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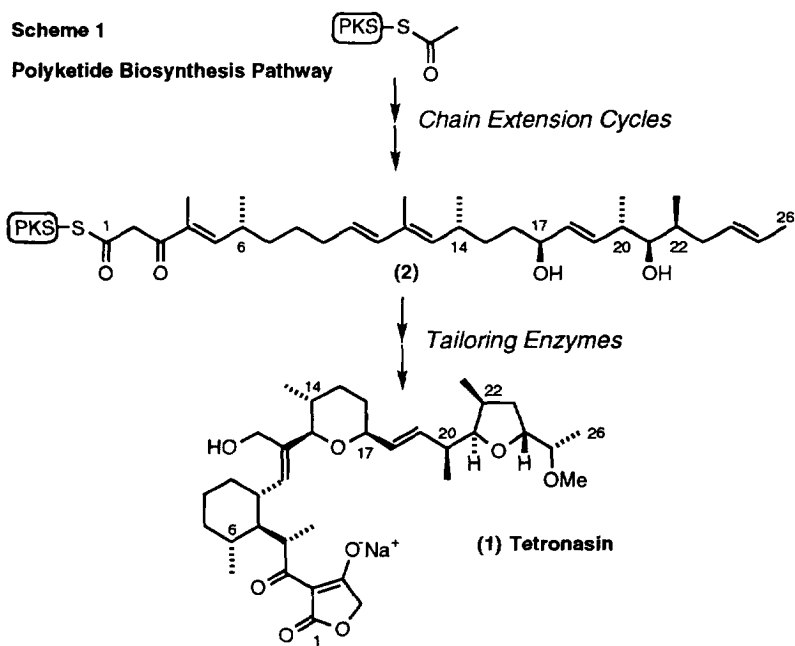
## Biosynthesis of Tetronasin: Part 4<sup>1</sup>, Preparation of Deuterium Labelled C19-C26, C17-C26, C11-C26 and C3-C26 Polyketide Fragments as Putative Biosynthetic Precursors of the Ionophore Antibiotic Tetronasin (ICI 139603)

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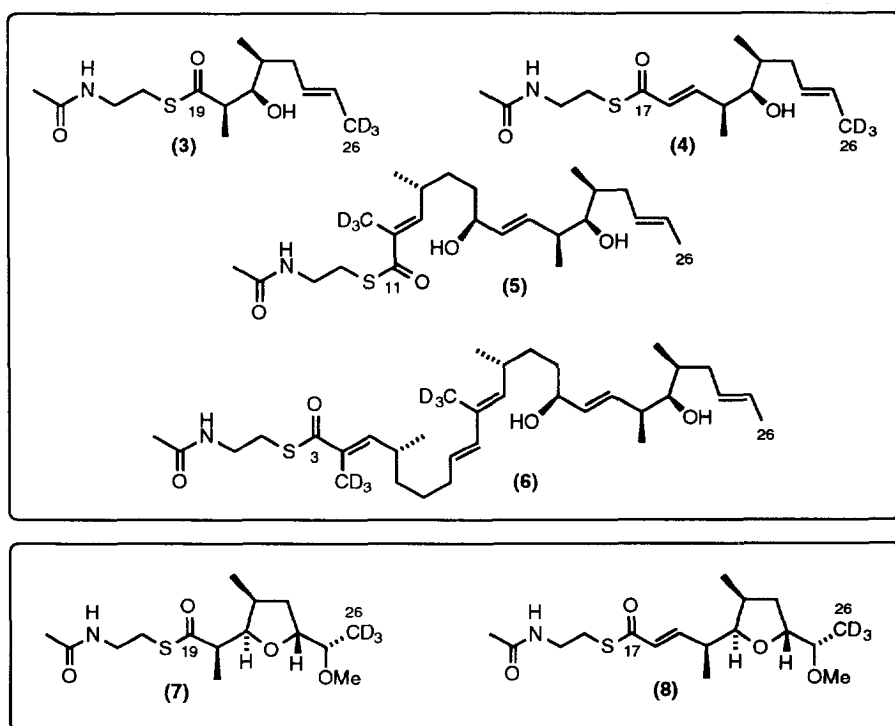
**Abstract:** Six deuterium labelled *N*-acylcysteamine polyketide derivatives (3) - (8) have been prepared as putative precursors for incorporation in studies of the biosynthesis of the ionophore antibiotic tetronasin (1). The route to these compounds was designed to be flexible and to maximise the use of common synthetic fragments.

Tetronasin (ICI 139603) (1) is an acyltetronic acid ionophore produced by *Streptomyces longisporoflavus*<sup>2</sup> and is of commercial interest owing to its biological activity as an antibiotic, antiparasitic and growth promotion agent in ruminants.<sup>3</sup> Several studies have been reported on its structure,<sup>2</sup> properties,<sup>4</sup> biosynthesis<sup>1,5</sup> and synthesis.<sup>6</sup> In preliminary studies into the biosynthetic pathway it has been determined that the carbon skeleton has been largely built up by normal polyketide coupling of seven acetate and six propionate units.<sup>5e,f</sup> Furthermore it has been speculated that this pathway progresses by a processive sequence involving assembly on a polyketide synthase (PKS) enzyme complex,<sup>5d</sup> *via* a number of enzyme-bound intermediates. These eventually lead to a linear polyene species such as (2) in which a total of twelve chain extension cycles have occurred from the initial thioacetyl loaded PKS (Scheme 1).



The final polyene (**2**) can then be elaborated by post-PKS tailoring enzymes to afford (**1**).

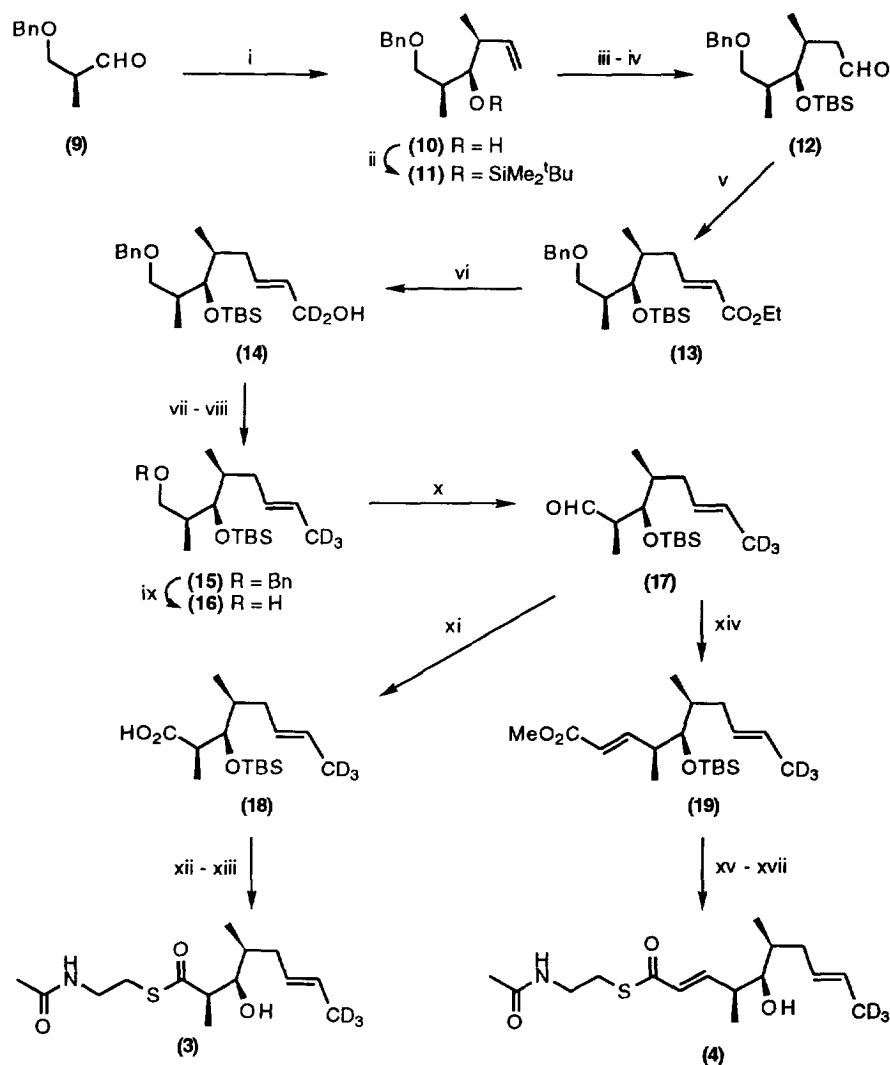
In this work we report the synthesis of a number of the putative polyketide intermediates on this pathway which have been specifically labelled with deuterium and substituted as *N*-acylcysteamine thioester derivatives (NAC-thioesters) for potential incorporation into the biosynthetic machinery.<sup>7</sup> The synthetic route has been designed to be extremely flexible, allowing for the preparation of any potential precursor polyketide on the biosynthetic pathway. For this particular study, however, we restricted our efforts towards the synthesis of two groups of NAC-thioesters. The first group of compounds (**3**) - (**6**) (Figure 1) are designed to probe the involvement of a particular processive pathway and can be considered as representative examples of polyketides on the extended chain processive route to (**1**).<sup>5d</sup> The second group of NAC-thioesters which have been prepared, compounds (**7**) and (**8**), were synthesised to be complementary to the open chain precursors (**3**) and (**4**) in order to investigate whether the terminal furan ring is formed early in the biosynthetic pathway and could thus be incorporated and processed as an intact motif.



**Figure 1: Labeled Polyketide Precursors for Biosynthetic Investigation**

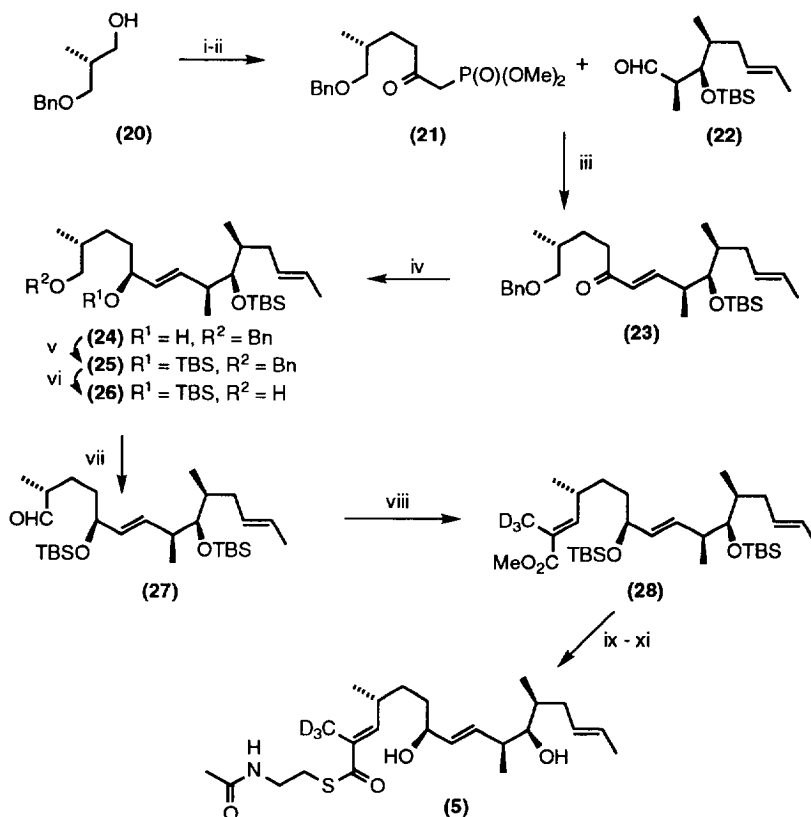
The first set of compounds were prepared from the readily available aldehyde (**9**)<sup>8</sup> (Scheme 2). Reaction of (**9**) with (*Z*)-crotyl-(+)-diisopinocampheylborane<sup>9</sup> and oxidative work up gave (**10**), in which three of the required stereogenic centres are in place, in essentially one step. The alcohol (**10**) was readily protected as its *t*-butyldimethylsilyl ether (**11**) using *t*-butyldimethylsilyl triflate.<sup>10</sup> The double bond of (**11**) was then transformed to the aldehyde (**12**) by hydroboration using 9-BBN followed by oxidative work up, and subsequent Swern oxidation.<sup>11</sup> This aldehyde (**12**) serves as a synthetic precursor for all the NAC-thioester derivatives reported here. Homologation of (**12**) with triethyl phosphonoacetate under the Masamune-Roush

conditions<sup>12</sup> gave the ester (13) which was then reduced with DIBAL-D<sup>13</sup> to give the dideuterio allylic alcohol (14).



**Scheme 2** (i) (Z)-crotyl-(+)-diisopinocampheylborane, THF, Et<sub>2</sub>O, -100°C (71%). (ii) TBDMSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub> (100%). (iii) 9-BBN, THF, Δ; then H<sub>2</sub>O<sub>2</sub>, NaOH, 0°C - rt (95%). (iv) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60°C - rt (85%). (v) EtO<sub>2</sub>CH<sub>2</sub>P(O)(OEt)<sub>2</sub>, LiCl, DIPEA, CH<sub>3</sub>CN (93%). (vi) DIBAL-D, THF, -78°C (85%). (vii) TsCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (90%). (viii) LiEt<sub>3</sub>BD, THF, -78°C (85%). (ix) Li/NH<sub>3</sub>, Et<sub>2</sub>O, -78°C (97%). (x) <sup>n</sup>Pr<sub>4</sub>NRuO<sub>4</sub>, NMO, 4 Å powdered sieves, CH<sub>2</sub>Cl<sub>2</sub> (95%). (xi) NaClO<sub>2</sub>, 2-methyl-2-butene, KH<sub>2</sub>PO<sub>4</sub>, <sup>t</sup>BuOH/H<sub>2</sub>O. (xii) *N*-acetylcysteamine, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (77% over two steps). (xiii) HF, pyridine, MeCN (80%). (xiv) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me, CHCl<sub>3</sub>, Δ (95%). (xv) LiOH, EtOH/H<sub>2</sub>O, 40°C. (xvi) *N*-acetylcysteamine, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (49% over two steps). (xvii) HF, pyridine, MeCN (98%).

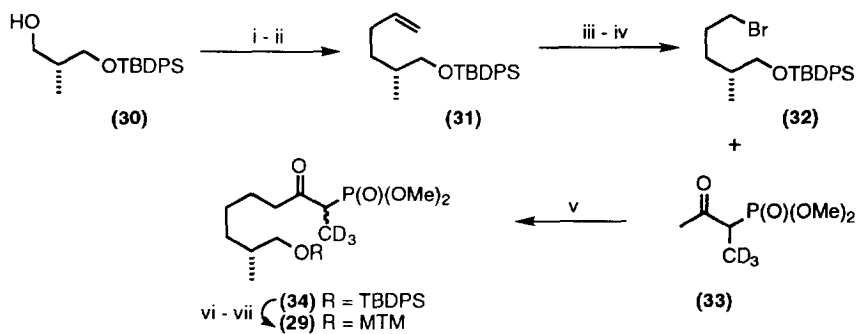
Further reduction of (14) was achieved *via* intermediate conversion to the corresponding chloride using tosyl chloride in CH<sub>2</sub>Cl<sub>2</sub> containing DMAP<sup>14</sup> and then treatment with lithium triethylborodeuteride (Super-Deuteride®) to give (15) in excellent overall yield. In fact, all reactions in Scheme 2 proceeded in better than 80% yield for any individual step. Deprotection of (15) to (16) with lithium in ammonia at -78 °C was straightforward and the product was subsequently oxidised to the aldehyde (17) using tetra-*n*-propylammonium perruthenate (TPAP).<sup>15</sup> This material was then diverted through two pathways to the NAC-thioesters (3) and (4). In the first case, oxidation with sodium chlorite, in the presence of 2-methyl-2-butene as a chlorine scavenger, afforded the acid (18) which was coupled with *N*-acetylcysteamine<sup>16</sup> using DCC/DMAP. Subsequent deprotection with hydrogen fluoride in pyridine gave the NAC-thioester (3) (Scheme 2). Alternatively, the homologated pentaketide ester (4) was obtained by reacting the aldehyde (17) with carbomethoxymethylene triphenylphosphorane to produce (19) which was then hydrolysed with lithium hydroxide. The resulting acid was coupled with *N*-acetylcysteamine as before and deprotection then afforded (4) (Scheme 2).



**Scheme 3** (i) NBS, PPh<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (87%). (ii) Dimethyl (2-oxopropyl)phosphonate, NaH, <sup>n</sup>BuLi, THF, -10 °C (70%). (iii) DIPEA, LiCl, MeCN (88%). (iv) (*S*)-BINAL-H, THF, -100 °C (77%). (v) TBDMSCl, imidazole, DMF, 0 °C (98%). (vi) Li/NH<sub>3</sub>, Et<sub>2</sub>O, -78 °C (99%). (vii) <sup>n</sup>Pr<sub>4</sub>NRuO<sub>4</sub>, NMO, 4 Å powdered sieves, CH<sub>2</sub>Cl<sub>2</sub> (97%). (viii) Ph<sub>3</sub>P=C(CD<sub>3</sub>)CO<sub>2</sub>Me, CHCl<sub>3</sub>, Δ (88%). (ix) LiOH/H<sub>2</sub>O, EtOH/H<sub>2</sub>O, 60 °C. (x) *N*-acetylcysteamine, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (82% over two steps). (xi) AcOH/H<sub>2</sub>O/THF (3:3:1), rt 24 hrs and 45 °C 48 hrs (63%, after recycling monodeprotected material).

For the preparation of the larger polyketide precursors (**5**) and (**6**), further coupling components required synthesis. The first of these was prepared by converting the known alcohol (**20**)<sup>8</sup> (Scheme 3), which is also the precursor to aldehyde (**9**) used in Scheme 2, to the corresponding bromide with *N*-bromosuccinimide and triphenylphosphine. This intermediate bromide was then used to alkylate the dianion generated from dimethyl 2-(oxopropyl)phosphonate<sup>17</sup> to give (**21**), a key six-carbon coupling fragment. Compound (**21**) was coupled with the aldehyde (**22**) to afford the unsaturated ketone (**23**) using the Masamune-Roush conditions.<sup>12</sup> The aldehyde (**22**) was prepared using similar chemistry to that described in Scheme 2, but using non-deuterated reagents. Next, we required to effect a stereoselective reduction of the carbonyl group of (**23**). This asymmetric reduction was best achieved by using 2.2 equivalents of (*S*)-BINAL-H<sup>18</sup> in THF at -100 °C to provide (**24**) in 97% d.e.. The stereochemical outcome of this reduction is important for further transformations and was first assigned based on the Noyori model.<sup>18</sup> However, as we could not establish unambiguous proof of this stereochemistry by X-ray crystallographic or Mosher ester methods, further structural evidence was required. This was provided by data obtained by examining the Sharpless kinetic resolution procedure<sup>19</sup> using a 1:1 mixture of diastereomeric alcohols and matching these predicted product ratios with that obtained from the Noyori protocol. Thus, we were able to use a second asymmetric sequence to aid in a stereochemical assignment of the first asymmetric process. Full details of these experiments and procedures will be reported on completion of the total synthesis of (**1**).

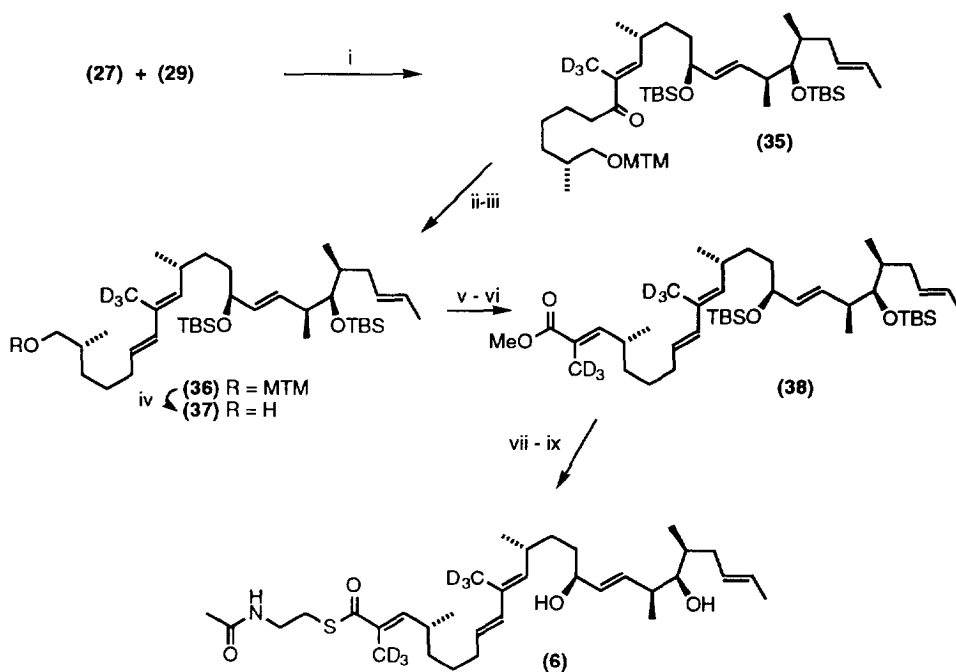
The synthesis of the required NAC-thioester (**5**) was continued as outlined in Scheme 3. The alcohol (**24**) was protected as its *t*-butyldimethylsilyl ether (**25**) using standard conditions and the benzyl group was then removed using lithium in ammonia to give (**26**). Oxidation of (**26**) with TPAP<sup>15</sup> produced the aldehyde (**27**) in excellent yield with no detectable racemisation of the sensitive adjacent stereogenic centre. The aldehyde (**27**) was then homologated by reaction with trideuteriomethyl( $\alpha$ -carbomethoxymethyl)triphenylphosphorane<sup>20</sup> to give (**28**), incorporating an appropriate deuterium-labelled substituent to facilitate tracking during the biosynthetic studies. The remaining steps of the synthesis were straightforward, involving hydrolysis to the acid with lithium hydroxide, coupling with *N*-acetylcysteamine and removal of the silicon protecting groups with aqueous acetic acid to give (**5**) (Scheme 3).



**Scheme 4** (i) Tf<sub>2</sub>O, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>. (ii) Allyl magnesium bromide, CuBr, Et<sub>2</sub>O, -78 °C (84%, over two steps). (iii) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOH, -78 °C, followed by NaBH<sub>4</sub>, rt (83%). (iv) Ph<sub>3</sub>PBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (81%). (v) (**33**) + NaH, THF, 0 °C, then <sup>n</sup>BuLi, -10 °C, then (**32**) (70%). (vi) TBAF, THF, rt (71%). (vii) DMSO/Ac<sub>2</sub>O/AcOH (10:6:0.5), 4 days (70%).

For the preparation of the final putative polyketide open-chain precursor (**6**) it was necessary to prepare an additionally labelled ketophosphonate (**29**) for the coupling studies. This was achieved in a short sequence

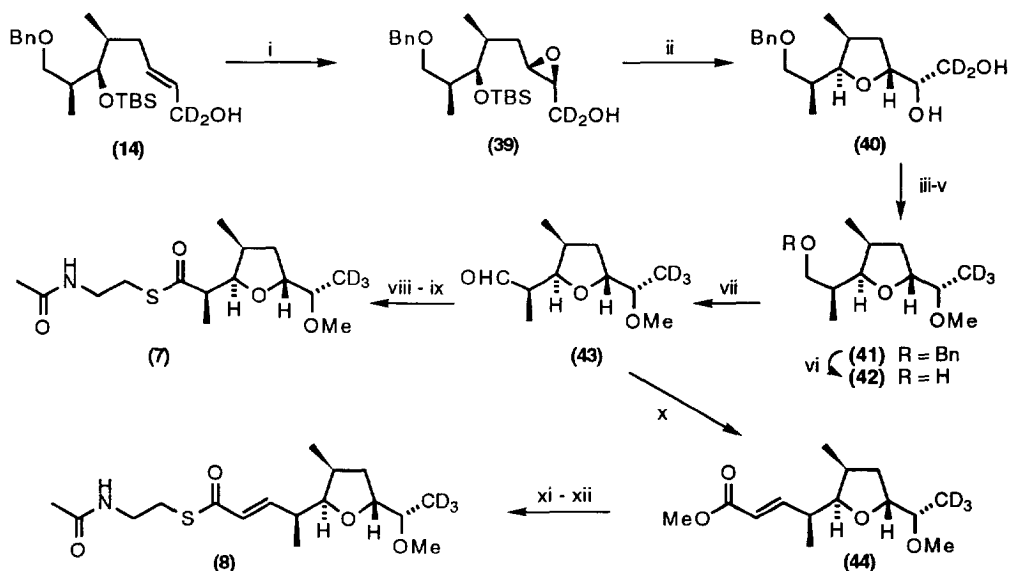
of high-yielding steps from the known alcohol (30) (Scheme 4). Conversion of (30) to (31) was effected by a two-step process involving formation of an intermediate triflate using triflic anhydride and subsequent displacement with allyl magnesium bromide in the presence of copper(I) bromide.<sup>21</sup> Next the double bond of (31) was cleaved by ozonolysis and reductive workup with sodium borohydride to afford an alcohol which was immediately converted into the bromide (32) with triphenylphosphine dibromide in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C. This was coupled to the dianion of the labelled ketophosphonate (33) to give (34). For procedural reasons the protecting group in (34) was exchanged *via* tetra-*n*-butylammonium fluoride deprotection and then reaction with DMSO and acetic anhydride in the presence of acetic acid to give the required labelled ketophosphonate (29), suitably protected as its methylthiomethyl (MTM) ether<sup>22</sup> (Scheme 4).



**Scheme 5** (i) LiHMDS, THF, -78 °C, 3 days (83%, 50% *E*-isomer). (ii) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 0 °C (91%). (iii) MsCl, NEt<sub>3</sub>, 0 °C-rt (90%). (iv) MeI, acetone, H<sub>2</sub>O, NaHCO<sub>3</sub>, 50 °C (96%). (v) <sup>10</sup>Pr<sub>4</sub>RuO<sub>4</sub>, NMO, 4 Å powdered sieves, CH<sub>2</sub>Cl<sub>2</sub> (94%). (vi) Ph<sub>3</sub>P=C(CD<sub>3</sub>)CO<sub>2</sub>Me, CHCl<sub>3</sub>, Δ (75%). (vii) LiOH·H<sub>2</sub>O, EtOH/H<sub>2</sub>O, 60 °C (97%). (viii) *N*-acetyl cysteamine, DCC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (85%). (ix) Dowex 50W (H<sup>+</sup>) ion exchange resin, MeOH, rt, (66%).

Coupling of the previously described aldehyde (27) with the phosphonate (29), using lithium hexamethyldisilazide as the base, gave the desired (*E*)-enone (35) in 50% yield (Scheme 5). The low yield was due to competitive formation of the undesired (*Z*)-enone which could be easily separated from (35) by flash column chromatography. The enone (35) was then transformed to the (*E,E*)-diene (36) by reduction under the Luche conditions,<sup>23</sup> mesylate formation and spontaneous elimination. The MTM protecting group could be selectively removed to give (37) using the standard conditions of iodomethane in aqueous acetone containing NaHCO<sub>3</sub> at 50 °C.<sup>22</sup> The last steps of the synthesis proceeded using similar steps to those described for the preparation of the earlier NAC-thioesters, namely oxidation with TPAP<sup>15</sup> and reaction with

trideuteriomethyl( $\alpha$ -carbomethoxymethyl)triphenylphosphorane<sup>20</sup> to give (38), containing two trideuteriomethyl labels. Hydrolysis with lithium hydroxide and coupling with *N*-acetylcysteamine as before afforded an intermediate NAC-thioester which was smoothly deprotected upon treatment with Dowex-50 (H<sup>+</sup> form) in methanol, to give the desired compound (6) (Scheme 5).



**Scheme 6** (i)  $\text{Ti}(\text{O}^i\text{Pr})_4$ ,  $^t\text{BuOOH}$ , (+)-DET,  $\text{CH}_2\text{Cl}_2$ ,  $-20^\circ\text{C}$  (80%). (ii)  $^n\text{Bu}_4\text{NF}$ , THF,  $60^\circ\text{C}$  (70%). (iii)  $\text{Bu}_2\text{SnO}$ , MeOH,  $\Delta$ ,  $\text{Et}_3\text{N}$ , TsCl (81%). (iv)  $\text{LiEt}_3\text{BD}$ , THF,  $0^\circ\text{C}$  (92%). (v) MeI, KH, THF,  $0^\circ\text{C}$  (94%). (vi)  $\text{H}_2$ , Pd/C, MeOH (100%). (vii)  $^n\text{Pr}_4\text{NRuO}_4$ , NMO, 4Å powdered sieves,  $\text{CH}_2\text{Cl}_2$  (94%). (viii) NaOCl, 2-methyl-2-butene,  $\text{KH}_2\text{PO}_4$ ,  $^t\text{BuOH}/\text{H}_2\text{O}$ . (ix) *N*-acetyl cysteamine, DCC, DMAP,  $\text{CH}_2\text{Cl}_2$  (76% over two steps). (x)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ ,  $\text{CHCl}_3$ ,  $\Delta$  (86%). (xi) LiOH, EtOH/ $\text{H}_2\text{O}$ ,  $40^\circ\text{C}$ . (xii) *N*-acetyl cysteamine, DCC, DMAP,  $\text{CH}_2\text{Cl}_2$  (41% over two steps).

The last two putative polyketide precursors (7) and (8) were again prepared from common intermediates. For example, the dideuterio labelled alcohol (14), the preparation of which has already been described, was epoxidised using the Sharpless asymmetric procedure<sup>19,24</sup> with (+)-diethyl tartrate as the chiral auxiliary to give (39). This was readily transformed to the tetrahydrofuran (40) by reaction with tetrabutylammonium fluoride in THF at  $60^\circ\text{C}$ . In order to elaborate (40) to the correct substitution and oxidation pattern found in the natural product, the terminal primary hydroxyl group of (40) was selectively tosylated using dibutyltin oxide and tosyl chloride with triethylamine as base.<sup>25</sup> This was then reduced with lithium triethylborodeuteride (Super-Deuteride®) in THF to establish the desired terminal trideuteriomethyl substituent. The free secondary hydroxyl group was then methylated using iodomethane and potassium hydride to give (41) (Scheme 6). This compound was deprotected to (42) with lithium in ammonia and oxidised to the aldehyde (43) with TPAP.<sup>15</sup> Compound (43) served as the pivotal point between the preparation of the two tetrahydrofuran NAC-thioester derivatives (7) and (8) using similar methodology to that established previously. Thus (43) was further oxidised to the corresponding acid with sodium chlorite and coupled with *N*-acetylcysteamine in the normal way to afford (7). Alternatively (43) was homologated with carbomethoxymethylenetriphenylphosphorane to give (44). The ester was subsequently hydrolysed and

the acid was coupled with *N*-acetylcysteamine to afford the last of the required NAC-thioester derivatives (**8**) (Scheme 6).

The synthetic polyketide NAC-thioester derivatives prepared above have proved extremely useful in detailing the processive biosynthetic pathway to the natural product tetronasin (**1**).<sup>26</sup> Full details of these and other biosynthetic studies will be reported separately. We have established, therefore, a general and flexible strategy to various putative polyketide precursors of the ionophore (**1**). These compounds are labelled with deuterium to track their progress by nmr during incorporation studies and NAC-thioesters have been prepared to facilitate incorporation of the compounds into senescent cells<sup>7</sup> and, in later studies, to be suitable for loading *in vitro* onto isolated acyl carrier proteins of the PKS complex.

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### Experimental Section:

**General:** Infrared spectra were recorded on a Perkin Elmer 983G Infrared Spectrometer. <sup>1</sup>H nmr spectra were recorded at 250, 270 or 500 MHz on Bruker WM 250, Jeol GSX 270 or Bruker AM 500 spectrometers respectively. Residual protic solvent, *i.e.* CHCl<sub>3</sub> ( $\delta_{\text{H}}=7.26$  ppm), was used as internal reference. Mass spectra were recorded on a VG micromass 7070B spectrometer in the Imperial College Chemistry Department mass spectroscopy laboratory, or VG12-253 and VG ZAB-E instruments at the SERC Mass Spectrometry Service in Swansea. Optical rotations were measured on an Optical Activity AA-1000 polarimeter. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Elemental microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory or at the laboratory of MEDAC Ltd., Brunel University Chemistry Department.

Diethyl ether and THF were distilled from sodium-benzophenone ketyl; dichloromethane from phosphorous pentoxide; toluene from sodium and acetonitrile from calcium hydride. Other solvents and reagents were purified by standard procedures as necessary. Petrol refers to light petroleum ether, b.p. 40–60 °C and was distilled prior to use. Ether refers to diethyl ether.

Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F<sub>254</sub>) and was visualised by using U.V., acidic ammonium molybdate(IV), acidic palladium(II) chloride or iodine. Chromatography was performed under pressure on Merck Kieselgel 60 (230–400 mesh) unless otherwise stated. Florisil<sup>®</sup> refers to 230–300 mesh Florisil<sup>®</sup> as supplied by BDH Ltd. Normal phase HPLC was carried using a Gilson system and an ultra-violet detector.

**(2S,3R,4S) 1-Benzyloxy-2,4-dimethyl-5-hexen-3-ol (10):** *Cis*-2-butene (40 ml) was condensed into a measuring cylinder at -78 °C and transferred by cannula into a stirred solution of potassium-*t*-butoxide (15.6 g, 0.14 mol) in THF (250 ml) at -78 °C. *n*-Butyllithium (2.5 M in hexanes, 60 ml, 0.14 mol) was added dropwise and the mixture was warmed to -45 °C for 10 min. The solution was recooled to -78 °C before adding (+)-*B*-methoxydiisopinocampheylborane (53 g, 0.16 mol) in ether (100 ml) by cannula. Stirring was continued for 45 min after which the mixture was cooled to -90 °C. Boron trifluoride etherate (25 ml, 0.2 mol) was added, followed immediately by a precooled (-78 °C) solution of the aldehyde (**9**)<sup>8</sup> in ether (100



ml). Stirring was continued at  $-90\text{ }^{\circ}\text{C}$  for 16 h after which the reaction mixture was allowed to warm to room temperature. 3N Sodium hydroxide (250 ml) was added and the mixture was heated to a gentle reflux before adding 30% hydrogen peroxide (80 ml) dropwise. The resulting mixture was heated at reflux for 5 h, cooled to room temperature and the organic phase was separated and washed with saturated  $\text{Na}_2\text{SO}_3$ . The combined aqueous phases were extracted with ethyl acetate ( $4 \times 150$  ml) and the combined organic layers were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10–20% ether-petrol) yielded the *alkene* (**10**) (18 g, 71%) as a colourless oil;  $[\alpha]_{\text{D}}^{20} -21.4$  (*c* 4.7, MeOH) [lit.,<sup>9b</sup>  $[\alpha]_{\text{D}}^{23} -17.5$  (*c* 4.7, MeOH) (95:5 mixture)];  $\nu_{\text{max}}$  (film) 3478, 3029, 2960, 1636, 1498, 1206, 1028 and 698  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.96 (3H, d, *J* 7.0 Hz, 2-Me), 1.04 (3H, d, *J* 6.8 Hz, 4-Me), 1.92–1.97 (1H, m, H-2), 2.33 (1H, m, H-4), 3.17 (1H, d, *J* 4.3 Hz, OH), 3.40 (1H, m, H-3), 3.48 (1H, dd, *J* 9.1 and 6.2 Hz, H-1), 3.64 (1H, dd, *J* 9.1 and 4.2 Hz, H-1), 4.51 (2H, s,  $\text{CH}_2\text{Ph}$ ), 5.02 (1H, dd, *J* 9.0 and 1.1 Hz, H-6 *cis*), 5.05 (1H, dd, *J* 16.9 and 4.2 Hz, H-6 *trans*), 5.83 (1H, ddd, *J* 17.1, 10.6 and 7.3 Hz, H-5), 7.27–7.39 (5H, m, ArH); *m/z* (EI) 235 ( $\text{MH}^+$ ), 234 ( $\text{M}^+$ ), 179, 107 and 91 ( $\text{C}_7\text{H}_7^+$ ); Observed (CI,  $\text{NH}_3$ )  $\text{MH}^+$  235.1698; Calc. for  $\text{C}_{15}\text{H}_{23}\text{O}_2$  *MH* 235.1698; Found C, 77.15; H, 9.53%; Calc. for  $\text{C}_{15}\text{H}_{22}\text{O}_2$  C, 76.88; H, 9.46%.

(3*S*,4*R*,5*S*) 6-Benzyloxy-4-(*t*-butyldimethylsilyloxy)-3,5-dimethylhex-1-ene (**11**): A solution of the alcohol (**10**) (14.6 g, 62.4 mmol) and triethylamine (26 ml, 187 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 ml) was cooled to  $-30\text{ }^{\circ}\text{C}$  and *t*-butyldimethylsilyl triflate (16 ml, 68.6 mmol) was added dropwise over 30 min. The mixture was then stirred at  $-30\text{ }^{\circ}\text{C}$  for a further 30 minutes before being allowed to warm to room temperature. The reaction mixture was poured into saturated  $\text{NaHCO}_3$  (200 ml) and extracted with ether ( $3 \times 150$  ml). The combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (2% ether-petrol) yielded the *silyl ether* (**11**) (22.9 g, 100%) as a colourless oil;  $[\alpha]_{\text{D}}^{20} -18.2$  (*c* 2,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3066, 3023, 2956, 2853, 1948, 1600, 1470, 1305, 1096, 911, and 774  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.03 (6H, s,  $\text{SiMe}_2$ ), 0.88 (9H, s,  $\text{tBu}$ ), 0.97 (3H, d, *J* 4.8 Hz, 5-Me), 0.99 (3H, d, *J* 4.9 Hz, 3-Me), 1.98–2.06 (1H, m, H-5), 2.35–2.39 (1H, m, H-3), 3.26 (1H, dd, *J* 9.2 and 8.1 Hz, H-6), 3.50 (1H, t, *J* 5.1 Hz, H-4), 3.57 (1H, dd, *J* 9.2 and 4.8 Hz, H-6), 4.44 (1H, d, *J* 16.0 Hz,  $\text{CH}_2\text{Ph}$ ), 4.46 (1H, d, *J* 16.0 Hz,  $\text{CH}_2\text{Ph}$ ), 4.93–5.00 (2H, m, H<sub>2</sub>-1), 5.76–5.83 (1H, m, H-2), 7.27–7.33 (5H, m, ArH); *m/z* (CI,  $\text{NH}_3$ ) 349 ( $\text{MH}^+$ ), 348 ( $\text{M}^+$ ), 293 ( $\text{M}^+ - \text{C}_4\text{H}_7$ ), 291 ( $\text{M}^+ - \text{C}_4\text{H}_9$ ), 221, 199, 187 and 91 ( $\text{C}_7\text{H}_7^+$ ); Observed (CI,  $\text{NH}_3$ )  $\text{MH}^+$  349.2563.  $\text{C}_{21}\text{H}_{37}\text{O}_2\text{Si}$  requires *MH* 349.2563; Found C, 72.45; H, 10.50%;  $\text{C}_{21}\text{H}_{36}\text{O}_2\text{Si}$  requires C, 72.36; H, 10.41%.

(3*S*,4*R*,5*S*) 6-Benzyloxy-4-(*t*-butyldimethylsilyloxy)-3,5-dimethylhexanal (**12**): A solution of 9-BBN (344 ml, 0.5 M in THF, 172 mmol) was added by cannula to a solution of the alkene (**11**) (20 g, 57 mmol) in THF (100 ml) and heated at reflux for 2 h. The mixture was cooled to  $0\text{ }^{\circ}\text{C}$ , water (20 ml) was added carefully followed by 2N NaOH (200 ml) and 30%  $\text{H}_2\text{O}_2$  (80 ml). The reaction mixture was warmed to room temperature and stirred for 1 h, after which the organic phase was separated and washed with saturated  $\text{Na}_2\text{SO}_3$ . The aqueous layers were combined, saturated with  $\text{K}_2\text{CO}_3$  and extracted with ether ( $3 \times 200$  ml). The combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* and the residue was purified by chromatography on silica gel (40% ether-petrol) to yield (3*S*,4*R*,5*S*) 6-benzyloxy-4-(*t*-butyldimethylsilyloxy)-3,5-dimethylhexan-1-ol (19.94 g, 95%) as a colourless oil;  $[\alpha]_{\text{D}}^{20} -11.4$  (*c* 1.76,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  3379, 3063, 3030, 2954, 2244, 1493, 1379, 1203, 1095, 909 and 773  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz) 0.03 (3H, s,  $\text{SiMe}$ ), 0.04 (3H, s,  $\text{SiMe}$ ), 0.88 (9H, s,  $\text{tBu}$ ), 0.89 (3H, d, *J* 7.0 Hz, 3-Me), 0.97 (3H, d, *J* 7.0 Hz, 5-Me), 1.39–1.46 (1H, m, H-2), 1.59 (1H, t, *J* 5.5 Hz, OH), 1.66 (1H, sept., *J* 6.5 Hz, H-3), 1.76–1.83 (1H, m, H-2), 1.99–2.04 (1H, m, H-5), 3.29 (1H, dd, *J* 9.2 and 7.2 Hz, H-6), 3.53–3.59 (2H, m, H-4, H-6), 3.60–3.66 (1H, m, H-1),

3.67-3.72 (1H, m, H-1), 4.44 (1H, d,  $J$  12.0 Hz,  $\text{CH}_2\text{Ph}$ ), 4.47 (1H, d,  $J$  12.1 Hz,  $\text{CH}_2\text{Ph}$ ), 7.27-7.33 (5H, m, ArH);  $m/z$  (EI) 309 ( $\text{M}^+$ - $\text{C}_4\text{H}_9$ ), 293, 217, 201, 187 and 91 ( $\text{C}_7\text{H}_7^+$ ); Observed (EI)  $\text{M}^+$ - $\text{C}_4\text{H}_9$  309.1886;  $\text{C}_{17}\text{H}_{29}\text{O}_3\text{Si}$  requires  $M$  309.1886; Found C, 69.00%; H, 10.53%;  $\text{C}_{21}\text{H}_{38}\text{O}_3\text{Si}$  requires C, 68.80%; H, 10.45%.

Oxalyl chloride (6.84 ml, 76.6 mmol) was added slowly to a solution of dimethyl sulfoxide (11 ml, 153 mmol) in  $\text{CH}_2\text{Cl}_2$  (500 ml) at  $-78^\circ\text{C}$ . The mixture was stirred at  $-78^\circ\text{C}$  for 10 min after which (3*S*,4*R*,5*S*) 6-benzyloxy-4-(*t*-butyldimethyl silyloxy)-3,5-dimethylhexan-1-ol (14 g, 38.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 ml) was added. After stirring at  $-78^\circ\text{C}$  for a further 1 h, triethylamine (27 ml, 192 mmol) was added and the temperature was maintained at  $-78^\circ\text{C}$  for 15 min before allowing the mixture to warm to room temperature. Ether (600 ml) was added and the organic phase was separated and washed with 2%  $\text{KHSO}_4$ , dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10% ether-petrol) yielded the aldehyde (**12**) (11.7 g, 85%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -2.9 ( $c$  1.87,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3029, 2954, 2882, 1723, 1459, 1380, 1252, 1095, 836 and 774  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.03 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.88 (9H, s,  $^t\text{Bu}$ ), 0.92 (3H, d,  $J$  6.6 Hz, 3-Me), 0.99 (3H, d,  $J$  7.0 Hz, 5-Me), 1.91-1.97 (1H, m, H-3), 2.27-2.33 (2H, m, H-2, H-5), 2.50-2.55 (1H, m, H-2), 3.27 (1H, dd,  $J$  9.1 and 7.1 Hz, H-6), 3.52-3.56 (2H, m, H-4, H-6), 4.44 (1H, d,  $J$  12.0 Hz,  $\text{CH}_2\text{Ph}$ ), 4.49 (1H, d,  $J$  12.0 Hz,  $\text{CH}_2\text{Ph}$ ), 7.27-7.33 (5H, m, ArH), 9.72 (1H, t,  $J$  1.82, H-1);  $m/z$  (EI) 365 ( $\text{MH}^+$ ), 307 ( $\text{M}^+$ - $\text{C}_4\text{H}_9$ ), 293 ( $\text{M}^+$ - $\text{C}_4\text{H}_7\text{O}$ ), 263, 215, 199, 149 and 91 ( $\text{C}_7\text{H}_7^+$ ); Observed (CI,  $\text{NH}_3$ )  $\text{MH}^+$  365.2512;  $\text{C}_{21}\text{H}_{37}\text{O}_3\text{Si}$  requires  $MH$  365.2512.

(2*E*,5*S*,6*R*,7*S*) Ethyl 8-benzyloxy-6-(*t*-butyldimethylsilyloxy)-5,7-dimethyloct-2-enoate (**13**): Triethyl phosphonoacetate (9 ml, 45 mmol) and diisopropylethylamine (8 ml, 45 mmol) were added to a suspension of lithium chloride (1.9 g, 45 mmol) in acetonitrile (250 ml). The suspension was stirred for 15 min after which the aldehyde (**12**) (11.7 g, 32 mmol) in acetonitrile (50 ml) was added. The reaction mixture was stirred for 20 h, then poured into saturated  $\text{NaHCO}_3$  and ether. The organic phase was separated and the aqueous phase was extracted with ether (3  $\times$  200 ml). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (7% ether-petrol) yielded the ester (**13**) (12.95 g, 93%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -6.0 ( $c$  2.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3029, 2930, 1718, 1649, 1459, 1256, 1096, 982 and 774  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.03 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.85 (3H, d,  $J$  6.8 Hz, 5-Me), 0.89 (9H, s,  $^t\text{Bu}$ ), 0.97 (3H, d,  $J$  6.9 Hz, 7-Me), 1.28 (3H, t,  $J$  7.1 Hz, 2'-Me), 1.77-1.85 (1H, m, H-5), 1.93-2.02 (1H, m, H-4), 2.06-2.11 (1H, m, H-4), 2.26-2.31 (1H, m, H-7), 3.27 (1H, dd,  $J$  9.1 and 7.3 Hz, H-8), 3.50 (1H, dd,  $J$  9.1 and 4.8 Hz, H-8), 3.53 (1H, dd,  $J$  6.0 and 3.0 Hz, H-6), 4.16 (2H, q,  $J$  7.2 Hz,  $\text{H}_2$ -1'), 4.44 (1H, dt,  $J$  12.1 Hz,  $\text{CH}_2\text{Ph}$ ), 4.49 (1H, d,  $J$  12.1 Hz,  $\text{CH}_2\text{Ph}$ ), 5.78 (1H, dt,  $J$  15.6 and 1.4 Hz, H-2), 6.87-6.95 (1H, m, H-3), 7.27-7.33 (5H, m, ArH);  $m/z$  (EI) 389 ( $\text{M}^+$ - $\text{C}_2\text{H}_5\text{O}$ ), 377 ( $\text{M}^+$ - $\text{C}_4\text{H}_9$ ), 293, 285, 187, 145 and 91 ( $\text{C}_7\text{H}_7^+$ ); Observed (EI)  $\text{M}^+$ - $\text{C}_4\text{H}_9$  377.2148;  $\text{C}_{21}\text{H}_{33}\text{O}_4\text{Si}$  requires  $M$  377.2148; Found C, 69.03%; H, 9.88%;  $\text{C}_{25}\text{H}_{42}\text{O}_4\text{Si}$  requires C, 69.08%; H, 9.74%.

(2*E*,5*S*,6*R*,7*S*) 8-Benzyloxy-6-(*t*-butyldimethylsilyloxy)-1,1-dideuterio-5,7-dimethyloct-2-en-1-ol (**14**): DIBAL- $\text{D}^{13}$  (7.2 ml, 1.4 M in hexane, 10 mmol) was added to the allylic ester (**13**) (1.74 g, 4 mmol) in THF (50 ml) at  $-78^\circ\text{C}$ . The reaction mixture was stirred at  $-78^\circ\text{C}$  for 2 h and at  $-30^\circ\text{C}$  for 30 min before being cooled back to  $-78^\circ\text{C}$ , at which temperature water (4.5 ml) was added dropwise, followed by saturated  $\text{Na}_2\text{SO}_4$ . The mixture was allowed to warm to room temperature over 2 h, solid  $\text{Na}_2\text{SO}_4$  was then added and the mixture was filtered. The collected solids were rinsed with ethyl acetate and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (40% ether-petrol) yielded the allylic alcohol (**14**) (1.5 g, 85%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -6.2 ( $c$  1.5,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3352, 3086, 3062, 2954, 2854, 2707, 2182, 1942, 1459, 1379, 1359, 1252, 1084, 836 and 697  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,

CDCl<sub>3</sub>) 0.03 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.85 (3H, d, *J* 6.8 Hz, 5-Me), 0.89 (9H, s, <sup>t</sup>Bu), 0.97 (3H, d, *J* 7.0 Hz, 7-Me), 1.25 (1H, s, OH), 1.62-1.67 (1H, m, H-5), 1.85-1.89 (1H, m, H-4), 1.96 (1H, sept, *J* 4.0 Hz, H-7), 2.09-2.14 (1H, m, H-4), 3.28 (1H, dd, *J* 9.2 and 7.4 Hz, H-8), 3.48-3.55 (2H, m, H-6, H-8), 4.47 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 4.49 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 5.60-5.63 (2H, m, H-2, H-3), 7.27-7.36 (5H, m, ArH); *m/z* (EI) 337 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 293, 245, 229, 187, 145 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 337.2168; C<sub>19</sub>H<sub>29</sub>D<sub>2</sub>O<sub>3</sub>Si requires *M* 337.2168; Found C, 70.07; H+D, 10.44%; C<sub>23</sub>H<sub>38</sub>D<sub>2</sub>O<sub>3</sub>Si requires C, 70.00; H+D, 10.73%.

**(2S,3R,4S,6E) 1-Benzyloxy-3-(*t*-butyldimethylsilyloxy)-8,8,8-trideuterio-2,4-dimethyloct-6-ene (15):**

DMAP (0.56 g, 4.56 mmol) and *p*-toluenesulfonyl chloride (0.87 g, 4.56 mmol) were added sequentially to a solution of the allylic alcohol (14) (1.5 g, 3.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 16 h the mixture was diluted with ether (100 ml), filtered and the solid was washed with ether. The combined filtrates were washed with 10% CuSO<sub>4</sub>, saturated NaHCO<sub>3</sub> and brine and the organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (7% ether-petrol) yielded (2*E*,5*S*,6*R*,7*S*) 8-benzyloxy-6-(*t*-butyldimethylsilyloxy)-1-chloro-1,1-dideuterio-5,7-dimethyloct-2-ene (1 g, 64%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -5.8 (*c* 1.9, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3023, 2928, 2304, 2161, 1661, 1459, 1252, 1098, 773 and 697 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.03 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.85 (3H, d, *J* 6.8 Hz, 5-Me), 0.89 (9H, s, <sup>t</sup>Bu), 0.97 (3H, d, *J* 7.0 Hz, 7-Me), 1.65-1.70 (1H, m, H-5), 1.88-1.99 (2H, m, H-4, H-7), 2.12-2.18 (1H, m, H-4), 3.29 (1H, dd, *J* 9.1 and 7.3 Hz, H-8), 3.51-3.54 (2H, m, H-6, H-8), 4.47 (1H, d, *J* 12.5 Hz, CH<sub>2</sub>Ph), 4.52 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 5.59 (1H, d, *J* 15.2 Hz, H-2), 5.70 (1H, ddd, *J* 14.1, 7.5 and 6.4 Hz, H-3), 7.27-7.35 (5H, m, ArH); *m/z* (EI) 413 (M<sup>+</sup>-H, <sup>37</sup>Cl), 411 (M<sup>+</sup>-H, <sup>35</sup>Cl), 377 (M<sup>+</sup>-Cl), 357 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub><sup>+</sup>, <sup>37</sup>Cl), 355 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>, <sup>35</sup>Cl) and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Observed (EI) M<sup>+</sup>-Cl 377.2845; C<sub>23</sub>H<sub>37</sub>D<sub>2</sub>O<sub>2</sub>Si requires *M* 377.2845; Found C, 66.91; H+D, 9.41%; C<sub>23</sub>H<sub>37</sub>D<sub>2</sub>ClO<sub>2</sub>Si requires C, 66.87; H+D, 9.51%.

Super-Deuteride<sup>®</sup> (5.8 ml, 1.0 M in THF, 5.8 mmol) was added slowly to a solution of the chloride (1.2 g, 2.9 mmol) in THF (10 ml) at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Brine (10 ml) was added carefully, the mixture was extracted with ether (4 × 50 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (3% ether-petrol) yielded the *trideuteride* (15) (970 mg, 88%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -9.3 (*c* 1.9, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 2928, 2854, 2210, 1459, 1360, 1252, 1095, 836, 733 and 696 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.02 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 4-Me), 0.88 (9H, s, <sup>t</sup>Bu), 0.97 (3H, d, *J* 6.9 Hz, 2-Me), 1.59-1.64 (1H, m, H-4), 1.83 (1H, ddd, *J* 13.4, 9.0 and 6.0 Hz, H-5), 1.95 (1H, sept, *J* 4.8 Hz, H-2), 2.06 (1H, dt, *J* 13.7 and 5.0 Hz, H-5), 3.27 (1H, dd, *J* 9.0 and 7.8 Hz, H-1), 3.51 (1H, dd, *J* 6.0 and 3.0 Hz, H-3), 3.54 (1H, dd, *J* 9.1 and 4.6 Hz, H-1), 4.48 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 4.52 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 5.33-5.44 (2H, m, H-6, H-7), 7.27-7.34 (5H, m, ArH); *m/z* (EI) 379 (M<sup>+</sup>), 322 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 293, 230 (C<sub>13</sub>H<sub>24</sub>D<sub>3</sub>O<sub>3</sub>Si), 187, 145 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 322.2282; C<sub>23</sub>H<sub>37</sub>D<sub>3</sub>O<sub>2</sub>Si requires *M*-C<sub>4</sub>H<sub>9</sub> 322.2282; Found C, 72.89; H+D, 10.62%; C<sub>23</sub>H<sub>37</sub>D<sub>3</sub>O<sub>2</sub>Si requires C, 72.76; H+D, 10.62%.

**(2S,3R,4S,6E) 3-(*t*-Butyldimethylsilyloxy)-8,8,8-trideuterio-2,4-dimethyloct-6-en-1-ol (16):** A solution of the benzyl ether (15) (690 mg, 1.82 mmol) in ether (5 ml), was added to a blue solution of lithium metal (100 mg, 7 mmol) in liquid ammonia (50 ml) at -78 °C over a period of 5 min. The mixture was stirred for 1 h at -78 °C after which solid ammonium chloride (excess) was added and the mixture warmed to room temperature, allowing the ammonia to evaporate. Brine (50 ml) was added to the residue and the resulting mixture was extracted with ether (3 × 100 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered

and concentrated *in vacuo*. Chromatography of the residue on silica gel (25% ether-petrol) yielded the alcohol (**81**) (477 mg, 91%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -5.5 (*c* 1.5, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3363, 2954, 2855, 2735, 2707, 2218, 2203, 2118, 2063, 1864, 1662, 1469, 1405, 1379, 1253, 1090 and 1028 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.09 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.88 (3H, d, *J* 6.6 Hz, 4-Me), 0.92 (9H, s, <sup>t</sup>Bu), 0.96 (3H, d, *J* 7.1 Hz, 2-Me), 1.63-1.69 (1H, m, H-4), 1.83-1.89 (2H, m, H-2, H-5), 2.17 (1H, dt, *J* 13.7 and 5.1 Hz, H-5), 2.52 (1H, dd *J* 6.3 and 5.4 Hz, OH), 3.53 (1H, dd, *J* 5.2 and 4 Hz, H-3), 3.59-3.63 (2H, m, H<sub>2</sub>-1), 5.32-5.43 (2H, m, H-6, H-7); *m/z* (EI) 290 (MH<sup>+</sup>), 289 (M<sup>+</sup>), 274 (M<sup>+</sup>-Me), 258 (M<sup>+</sup>-CH<sub>2</sub>OH), 232 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 230 (C<sub>13</sub>H<sub>24</sub>D<sub>3</sub>OSi), 203, 140 and 119; Found C, 66.48; H+D, 11.86%; C<sub>16</sub>H<sub>31</sub>D<sub>3</sub>O<sub>2</sub>Si requires C, 66.37; H+D, 11.84%.

**(2R,3R,4S,6E) 3-(*t*-Butyldimethylsilyloxy)-8,8,8-trideuterio-2,4-dimethyloct-6-enal (17)**: Powdered 4 Å molecular sieves (excess) were added to a solution of the alcohol (**16**) (0.32 g, 1.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml), followed by *N*-methylmorpholine-*N*-oxide monohydrate (0.26 g, 2.24 mmol) and tetra-*n*-propylammonium perruthenate (20 mg, 0.06 mmol). The mixture was stirred at room temperature for 1 hour, then filtered through Florisil<sup>®</sup> washing with CH<sub>2</sub>Cl<sub>2</sub>. The combined solvents were concentrated *in vacuo* to afford the aldehyde (**17**) which was used without further purification.

**(2R,3R,4S,6E) 3-(*t*-Butyldimethylsilyloxy)-8,8,8-trideuterio-2,4-dimethyloct-6-enoic acid (18)**: 2-Methyl-2-butene (8 ml), potassium dihydrogen orthophosphate (1.6 g) and sodium chlorite (0.45 g, 5 mmol) were added to a solution of the aldehyde (**17**) (0.31 g, 1.1 mmol) in *t*-butanol (10 ml) and water (10 ml) at room temperature and the mixture was stirred for 60 min. After being cooled to 0 °C, saturated sodium sulphite (10 ml) was added and the resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 15 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford the crude carboxylic acid (**18**) which was used without further purification.

**(2R,3R,4S,6E) S-[2-(Acetylamino)ethyl] 8,8,8-trideuterio-3-hydroxy-2,4-dimethyloct-6-enethioate (3)**: A solution of the crude acid (**18**) (0.33 g, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was stirred at 0 °C and DMAP (14 mg, 0.112 mmol) followed by *N*-acetylcysteamine<sup>16</sup> (175 mg, 1.46 mmol, freshly prepared) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) and DCC (325 mg, 1.57 mmol) were added. The reaction mixture was stirred at 0 °C for 30 min, before being warmed to room temperature and stirred for a further 16 h. Precipitated DCU was removed by filtration, rinsed with ethyl acetate and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (50% ethyl acetate-petrol) yielded (2R,3R,4S,6E) S-[2-(acetylamino)ethyl] 3-(*t*-butyldimethylsilyloxy)-8,8,8-trideuterio-2,4-dimethyloct-6-enethioate (330 mg, 73% over three steps) as a viscous colourless oil;  $[\alpha]_{\text{D}}^{20}$  -69.0 (*c* 1.36, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3282, 3076, 2930, 2850, 2218, 1656, 1549, 1459, 1374, 1253, 1198, 1059 and 967 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) -0.04 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.84 (3H, d, *J* 6.8 Hz, 4-Me), 0.87 (9H, s, <sup>t</sup>Bu), 1.10 (3H, d, *J* 7.1 Hz, 2-Me), 1.56-1.61 (1H, m, H-4), 1.84-1.88 (1H, m, H-5), 1.96 (3H, s, CH<sub>3</sub>CO), 2.01-2.06 (1H, m, H-5), 2.87 (2H, m, CH<sub>2</sub>S), 3.10 (1H, p, *J* 6.9 Hz, H-2), 3.42 (2H, q, *J* 6.2 Hz, CH<sub>2</sub>N), 3.94 (1H, dd, *J* 7.9 and 2.4 Hz, H-3), 5.29-5.46 (2H, m, H-6, H-7), 5.78 (1H, br s, NH); *m/z* (CI, NH<sub>3</sub>) 405 (MH<sup>+</sup>), 389 (M<sup>+</sup>-Me), 361 (M<sup>+</sup>-CH<sub>3</sub>CO), 347 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 232, 199, 176, 147 and 86; Observed (CI, NH<sub>3</sub>) MH<sup>+</sup> 405.2687; C<sub>20</sub>H<sub>37</sub>D<sub>3</sub>NO<sub>3</sub>SSi requires *MH* 405.2686.

Pyridine (200 μl, 2.37 mmol) was added to the silyl ether (160 mg, 0.395 mmol) in acetonitrile (5 ml) in a teflon flask. HF (2 ml, 40% solution in H<sub>2</sub>O) was added dropwise and the mixture was stirred at 40 °C for 16 h, then poured into saturated NaHCO<sub>3</sub> (20 ml). The solution was extracted with ether (4 × 20 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the

residue on silica gel (ethyl acetate) and further purification by HPLC (23% IPA-petrol) yielded the *alcohol* (**3**) (95 mg, 80%) as a viscous colourless oil;  $[\alpha]_{\text{D}}^{20}$  -9.6 (*c* 1.0, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3304, 3085, 2966, 2931, 2217, 2118, 2063, 1653, 1545, 1451, 1373, 1290, 1198, 1046 and 965 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.87 (3H, d, *J* 6.8 Hz, 4-Me), 1.15 (3H, d, *J* 7.1 Hz, 2-Me), 1.63 (1H, qd, *J* 6.9 and 3.3 Hz, H-4), 1.95 (3H, s, CH<sub>3</sub>CO), 1.95-1.99 (1H, m, H-5), 2.05-2.10 (1H, m, H-5), 2.19 (1H, d, *J* 6.0 Hz, OH), 2.83 (1H, m, H-2), 3.03-3.11 (2H, m, CH<sub>2</sub>S), 3.40-3.48 (2H, m, CH<sub>2</sub>N), 3.72 (1H, m, H-3), 5.38 (1H, dt, *J* 15.2 and 6.6 Hz, H-6), 5.43 (1H, d, *J* 15.3 Hz, H-7), 5.90 (1H, br s, NH); *m/z* (CI, NH<sub>3</sub>) 291 (MH<sup>+</sup>), 281, 278, 272 (M<sup>+</sup>-H<sub>2</sub>O), 204, 171, 154 and 43 (CH<sub>3</sub>CO<sup>+</sup>); Observed (CI, NH<sub>3</sub>) MH<sup>+</sup> 291.1829; C<sub>14</sub>H<sub>23</sub>D<sub>3</sub>NO<sub>3</sub>S requires *MH* 291.1822.

**(2E,4S,5R,6S,8E) Methyl 5-(*t*-butyldimethylsilyloxy)-10,10,10-trideuterio-4,6-dimethyldeca-2,8-dienoate (19):** Carbomethoxymethylenetriphenyl phosphorane (1.2 g, 3.34 mmol) was added to a solution of the crude aldehyde (**17**) (248 mg, 0.87 mmol) in chloroform (20 ml, filtered through basic alumina). The reaction mixture was heated at reflux for 16 h after which the solvent was removed by rotary evaporation and the residue was filtered through a silica plug (25% ether-petrol). The solvents were concentrated *in vacuo* and the residue was purified by chromatography on silica gel (5% ether-petrol), to yield the *ester* (**19**) (282 mg, 95%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -25.4 (*c* 0.89, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2953, 2929, 2854, 2219, 2063, 1724, 1652, 1459, 1432, 1379, 1254, 1192, 1176, 1032 and 987 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.03 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.84 (3H, d, *J* 6.8 Hz, 6-Me), 0.90 (9H, s, <sup>t</sup>Bu), 1.03 (3H, d, *J* 7.0 Hz, 4-Me), 1.56-1.60 (1H, m, H-6), 1.75 (1H, ddd *J* 13.8, 9.1 and 7.1 Hz, H-7), 2.07 (1H, dt, *J* 13.4 and 5.3 Hz, H-7), 2.50-2.55 (1H, m, H-4), 3.49 (1H, dd, *J* 4.6 and 4.0 Hz, H-5), 3.73 (3H, s, CO<sub>2</sub>Me), 5.29-5.41 (2H, m, H-8, H-9), 5.78 (1H, dd, *J* 15.7 and 1.0 Hz, H-2), 7.02 (1H, dd, *J* 15.8 and 8.3 Hz, H-3); *m/z* (EI) 344 (MH<sup>+</sup>), 343 (M<sup>+</sup>), 342 (M<sup>+</sup>-H), 328 (M<sup>+</sup>-OMe), 312, 300, 286 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 284 (M<sup>+</sup>-CO<sub>2</sub>Me), 257, 230 (C<sub>13</sub>H<sub>24</sub>D<sub>3</sub>OSi), 171, 89 and 73; Found C, 66.72; H+D, 10.67%; C<sub>19</sub>H<sub>33</sub>D<sub>3</sub>O<sub>3</sub>Si requires C, 66.42; H+D, 10.56%.

**(2E,4S,5R,6S,8E) S-[2-(Acetylamino)ethyl] 10,10,10-trideuterio-5-hydroxy-4,6-dimethyldeca-2,8-dienethioate (4):** Lithium hydroxide monohydrate (294 mg, 7 mmol) was added to a solution of the ester (**19**) (240 mg, 0.7 mmol) in ethanol (8 ml) and water (2 ml). The mixture was heated at 40 °C for 16 h and the ethanol was then removed by rotary evaporation. The aqueous phase was acidified with 10% citric acid (10 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford crude (2E,4S,5R,6S,8E) 5-(*t*-butyldimethylsilyloxy)-10,10,10-trideuterio-4,6-dimethyldeca-2,8-dienoic acid which was used without further purification.

Previously prepared *N*-acetylcysteamine<sup>16</sup> (130 mg, 0.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added to a solution of the acid (246 mg, 0.74 mmol), DMAP (18 mg, 0.15 mmol) and DCC (220 mg, 1.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, allowed to warm to room temperature and stirred for 16 hours. Precipitated DCU was removed by filtration, the solids were rinsed with ethyl acetate (3 × 25 ml) and the combined solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (60% ethyl acetate-petrol) yielded (2E,4S,5R,6S,8E) S-[2-(acetylamino)ethyl] 5-(*t*-butyldimethylsilyloxy)-10,10,10-trideuterio-4,6-dimethyldeca-2,8-dienethioate (146 mg, 49%) as a colourless viscous oil;  $[\alpha]_{\text{D}}^{20}$  -31.5 (*c* 0.68, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3285, 3074, 2928, 2854, 2218, 2117, 2063, 1652, 1547, 1459, 1403, 1373, 1288, 1198, 1098, 1021 and 969 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.03 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.84 (3H, d, *J* 6.8 Hz, 6-Me), 0.91 (9H, s, <sup>t</sup>Bu), 1.05 (3H, d, *J* 7.0 Hz, 4-Me), 1.58-1.64 (1H, m, H-6), 1.74 (1H, ddd *J* 13.9, 9.3 and 7.2 Hz, H-7), 1.96 (3H, s, COCH<sub>3</sub>), 2.08 (1H, dt, *J* 13.0 and 5.9 Hz, H-7), 2.48-2.55 (1H, m, H-4), 3.09 (2H, td, *J* 6.3 and 1.2 Hz, CH<sub>2</sub>S), 3.46 (2H, q, *J* 6.2 Hz, CH<sub>2</sub>N), 3.51 (1H, t, *J* 4.4 Hz, H-5), 5.29-5.41 (2H, m, H-8, H-9), 5.89 (1H, br s, NH), 6.09 (1H, dd, *J* 15.7 and 1.1 Hz, H-2), 7.01 (1H, dd, *J* 15.8 and 8.4 Hz, H-3);

$m/z$  (FAB) 861 ( $2M^+ + H$ ), 545, 431 ( $MH^+$ ), 373 ( $M^+ - C_4H_9$ ), 316, and 73; Observed (FAB)  $MH^+$  431.2840;  $C_{22}H_{39}D_3NO_3SSi$  requires  $MH$  431.2843; Found C, 61.37; H+D, 9.76; N, 3.25%;  $C_{22}H_{38}D_3NO_3SSi$  requires C, 61.35; H+D, 9.59; N, 3.25%.

HF (-0.5 ml, 40% solution in  $H_2O$ ) was added dropwise to a solution of the silyl ether (120 mg, 0.28 mmol) in acetonitrile (10 ml), in a teflon flask. The mixture was stirred at room temperature for 16 h and then poured into saturated  $NaHCO_3$  (30 ml). The mixture was extracted with  $CH_2Cl_2$  ( $4 \times 25$  ml) and the combined organic solvents dried ( $MgSO_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (ethyl acetate) yielded the alcohol (**4**) (89 mg, 98%) as a colourless viscous oil;  $[\alpha]_D^{20}$  -13.3 ( $c$  0.86,  $CHCl_3$ );  $\nu_{max}$  (film) 3296, 3088, 2963, 2927 2218, 2130, 2074, 1654, 1547, 1439, 1372, 1288, 1161 and 1046  $cm^{-1}$ ;  $\delta_H$  (500 MHz,  $CDCl_3$ ) 0.88 (3H, d,  $J$  6.9 Hz, 6-Me), 1.05 (3H, d,  $J$  6.8 Hz, 4-Me), 1.48 (1H, br d,  $J$  3.4 Hz, OH), 1.68 (1H, qd,  $J$  6.8 and 3.9 Hz, H-6), 1.96 (3H, s, COCH<sub>3</sub>), 1.93-1.99 (1H, m, H-7), 2.03-2.09 (1H, m, H-7), 2.49 (1H, sextet,  $J$  7.4 Hz, H-4), 3.09 (2H, t,  $J$  6.6 Hz, CH<sub>2</sub>S), 3.35-3.40 (1H, m, H-5), 3.46 (2H, q,  $J$  6.2 Hz, CH<sub>2</sub>N), 5.39 (1H, dt,  $J$  15.1 and 6.7 Hz, H-8), 5.45 (1H, d,  $J$  15.3 Hz, H-9), 5.90 (1H, br s, NH), 6.18 (1H, dd,  $J$  15.6 and 0.9 Hz, H-2), 6.96 (1H, dd,  $J$  15.6 and 8.5 Hz, H-3);  $m/z$  (EI) 316 ( $M^+$ ), 298 ( $M^+ - H_2O$ ), 273 ( $M^+ - COCH_3$ ), 257, 240, and 201; Observed (FAB)  $MH^+$  317.1978;  $C_{16}H_{25}D_3NO_3S$  requires  $MH$  317.1978; Found C, 60.10; H+D, 8.63; N, 4.23%;  $C_{16}H_{24}D_3NO_3S$  requires C, 60.11; H+D, 8.52; N, 4.37%.

**(5R) Dimethyl (6-benzyloxy-5-methyl-2-oxohexyl)phosphonate (21)**: A solution of NBS (19.8 g, 0.111 mmol) in  $CH_2Cl_2$  (100 ml) was added carefully to a solution of the alcohol (**20**) (20 g, 0.110 mmol) and triphenylphosphine (29.1 g, 0.110 mmol) in  $CH_2Cl_2$  (200 ml). The mixture was stirred for 1.5 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in ether (400 ml), washed with water and brine, dried, filtered and the solvent concentrated *in vacuo*. The residue was triturated with petrol, the solid filtered and the filtrate concentrated *in vacuo* to afford an oil which was purified by column chromatography on silica gel (5% ether-petrol) to yield (2*S*) 3-benzyloxy-1-bromo-2-methylpropane (24 g, 89%) as a colourless oil;  $[\alpha]_D^{20}$  12.3 ( $c$  1.00, EtOH);  $\nu_{max}$  (film) 2962, 2858, 1493, 1450, 1361, 1333, 1254, 1231, 1098, 1027, 736 and 697  $cm^{-1}$ ;  $\delta_H$  (500 MHz,  $CDCl_3$ ) 1.04 (3H, d,  $J$  6.8, 2-Me), 2.11-2.15 (1H, m, H-2), 3.39-3.47 (2H, m,  $2 \times H-1$ ), 3.50-3.56 (2H, m,  $2 \times H-3$ ), 4.53 (2H, m, CH<sub>2</sub>Ph), 7.34 (5H, m, ArH);  $m/z$  (EI) 244, 242 ( $M^+$ ), 163 ( $M^+ - Br$ ), 153, 151 ( $M^+ - C_7H_7$ ), 91; Found C, 54.30; H, 6.22;  $C_{11}H_{15}OBr$  requires C, 54.43, H, 6.22%.

A suspension of KH (1.15 g, 28.8 mmol) in THF was stirred at room temperature and dimethyl (2-oxopropyl)phosphonate (4.10 g, 24.7 mmol) was added dropwise by syringe to form a thick suspension. After stirring for 45 min, *n*-butyllithium (18 ml, 1.6 M in hexanes, 28.8 mmol) was added slowly and the resulting deep orange solution was stirred for a further 30 min before a solution of the bromide (5.00 g, 20.6 mmol) in THF (25 ml) was added. The mixture was stirred for 24 h before saturated  $NH_4Cl$  (15 ml) was added, followed by sufficient water to dissolve the solids. The organics were washed with brine (50 ml) and the combined aqueous layers extracted with ether ( $2 \times 50$  ml). The combined organics were dried ( $MgSO_4$ ) and concentrated *in vacuo*. Chromatography of the residue on silica gel (5%-20% acetone-petrol) afforded unreacted bromide (0.84 g) followed by the phosphonate (3.53 g, 63% based on recovered bromide) as a colourless oil;  $[\alpha]_D^{20}$  -1.5 ( $c$  2.67,  $CHCl_3$ );  $\nu_{max}$  (film) 3027, 2925, 2853, 1710, 1494, 1403, 1366, 1262, 1184, 1033, 813, 739 and 700  $cm^{-1}$ ;  $\delta_H$  (270 MHz,  $CDCl_3$ ) 0.92 (3H, d,  $J$  6.6 Hz, 5-Me), 1.41-1.49 (1H, m, H-5), 1.70-1.81 (2H, m,  $2 \times H-4$ ), 2.60-2.70 (2H, m,  $2 \times H-3$ ), 3.06 (2H, d,  $J$  23 Hz,  $2 \times H-1$ ), 3.29 (2H, d,  $J$  5.8 Hz,  $2 \times H-6$ ), 3.76 (6H, d,  $J$  11.2 Hz,  $2 \times OMe$ ), 4.48 (2H, s, CH<sub>2</sub>Ph), 7.27-7.37 (5H, m, ArH);  $m/z$  (EI)

329 (MH<sup>+</sup>), 237 (M<sup>+</sup>-C<sub>7</sub>H<sub>7</sub>), 219, 193, 179, 166, 124, 109 and 91; Observed (EI) MH<sup>+</sup> 329.1519; C<sub>16</sub>H<sub>26</sub>O<sub>5</sub>P requires MH 329.1518.

**(2R,6E,8S,9R,10S,12E) 1-Benzoyloxy-9-(*t*-butyldimethylsilyloxy)-2,8,10-trimethyltetradeca-6,12-dien-5-one (23):** A solution of the ketophosphonate (**21**) (4.2 g, 12.8 mmol) in acetonitrile (15 ml) was added to a suspension of lithium chloride (0.54 g, 12.8 mmol) and diisopropylethylamine (2.3 ml, 12.8 mmol) in acetonitrile (100 ml). The mixture was stirred for 15 min after which a solution of the aldehyde (**22**) (2.3 g, 8 mmol) in acetonitrile (10 ml) was added by cannula. The resulting solution was stirred at room temperature for 20 h before being poured into saturated NaHCO<sub>3</sub> (100 ml). The mixture was extracted with ether (4 × 100 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10% ether-petrol) yielded the *enone* (**23**) (3.43 g, 88%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -24.3 (*c* 1.1, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3061, 3025, 2955, 2854, 2360, 1695, 1670, 1626, 1451, 1376, 1252, 1185, 1028, 966 and 774 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.03 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.84 (3H, d, *J* 6.8 Hz, 10-Me), 0.9 (9H, s, <sup>t</sup>Bu), 0.94 (3H, d, *J* 6.6 Hz, 2-Me), 1.05 (3H, d, *J* 6.9 Hz, 8-Me), 1.45-1.60 (2H, m, H-3, H-10), 1.64 (3H, dd, *J* 6.2 and 1.2 Hz, H<sub>3</sub>-14), 1.70-1.82 (3H, m, H-2, H-3, H-11), 2.09-2.13 (1H, m, H-11), 2.50-2.62 (3H, m, H<sub>2</sub>-4, H-8), 3.27 (1H, dd, *J* 9.2 and 6.2 Hz, H-1), 3.31 (1H, dd, *J* 9.1 and 5.9 Hz, H-1), 3.51 (1H, t, *J* 4.1 Hz, H-9), 4.46 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 4.49 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 5.29-5.41 (2H, m, H-12, H-13), 6.05 (1H, dd, *J* 16.1 and 0.8 Hz, H-6), 6.89 (1H, dd, *J* 16.1 and 8.4 Hz, H-7), 7.33 (5H, m, ArH); *m/z* (EI) 486 (M<sup>+</sup>), 429 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 403, 317, 227 (C<sub>13</sub>H<sub>27</sub>OSi), 105 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Observed (EI) M<sup>+</sup> 486.3529; C<sub>30</sub>H<sub>50</sub>O<sub>3</sub>Si requires *M* 486.3529; Found C, 73.94; H, 10.19%; C<sub>30</sub>H<sub>50</sub>O<sub>3</sub>Si requires C, 74.02; H, 10.35%.

**(2R,5S,6E,8S,9R,10S,12E) 1-Benzoyloxy-9-(*t*-butyldimethylsilyloxy)-2,8,10-trimethyltetradeca-6,12-dien-5-ol (24):** Methanol (9.05 ml of a 2.0 M solution in THF, 18.1 mmol) was added to a stirred solution of LiAlH<sub>4</sub> (18.1 ml of a 1.0 M solution in THF, 18.1 mmol) at room temperature. After 5 min (*S*)-1,1'-bi-2-naphthol (5.18 g, 18.1 mmol) in THF (15 ml) was added and the mixture stirred for a further 30 min at room temperature. After cooling the mixture to -100 °C a solution of the *enone* (**23**) (4.4 g, 9.05 mmol) in THF (25 ml) was added over 30 min. The mixture was stirred at -100 °C for 44 h and then quenched by the sequential addition of methanol (4 ml) and water (4 ml). The mixture was allowed to warm to room temperature then poured into brine, extracted with ether (4 × 100 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10% ether-petrol) yielded unreacted *enone* (**23**) (1.3 g) followed by the *alcohol* (**24**) (3 g, 77%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -9.2 (*c* 1.3, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3414, 3024, 2955, 2929, 1451, 1374, 1252, 1204, 1028, 836 and 734 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.04 (6H, s, SiMe<sub>2</sub>), 0.84 (3H, d, *J* 6.9 Hz, 10-Me), 0.91 (9H, s, <sup>t</sup>Bu), 0.94 (3H, d, *J* 6.7 Hz, 2-Me), 0.99 (3H, d, *J* 7.0 Hz, 8-Me), 1.09-1.13 (1H, m, H-3), 1.40 (1H, d, *J* 3.5 Hz, OH), 1.53-1.59 (4H, m, H-3, H<sub>2</sub>-4, H-10), 1.64 (3H, dd, *J* 6.1 and 1.2 Hz, H<sub>3</sub>-14), 1.75-1.79 (2H, m, H-2, H-11), 2.04-2.08 (1H, m, H-11), 2.35-2.39 (1H, m, H-8), 3.24 (1H, dd, *J* 9.1 and 6.7 Hz, H-1), 3.32 (1H, dd, *J* 9.1 and 6.1 Hz, H-1), 3.42 (1H, t, *J* 4.1 Hz, H-9), 3.99-4.02 (1H, broad m, H-5), 4.49 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 4.52 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 5.35-5.41 (2H, m, H-12, H-13), 5.41, (1H, ddd, *J* 15.5, 7.5 and 0.9 Hz, H-6), 5.71 (1H, ddd, *J* 15.6, 7.8 and 0.8 Hz, H-7), 7.33 (5H, m, ArH); *m/z* (EI) 488 (M<sup>+</sup>), 472, 470 (M<sup>+</sup>-H<sub>2</sub>O), 429, 431 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 415, 387, 323, 317, 227 (C<sub>13</sub>H<sub>27</sub>OSi) and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Found C, 73.74; H, 10.80%; C<sub>30</sub>H<sub>52</sub>O<sub>3</sub>Si requires C, 73.71; H, 10.72%.

**(2R,5S,6E,8S,9R,10S,12E) 1-Benzyloxy-5,9-di(*t*-butyldimethylsilyloxy)-2,8,10-trimethyltetradeca-6,12-diene (25):** DMF (12 ml) was added to a mixture of the alcohol (**24**) (3.2 g, 6.73 mmol), *tert*-butyldimethylsilyl chloride (1.3 g, 8.5 mmol) and imidazole (0.58 g, 8.51 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred for a further 16 h. The solution was then poured into brine, extracted with ether (4 × 50 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10% ether-petrol) yielded the *bis*(silyl ether) (**25**) (3.96 g, 98%) as a colourless oil; [ $\alpha_D^{20}$  -9.2 (*c* 1.9, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3062, 3024, 2954, 2929, 2884, 2854, 2707, 1588, 1459, 1359, 1203, 1096, 939 and 810 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.02 (3H, s, SiMe), 0.04 (6H, s, SiMe<sub>2</sub>), 0.05 (3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 10-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.93 (3H, d, *J* 6.8 Hz, 2-Me), 0.99 (3H, d, *J* 7.0 Hz, 8-Me), 1.04-1.08 (1H, m, H-2), 1.44-1.62 (4H, m, H<sub>2</sub>-3, H-4, H-11), 1.63 (3H, dd, *J* 6.1 and 1.1 Hz, H<sub>3</sub>-14), 1.72-1.77 (2H, m, H-4, H-10), 2.06-2.09 (1H, m, H-11), 2.32-2.37 (1H, m, H-8), 3.21 (1H, dd, *J* 9.1 and 7 Hz, H-1), 3.31 (1H, dd, *J* 9.1 and 5.9 Hz, H-1), 3.40 (1H, dd, *J* 4.7 and 3.3 Hz, H-9), 4.01 (1H, br q, *J* 5.9 Hz, H-5), 4.49 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 4.50 (1H, d, *J* 12.1 Hz, CH<sub>2</sub>Ph), 5.35-5.41 (3H, m, H-6, H-12, H-13), 5.61 (1H, ddd, *J* 15.6, 7.9 and 0.7 Hz, H-7), 7.33 (5H, m, ArH); *m/z* (EI) 545 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 470, 413, 387, 247 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 545.3842; C<sub>32</sub>H<sub>57</sub>O<sub>3</sub>Si<sub>2</sub> requires *M*-545.3846; Found C, 71.68; H, 11.07%; C<sub>36</sub>H<sub>66</sub>O<sub>3</sub>Si<sub>2</sub> requires C, 71.70; H, 11.03%.

**(2R,5S,6E,8S,9R,10S,12E) 5,9-Di(*t*-butyldimethylsilyloxy)-2,8,10-trimethyltetradeca-6,12-dien-1-ol (26):** Lithium metal (242 mg, 34.8 mmol) was added to a solution of the benzyl ether (**25**) (2.1 g, 3.48 mmol) in liquid ammonia (100 ml) at -78 °C. The resulting blue solution was stirred at -78 °C for 2 h after which solid ammonium chloride was added and the ammonia was allowed to evaporate by warming the mixture to room temperature. The residue was diluted with brine, extracted with ether (4 × 200 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (20% ether-petrol) yielded the alcohol (**26**) (1.76 g, 99%) as a colourless oil; [ $\alpha_D^{20}$  -7.5 (*c* 1.4, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3343, 2929, 2855, 2734, 2707, 1459, 1375, 1253, 1034, 967 and 810 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.02 (3H, s, SiMe), 0.04 (6H, s, SiMe<sub>2</sub>), 0.05 (3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 10-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.92 (3H, d, *J* 6.6 Hz, 2-Me), 0.99 (3H, d, *J* 7.0 Hz, 8-Me), 1.02-1.06 (1H, m, H-2), 1.26 (1H, br s, OH), 1.39-1.62 (5H, m, H<sub>2</sub>-3, H<sub>2</sub>-4, H-11), 1.65 (3H, dd, *J* 6.1 and 1.1 Hz, H<sub>3</sub>-14), 1.72-1.77 (1H, m, H-10), 2.05-2.09 (1H, m, H-11), 2.31-2.37 (1H, m, H-8), 3.41 (2H, dd, *J* 4.8 and 3.2 Hz, H<sub>2</sub>-1), 3.50 (1H, m, H-9), 4.02 (1H, br q, *J* 6.2 Hz, H-5), 5.28-5.41 (3H, m, H-6, H-12, H-13), 5.60 (1H, ddd, *J* 15.6, 8.7 and 0.8 Hz, H-7); *m/z* (EI) 512 (M<sup>+</sup>), 497 (M<sup>+</sup>-CH<sub>3</sub>), 455 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 427, 365, 341, 227 (C<sub>13</sub>H<sub>27</sub>OSi), 89 and 75; Observed (EI) M<sup>+</sup> 512.4080; C<sub>29</sub>H<sub>60</sub>O<sub>3</sub>Si<sub>2</sub> requires *M* 512.4081; Observed M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 455.3377; C<sub>25</sub>H<sub>51</sub>O<sub>3</sub>Si<sub>2</sub> requires *M*-455.3377; Found C, 67.87; H, 11.82%; C<sub>29</sub>H<sub>60</sub>O<sub>3</sub>Si<sub>2</sub> requires C, 67.90; H, 11.79%.

**(2R,5S,6E,8S,9R,10S,12E) 5,9-Di(*t*-butyldimethylsilyloxy)-2,8,10-trimethyltetradeca-6,12-dienal (27):** Tetra-*n*-propylammonium perruthenate (60 mg, 0.17 mmol) was added to a slurry of powdered 4 Å sieves (excess) in a solution of the alcohol (**26**) (1.76 g, 3.43 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (0.5 g, 4.63 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) at room temperature. The mixture was stirred at room temperature for 30 min and filtered through Florisil<sup>®</sup>, eluting with ethyl acetate. The solvents were concentrated *in vacuo* and chromatography of the residue on silica gel (5% ether-petrol) yielded the aldehyde (**27**) (1.7 g, 97%) as a colourless oil; [ $\alpha_D^{20}$  -13.8 (*c* 0.9, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3203, 2956, 2929, 2855, 2706, 1726, 1459, 1374, 1250, 1094, 967 and 938 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 0.02 (3H, s, SiMe), 0.04 (3x3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 10-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.99 (3H, d, *J* 7.1 Hz, 8-Me), 1.08 (3H, d, *J* 7.1 Hz, 2-Me),



1.28-1.59 (5H, m), 1.64 (3H, d,  $J$  4.9 Hz, H<sub>3</sub>-14), 1.70-1.77 (1H, m, H-10), 2.14-2.18 (1H, m, H-11), 2.30-2.35 (2H, m, H-2, H-8), 3.40 (1H, dd,  $J$  4.6 and 3.2 Hz, H-9), 4.04 (1H, br q,  $J$  5.8 Hz, H-5), 5.28-5.41 (3H, m, H-6, H-12, H-13), 5.62 (1H, dd,  $J$  15.6 and 7.8 Hz, H-7), 9.60 (1H, d,  $J$  2.0 Hz, H-1);  $m/z$  (EI) 453 ( $M^+$ -C<sub>4</sub>H<sub>9</sub>), 427, 341, 301, 267, 89 and 73; Observed (EI)  $M^+$ -C<sub>4</sub>H<sub>9</sub> 453.3220; C<sub>25</sub>H<sub>49</sub>O<sub>3</sub>Si<sub>2</sub> requires  $M$ -453.3220.

**(2*E*,4*R*,7*S*,8*E*,10*S*,11*R*,12*S*,14*E*) Methyl 7,11-di-(*t*-butyldimethylsilyloxy)-4,10,12-trimethyl-2-(trideuteriomethyl)hexadeca-2,8,14-trienoate (28):** Trideuteriomethyl( $\alpha$ -carbomethoxymethyl)triphenylphosphonium iodide<sup>20</sup> (1.5 g, 2.94 mmol) was dissolved in CHCl<sub>3</sub> (20 ml) and washed with 1 N NaOH (25 ml). The organic phase was dried (MgSO<sub>4</sub>) and filtered and the filtrate was added to aldehyde (27) (470 mg, 0.98 mmol) and the resulting solution heated at reflux for 16 h. The solvent was concentrated *in vacuo*, the residue passed down a plug of silica (25% ether-petrol) and the eluant concentrated *in vacuo*. Chromatography of the residue on silica gel (5% ether-petrol) yielded the *ester* (28) (506 mg, 88%) as a colourless oil; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -16.0 ( $c$  1.0, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 2954, 2855, 2706, 2211, 1715, 1640, 1457, 1375, 1252, 1069, 1005 and 967 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.01 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.036 (2x3H, s, SiMe), 0.83 (3H, d,  $J$  6.8 Hz, 12-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.98 (3H, d,  $J$  7.1 Hz, 4-Me or 10-Me), 0.99 (3H, d,  $J$  6.7 Hz, 4-Me or 10-Me), 1.35-1.39 (4H, m, H<sub>2</sub>-5, H<sub>2</sub>-6), 1.56-1.61 (1H, m, H-13), 1.63 (3H, dd,  $J$  6.2 and 1.2 Hz, H<sub>3</sub>-16), 1.70-1.77 (1H, m, H-12), 2.05-2.09 (1H, m, H-13), 2.36 (1H, dt,  $J$  7.2 and 3.2 Hz, H-10), 2.45-2.52 (1H, m, H-4), 3.40 (1H, dd,  $J$  4.8 and 3.3 Hz, H-11), 3.73 (3H, s, CO<sub>2</sub>Me), 4.00 (1H, m, H-7), 5.30-5.37 (3H, m, H-8, H-14, H-15), 5.59 (1H, ddd,  $J$  15.6, 7.9 and 0.9 Hz, H-9), 6.52 (1H, d,  $J$  10.1 Hz, H-3);  $m/z$  (EI) 568 ( $M^+$ -Me), 526 ( $M^+$ -C<sub>4</sub>H<sub>9</sub>), 509, 471, 368, 301, 227 (C<sub>13</sub>H<sub>27</sub>OSi) and 89; Observed (EI)  $M^+$ -C<sub>4</sub>H<sub>9</sub> 526.3827; C<sub>29</sub>H<sub>52</sub>D<sub>3</sub>O<sub>4</sub>Si<sub>2</sub> requires  $M$ -526.3827; Found C, 67.87; H, 11.18%; C<sub>33</sub>H<sub>61</sub>D<sub>3</sub>O<sub>4</sub>Si<sub>2</sub> requires C, 67.86; H, 11.04%.

**(2*E*,4*R*,7*S*,8*E*,10*S*,11*R*,12*S*,14*E*)S-[2-(Acetylamino)ethyl] 7,11-dihydroxy--4,10,12-trimethyl-2-(trideuteriomethyl)hexadeca-2,8,14-trienethioate (5):** Lithium hydroxide monohydrate (144 mg, 3.4 mmol) was added to a solution of the ester (28) (250 mg, 0.43 mmol) in ethanol (8 ml) and water (0.8 ml). The mixture was stirred at 60 °C for 8 h and then at room temperature overnight. The solvents were concentrated *in vacuo* and the residue partitioned between 10% citric acid (30 ml) and CH<sub>2</sub>Cl<sub>2</sub> (30 ml). The organic layer was separated, the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to yield crude (2*E*,4*R*,7*S*,8*E*,10*S*,11*R*,12*S*,14*E*) 7,11-di-(*t*-butyldimethylsilyloxy)-4,10,12-trimethyl-2-(trideuteriomethyl)hexadeca-2,8,14-trienic acid as a colourless oil which was used without further purification.

A solution of the crude carboxylic acid in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was stirred at 0 °C and DMAP (11 mg, 90  $\mu$ mol) followed by freshly prepared *N*-acetylcysteamine<sup>16</sup> (80 mg, 0.67 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) and DCC (150 mg, 0.72 mmol) were added. The mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature and stirred for a further 16 h. The precipitated DCU was removed by filtration, rinsed with ethyl acetate and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (80% ether-petrol-100% ether) yielded (2*E*,4*R*,7*S*,8*E*,10*S*,11*R*,12*S*,14*E*) S-[2-(acetylamino)ethyl] 7,11-di-(*t*-butyldimethylsilyloxy)-4,10,12-trimethyl-2-(trideuteriomethyl)hexadeca-2,8,14-trienethioate (221 mg, 77%) as a viscous colourless oil; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -27.4 ( $c$  0.7, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3283, 3076, 2928, 2854, 2064, 1653, 1548, 1458, 1360, 1290, 1069, 967 and 774 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.015 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.036 (3H, s, SiMe), 0.038 (3H, s, SiMe), 0.85 (3H, d,  $J$  6.8 Hz, 12-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91

(9H, s, <sup>1</sup>Bu), 0.99 (3H, d, *J* 7.0 Hz, 4-Me or 10-Me), 1.02 (3H, d, *J* 6.7 Hz, 4-Me or 10-Me), 1.35-1.39 (4H, m, H<sub>2</sub>-5, H<sub>2</sub>-6), 1.53-1.58 (1H, m, H-13), 1.64 (3H, dd, *J* 6.0 and 1.1 Hz, H<sub>3</sub>-16), 1.72-1.77 (1H, m, H-12), 1.97 (3H, s, CH<sub>3</sub>CO), 2.09 (1H, m, H-13), 2.36 (1H, dt, *J* 7.1 and 3.2 Hz, H-10), 2.44-2.50 (1H, m, H-4), 3.06 (2H, dt, *J* 6.4 and 3.3 Hz, CH<sub>2</sub>S), 3.41 (1H, dd, *J* 4.9 and 3.3 Hz, H-11), 3.45 (2H, q, *J* 6.2 Hz, CH<sub>2</sub>N), 3.98-4.02 (1H, m, H-7), 5.29-5.40 (3H, m, H-8, H-14, H-15), 5.60 (1H, ddd, *J* 15.5, 7.9 and 0.8 Hz, H-9), 5.86 (1H, br s, NH), 6.52 (1H, d, *J* 9.9 Hz, H-3); *m/z* (FAB, 1:1 NaCl/LiCl + aqueous glycerol) 677 (MLi<sup>+</sup>), 655 (M<sup>+</sup>-Me), 613 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 539, 427, 227 (C<sub>13</sub>H<sub>27</sub>OSi) and 73; Observed (FAB) MNa<sup>+</sup> 693.4570; C<sub>36</sub>H<sub>66</sub>D<sub>3</sub>NNaO<sub>4</sub>SSi<sub>2</sub> requires *M* 693.4572; Found C, 64.33; H+D, 10.49; N, 1.90%; C<sub>36</sub>H<sub>66</sub>D<sub>3</sub>NO<sub>4</sub>SSi<sub>2</sub> requires C, 64.42; H+D, 10.36; N, 2.09%.

A solution of the bis(silyl ether) (67 mg, 0.1 mmol) in acetic acid, water and THF (3:3:1, 3 ml) was stirred at room temperature for 2 days and at 50 °C for a further 2 days. The mixture was concentrated *in vacuo*, water (1 ml) was added and the mixture was concentrated *in vacuo* again (repeated three times). Chromatography of the residue on silica gel (80% ethyl acetate-petrol to 1% methanol-ethyl acetate) yielded material deprotected at C(7) only (31 mg, 55%) followed by the *diol* (**5**) (13 mg, 30%) as a viscous colourless oil;  $[\alpha]_{\text{D}}^{20}$  -28.7 (*c* 0.46, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3292, 2959, 2927, 1653, 1547, 1448, 1371, 1292, 1074, 969 and 901 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.86 (3H, d, *J* 6.9 Hz, 12-Me), 0.96 (3H, d, *J* 6.8 Hz, 10-Me), 1.04 (3H, d, *J* 6.7 Hz, 4-Me), 1.43-1.47 (4H, m, H<sub>2</sub>-5, H<sub>2</sub>-6), 1.65 (3H, dd, *J* 6.0 and 1.1 Hz, H<sub>3</sub>-16), 1.67 (3H, m, H-12, 2xOH), 1.96 (1H, m, H-13), 1.97 (3H, s, CH<sub>3</sub>CO), 2.12 (1H, m, H-13), 2.27 (1H, sextet, *J* 7.1 Hz, H-10), 2.50-2.55 (1H, m, H-4), 3.06 (2H, dt, *J* 6.5 and 2.1 Hz, CH<sub>2</sub>S), 3.22 (1H, dd, *J* 7.9 and 3.6 Hz, H-11), 3.45 (2H, dq, *J* 5.7 and 1.2 Hz, CH<sub>2</sub>N), 4.00-4.04 (1H, m, H-7), 5.38-5.44 (2H, m, H-14, H-15), 5.52-5.60 (2H, m, H-8, H-9), 5.91 (1H, br s, NH), 6.52 (1H, d, *J* 9.9 Hz, H-3); *m/z* (FAB) 465 (MNa<sup>+</sup>), 447 (MNa<sup>+</sup>-H<sub>2</sub>O), 425 (MH<sup>+</sup>-H<sub>2</sub>O), 407 (MH<sup>+</sup>-2xH<sub>2</sub>O), 370, 327 (M<sup>+</sup>-C<sub>4</sub>H<sub>8</sub>NOS), 313, 194 and 116; Observed (FAB) MNa<sup>+</sup> 465.2842; C<sub>24</sub>H<sub>38</sub>D<sub>3</sub>NNaO<sub>4</sub>S requires *M* 465.2842; Found C, 64.81; H+D, 9.40; N, 3.06%; C<sub>24</sub>H<sub>38</sub>D<sub>3</sub>NO<sub>4</sub>S requires C, 65.12; H+D, 9.34; N, 3.16%.

The monodeprotected material (31 mg, 0.06 mmol) was recycled to give a further quantity of *diol* (**5**) (8 mg, 30%) and some unreacted starting material (15 mg). The recovered starting material was further reacted to give the *diol* (**5**) (7 mg, 55%). Thus the total yield of the *diol* (**18**) from the bis(silyl ether) was 63%.

**(5R) 6-(*t*-Butyldiphenylsilyloxy)-5-methylhex-1-ene (31):** Trifluoromethanesulfonic anhydride (7.7 ml, 45.7 mmol) was added dropwise to a solution of the alcohol (**30**) (10 g, 30.4 mmol) and triethylamine (12.7 ml, 91.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) at -15 °C. The reaction mixture was stirred at this temperature for 30 min, warmed to room temperature, then washed with saturated NaHCO<sub>3</sub> (40 ml) and brine (40 ml). The organic phase was dried (MgSO<sub>4</sub>) and then passed through a plug of silica gel, eluting with ether. The combined organics were concentrated *in vacuo* and the resulting crude triflate was used without further purification.

Allylmagnesium bromide (46 ml, 1.0 M in ether, 46 mmol) and copper(I) bromide (0.88 g, 6.1 mmol) were added sequentially to a solution of the crude triflate in ether (100 ml), at -78 °C. The mixture was stirred at -78 °C for 3 h before being allowed to warm slowly to room temperature. After stirring the mixture at room temperature for 12 h, 10% NH<sub>4</sub>OH/NH<sub>4</sub>Cl (100 ml) was added carefully. The mixture was passed down a plug of Celite<sup>®</sup> and the organic phase was separated and washed with brine (40 ml) and saturated NaHCO<sub>3</sub> (40 ml). The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (petrol) yielded the *alkene* (**31**) (9 g, 84%) as a colourless liquid;  $[\alpha]_{\text{D}}^{20}$  -0.43 (*c* 3.5,

CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3069, 2958, 2855, 1636, 1583, 1428, 1387, 1188, 997 and 823 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.93 (3H, d, *J* 6.7 Hz, 5-Me), 1.06 (9H, s, <sup>t</sup>Bu), 1.20-1.24 (1H, m, H-4), 1.50-1.55 (1H, m, H-4), 1.68 (1H, octet, *J* 6.2 Hz, H-5), 1.98-2.11 (2H, m, H<sub>2</sub>-3), 3.45 (1H, dd, *J* 10.0 and 6.3 Hz, H-6), 3.52 (1H, dd, *J* 10.0 and 5.7 Hz, H-6), 4.91 (1H, ddt, *J* 10.2, 2.6 and 1.3 Hz, H-1<sub>[cis]</sub>), 4.97 (1H, ddd, *J* 17.2, 3.6 and 1.7 Hz, H-1<sub>[trans]</sub>), 5.78 (1H, ddt, *J* 16.9, 10.2 and 6.6 Hz, H-2), 7.23-7.72 (10H, m, ArH); *m/z* (EI) 295 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 258, 240, 201 and 183; Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 295.1518; C<sub>19</sub>H<sub>23</sub>OSi requires *M* 295.1518; Found C, 78.36; H, 9.25%; C<sub>23</sub>H<sub>32</sub>O<sub>2</sub>Si requires C, 78.35; H, 9.15%.

**(2R) 5-Bromo-1-(*t*-butyldiphenylsilyloxy)-2-methylpentane (32):** Ozone (40 L/h, 140 V) was passed through a solution of the alkene (31) (7 g, 19.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 ml) and ethanol (100 ml), at -78 °C for 8 h. The solution was flushed with argon and sodium borohydride (3.8 g, 99 mmol) was added. The resulting mixture was allowed to warm to room temperature and stirred for 16 h after which saturated ammonium chloride was added carefully until effervescence ceased. The organic solvents were removed by evaporation and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (50% ether-petrol) yielded (4R) 5-(*t*-butyldiphenylsilyloxy)-4-methylpentan-1-ol (5.9 g, 83%) as a colourless oil; [ $\alpha_{\text{D}}^{20}$ ] -2.7 (*c* 1.72, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3327, 3066, 2990, 2738, 1656, 1588, 1428, 1426, 1387, 1261, 1111 and 939 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (270 MHz, CDCl<sub>3</sub>) 0.93 (3H, d, *J* 6.6 Hz, 4-Me), 1.06 (9H, s, <sup>t</sup>Bu), 1.15-1.19 (1H, m, H-3), 1.22-1.26 (1H, m, OH), 1.44-1.55 (3H, m, H<sub>2</sub>-2, H-3) 1.60 (1H, octet, *J* 6.6 Hz, H-4), 3.45 (1H, dd, *J* 10.0 and 6.1 Hz, H-5), 3.53 (1H, dd, *J* 9.8 and 5.9 Hz, H-5), 3.58-3.63 (2H, m, H<sub>2</sub>-1), 7.35-7.69 (10H, m, ArH); *m/z* (EI) 299 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 229, 281 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>-H<sub>2</sub>O), 239 (TBDPSi<sup>+</sup>) and 199; Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 299.1467; C<sub>18</sub>H<sub>23</sub>O<sub>2</sub>Si requires *M* 299.1467; Found C, 74.27; H, 9.00%; C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>Si requires C, 74.10; H, 9.05%.

Triphenylphosphine dibromide (11.9 g, 28.1 mmol) was added portionwise to a solution of the alcohol (7.7 g, 21.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml), maintaining the internal temperature at 0 °C. After complete addition of the reagent the reaction was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred for a further 1 h. The mixture was concentrated *in vacuo*, the residue triturated with petrol and the triphenylphosphine oxide removed by filtration. The collected solids were rinsed with petrol (3 × 50 ml) and the combined filtrates were concentrated *in vacuo*. Chromatography of the residue on silica gel (2% ether-petrol) yielded the bromide (32) (7.3 g, 81%) as a colourless oil; [ $\alpha_{\text{D}}^{20}$ ] +4.5 (*c* 1.6, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3068, 3046, 2956, 2929, 2855, 1538, 1459, 1260, 1188 and 828 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (270 MHz, CDCl<sub>3</sub>) 0.91 (3H, d, *J* 6.6 Hz, 2-Me), 1.06 (9H, s, <sup>t</sup>Bu), 1.24-1.28 (1H, m, H-3), 1.53-1.88 (4H, m, H<sub>2</sub>-4, H-3, H-2), 3.37 (2H, dt, *J* 6.8 and 0.5 Hz, H<sub>2</sub>-1), 3.47 (2H, dd, *J* 5.9 and 1.5 Hz, H<sub>2</sub>-5), 7.37-7.68 (10H, m, ArH); *m/z* (EI) 363 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>, <sup>81</sup>Br), 361 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>, <sup>79</sup>Br), 293/291, 263/261, 199 and 83; Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 361.0623; C<sub>18</sub>H<sub>22</sub><sup>79</sup>BrOSi requires *M* 361.0624; Found C, 62.97; H, 7.45; Br, 19.12%; C<sub>22</sub>H<sub>31</sub>BrOSi requires C, 62.99; H, 7.45; Br 19.05%.

**Dimethyl [2-oxo-1-(trideuteriomethyl)propyl]phosphonate (33):** Trideuteriodomethane (1.7 ml, 26.4 mmol) was added to a mixture of potassium carbonate (4.3 g, 31 mmol) and dimethyl (2-oxopropyl)phosphonate (4 g, 24.1 mmol) in acetone (40 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for a further 16 h. Saturated ammonium chloride (30 ml) was added, the organic solvents were removed by rotary evaporation and the aqueous phase was extracted with ethyl acetate (4 × 60 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (40-50% acetone-petrol) yielded the deuterated phosphonate (33) (3.2 g, 71%) as a pale yellow oil;  $\nu_{\max}$  (film) 3478, 2957, 2853, 2239, 2140, 2081, 2027,

1709, 1459, 1359, 1292, 1191, 1031 and 772  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 2.32 (3H, s,  $\text{CH}_3\text{CO}$ ), 3.22 (1H, d,  $J$  25.0 Hz, H-1), 3.74 (3H, d,  $J$  1.7 Hz, OMe), 3.78 (3H, d,  $J$  1.7 Hz, OMe);  $m/z$  (EI) 184 ( $\text{MH}^+$ ), 183 ( $\text{M}^+$ ), 168 ( $\text{M}^+-\text{Me}$ ), 158, 156, 152, 141, 109 and 79; Observed (EI)  $\text{M}^+$  183.0738;  $\text{C}_6\text{H}_{10}\text{D}_3\text{O}_4\text{P}$  requires  $M$  183.0734; Found C, 38.41; H+D, 7.23; P, 16.54%;  $\text{C}_6\text{H}_{10}\text{D}_3\text{O}_4\text{P} \cdot 0.25 \text{H}_2\text{O}$  requires C, 38.40; H+D, 7.25; P, 16.51%.

**(1*RS*,7*R*) Dimethyl [8-(*t*-butyldiphenylsilyloxy)-7-methyl-2-oxo-1-(trideuteriomethyl)octyl]phosphonate (34):** A solution of the phosphonate (33) (2.56 g, 13.94 mmol) in THF (10 ml) was added to a suspension of sodium hydride (640 mg, 17.3 mmol, 60% dispersion) in THF (10 ml) at 0 °C. The viscous mixture was stirred for 1 h at room temperature, cooled to -10 °C and *n*-butyllithium (6.4 ml, 2.5 M in hexanes, 16.1 mmol) was added dropwise over 10 min. The resulting solution was stirred at 0 °C for 20 min, after which a solution of the bromide (32) (4.5 g, 10.72 mmol) in THF (10 ml) was added by cannula. The reaction mixture was stirred at room temperature for 16 h, poured into saturated ammonium chloride (100 ml) and extracted with ethyl acetate (4 × 100 ml). The combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (25% acetone-petrol) yielded unreacted bromide (32) (1.84 g) followed by the *ketophosphonate* (34) (2.27g, 41%) as colourless oils;  $[\alpha_{\text{D}}^{20}] +1.1$  ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3067, 2952, 2855, 2235, 2079, 1959, 1887, 1823, 1735, 1708, 1587, 1406, 1255, 1111 and 1033  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.89 (3H, d,  $J$  6.7 Hz, 7-Me), 1.04 (9H, s, <sup>t</sup>Bu), 1.06-1.11 (1H, m, H-5), 1.17-1.23 (1H, m, H-5), 1.29-1.33 (1H, m, H-6), 1.41-1.46 (1H, m, H-6), 1.54-1.61 (2H, m, H<sub>2</sub>-4), 1.63 (1H, octet,  $J$  6.8 Hz, H-7), 2.46-2.51 (1H, m, H-3), 2.71-2.76 (1H, m, H-3), 3.20 (1H, d,  $J$  24.9 Hz, H-1), 3.42 (1H, dd,  $J$  9.8 and 6.4 Hz, H-8), 3.49 (1H, dd,  $J$  9.8 and 5.8 Hz, H-8), 3.75 (6H, m, 2xOMe), 7.33-7.40 (6H, m, ArH), 7.60-7.68 (4H, m, ArH);  $m/z$  (EI) 521 ( $\text{M}^+$ ), 520 ( $\text{M}^+-\text{H}$ ), 506 ( $\text{M}^+-\text{Me}$ ), 490 ( $\text{M}^+-\text{OMe}$ ), 478, 464 ( $\text{M}^+-\text{C}_4\text{H}_9$ ), 386 and 199; Observed (EI)  $\text{M}^+-\text{Me}$  506.2571;  $\text{C}_{27}\text{H}_{37}\text{D}_3\text{O}_5\text{PSi}$  requires  $M$  506.2571.

**(1*RS*,7*R*)-(-)-Dimethyl [7-methyl-8-methylthiomethoxy-2-oxo-1-(trideuteriomethyl)octyl]phosphonate (29):** TBAF (5.5 ml, 1 M in THF) was added to a solution of the silyl ether (34) (2.2 g, 4.22 mmol) in THF (10 ml). The resulting mixture was stirred at room temperature for 6 h, then poured into saturated  $\text{NaHCO}_3$  and extracted with ethyl acetate (3 × 100 ml). The combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (50% acetone-petrol) yielded (1*RS*,7*R*) dimethyl [8-hydroxy-7-methyl-2-oxo-1-(trideuteriomethyl)octyl]phosphonate (844 mg, 71%) as a colourless oil.

A premixed solution of acetic anhydride (2.5 ml) and acetic acid (0.2 ml) was added to the alcohol (2 g, 6.5 mmol) in DMSO (4 ml). The mixture was shaken, then allowed to stand for 4 days before being neutralised by stirring with saturated  $\text{NaHCO}_3$  for 3 h. The resulting solution was extracted with ethyl acetate (5 × 100 ml), the combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (25% acetone-petrol) yielded the *methylthiomethyl ether* (29) (522 mg, 51%) as a colourless oil;  $[\alpha_{\text{D}}^{20}] -3.4$  ( $c$  1.1,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2951, 2922, 2853, 2235, 2079, 1707, 1459, 1367, 1253, 1184, 1031 and 961  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.90 (3H, d,  $J$  6.7 Hz, 7-Me), 1.10-1.14 (1H, m, H-5), 1.25-1.42 (3H, m, H-5, H<sub>2</sub>-6), 1.53-1.58 (2H, m, H<sub>2</sub>-4), 1.71 (1H, octet,  $J$  6.5 Hz, H-7), 2.12 (3H, s,  $\text{SCH}_3$ ), 2.51 (1H, m, H-3), 2.77 (1H, m, H-3), 3.21 (1H, d,  $J$  24.9 Hz, H-1), 3.28 (1H, dd,  $J$  9.1 and 6.6 Hz, H-8), 3.36 (1H, dd,  $J$  9.1 and 6.1 Hz, H-8), 3.76 (6H, 2xd,  $J$  5 Hz, 2 × OMe), 4.60 (2H, d,  $J$  0.9 Hz,  $\text{OCH}_2\text{S}$ );  $m/z$  (EI) 343 ( $\text{M}^+$ ), 328 ( $\text{M}^+-\text{Me}$ ), 296 ( $\text{M}^+-\text{SMe}$ ), 282 ( $\text{M}^+-\text{CH}_2\text{SCH}_3$ ), 266 ( $\text{M}^+-\text{OCH}_2\text{SCH}_3$ ), 224, 196, 183 and 109; Observed (EI)  $\text{M}^+-\text{Me}$  328.1428;  $\text{C}_{13}\text{H}_{23}\text{D}_3\text{O}_5\text{PS}$  requires  $M$  328.1427.

**(2*R*,8*E*,10*R*,13*S*,14*E*,16*S*,17*R*,18*S*,20*E*) 13,17-Di(*t*-butyldimethylsilyloxy)-2,10,16,18-tetramethyl-1-methylthiomethoxy-8-(trideuteriomethyl)docosa-8,14,20-trien-7-one (35):** LHMDs (1.27 ml, 1.0 M in hexanes, 1.27 mmol) was added dropwise to a solution of the deuterated ketophosphonate (**29**) (458 mg, 1.34 mmol) in THF (7 ml), at -78 °C. The mixture was stirred for 10 min at this temperature, before warming to room temperature and stirring for a further 30 min. The solution was cooled back to -78 °C and a solution of the aldehyde (**27**) (529 mg, 1.04 mmol) in THF (7 ml) was added by cannula. The resulting mixture was stirred at -78 °C for 30 min before being allowed to warm to room temperature and stirred for 3 days. The mixture was poured into saturated ammonium chloride and extracted with ether (4 × 100 ml). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (5-10% ether-petrol) yielded the undesired (*Z*)-enone (248 mg, 33%) followed by the (*E*)-enone (**35**) (380 mg, 50%) as colourless oils.

(*Z*)-enone;  $[\alpha]_{\text{D}}^{20} +4.5$  (*c* 1.2, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2954, 2927, 2854, 2234, 2215, 2203, 2068, 1687, 1618, 1459, 1360, 1300, 1078 and 966 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.006 (3H, s, SiMe), 0.027 (3H, s, SiMe), 0.032 (3H, s, SiMe), 0.036 (3H, s, SiMe), 0.82 (3H, d, *J* 6.8 Hz, 18-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.92 (3H, d, *J* 6.9 Hz, 2-Me), 0.95 (3H, d, *J* 6.7 Hz, 16-Me), 0.98 (3H, d, *J* 7.0 Hz, 10-Me), 1.12-1.16 (1H, m, H-4), 1.22-1.47 (7H, m, H-2, H<sub>2</sub>-3, H-4, H<sub>2</sub>-11, H-18), 1.55-1.62 (3H, m, H<sub>2</sub>-5, H-12), 1.63 (3H, dd, *J* 6.1 and 1 Hz, H<sub>3</sub>-22), 1.68-1.78 (2H, m, H-12, H-19), 2.05-2.10 (1H, m, H-19), 2.14 (3H, s, SCH<sub>3</sub>), 2.35 (1H, td, *J* 7.1 and 3.3 Hz, H-16), 2.46-2.50 (2H, m, H<sub>2</sub>-6), 2.58-2.63 (1H, m, H-10), 3.30 (1H, dd, *J* 9.0 and 6.5 Hz, H-1), 3.36 (1H, dd, *J* 9.1 and 6 Hz, H-1), 3.40 (1H, dd, *J* 4.7 and 3.3 Hz, H-17), 3.99 (1H, q, *J* 6.0 Hz, H-13), 4.60 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 4.63 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 5.27-5.39 (4H, m, H-9, H-14, H-20, H-21), 5.57 (1H, ddd, *J* 16.3, 7.8 and 0.7 Hz, H-15);

(*E*)-enone (**35**);  $[\alpha]_{\text{D}}^{20} -13.8$  (*c* 1.1, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 2954, 2927, 2854, 2234, 2215, 2203, 2068, 1687, 1618, 1459, 1360, 1300, 1078 and 966 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.013 (3H, s, SiMe), 0.034 (3x3H, s, SiMe), 0.83 (3H, d, *J* 6.9 Hz, 18-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.92 (3H, d, *J* 6.8 Hz, 2-Me), 0.99 (3H, d, *J* 7.0 Hz, 16-Me), 1.01 (3H, d, *J* 6.7 Hz, 10-Me), 1.14-1.18 (1H, m, H-4), 1.27-1.43 (7H, m, H-2, H<sub>2</sub>-3, H-4, H<sub>2</sub>-11, H-18), 1.54-1.63 (3H, m, H<sub>2</sub>-5, H-12), 1.63 (3H, dd, *J* 5.9 and 1.1 Hz, H<sub>3</sub>-22), 1.72-1.78 (2H, m, H-12, H-19), 2.06-2.09 (1H, m, H-19), 2.14 (3H, s, SCH<sub>3</sub>), 2.35 (1H, td, *J* 7.1 and 3.9 Hz, H-16), 2.48-2.54 (1H, m, H-10), 2.60-2.65 (2H, m, H<sub>2</sub>-6), 3.30 (1H, dd, *J* 9.1 and 6.6 Hz, H-1), 3.36 (1H, dd, *J* 9.1 and 5.9 Hz, H-1), 3.40 (1H, dd, *J* 4.8 and 3.3 Hz, H-17), 4.00 (1H, br q, *J* 6.0 Hz, H-13), 4.60 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 4.63 (1H, d, *J* 11.3 Hz, CH<sub>2</sub>S), 5.29-5.39 (3H, m, H-14, H-20, H-21), 5.59 (1H, dd, *J* 15.6 and 7.9 Hz, H-15), 6.33 (1H, d, *J* 9.7 Hz, H-9); *m/z* (EI) 728 (MH<sup>+</sup>), 727 (M<sup>+</sup>), 712 (M<sup>+</sup>-Me), 670 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 616, 558 (M<sup>+</sup>-2xC<sub>4</sub>H<sub>9</sub>-C<sub>4</sub>H<sub>7</sub>), 301 and 227 (C<sub>13</sub>H<sub>27</sub>OSi); Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 670.4800; C<sub>37</sub>H<sub>68</sub>D<sub>3</sub>O<sub>4</sub>SSi requires *M* 670.4803; Found C, 67.53; H+D, 11.26%; C<sub>41</sub>H<sub>77</sub>D<sub>3</sub>O<sub>4</sub>SSi<sub>2</sub> requires C, 67.61; H+D, 11.07%.

**(2*R*,6*E*,8*E*,10*R*,13*S*,14*E*,16*S*,17*R*,18*S*,20*E*) 13,17-Di(*t*-butyldimethylsilyloxy)-2,10,16,18-tetramethyl-1-methylthiomethoxy-8-(trideuteriomethyl)docosa-6,8,14,20-tetraene (36):** Sodium borohydride (20 mg, 0.5 mmol) was added to a solution of the enone (**35**) (380 mg, 0.52 mmol) and cerium trichloride heptahydrate (186 mg, 0.50 mmol) in methanol (10 ml) at 0 °C. The mixture was stirred at 0 °C for 15 min, then poured into brine and extracted with ether (4 × 30 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (20-30% ether-petrol) yielded (2*R*,7*R*,8*E*,10*R*,13*S*,14*E*,16*S*,17*R*,18*S*,20*E*) 13,17-di(*t*-butyldimethylsilyloxy)-2,10,16,18-tetramethyl-1-methylthiomethoxy-8-(trideuteriomethyl)docosa-8,14,20-trien-7-ol and its 7*S* diastereomer as separable colourless oils.

Less polar (260 mg, 68%);  $[\alpha]_{\text{D}}^{20} -10.9$  (*c* 1.1, CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (film) 3468, 2930, 1462, 1360, 1253, 1078, 966, 836 and 773 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.016 (3H, s, SiMe), 0.037 (6H, s, 2 x SiMe), 0.043 (3H, s, SiMe),

0.83 (3H, d, *J* 6.8 Hz, 18-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.87-0.98 (6H, 2 x d, obscured, 2-Me, 16-Me), 0.99 (3H, d, *J* 7.0 Hz, 10-Me), 1.12-1.55 (11H, m, H-2, H<sub>2</sub>-3, H<sub>2</sub>-4, H<sub>2</sub>-5, H<sub>2</sub>-11, H<sub>2</sub>-12), 1.30 (1H, d, *J* 3.3 Hz, OH), 1.59-1.62 (1H, m, H-18), 1.63 (3H, dd, *J* 5.9 and 0.9 Hz, H<sub>3</sub>-22), 1.69-1.79 (2H, m, H-10, H-19), 2.04-2.11 (1H, m, H-19), 2.14 (3H, s, SCH<sub>3</sub>), 2.32-2.38 (3H, m, H<sub>2</sub>-6, H-16), 3.29 (1H, dd, *J* 9.1 and 6.7 Hz, H-1), 3.38 (1H, dd, *J* 9.1 and 5.9 Hz, H-1), 3.41 (1H, dd, *J* 4.8 and 3.3 Hz, H-17), 3.95 (1H, td, *J* 6.7 and 3.1 Hz, H-7), 4.00 (1H, q, *J* 6.1 Hz, H-13), 4.62 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 4.64 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 5.12 (1H, d, *J* 9.5 Hz, H-9), 5.31-5.40 (3H, m, H-14, H-20, H-21), 5.59 (1H, ddd, *J* 15.7, 7.9 and 0.7 Hz, H-15).

More polar (87 mg, 23%); [ $\alpha$ ]<sub>D</sub><sup>20</sup> -10.0 (*c* 0.84, CHCl<sub>3</sub>);  $\delta$ <sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.012 (3H, s, SiMe), 0.033 (3H, s, SiMe), 0.037 (3H, s, SiMe), 0.041 (3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 18-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.91-0.94 (6H, 2 x d, obscured, 2-Me, 16-Me), 0.98 (3H, d, *J* 7.1 Hz, 10-Me), 1.11-1.56 (11H, m, H-2, H<sub>2</sub>-3, H<sub>2</sub>-4, H<sub>2</sub>-5, H<sub>2</sub>-11, H<sub>2</sub>-12), 1.32 (1H, d, *J* 3.2 Hz, OH), 1.59-1.63 (1H, m, H-18), 1.64 (3H, dd, *J* 5.8 and 0.8 Hz, H<sub>3</sub>-22), 1.71-1.78 (2H, m, H-10, H-19), 2.05-2.10 (1H, m, H-19), 2.14 (3H, s, SCH<sub>3</sub>), 2.31-2.37 (3H, m, H<sub>2</sub>-6, H-16), 3.29 (1H, dd, *J* 9.0 and 6.7 Hz, H-1), 3.37 (1H, dd, *J* 9.0 and 5.8 Hz, H-1), 3.40 (1H, dd, *J* 4.8 and 3.2 Hz, H-17), 3.94 (1H, td, *J* 6.9 and 3.2 Hz, H-7), 3.98 (1H, q, *J* 6.5 Hz, H-13), 4.60 (1H, d, *J* 11.3 Hz, CH<sub>2</sub>S), 4.63 (1H, d, *J* 11.3 Hz, CH<sub>2</sub>S), 5.11 (1H, d, *J* 9.4 Hz, H-9), 5.30-5.40 (3H, m, H-14, H-20, H-21), 5.59 (1H, dd, *J* 15.6 and 8.8 Hz, H-15); *m/z* (EI) 729 (M<sup>+</sup>), 714 (M<sup>+</sup>-Me), 711 (M<sup>+</sup>-H<sub>2</sub>O), 672 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 485, 428, 301 and 227 (C<sub>13</sub>H<sub>27</sub>OSi); Observed (EI) M<sup>+</sup> 729.5660; C<sub>41</sub>H<sub>79</sub>D<sub>3</sub>O<sub>4</sub>SSi<sub>2</sub> requires *M* 729.5661; Found C, 67.43; H+D, 11.35%; C<sub>41</sub>H<sub>79</sub>D<sub>3</sub>O<sub>4</sub>SSi<sub>2</sub> requires C, 67.43; H+D, 11.32.

Methanesulphonyl chloride (65  $\mu$ l, 0.82 mmol) was added to a solution of the major, less polar, allylic alcohol (200 mg, 0.274 mmol) and triethylamine (385  $\mu$ l, 2.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and stirred overnight. The mixture was poured into saturated NaHCO<sub>3</sub> and extracted with ether (4  $\times$  100 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (2-4% ether-petrol) yielded the diene (**36**) (120 mg, 62%) as a colourless oil; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -9.6 (*c* 1.1, CHCl<sub>3</sub>);  $\nu$ <sub>max</sub> (film) 2957, 2930, 2856, 2741, 2713, 2243, 2201, 2130, 2074, 1461, 1360, 1254, 1079, 1006 and 965 cm<sup>-1</sup>;  $\delta$ <sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.01 (3H, s, SiMe), 0.032 (3H, s, SiMe), 0.036 (3H, s, SiMe), 0.039 (3H, s, SiMe), 0.83 (3H, d, *J* 6.8 Hz, 18-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.93 (3H, d, *J* 6.7 Hz, 2-Me or 16-Me), 0.94 (3H, d, *J* 6.6 Hz, 2 or 16-Me), 0.98 (3H, d, *J* 7.0 Hz, 10-Me), 1.16 (1H, m, H-3), 1.24-1.54 (7H, m, H-2, H-3, H<sub>2</sub>-4, H<sub>2</sub>-11, H-12), 1.56-1.61 (1H, m, H-18), 1.63 (3H, dd, *J* 5.9 and 0.7 Hz, H<sub>3</sub>-22), 1.71-1.78 (2H, m, H-12, H-19), 2.04-2.11 (3H, m, H<sub>2</sub>-5, H-19), 2.14 (3H, s, SCH<sub>3</sub>), 2.30-2.36 (1H, m, H-16), 2.40-2.45 (1H, m, H-10), 3.30 (1H, dd, *J* 9.1 and 6.7 Hz, H-1), 3.38 (1H, dd, *J* 9.1 and 5.9 Hz, H-1), 3.40-3.45 (1H, m, H-17), 4.00 (1H, q, *J* 6.3 Hz, H-13), 4.62 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 4.62 (1H, d, *J* 11.4 Hz, CH<sub>2</sub>S), 5.12 (1H, d, *J* 9.5 Hz, H-9), 5.30-5.40 (3H, m, H-14, H-20, H-21), 5.53 (1H, dt, *J* 15.5 and 7 Hz, H-6), 5.57 (1H, dd, *J* 15.5 and 8.0 Hz, H-15), 6.01 (1H, d, *J* 15.6 Hz, H-7); *m/z* (EI) 711 (M<sup>+</sup>), 654 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 456, 301 and 227 (C<sub>13</sub>H<sub>27</sub>OSi); Observed (EI) M<sup>+</sup> 711.5555; C<sub>41</sub>H<sub>77</sub>D<sub>3</sub>O<sub>3</sub>SSi<sub>2</sub> requires *M* 711.5555.

Similar treatment of the minor, more polar, allylic alcohol afforded a 3:1 mixture of the diene (**36**) and its 6*Z*,8*E* diastereomer in 65% yield.

**(2*R*,6*E*,8*E*,10*R*,13*S*,14*E*,16*S*,17*R*,18*S*,20*E*) 13,17-Di(*t*-butyldimethylsilyloxy)-2,10,16,18-tetramethyl-8-(trideuteriomethyl)docosa-6,8,14,20-tetraen-1-ol (**37**):** Iodomethane (5 ml) was added to a mixture of the diene (**36**) (160 mg, 0.23 mmol), NaHCO<sub>3</sub> (60 mg, 0.67 mmol), acetone (10 ml) and water (0.5 ml) at room temperature. The mixture was heated at 50 °C for 20 h, the volatiles were removed by rotary evaporation and

then brine (50 ml) and ether (100 ml) were added. The organic phase was separated and the aqueous phase was extracted with ether (3 × 100 ml). The combined organic solvents were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (25% ether-petrol) yielded the *alcohol* (**37**) (140 mg, 96%) as a colourless oil;  $[\alpha]_D^{20}$  -6.2 (*c* 1.3, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3344, 2930, 2856, 2741, 2713, 2243, 2205, 2074, 1461, 1360, 1253, 1035, 1006 and 965 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.01 (3H, s, SiMe), 0.032 (3H, s, SiMe), 0.035 (3H, s, SiMe), 0.039 (3H, s, SiMe), 0.83 (3H, d, *J* 6.9 Hz, 18-Me), 0.88 (9H, s, <sup>t</sup>Bu), 0.91 (9H, s, <sup>t</sup>Bu), 0.92 (3H, d, *J* 6.8 Hz, 2-Me or 16-Me), 0.94 (3H, d, *J* 6.7 Hz, 2 or 16-Me), 0.98 (3H, d, *J* 7.0 Hz, 10-Me), 1.15 (1H, m, H-3), 1.22-1.31 (3H, m, H-3, H<sub>2</sub>-4), 1.35-1.49 (6H, m, H-2, H<sub>2</sub>-11, H<sub>2</sub>-12, OH), 1.57-1.61 (1H, m, H-18), 1.63 (3H, dd, *J* 6.7 and 0.9 Hz, H<sub>3</sub>-22), 1.74-1.78 (1H, m, H-19), 2.06-2.12 (3H, m, H<sub>2</sub>-5, H-19), 2.31-2.36 (1H, m, H-16), 2.39-2.44 (1H, m, H-10), 3.37-3.42 (1H, m, H-17), 3.40-3.45 (1H, m, H-1), 3.49-3.53 (1H, m, H-1), 4.00 (1H, q, *J* 6.3 Hz, H-13), 5.12 (1H, d, *J* 9.5 Hz, H-9), 5.29-5.40 (3H, m, H-14, H-20, H-21), 5.51 (1H, dt, *J* 15.6 and 7.1 Hz, H-6), 5.58 (1H, dd, *J* 15.2 and 7.8 Hz, H-15), 6.03 (1H, d, *J* 15.6 Hz, H-7); *m/z* (EI) 651 (M<sup>+</sup>), 594 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 566, 519, 462, 301, 228 and 227 (C<sub>13</sub>H<sub>27</sub>OSi); Observed (EI) M<sup>+</sup> 651.5520; C<sub>39</sub>H<sub>73</sub>D<sub>3</sub>O<sub>3</sub>Si<sub>2</sub> requires *M* 651.5521.

**(2E,4R,8E,10E,12R,15S,16E,18S,19R,20S,22E) Methyl 15,19-di(*t*-butyldimethylsilyloxy)-4,12,18,20-tetramethyl-2,4-di(trideuteriomethyl)tetracos-2,8,10,16,22-pentaenoate (38):** Tetra-*n*-propylammonium perruthenate (4 mg, 10 μmol) was added to a slurry of powdered 4 Å sieves in a solution of the alcohol (**37**) (130 mg, 0.2 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (40 mg, 0.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at room temperature. The mixture was stirred for 15 min, filtered through Florisil®, eluting with ethyl acetate, and the combined solvents were concentrated *in vacuo*. The crude (2R,6E,8E,10R,13S,14E,16S,17R,18S,20E) 13,17-di(*t*-butyldimethylsilyloxy)-2,10,16,18-tetramethyl-8-(trideuteriomethyl)docosa-6,8,14,20-tetraenal was used without further purification.

Trideuteriomethyl(α-carbomethoxymethyl)triphenylphosphonium iodide<sup>20</sup> (1.5 g, 2.94 mmol) was dissolved in CDCl<sub>3</sub> (10 ml) and washed with 1 N NaOH (15 ml) and the organic phase was dried (MgSO<sub>4</sub>) and filtered. The filtrate was added to the crude aldehyde and the solution was heated at reflux for 24 h. The solvent was concentrated *in vacuo*, the residue passed down a plug of silica (20% ether-petrol) and the eluant concentrated *in vacuo*. Chromatography of the residue on silica gel (3-5% ether-petrol) yielded the *ester* (**38**) (100 mg, 69%) as a colourless oil;  $[\alpha]_D^{20}$  -21.0 (*c* 0.8, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 2956, 2930, 2857, 2732, 2713, 2241, 2215, 2121, 2074, 1714, 1643, 1459, 1361, 1252, 1063, 1006 and 966 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.01 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.034 (3H, s, SiMe), 0.037 (3H, s, SiMe), 0.83 (3H, d, *J* 6.9 Hz, 20-Me), 0.88 (9H, s, <sup>t</sup>Bu), 0.91 (9H, s, <sup>t</sup>Bu), 0.93 (3H, d, *J* 6.7 Hz, 18-Me), 0.98 (3H, d, *J* 6.7 Hz, 4 or 12-Me), 1.0 (3H, d, *J* 6.6 Hz, 4 or 12-Me), 1.24-1.46 (8H, m, H<sub>2</sub>-5, H<sub>2</sub>-6, H<sub>2</sub>-13, H<sub>2</sub>-14), 1.56-1.61 (1H, m, H-20), 1.64 (3H, dd, *J* 5.6 and 0.6 Hz, H<sub>3</sub>-24), 1.71-1.76 (1H, m, H-21), 2.03-2.11 (3H, m, H<sub>2</sub>-7, H-21), 2.31-2.36 (1H, m, H-18), 2.40-2.44 (1H, m, H-12), 2.45-2.49 (1H, m, H-4), 3.40 (1H, dd, *J* 4.7 and 3.3 Hz, H-19), 3.73 (3H, s, CO<sub>2</sub>Me), 3.99 (1H, q, *J* 6.1 Hz, H-15), 5.11 (1H, d, *J* 9.5 Hz, H-11), 5.29-5.40 (3H, m, H-16, H-22, H-23), 5.49 (1H, dt, *J* 15.5 and 7.1 Hz, H-8), 5.57 (1H, dd, *J* 15.6 and 7.4 Hz, H-17), 6.00 (1H, d, *J* 15.7 Hz, H-9), 6.53 (1H, d, *J* 10.1 Hz, H-3); *m/z* (EI) 722 (M<sup>+</sup>), 707 (M<sup>+</sup>-Me), 665 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 637, 590, 533, 467, 301 and 227 (C<sub>13</sub>H<sub>27</sub>OSi); Observed (EI) M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub> 665.5285; C<sub>39</sub>H<sub>65</sub>D<sub>6</sub>O<sub>4</sub>Si<sub>2</sub> requires *M* 665.5268.

**(2E,4R,8E,10E,12R,15S,16E,18S,19R,20S,22E) S-[2-(Acetylamino)ethyl] 15,19-dihydroxy-4,12,18,20-tetramethyl-2,10-di(trideuteriomethyl)tetracos-2,8,10,16,22-pentaenethioate (6):** Lithium hydroxide monohydrate (50 mg, 1.3 mmol) was added to a solution of the ester (**38**) (90 mg, 0.13 mmol) in ethanol (4 ml) and water (0.5 ml). The mixture was stirred at 60 °C for 8 h and then at room temperature overnight. The

solvents were concentrated *in vacuo* and the residue was partitioned between 10% citric acid (30 ml) and CH<sub>2</sub>Cl<sub>2</sub> (30 ml). The organic layer was separated, the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 ml) and the combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to yield the crude (2*E*,4*R*,8*E*,10*E*,12*R*,15*S*,16*E*,18*S*,19*R*,20*S*,22*E*) 15,19-di(*t*-butyldimethylsilyloxy)-4,12,18,20-tetramethyl-2,4-di(trideuteriomethyl)tetracos-2,8,10,16,22-pentaenoic acid as a colourless oil.

A solution of the crude acid in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was stirred at 0 °C and DMAP (4 mg, 28 μmol) followed by *N*-acetylcysteamine<sup>16</sup> (27 mg, 0.23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) and DCC (52 mg, 0.25 mmol) were added. The mixture was stirred at 0 °C for 30 min, before being warmed to room temperature and stirred for a further 16 h. The precipitated DCU was removed by filtration, rinsed with ethyl acetate and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (ether) yielded (2*E*,4*R*,8*E*,10*E*,12*R*,15*S*,16*E*,18*S*,19*R*,20*S*,22*E*) *S*-[2-(acetylamino)ethyl] 15,19-di(*t*-butyldimethylsilyloxy)-4,12,18,20-tetramethyl-2,10-di(trideuteriomethyl)tetracos-2,8,10,16,22-pentaenethioate (81 mg, 82%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -34.7 (*c* 0.6, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3319, 2957, 2930, 2856, 2741, 2703, 2243, 2201, 2121, 2074, 1655, 1550, 1459, 1360, 1292, 1253, 1075 and 1006 cm<sup>-1</sup>; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.01 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.034 (3H, s, SiMe), 0.037 (3H, s, SiMe), 0.83 (3H, d, *J* 6.9 Hz, 20-Me), 0.88 (9H, s, <sup>1</sup>Bu), 0.91 (9H, s, <sup>1</sup>Bu), 0.94 (3H, d, *J* 6.7 Hz, 18-Me), 0.99 (3H, d, *J* 6.7 Hz, 12-Me), 1.02 (3H, d, *J* 6.7 Hz, 4-Me), 1.24-1.46 (8H, m, H<sub>2</sub>-5, H<sub>2</sub>-6, H<sub>2</sub>-13, H<sub>2</sub>-14), 1.56-1.61 (1H, m, H-20), 1.63 (3H, dd, *J* 6.2 and 0.7 Hz, H<sub>3</sub>-24), 1.71-1.77 (1H, m, H-21), 1.97 (3H, s, CH<sub>3</sub>CO), 2.03-2.10 (3H, m, H<sub>2</sub>-7, H-21), 2.30-2.35 (1H, m, H-18), 2.39-2.44 (1H, m, H-12), 2.50-2.56 (1H, m, H-4), 3.06 (2H, td, *J* 6.0 and 1.1 Hz, CH<sub>2</sub>S), 3.40 (1H, dd, *J* 4.7 and 3.3 Hz, H-19), 3.46 (2H, q, *J* 6.2 Hz, CH<sub>2</sub>N), 3.99 (1H, q, *J* 6.1 Hz, H-15), 5.12 (1H, d, *J* 9.5 Hz, H-11), 5.29-5.40 (3H, m, H-16, H-22, H-23), 5.49 (1H, dt, *J* 15.5 and 7 Hz, H-8), 5.58 (1H, ddd, *J* 15.7, 7.3 and 0.6 Hz, H-17), 5.86 (1H, br s, NH), 6.02 (1H, d, *J* 15.6 Hz, H-9), 6.53 (1H, d, *J* 9.9 Hz, H-3); *m/z* (FAB) 833 (MNa<sup>+</sup>), 753 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 679, 567, 227 (C<sub>13</sub>H<sub>27</sub>OSi) and 147; Observed (FAB) MNa<sup>+</sup> 832.6012; C<sub>46</sub>H<sub>79</sub>D<sub>6</sub>NNaO<sub>4</sub>SSi<sub>2</sub> requires *M* 832.6012; Found C, 68.39; H+D, 10.48; N, 1.76%; C<sub>46</sub>H<sub>79</sub>D<sub>6</sub>NO<sub>4</sub>SSi<sub>2</sub> requires C, 68.17; H+D, 10.57; N, 1.73%.

Dowex 50W-X8 (H<sup>+</sup>) ion exchange resin (excess) was added to a solution of the bis(silyl ether) (45 mg, 0.056 mmol) in methanol (2 ml) and stirred for 24 h. The resin was removed by filtration, rinsed with ethyl acetate (25 ml) and the combined filtrates were concentrated *in vacuo*. Chromatography of the residue on silica gel (60% ethyl acetate-petrol to ethyl acetate) yielded the C(19)-monosilyl ether (25 mg, 65%) and the diol (**6**) (8.5 mg, 26%) as viscous colourless oils. The C(19)-monosilyl ether was recycled (three times) to yield further diol (**19**) (21.5 mg, 66% overall yield) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -26.5 (*c* 0.5, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 3298, 3082, 2960, 2928, 2854, 2243, 2203, 2121, 2064, 1657, 1550, 1452, 1372, 1293, 1142 and 1076; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.86 (3H, d, *J* 6.8 Hz, 20-Me), 0.96 (3H, d, *J* 6.7 Hz, 12 or 18-Me), 0.97 (3H, d, *J* 6.7 Hz, 12 or 18-Me), 1.03 (3H, d, *J* 6.7 Hz, 4-Me), 1.30-1.38 (6H, m, H-5, H<sub>2</sub>-6, H<sub>2</sub>-13, H-14), 1.42-1.48 (1H, m, H-5), 1.49-1.55 (1H, m, H-14), 1.59-1.63 (1H, br s, OH), 1.64-1.68 (1H, m, H-20), 1.67 (3H, dd, *J* 5.9 and 0.9 Hz, H<sub>3</sub>-24), 1.70-1.75 (1H, br s, OH), 1.97 (3H, s, CH<sub>3</sub>CO), 1.95-2.01 (1H, m, H-21), 2.09-2.15 (3H, m, H<sub>2</sub>-7, H-21), 2.25-2.30 (1H, m, H-18), 2.41-2.47 (1H, m, H-12), 2.53-2.57 (1H, m, H-4), 3.07 (2H, t, *J* 6.5 Hz, CH<sub>2</sub>S), 3.22 (1H, dd, *J* 8 and 3.7 Hz, H-19), 3.46 (2H, q, *J* 6.1 Hz, CH<sub>2</sub>N), 4.00-4.04 (1H, m, H-15), 5.12 (1H, d, *J* 9.6 Hz, H-11), 5.16-5.47 (2H, m, H-22, H-23), 5.51 (1H, dt, *J* 15.6 and 7.1 Hz, H-8), 5.57 (2H, m, H-16, H-17), 5.88 (1H, br s, NH), 6.01 (1H, d, *J* 15.6 Hz, H-9), 6.54 (1H, d, *J* 9.9 Hz, H-3); *m/z* (CI, NH<sub>3</sub>) 581 (M<sup>+</sup>), 564 (MH<sup>+</sup>-H<sub>2</sub>O), 546 (MH<sup>+</sup>-2xH<sub>2</sub>O), 427, 333, 237, 95, 55 and 43 (CH<sub>3</sub>CO<sup>+</sup>); Observed (CI, NH<sub>3</sub>) M<sup>+</sup> 581.4380; C<sub>34</sub>H<sub>51</sub>D<sub>6</sub>NO<sub>4</sub>S requires *M* 581.4385.



**(2S,3S,5S,6R,7S) 8-Benzoyloxy-6-(*t*-butyldimethylsilyl)-1,1-dideuterio-2,3-epoxy-5,7-dimethyloctanol (39):** A suspension of activated powdered 4 Å molecular sieves (250 mg) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was stirred at -20 °C and a solution of L-(+)-diethyl tartrate (80 mg, 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added, followed by titanium(IV) isopropoxide (0.1 ml, 0.32 mmol). *t*-Butyl hydroperoxide (3.0 M in isooctane, 1.8 ml, 5.4 mmol) (dried over 4 Å molecular sieves) was added dropwise and the mixture was stirred at -20 °C for 30 min before the allylic alcohol (**14**) (1.0 g, 2.54 mmol, dried over 4 Å molecular sieves) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added. The reaction was stirred at -20 °C for 4 h and then quenched by the addition of a solution of citric acid monohydrate (64 mg) in 10% acetone-ether (25 ml). The mixture was allowed to warm to room temperature, stirred for 20 min, filtered through Celite<sup>®</sup>, rinsed with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 ml) and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (40% ether-petrol) yielded the epoxide (**39**) (0.65 g, 62%) as a colourless oil;  $[\alpha]_D^{20}$  -21.2 (*c* 1.0, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3434, 3062, 3026, 2954, 2927, 2854, 2204, 2092, 1604, 1493, 1459, 1380, 1252, and 1186 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.03 (6H, s, SiMe<sub>2</sub>), 0.88 (9H, s, <sup>t</sup>Bu), 0.93 (3H, d, *J* 6.8 Hz, 5-Me), 0.97 (3H, d, *J* 7.0 Hz, 7-Me), 1.40 (1H, ddd, *J* 15.7, 13.7 and 5.7 Hz, H-4), 1.63-1.66 (1H, m, H-4), 1.67 (1H, s, OH), 1.84-1.88 (1H, m, H-5), 1.92-1.96 (1H, m, H-7), 2.88 (1H, d, *J* 2.3 Hz, H-2), 2.95 (1H, dt, *J* 6.0 and 2.4 Hz, H-3), 3.29 (1H, dd, *J* 9.1 and 7.4 Hz, H-6), 3.54 (2H, m, 2 × H-8), 4.46 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 4.51 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 7.27-7.33 (5H, m, ArH); *m/z* (EI) 411 (MH<sup>+</sup>), 353 (M<sup>+</sup>-C<sub>4</sub>H<sub>9</sub>), 335, 321, 293 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Found C, 66.98; H+D, 9.92%; C<sub>23</sub>H<sub>38</sub>D<sub>2</sub>O<sub>4</sub>Si requires C, 67.27; H+D, 9.82%.

**[2R(S),3S,5R(S)] 2-(1-Benzoyloxy-2-propyl)-5-(2,2-dideuterio-1,2-dihydroxyethyl)-3-methyltetrahydrofuran (40):** A solution of TBAF (4 ml, 1 M in THF, 4 mmol) was added to the epoxide (**39**) (0.6 g, 1.46 mmol) in THF (4 ml). The mixture was heated at 60 °C for 4 h, cooled to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 ml) and washed with brine (50 ml). The organic phase was dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (75% ethyl acetate-petrol) yielded the diol (**40**) (0.33 g, 76%) as a colourless oil;  $[\alpha]_D^{20}$  -7.1 (*c* 1.1, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3292, 3022, 2964, 2918, 2883, 2854, 2219, 2104, 1492, 1448, 1379 and 1068 cm<sup>-1</sup>;  $\delta_H$  (270 MHz, CDCl<sub>3</sub>) 0.91 (3H, d, *J* 6.8 Hz, 3-Me), 0.95 (3H, d, *J* 6.9 Hz, 2'-Me), 1.73 (1H, dd, *J* 12.5 and 6.6 Hz, H<sub>α</sub>-4), 1.82-1.86 (1H, m, H-2'), 1.95-1.99 (1H, m, H<sub>β</sub>-4), 2.28-2.33 (1H, m, H-3), 2.43 (2H, br s, 2 × OH), 3.43 (1H, dd, *J* 9.0 and 6.6 Hz, H-1'), 3.57-3.64 (3H, m, H-2, H-1', H-1''), 4.06 (1H, dt, *J* 12.2 and 6.3 Hz, H-5), 4.49 (1H, d, *J* 12.2 Hz, CH<sub>2</sub>Ph), 4.53 (1H, d, *J* 12.0 Hz, CH<sub>2</sub>Ph), 7.26-7.34 (5H, m, ArH); *m/z* (EI) 296 (M<sup>+</sup>), 278 (M<sup>+</sup>-H<sub>2</sub>O), 267, 263, 251, 245 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>).

**[2R(S),3S,5R(S)] 2-(1-Benzoyloxy-2-propyl)-5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran (41):** Dibutyltin oxide (0.28 g, 1.22 mmol) was added to a solution of the diol (**40**) (0.3 g, 1.01 mmol) in methanol (10 ml) and the resulting mixture was heated at reflux for 45 min. After cooling to room temperature, triethylamine (1.15 ml, 3.7 mmol) and *p*-toluenesulfonyl chloride (1.28 g, 6.62 mmol) were added sequentially. The mixture was stirred at room temperature for 15 min, poured into saturated NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 50 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (35-60% ether-petrol) yielded [2R(S),3S,5R(S)] 2-(1-Benzoyloxy-2-propyl)-5-[2,2,-dideuterio-1-hydroxy-2(*p*-toluenesulfonyloxy)ethyl]-3-methyltetrahydrofuran (0.37 g, 81%) as a colourless oil;  $[\alpha]_D^{20}$  -20.8 (*c* 1.4, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3383, 2961, 2206, 1596, 1450, 1357, 1188 and 1176 cm<sup>-1</sup>;  $\delta_H$  (500 MHz, CDCl<sub>3</sub>) 0.88 (3H, d, *J* 7.0 Hz, 3-Me), 0.94 (3H, d, *J* 6.8 Hz, 2'-Me), 1.73 (1H, ddd, *J* 12.5, 6.7 and 0.5 Hz, H<sub>α</sub>-4), 1.77-1.81 (1H, m, H-2'), 1.96 (1H, ddd, *J* 15.8, 9.4 and 6.5 Hz, H<sub>β</sub>-4), 2.20 (1H, d, *J* 4.6 Hz, OH), 2.25 (1H, m, H-3),

2.44 (3H, s, MeAr), 3.34 (1H, dd,  $J$  8.8 and 7 Hz, H-1'), 3.53 (1H, dd,  $J$  10.3 and 3.9 Hz, H-2), 3.57 (1H, dd,  $J$  8.8 and 3.2 Hz, H-1'), 3.74 (1H, dd,  $J$  6.7 and 4.6 Hz, H-1''), 3.93 (1H, dt,  $J$  13.3 and 6.7 Hz, H-5), 4.44 (1H, d,  $J$  12.1 Hz, CH<sub>2</sub>Ph), 4.54 (1H, d,  $J$  12.1 Hz, CH<sub>2</sub>Ph), 7.26-7.35 (7H, m, ArH), 7.78 (2H, d,  $J$  8.3 Hz, ArH);  $m/z$  (EI) 450 (M<sup>+</sup>), 359 (M<sup>+</sup>-C<sub>7</sub>H<sub>7</sub>), 342, 329, 301 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Found C, 64.10; H+D, 7.35%; C<sub>24</sub>H<sub>30</sub>D<sub>2</sub>O<sub>6</sub>S requires C, 63.98; H+D, 7.16%.

A solution of the tosylate (370 mg, 0.82 mmol) in THF (3 ml) was added dropwise to Super-Deuteride<sup>®</sup> (3.5 ml, 1 M in THF, 3.5 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min and then quenched by the careful addition of brine (5 ml). The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 ml) and the organic phase was washed with brine (2 × 10 ml), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (50-60% ether-petrol) yielded [2*R*(*S*),3*S*,5*R*(*S*)] 2-(1-Benzyloxy-2-propyl)-5-(2,2,2-trideuterio-1-hydroxyethyl)-3-methyltetrahydrofuran (212 mg, 92%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -5.6 (*c* 1.2, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3438, 3027, 2961, 2925, 2873, 2225, 2123, 1602, 1494, 1362, 1310 and 1075 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.93 (3H, d,  $J$  7.0 Hz, 3-Me), 0.96 (3H, d,  $J$  6.7 Hz, 2'-Me), 1.56 (1H, dd,  $J$  11.5 and 5.6 Hz, H<sub>α</sub>-4), 1.83 (1H, d,  $J$  3.3 Hz, OH), 1.84-1.88 (1H, m, H-2'), 2.03 (1H, ddd,  $J$  16.4, 10.0 and 6.4 Hz, H<sub>β</sub>-4), 2.25-2.30 (1H, m, H-3), 3.44 (1H, dd,  $J$  8.9 and 7.1 Hz, H-1'), 3.63 (1H, dd,  $J$  10.4 and 4 Hz, H-2), 3.67 (1H, dd,  $J$  8.8 and 3.2 Hz, H-1'), 3.90 (1H, br s, H-1''), 3.98 (1H, ddd,  $J$  10.1, 6.4 and 3.7 Hz, H-5), 4.49 (1H, d,  $J$  12.1 Hz CH<sub>2</sub>Ph), 4.58 (1H d,  $J$  12.0, Hz CH<sub>2</sub>Ph), 7.17-7.31 (5H, m, ArH);  $m/z$  (EI) 282 (MH<sup>+</sup>), 281 (M<sup>+</sup>), 233 (M<sup>+</sup>-C<sub>2</sub>H<sub>2</sub>D<sub>3</sub>O), 127 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>).

A solution of the alcohol (206 mg, 0.73 mmol) in THF (3 ml) was added to a suspension of KH (180 mg of a 35% dispersion in oil, 1.5 mmol) in THF (2 ml) at 0 °C and stirred for 15 min. Iodomethane (0.2 ml, 3.2 mmol) was then added and the mixture was allowed to warm to room temperature. Stirring was continued for 3 h, before methanol (2 ml) was added. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml), washed with brine (2 × 25 ml) and the organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel (10% ether-petrol) yielded the *methyl ether* (**41**) (203 mg, 94%) as a colourless oil; [α]<sub>D</sub><sup>20</sup> -6.9 (*c* 1.0, CHCl<sub>3</sub>);  $\nu_{\max}$  (film) 3027, 2962, 2928, 2874, 2224, 2123, 1493, 1450, 1373, 1239 and 1198 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.91 (3H, d,  $J$  7.0 Hz, 3-Me), 0.96 (3H, d,  $J$  6.7 Hz, 2'-Me), 1.67 (1H, ddd,  $J$  12.6, 6.7 and 0.5 Hz, H<sub>α</sub>-4), 1.82-1.87 (1H, m, H-2'), 1.96 (1H, ddd,  $J$  15.9, 9.3 and 6.6 Hz, H<sub>β</sub>-4), 2.20-2.24 (1H, m, H-3), 3.30 (1H, d,  $J$  4.8 Hz, H-1''), 3.37 (3H, s, OMe), 3.41 (1H, dd,  $J$  9.0 and 7.4 Hz, H-1'), 3.58 (1H, dd,  $J$  10.4 and 3.9 Hz, H-2), 3.71 (1H, dd,  $J$  8.9 and 3.3 Hz, H-1'), 3.98 (1H, ddd,  $J$  11.6, 6.8 and 4.9 Hz, H-5), 4.49 (1H, d,  $J$  12.0 Hz CH<sub>2</sub>Ph), 4.56 (1H d,  $J$  12.0, Hz CH<sub>2</sub>Ph), 7.17-7.31 (5H, m, ArH);  $m/z$  (EI) 295 (M<sup>+</sup>), 263 (M<sup>+</sup>-CH<sub>3</sub>OH), 233 (M<sup>+</sup>-C<sub>3</sub>H<sub>4</sub>D<sub>3</sub>O), 127 and 91 (C<sub>7</sub>H<sub>7</sub><sup>+</sup>); Found C, 73.07; H+D, 9.62%; C<sub>18</sub>H<sub>25</sub>D<sub>3</sub>O<sub>3</sub> requires C, 73.18; H, 9.55%.

**[2*R*(*S*),3*S*,5*R*(*S*)] 2-(1-Hydroxy-2-propyl)-5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran (**42**):** 10% Palladium on carbon (50 mg) was added to a solution of the benzyl ether (**41**) (207 mg, 0.70 mmol) in methanol (5 ml) under an argon atmosphere. The flask was flushed with hydrogen and the mixture was stirred under a hydrogen atmosphere for 16 h. The flask was flushed with argon, the catalyst removed by filtration and the solvent concentrated *in vacuo*. Chromatography of the residue on silica gel (60% ether-petrol) yielded the alcohol (**42**) (143 mg, 100%) as a low melting solid; [α]<sub>S</sub>(20,D) +38.6 (*c* 0.9 CHCl<sub>3</sub>) (lit., <sup>18</sup> [α]<sub>D</sub><sup>20</sup> +38.8 [*c* 5.0, CHCl<sub>3</sub>], for the non-labelled material);  $\nu_{\max}$  (film) 3452, 2965, 2877, 2221, 2124, 1459, 1374, 1150, 1090, 1009, 965, 894 and 800 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 0.77 (3H, d,  $J$  6.8 Hz, 3-Me), 0.92 (3H, d,  $J$  7.1 Hz, 2'-Me), 1.65 (1H, dd,  $J$  12.7 and 6.7 Hz, H<sub>α</sub>-4), 1.82-1.88 (1H, m, H-2'), 1.97 (1H, ddd,  $J$  12.5, 9.6 and 6.6 Hz, H<sub>β</sub>-4), 2.27-2.33 (1H, m, H-3), 2.60 (1H, br s, OH), 3.34 (1H, d,  $J$  4.5 Hz, H-1''), 3.38

(3H, s, OMe), 3.53-3.57 (2H, m,  $2 \times \text{H-1}'$ ), 3.63 (1H, dd,  $J$  10.1 and 4.0 Hz, H-2), 3.99 (1H, ddd,  $J$  9.5, 6.4 and 5.0 Hz, H-5)

**[2R[2R,3S,5R(S)]] 2-[5-(2,2,2-Trideuterio-1-methoxy-ethyl)-3-methyltetrahydrofuran-2-yl]propanal (43)**: Tetra-*n*-propylammonium perruthenate (4 mg, 12  $\mu\text{mol}$ ) was added to a suspension of 4 Å molecular sieves (excess) in a solution of the alcohol (42) (50 mg, 0.24 mmol) and *N*-methylmorpholine-*N*-oxide monohydrate (54 mg, 0.47 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml). The mixture was stirred at room temperature for 1 h, then filtered through Florisil®, washing with  $\text{CH}_2\text{Cl}_2$ , and the combined solvents were concentrated *in vacuo* to afford the aldehyde (43), which was used without further purification.

**[2R[2R,3S,5R(S)]](-)-S-[2-(Acetylamino)ethyl] 2-[5-(1-methoxy-2,2,2-trideuterioethyl)-3-methyl-2-tetrahydrofuranyl]propanethioate (7)**: A solution of the aldehyde (43) (49 mg, 0.24 mmol) in *t*-butanol (2.5 ml) and water (2.5 ml) was stirred at room temperature and 2-methyl-2-butene (2 ml), potassium dihydrogen phosphate (0.42 g, 3.1 mmol) and sodium chlorite (90 mg, 1 mmol) were added. The mixture was stirred for 60 min, cooled to 0 °C, saturated sodium sulphite (3 ml) was added and the resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$  ( $4 \times 15$  ml). The combined organic solvents were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford crude [2R[2R,3S,5R(S)]] 2-[5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran-2-yl]propanoic acid which was used without further purification.

A solution of the crude acid in  $\text{CH}_2\text{Cl}_2$  (1 ml) was stirred at 0 °C and DMAP (4 mg, 0.032 mmol), followed by *N*-acetylcysteamine<sup>16</sup> (175 mg, 1.46 mmol, freshly prepared) in  $\text{CH}_2\text{Cl}_2$  (1 ml) and DCC (81 mg, 0.39 mmol) were added. The mixture was stirred at 0 °C for 30 min, before being warmed to room temperature and stirred for a further 16 h. Precipitated DCU was removed by filtration, the solids were rinsed with ethyl acetate and the combined organic solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (90% ethyl acetate-petrol to 1% methanol-ethyl acetate) and further purification by HPLC (25% IPA-petrol) yielded the thioester (7) (55 mg, 71%) as a viscous colourless oil;  $[\alpha]_{\text{D}}^{20}$  -0.48 ( $c$  0.83,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 3301, 2969, 2934, 2234, 1684, 1543, 1451, 1374, 1289 and 1196  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.92 (3H, d,  $J$  7.0 Hz, 3'-Me), 1.11 (3H, d,  $J$  6.9 Hz, 2-Me), 1.66 (1H, ddd,  $J$  12.5, 6.9 and 1 Hz,  $\text{H}_{\alpha-4'}$ ), 1.95 (3H, s,  $\text{CH}_3\text{CO}$ ), 2.00 (1H, ddd,  $J$  15.9, 9.1 and 6.7 Hz,  $\text{H}_{\beta-4'}$ ), 2.31 (1H, m, H-3'), 2.71-2.76 (1H, m, H-2), 3.06 (2H, m,  $\text{CH}_2\text{S}$ ), 3.31 (1H, d,  $J$  4.0 Hz, H-1''), 3.35 (3H, s, OMe), 3.36-3.50 (2H, m,  $\text{CH}_2\text{N}$ ), 3.98 (1H, dd,  $J$  10.2 and 4.1 Hz, H-2'), 4.06 (1H, ddd,  $J$  11.0, 6.9 and 4.1 Hz, H-5'), 5.78 (1H, broad s, NH);  $m/z$  (EI) 321 ( $\text{MH}^+$ ), 305, 288 ( $\text{M}^+ - \text{MeOH}$ ), 277 ( $\text{M}^+ - \text{C}_2\text{H}_3\text{O}$ ), 258 and 146.

**[2E,4S[2R,3S,5R(S)]] Methyl 4-[5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran-2-yl]pent-2-enoate (44)**: Carbomethoxymethylene triphenylphosphorane (240 mg, 0.67 mmol) was added to a solution of the crude aldehyde (43) (45 mg, 0.2 mmol) in  $\text{CHCl}_3$  (5 ml, filtered through basic alumina). The reaction mixture was heated at reflux for 16 h, cooled to room temperature, the solvent removed by rotary evaporation and the residue filtered through a silica plug (25% ether-petrol). The combined organic solvents were concentrated *in vacuo* and the residue was purified by chromatography on silica gel (50% ether-petrol) to yield the ester (44) (40 mg, 77%) as a colourless oil;  $[\alpha]_{\text{D}}^{20}$  -7.0 ( $c$  1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (film) 2967, 2881, 2227, 1724, 1657, 1434, 1382, 1314 and 1276  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 0.93 (3H, d,  $J$  7.0 Hz, 3'-Me), 0.99 (3H, d,  $J$  6.8 Hz, 4-Me), 1.66 (1H, ddd,  $J$  12.5, 6.9 and 1.4 Hz,  $\text{H}_{\alpha-4'}$ ), 2.03 (1H, ddd,  $J$  15.5, 8.8 and 6.7 Hz,  $\text{H}_{\beta-4'}$ ), 2.28-2.33 (1H, m, H-3'), 2.40-2.45 (1H, m, H-4), 3.34 (1H, d,  $J$  4.7 Hz, H-1''), 3.37 (3H, s, OMe), 3.62 (1H, dd,  $J$  9.5 and 4.2 Hz, H-2'), 3.72 (3H, s,  $\text{CO}_2\text{Me}$ ), 3.99 (1H, ddd,  $J$  11.6, 7.0 and 4.6 Hz, H-5'), 5.90

(1H, dd, *J* 15.8 and 1.2 Hz, H-2), 7.03 (1H, dd, *J* 15.8 and 7.4 Hz, H-3); *m/z* (EI) 259 (M<sup>+</sup>), 227 (M<sup>+</sup>-MeOH), 223, 197 (M<sup>+</sup>-C<sub>3</sub>H<sub>4</sub>D<sub>3</sub>O), 165 and 146.

**[2*E*,4*S*[2*R*,3*S*,5*R*(*S*)] S-[2-(Acetylamino)ethyl] 4-[5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran-2-yl]pent-2-enoate (8)**: Lithium hydroxide monohydrate (63 mg, 1.5 mmol) was added to a solution of the ester (**44**) (40 mg, 0.15 mmol) in ethanol (2 ml) and water (0.2 ml). The mixture was heated at 40 °C for 6 h after which the ethanol was removed by evaporation. The aqueous phase was acidified with 10% citric acid (10 ml) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 10 ml). The combined organic solvents were dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford crude [2*E*,4*S*[2*R*,3*S*,5*R*(*S*)] 4-[5-(2,2,2-trideuterio-1-methoxyethyl)-3-methyltetrahydrofuran-2-yl]pent-2-enoic acid which was used without further purification.

Freshly prepared *N*-acetylcysteamine<sup>16</sup> (32 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was added to a solution of the acid, DMAP (5 mg, 0.04 mmol) and DCC (62 mg, 0.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h before being allowed to warm to room temperature and stirred for a further 16 h. The precipitated DCU was removed by filtration, the solids were rinsed with ethyl acetate (3 × 10 ml) and the combined solvents were concentrated *in vacuo*. Chromatography of the residue on silica gel (50-80% ethyl acetate-petrol) yielded the *thioester* (**8**) (25 mg, 41%) as a colourless viscous oil; [α]<sub>D</sub><sup>20</sup> -2.7 (*c* 0.45, CHCl<sub>3</sub>); *v*<sub>max</sub> (film) 3303, 2923, 1656, 1397, 1461, 1373, 1288, 1084; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.93 (3H, d, *J* 6.9 Hz, 3'-Me), 1.02 (3H, d, *J* 7.7 Hz, 4-Me), 1.68 (1H, ddd, *J* 12.1, 7.0 and 1.3 Hz, H<sub>α</sub>-4'), 1.95 (3H, s, CH<sub>3</sub>CO), 2.00-2.24 (1H, m, H<sub>β</sub>-4'), 2.29-2.33 (1H, m, H-3'), 2.39-2.43 (1H, m, H-4), 3.07-3.13 (2H, m, CH<sub>2</sub>S), 3.33 (1H, d, *J* 4.4 Hz, H-1''), 3.37 (3H, s, OMe), 3.40-3.47 (2H, m, CH<sub>2</sub>N), 3.63 (1H, dd, *J* 9.5 and 4.2 Hz, H-2'), 3.95-4.01 (1H, m, H-5'), 5.88 (1H, broad s, NH), 6.22 (1H, dd, 14.8 and 0.8 Hz, H-2), 7.02 (1H, dd, 14.8 and 7.2 Hz, H-3); *m/z* (EI) 346 (M<sup>+</sup>), 330, 299, 284 (M<sup>+</sup>-C<sub>3</sub>H<sub>4</sub>D<sub>3</sub>O), 201, 88 and 43 (C<sub>2</sub>H<sub>3</sub>O).

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