Reversal of facial selectivity in a thia-Claisen rearrangement by incorporation of a vinylic bromine substituent

Adam R. Ellwood,[a] Anne J. Price Mortimer,[a] Jonathan M. Goodman[b] and Michael J. Porter*[a]

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Preparation of Allylic Bromides

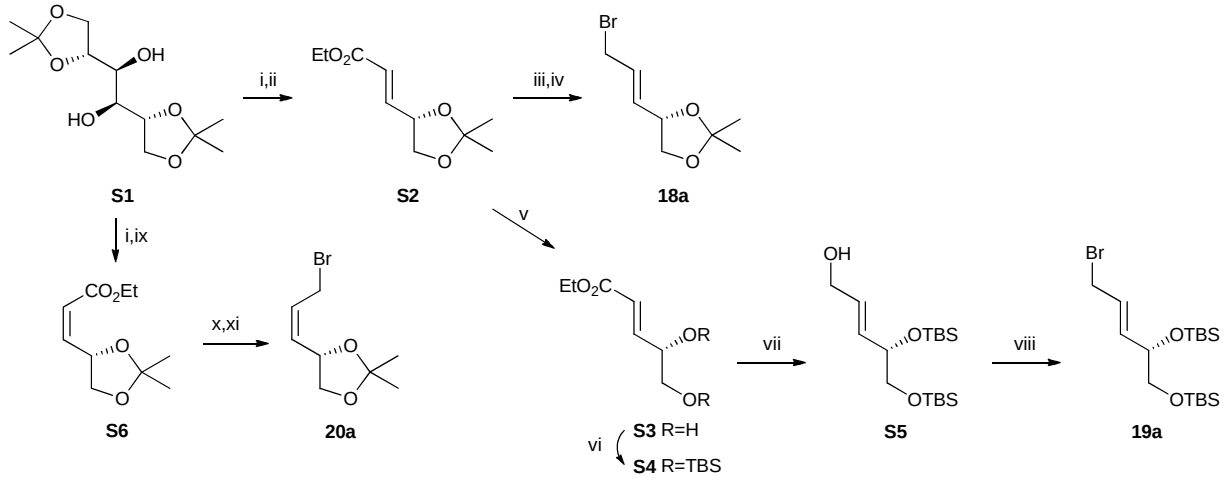
Allylic bromides **18a**–**20b** were all synthesised from 1,2:5,6-diisopropylidene-D-mannitol **S1** (Scheme S1).[1] Cleavage of the central vicinal diol and subsequent Wadsworth-Emmons olefination with triethyl phosphonoacetate were carried out in one pot[2] to give the (*E*)-unsaturated ester **S2** as a single geometrical isomer. DIBAL reduction to an allylic alcohol was followed by treatment with *N*-bromosuccinimide and triphenylphosphine, affording allylic bromide **18a**.[3]

Exchange of the acetonide protecting group for silyl ethers was carried out at the ester stage: unsaturated ester **S2** was treated with aqueous acetic acid to give diol **S3**. Reprotection with TBS-Cl afforded a bis-silyl ether **S4**, which was reduced with DIBAL as previously to give allylic alcohol **S5**. Bromination then led to allylic bromide **19a**.

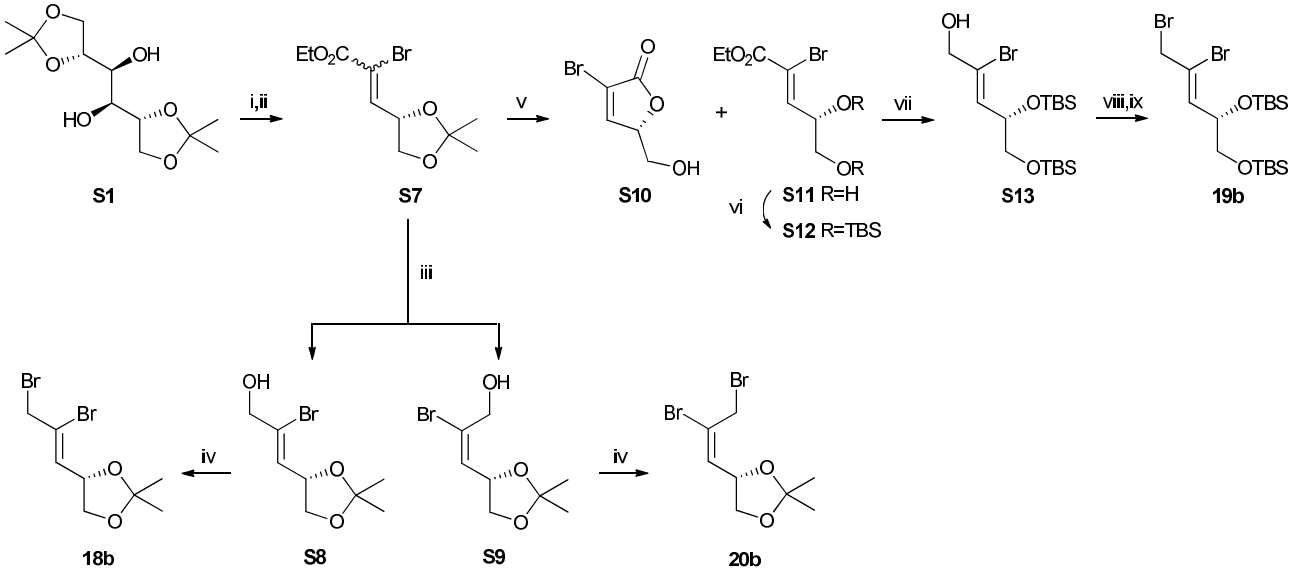
The *Z*-enoate **S6** could be prepared by following the oxidative cleavage of **S1** with a Wittig reaction in methanol.[4] Reduction and bromination proceeded as previously to give bromide **20a**.

Use of triethyl bromophosphonoacetate[5] in the olefination step gave the α-bromo-α,β-unsaturated ester **S7** as an inseparable 1.6:1 *Z*:*E* mixture (Scheme S2). Following DIBAL reduction, the geometrical isomers *Z*-**S8** and *E*-**S9** were separated and individually converted to the corresponding allylic bromides **18b** and **20b**.

Preparation of dibromide **19b** required some minor modifications to the synthetic sequence used previously; upon hydrolysis of the acetonide in **S7**, the *E*-diol spontaneously lactonised to give butenolide **S10**, which was readily separated from the *Z*-diol **S11**. Following silylation of this diol to give **S12**, attempts to use DIBAL reduction were thwarted by the unexpected loss of one of the silyl protecting groups. No such problems were encountered when $LiAlH_4$ was used as the reducing agent, and alcohol **S13** was obtained in 91% yield. Conversion of this alcohol to the corresponding bromide using NBS/PPh_3 was not a clean reaction; however a two-step sequence of sulfonylation with tosyl chloride followed by displacement of the allylic sulfonate using lithium bromide was successful in affording **19b**.



Scheme S1 *Reagents and conditions:* (i) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, 0 °C to rt; (ii) $EtO_2CCH_2PO(OEt)_2$, K_2CO_3, H_2O, 0 °C to rt; 96% (two steps); (iii) DIBAL, CH_2Cl_2, –78 °C, 77%; (iv) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 93%; (v) AcOH, H_2O, 98%; (vi) TBSCl, imidazole, CH_2Cl_2, 77%; (vii) DIBAL, CH_2Cl_2, hexane, –78 °C, 93%; (viii) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 71%; (ix) $EtO_2CCH{=}PPh_3$, MeOH, H_2O, –60 °C to 0 °C, 81% (two steps); (x) DIBAL, CH_2Cl_2, –78 °C, 89%; (xi) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 72%.



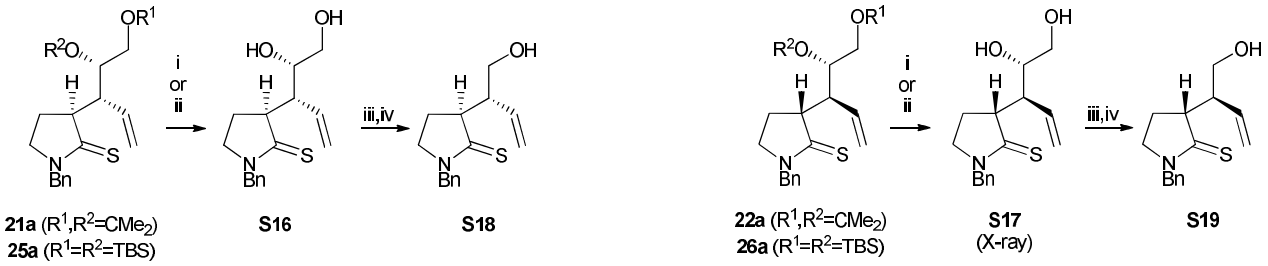
Scheme S2 *Reagents and conditions:* (i) $NaIO_4$, $NaHCO_3$, H_2O, 0 °C to rt; (ii) $EtO_2CCHBrPO(OEt)_2$, K_2CO_3, H_2O, 0 °C to rt; (iii) DIBAL, CH_2Cl_2, –78 °C, 41% **S8** + 25% **S9** (three steps); (iv) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 67% (**18b**), 54% (**20b**); (v) AcOH, H_2O, 35% **S10** + 54% **S11**; (vi) TBSCl, imidazole, CH_2Cl_2, 87%; (vii) $LiAlH_4$, THF, Et_2O, 0 °C 91%; (viii) TsCl, Et_3N, DMAP, CH_2Cl_2, 60%; (ix) LiBr, MeCN, 60%.

Stereochemical Assignment of Thiolactam Products

The stereochemical assignment of the thiolactam products was achieved through a combination of X-ray crystallography and chemical correlation. Initial deprotection of the acetonide-containing products **21a** and **22a** led to diols **S16** and **S17** respectively (Scheme S3). Diol **S17** proved to be crystalline, and its stereochemistry (and hence that of **22a**) was established by single-crystal X-ray diffraction.[11]

The stereochemistry of diol **S16** was correlated with that of **S17** through oxidative cleavage; thus cleavage of **S16** with silica-supported sodium periodate[6] and reduction of the aldehyde product gave alcohol **S18** while similar treatment of **S17** afforded the enantiomeric alcohol **S19**. As the stereostructure of **S19** could be deduced from the crystal structure of **S17**, the structure of **S18** and hence those of **S16** and **21a** must be as depicted in Scheme S3.

Desilylation of bis-silyl ethers **25a** and **26a** (AcOH, H_2O, 55 °C) led to diols **S16** and **S17** in 67% and 95% yield respectively, thus establishing the stereochemical correspondence between the acetonide and silyl ether series.



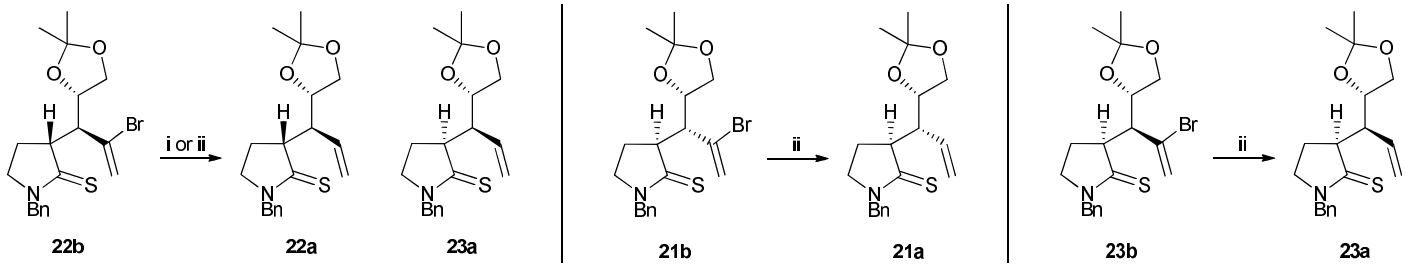
Scheme S3 *Reagents and conditions:* (i) AcOH, H_2O, 98% **S16** from **21a**, 92 % **S17** from **22a**; (ii) AcOH, THF, 50 °C, 93% **S16** from **25a**, 67% **S17** from **26a**; (iii) $NaIO_4$, SiO_2, CH_2Cl_2, H_2O; (iv) $NaBH_4$, EtOH, THF, 51% **S18**, 31% **S19** (two steps).

Having established the stereochemistry of the major products in the bromine-free series, we turned our attention to the compounds containing a vinyl bromide moiety. To this end, lactam **22b**, the major product from thia-Claisen rearrangement of bromide **18b**, was subjected to palladium-catalysed debromination with triethylammonium formate (Scheme S4).[7] Under these conditions significant epimerisation occurred and both **22a** and **23a** were obtained. While this did not allow unambiguous assignment of the stereostructure of **22b**, it implied that **22a** and **23a** differed at the configuration α- to the thiocarbonyl group. As the structure of **22a** had already been confirmed, this allowed assignment of the stereochemistry of **23a**.

Debromination of **22b** without concomitant epimerisation could be effected by carrying out the reduction with tributyltin hydride in the presence of $Pd(PPh_3)_4$.[8] Under these conditions, only **22a** was obtained, and the stereochemistry of **22b** was thereby confirmed. Likewise, debromination of **21b** with tin hydride afforded solely **21a**, and debromination of **23b** afforded solely **23a**, establishing the stereochemistry of these two brominated compounds.

The unambiguous elucidation of the stereochemistry of compounds **21b**, **22b** and **23b** means that the one remaining stereoisomer, compound **24b**, must have the stereochemistry depicted in Scheme 7.

Hence, through X-ray crystallography and a series of chemical correlations, the stereochemical assignments of all nine isolated thia-Claisen products were firmly established.



Scheme S4 *Reagents and conditions:* (i) Et_3N, HCOOH, $Pd(OAc)_2$, PPh_3, DMF, 65 °C, 35% **22a** + 21% **23a**; (ii) Bu_3SnH, $Pd(PPh_3)_4$, THF, reflux, 50% **22a** from **22b**; 60% **21a** from **21b**, 49% **23a** from **23b**.

Experimental Section

General Experimental Procedures

All non-aqueous reactions were carried out under argon with dry solvents. Dry THF, MeCN and CH_2Cl_2 were obtained by passage through activated alumina columns under nitrogen; pyridine, Et_3N and DMF were distilled from CaH_2 prior to use. Where petrol is specified this refers to the fraction that boils in the range 40–60 ˚C. Reagents were used as obtained from commercial sources. Flash column chromatography was carried out on BDH silica gel (Kieselgel 600). TLC was carried out on aluminium plates coated with 0.2mm silica gel 60 F_{254}, which were visualised either by UV light (254 nm), aq $KMnO_4$ or vanillin in ethanol. IR spectra were recorded as KBr discs, chloroform casts or neat solids or liquids using either a SHIMADZU FT-IR 8700 spectrometer or a PerkinElmer Spectrum 100 spectrometer fitted with an ATR accessory. Broad peaks are denoted using the abbreviation br. ^{1}H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on Bruker AMX-300, Bruker AVANCE-500 or Bruker AVANCE-600 spectrometers. Chemical shifts are reported in parts per million and are referenced to the residual solvent signal (^{1}H 7.26 ppm and ^{13}C 77.0 ppm). Coupling constants are given in Hz. Peaks are described using the following abbreviations: br, broad; app, apparent; s, singlet; d, doublet, t, triplet, q, quartet, m, multiplet. Mass spectra were recorded on a VG70-SE instrument or a Thermo MAT 900 instrument. Major peaks are listed with intensities quoted as percentages of the base peak. Melting points were measured on a Reichert-Jung THERMOVAR instrument or an Electrothermal 9100 apparatus and are uncorrected. Optical rotations were recorded on a POLAAR 2000 Automatic Polarimeter or a PerkinElmer Model 343 Polarimeter using the sodium D line (589 nm). $[\alpha]_D$ is given in units of 0.1 deg cm^2 g^{-1}; concentrations are quoted in g/100 mL.

Diacetonide **S1**,[1] esters **S2**[2b] and **S6**,[4b] bromide **18a**,[3] triethyl bromophosphonoacetate[5] and 1-benzylpyrrolidine-2-thione **13**[9] were prepared by literature procedures. Other starting materials and reagents were used as obtained from commercial sources.

Synthesis of Allylic Bromide Substrates

Ethyl (*S*,*E*)-4,5-dihydroxypent-2-enoate (S3)

A solution of ester **S2**[2b] (1.00 g, 5.0 mmol) in 3:2 AcOH/H_2O (50 mL) was stirred at room temperature for 24 h. Petrol (50 mL) was added, and the aqueous layer separated and concentrated *in vacuo*. The residue was dried by evaporation successively of EtOH (3 × 50 mL) and toluene (3 × 50 mL) to give diol **S3** (0.78 g, 98%) as a cloudy oil: R_f = 0.16 (petrol/EtOAc 1:1); $[\alpha]_D^{17}$ –8.0 (*c* 1.03, $CHCl_3$) [lit.[10] $[\alpha]_D^{25}$ –5.0 (*c* 0.5, $CHCl_3$)]; ν_{max}/cm^{-1} (film) 3398br (OH), 2937 (CH), 1715 (C=O), 1659 (C=C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (3H, t, *J* 7.2 Hz, CH_3), 2.34–2.89 (2H, br s, O*H*), 3.55 (1H, dd, *J* 11.2, 6.9 Hz) and 3.77 (1H, dd, *J* 11.2, 3.2 Hz, CH_2OH), 4.22 (2H, q, *J* 7.2 Hz, CH_3CH_2), 4.43 (1H, br s, C*H*OH), 6.14 (1H, dd, *J* 15.7, 1.7 Hz, EtO_2CCH=CH), 6.90 (1H, dd, *J* 15.7, 4.4 Hz, EtO_2CCH=C*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2 (*C*H_3), 60.7 (CH_3CH_2), 65.5 (*C*H_2OH), 71.7 (*C*HOH), 122.0 (EtO_2CCH=CH), 146.2 (EtO_2CCH=*C*H), 166.6 (*C*=O); *m*/*z* (CI$^+$) 161 (MH$^+$, 51%), 143 (MH$^+$–H_2O, 55), 115 (52), 97 (100); HRMS found 161.0803, $C_7H_{13}O_4$ (MH$^+$) requires 161.0808.

Ethyl (*S*,*E*)-4,5-di(*tert*-butyldimethylsilanyloxy)pent-2-enoate (S4)

To a solution of diol **S3** (5.00 g, 31.2 mmol) and imidazole (8.50 g, 125 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added *tert*-butylchlorodimethylsilane (10.4 g, 68.7 mmol) and the mixture stirred at room temperature for 4 h. The solution was diluted with H_2O (250 mL), the organic material extracted with CH_2Cl_2 (3 × 150 mL), washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 98:2) afforded ester **S4** (9.35 g, 77%) as a colourless oil: R_f = 0.45 (petrol/EtOAc 19:1); $[\alpha]_D^{19}$–25.2 (*c* 0.68, $CHCl_3$); ν_{max}/cm^{-1} (film) 2930 (CH), 1725 (C=O), 1661 (C=C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (6H, s), 0.06 (3H, s) and 0.07 (3H, s, 2 × Si(CH_3)$_2$), 0.87 (9H, s) and 0.89 (9H, s, 2 × C(CH_3)$_3$), 1.27 (3H, t, *J* 7.1 Hz, CH_3CH$_2$), 3.48 (1H, dd, *J* 9.9, 6.5 Hz) and 3.58 (1H, dd, *J* 9.9, 6.3 Hz, TBSOCH_2), 4.19 (2H, q, *J* 7.1 Hz, CH_3CH_2), 4.33 (1H, m, TBSOC*H*), 6.04 (1H, dd, *J* 15.6, 1.8 Hz, EtO_2CCH=CH), 7.01 (1H, dd, *J* 15.6, 4.2 Hz, EtO_2CCH=C*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.5, –5.3, –4.9 and –4.8 (2 × Si(*C*H_3)$_2$), 14.2 (*C*H_3CH$_2$), 18.2 and 18.3 (2 × *C*(CH$_3$)$_3$), 25.8 and 25.9 (2 × C(*C*H$_3$)$_3$), 60.3 (CH_3CH_2), 67.2 (TBSO*C*H$_2$), 72.7 (TBSO*C*H), 120.8 (EtO_2CCH=CH), 148.5 (EtO_2CCH=*C*H), 166.6 (O=*C*); *m*/*z* (ESI$^+$) 411 (MNa$^+$, 100%), 389 (MH$^+$, 50), 257 (64); HRMS found 389.2556, $C_{19}H_{41}O_4Si_2$ (MH$^+$) requires 389.2538.

(*S*,*E*)-4,5-Di(*tert*-butyldimethylsilanyloxy)pent-2-en-1-ol (S5)

To a solution of ester **S4** (600 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DIBAL (1.0 M in hexane, 3.9 mL, 3.9 mmol) dropwise, and the resulting mixture stirred for 4 h at –78 °C. After warming the reaction mixture to room temperature, MeOH (5 mL), Et_2O (5 mL) and sat. aq. potassium sodium tartrate (10 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (5 mL) and the organic material extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 19:1) provided alcohol **S5** (500 mg, 93%) as a colourless oil: R_f = 0.23 (petrol/EtOAc 9:1); $[\alpha]_D^{19}$ –16.8 (*c* 0.63, $CHCl_3$); ν_{max}/cm^{-1} (film) 3332br (OH), 2929 (CH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (6H, s), 0.05 (3H, s) and 0.07 (3H, s, 2 × Si(CH_3)$_2$), 0.88 (9H, s) and 0.89 (9H, s, 2 × C(CH_3)$_3$), 1.41 (1H, br s, O*H*), 3.44 (1H, dd, *J* 10.0, 5.9 Hz) and 3.53 (1H, dd, *J* 10.0, 6.5 Hz, TBSOCH_2), 4.14–4.21 (3H, m, TBSOC*H* and CH_2OH), 5.72 (1H, dd, *J* 15.5, 3.8 Hz, $HOCH_2CH$=C*H*) 5.87 (1H, dt, *J* 15.5, 5.2 Hz, $HOCH_2C$*H*=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.4, –5.2 and –4.6 (2 × Si(*C*H_3)$_2$), 18.3 and 18.4 (2 × *C*(CH$_3$)$_3$), 25.9 and 26.0 (2 × C(*C*H$_3$)$_3$), 63.2 (*C*H_2OH), 68.0 (TBSO*C*H$_2$), 73.4 (TBSO*C*H), 129.6 ($HOCH_2C$H=CH), 132.3 ($HOCH_2CH$=*C*H); *m*/*z* (ESI$^+$) 369 (MNa$^+$, 100%), 215 (17); HRMS found 369.2268, $C_{17}H_{38}O_3Si_2Na$ (MNa$^+$) requires 369.2252.

(*S*,*E*)-1-Bromo-4,5-di(*tert*-butyldimethylsilanyloxy)pent-2-ene (19a)

To a stirred solution of alcohol **S5** (2.85 g, 8.2 mmol) in CH_2Cl_2 (80 mL) at 0 °C, triphenylphosphine (2.37 g, 9.0 mmol) was added, followed by *N*-bromsuccinimide (1.54 g, 8.6 mmol) portionwise over several minutes. The solution was stirred at room temperature for 3 h, then quenched with H_2O (100 mL). The organic material was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts

washed with brine (170 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 96:4) afforded bromide **19a** (2.37 g, 71%) as a colourless oil: R_f = 0.71 (petrol/EtOAc 19:1); $[\alpha]_D^{19}$ –18.7 (*c* 0.73, $CHCl_3$); ν_{max}/cm^{-1} (film) 2929 (CH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (3H, s), 0.07 (6H, s) and 0.08 (3H, s, 2 × Si(C*H*$_3$)$_2$), 0.89 (9H, s) and 0.90 (9H, s, 2 × C(C*H*$_3$)$_3$), 3.42 (1H, dd, *J* 9.9, 6.2 Hz) and 3.54 (1H, dd, *J* 9.9, 6.2 Hz, TBSOC*H*$_2$), 3.96 (2H, d, *J* 7.2 Hz, BrC*H*$_2$), 4.19 (1H, m, TBSOC*H*), 5.75 (1H, dd, *J* 15.3, 5.0 Hz, BrCH$_2$CH=C*H*), 5.91 (1H, m, BrCH$_2$C*H*=CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ –5.3, –5.3, –4.7 and –4.6 (2 × Si(*C*H$_3$)$_2$), 18.3 and 18.4 (2 × *C*(CH$_3$)$_3$), 25.9 and 26.0 (2 × C(*C*H$_3$)$_3$), 32.5 (Br*C*H$_2$), 67.7 (TBSO*C*H$_2$), 73.0 (TBSO*C*H), 126.7 (BrCH$_2$*C*H=CH), 136.0 (BrCH$_2$CH=*C*H); *m/z* (EI$^+$) 431/433 (MNa$^+$, 12/13%), 351/353 (40/40), 330 (38), 329 (84), 307 (45), 197 (56), 189 (61), 177 (81), 176 (100); HRMS found 431.1418, $C_{17}H_{37}{}^{79}BrO_2Si_2Na$ (MNa$^+$) requires 431.1413.

(*S*,*Z*)-4-(3-Bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (20a)

To a solution of ester **S6**[4b] (2.46 g, 12.3 mmol) in CH_2Cl_2 (40 mL) at –78 °C was added DIBAL (1.2 M in toluene, 25.5 mL, 30.7 mmol) dropwise, and the solution stirred for 2 h at –78 °C. After warming the reaction mixture to room temperature, MeOH (80 mL), Et_2O (100 mL) and sat. aq. potassium sodium tartrate (100 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (60 mL) and the organic material extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a cloudy liquid. Purification by flash chromatography (SiO_2, petrol/EtOAc 8:2–7:3) afforded (*S*,*Z*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (1.73 g, 89%) as a colourless liquid. R_f = 0.32 (petrol/EtOAc 1:1); $[\alpha]_D^{20}$ +12.8 (*c* 1.08, $CHCl_3$) [lit.[2a] $[\alpha]_D$ –16.5 (*c* 0.22, $CHCl_3$) for enantiomer]; ν_{max}/cm^{-1} ($CDCl_3$ cast) 3395 (OH), 2987, 2936, 2873 (CH), 1647 (C=C); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (3H, s) and 1.42 (3H, s, C(C*H*$_3$)$_2$), 1.85 (1H, br s, O*H*), 3.58 (1H, t, *J* 7.9 Hz) and 4.10 (1H, dd, *J* 8.2, 6.2 Hz, OCHC*H*$_2$O), 4.20 (1H, ddd, *J* 13.1, 6.1, 1.1 Hz) and 4.31 (1H, ddd, *J* 13.1, 7.1, 1.2 Hz, C*H*$_2$OH), 4.87 (1H, tdd, *J* 7.8, 6.2, 1.2 Hz, OC*H*), 5.58 (1H, ddt, *J* 11.1, 8.2, 1.3 Hz, HOCH$_2$CH=C*H*), 5.85 (1H, dddd, *J* 11.1, 7.1, 6.1, 1.3 Hz HOCH$_2$C*H*=CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.9 and 26.7 (C(*C*H$_3$)$_2$), 58.7 (*C*H$_2$OH), 69.5 (O*C*H$_2$), 71.2 (O*C*H), 109.5 (*C*Me$_2$), 129.6 (HOCH$_2$CH=*C*H), 133.1 (HOCH$_2$*C*H=CH). *m/z* (CI$^+$) 159 (MH$^+$, 85%), 143 (52), 137 (64), 111 (65), 101 (47), 84 (50), 83 (100); HRMS found 159.1018, $C_8H_{15}O_3$ (MH$^+$) requires 159.1021.

To a stirred solution of this alcohol (1.61 g, 10.2 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added triphenylphosphine (2.94 g, 11.2 mmol), followed by *N*-bromosuccinimide (1.90 g, 10.6 mmol) portionwise over a few minutes. The solution was stirred at room temperature for 3 h. H_2O (80 mL) was added and the organic material extracted with CH_2Cl_2 (3 × 80 mL). The combined extracts were washed with brine (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 85:15) afforded bromide **20a** (1.63 g, 72%) as a colourless oil. R_f = 0.32 (petrol/EtOAc 4:1); $[\alpha]_D^{20}$ –146.9 (*c* 0.98, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast) 2986, 2936, 2873 (CH), 1056; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (3H, s) and 1.44 (3H, s, C(C*H*$_3$)$_2$), 3.61 (1H, t, *J* 8.0 Hz, OC*H*H), 3.99 (1H, dd, *J* 10.4, 7.9 Hz) and 4.09 (1H, ddd, *J* 10.4, 9.3, 0.8 Hz, CH_2Br), 4.16 (1H, dd, *J* 8.3, 6.2 Hz, OCH*H*), 4.90 (1H, m, OC*H*), 5.60 (1H, dd, *J* 10.6, 8.4 Hz, BrCH$_2$CH=C*H*), 5.94 (1H, dddd, *J* 10.6, 9.3, 7.9, 1.1 Hz, BrCH$_2$C*H*=CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.9 (*C*H$_3$CCH$_3$), 25.9 (*C*H$_2$Br), 26.7 (CH$_3$C*C*H$_3$), 69.1 (O*C*H$_2$), 71.2 (O*C*H), 109.7 (*C*Me$_2$), 129.3 (BrCH$_2$*C*H=CH), 132.2 (BrCH$_2$CH=*C*H); *m/z* (CI$^+$) 221/223 (MH$^+$, 6/5%), 142 (83), 112 (32), 84 (100); HRMS found 221.0181, $C_8H_{14}{}^{79}BrO_2$ (MH$^+$) requires 221.0177.

Ethyl (*S*)-2-bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-enoate (S7)

To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**S1**)[13] (2.49 g, 9.50 mmol) in aq. $NaHCO_3$ (5% *w*/*v*, 25 mL) at 0 °C was added a solution of $NaIO_4$ (2.48 g, 11.4 mmol) in H_2O (25 mL). After stirring for 1 h at room temperature, the solution was cooled to 0 °C. Triethyl bromophosphonoacetate[5] (12.0 g, 39.4 mmol) and aq. K_2CO_3 (6M, 70 mL) were added successively and the reaction was stirred overnight at room temperature. After addition of H_2O (50 mL) to dissolve residual solids, the organic material was extracted with CH_2Cl_2 (3 × 150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 98:2) afforded ester **S7** as an inseparable 3:2 mixture of *Z* and *E* esters (4.57g, 86%), as a colourless oil. R_f = 0.27 (petrol/EtOAc 19:1); ν_{max}/cm^{-1} ($CDCl_3$ cast) 2985, 2935, 1783, 1729 (C=O), 1631(C=C); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31–1.41 (3H, m, C*H*$_3$CH$_2$), 1.35 (0.4 × 3H, s) and 1.39 (0.4 × 3H, s, C(C*H*$_3$)$_2$ of *E*-isomer), 1.42 (0.6 × 3H, s) and 1.47 (0.6 × 3H, s, C(C*H*$_3$)$_2$ of *Z*-isomer), 3.70–3.76 (1H, m) and 4.24–4.36 (3H, m, OC*H*$_2$CH and OC*H*$_2$CH$_3$), 4.97 (0.6 × 1H, q, *J* 6.7 Hz, OC*H* of *Z*-isomer), 5.24 (0.4 × 1H, q, *J* 7.3 Hz, OC*H* of *E*-isomer), 6.82 (0.4 × 1H, d, *J* 6.9 Hz, C(Br)=C*H* of *E*-isomer), 7.38 (0.6 × 1H, d, *J* 6.7 Hz, C(Br)=C*H* of *Z*-isomer); *m/z* (CI$^+$) 279/281 (MH$^+$, 8/5%), 263/265 (100/100); HRMS found 279.0229, $C_{10}H_{16}{}^{79}BrO_4$ (MH$^+$) requires 279.0226.

(*S*,*Z*)-2-Bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (S8) and (*S*,*E*)-2-Bromo-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (S9)

To a solution of the *E*- and *Z*-esters (**S7**) from the preceding procedure (3.15 g, 11.3 mmol) in CH_2Cl_2 (30 mL) at –78 °C was added DIBAL (1.2 M in toluene, 22.7 mL, 27.2 mmol) dropwise, and the solution stirred for 6 h at –78 °C. After allowing the reaction mixture to warm to room temperature, MeOH (50 mL), Et_2O (60 mL) and sat. aq. potassium sodium tartrate (60 mL) were added successively, and the mixture stirred for 1 h. The solution was diluted with H_2O (50 mL), then the organic material was extracted with EtOAc (3 × 50 mL), washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 95:5–90:10) afforded *Z*-alcohol **S8** (1.35 g, 41% from **S1**) and *E*-alcohol **S9** (0.81 g, 25% from **S1**) as colourless oils:

Z-Alcohol **S8**: R_f = 0.43 (petrol/EtOAc 7:3); $[\alpha]_D^{20}$ +10.2 (*c* 0.12, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3439br (OH), 2987, 2929, 2869 (CH), 1667 (C=C); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (3H, s) and 1.44 (3H, s, C(C*H*$_3$)$_2$), 3.65 (1H, dd, *J* 8.3, 7.1 Hz) and 4.12 (1H, dd, *J* 8.3, 6.3 Hz, OC*H*$_2$), 4.25 (2H, s, C*H*$_2$OH), 4.92 (1H, td, *J* 7.1, 6.3 Hz, OC*H*), 6.20 (1H, d, *J* 7.1 Hz, C(Br)=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7 and 26.6 (C(*C*H$_3$)$_2$), 67.8 (O*C*H$_2$), 68.6 (*C*H$_2$OH), 75.2 (O*C*H), 109.7 (*C*(CH$_3$)$_2$) 128.1 (C(Br)=*C*H), 129.0 (*C*(Br)=CH); *m/z* (CI$^+$) 254/256 (MNH$_4^+$, 12/11%), 237/239 (MH$^+$, 56/52) 223 (23), 221 (30), 198 (100), 196 (98); HRMS found 237.0119, $C_8H_{14}{}^{79}BrO_3$ (MH$^+$) requires 237.0121.

E-Alcohol **S9**: R_f = 0.33 (petrol/EtOAc 7:3); $[\alpha]_D^{22}$ +12.1 (*c* 1.34, $CHCl_3$); ν_{max}/cm^{-1} (CH_2Cl_2 cast) 3421 br (OH), 2976, 2903 (CH), 1665 (C=C); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36 (3H, s) and 1.40 (3H, s, C(C*H*$_3$)$_2$), 3.62 (1H, dd, *J* 8.4, 7.1 Hz) and 4.10 (1H, dd, *J* 8.4, 6.3

Hz, OCH_2), 4.40 (2H, s, CH_2OH), 4.83 (1H, ddd, *J* 8.2, 7.1, 6.3 Hz, OC*H*), 6.05 (1H, d, *J* 8.2 Hz, C(Br)=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8 and 26.7 (C(CH_3)$_2$), 63.8 (*C*H$_2$OH), 69.1 (O*C*H$_2$), 72.5 (O*C*H), 109.9 (*C*(Me)$_2$), 129.6 (*C*Br) 132.3 (C(Br)=*C*H); *m/z* (CI^+) 237/239 (MH^+, 23/21%), 221/223 (41/38) 181 (100), 179 (97); HRMS found 237.0117, $C_8H_{14}{}^{79}BrO_3$ (MH^+) requires 237.0121.

(*S*,*Z*)-4-(2,3-Dibromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (18b)

To a solution of alcohol **S8** (0.95 g, 4.0 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added triphenylphosphine (1.16 g, 4.4 mmol), followed by *N*-bromosuccinimide (0.75 g, 4.2 mmol) portionwise over several minutes. The solution was stirred at room temperature for 3 h. The reaction was quenched with H_2O (50 mL) and the organic material extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 92:8) afforded bromide **18b** (0.80 g, 67%) as a yellow oil: R_f = 0.47 (petrol/EtOAc 9:1); $[\alpha]_D^{22}$ +22.5 (*c* 1.2, $CHCl_3$) ν_{max}/cm^{-1} ($CHCl_3$ cast) 2986, 2932 (CH), 1647 (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (3H, s) and 1.45 (3H, s, C(CH_3)$_2$), 3.67 (1H, dd, *J* 8.4, 6.8 Hz, OC*H*H), 4.21 (1H, d, *J* 11.7 Hz) and 4.24 (1H, d, *J* 11.7 Hz, CH_2Br), 4.25 (1H, dd, *J* 8.4, 6.4 Hz, OCH*H*), 4.86 (1H, q, *J* 6.9 Hz, OC*H*), 6.29 (1H, d, *J* 7.1 Hz, C(Br)=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.6 and 26.6 (C(*C*H$_3$)$_2$), 64.6 (*C*H$_2$Br), 68.4 (O*C*H$_2$), 75.7 (O*C*H), 110.0 (*C*(Me)$_2$), 124.2 (*C*Br), 132.7 (C(Br)=*C*H); *m/z* (CI^+) 299/301/303 (MH^+, 28/52/22%), 241/243/245 ([MH–Me$_2$CO]$^+$, 27/53/23), 219/221 ([MH–HBr]$^+$, 27/27), 189/191 (50/50), 161/163 (100/99); HRMS found 298.9289, $C_8H_{13}{}^{79}Br_2O_2$ (MH^+) requires 298.9282.

(*S*,*E*)-4-(2,3-Dibromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (20b)

To a stirred solution of alcohol **S9** (0.43 g, 1.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added triphenylphosphine (0.52 g, 2.0 mmol), followed by *N*-bromosuccinimide (0.34 g, 1.9 mmol) portionwise over a few minutes. The solution was stirred at room temperature for 24 h. The reaction was quenched with H_2O (30 mL), and the organic material extracted with CH_2Cl_2 (3 × 30 mL), washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/Et_2O 97:3) afforded bromide **20b** (0.29 g, 54%) as a colourless oil: R_f = 0.33 (petrol/EtOAc 7:3); $[\alpha]_D^{20}$ –4.0 (*c* 0.43, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 2986, 2933, 2873 (CH), 1638 (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (3H, s) and 1.44 (3H, s, C(CH_3)$_2$), 3.69 (1H, dd, *J* 8.5, 7.0 Hz) and 4.18 (1H, dd, *J* 8.5, 6.2 Hz, OCH_2), 4.23 (1H, d, J 11.3 Hz) and 4.46 (1H, d, *J* 11.3 Hz, CH_2Br), 4.75 (1H, ddd, *J* 8.3, 7.0, 6.2 Hz, OC*H*) 6.08 (1H, d, *J* 8.3 Hz, C(Br)=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7 and 26.6 (C(*C*H$_3$)$_2$), 32.2 (*C*H$_2$Br), 68.5 (O*C*H$_2$), 72.7 (O*C*H), 110.1 (*C*(Me)$_2$), 124.2 (*C*(Br)=CH) 134.8 (C(Br)=*C*H); *m/z* (CI^+) 299/301/303 (MH^+, 17/27/15%), 283/285/287 (26/48/25), 241/243/245 ([MH–Me$_2$CO]$^+$, 50/95/45), 227/229/231 (63/100/47); HRMS found 298.9279, $C_8H_{13}{}^{79}Br_2O_2$ (MH^+) requires 298.9282.

(*S*)-3-Bromo-5-hydroxymethyl-5(*H*)furan-2-one (S10) and ethyl (*S*,*Z*)-2-bromo-4,5-dihydroxypent-2-enoate (S11)

Ester **S7** (mixture of isomers, 3.20 g, 11.5 mmol) and aq. AcOH (60% *v*/*v*, 60 mL) were stirred at room temperature for 2 d. Petrol (60 mL) was added, then the aqueous layer was separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 60 mL) and toluene (3 × 60 mL), and purification by flash chromatography (SiO_2, petrol/Et_2O 40:60) afforded butenolide **S10** (0.76 g, 35%) as a yellow oil and diol **S11** (1.49 g, 6.2 mmol, 54%) as a colourless oil.

Butenolide **S10**: R_f = 0.20 (petrol/Et_2O 2:8); $[\alpha]_D^{20}$ –51.5 (*c* 0.20, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3400br (OH), 2930 (CH), 1756 (C=O), 1607 (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.83 (1H, dd, *J* 12.3, 4.8 Hz) and 3.99 (1H, dd, *J* 12.3, 3.9 Hz, CH_2), 5.08 (1H, ddd, *J* 4.8, 3.9, 1.8 Hz, CH$_2$C*H*), 7.54 (1H, d, *J* 1.8 Hz, CBr=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.2 (*C*H$_2$), 83.0 (CH$_2$*C*H), 114.4 (*C*Br), 149.7 (CBr=*C*H) 168.2 (*C*=O); *m/z* (CI^+) 193/195 (MH^+, 46/46%), 175/177 ([MH–H_2O]$^+$, 100/99); HRMS found 192.9495, $C_5H_6{}^{79}BrO_3$ (MH^+) requires 192.9500.

Diol **S11**: R_f = 0.23 (petrol/Et_2O 2:8); $[\alpha]_D^{20}$ +27.0 (*c* 0.91, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3397br (OH), 2984 (CH), 1713 (C=O), 1627 (C=C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (3H, t, *J* 7.2 Hz, CH_3), 3.65 (1H, dd, *J* 11.2, 7.2 Hz) and 3.83 (1H, dd, *J* 11.2, 3.2 Hz, CH_2OH), 4.30 (2H, q, *J* 7.2 Hz, CH$_3$CH_2), 4.71 (1H, td, *J* 7.2, 3.2 Hz, C*H*OH), 7.30 (1H, d, *J* 7.4 Hz, CBr=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (*C*H$_3$), 62.9 (CH$_3$*C*H$_2$), 64.0 (*C*H$_2$OH), 72.5 (*C*HOH), 117.3 (*C*Br), 143.2 (CBr=*C*H), 161.8 (*C*=O); *m/z* (CI^+) 239/241 (MH^+, 8/7%), 221/223 ([MH–H_2O]$^+$, 100/97), 193/195 ([MH–EtOH]$^+$, 48/45), 175/177 ([MH–H_2O–EtOH]$^+$, 94/93); HRMS found 238.9915, $C_7H_{12}{}^{79}BrO_4$ (MH^+) requires 238.9919.

Ethyl (*S*,*Z*)-2-bromo-4,5-di(*tert*-butyldimethylsilanyloxy)pent-2-enoate (S12)

To a solution of diol **S11** (1.23 g, 5.1 mmol) and imidazole (1.75 g, 25.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added *tert*-butylchlorodimethylsilane (2.33 g, 15.4 mmol) and the solution stirred for 3 h at room temperature. The reaction was quenched with H_2O (50 mL) and the organic material extracted with CH_2Cl_2 (3 × 50 mL), then the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 95:5) afforded ester **S12** (2.09 g, 87%) as a colourless oil: R_f = 0.38 (petrol/EtOAc 19:1); $[\alpha]_D^{20}$ +1.9 (*c* 0.57, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 2955, 2929, 2886, 2858 (CH), 1723 (C=O), 1630 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (3H, s), 0.07 (3H, s), 0.07 (3H, s) and 0.10 (3H, s, 2 × Si(CH_3)$_2$), 0.89 (18H, s, 2 × C(CH_3)$_3$), 1.34 (3H, t, *J* 7.1 Hz, CH_3CH$_2$), 3.60 (1H, dd, *J* 10.3, 4.9 Hz) and 3.66 (1H, dd, *J* 10.3, 6.3 Hz, TBSOCH_2), 4.28 (1H, dq, *J* 10.7, 7.1 Hz) and 4.31 (1H, dq, *J* 10.7, 7.1 Hz, CH$_3$CH_2), 4.65 (1H, ddd, *J* 8.0, 6.3, 4.9 Hz, TBSOC*H*), 7.15 (1H, d, *J* 8.0 Hz, CBr=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4, –5.3 and –4.7 (2 × Si(*C*H$_3$)$_2$), 14.1 (*C*H$_3$CH$_2$), 18.2 and 18.4 (2 × *C*(CH$_3$)$_3$), 25.8, 25.9 (2 × C(*C*H$_3$)$_3$), 62.6 (CH$_3$*C*H$_2$), 66.1 (TBSO*C*H$_2$), 74.0 (TBSO*C*H), 115.8 (*C*Br) 145.8 (CBr=*C*H), 162.1 (*C*=O). *m/z* (CI^+) 467/469 (MH^+, 2/3%), 335/337 (100/99); HRMS found 467.1637, $C_{19}H_{40}{}^{79}BrO_4Si_2$ (MH^+) requires 467.1649.

(*S*,*Z*)-2-Bromo-4,5-di(*tert*-butyldimethylsilanyloxy)pent-2-en-1-ol (S13)

To a solution of $LiAlH_4$ (1M solution in THF, 1.2 mL, 1.2 mmol) in Et_2O (15 mL) at 0 °C was added a solution of ester **S12** (500 mg, 1.1 mmol) in Et_2O (15 mL) over a few minutes. The solution was stirred at 0 °C for 15 minutes, then H_2O (20 mL) was added and the mixture stirred for a further 30 minutes. The organic material was extracted with Et_2O (3 × 200 mL), washed with H_2O (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo* to afford alcohol **S13** (403 mg, 91%) as a pale yellow oil: R_f = 0.58 (petrol/EtOAc 4:1); $[\alpha]_D^{20}$ +0.5 (*c* 0.78, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3369br (OH), 2954, 2929, 2886, 2857 (CH), 1664 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ

0.06 (3H, s), 0.07 (3H, s), 0.08 (3H, s) and 0.10 (3H, s, 2 × Si(CH_3)$_2$), 0.89 (9H, s) and 0.90 (9H, s, 2 × C(CH_3)$_3$), 1.89 (1H, t, *J* 6.9 Hz, O*H*), 3.55 (1H, dd, *J* 10.4, 5.1 Hz) and 3.59 (1H, dd, *J* 10.4, 6.4 Hz, TBSOCH_2), 4.23–4.28 (2H, m, CH_2OH), 4.57 (1H, ddd, *J* 7.8, 6.4, 5.1 Hz, TBSOCH), 5.99 (1H, dt, *J* 7.8, 1.1 Hz, C(Br)=C*H*); ^{13}C NMR (CDCl$_3$, 125 MHz) δ –5.3, –5.2, –4.6 and –4.6 (2 × Si(*C*H$_3$)$_2$), 18.2 and 18.4 (2 × *C*(CH$_3$)$_3$), 25.9 and 26.0 (2 × C(*C*H$_3$)$_3$), 66.7 (TBSO*C*H$_2$), 68.1 (*C*H$_2$OH), 73.5 (TBSO*C*H), 126.7 (*C*Br), 130.8 (C(Br)=*C*H); *m*/*z* (FAB$^+$) 447/449 (MNa$^+$, 41/40%), 369 (72), 367 (70), 295 (65), 293 (69), 189 (100); HRMS found 447.1370, C$_{17}$H$_{37}$^{79}BrO$_3$Si$_2$Na (MNa$^+$) requires 447.1362.

(*S*,*Z*)-1,2-Dibromo-4,5-di(*tert*-butyldimethylsilanyloxy)pent-2-ene (19b)

To a solution of alcohol **S13** (120 mg, 0.3 mmol), triethylamine (120 μL, 0.8 mmol) and DMAP (5.2 mg, 40 μmol) in CH_2Cl_2 (3 mL) at 0 °C was added TsCl (64 mg, 0.3 mmol), and the solution stirred for 5 h at rt. The solution was diluted with CH_2Cl_2 (10 mL), washed successively with HCl (1M, 5 mL), sat. aq. $NaHCO_3$ (5 mL) and brine (2 × 5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2; petrol/EtOAc 99:1) afforded (*S*,*Z*)-2-bromo-4,5-di(*tert*-butyldimethylsilanyloxy)-1-(4-toluenesulfonyloxy)-pent-2-ene (82 mg, 60%) as a colourless oil: R_f = 0.73 (petrol/EtOAc 9:1); $[\alpha]_D^{20}$ –12.5 (*c* 0.42, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast) 2954, 2929, 2857 (CH), 1599 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (3H, s), 0.04 (6H, s) and 0.06 (3H, s, 4 × Si(C*H*$_3$)$_2$), 0.86 (9H, s) and 0.88 (9H, s, 2 × C(C*H*$_3$)$_3$), 2.46 (3H, s, ArC*H*$_3$), 3.47 (1H, dd, *J* 10.3, 4.9 Hz) and 3.53 (1H, dd, *J* 10.3, 6.4 Hz, TBSOCH_2), 4.48 (1H, ddd, *J* 7.7, 6.4, 4.9 Hz, OC*H*) , 4.61 (1H, d, *J* 12.4 Hz) and 4.65 (1H, d, *J*, 12.4 Hz, CH_2OTs), 6.03 (1H, d, *J* 7.7 Hz, C(Br)=C*H*), 7.36 (2H, d, *J* 8.3 Hz) and 7.82 (2H, d, *J* 8.3 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4, –5.3, –4.7 and –4.7 (2 × Si(*C*H$_3$)$_2$), 18.1 and 18.3 (2 × *C*(CH$_3$)$_3$), 21.7 (Ar*C*H$_3$), 25.8 and 25.9 (2 × C(*C*H$_3$)$_3$), 60.4 (TBSO*C*H$_2$), 73.2 (*C*H$_2$OTs) 73.5 (TBSO*C*H), 117.8 (*C*Br), 128.0 and 129.9 (aromatic *C*H), 132.8 (aromatic *C*), 135.9 (C(Br)=*C*H), 145.1 (aromatic *C*); *m*/*z* (CI$^+$) 579/581 (MH$^+$, 8/8%), 449 (100), 447 (66), 409 (76), 407 (58), 345 (45), 277 (75); HRMS found 579.1647, C$_{24}$H$_{44}$^{79}BrO$_5$SSi$_2$ (MH$^+$) requires 579.1631.

To a solution of this tosylate (510 mg, 0.9 mmol) in MeCN (30 mL) at 0 °C was added LiBr (0.38 g, 4.4 mmol) and the solution stirred at room temperature for 24 h. After removal of the MeCN *in vacuo*, brine (30 mL) was added and the organic material extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield bromide **19b** (250 mg, 60%) as a colourless oil: R_f = 0.50 (petrol/EtOAc 19:1); $[\alpha]_D^{20}$ +38.4 (*c* 0.85, $CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$ cast) 2954, 2929, 2857 (CH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.06 (3H, s), 0.07 (3H, s), 0.08 (3H, s) and 0.10 (3H, s, 2 × Si(C*H*$_3$)$_2$), 0.89 (9H, s) and 0.90 (9H, s, 2 × C(C*H*$_3$)$_3$), 3.54 (1H, dd, *J* 10.3, 5.2 Hz) and 3.60 (1H, dd, *J* 10.3, 6.2 Hz, OCH_2), 4.20 (1H, dd, *J* 11.3, 0.6 Hz) and 4.24 (1H, dd, *J* 11.3, 0.5 Hz, CH_2Br), 4.50 (1H, ddd, *J* 7.9, 6.2, 5.2 Hz, OC*H*), 6.06 (1H, d, *J* 7.9 Hz, C(Br)=C*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4, –5.3, –4.7 and –4.5 (2 × Si(*C*H$_3$)$_2$), 18.1 and 18.4 (2 × *C*(CH$_3$)$_3$), 25.8 and 25.9 (2 × C(*C*H$_3$)$_3$), 38.1 (*C*H$_2$Br), 66.4 (O*C*H$_2$), 73.9 (O*C*H), 122.2 (CBr), 135.3 (C(Br)=*C*H); *m*/*z* (EI) 429/431/433 ([M–^{t}Bu]$^+$, 6/11/6%), 207 (22), 205 (17), 189 (30), 148 (15), 147 (100); HRMS found 428.9903, C$_{17}$H$_{27}$^{79}Br$_2$O$_2$Si$_2$ ([M–^{t}Bu]$^+$) requires 428.9916.

Assignment of Stereochemistry of Thia-Claisen products

(3*S*,3'*R*,4'*S*)-1-Benzyl-3-(4,5-dihydroxypent-1-en-3-yl)pyrrolidine-2-thione (S16)

Acetonide **21a** (270 mg, 0.8 mmol) and aq. AcOH (60%, 15 mL) were stirred at room temperature for 24 h. Petrol (15 mL) was added, then the aqueous layer was separated and concentrated *in vacuo*. The residue was dried azeotropically by concentrating successively from EtOH (3 × 15 mL) and toluene (3 × 15 mL) to give diol **S16** (232 mg, 98%) as a pale yellow oil: R_f = 0.20 (petrol/EtOAc 1:1); $[\alpha]_D^{17}$ –159.3 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3362br (OH), 3069, 3030, 2922, 2878 (CH), 1637 (C=C), 1510, 1452, 1310 (C=S); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.04 (1H, ddt, *J* 13.0, 8.9, 6.9 Hz, NCH$_2$C*H*H), 2.11 (1H, br s, O*H*), 2.24 (1H, dtd, *J* 13.0, 9.0, 5.1 Hz, NCH$_2$CH*H*), 2.60 (1H, dt, *J* 9.8, 2.8 Hz, CH$_2$=CHC*H*), 3.31 (1H, m, C=SC*H*), 3.45 (1H, ddd, *J* 11.1, 8.7, 6.7 Hz) and 3.56 (1H, ddd, *J* 11.1, 9.0, 5.2 Hz, NCH_2CH$_2$), 3.62 (2H, m, CH_2OH), 3.95 (1H, d, *J* 2.8 Hz, O*H*), 4.14 (1H, tt, *J* 5.7, 2.8 Hz, C*H*OH), 4.94 (1H, d, *J* 14.3, Hz) and 5.08 (1H, d, *J* 14.3, Hz, NCH_2Ph), 5.15–5.22 (2H, m, CH_2=CH), 5.99 (1H, dt, *J* 16.9, 10.1 Hz, CH$_2$=C*H*), 7.31–7.38 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.7 (NCH$_2$*C*H$_2$), 50.0 (CH$_2$=CH*C*H)), 52.1 (N*C*H$_2$Ph), 52.7 (N*C*H$_2$CH$_2$), 58.4 (C=S*C*H), 65.1 (*C*H$_2$OH), 72.8 (*C*HOH), 119.7 (*C*H$_2$=CH), 128.1, 128.3, 128.8 (aromatic *C*H), 134.2 (CH$_2$=*C*H), 134.7 (aromatic *C*), 202.1 (*C*=S); *m*/*z* (CI$^+$) 292 (MH$^+$, 25%), 274 (10), 230 (32), 191 (78), 91 (100); HRMS found 292.1364, C$_{16}$H$_{22}$NO$_2$S (MH$^+$) requires 292.1371.

(3*R*,3'*S*,4'*S*)-1-Benzyl-3-(4,5-dihydroxypent-1-en-3-yl)pyrrolidine-2-thione (S17)

Acetonide **22a** (100 mg, 0.3 mmol) by the above procedure afforded diol **S17** (80 mg, 92%) as a white solid: m.p. 111-112 °C; R_f = 0.15 (petrol/EtOAc 1:1); $[\alpha]_D^{17}$ +10.3 (*c* 0.51, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3368br (OH), 2920, 2873 (CH), 1630 (C=C), 1518 (C=S); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (1H, ddt, *J* 13.0, 8.6, 4.6 Hz) and 2.27 (1H, dtd, *J* 13.0, 9.5, 7.2 Hz, NCH$_2$CH_2), 2.56 (1H, td, *J* 9.7, 3.5 Hz, CH$_2$=CHC*H*), 3.42–3.57 (3H, m, NCH_2CH$_2$ and C*H*HOH), 3.62 (1H, dt, *J* 9.5, 4.5 Hz, C=SC*H*), 3.72 (1H, br d, *J* 11.7 Hz, CH*H*OH), 4.16 (1H, br s, C*H*OH), 4.92 (1H, d, *J* 14.3 Hz) and 5.07 (1H, d, *J* 14.3 Hz, NCH_2Ph), 5.10 (1H, dd, *J* 10.1, 1.7 Hz) and 5.20 (1H, dd, *J* 17.1, 1.7 Hz, CH_2=CH), 5.54 (1H, dt, *J* 17.1, 10.1 Hz, CH$_2$=C*H*), 7.32–7.38 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.0 (NCH$_2$*C*H$_2$), 51.4 (CH$_2$=CH*C*H), 51.8 (N*C*H$_2$Ph), 53.2 (N*C*H$_2$CH$_2$), 54.1 (C=S*C*H), 64.7 (*C*H$_2$OH), 71.3 (*C*HOH), 119.9 (*C*H$_2$=CH), 128.2, 128.3, 128.8 (aromatic *C*H), 134.8 (aromatic *C*), 135.1 (CH$_2$=*C*H), 201.9 (*C*=S); *m*/*z* (CI$^+$) 292 (MH$^+$, 100%), 279 (31); HRMS found 292.1367, C$_{16}$H$_{22}$NO$_2$S (MH$^+$) requires 292.1371.

Deprotection of silyl ethers 25a and 26a: General Procedure

A solution of lactam **25a** (100 mg, 0.2 mmol) in a 1:1 mixture of AcOH (10 mL) and THF (10 mL) was stirred at 50 °C for 24 h. Petrol (30 mL) was added, then the aqueous layer separated and concentrated *in vacuo*. The residue was dried by azeotroping successively with EtOH (3 × 40 mL) and toluene (3 × 40 mL) to give **S16** (52 mg, 93%) as a yellow oil.

Similar treatment of lactam **26a** (6 mg, 12 μmol) afforded **S17** (2.3 mg, 67%) as a white solid.

(3*S*,1'*R*)-1-Benzyl-3-(1-hydroxymethylallyl)pyrrolidine-2-thione (S18)

To a solution of $NaIO_4$ (2.57 g, 12.0 mmol) in H_2O (5 mL) at *ca.* 70 °C was added flash silica gel (10.0 g), and the contents shaken vigorously until a free flowing powder had formed.[6]
To a suspension of this silica-supported $NaIO_4$ powder (0.32 g, *ca.* 0.31 mmol) in CH_2Cl_2 (2 mL) was added a solution of diol **S16** (102 mg, 0.3 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 1 h at room temperature. After removal of the solid by filtration, and removal of CH_2Cl_2 *in vacuo*, the intermediate aldehyde was dissolved in EtOH/THF (2:1 *v*/*v*, 6 mL), and $NaBH_4$ (130 mg, 3.5 mmol) was added. The solution was stirred for 15 minutes at room temperature, then HCl (1 M) added until the mixture was neutral. The organic material was extracted with EtOAc (3 × 40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, petrol:EtOAc 70:30) afforded alcohol **S18** (46 mg, 51%) as a pale yellow oil: R_f 0.23 (EtOAc:petrol 30:70); $[\alpha]_D^{20}$ −73.2 (*c* 0.40, $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$ cast) 3399br (OH), 2923, 2875 (CH), 1635 (C=C), 1508, 1453, 1310 (C=S); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (1H, ddt, *J* 12.7, 8.7, 6.2 Hz) and 2.21 (1H, dtd, *J* 12.7, 9.1, 5.9 Hz, NCH_2CH_2), 2.66 (1H, br s, O*H*), 3.06 (1H, m, H_2C=CHC*H*), 3.37 (1H, ddd, *J* 9.2, 6.1, 3.6 Hz, C*H*C=S), 3.47 (1H, ddd, *J* 11.1, 9.0, 5.8 Hz) and 3.55 (1H, ddd, *J* 11.1, 8.7, 5.9 Hz, NCH_2CH_2), 3.75 (1H, dd, *J* 11.4, 6.5 Hz) and 3.89 (1H, br dd, *J* 11.4, 9.0 Hz, CH_2OH), 4.94 (1H, d, *J* 14.3 Hz) and 5.08 (1H, d, *J* 14.3 Hz, $PhCH_2$), 5.13 (1H, d, *J* 10.3 Hz) and 5.21 (1H, d, *J* 17.1 Hz, CH=CH_2), 5.67 (1H, ddd, *J* 17.1, 10.3, 8.8 Hz, C*H*=CH_2), 7.31–7.37 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.1 (NCH_2CH_2), 49.3 (H_2C=CH*C*H), 51.8 ($PhCH_2$), 52.8 (NCH_2CH_2), 55.1 (*C*HC=S), 63.0 (CH_2OH), 118.4 (CH=*C*H_2), 128.1, 128.3 and 128.8 (aromatic *C*H), 134.9 (aromatic *C*), 135.6 (*C*H=CH_2), 202.7 (*C*=S); *m/z* (CI^+, CH_4) 290 ($[M+C_2H_5]^+$, 22%), 262 (MH^+, 100), 244 ($[MH–H_2O]^+$, 32), 191 (25); HRMS found 262.1260, $C_{15}H_{20}NOS$ (MH^+) requires 262.1266.

(3*R*,1'*S*)-1-Benzyl-3-(1-hydroxymethylallyl)pyrrolidine-2-thione (S19)

The title compound (13 mg, 31%) was prepared from diol **S17** (47 mg, 0.2 mmol) as for compound **S18** and purified by preparative thin layer chromatography (SiO_2, petrol:EtOAc 50:50). It displayed identical spectroscopic characteristics to **S18**. $[\alpha]_D^{20}$ +71.4 (*c* 0.28, $CHCl_3$).

Debromination of 22b with triethylammonium formate

To a solution of bromide **22b** (60 mg, 0.1 mmol), PPh_3 (3.1 mg, 0.01 mmol), NEt_3 (0.60 mL, 4.4 mmol) and $Pd(OAc)_2$ (1.3 mg, 0.004 mmol) in DMF (1 mL) was added HCOOH (0.11 mL, 2.3 mmol). The solution was heated to 65 °C with stirring for 6 h. After cooling to room temperature, the reaction mixture was diluted with brine (10 mL) and the organic material extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography (SiO_2, petrol/EtOAc 95:5) afforded thiolactams **22a** (17 mg, 35%) and **23a** (10 mg, 21%) as colourless oils.

Debromination of 21b, 22b and 23b with tributyltin hydride

To a solution of $Pd(PPh_3)_4$ (0.5 mg, 0.4 μmol) in THF (0.2 mL) was added a solution of bromide **21b** (9.0 mg, 20 μmol), and Bu_3SnH (9 μL, 30 μmol) in THF (0.3 mL). The solution was heated to reflux overnight. The mixture was cooled to room temperature, diluted with brine (5 mL) and the organic material extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by preparative TLC (SiO_2, petrol/EtOAc 90:10, triple elution) afforded thiolactam **21a** (4.0 mg, 60%) as a pale yellow oil.
Similar treatment of bromide **22b** (50 mg, 0.1 mmol) afforded thiolactam **22a** (20 mg, 50%); bromide **23b** (10 mg, 24 μmol) afforded thiolactam **23a** (3.9 mg, 49%).

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