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ASYMMETRIC MICHAEL ADDITIONS OF ESTER ENOLATES TO ENANTIOMERICALLY PURE VINYLIC SULFOXIDES

SYNTHESIS OF 3-SUBSTITUTED GLUTARATE ESTERS IN HIGH ENANTIOMERIC PURITY

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Abstract—Various ester enolate ions add as Michael donors to enantiomerically pure Michael acceptor cycloalkenone sulfoxides **1a** and **1b** and unsaturated lactone sulfoxides **3a** and **3b**. The level of asymmetric induction in some cases is extraordinarily high (≥95% e.e. of final 1,5-dicarbonyl products). Adduct ester lactones **5** and **6** can be converted easily into some synthetically versatile, trifunctional, 3-substituted glutarate esters of high enantiomeric purity. An efficient route to enantiomerically pure pentenolide sulfoxide (*S*)-(+)-**3b** is presented.

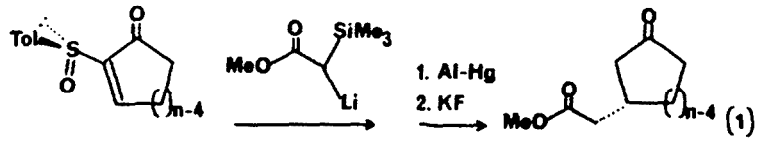
Asymmetric Michael additions of enolate ions present a significant stereochemical challenge of substantial current interest worldwide.[1] Previously, we have shown that conjugate additions of hydrocarbon groups (i.e. organometallic reagents) to 2-arylsulfinylcycloalkenones and to a 2-arylsulfinylbutenolide proceed in a very highly stereocontrolled fashion via either chelate or non-chelate pathways depending on the reaction conditions chosen.[2] We report here some highly diastereoselective non-chelate Michael additions of various ester enolate ions to several enantiomerically pure 2-arylsulfinylcycloalkenones and 2-arylsulfinyl unsaturated lactones producing ultimately 1,5-dicarbonyl adducts (i.e. ester ketones and ester lactones) in very good to excellent enantiomeric purity.

RESULTS AND DISCUSSION

Methyl α-lithioacetate added to the potent, doubly-activated, enantiomerically pure Michael acceptor (*S*)-(+)-2-(*p*-tolylsulfinyl)-2-cyclopentenone (**1a**)[2f] at −78° in THF to form conjugate adduct (*S*)-(−)-methyl 3-oxocyclopentylacetate (**2a**), after reductive cleavage of the sulfinyl group, in good chemical yield and in 60% enantiomeric purity as assayed by ^{13}C-NMR analysis of the corresponding ketals formed using enantiomerically pure (*R*,*R*)-2,3-butanediol;[3] comparison was made with the ^{13}C-NMR spectrum of the corresponding ketals formed from independently prepared *racemic* ester ketone **2a**. This result stands in contrast to a literature report[4] that *methyl* α-lithioacetate is not useful in some carbon–carbon bond-forming alkylation reactions. A comparable result (68% enantiomeric excess, e.e.) was obtained using diethyl sodiomalonate as Michael donor in ethanol solvent at +25°. Attempting to promote chelate-mode conjugate addition by treating Michael acceptor (*S*)-(+)-**1a** with zinc dibromide[2] *before* adding methyl α-lithioacetate still resulted in predominant non-chelate Michael addition. Lowering the reaction temperature to −105°, changing the solvent from THF to the more strongly chelating solvent 1,2-dimethoxyethane (DME),[2b] or adding 12-crown-4 to the THF solvent did not increase the degree of non-chelate asymmetric induction. Non-chelate asymmetric induction to the extent of 70% was achieved in excellent chemical yield using methyl α-trimethylsilyl-α-lithioacetate[5–7] at −78° in THF (Eq. 1). The absolute (*S*)-stereochemistry of Michael adduct (−)-**2a**, which is consistent with our proposed[2] non-chelate mode of addition involving approach of the Michael donor to the less-hindered *si* face of the prochiral β-carbon atom, was established by comparison with literature data.[8] We have very recently applied this type of stereocontrolled Michael addition of an acetate ester to an asymmetric total synthesis of fragrant, natural (−)-methyl jasmonate in extremely high enantiomeric purity.[9] We have also found that some *ketone* enolate ions add in a non-chelate conjugate mode to cyclopentenone sulfoxide (*S*)-(+)-**1a**, as exemplified by an asymmetric total synthesis of estrone methyl ether in high enantiomeric purity.[10]

Extremely high (i.e. 95%) asymmetric induction was accomplished during α-trimethylsilyl-α-lithioacetate addition to the cyclo*hex*enone sulfoxide *S*-(+)-**1b** (Eq. 1). The (*S*)-stereochemistry of conjugate adduct (−)-**2b** was established unambiguously by converting ester (−)-**2b** into the corresponding methyl ketone (i.e. 3-oxocyclohexylacetone) of known absolute stereochemistry.[11]

The ground-state conformation of β-carbonyl sulfoxides is reasonably expected to be such that the carbon–oxygen and sulfur–oxygen bond dipoles are oriented roughly in opposite directions to minimize dipole–dipole interactions.[12] Single-crystal X-ray analysis of cyclopentenone sulfoxide (*S*)-(+)-**1a** and



(S)-(+)-1a, n=5 (S)-(−)-2a, n=5, 70% e.e.

(S)-(+)-1b, n=6 (S)-(−)-2b, n=6, 95% e.e.

of butenolide sulfoxide (*S*)-(+)-**3a** confirmed this expectation, as shown in the accompanying drawings (Figs 1 and 2).

Asymmetric Michael addition of various ester enolate ions[13] to butenolide sulfoxide (*S*)-(+)-**3a**[2] proceeded smoothly in a non-chelate mode to form, after reductive cleavage of the sulfinyl group, 1,5-dicarbonyl adduct (*S*)-(+)-**5** in 27–91% enantiomeric excess (see Scheme 1 and Table 1). The best results (78–91% e.e.) were obtained using α-lithio α-phenylthioacetates[14] as Michael donors. Modest asymmetric induction was found using t-butyl acetate as a Michael donor. Benzyl acetate and t-butyl *p*-tolylthioacetate gave modest chemical yields of Michael adducts, and methyl trimethylsilylacetate gave erratic results. The enantiomeric purity of the MEM ester adduct was assayed by converting it into the corresponding methyl ester (Eq. 2),[15] which was exposed to the ^{1}H-NMR chiral shift reagent Eu(hfc)$_3$; the methyl ester region of its ^{1}H-NMR spectrum was compared with that of independently prepared racemic methyl ester lactone **5a** in the presence of Eu(hfc)$_3$. The absolute (*S*)-stereochemistry of adduct (+)-**5c** was established by correlating it with (*R*)-(+)-3-methylvalerolactone (see Scheme 2).[16] Because t-butyl ester lactone (*S*)-(+)-**5c** can be prepared from the corresponding MEM[15] ester (via the carboxylic acid as in Eq. 2), t-butyl ester lactone (+)-**5c** should be available in 78% e.e. An intermediate in the correlation (Scheme 2) is 3-phenylselenomethyl glutaric acid methyl t-butyl mixed diester (*S*)-(+)-**8**, which is a small, chiral, non-racemic molecule having three different functional groups and thereby possessing a great versatility for various chemoselective transformations (e.g. **8** → **9**).

Asymmetric Michael addition of MEM α-lithio-

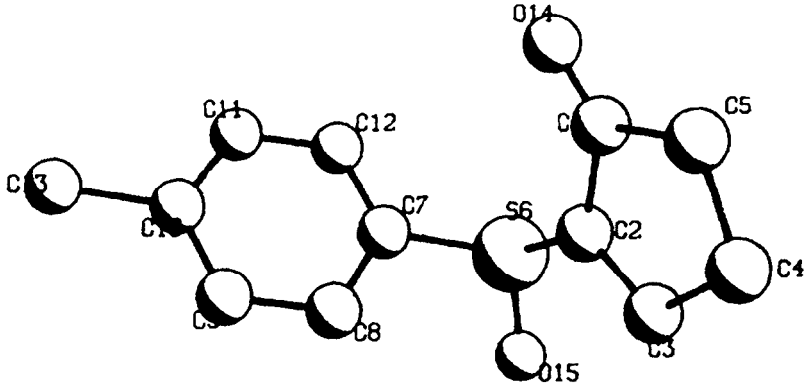


Fig. 1. (*S*)-(+)-**1a**.

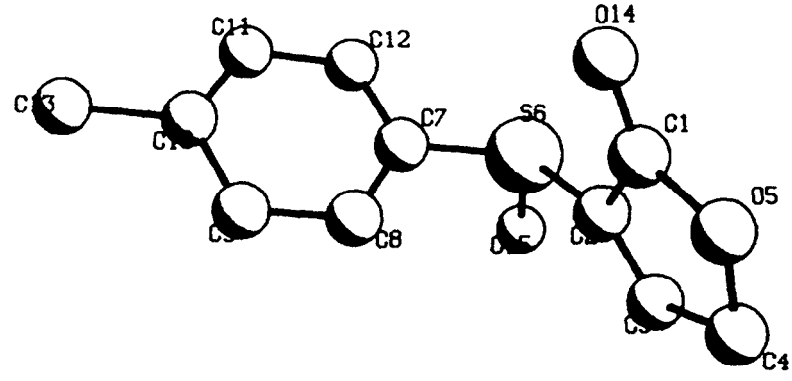
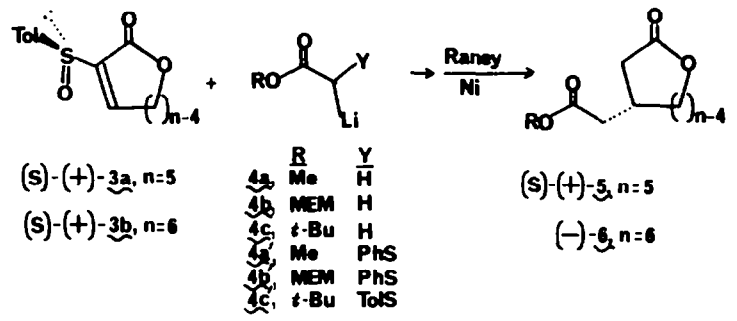
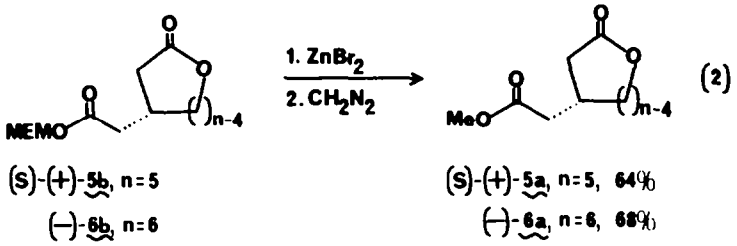


Fig. 2. (*S*)-(+)-**3a**.



Scheme 1.



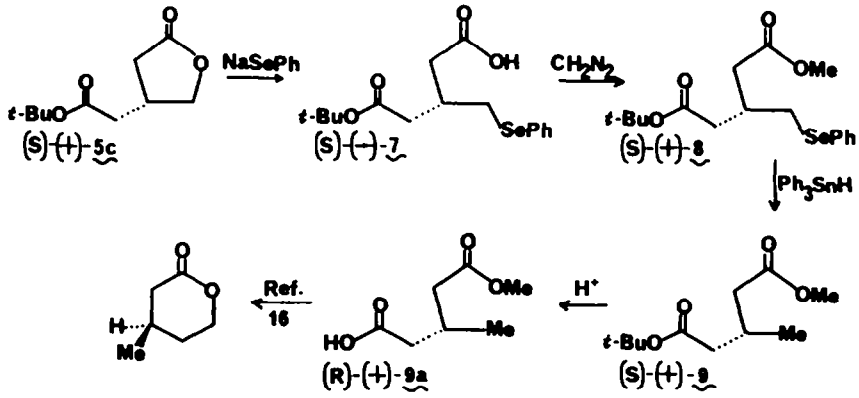
acetate[17] and of the corresponding α-phenylthio analog to pentenolide sulfoxide (*S*)-(+)-**3b** proceeded with almost complete π-facial diastereoselectivity (>96% e.e. after one-pot reductive removal of *both* the sulfinyl and the thioether sulfur groups, Table 1).

Table 1. Conversion of **3a** → **5** and **3b** → **6** via Scheme 1

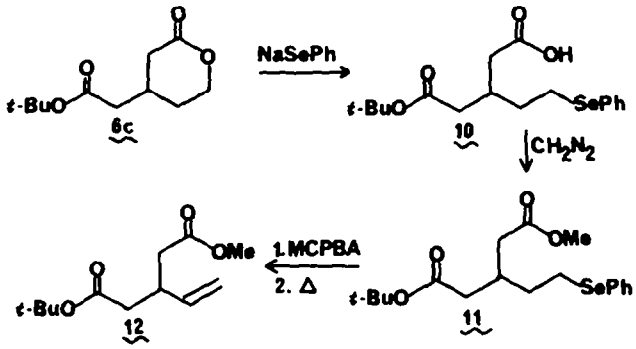
Reactant	Reagent	Product, R	% yield	% e.e.
3a	4a	Me	65	80
3a	4b	MEM	71	—
3a	4c	t-Bu	82	43
3a	4a'	Me	100	91
3a	4b'	MEM	79	78
3b	4b	MEM	62	>96
3b	4c	t-Bu	92	63
3b	4a'	Me	92	91
3b	4b'	MEM	94	>96
3b	4c'	t-Bu	29	88

Although no simple compound of known absolute stereochemistry was available for correlation with (−)-**6**, we assume that, in excellent analogy with the very closely related five-membered ring lactone homolog, the absolute stereochemistry of (−)-**6** is as shown (i.e. *S*), consistent with a non-chelate mode of Michael addition.

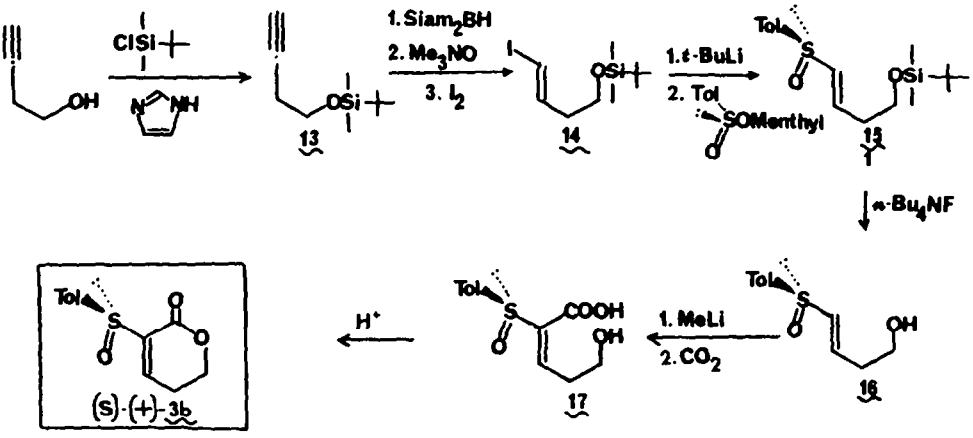
MEM ester (−)-**6b** of >96% e.e. can be hydrolyzed into the corresponding acid[15] and then converted into t-butyl ester (−)-**6c**. We have shown (Scheme 3) that the lactone ring of such a t-butyl ester pentanolide can be opened chemospecifically with sodium phenylselenide[18] and that the resultant carboxylic acid **10** can be converted into its methyl ester **11**. Like glutarate mixed diester (*S*)-(+)-**8**, 3-selenyl glutarate mixed diester **11** is a small, chiral molecule having three different functional groups and is thereby able to undergo many chemoselective operations. One example involved selenoxide formation and β-elimination[19] to form very versatile tri-functional synthon **12**. Because the phenylselenyl group can be replaced by various alkyl



Scheme 2.



Scheme 3.

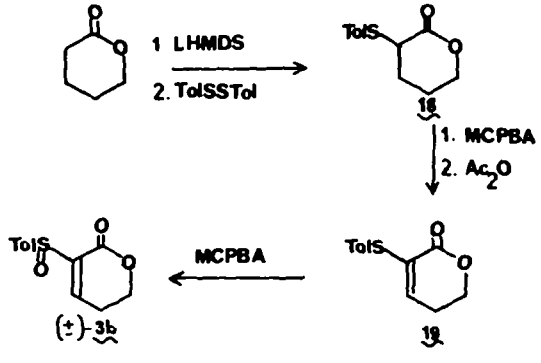


Scheme 4.

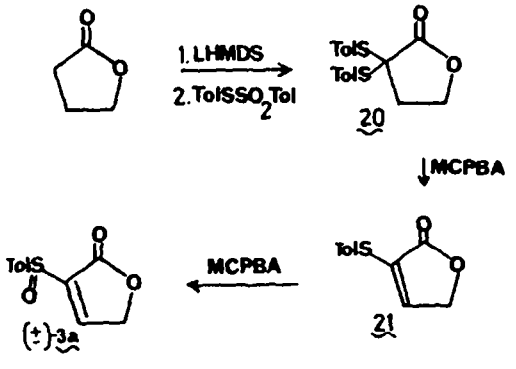
groups via coupling with organometallic reagents[20] and can also serve as a precursor to carbon-based radicals which can enter into intramolecular and intermolecular carbon–carbon bond-forming reactions,[21] tri-functional gluturate **11** is indeed a flexible, chiral synthon of very considerable synthetic potential.

3-Substituted glutaric acid mono-esters (e.g. **9a**, **10**) are extremely versatile building blocks which have already been used effectively in synthesis, for example, of radiolabelled myocardial imaging agents,[22] insect pheromones[16] and steroid side-chains.[23] Enzymatic procedures have been applied successfully to kinetic resolution of *meso*-glutarate diesters via stereocontrolled hydrolysis of one enantiotopic ester group.[24] Our results represent a useful chemical process complementary to the enzymatic procedure for asymmetric synthesis of 3-substituted glutaric acid mono-esters of high enantiomeric purity.

Preparations of enantiomerically pure and of racemic pentenolide sulfoxides (*S*)-(+)-**3b** and (±)-**3b**[25a] and of racemic butenolide sulfoxide (±)-**3a**[25b–d] are summarized in Schemes 4–6, respectively.



Scheme 5.



Scheme 6.

EXPERIMENTAL

M.ps were determined using a Mel-Temp m.p. apparatus or a Sybron/Thermolyne Model MP-12615 m.p. apparatus; m.ps and b.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 599B spectrometer and were calibrated using the 1601 cm^{-1} polystyrene absorption as reference. ^{1}H-NMR spectra were obtained using a Varian CFT-20 or a Varian XL-400 spectrometer operating at 80 or 400 MHz, respectively. Chemical shifts are reported in ppm downfield from a TMS internal standard, and the resonances are noted as being a singlet (s), a doublet (d), a triplet (t), or a multiplet (m). Compounds containing silicon were run without TMS and were referenced to $CHCl_3$ (singlet at 578.1 Hz at 80 MHz). ^{13}C-NMR spectra were recorded using a Varian XL-400 spectrometer operating at 100 MHz; all spectra reported are proton-noise decoupled and the chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (76.9 ppm). Specific rotations were determined with a Perkin–Elmer 141 variable wavelength polarimeter using a thermostated 1 dm quartz window cell of 1 ml capacity. Concentrations (c) for specific rotations are reported in units of g/100 ml. Gas–liquid phase chromatography (GLPC) was performed on a Hewlett-Packard 5890 capillary gas chromatograph. Mass spectra were performed by the Middle-Atlantic Regional Mass Spectrometry Facility, Johns Hopkins University, Baltimore, Maryland. Microanalytical combustion analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

The tetrahydrofuran (THF), 2,5-dimethyltetrahydrofuran (DMTHF) and diethyl ether (Et_2O) were distilled from Na/benzophenone. The methylene chloride (CH_2Cl_2) was dried over 3 Å sieves. The hexamethyldisilazane and dimethyl formamide (DMF) were distilled from CaH_2, and the *m*-chloroperbenzoic acid was stirred with phosphate buffer (pH 7.5) prior to use. Alkyllithiums were titrated using diphenylacetic acid/THF (MeLi)[26] or 2,5-dimethoxybenzyl alcohol/C_6H_6 (n-BuLi, t-BuLi).[27]

The following reagents were used as received: Ac_2O, methanesulfonic acid, tetra-n-butylammonium fluoride (1 M THF), 1 M borane–THF soln, 2 M 2-methyl-2-butene soln, t-butyldimethylsilyl chloride, imidazole, 3-butyn-1-ol, ditolyl disulfide, δ-valerolactone, trimethylamine-N-oxide dihydrate and (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (Aldrich).

*Conjugate addition to cyclopentenone sulfoxide (S)-(+)-**1a***

A flame-dried 10 ml round-bottomed flask was charged with 1 ml of dry THF and 266 μl (1.26 mmol) of hexamethyldisilazane and cooled to −78°. After 10 min, 800 μl of 1.5 M n-BuLi (1.20 mmol) was added and the mixture was stirred for 40 min at −78° under N_2. Methyl trimethylsilylacetate (Aldrich, 197 μl, 1.20 mmol) was added and, after 2 h, a −78° soln of 132 mg (0.60 mmol) of (*S*)-(+)-**1a** in 5 ml of THF was added dropwise over 10 min via precooled cannula. After the addition, the pale yellow soln was stirred for 30 min at −78°. The mixture was then quenched by adding a sat soln of sodium hydrogen phosphate and warmed to room temp. The contents in the flask were extracted with Et_2O (3 × 10 ml) and the combined organic layers were washed with H_2O and dried over $MgSO_4$. Filtration and solvent evaporation gave a white solid, which was used directly in the next step without further purification.

The crude conjugate adduct from the previous reaction was dissolved in 10 ml of aq THF soln (THF–H_2O, 9:1) and cooled to −15°. Al amalgam (6.0 mmol) was added and the mixture was warmed slowly to room temp and stirred overnight.[28] Anhyd $MgSO_4$ was added to the gray slurry and the organic layer was filtered off. The slurry was washed with Et_2O (2 × 10 ml). Evaporation of the solvent under reduced pressure gave a pale yellow liquid which was purified by column chromatography (eluting solvent: Et_2O–hexane, 1:9) to give 133 mg [97% from (*S*)-(+)-**1a**] of the desulfurized keto ester: ^{1}H-NMR ($CDCl_3$) δ 0.06 (s, 9H), 2.10–3.15 (m, 8H), 3.61 (s, 3H).

Protodesilylation was carried out in a 20% aq MeOH soln (8 ml) of the above trimethylsilyl ester (130 mg, 0.54 mmol) with KF (63 mg, 1.14 mmol) stirred at room temp for 6 h.[29] The mixture was concentrated under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 10 ml). The combined extracts were washed with H_2O and dried over $MgSO_4$. Filtration and solvent evaporation gave 88 mg of a pale yellow liquid which was purified by column chromatography (eluting solvent: Et_2O–hexane, 2:8) to give 80 mg (95%) of (−)-**2a**: IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4–2.8 (m, 9H), 3.70 (s, 3H); mass spectrum *m/z* 156 (M^+). Kugelrohr distillation gave 70 mg of a colorless liquid: $[\alpha]_D^{18}$ −82.2° (*c* 1.46, $CHCl_3$). Lit. value: $[\alpha]_D^{18}$ −121.0° (*c* 1.47, $CHCl_3$).[8]

Keto ester (−)-**2a** (65 mg, 0.416 mmol) was dissolved in 15 ml of C_6H_6 along with 76 μl (0.833 mmol) of (*R*,*R*)-(−)-2,3-butanediol (Aldrich) and a catalytic amount of *p*-toluenesulfonic acid in a 25 ml round-bottomed flask fitted with a Dean–Stark trap. The ketone was ketalized by heating to reflux for 50 h and removing the H_2O generated by azeotropic distillation. The reaction mixture was cooled to room temp, the C_6H_6 was removed under vacuum and the residue was dissolved in 20 ml of pentane. The pentane was washed with sat $NaHCO_3$ aq and $NaHSO_3$ aq (5%) and dried over $MgSO_4$. Filtration and solvent evaporation gave an oil which was purified by column chromatography (eluting solvent: Et_2O–hexane, 1:9) to give 50 mg (53%) of the desired ketal. No starting ketone **2a** was detectable. Relative integration of the diastereotopic carbon resonances at 30.108 ppm and at 29.720 ppm in the ^{13}C-NMR spectrum indicated a 70% diastereomeric excess. For comparison, the diastereomeric ketals of (±)-**2a** were prepared and showed a 1.07:1.00 ratio of resonances at 30.061 and at 29.667 ppm.

*Conjugate addition to cyclohexenone sulfoxide (S)-(+)-**1b***

Conjugate addition of methyl trimethylsilylacetate to cyclohexenone sulfoxide (*S*)-(+)-**1b** was performed in a similar manner as described above for cyclopentenone sulfoxide (*S*)-(+)-**1a**. Lithium hexamethyldisilazide was prepared as usual and then 164 μl (1.00 mmol) of methyl trimethylsilylacetate was added and stirred for 2 h at −78°. A precooled (−78°) THF (4 ml) soln of (*S*)-(+)-**1b** was added dropwise via a cannula over 10 min. The mixture was quenched with a sat soln of sodium hydrogen phosphate after being stirred for 30 min. Usual workup gave 212 mg of a colorless oil, which was reductively cleaved using 40.5 mg (1.5 mmol) of Al–Hg in aq THF soln. The crude colorless oil (150 mg) obtained from this reaction was purified by column chromatography (eluting solvent: Et_2O–hexane, 1:9) to give 95 mg [78% from (*S*)-(+)-**1b**] of desulfurized keto ester: ^{1}H-NMR ($CDCl_3$) δ 0.05 (s, 9H), 2.05–3.10 (m, 10H), 3.54 (s, 3H).

Protodesilylation of 80 mg (0.33 mmol) of the above trimethylsilyl-ketomethylester with 30 mg (0.66 mmol) of KF in 10 ml of 20% aq MeOH gave 51 mg (90%) of (−)-**2b**: IR (neat) 1740–1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4–2.5 (m, 11H), 3.66 (s, 3H); $[\alpha]_D^{25}$ −10.0° (*c* 1.50, $CHCl_3$).

Diastereomeric ketals were prepared from 26 mg (0.153 mmol) of (−)-**2b** and 27 mg (0.306 mmol) of (*R*,*R*)-(−)-2,3-butanediol in refluxing C_6H_6 (50 h) with a catalytic amount of *p*-toluenesulfonic acid. The crude product (51 mg) obtained from this reaction was purified by column chromatography (eluting solvent: Et_2O–hexane, 1:9) to give 30 mg (80%) of the desired ketals. No starting ketone (−)-**2b** was detectable. Relative integration of the diastereotopic carbon resonances at 36.654 ppm and at 35.645 ppm in the ^{13}C-NMR spectrum indicated 95% diastereomeric excess. For comparison, the diastereomeric ketals of (±)-**2b** were prepared and showed a 1.10:1.00 ratio of resonances at 36.655 ppm and at 35.647 ppm.

*Preparation of (±)-butenolide sulfoxide **3a**[25b–d]*

A soln of 11.58 ml (19.1 mmol) of 1.55 M n-BuLi in hexane was added dropwise to a cooled (−78°) soln of 4.17 ml (19.7 mmol) of hexamethyldisilazane in 15 ml of THF. After 45 min, 690 μl (898 mmol) of γ-butyrolactone was introduced slowly. After an additional 30 min at −78°, a soln of 5.0 g of *p*-tolyl *p*-toluenesulfinate in 25 ml of THF was added via a cannula. Stirring was continued for another 4 h, at which time heavy precipitation was observed. The reaction was allowed to warm

slowly to room temp overnight and then quenched with H_2O. The soln was extracted with Et_2O and EtOAc. The combined organic layers were washed with sat $NaHCO_3$ aq and H_2O. The soln was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil which, after crystallization (CH_2Cl_2–hexane), afforded 2.43 g (82%) of **20** as white prismatic crystals: m.p. 66–67°; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.54 (4H, d, J = 8.30 Hz), 7.161 (4H, d, J = 8.30 Hz), 4.163 (2H, t, J = 6.35 Hz), 2.395 (2H, t, J = 6.35 Hz), 2.35 (6H, s); IR ($CHCl_3$) 1780 cm^{-1}; MS (70 eV) *m/z* 330 (M^+). (Found: C, 65.38; H, 5.27; S, 19.21. Calc for $C_{18}H_{18}O_2S_2$: C, 65.53; H, 5.49; S, 19.67%.)

A cooled (0°) soln of **20** (2.17 g, 6.57 mmol) in 25 ml of $CHCl_3$ was treated with 1.25 g (7.23 mmol) of 99% *m*-chloroperbenzoic acid. After 10 min, a sat soln of $NaHCO_3$ aq was added and the mixture was diluted with $CHCl_3$ (50 ml), washed with $NaHCO_3$ aq (2 ×) and then with H_2O (2 ×). The organic soln was dried over $MgSO_4$ and filtered, then boiled for 2.5 h. Thereafter, it was concentrated *in vacuo*. The residual oil was purified by short path chromatography (25 g silica, 20% Et_2O–hexane) to give, after recrystallization from Et_2O–hexane, 1.21 g (89.1%) of **21** as white cubic crystals: m.p. 64–65°; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.50–7.18 (4H, AB, J_{AB} = 8.3 Hz), 6.57 (1H, t, J = 2.1 Hz), 4.76 (2H, d, J = 2.1 Hz), 2.38 (3H, s); IR ($CHCl_3$) 1760 cm^{-1}; MS (70 eV) *m/z* 206 (M^+). (Found: C, 64.26; H, 4.97; S, 15.68. Calc for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54%.)

A cooled (0°) soln of **21** (65 mg, 0.31 mmol) in 25 ml of $CHCl_3$ was treated with 57 mg (0.33 mmol) of 99% *m*-chloroperbenzoic acid. After 10 min at 0°, the soln was diluted with 25 ml of $CHCl_3$ and washed with sat $NaHCO_3$ aq, then with brine (3 ×), dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from CH_2Cl_2–Et_2O–hexane afforded 65.5 mg (93.5%) of (±)-**3a**, as white prismatic crystals, m.p. 113–119°.[25b–d]

Preparation of (±)-pentenolide sulfoxide **3b**[25a]

A soln of 2.15 ml (10.2 mmol) of hexamethyldisilazane in 10 ml of THF was cooled to −35° and treated with 4.32 ml (10.2 mmol) of 2.36 M n-BuLi in hexane. This soln was stirred for 30 min at −35° and then cooled to −78°. A soln of 450 μl of δ-valerolactone (4.85 mmol) in 4.85 ml of THF was added via a syringe over 15 min. After stirring for 30 min at −78°, a soln of 2.51 g (10.2 mmol) of *p*-tolyl disulfide in 10 ml of THF was added. The mixture was stirred as it was warmed to room temp. After stirring overnight, the resulting clear yellow soln was quenched with sat NH_4Cl aq. This was poured into a separatory funnel, diluted with H_2O, and extracted with Et_2O (3 × 50 ml). The Et_2O layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 2.65 g of a yellow liquid which had a stench. The product was isolated via short path chromatography (20 g silica, 50% Et_2O–hexane) which gave 450 mg (42%) of clear, colorless, oily sulfide **18** which solidified on standing: m.p. 44–45°; ^{1}H-NMR ($CDCl_3$) δ 7.50–7.09 (4H, m), 4.40 (2H, m), 3.85 (1H, t, J = 3.4 Hz), 2.34 (3H, s), 2.2–1.8 (4H, m); IR ($CHCl_3$) 1725 cm^{-1}; MS (70 eV) *m/z* 222 (M^+). (Found: C, 65.09; H, 6.32; S, 14.74. Calc for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42%.)

A soln of 1.05 g (4.73 mmol) of **18** in 35 ml of CH_2Cl_2 was cooled to 0° and treated with 844 mg (4.55 mmol) of 93% *m*-chloroperbenzoic acid in four portions over 10 min. The ice bath was removed, and the soln was stirred at 25° for 25 min. The clear colorless soln was then treated with 625 μl (6.62 mmol) of Ac_2O and 40 μl (0.62 mmol) of methanesulfonic acid. The pale yellow soln was stirred overnight at 25°, giving a clear, dark orange soln. The reaction was diluted with H_2O and then washed with sat $NaHCO_3$ aq. The aq layers were back-extracted with CH_2Cl_2. The opaque, pink CH_2Cl_2 layers were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 1.39 g of a dark orange liquid. The product was purified via short path chromatography (14 g silica, 50% Et_2O–hexane) giving 848.3 mg (81.6%) of **19** as a yellow solid. The solid was washed with Et_2O. After decanting the Et_2O, 667.7 mg (64%) of white solid **19** remained: m.p. 75–77°; ^{1}H-NMR ($CDCl_3$) δ 7.39–7.00 (4H, m), 6.06 (1H, t, J = 4.6 Hz), 4.30 (2H, t, J = 6.1 Hz), 2.28 (3H, s), 2.44–2.22 (2H, m); IR ($CHCl_3$) 1710 cm^{-1}; MS (70 eV) *m/z* 220 (M^+). (Found: C, 65.76; H, 5.67. Calc for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49%.)

A soln of 667 mg (3.03 mmol) of **19** in 25 ml of CH_2Cl_2 was cooled to 0° and treated with 534 mg (2.88 mmol) of 93% *m*-chloroperbenzoic acid in three portions over 10 min. The soln was stirred for 10 min at 0° and then 30 min at 25°. The mixture was placed in a separatory funnel and washed with $NaHCO_3$ aq. The aq layers were combined and back-extracted with CH_2Cl_2. The CH_2Cl_2 layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* leaving 718.3 mg which was purified by short path chromatography (7.2 g silica, EtOAc) to give 642 mg (89.7%) of a pale pink solid. This was recrystallized (EtOAc–Et_2O–petroleum ether) to give 534.1 mg (74.6%) of white, free-flowing solid pentenolide sulfoxide (±)-**3b**: m.p. 95–96.5°; ^{1}H-NMR ($CDCl_3$) δ 7.68–7.25 (5H, m), 4.44 (1H, m), 4.27 (1H, m), 2.70 (2H, m), 2.38 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 159.68, 143.23, 142.24, 139.6, 139.24, 129.84, 125.42, 66.16, 24.68, 21.34; IR ($CHCl_3$) 1720 cm^{-1}; MS (70 eV) *m/z* 236 (M^+). (Found: C, 60.92; H, 5.00; S, 13.76. Calc for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57%.)

Preparation of (+)-pentenolide sulfoxide **3b**

Acetylenic silyl ether **13**. A soln of 9 g (59.7 mmol) of t-butyldimethylsilyl chloride, 8.5 g (124.9 mmol) of imidazole, 8.2 ml (54.2 mmol) of 3-butyn-1-ol in 10 ml of DMF was heated to 35° in an oil bath overnight. The soln was diluted with H_2O and extracted with Et_2O (3 × 50 ml). The Et_2O extracts were combined and washed with H_2O (2 × 25 ml) dried with $MgSO_4$, filtered and concentrated *in vacuo*. Kugelrohr distillation (50° at 2.8 mmHg) yielded 9.35 g of clear, colorless liquid **13** (93.8%): ^{1}H-NMR ($CDCl_3$) δ 3.75 (2H, t, J = 7.0 Hz), 2.40 (2H, dt, J_t = 7.0 Hz, J_d = 2.6 Hz), 1.96 (1H, t, J = 2.6 Hz), 0.90 (9H, s), 0.08 (6H, s); IR ($CHCl_3$) 3200, 2110 (weak), 1100, 640 cm^{-1}.

(E)-Vinylic iodide silyl ether **14**

To 50 ml (50 mmol) of a 1 M borane–THF soln at −10° was added 50 ml (100 mmol) of a 2 M 2-methyl-2-butene soln dropwise at a rate to ensure that the temp of the mixture remained at 0°. After stirring for 2 h, 4.86 g (26.4 mmol) of alkyne **13** was added over 20 min. After stirring for 30 min at 0°, the mixture was warmed to 25° and stirred for an additional 2 h. After cooling to 0°, 10.96 g (98.6 mmol) of $Me_3NO \cdot 2H_2O$ was added in three portions over 15 min. The mixture was warmed to 25° and stirred for 30 min. This was then poured into 425 ml of 15% NaOH aq, immediately followed by a soln of 18.7 g (73.7 mmol) of I_2 in 53 ml of THF. After stirring for 30 min at 25°, the layers were separated and the aq layer was extracted with Et_2O. The organic layers were combined and then washed with 2% sodium thiosulfate (2 ×) and sat Na_2SO_4 (1 ×). After drying with $MgSO_4$, the soln was filtered and concentrated *in vacuo* leaving 12.77 g of a yellow liquid. Purification by short path chromatography (120 g silica, hexane) gave 7.24 g (88%) of silyl ether **14**: ^{1}H-NMR ($CDCl_3$) δ 6.55 (1H, dt, J_d = 14.4 Hz, J_t = 7.1 Hz), 6.06 (1H, dt, J_d = 14.4 Hz, J_t = 1.0 Hz), 3.65 (2H, m), 2.25 (2H, m), 0.88 (9H, s), 0.04 (6H, s); IR ($CHCl_3$) 1605, 1035, 840 cm^{-1}.

(E)-Vinylic sulfoxide silyl ether **15**

To a soln of 1.99 g (6.83 mmol) of **14** in 44 ml of Et_2O at −78° was added 7.5 ml (13.4 mmol) of 1.78 M t-BuLi in hexane via a syringe pump over 1 h giving a clear yellow soln. After stirring for an additional hour at −78°, this vinyl anion soln was added over 1 h via a dry-ice cooled cannula to a −78° soln of 2.25 g (7.65 mmol) of (−)-menthyl-(*S*)-*p*-toluenesulfinate in 115 ml of THF. After stirring for 1 h at −78°, the soln was warmed to −40° over 1.75 h and then quenched with sat NH_4Cl aq, diluted with H_2O and extracted with Et_2O. The soln was dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 3.86 g of an orange–brown liquid which was purified via short path chromatography (30 g silica, 1 : 1 hexane–Et_2O) to give 1.347 g (65.2%) of **15**: ^{1}H-NMR ($CDCl_3$) δ 7.37–7.04 (4H, m), 6.5–5.9 (2H, m), 3.52 (2H, m), 2.26 (2H, m), 2.20 (3H, s), 0.66 (9H, s), 0.16 (6H, s); IR ($CHCl_3$) 1035 cm^{-1}.

(E)-(+)-Vinylic sulfoxide alcohol **16**

A soln of 232.2 mg (0.715 mmol) of **15** in 2.3 ml of THF was cooled to 0° and treated with 1.4 ml of 1.0 M (1.4 mmol) tetra-n-butylammonium fluoride in THF via a syringe over 5 min. The clear orange soln was stirred for 40 min at 0°. After diluting with H_2O, and concentrating by rotary evaporation, the residue was extracted with CH_2Cl_2, dried with $MgSO_4$, filtered and concentrated *in vacuo*, leaving 203.4 mg of a dark yellow oil. The product was isolated by short path chromatography (4 g silica, 10% Me_2CO–Et_2O) to give 124.2 mg (82.7%) of **16**: ^{1}H-NMR ($CDCl_3$) δ 7.57–7.35 (4H, m), 6.62–6.21 (2H, m), 3.78 (2H, m), 2.41 (3H, s), 2.49 (2H, m), 1.58 (1H, t, J = 2.7 Hz). When shaken with D_2O the 1.58 triplet disappeared and the 3.78 multiplet became a triplet (J = 6.3 Hz). IR ($CHCl_3$) 3360 (br), 1030 cm^{-1}; MS (70 eV) *m/z* 210 (M^+); $[\alpha]_D^{25}$ + 162.7° (*c* 0.49, $CHCl_3$).

(+)-Hydroxycarboxylic acid **17**

A soln of 532.2 mg (2.53 mmol) of **16** in 12 ml of THF was cooled to − 78° and treated with 7.44 ml (6.84 mmol) of a 0.92 M soln of MeLi in Et_2O via a syringe, resulting in a yellow opaque soln. After stirring for 1 h at − 78°, dry gaseous CO_2 was introduced into the vessel, causing the soln to change to opaque white. The mixture was stirred for 2.5 h as it was warmed to 0°. The reaction was quenched with sat NH_4Cl aq, diluted with brine and extracted with CH_2Cl_2 removing any unreacted starting material. The aq layer was returned to the separatory funnel, EtOAc was added, and the aq layer was acidified with 20% HCl giving a white milky soln, which was immediately shaken with the EtOAc. After extracting with EtOAc, the EtOAc was dried with $MgSO_4$, filtered and concentrated *in vacuo* to give 598.6 mg (93%) of a yellow oil. Hydroxycarboxylic acid **17** crystallized after being placed in the refrigerator overnight: m.p. 117–124°; $[\alpha]_D^{25}$ + 235.6° (*c* 0.24, Me_2CO); ^{1}H-NMR ($CDCl_3$) δ 7.77–7.21 (5H, m), 3.92 (2H, t, J = 6.2 Hz), 3.1 (2H, m), 2.50 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 162.2, 142.3, 140.7, 140.1, 137.9, 128.2, 124.6, 59.4, 31.8, 19.6; IR ($CHCl_3$) 3350 (broad), 1710 cm^{-1}.

(+)-Pentenolide sulfoxide **3b**

A soln of 598 mg (2.35 mmol) of **17** in 500 ml of $CHCl_3$ with 2 ml of AcOH, was stirred under N_2 at 25° for 8 days. The $CHCl_3$ was washed with H_2O, and the aq layer was back-extracted with $CHCl_3$. The $CHCl_3$ was dried with $MgSO_4$, filtered and concentrated *in vacuo* leaving 429.8 mg of an orange oil. Short path chromatography (4.5 g silica, EtOAc) led to 255 mg of an off-white solid which was recrystallized from EtOAc–Et_2O–petroleum ether to yield 225 mg (42%) of white solid **3b**: m.p. 93–94°; ^{1}H-NMR ($CDCl_3$) δ 7.68–7.25 (5H, m), 4.45 (1H, m), 4.27 (1H, m), 2.70 (2H, m), 2.37 (3H, s); IR ($CHCl_3$) 1720 cm^{-1}; $[\alpha]_D^{25}$ + 212.78° (*c* 0.27, $CHCl_3$). (Found: C, 61.15; H, 5.30; S, 13.71. Calc for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12; S, 13.57%.)

The enantiomeric purity (>98% e.e.) of (+)-**3b** was determined using the chiral NMR shift reagent Eu(hfc)$_3$.[30] Complexation of racemic pentenolide sulfoxide with 0.68 equiv of Eu(hfc)$_3$ produced two diastereotopic signals of equal intensity for H-3 at δ 14.63 and δ 14.33. Complexation of pentenolide sulfoxide (+)-**3b** with 0.67 equiv of Eu(hfc)$_3$ produced a similar downfield shift for H-3 (from δ 7.67 to δ 13.88) with only one diastereotopic resonance present.

MEM phenylthioacetate (**4b'**)

A cooled (0°) soln of 1 g (5.94 mmol) of thiophenoxyacetic acid and 2.59 ml (14.8 mmol) of diisopropylethylamine in 12 ml of CH_2Cl_2 was stirred for 30 min, at which time 1.70 ml (14.8 mmol) of methoxyethoxymethyl (MEM) chloride was added slowly. After 20 min at 0°, the soln was allowed to warm slowly to room temp for 30 min and then set $NaHCO_3$ aq was introduced and the soln was stirred for an additional 20 min. After diluting with 80 ml of Et_2O, the soln was washed with brine (3 ×), dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by Kugelrohr distillation at 140°C/1 mmHg to yield 1.2 g (78.7%) of light yellow, oily MEM phenylthioacetate (**4b'**): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.44–7.26 (5H, m), 5.38 (2H, s), 3.76–3.51 (4H, m), 3.71 (2H, s), 3.40 (3H, s); IR ($CHCl_3$) 1740 cm^{-1}.

t-*Butyl p-tolylthioacetate* (**4c'**)

A soln of 1.46 ml (2.1 mmol) of 1.47 M n-BuLi in hexane was added dropwise to a cooled (− 78°) soln of 332 μl (2.4 mmol) of diisopropylamine in 20 ml of THF. After 1 h at − 78°, 377 μl (2.8 mmol) of t-butyl acetate (**4c**) was added and stirring was continued at − 78° for an additional 15 min. A soln of 0.6 g (2.1 mmol) of *p*-tolyl *p*-toluenethiosulfinate in 10 ml of THF was added slowly via a cold cannula. After 10 min, the reaction was warmed slowly to 0° and then quenched with H_2O, diluted with Et_2O (100 ml) and washed in brine (5 ×). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was purified by short path chromatography [15 g silica, (a) hexane, (b) 20% Et_2O–hexane] to yield 295 mg (57%) of slightly yellow, oily ester **4c'**: ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.28–7.14 (4H, AB), 3.50 (2H, s), 2.31 (3H, s), 1.40 (9H, s); IR ($CDCl_3$) 1740 cm^{-1}.

(+)-Methyl ester butanolide **5a**

(a) A soln of 81 μl (0.12 mmol) of 1.5 M n-BuLi in hexane was added slowly to a cooled (− 78°) soln of 26 μl (0.12 mmol) of hexamethyldisalazane in 1.0 ml of THF. After 45 min, 172 μl (0.1 mmol) of a 0.576 M soln of **4a'** in 1:1 hexane–cyclohexane was introduced slowly and stirring was continued for an additional hour. This soln was treated with 18.3 mg (0.082 mmol) of cold (− 78°) (+)-**3a** soln in 4 ml of THF, which was added via a cold (− 78°) cannula. After 5 min at − 78°, the mixture was quenched with 0.6 ml of 1 N HCl and allowed to warm slowly to room temp. Brine was added, followed by successive extractions with Et_2O (2 × 5 ml) and EtOAc (2 × 10 ml). The combined organic layers were washed with brine (3 ×), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a light yellow oil.

The oil was dissolved in 15 ml of Me_2CO together with 1 ml of Raney Ni, prewashed (4 ×) with Me_2CO. This mixture was stirred rapidly overnight at room temp. The Raney Ni was filtered and washed successively with Me_2CO (2 × 10 ml) and EtOAc (2 × 10 ml). Evaporation of the combined organic solvents afforded 13.0 mg (100%) of colorless oily, Michael adduct **5a** which was homogeneous by capillary GC: $[\alpha]_{589}^{25}$ 14.65° (*c* 1.2, $CHCl_3$); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.63–3.73 (2H, ABX), 3.71 (3H, s), 3.2–2.9 (1H, m), 2.90–2.18 (4H, m); IR ($CHCl_3$) 1770, 1730 cm^{-1}. Precise mass calc for $C_7H_{10}O_4$ *m/z* 158.0579. Found: 158.0586. Using Eu(hfc)$_3$ as a chiral ^{1}H-NMR shift reagent, the e.e. was found to be 91% by comparing the characteristic methyl peaks at 7.68 and at 7.60 ppm with those from racemic **5a** prepared independently.

(b) The same product **5a** was obtained by following the above procedure with 2 equiv of methyl acetate (**4a**). The yield was 65.1% and the e.e. was 80%.

(+)-MEM ester butanolide **5b**

The product (+)-**5b** was obtained as a light yellow oil in 79% yield by following the same procedure as for (+)-**5a**, with 1.5 equiv of the MEM phenylthioacetate **4b'**. This material was homogeneous on capillary GC: $[\alpha]_{589}^{25}$ 6.81° (*c* 1.6, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.325 (2H, s), 4.564–3.986 (2H, ABX), 3.794–3.523 (4H, m), 3.365 (3H, s), 2.980 (1H, heptet, J = 7.33 Hz), 2.765–2.227 (4H, m); IR ($CHCl_3$) 1735, 1775 cm^{-1}. Precise mass calc for $C_8H_{11}O_5$ *m/z* 187.0607. Found 187.0609.

(+)-t-Butyl ester butanolide **5c**

The product **5c** was obtained as a colorless oil in 82% yield by following the same procedure as for the preparation of **5a** but using 3 equiv of t-butyl acetate (**4c**): $[\alpha]_D^{25}$ 4.51° (*c* 1.4, $CHCl_3$); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.62–3.90 (2H, ABX), 2.95–2.18 (5H, m), 1.45 (s, 9H); IR ($CHCl_3$) 1740 cm^{-1}; MS (70 eV) *m/z* 199 ($M-1$)$^+$. The e.e. was found to be 43% by comparison with 3-phenylselenyl glutarate mixed diester (+)-**8** which was derived from this product.

(−)-Methyl ester pentanolide **6a**

The product (−)-**6a** was obtained as a colorless oil, homogeneous by capillary GC, in 91.6% yield by following the same procedure as for **5a** and by using 1.3 equiv of **4a'** with (+)-**3b**: $[\alpha]_{589}^{25}$ −8.75° (*c* 2.0, $CHCl_3$); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.54–4.14 (2H, m), 3.70 (3H, s), 2.17–1.79 (5H, m), 1.97–1.55 (2H, m); IR ($CHCl_3$) 1730 cm^{-1}. Precise mass calc for $C_8H_{12}O_4$ *m/z* 172.0736. Found: 172.0747.

Using Eu(hfc)$_3$ as a chiral ^{1}H-NMR shift reagent, the e.e. was found to be 91% by comparison of the characteristic peaks at 7.93 and 7.80 ppm, as compared to those peaks of independently prepared racemic **6a** plus Eu(hfc)$_3$.

(−)-MEM ester pentanolide **6b**

The product (−)-**6b** was obtained in 62.3% yield by following the same procedure as for **5a**, with 2.0 equiv of **4b** with (+)-**3b**. Treating 1.5 equiv of **4b'** with (+)-**3b** gave rise to a 94% yield of (−)-**6b**, as a colorless oil which was homogeneous by capillary GC: $[\alpha]_{589}^{25}$ −9.5° (*c* 1.6, $CHCl_3$, for both cases); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 5.33 (3H, s), 4.44–4.24 (2H, m), 3.84–3.47 (4H, m), 3.37 (3H, s), 2.70–2.08 (7H, m); IR ($CHCl_3$) 1732 cm^{-1}. Precise mass calc for $C_7H_9O_3$ *m/z* 141.0552. Found: 141.0537.

Conversion of (−)-MEM into (−)-methyl ester pentanolide **6a**

A soln of 405 μl (0.43 mmol) of 1.052 M $ZnBr_2$ in DMTHF was injected into a stirred soln of 21 mg (0.85 mmol) of (−)-**6b** in 3 ml of CH_2Cl_2 at room temp. After 8 h, 0.5 ml of 1 N HCl was added, followed by 3 ml of brine. The mixture was diluted with EtOAc (25 ml) and the organic layer was washed in brine (2 ×), dried over $MgSO_4$ and concentrated *in vacuo*. NMR of the crude showed the absence of the MEM group and the IR spectrum showed two characteristic bands at 1735 and 1708 cm^{-1}. Ethylene glycol monomethylether was the main contamination observed in the NMR spectrum. The resultant oil was dissolved in 10 ml of Et_2O and was treated with excess diazomethane for 10 min at room temp. The yield of (−)-**6a** was established by GC analysis to be 68%. The e.e. was established by the same method as described for the direct preparation of **6a** using Eu(hfc)$_3$ and was found to be higher than 96%.

(−)-t-Butyl ester pentanolide **6c**

A cooled (−78°) soln of 216 μl (0.216 mmol) of 1 M lithium hexamethyldisalazide in hexane in 6 ml of THF was treated with 30 μl (0.216 mmol) of t-butyl acetate. After 15 min at −78°, the mixture was cooled to −94° (toluene–liquid N_2). This soln was treated with 17.0 mg (0.072 mmol) of cooled (−94°) (+)-**3b** soln in 5 ml of THF, which was added slowly via a cannula. After 15 min at −94°, the mixture was quenched with 0.8 ml 1 N HCl and allowed to warm to room temp. Brine was added, followed by successive extractions with Et_2O (2 × 5 ml) and EtOAc (2 × 10 ml). The combined organic layers were washed with brine (3 ×), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a light yellow oil. The oil was dissolved in 20 ml of Me_2CO together with 1 ml of Raney Ni, prewashed (4 ×) with Me_2CO. This mixture was stirred rapidly overnight at room temp. The Raney Ni was filtered and washed successively with Me_2CO (2 × 10 ml) and EtOAc (2 × 10 ml). Evaporation of the combined organic solvents afforded 14.1 mg (91.5%) of (−)-**6c** as a colorless oil: $[\alpha]_{589}^{25}$ −7.23° (*c* 1.4, $CHCl_3$). Using Eu(hfc)$_3$ as a chiral ^{1}H-NMR shift reagent, the e.e. was found to be 63% by comparing the characteristic peaks of the t-Bu group at 5.28 and 5.23 ppm.

(+)-t-Butyl ester pentanolide **6c**

The product **6c** was obtained as a colorless oil in 29.1% yield by following the same procedures as for **5a** and by using 3 equiv of t-butyl *p*-tolylthioacetate (**4c'**) with (+)-**3b**: ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.43–4.24 (m, 2H), 2.45–1.64 (m, 7H), 1.45 (9H, s); IR ($CHCl_3$) 1720 cm^{-1}. Precise mass calc for $C_{10}H_{15}O_4$ (M − CH_3) *m/z* 199.0970. Found: 199.0979.

(+)-3-Phenylselenyl glutarate mono-ester **7**

A soln of 27.1 mg (0.87 mmol) of freshly recrystallized (hexane) diphenyl diselenide in 0.55 ml of DMF was purged with N_2 for 1 h and treated with 8 mg (0.21 mmol) of $NaBH_4$. After the evolution of H_2 ceased, the temp was raised to 100°. A soln of 14.5 mg (0.072 mmol) of (+)-**5c** in 2.0 ml of DMF, prepurged with N_2, was added via a cannula and the temp was raised to 120° for 4 h, then raised again to 130° for an additional 45 min. After cooling to room temp, the soln was diluted with Et_2O (30 ml), washed with 5% HCl and then with brine (3 ×), dried over $MgSO_4$ and concentrated *in vacuo*. The product (+)-**7** was isolated via short path chromatography [2 g silica, (a) pentane, (b) 40% Et_2O in pentane] which yielded 13.2 mg (51%): $[\alpha]_{436}^{25}$ 14.1° (*c* 1.3, $CHCl_3$); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.59–7.18 (5H, m), 3.09–2.95 (2H, m), 2.63–2.39 (5H, m), 1.41 (9H, s); IR ($CHCl_3$) 1735, 1710 cm^{-1}; MS (70 eV) *m/z* 358 (M^+).

(+)-3-Phenylselenyl glutarate diester **8**

A soln of 13.2 mg (0.037 mmol) of (+)-**7** in 5 ml of Et_2O was treated with excess diazomethane at room temp for 5 min. Evaporation of the solvent and the excess of diazomethane *in vacuo* afforded 13.7 mg (100%) of the product (+)-**8**: $[\alpha]_{589}^{25}$ 3.72° (*c* 1.4, $CHCl_3$); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.54–7.20 (5H, m), 3.62 (3H, s), 3.08–2.98 (2H, m), 2.52–2.41 (5H, m), 1.41 (9H, s); IR ($CHCl_3$) 1735 cm^{-1}; MS (70 eV) *m/z* 372 (M^+). Using Eu(hfc)$_3$ as a chiral ^{1}H-NMR shift reagent, the e.e. was found to be 43% by comparing the characteristic peaks at 7.32 and 7.17 ppm for the methyl group and the peaks at 4.21 and 4.16 ppm for the t-butyl group.

(+)-3-Methylglutarate mixed diester **9**

(a) A soln of 5.3 mg (0.024 mmol) of (+)-**8** in 2 ml of toluene was treated with 9.8 mg (0.08 mmol) of triphenyltin hydride. The mixture was refluxed overnight. After cooling to room temp, the soln was diluted with 20 ml of Et_2O, washed with 1 N HCl and then with brine (3 ×), dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was diluted with 2 ml of Et_2O and the yield of (+)-**9** was established by GC, in comparison to an authentic sample, to be 96% (59% by PTLC on silica with 15% Et_2O in hexane).

(b) A soln of 150 mg (1.17 mmol) of 3-methyl glutaric anhydride in 5 ml of THF was treated with 190 mg (1.34 mmol) of t-BuOK. After 1 h at room temp, the mixture was diluted with 40 ml of Et_2O and washed with 1 N HCl and brine (3 ×), dried over $MgSO_4$ and concentrated *in vacuo* to yield 118 mg (49.8%) of t-butyl 3-methyl glutarate mono-ester as a colorless oil: ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.40–2.22 (5H, m), 1.45 (9H, s), 1.04 (3H, d, J = 5.7 Hz); IR ($CDCl_3$) 1730, 1710 cm^{-1}; MS (70 eV) *m/z* 202 (M^+).

A soln of 100 mg (4.95 mmol) of this half ester in 15 ml of Et_2O was treated with excess diazomethane for 10 min at 25°. Evaporation of the solvent *in vacuo* afforded the product (+)-**9** in quantitative yield: ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.67 (3H, s), 2.35–2.22 (5H, m), 1.44 (9H, s), 1.24 (3H, d, J = 5.8 Hz); IR ($CDCl_3$) 1735 cm^{-1}; MS (70 eV) *m/z* 216 (M^+).

(+)-3-Methyl glutarate mono-ester **9a**

A soln of 3.8 mg of (+)-**9** in 0.5 ml of 95% formic acid was stirred at room temp for 1.5 h. Removal of the solvent *in vacuo* afforded the (+)-mono-ester **9a** as a yellow oil which was converted via Ref. 16 into (*R*)-(+)-3-methylvalerolactone.

(±)-t-Butyl ester pentanolide **6c**

Cleavage of the MEM group was performed by the same procedure as described for the preparation of **6a** from **6b**. The resulting 10.2 mg (0.064 mmol) of a yellow oil was dissolved in 2 ml of EtOAc together with 14 mg (0.067 mmol) of dicyclohexylcarbodiimide and excess t-BuOH for 36 h at room temp. The solid was filtered and the yield of **6c** was established by GC analysis to be 64%.

(±)-3-Phenylselenyl glutarate mixed diester **11**

A soln of 45 mg (0.29 mmol) of benzeneselenol and 12 mg (0.056 mmol) of (±)-**6c** in 2.5 ml of THF and 41 μl (0.23 mmol) HMPA were introduced via a cannula into a soln containing 14.5 mg (0.3 mmol) of 50% NaH (prewashed twice with THF) in 1 ml of THF. The mixture was brought to reflux under N_2 for 4.5 h. After cooling, EtOAc (20 ml) and Et_2O (10 ml) were added and the mixture was washed consecutively with 1 N HCl and brine (3 ×), dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was dissolved in 10 ml of Et_2O and was treated with excess diazomethane which gave, after evaporation, 60 mg of crude oil. The product **11** was purified by PTLC on silica (250 μm, 15% Et_2O in hexane), to yield 6.4 mg (29.3%) of **11**, as a slightly yellow oil: ^{1}H-NMR (80 MHz, $CDCl_3$) δ 7.56–7.20 (5H, m), 3.64 (3H, s), 3.27–2.81 (2H, m), 2.39–2.24 (5H, m), 1.51–1.37 (2H, m), 1.42 (9H, s); IR ($CHCl_3$) 1735 cm^{-1}.

Olefinic glutarate mixed diester (±)-**12**

A soln of 70 μl (0.01 mmol) of 0.149 M 99% *m*-chloroperbenzoic acid in $CDCl_3$ was injected into an NMR tube which contained a cooled (−78°) soln of 4.0 mg (0.01 mmol) of (±)-**11** in 0.4 ml of $CDCl_3$ under N_2. Upon warming to room temp, a downfield shift of 0.2 ppm was observed for the multiplet at 3.17–2.81 ppm. The extent of the reaction was monitored by NMR. Three days were required for complete elimination. Purification by PTLC (7% Et_2O in hexane) afforded 1.6 mg (67.5%) of (±)-**12** as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.776–5.688 (1H, m), 5.104–5.012 (2H, m), 3.655 (3H, s), 3.003–2.965 (1H, m), 2.479–2.249 (4H, m), 1.422 (9H, s); IR ($CHCl_3$) 1720, 1600 cm^{-1}. Precise mass calc for $C_8H_{11}O_4$ (M − *t*-Bu) *m/z* 171.0657. Found: 171.0654.

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Table 2. Fractional coordinates and thermal parameters for (*S*)-(+)-**1a**[a]

Atom	*x*	*y*	*z*	*B*
C1	0.2537(9)	0.0992(12)	0.4899(6)	7.1(4)*
C2	0.2040(8)	0.2681(12)	0.4150(5)	6.3(3)*
C3	0.2071(9)	0.4471(13)	0.4684(6)	7.6(4)*
C4	0.2655(10)	0.4181(15)	0.5891(5)	8.2(4)*
C5	0.3030(11)	0.1985(13)	0.6007(5)	8.2(4)*
S6	0.1289(2)	0.2469(0)	0.2766(1)	7.5(1)*
C7	0.3414(9)	0.1452(12)	0.2137(5)	6.8(4)*
C8	0.4888(9)	0.2824(13)	0.2002(5)	7.1(4)*
C9	0.6483(9)	0.2077(15)	0.1476(5)	7.9(4)*
C10	0.6602(9)	0.0070(14)	0.1128(5)	7.5(4)*
C11	0.5119(10)	−0.1281(14)	0.1289(5)	7.8(4)*
C12	0.3488(10)	−0.0585(12)	0.1799(5)	7.3(4)*
C13	0.8378(10)	−0.0796(19)	0.0566(6)	10.3(6)*
O14	0.2581(8)	−0.0782(9)	0.4650(4)	9.8(3)*
O15	0.0974(7)	0.4572(10)	0.2345(4)	9.2(3)*
HC3	0.191(7)	0.619(9)	0.428(4)	4.1(15)
HC4A	0.208(8)	0.492(12)	0.626(5)	6.8(19)
HC4B	0.396(8)	0.492(11)	0.617(5)	6.7(18)
HC5A	0.272(9)	0.083(15)	0.585(6)	9.3(23)
HC5B	0.286(13)	0.146(18)	0.688(8)	17.7(43)
HC8	0.487(8)	0.452(11)	0.234(5)	6.0(17)
HC9	0.746(10)	0.341(17)	0.126(6)	12.1(27)
HC11	0.490(9)	−0.310(12)	0.093(5)	7.6(20)
HC12	0.231(8)	−0.168(13)	0.191(5)	8.1(21)
HC13A	0.854(13)	−0.266(19)	0.092(7)	17.3(38)
HC13B	0.821(10)	0.046(16)	−0.019(6)	12.1(28)
HC13C	0.939(15)	−0.085(22)	0.093(8)	22.2(48)

[a] Standard deviations of the least significant figures are given in parentheses. The isotropic equivalent thermal parameter is given for anisotropic atoms (denoted by an asterisk).

Table 3. Bond distances for (*S*)-(+)-**1a**[a]

C1–C2	1.466(10)	S6–O15	1.475(6)
C1–C5	1.323(10)	C7–C8	1.398(10)
C1–O14	1.190(10)	C7–C12	1.384(11)
C2–C3	1.327(11)	C8–C9	1.396(10)
C2–S6	1.762(6)	C9–C10	1.371(13)
C3–C4	1.527(10)	C10–C11	1.398(11)
C4–C5	1.458(13)	C10–C13	1.550(11)
S6–C7	1.828(7)	C11–C12	1.398(10)
S6–O14	3.242(6)		

[a] The standard deviation of the least significant figure of each distance is given in parentheses.

Table 4. Bond angles (°) for (*S*)-(+)-**1a**[a]

C2–C1–C5	106.3(6)
C2–C1–O14	125.2(6)
C5–C1–O14	128.4(7)
C1–C2–C3	110.7(6)
C1–C2–S6	127.0(6)
C3–C2–S6	122.1(6)
C2–C3–C4	110.9(7)
C3–C4–C5	105.4(7)
C1–C5–C4	106.5(6)
C2–S6–C7	98.5(3)
C2–S6–O15	107.6(3)
C7–S6–O15	109.0(3)
S6–C7–C8	117.0(6)
S6–C7–C12	119.6(5)
C8–C7–C12	123.3(6)
C7–C8–C9	117.2(7)
C8–C9–C10	121.1(7)
C9–C10–C11	120.6(7)
C9–C10–C13	121.7(7)
C11–C10–C13	117.6(8)
C10–C11–C12	120.0(8)
C7–C12–C11	117.8(7)

[a] The standard deviation of the least significant figure of each angle is given in parentheses.

[31] All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 78, MULTAN 80 and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declerq and M. M. Woolfson, University of York, U.K., 1978 and 1980; DIRDIF, written by P. T. Beurskens *et al.*, University of Nijmegen, The Netherlands, 1981; MITHRIL, an automatic solution package written by C. J. Gilmore, University of Glasgow, Scotland, 1983; BLS78A, an anisotropic block diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, U.K., 1978; and BOND, a program to calculate molecular parameters and prepare tables, written by K. Hirotsu, Cornell University, 1978.

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Single-crystal X-ray structure determination of (*S*)-(+)-**1a**. Preliminary X-ray photographs displayed monoclinic symmetry. Precise lattice constants of $a = 7.244(1)$, $b = 6.493(1)$, $c = 12.004(2)$ Å, and $\beta = 89.172°$ were determined from a least-squares fit of 15 moderate 2θ-values. Systematic extinctions, crystal density and the presence of chirally pure molecules were uniquely accommodated by space group $P2_1$ with one molecule of composition $C_{12}H_{12}SO_2$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leqslant 114°$ were collected using variable speed, 1° ω-scans and

Table 5. Fractional coordinates and thermal parameters for (*S*)-(+)-**3a**[a]

Atom	*x*	*y*	*z*	*B*
C1	0.4396(16)	−0.2328(28)	0.3789(11)	4.9(7)*
C2	0.2971(16)	−0.0524(28)	0.3939(9)	4.1(7)*
C3	0.2036(16)	−0.0998(30)	0.4879(11)	5.1(8)*
C4	0.2667(17)	−0.3258(35)	0.5406(10)	5.7(7)*
O5	0.4155(11)	−0.3862(18)	0.4656(7)	5.4(5)*
S6	0.2835(5)	0.1978(0)	0.3040(3)	5.1(2)*
C7	0.2610(14)	0.0432(27)	0.1770(9)	3.9(7)*
C8	0.1713(15)	−0.1607(29)	0.1732(10)	4.4(7)*
C9	0.1468(17)	−0.2594(31)	0.0698(11)	5.2(7)*
C10	0.2231(16)	−0.1398(31)	−0.0297(10)	4.3(7)*
C11	0.3120(16)	0.0648(31)	−0.0241(10)	4.9(7)*
C12	0.3338(15)	0.1592(30)	0.0822(11)	4.5(7)*
C13	0.1994(21)	−0.2517(44)	−0.1428(11)	7.7(10)*
O14	0.5555(10)	−0.2432(22)	0.3014(7)	6.0(6)*
O15	0.1202(12)	0.3214(20)	0.3525(7)	5.6(5)*
HC3	0.130(17)	0.048(38)	0.518(12)	8.9(50)
HC4A	0.293(19)	−0.242(41)	0.649(12)	10.0(55)
HC4B	0.174(26)	−0.501(56)	0.631(17)	18.0(89)
HC8	0.130(14)	−0.258(28)	0.228(9)	4.3(34)
HC9	0.085(14)	−0.414(28)	0.087(10)	4.9(38)
HC11	0.342(12)	0.154(22)	−0.076(7)	1.6(25)
HC12	0.404(13)	0.307(24)	0.064(8)	2.6(29)
HC13A	0.085(14)	−0.356(29)	−0.113(10)	5.4(38)
HC13B	0.231(16)	−0.148(31)	−0.191(11)	6.1(41)
HC13C	0.213(16)	−0.415(34)	−0.120(11)	6.9(45)

[a] Standard deviations of the least significant figures are given in parentheses. The isotropic equivalent thermal parameter is given for anisotropic atoms (denoted by an asterisk).

Table 6. Bond distances for (*S*)-(+)-**3a**[a]

C1–C2	1.514(20)	S6–O15	1.527(10)
C1–O5	1.327(17)	C7–C8	1.336(20)
C1–O14	1.222(15)	C7–C12	1.357(18)
C2–C3	1.288(16)	C8–C9	1.400(20)
C2–S6	1.755(14)	C9–C10	1.419(19)
C3–C4	1.512(24)	C10–C11	1.338(22)
C4–O5	1.434(15)	C10–C13	1.532(21)
S6–C7	1.781(13)	C11–C12	1.418(19)
S6–O14	3.272(13)		

[a] The standard deviation of the least significant figure of each distance is given in parentheses.

Table 7. Bond angles (°) for (*S*)-(+)-**3a**[a]

C2–C1–O5	107.4(10)
C2–C1–O14	127.7(13)
O5–C1–O14	124.9(13)
C1–C2–C3	108.3(13)
C1–C2–S6	123.6(9)
C3–C2–S6	127.7(12)
C2–C3–C4	109.7(12)
C3–C4–O5	103.6(10)
C1–O5–C4	110.9(11)
C2–S6–C7	100.9(6)
C2–S6–O15	104.0(6)
C7–S6–O15	109.5(6)
S6–C7–C8	123.7(9)
S6–C7–C12	114.3(11)
C8–C7–C12	121.9(12)
C7–C8–C9	120.5(12)
C8–C9–C10	118.0(14)
C9–C10–C11	120.6(12)
C9–C10–C13	117.9(14)
C11–C10–C13	121.5(13)
C10–C11–C12	119.7(12)
C7–C12–C11	119.3(14)

[a] The satandard deviation of the least significant figure of each angle is given in parentheses.

graphite monochromated Cu $K\bar{\alpha}$ radiation (1.54178 Å). Of the 836 reflections that were collected in this fashion, 764 (91%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization and background effects.[31] The structure was solved uneventfully by direct methods. All of the hydrogen atoms were located on a difference synthesis following preliminary refinement of the non-hydrogen structure. Block diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens converged to a conventional crystallographic residual of 0.048 for the observed data. The absolute configuration was established by carefully remeasuring 15 Friedel pairs of reflections that were calculated to give a relatively large difference based on the anomalous scattering of sulfur. Thirteen of the fifteen clearly indicated the absolute configuration shown in Fig. 1. The structure shown in Fig. 1 was also selected by Hamilton's test by refining both enantiomers.[32]

Single crystal X-ray structure determination of (*S*)-(+)-**3a**. Preliminary X-ray photographs indicated that the crystals belonged to the monoclinic system. Precise lattice constants of $a = 8.185(3)$, $b = 5.445(2)$, $c = 12.047(5)$ Å and $\beta = 80.86(3)°$ were determined from a least-squares fit of 15 moderate 2θ-values. The systematic extinctions, crystal density and chirally pure starting material were uniquely accommodated by space group $P2_1$ with one molecule of composition $C_{11}H_{10}SO_3$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected using variable speed, 1° ω-scans and graphite monochromated Cu $K\bar{\alpha}$ radiation (1.54178 Å). Of the 798 reflections collected in this fashion, 475 (59%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization and background effects. The structure was solved uneventfully using direct methods. Hydrogens were located on a difference electron density synthesis following partial refinement of the non-hydrogen atom structure. Block diagonal least-squares refinements with anisotropic non-hydrogen atoms and isotropic hydrogens converged to a standard crystallographic residual of 0.0586 for the observed reflections.