1,2-Asymmetric induction in conjugate additions to nitroalkenes

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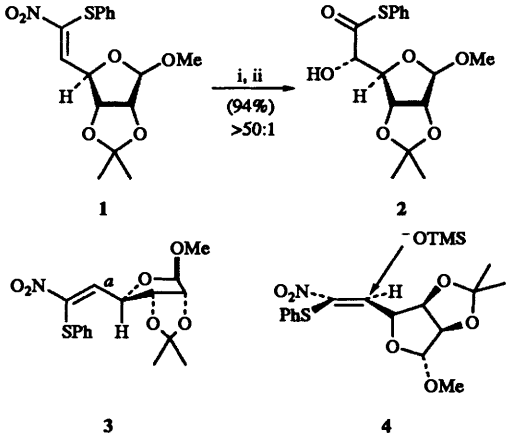
Conjugate addition of nucleophiles to the nitroalkenes **8** and **11** followed by *in situ* ozonolysis resulted in the formation of α-substituted thioesters exhibiting the 'unexpected' *syn* relative configuration between the C-3 and newly formed stereogenic centre in all cases but one. The relative stereochemistry in many instances was determined by examination of the ^{1}H NMR coupling constants of the thioesters.

Introduction

Addition of nucleophiles to 1-nitro-1-(phenylsulfanyl)alkenes, followed by ozonolysis of the intermediate nitronates, represent a convenient method for the synthesis of α-substituted thioesters.[1] This chemistry is useful for the preparation of acyclic systems,[2] bicyclic β-lactams,[3] and tetrahydrofuran and tetrahydropyran derivatives.[4] Recently, during the total synthesis of polyoxin C,[5] we observed high diastereoselectivities in conjugate addition of nucleophiles to the nitroalkene **1**. Michael addition of potassium trimethylsilanolate, *in situ* ozonolysis, followed by hydrolytic work-up afforded the 5(*S*) α-hydroxy thioester **2** (94%) as a single diastereoisomer (Scheme 1). The

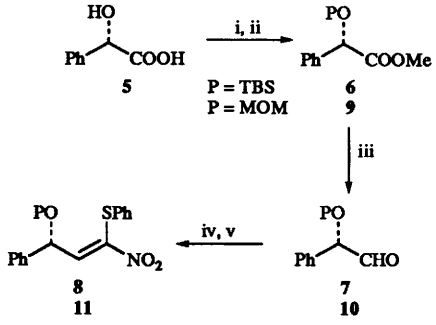


Scheme 1 *Reagents:* i, $KOSiMe_3$, DMF; ii, O_3, CH_2Cl_2, −78 °C

remarkable diastereoselectivity of the conjugate addition reaction is due to steric and stereoelectronic control.[1] The eclipsed conformation **3** is strongly favoured due to avoidance of 1,3-allylic strain.[6] However, partial rotation (~30°) about bond *a* allows the system to adopt conformation **4** where the carbon–oxygen bond is aligned with the p-orbitals of the π-system. This conformation meets the stereoelectronic requirements for antiperiplanar addition of the nucleophile resulting in the high (>50:1) 5(*S*) stereochemical bias. However, Michael addition of potassium-phthalimide and -succinimide to the nitroalkene **1** gave adducts with the 5(*R*) configuration (≥15:1). This curious reversal was attributed to the unique steric requirements of the phthalimide and succinimide carbonyl substituents during the addition and termed 'stealth stereocontrol'.[7] Herein, we report studies on the diastereoselectivity of Michael addition to the nitroalkenes **8** and **11**.

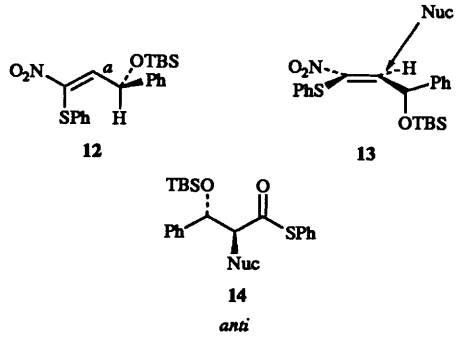
Results and discussion

The nitroalkene **8** was readily synthesised from (*S*)-mandelic acid **5** by esterification (CH_2N_2, diethyl ether) and protection of the alcohol (TBSCl, imidazole, catalytic DMAP, DMF)† to afford the methyl ester **6** (Scheme 2). Reduction to the aldehyde



Scheme 2 *Reagents:* i, CH_2N_2, ether; ii, TBSCl, imidazole, DMAP, DMF; or MOMCl, Pr^i_2EtN, CH_2Cl_2; iii, DIBAL-H, CH_2Cl_2, −78 °C; iv, $PhSCH_2NO_2$, $KOBu^t$, Bu^tOH–THF, 0 °C; v, MsCl, Et_3N, CH_2Cl_2, 0 °C

7 (DIBAL-H,† −78 °C), Henry reaction with (phenylsulfanyl)-nitromethane[8] ($KOBu^t$, Bu^tOH/THF, 0 °C), and elimination (MsCl, Et_3N, 0 °C) provided the nitroalkene **8**. We predicted that the stereogenic centre adjacent to the olefin would influence the diastereoselectivity of conjugate additions to **8** in a manner analogous to that for the nitroalkene **1**. As previously described 1,3-allylic strain dictates that the eclipsed conformation **12** should be strongly favoured, similar to **3**. Partial rotation about bond *a* (~30°) aligns the carbon–oxygen bond with p-orbitals of the π-system and antiperiplanar to nucleophilic addition **13**. We reasoned that conjugate additions of nucleophiles would occur at the less sterically congested *si* face



† TBSCl = *tert*-butyldimethylsilyl chloride, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, DIBAL-H = diisobutylaluminium hydride, PPTS = pyridinium toluene-*p*-sulfonate, TBAF = tetrabutylammonium fluoride, THF = tetrahydrofuran, MOMCl = methoxymethyl chloride, TMSBr = trimethylsilyl bromide.

Table 1 Michael additions to the nitroalkenes **8** and **11**

Entry	Nitroalkene	Nucleophile	Product	Yield (%)	C-2 config.[a]	Isomeric ratio
1	**8**	KOTMS	**15**	65	*anti*	4.4:1
2	**8**	K-phthal	**16**	59	*syn*	7:1
3	**8**	Me_2CuLi	**17**	41	*syn*	2.2:1
4	**8**	NaOMe	**18**	58	*syn*	1.6:1
5	**8**	K-NHTs	**19**	50	*syn*	3.1:1
6	**11**	KOTMS	**25**	44	*syn*	2.5:1
7	**11**	K-phthal	**26**	58	*syn*	2.7:1

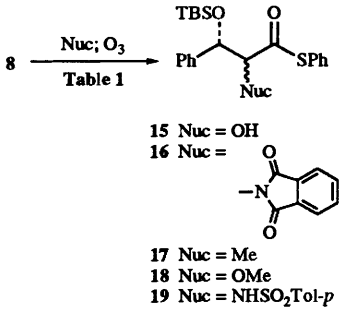
[a] Configuration of major diastereoisomer relative to C-3.

Table 2 Coupling constants of cyclic ketals

Entry	Ketal	J_{ab}/Hz
1	**20**	8.9
2	**21**	1.8
3	**22**	2.7
4	**23**	10.3
5	**24**	1.9

of the olefin **8** resulting in the formation, after ozonolysis, of thioesters with the *anti* relative configuration **14**.

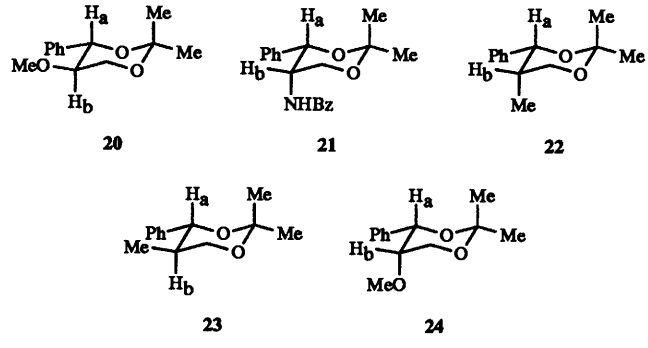
The conjugate addition of potassium trimethylsilanolate to the nitroalkene **8** (0.3 mol dm^{-3} DMF, −55 °C) followed by *in situ* ozonolysis (0.1 mol dm^{-3} CH_2Cl_2, −78 °C) and selective cleavage of the trimethylsilyl ether (10% methanolic citric acid) afforded the thioester **15** (Scheme 3) as a 4.4:1 mixture of



Scheme 3

diastereoisomers (Table 1) which were separable by flash chromatography. The relative configuration of the major diastereoisomer was assigned as *anti* by conversion of the compound into the ketal **20** and examination of its ^1H NMR spectrum. The major diastereoisomer of **15** was methylated (MeOTf, 2-*tert*-butyl-1′,1′,3″,3″-tetramethylguanidine,[9] −78 °C), reduced ($NaBH_4$, Pr^iOH), desilylated ($Bu_4N^+F^-$, THF) and cyclised [$Me_2C(OMe)_2$, PPTS]† to afford the target ketal **20**. The ^1H NMR coupling constant between H_a and H_b (Table 2) indicated an axial–axial relationship (J_{ab} 8.9 Hz) and was consistent with the assignment of *anti* stereochemistry. Thus, the conjugate addition must have occurred from the *si* face of the nitroalkene **8**, in agreement with our hypothesis. Nucleophilic Michael addition of potassium phthalimide to the nitroalkene **8** (0.1 mol dm^{-3} DMF, −40 °C) followed by *in situ* ozonolysis (0.03 mol dm^{-3} CH_2Cl_2, −78 °C) resulted in formation of the thioester **16** as a 7:1 mixture of diastereoisomers which were also separable by flash chromatography. Reduction of the major diastereoisomer of the imide ester **16** to the amino alcohol ($NaBH_4$, Pr^iOH, H_2O), selective protection of the amine (BzCN, CH_2Cl_2), desilylation (TBAF. THF)† and cyclisation [$Me_2C(OMe)_2$, PPTS] yielded the ketal **21**. To our surprise, the ^1H NMR coupling constant between H_a and H_b of this compound was consistent with the axial–equatorial relationship depicted (J_{ab} 1.8 Hz). This is consistent with the major diastereoisomer of the imide **16** having the *syn* stereochemistry and thus the conjugate addition of potassium phthalimide to the nitroalkene **8** must have occurred from the *re* face.

This curious reversal of reaction diastereoselectivity prompted us to investigate several other nucleophilic species. Conjugate addition of (dimethylcopper)lithium to the nitroalkene **8** [CuBr(SMe_2), MeLi, 0.5 mol dm^{-3} Et_2O, −40 °C] yielded the corresponding nitroalkane. Subsequent ozonolysis (O_3, 0.1 mol dm^{-3} THF, $KOBu^t$, −78 °C) gave the thioester **17** as a 2.2:1 mixture of diastereoisomers. This mixture was reduced to the primary alcohol ($LiAlH_4$, Et_2O), desilylated (TBAF, THF) and cyclised [$Me_2C(OMe)_2$, PPTS] to produce both cyclic ketals **22** and **23**. Again close examination of the ^1H NMR spectra was used to assign stereochemistry. The coupling constant between H_a and H_b of the major diastereoisomer **22** (J_{ab} 2.7 Hz) was consistent with an axial–equatorial relationship. Since the two diastereoisomers **22** and **23** were inseparable by flash chromatography throughout this sequence, the minor



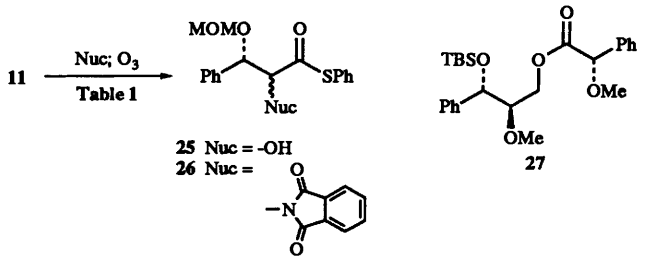
cyclic ketal **23** was also present in the product mixture. By contrast, the coupling constant for the isomer **23** (J_{ab} 10.3 Hz) clearly indicates an axial–axial relationship. It is clear from this analysis that the major diastereoisomer of thioester **17** possessed *syn* stereochemistry.

Conjugate addition of sodium methoxide to the nitroalkene **8** (25% NaOMe in MeOH, 0.15 mol dm^{-3} DMF, −45 °C) and *in situ* ozonolysis (0.05 mol dm^{-3} CH_2Cl_2, −78 °C) gave the thioester **18** as a 1.6:1 mixture of diastereoisomers. The epimeric mixture was reduced ($NaBH_4$, Pr^iOH, 0 °C), desilylated (TBAF, THF) and cyclised [$Me_2C(OMe)_2$, PPTS] to yield both cyclic ketals **24** and **20**. These derivatives were separable by flash chromatography. The ketal **24**, the major diastereoiso-

† See footnote on p. 1009.

Table 3 Coupling constants of thioesters

Entry	Thioester	J_{syn}/Hz	J_{anti}/Hz
1	**15**	1.0	4.6
2	**16**	9.0	8.9
3	**17**	6.5	9.2
4	**18**	3.4	5.7
5	**19**	1.9	5.2
6	**25**	2.2	4.5
7	**26**	9.4	9.4



Scheme 4

meric product, exhibited an axial–equatorial coupling constant (J_{ab} 1.9 Hz) while the minor diastereoisomeric product was identical with the previously characterised compound **20** (^{1}H NMR). As a result, the major and minor diastereoisomeric products of sodium methoxide conjugate addition to **8** are *syn* and *anti*, respectively. Conjugate addition of potassium toluene-4-sulfonamide to the nitroalkene **8** (Tol-*p*-SO_2NH_2, KOBu^t, 0.1 mol dm^{-3} DMF, 0 °C) and ozonolysis (0.05 mol dm^{-3} CH_2Cl_2, −78 °C) afforded the thioester **19** as a 3.1 : 1 mixture of *syn*/*anti* diastereoisomers. The relative stereochemistry of each diastereoisomer was assigned without further transformations by comparison of the H_α–H_β coupling constants in the ^{1}H NMR spectrum of the thioester **19** with corresponding values for the thioesters **15** to **18**. This coupling constant for *anti* thioesters was significantly larger in magnitude (> 2 Hz) than for the *syn* isomers (Table 3) in every case except the phthalimide derivative **16** (entry 2). Consequently, the major and minor diastereoisomers were, respectively, assigned as *syn*-**19** (*J* 1.9 Hz) and *anti*-**19** (*J* 5.2 Hz). All these results show, with the exception of potassium trimethylsilanolate, preferential formation of adducts with the 'unexpected' *syn* relative configuration.

In attempting to ascertain the origin of the *syn* diastereoselectivity, we briefly examined the effect of replacing the *tert*-butyldimethylsilyl hydroxy protecting group of the nitroalkene **8** with (methoxy)methyl. The nitroalkene **11**, which reflects this alteration, was synthesised by esterification (CH_2N_2, ether), protection (MOMCl, Pr$^i_2$EtN, CH_2Cl_2), reduction (DIBAL-H, −78 °C), Henry reaction (KOBu^t, Bu^{t}OH/THF, 0 °C) and elimination (MsCl, Et_3N, 0 °C) in a sequence analogous to that for the synthesis of **8** (Scheme 2). Conjugate addition of potassium trimethylsilanolate (0.1 mol dm^{-3} DMF, −45 °C), ozonolysis (0.02 mol dm^{-3} CH_2Cl_2, −78 °C) and cleavage of the trimethylsilyl protecting group (10% methanolic citric acid) gave the thioester **25** as a mixture (2.5 : 1) of diastereoisomers (Scheme 4). Assignment of the relative stereochemistry as *syn* for the major diastereoisomer followed from the ^{1}H NMR H_α–H_β coupling constant (Table 3, entry 6).

The Michael addition of potassium phthalimide to the nitroalkene **11** (0.1 mol dm^{-3} DMF, −40 °C) and ozonolysis (0.02 mol dm^{-3} CH_2Cl_2, −78 °C) also resulted in preferential formation of the *syn* thioester **26** (2.7 : 1). As with the imide **16**, the ^{1}H NMR H_α–H_β coupling constants of both *syn*- and *anti*-**26** were approximately equal (Table 3, entry 7) and of no value in the assignment of stereochemistry. Thus, the stereochemical assignment was made by converting the thioester **26**

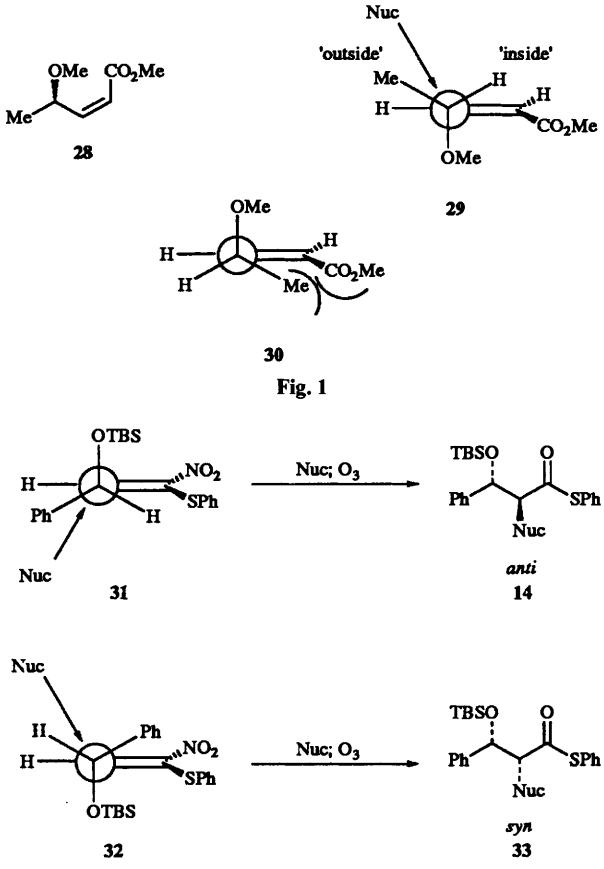


Fig. 1

Fig. 2

into the thioester **16**. Deprotection of the methoxymethyl group (TMSBr, THF)† and *tert*-butyldimethylsilylation (TBSOTf, 2,6-dimethylpyridine) of the major isomer of the imide **26** gave a product identical with the *syn* diastereoisomer of the imide **16**. It is clear that, as with the nitroalkene **8**, conjugate addition to the nitroalkene **11** favoured formation of *syn*- adducts and not the expected *anti*- thioesters. More remarkably, mere replacement of the *tert*-butyldimethylsilyl protecting group of the alkene **8** with a methoxymethyl group resulted in a *diastereoselective reversal* of the Michael addition of potassium trimethylsilanolate (Table 1, entries 1 and 6). Formation of the (*S*)-*O*-methyl mandelic ester **27** from the thioester **15** also indicates that racemisation did not occur at the C-3 stereocentre throughout these sequences (Schemes 2 and 3).

Contrary to our expectations, Michael addition to both nitroalkenes **8** and **11** followed by ozonolysis favoured formation of thioesters with the *syn* relative configuration in all but one instance. We erroneously predicted formation of *anti* products based on conjugate additions to α,β-unsaturated esters.[10,11] In a recent analysis of the (*Z*)-γ-alkoxy α,β-unsaturated ester **28**,[10] the predicted orientation of the γ-methoxy aligns the C–O bond antiperiplanar to the direction of nucleophilic attack (Fig. 1, **29**) in accordance with the Felkin–Anh model.[12] The larger methyl group occupies the 'outside' position while the 'inside' position is reserved for the smaller hydrogen. This conformation avoids the unfavourable 1,3-allylic strain present in the other possible rotamer (Fig. 1, **30**). Application of similar stereoelectronic arguments to the nitroalkene **8** would seem to dictate a reactive conformation in which the *tert*-butyldimethylsiloxy–carbon bond is aligned with the p-orbitals of the π system of the nitroalkene (Fig. 2, **31**). *The*

† See footnote on p. 1009.

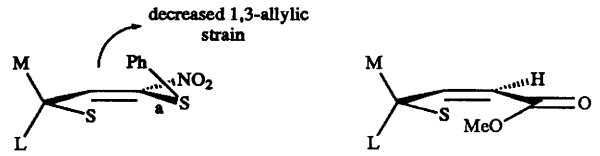


Fig. 3

hydrogen substituent should occupy the 'inside' position to avoid 1,3-allylic strain between the Z phenylsulfanyl substituent and the phenyl group. Nucleophilic attack of the nitroalkene from the less sterically congested *si* face followed by ozonolysis should lead predominantly to *anti* products **14**.

Experimental observations indicate that this clearly is not the case. However, formation of *syn* products could be accounted for by a conformation in which 1,3-*allylic strain is not a significant factor* (Fig. 2, **32**). Indeed, in this conformation the angle of attack (~120°)[13] allows the nucleophile to approach the nitroalkene in close proximity to the hydrogen as opposed to the sterically demanding phenyl substituent (Fig. 2). This difference would account for *syn* selectivity and forces us to speculate that 1,3-allylic strain does not contribute significantly to the reactive conformation of these nitroalkenes during conjugate addition. The longer carbon–sulfur bond (1.75 Å)[14] moves the *Z* phenylsulfanyl substituent further from the reactive arena lessening the effect of 1,3-allylic strain. Free rotation about the sulfur–phenyl bond allows the phenylsulfanyl ether to orientate itself out-of-the-plane of the π system. This lessens the effect of 1,3-allylic strain because the plane of conjugation is also the dimension in which an eclipsed substituent's steric influence is most pronounced. Rotation about bond *a* in the direction indicated (Fig. 3, **34**) moves the phenyl substituent farther away from the substituent (S) with which it is eclipsed. By comparison, a (*Z*)-α,β-unsaturated ester must necessarily remain in-the-plane as it extends conjugation of the π system (Fig. 3, **35**). While these arguments explain the general preference for *syn* thioesters, Fig. 2, **31** was not intended to account for the *anti* diastereoselectivity observed upon conjugate addition of potassium trimethylsilanolate to the nitroalkene **8**. It seems apparent that, in this instance, other factors, perhaps stereoelectronic, became more significant than the steric influences described herein.

Conclusion

Conjugate addition of nucleophiles to substituted nitroalkenes **8** and **11** appear to be controlled by steric factors in agreement with our earlier observations. However, 1,3-allylic strain appears not to play a significant role in Michael additions to the nitroalkenes **8** and **11**. The conformation Fig. 2, **32** is favoured during conjugate addition because the incoming nucleophile passes by the smaller hydrogen substituent in the 'outside' position as opposed to the larger phenyl substituent (Fig. 2, **31**). This is exhibited by a general preference, after ozonolysis, for *syn* thioesters as products. Double bond geometry has been shown to affect diastereoselectivity of conjugate additions.[15] Thus, conjugate additions of nucleophiles to 3-alkoxy-1-phenylsulfanyl-1-nitroalkenes represent a convenient stereoselective synthesis of α-substituted-β-alkoxy thioesters. Recently, Jackson and co-workers reported the synthesis of D-threonine and L-*allo*-threonine *via* stereoselective epoxidation of a 1-(4-tolylsulfanyl)-1-nitroalkene.[16]

Experimental

General procedures

All reactions were carried out under dry argon or nitrogen at room temperature unless otherwise stated. Low reaction temperatures were recorded as bath temperatures unless otherwise stated. Column chromatography was carried out on E. Merck silica gel 60, 230–400 mesh ASTM using flash chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F254 plates. Hexanes, dichloromethane, ethyl acetate, and ether used as eluents were ACS reagent grade solvent used undistilled. The following reaction solvents were purified by distillation: 2,2-dimethoxypropane, MeOH (from Mg, N_2), DMF (alumina), Bu^{t}OH (from CaH_2), CH_2Cl_2 (from CaH_2, N_2), Et_2O (from Ph_2CO–Na, N_2) and THF (from Ph_2CO–Na, N_2). Organic extracts were dried over Na_2SO_4, filtered and rotary evaporated at ≤50 °C; involatile oils further evaporated at <2 mmHg. Samples for combustion analysis were purified further by chromatography with rotary evaporation of the appropriate fraction and further evaporation (≤1 mmHg) for ≥10 h.

^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker 300 AC, JEOL 270 and Bruker 500. IR spectra were acquired on a Perkin-Elmer 1600 Series FTIR. Optical rotations were recorded at room temperature and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were determined either by G. D. Searle and Co., Skokie, IL or by the Department of Chemistry microanalytical laboratory at Imperial College.

Methyl (*S*)-*tert*-butyldimethylsiloxy(phenyl)acetate 6

To a solution of (*S*)-hydroxy(phenyl)acetic acid (41.3 g, 271 mmol) in Et_2O (700 cm^3) was added CH_2N_2 in Et_2O (~0.9 mol dm^{-3}; ~240 cm^3) until further addition ceased to cause bubbling. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (400 cm^3), separated and the aqueous phase extracted with Et_2O (3 × 200 cm^3). Evaporation of the combined organic layer and extracts and recrystallisation (EtOAc–hexanes) of the residue afforded crude methyl hydroxy(phenyl)acetate (43.4 g, 96%) which was dissolved in DMF (500 cm^3). To this solution was added *tert*-butyldimethylsilyl chloride (43.4 g, 288 mmol), imidazole (23.1 g, 339 mmol) and 4-dimethylaminopyridine (~0.5 g). After being stirred for 24 h, the reaction mixture was poured into water (500 cm^3) and extracted with Et_2O (3 × 300 cm^3). The combined extracts were dried and evaporated, and the residue was chromatographed on silica (eluent 90:10 hexanes–EtOAc, R_F 0.59) to afford the title compound **6** (70.58 g, 96%) as a clear oil (Found: C, 64.2; H, 8.5. Calc. for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63%); $[\alpha]_D$ +49.7 (*c* 1.24 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1760 (C=O); δ_H(500 MHz; $CDCl_3$) 0.04 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 3.69 (3 H, s, CO_2CH_3) 5.24 (1 H, s, $HCCO_2CH_3$) and 7.26–7.48 (5 H, m, Ph); δ_C(125 MHz, $CDCl_3$) 172.6, 139.1, 128.3, 128.1, 126.3, 74.4, 52.2, 25.7, 18.3, −5.1 and −5.2; *m/z* (EI) 265 (M − Me$^+$, 1%), 223 (M − Bu^{t+}, 55), 195 (25) and 89 (100).

(2*S*)-2-*tert*-Butyldimethylsiloxy(phenyl)acetaldehyde 7

To the methyl ester **6** (4.49 g, 16.0 mmol) in CH_2Cl_2 (30 cm^3) at −70 °C (solid CO_2–acetone, solution temperature) was added DIBAL-H in CH_2Cl_2 (1.0 mol dm^{-3}; 19 cm^3) so that the solution temperature never exceeded −65 °C. After 2 h, the reaction mixture was quenched with methanol (20 cm^3) at −78 °C and allowed to warm to room temperature. The gelatinous mixture was filtered through Celite, the latter then being washed with water (40 cm^3) and CH_2Cl_2 (50 cm^3). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined organic layer and extracts were dried and worked up. Chromatography of the residue on silica (eluent 90:10 hexanes–Et_2O, R_F 0.27) yielded the title compound **7** (3.53 g, 88%) as an unstable clear oil, δ_H(270 MHz; $CDCl_3$) 0.04 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.95 [9 H, s, $SiC(CH_3)_3$], 5.01 (1 H, d, *J* 2.2, C*H*CHO), 7.38–7.40 (5 H, m,

Ph) and 9.51 (1 H, d, *J* 2.2, CHO); δ_C(67.5 MHz; $CDCl_3$) 199.3, 136.5, 128.6, 128.3, 126.3, 79.9, 25.7, 25.5, 18.2 and −4.9; *m/z* (EI) 221 (M − CHO^+, 0.5%), 179 (10) and 75 (100). The product was used without further purification.

(*Z*,3*R*)-3-*tert*-Butyldimethylsiloxy-1-nitro-3-phenyl-1-phenylsulfanylpropene 8

To a solution of phenylsulfanyl(nitro)methane[8] (2.62 g, 15.5 mmol) in THF (18 cm^3) and Bu^{t}OH (19 cm^3) at 0 °C was added KOBu^t (0.171 g, 1.52 mmol) in Bu^{t}OH (1.4 cm^3). The aldehyde **7** (3.53 g, 14.1 mmol) in THF (40 cm^3) was added dropwise to this mixture with stirring. After 4 h, the reaction mixture was quenched with pH 7 phosphate buffer (50 cm^3), separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic layer and extracts were concentrated and filtered through silica. After work-up the crude product was dissolved in CH_2Cl_2 (100 cm^3) and the solution cooled to 0 °C. Methanesulfonyl chloride (2.2 cm^3, 28.4 mmol) and triethylamine (5.9 cm^3, 42.3 mmol) were added to the solution which was then stirred for 4 h. After this, the reaction mixture was quenched with 0.5 mol dm^{-3} acetic acid (50 cm^3) and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried and evaporated, and the residue chromatographed on silica (eluent 70:30 hexanes–CH_2Cl_2, R_F 0.29) to afford the nitroalkene **8** (3.37 g, 60%) as a yellow–green oil (Found: C, 62.7; H, 6.7; N, 3.45. Calc. for $C_{21}H_{27}NO_3SSi$: C, 62.81; H, 6.78; N, 3.49%); $[\alpha]_D$ −81.7 (*c* 2.41 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1538 (NO_2) and 1324 (NO_2); δ_H(300 MHz; $CDCl_3$) 0.0 (3 H, s, $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 5.88 (1 H, d, *J* 8.7, CHPh), 7.24–7.38 (10 H, m, Ph) and 7.64 [1 H, d, *J* 8.8, HC=C(SPh)NO_2]; δ_C(75 MHz; $CDCl_3$) 147.5, 145.0, 140.8, 131.5, 129.6, 128.8, 128.5, 127.8, 126.2, 72.9, 25.7, 18.1, −4.6 and −4.7; *m/z* (EI) 401 ($M^{+\bullet}$, 0.04%), 344 (M − Bu^{t+}, 40), 210 (40), 134 (75) and 73 (100).

Methyl (*S*)-methoxymethoxy(phenyl)acetate 9

To a solution of (*S*)-hydroxy(phenyl)acetic acid (8.52 g, 56.0 mmol) in methanol (200 cm^3) was added conc. H_2SO_4 (2 cm^3). After the mixture had been refluxed for 24 h, volatile organic material was removed by evaporation under reduced pressure and the residue diluted with Et_2O (100 cm^3). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 50 cm^3) and the aqueous phase back-extracted with Et_2O (3 × 25 cm^3). The combined organic layer and extracts were dried and evaporated to yield (*S*)-methyl hydroxy(phenyl)acetate (8.18 g, 88%) as a white solid. The product (0.582 g, 3.50 mmol) was dissolved in CH_2Cl_2 (35 cm^3) and Hunig's base (1.20 cm^3, 6.89 mmol) was added to the solution. After the mixture had been cooled to 0 °C, methoxymethyl chloride (1.0 cm^3, 13.2 mmol) was added to it. After being stirred for 16 h, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried and evaporated and chromatography of the residue on silica (eluent 90:10 hexanes–EtOAc, R_F 0.15) yielded the title compound **9** (0.574 g, 78%) as an oil (Found: C, 62.6; H, 6.45. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%); $[\alpha]_D$ +5.9 (*c* 1.11 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1753 (C=O); δ_H(270 MHz; $CDCl_3$) 3.30 (3 H, s, OCH_2OCH_3), 3.63 (3 H, s, CO_2CH_3), 4.59–4.68 (2 H, ABq, *J* 6.9, OCH_2OCH_3), 5.09 [1 H, s, CH(OMOM)] and 7.17–7.39 (5 H, m, Ph); δ_C(67.5 MHz; $CDCl_3$) 170.6, 135.6, 128.14, 128.06, 126.8, 94.4, 76.1, 55.3 and 51.6; *m/z* (CI, ammonia) 228 (M + NH_4^+, 85%), 211 (M + H^+, 10) and 179 (100).

(2*S*)-2-Methoxymethoxy(phenyl)acetaldehyde 10

To a solution of the ester **9** (4.92 g, 23.4 mmol) in CH_2Cl_2 (30 cm^3) at −70 °C (solid CO_2–acetone, solution temperature) was added DIBAL-H in CH_2Cl_2 (1.0 mol dm^{-3}; 23 cm^3) so that the solution temperature never exceeded −65 °C. After being stirred for 10 h, the reaction mixture was quenched with methanol (18 cm^3) and allowed to warm to room temperature. The gelatinous product was filtered through Celite, the latter then being washed with water (100 cm^3) and CH_2Cl_2 (200 cm^3). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic layer and extracts were dried and evaporated, and the residue was chromatographed on silica (eluent 80:20 hexanes–EtOAc, R_F 0.20) to yield the title compound **10** (3.94 g, 93%) as an unstable oil, δ_H(270 MHz; $CDCl_3$) 3.42 (3 H, s, OCH_3), 4.74–4.80 (2 H, ABq, *J* 6.7, OCH_2OCH_3), 5.04 [1 H, d, *J* 1.7, C(OMOM)*H*CHO], 7.36–7.42 (5 H, m, Ph) and 9.62 (1 H, d, *J* 1.7, CHO); δ_C(67.5 MHz; $CDCl_3$) 197.6, 133.4, 128.8, 128.7, 127.4, 95.0, 82.9 and 55.7; *m/z* (EI) 180 ($M^{+\bullet}$, 0.2%), 160 (0.4) and 151 (M − CHO^+, 100). The product was used without further purification.

(*Z*,3*R*)-3-Methoxymethoxy-1-nitro-3-phenyl-1-phenylsulfanylpropene 11

To a solution of phenylsulfanyl(nitro)methane[8] (1.40 g, 8.29 mmol) in THF (10 cm^3) and Bu^{t}OH (10 cm^3) at 0 °C was added KOBu^t (87.0 mg, 0.775 mmol) in Bu^{t}OH (1 cm^3). The aldehyde **10** (1.35 g, 7.49 mmol) in THF (15 cm^3) was added dropwise to this mixture with stirring. After 20 h, the reaction mixture was quenched with pH 7 phosphate buffer (20 cm^3) and separated, and the aqueous layer extracted with EtOAc (3 × 20 cm^3). The combined organic layer and extracts were concentrated and filtered through silica. This crude product was dissolved in CH_2Cl_2 (19 cm^3) and the solution cooled to 0 °C. Methanesulfonyl chloride (0.90 cm^3, 11.6 mmol) and triethylamine (2.50 cm^3, 17.9 mmol) were added to the solution which was then stirred for 1 h. The reaction mixture was quenched with pH 7 phosphate buffer (10 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried and evaporated, and the residue chromatographed on silica (eluent 50:50 hexanes–CH_2Cl_2, R_F 0.27) to yield the nitroalkene **11** (2.02 g, 81%) as a yellow–green oil, (Found: C, 61.5; H, 5.1; N, 4.3. Calc. for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23%); $[\alpha]_D$ +113 (*c* 0.995 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1536 (NO_2) and 1325 (NO_2); δ_H(270 MHz; $CDCl_3$) 3.41 (3 H, s, OCH_3), 4.74 (2 H, s, OCH_2OCH_3), 5.85 [1 H, *J* 8.9, CH(OMOM)Ph], 7.28–7.44 (10 H, m, Ph) and 7.74 [1 H, d, *J* 8.9, HC=C(SPh)NO_2]; δ_C(67.5 MHz, $CDCl_3$) 147.3, 145.0, 137.8, 131.2, 129.7, 129.5, 129.0, 128.9, 128.1, 127.1, 94.7, 75.9 and 55.8; *m/z* (EI) 331 ($M^{+\bullet}$, 3%), 255 (30), 218 (100) and 129 (100).

***S*-Phenyl (2*RS*,3*R*)-3-*tert*-butyldimethylsiloxy-2-hydroxy-3-phenylpropanethioate 15**

To the nitroalkene **8** (0.983 g, 2.45 mmol) in DMF (6 cm^3) at −55 °C was added potassium trimethylsilanolate (0.484 g, 3.77 mmol) in one portion. After being stirred for 4 h, the mixture was diluted with CH_2Cl_2 (20 cm^3) and cooled to −78 °C. Ozone was then bubbled through the mixture until a light blue colour was observed (~10 min). The reaction mixture was flushed with argon, quenched with water (10 cm^3) and allowed to warm to room temperature. The mixture was then extracted with Et_2O (3 × 10 cm^3) and the combined extracts were dried and evaporated to produce a crude oil which was immediately dissolved in 10% methanolic citric acid (20 cm^3). After 3 h, this mixture was quenched with pH 7 phosphate buffer and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried and evaporated and the residue was chromatographed on silica (eluent 90:10 hexanes–EtOAc) to yield the 2*S*-**15** (0.502 g, 53%, R_F 0.22) as an oil (Found: M + NH_4^+, 406.1890. $C_{21}H_{32}NO_3SSi$ requires *M*, 406.1872); $[\alpha]_D$ −65.3 (*c* 1.07 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1692 (C=O) and 1094 (C–S); δ_H(300 MHz; $CDCl_3$) −0.08 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 2.97 [1 H, br s, CH(O*H*)], 4.53 [1 H, dd, *J* 4.6, 5.6, *H*C(OH)], 5.08 [1 H, d, *J* 4.6,

HC(OTBS)] and 7.23–7.38 (10 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 199.2, 138.6, 134.5, 129.3, 129.1, 128.2, 128.1, 127.2, 126.9, 81.8, 76.0, 25.7, 18.2, −4.7 and −5.2; *m/z* (CI, ammonia) 406 ($M + NH_4^+$, 85%), 389 ($M^{+\bullet}$, 15), 274, (100), 268 (70), 251 (50) and 221 (45); and 2*R*-**15** (0.116 g, 12%; R_F 0.34) as an oil, δ_H(300 MHz; $CDCl_3$) −0.13 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$), 0.94 [9 H, s, $SiC(CH_3)_3$], 3.55 [1 H, d, *J* 10.4, CH(OH)], 4.19 [1 H, dd, *J* 0.8, 10.1, *H*C(OH)], 5.23 [1 H, d, *J* 1.0, HC(OTBS)] and 7.29–7.46 (10 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 140.7, 134.6, 129.4, 129.3, 129.2, 128.3, 128.0, 127.5, 126.1, 82.4, 74.6, 25.8, 18.2, −4.6 and −5.3; *m/z* (CI, ammonia) 406 ($M + NH_4^+$, 5%), 389 ($M^{+\bullet}$, 3), 274 (40), 268 (38), 251 (100) and 91 (45).

(4*S*,5*R*)-5-Methoxy-2,2-dimethyl-4-phenyl-1,3-dioxane 20

To the pure 2*S* diastereoisomer of **15** (0.183 g, 0.471 mmol) in CH_2Cl_2 (14 cm^3) at −78 °C was added 2-*tert*-butyl-1′,1′,3″,3″-tetramethylguanidine[9] (170 mm^3,‡ 0.960 mmol) and methyl trifluoromethanesulfonate (120 mm^3, 1.06 mmol). After 2.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 cm^3) and poured into water (20 cm^3). The aqueous mixture was extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined extracts were dried and evaporated. Chromatography of the residue on silica (eluent 95:5 hexanes–EtOAc) yielded the methyl-protected thioester (0.154 g, 81%) as an oil identical with the *R*-**18** (^1H NMR, *vide infra*).

To this thioester (62.3 mg, 0.155 mmol) in Pr^iOH (6 cm^3) at 0 °C was added $NaBH_4$ (30.7 mg, 0.812 mmol). After being stirred for 14 h, the reaction mixture was poured into water (10 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried, evaporated and filtered through silica. To the resulting crude primary alcohol (28.3 mg, 95.5 mm^3) in THF (2 cm^3) at 0 °C was added tetrabutylammonium fluoride in THF (1.0 mol dm^{-3}; 0.15 cm^3). After 2 h, the solvents were removed from the mixture by evaporation under reduced pressure and the residue was filtered through silica (EtOAc; 40 cm^3). This crude material was dissolved in 2,2-dimethoxypropane–benzene (1:1; 2 cm^3) along with a catalytic amount (~1 mg) of pyridinium toluene-4-sulfonate. After 5 days, the organic solvents were evaporated and the residue chromatographed on silica (eluent 90:10 hexanes–EtOAc) to yield the title compound **20** (13.8 mg, 64% overall) as an oil (Found: $M + H^+$, 223.1330. $C_{13}H_{19}O_3$ requires *M*, 223.1334); $[\alpha]_D$ −1.01 (*c* 0.69 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3029 (ArH), 2990 (aliph. CH), 1169, 1137 and 1089; δ_H(270 MHz; $CDCl_3$) 1.48 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 3.09 (3 H, s, OCH_3), 3.30 [1 H, dt *J* 5.2, 8.9, C*H*(OCH_3)], 3.76 [1 H, dd, *J* 8.9, 11.4, OC(H_{ax})H_{eq}], 4.06 [1 H, dd, *J* 5.2, 11.4, OC(H_{ax})H_{eq}], 4.59 [1 H, d, *J* 9.2, OC*H*(Ph)] and 7.30–7.47 (5 H, m, Ph); δ_C(67.5 MHz; $CDCl_3$) 139.9, 128.3, 128.0, 127.3, 99.2, 78.1, 75.4, 62.7, 58.1, 28.5 and 19.5; *m/z* (EI) 207 ($M - Me^+$, 3%), 147 (15), 134 (17), 91 (24) and 58 (100).

S-Phenyl (2*RS*,3*R*)-3-(*tert*-butyldimethylsiloxy)-3-phenyl-2-phthalimidopropanethioate 16

To the nitroalkene **8** (1.52 g, 3.79 mmol) in DMF (30 cm^3) at −40 °C was added potassium phthalimide (0.914 g, 4.93 mmol) over the course of 1 h. The mixture was stirred for 8 h before being diluted with CH_2Cl_2 (150 cm^3) and cooled to −78 °C. After this, ozone was bubbled through the solution until a faint blue colour appeared (~10 min). The reaction mixture was then flushed with argon, quenched with water and extracted with CH_2Cl_2. The extract was dried, evaporated and chromatographed on silica (eluent 2:1 hexanes–Et_2O) to yield 2*R*-**16** (1.01 g, 52%; R_F 0.45) as a solid, mp 84 °C (Found: $M + H^+$, 518.1804. $C_{29}H_{32}NO_4SSi$ requires *M*, 518.1821); $[\alpha]_D$ +101 (*c* 0.46 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1722 (C=O) and 1253 (C–S); δ_H(300 MHz; $CDCl_3$) −0.46 (3 H, s, $SiCH_3$), −0.22 (3 H, s, $SiCH_3$), 0.51 [9 H, s, $SiC(CH_3)_3$], 5.34 [1 H, d, *J* 9.0, HC(Nphthal)], 5.56 [1 H, d, *J* 9.0, PhCH(OTBS)], 7.25–7.52 (10 H, m, Ph) and 7.78–7.97 (4 H, m, phthalimido Ar); δ_C(75 MHz; $CDCl_3$) 192.4, 167.3, 141.6, 136.4, 134.5, 134.3, 133.5, 131.9, 131.3, 129.4, 129.3, 129.0, 128.7, 128.2, 128.1, 127.4, 126.3, 123.5, 71.2, 64.7, 25.1, 17.4 and −4.9; *m/z* (EI) 518 (M^+, 100%), 386 (35) and 221 (50); and the 2*S* epimer (0.14 g, 7%, R_F 0.34) as an oil; δ_H(300 MHz; $CDCl_3$) −0.24 (3 H, s, $SiCH_3$), 0.12 (3 H, s, $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 5.26 [1 H, d, *J* 8.9, HC(Nphthal)], 5.81 [1 H, d, *J* 8.9, PhHC(OTBS)], 7.11–7.39 (10 H, m, Ph) and 7.62–7.73 (4 H, m, phthalimido Ar); δ_C(75 MHz; $CDCl_3$) 191.8, 166.7, 134.5, 134.1, 131.1, 129.4, 129.2, 128.2, 128.1, 127.2, 123.5, 72.1, 64.4, 25.7, 18.0, −4.7 and −5.0; *m/z* (EI) 460 ($M - Bu^{t+}$, 13%), 354 (60) and 231 (40).

(4*S*,5*S*)-5-(*N*-Benzamido)-2,2-dimethyl-4-phenyl-1,3-dioxane 21

To the pure 2*R*-phthalimide **16** (0.155 g, 0.299 mmol) in Pr^iOH (4 cm^3) and water (0.3 cm^3) was added sodium boranuide (57.0 mg, 1.51 mmol) in one portion. The mixture was stirred for 24 h at room temperature after which glacial acetic acid (0.07 cm^3) was added to it and the whole refluxed for 2 h. The reaction mixture was then quenched with water and extracted with Et_2O (3 × 5 cm^3). The combined extracts were worked up and chromatographed on silica (eluent 95:5 CH_2Cl_2–methanol, 1% NH_4OH) to yield the amino alcohol (37.2 mg, 87%). To this substrate (0.130 g, 0.461 mmol) in CH_2Cl_2 (6 cm^3) at −15 °C was added benzoyl cyanide (60.1 mg, 0.458 mmol). The mixture was stirred for 12 h and then evaporated and chromatographed on silica (eluent 98:2 CH_2Cl_2–methanol, 1% NH_4OH) to afford the amido alcohol (120 mg, 68%) as an oil; δ_H(300 MHz; $CDCl_3$) −0.11 (3 H, s, $SiCH_3$), 0.11 (3 H, s, $SiCH_3$), 0.94 [9 H, s, $SiC(CH_3)_3$] 3.71–3.83 (AB dd, *J* 5.7, 11.0, HOCH_2), 4.23 [1 H, m, C(NHBz)H], 5.14 [1 H, d, *J* 3.1, CH(OTBS)], 6.74 (1 H, d, *J* 7.7, NH), 7.24–7.51 (8 H, m, Ph) and 7.68 (2 H, m, Ph).

This crude product (44.6 mg, 0.124 mmol) was dissolved in THF (1 cm^3) and treated with tetrabutylammonium fluoride in THF (1.0 mol dm^{-3}; 0.2 cm^3). After being stirred for 13 h, the mixture was evaporated and the product filtered through silica. The resulting oil was dissolved in CH_2Cl_2 (2 cm^3) and 2,2-dimethoxypropane (6 cm^3) and pyridinium toluene-4-sulfonate (~5 mg) were added to the solution. After being stirred for 15 h, the reaction mixture was quenched with triethylamine (0.1 cm^3), evaporated and chromatographed on silica (eluent 60:40 hexanes–EtOAc, R_F 0.22) to yield the title compound **21** (24.5 mg, 64%) as an oil (Found: $M + H^+$, 312.1620. $C_{19}H_{22}NO_3$ requires *M*, 312.1600); $[\alpha]_D$ +110 (*c* 1.42 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450, 3319 (N–H) and 1664 (C=O); δ_H(300 MHz; $CDCl_3$) 1.58 (3 H, s, Me), 1.62 (3 H, s, Me), 4.01 [1 H, dd, *J* 1.8, 12.0, OC(H_{ax})H_{eq}C(NHBz)H], 4.34 [1 H, dd, *J* 1.9, 12.0, OC(H_{ax})H_{eq}C(NHBz)H], 4.41 [1 H, dq, *J* 1.8, 9.0, C(NHBz)*H*], 5.30 [1 H, d, *J* 1.8, OC*H*PhC(NHBz)H], 6.68 (1 H, d, *J* 8.9, NHBz) and 7.20–7.52 (10 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 167.2, 138.4, 134.7, 131.4, 128.6, 128.5, 128.4, 127.7, 126.9, 125.4, 99.7, 72.2, 64.7, 47.4, 29.9 and 18.7; *m/z* (CI, ammonia) 312 ($M + H^+$, 65%), 254 (100), 147 (35) and 105 (35).

S-Phenyl (2*RS*,3*R*)-3-(*tert*-butyldimethylsiloxy)-2-methyl-3-phenylpropanethioate 17

Copper bromide–dimethyl sulfide complex (1.23 g, 5.98 mmol) was dissolved in Et_2O (4 cm^3) and methyl sulfide (4 cm^3) at room temperature. Methyllithium in Et_2O (1.4 mol dm^{-3}) was added dropwise to the solution until the initially bright yellow solution turned clear again. This solution was then cooled to −40 °C before being charged with a solution of the nitroalkene **8** (1.71 g, 4.26 mmol) in Et_2O (5 cm^3). After being stirred for

‡ 1 mm^3 = 1 μl.

2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and filtered through silica. The filtrate was evaporated and the crude product dissolved in THF (36 cm^3). Potassium *tert*-butoxide (0.797 g, 7.10 mmol) was added to the solution which turned red and was then cooled to −78 °C. Ozone was bubbled through the reaction mixture for 0.5 h after which it was quenched with water (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 cm^3) and the combined extracts were dried, evaporated and chromatographed on silica (eluent 95:5 hexanes–EtOAc, R_F 0.36) to afford the title compound **17** (0.676 g, 41%) as a 2.2:1 2*R*/2*S* mixture of diastereoisomers (Found: C, 68.1; H, 7.7. Calc. for $C_{22}H_{30}O_2SSi$: C, 68.34; H, 7.82%); ν_{max}(neat)/cm^{-1} 1704 (C=O) and 1257 (C–S); δ_H(300 MHz; $CDCl_3$) major diastereoisomer −0.20 (3 H, s, $SiCH_3$), 0.05 (3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.32 (3 H, d, *J* 6.9, $CHCH_3$), 2.96 (1 H, p, *J* 6.9, $CHCH_3$), 4.95 [1 H, d, *J* 6.5, C(OTBS)H] and 7.18–7.43 (10 H, m, Ph); minor diastereoisomer −0.31 (3 H, s, $SiCH_3$), 0.00 (3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 0.88 (3 H, d, obscured by Bu^t peak of major diastereoisomer, $CHCH_3$), 3.03 (1 H, dq, *J* 7.0, 9.2, $CHCH_3$), 4.79 [1 H, d, *J* 9.2, C(OTBS)H] and 7.18–7.43 (10 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 200.2, 199.4, 142.8, 142.2, 134.4, 134.3, 129.2, 129.0, 128.9, 128.2, 128.0, 127.9, 127.7, 127.5, 127.1, 126.7, 77.6, 76.3, 57.6, 57.1, 25.8, 25.7, 18.1, 18.0, 14.8, 12.9, −4.6, −4.7, −5.1 and −5.4; *m*/*z* (EI) 386 ($M^{+\cdot}$, 0.2%), 371 (M − Me^+, 0.2), 329 (M − Bu^{t+}, 40) and 115 (100).

(4*R*,5*R*)-2,2,5-Trimethyl-4-phenyl-1,3-dioxane 22

To the 2*R*/2*S* epimeric mixture of the thioester **17** (0.234 g, 0.605 mmol) in Et_2O (10 cm^3) at 0 °C was added lithium aluminium hydride (82.0 mg, 2.2 mmol). After being stirred for 5 h, the reaction mixture was quenched by the successive addition of water (80 mm^3), 12% NaOH (160 mm^3) and water (300 mm^3). The residue was filtered through Celite and the latter washed with Et_2O (3 × 10 cm^3). The combined extracts were dried and evaporated. The crude product (0.114 g) was dissolved in THF (10 cm^3) with tetrabutylammonium fluoride in THF (1.0 mol dm^{-3}, 0.9 cm^3). After being stirred for 5 h, the mixture was diluted with EtOAc (20 cm^3) and poured into water. The aqueous phase was separated and extracted with EtOAc (3 × 10 cm^3) and the combined organic layer and extracts were dried and evaporated. Chromatography of the residue on silica (eluent 1:1 hexanes–ethyl acetate) yielded (3*R*)-2-methyl-3-phenylpropane-1,3-diol as a mixture of epimers (64.6 mg, 64%) as a clear oil, δ_H(300 MHz; $CDCl_3$) major diastereoisomer 0.82 (3 H, d, *J* 7.0, $CHCH_3$), 2.78 (1 H, br s, OH), 3.64 (2 H, d, *J* 4.8, CH_2OH), 4.92 [1 H, d, *J* 3.7, PhC*H*(OH)] and 7.31 (5 H, m, Ph).

To the 1,3-diol (16.8 mg, 0.101 mmol) in benzene (1 cm^3) was added 2,2-dimethoxypropane (38 cm^3, 0.309 mmol) and pyridinium toluene-4-sulfonate (~5 mg). After being stirred for 16 h, the reaction mixture was quenched with triethylamine (1 cm^3), diluted with ethyl acetate (10 cm^3), filtered through a plug of silica, evaporated and chromatographed on silica (eluent 90:10 hexanes–EtOAc, R_F 0.40) to yield a mixture of compounds **22** and **23** (15.0 mg, 72%, 2.2:1) as an oil (Found: C, 75.5; H, 9.0. Calc. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%); ν_{max}(neat)/cm^{-1} 3030, 2992, 1381, 1108 and 1011; δ_H(300 MHz; $CDCl_3$) major diastereoisomer **22** 0.84 [3 H, d, *J* 7.0, $CH(CH_3)$], 1.53 [3 H, s, $C(CH_3)_2$], 1.54 [3 H, s, $C(CH_3)_2$], 1.77 [1 H, m, $CH(CH_3)$], 3.71 [1 H, dd, *J* 1.3, 11.3, $OC(H_{ax})H_{eq}C(Me)H_q$], 4.31 [1 H, dd, *J* 2.8, 11.4, $OC(H_{ax})H_{eq}C(Me)H_{eq}$], 5.16 [1 H, d, *J* 2.7, C(Ph)H] and 7.21–7.37 (5 H, m, Ph); minor diastereoisomer **23** 0.61 [3H, d, *J* 6.7, $CH(CH_3)$], 1.49 [3 H, s, $C(CH_3)_2$], 1.56 [3 H, s, $C(CH_3)_2$], 1.95 [1 H, m, $CH(CH_3)$], 3.68 [1 H, m, $OC(H_{ax})H_{eq}C(Me)H_{ax}$ obscured by major diastereoisomer], 3.83 [1 H, dd, *J* 5.1, 11.7, $OC(H_{ax})H_{eq}C(Me)H_{ax}$], 4.42 [1 H, d, *J* 10.3, C(Ph)H] and 7.21–7.37 (5 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 141.1, 140.4, 128.3, 128.0, 127.4, 126.8, 125.4, 99.0, 98.7, 78.9, 73.0, 66.5, 66.4, 36.1, 34.0, 29.9, 29.8, 26.9, 19.0, 12.5 and 10.8; *m*/*z* (EI) 206 ($M^{+\cdot}$, 5%), 191 (15), 148 (70), 107 (80) and 59 (100).

S-Phenyl (2*RS*,3*R*)-3-(*tert*-butyldimethylsiloxy)-2-methoxy-3-phenylpropanethioate 18

A solution of 25% sodium methoxide in methanol (0.3 cm^3, 1.50 mmol), methanol (1.2 cm^3) and DMF (7 cm^3) was added to the nitroalkene **8** (0.456 g, 1.14 mmol) in DMF (4.5 cm^3) at −45 °C. After being stirred for 2 h, the mixture was diluted with methanol (15 cm^3) and cooled to −78 °C. Ozone was flushed through the mixture until a faint blue colour appeared. After being quenched with water (20 cm^3), the mixture was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined extracts were washed with water (4 × 10 cm^3), dried, evaporated and chromatographed on silica (eluent 90:10 hexanes–EtOAc, R_F 0.31) to yield the title compound **18** (0.264 g, 58%) as a 1.6:1 2*R*/2*S* mixture of diastereoisomers (Found: C, 65.4; H, 7.7. Calc. for $C_{22}H_{30}O_3SSi$: C, 65.63; H, 7.51%); ν_{max}(neat)/cm^{-1} 1698 (C=O) and 1254 (C–S); δ_H(300 MHz; $CDCl_3$) major diastereoisomer −0.14 (3 H, s, $SiCH_3$), −0.01 (3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 3.31 (3 H, s, OCH_3), 3.78 [1 H, d, *J* 3.4, $HC(OCH_3)$], 5.06 [1 H, d, *J* 3.4, PhCH(OTBS)] and 7.24–7.44 (10 H, m, Ph); minor diastereoisomer −0.19 (3 H, s, $SiCH_3$), 0.03 (3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 3.46 (3 H, s, OCH_3), 3.85 [1 H, d, *J* 5.7, $HC(OCH_3)$], 4.95 [1 H, d, *J* 5.7, PhCH(OTBS)] and 7.24–7.43 (10 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 199.7, 198.7, 140.4, 140.3, 134.5, 129.2, 129.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.0, 92.4, 91.6, 77.2, 76.1, 75.9, 61.0, 60.1, 25.8, 25.7, 18.3, 18.1, −4.7, −4.8 and −5.2; *m*/*z* (EI) 345 (M − Bu^{t+}, 7.5%), 296 (4), 239 (40) and 221 (100).

(4*S*,5*S*)-5-Methoxy-2,2-dimethyl-4-phenyl-1,3-dioxane 24

To a 2*R*/2*S* epimeric mixture of thioester **18** (0.167 g, 0.415 mmol) in Pr^iOH (4.5 cm^3) at 0 °C was added sodium boranuide (64.0 mg, 1.69 mmol). The reaction mixture was stirred for 12 h during which time it was allowed to warm to room temperature. After being quenched with water (5 cm^3) the mixture was extracted with CH_2Cl_2 (3 × 5 cm^3), and the combined extracts were dried and evaporated to yield the crude primary alcohol (134 mg) as a yellow oil. This was dissolved in THF (5 cm^3) and charged with tetrabutylammonium fluoride in THF (1.0 mol dm^{-3}; 0.7 cm^3). After the mixture had been stirred for 2 h, it was evaporated and the resulting oil filtered through silica (EtOAc). The filtrate was dissolved in benzene (1 cm^3) and 2,2-dimethoxypropane (1 cm^3) and to this solution was added pyridinium toluene-4-sulfonate (~5 mg). After being stirred for 48 h, the mixture was quenched with triethylamine (0.1 cm^3), evaporated and chromatographed on silica (eluent 85:15 hexanes–EtOAc) to yield the title compound **24** (34.1 mg, 37% overall, R_F 0.16) as an oil (Found: M + NH_4^+, 240.1596. $C_{13}H_{22}NO_3$ requires *M*, 240.1600); $[\alpha]_D$ +77.7 (*c* 1.20 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3029 (arom. CH), 2990 (aliph. CH), 1169, 1137 and 1089; δ_H(300 MHz; $CDCl_3$) 1.55 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 3.06 (3 H, s, OCH_3), 3.19 [1 H, ddd, *J* 2.5, $CH(OCH_3)$], 4.05–4.15 [2 H, ABXdd, *J* 2.1, 12.7, $OCH_2CH(OCH_3)$], 5.02 [1 H, d, *J* 1.9, OCH(Ph)] and 7.27–7.45 (5 H, m, Ph); δ_C(75 MHz; $CDCl_3$) 138.7, 128.0, 127.3, 126.4, 99.0, 75.5, 73.2, 62.1, 58.2, 29.2 and 18.9; *m*/*z* (EI) 207 (M − Me^+, 0.5%), 147 (4), 134 (4), 91 (4.5) and 58 (100) and a compound identical with **20** (31.6 mg, 34%, R_F 0.47) by ^1H NMR.

S-Phenyl (2*RS*,3*R*)-3-(*tert*-butyldimethylsiloxy)-3-phenyl-2-(toluene-*p*-sulfonamido)propanethioate 19

To toluene-*p*-sulfonamide (108 mg, 0.631 mmol) and potassium *tert*-butoxide in THF (1.0 mol dm^{-3}; 0.65 cm^3) in DMF (4.0 cm^3) at 0 °C was added the nitroalkene **8** (0.195 g, 0.486 mmol)

in DMF (4 cm^3) at 0 °C dropwise *via* a cannula. After 5 h, the reaction mixture was diluted with CH_2Cl_2 (20 cm^3) and cooled to −78 °C. Ozone was bubbled through the solution until a faint blue colour appeared (~10 min). The reaction mixture was then quenched with dimethyl sulfide (0.5 cm^3), warmed to room temperature and poured into water (20 cm^3). The aqueous mixture was extracted with CH_2Cl_2 (3 × 10 cm^3), evaporated, diluted with EtOAc (30 cm^3), washed with water (3 × 10 cm^3), dried, evaporated and chromatographed on silica (90:10 hexanes–EtOAc) to yield the (2*R*)-**19** (99.5 mg, 38%; R_F 0.20), mp 124 °C (Found: C, 61.7; H, 6.6; N, 2.7. Calc. for $C_{28}H_{35}NO_4S_2Si$: C, 62.07; H, 6.51; N, 2.59%); $[\alpha]_D$ +96.9 (*c* 0.98 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3369 (NH), 1686 (C=O) and 1344 (S=O); δ_H(500 MHz; $CDCl_3$) −0.19 (3 H, s, $SiCH_3$), −0.04 (3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 2.36 (3 H, s, SO_2PhCH_3), 4.15 [1 H, dd, *J* 2.0, 9.0, *HC*(NHTs-*p*)], 5.27 [1 H, d, *J* 1.9, PhCH(OTBS)], 5.60 (1 H, d, *J* 9.0, NHTs), 7.05 (1 H, d, *J* 8.1, Ph) and 7.13–7.41 (13 H, m, Ph); δ_H(125 MHz; $CDCl_3$) 198.5, 143.1, 139.7, 137.0, 134.4, 129.5, 129.2, 128.2, 127.7, 127.5, 126.8, 125.9, 74.6, 69.3, 25.8, 21.4, 18.2, −4.7 and −5.3; *m/z* (EI) 484 (M − Bu^{t+}, 0.5%), 404 (8), 346 (20), 221 (100) and 190 (40); and the 2*S* epimer (32.1 mg, 12%, R_F 0.10); δ_H(270 MHz; $CDCl_3$) −0.18 (3 H, s, $SiCH_3$), 0.01 (3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 2.41 (3 H, s, SO_2PhCH_3), 4.32 [1 H, dd, *J* 5.2, 9.4, *HC*(NHTs-*p*)], 5.04 [1 H, d, *J* 5.2, PhCH(OTBS)], 5.12 (1 H, d, *J* 9.4, NHTs) and 7.07–7.67 (14 H, m, Ph); δ_C(67.5 MHz; $CDCl_3$) 196.3, 143.5, 138.8, 137.0, 134.1, 129.55, 129.48, 129.0, 128.3, 127.3, 126.8, 126.7, 75.7, 68.0, 25.7, 21.4, 18.1, −4.9 and −5.3; *m/z* (EI) 484 (M − Bu^{t+}, 2%), 346 (26) and 248 (80).

S-Phenyl (2*RS*,3*R*)-2-hydroxy-3-methoxymethyl-3-phenylpropanethioate 25

To a solution of the nitroalkene **11** (0.215 g, 0.649 mmol) in DMF (7 cm^3) at −45 °C was added potassium trimethylsilanolate (0.1126 g, 0.98 mmol) in one portion. After being stirred for 5 h, the mixture was diluted with CH_2Cl_2 (20 cm^3) and cooled to −78 °C. Ozone was bubbled through the solution until a light blue colour was observed (~10 min). The reaction mixture was then quenched with Me_2S (0.5 cm^3), poured into water (30 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were evaporated and diluted with EtOAc (30 cm^3), and then washed with water (3 × 15 cm^3), dried and evaporated. The residue was dissolved in 10% methanolic citric acid (15 cm^3) and stirred for 1 h, before being poured into water (30 cm^3) and extracted with EtOAc (3 × 10 cm^3). The combined extracts were dried, evaporated and chromatographed on silica (eluent 80:20 hexanes–EtOAc) to yield (2*R*)-**25** (68.7 mg, 33%; R_F 0.34) as a white solid, mp 94 °C (Found: C, 64.1; H, 5.4. Calc. for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70); $[\alpha]_D$ +181 (*c* 0.96 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3429 (OH), 1697 (C=O), 1440, 1070 and 1019 (C–O–C); δ_H(270 MHz; $CDCl_3$) 3.32 (3 H, s, OCH_3), 3.39 (1 H, d, *J* 9.2, OH), 4.36 [1 H, dd, *J* 2.2, 8.9, CH(OH)], 4.57–4.63 (2 H, ABq, *J* 6.7, OCH_2O), 5.19 [1 H, d, *J* 2.2, CH(OMOM)] and 7.33–7.46 (10 H, m, Ph); δ_C(67.5 MHz; $CDCl_3$) 200.43, 137.1, 134.5, 129.4, 129.2, 128.5, 128.4, 127.3, 94.3, 81.3, 77.5 and 55.9; *m/z* (CI, ammonia) 336 (M + NH_4^+, 100%), 304 (60), 274 (50) and 198 (40); and the 2*S* epimer (34.3 mg, 17%; R_F 0.28); δ_H(270 MHz; $CDCl_3$) 3.24 (1 H, d, *J* 6.9, OH), 3.41 (3 H, s, OCH_3), 4.63–4.71 (2 H, ABq, *J* 6.7, OCH_2O), 4.71 [1 H, dd, *J* 4.2, 6.9, C*H*(OH)], 5.05 [1 H, d, *J* 4.5, CH(OMOM)] and 7.25–7.40 (10 H, m, Ph); δ_C(67.5 MHz; $CDCl_3$) 199.0, 135.5, 134.5, 129.4, 129.2, 128.6, 128.4, 127.9, 126.8, 94.9, 80.3, 79.3 and 56.1; *m/z* (CI, ammonia) 336 (M + NH_4^+, 100%), 319 (M + H^+, 20), 287 (60) and 198 (50).

S-Phenyl (2*RS*,3*R*)-3-methoxymethyl-3-phenyl-2-phthalimidopropanethioate 26

To the nitroalkene **11** (0.193 g, 0.581 mmol) in DMF (6 cm^3) at −40 °C was added potassium phthalimide (0.139 g, 0.581 mmol) in one portion. The mixture was stirred for 16 h before being diluted with CH_2Cl_2 (18 cm^3) and cooled to −78 °C. Ozone was bubbled through the mixture until the bright yellow colour became pale blue. The reaction mixture was then flushed with nitrogen and quenched with Me_2S (0.5 cm^3). The solution was poured into water (20 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined extracts were evaporated, diluted with EtOAc (30 cm^3), washed with water (2 × 20 cm^3), dried and evaporated. Chromatography of the residue (eluent 80:20 hexanes–EtOAc) yielded (2*R*)-**26** (0.109 g, 42%; R_F 0.20) as a solid, mp 39 °C; (Found M + H^+, 448.1229. $C_{25}H_{22}NO_5S$ requires *M*, 448.1219); $[\alpha]_D$ +113 (*c* 0.99 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1723 (C=O) and 1711 (C=O); δ_H(270 MHz; $CDCl_3$) 3.02 (3 H, s, OCH_3), 4.38 (2 H, s, OCH_2OCH_3), 5.43 [1 H, d, *J* 9.4, C(=O)C*H*(N-phthal)], 5.58 [1 H, d, *J* 9.4, PhC*H*(OMOM)], 7.22–7.53 (10 H, m, Ph) and 7.74–7.99 (4 H, m, phthal); δ_C(125 MHz; $CDCl_3$) 192.1, 167.4, 138.6, 134.6, 134.4, 134.3, 131.9, 129.6, 129.2, 128.6, 128.5, 126.4, 123.8, 123.6, 94.4, 74.2, 63.4 and 55.8; *m/z* (CI, ammonia), 465 (M + NH_4^+, 50%), 448 (M + H^+, 35), 386 (80), 293 (97) and 276 (100); and the 2*S* epimer (40.7 mg, 16%; R_F 0.27) as an oil; δ_H(270 MHz; $CDCl_3$) 3.23 (3 H, s, OCH_3), 4.59 (1 H, d, *J* 6.7, OCH_2OCH_3), 4.78 (1 H, d, *J* 6.7, OCH_2OCH_3), 5.38 [1 H, d, *J* 9.4, C(=O)CH(N-phthal)], 5.66 [1 H, d, *J* 9.4, PhC*H*-(OMOM)], 7.10–7.40 (10 H, m, Ph) and 7.62–7.74 (4 H, m, phthal); δ_C(67.5 MHz; $CDCl_3$) 192.1, 167.4, 138.6, 134.6, 134.4, 134.3, 131.9, 129.6, 129.2, 128.6, 128.5, 126.4, 123.8, 123.6, 94.4, 74.2, 63.4 and 55.8; *m/z* (CI, ammonia) 465 (M + NH_4^+, 45%), 448 (M + H^+, 25), 416 (100), 386 (95) and 276 (80).

S-Phenyl (2*R*,3*R*)-3-(*tert*-butyldimethylsiloxy)-3-phenyl-2-phthalimidopropanethioate 16 (from 26)

To the (2*R*)-**26** (0.124 g, 0.277 mmol) in CH_2Cl_2 (3 cm^3) was added trimethylsilyl bromide (0.30 cm^3, 2.27 mmol at 0 °C. The reaction mixture was allowed to warm to room temperature and then stirred for 3 days before being quenched with water (1 cm^3). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic layer and extracts were dried and chromatographed on silica (80:20 hexanes–EtOAc) to yield the alcohol (72.3 mg, 65%) along with recovered starting material (36.5 mg, 29%). To a solution of the alcohol (31.4 mg, 77.8 μmol) in CH_2Cl_2 (1 cm^3) at −78 °C was added *tert*-butyldimethylsilyl triflate (0.4 cm^3, 1.7 mmol) and 2,6-dimethylpyridine (27 mm^3, 0.234 mmol). The reaction mixture was allowed to warm to room temperature (~1 h) and stirred for a further 12 h before being quenched with water. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic layer and extracts were dried and evaporated, and the residue was chromatographed on silica (2:1 hexanes–Et_2O, R_F 0.45) to afford the (2*R*)-**16** (38.6 mg, 96%) identical with the previously synthesised material (^1H NMR).

(2*R*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-methoxy-3-phenylpropyl (*S*)-methoxy(phenyl)acetate 27

To the primary alcohol (12.6 mg, 42.5 μmol), resulting from methylation and reduction of **15** (see Experimental detail for **20**), in CH_2Cl_2 (1 cm^3) at 0 °C was added dicyclohexylcarbodiimide (16.5 mg, 80 μmol), (*S*)-methoxy(phenyl)acetic acid (9.8 mg, 59 μmol) and 4-dimethylaminopyridine (~1 mg). After 1 h, the reaction mixture was poured into cold 1 mol dm^{-3} HCl (5 cm^3) and extracted with CH_2Cl_2 (3 × 5 cm^3). The combined extracts were washed with saturated aqueous $NaHCO_3$ and then saturated brine, dried and evaporated. The residue was filtered through silica to yield the title compound **27** (16.2 mg, 86%) as a single diastereoisomer by ^1H NMR δ_H(270 MHz; $CDCl_3$) −0.18 (3 H, s, $SiCH_3$), −0.02 (3 H, s, $SiCH_3$), 0.89

[9 H, s, $SiC(CH_3)_3$], 3.08 [3 H, s, $OC(O)CH(OCH_3)$], 3.45 [m, 1 H, $CH(OCH_3)CH(OTBS)$], 3.48 [3 H, s, $(TBSO)CH-CH(OCH_3)$], 4.29 (1 H, dd, *J* 6.4, 11.6, CH_2), 4.47 (1 H, dd, *J* 3.0, 11.6, CH_2), 4.65 [1 H, d, *J* 6.2, $PhCH(OTBS)$], 4.83 [1 H, s, $OC(O)CH(OCH_3)$] and 7.53–7.31 (10 H, m, Ph). ^1H NMR for (*R*)-ester: δ_H(270 MHz; $CDCl_3$) 3.02 [3 H, s, $OC(O)-CH(OCH_3)$].

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