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

Adam R. Ellwood,* Anne J. Price Mortimer,* Jonathan M. Goodman† and Michael J. Porter*

Supporting Information

Contents

SI1: Experimental Details
Preparation of allylic bromide substrates S2
Stereochemical assignment of thiolactam products S3
Experimental details S4
References S8

SI2: Computational Details
Details of computational work S9
References S9
Summary of transition state energies S10
Cartesian coordinates and energies for all computed structures

Substrate 27a
Starting material S11
TS Ia S12
TS Ia* S13
TS Ila S14
TS Ila* S15
TS Ib S16
TS Ib* S17
TS I Ib S18
TS I Ib* S19
TS Ic S20
TS Ic* S21
TS I Ic S22
TS I Ic* S23

Substrate 27b
Starting material S24
TS Ia S25
TS Ia* S26
TS Ila S27
TS Ila* S28
TS Ib S29
TS Ib* S30
TS I Ib S31
TS I Ib* S32
TS Ic S33
TS Ic* S34
TS I Ic S35
TS I Ic* S36

SI3: NMR Spectra
21a – H S37
22a – H & 13C S38
23a – H & 13C S40
21b – H & 13C S42
22b – H & 13C S44
23b – H & 13C S46
24b – H S48
25a – H & 13C S49
26a – H & 13C S51
27a – H & 13C S53
28a – H & 13C S55
29a – H & 13C S57
30a – H & 13C S59
31a – H & 13C S61
32a – H & 13C S63

SI4: NMR Spectra (continued)
19a – H & 13C S65
20a precursor – H & 13C S67
19b – H & 13C S69
20b – H & 13C S71
21b – H & 13C S72
22b – H & 13C S74
23b – H & 13C S76
24b – H & 13C S78
25b – H & 13C S80
19b precursor – H & 13C S82
19b – H & 13C S84
20b – H & 13C S86
21b – H & 13C S88
22b – H & 13C S90
Preparation of Allylic Bromides

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

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. Reduction and bromination proceeded as previously to give bromide 20a.

Use of triethyl bromophosphonoacetate 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 LiAlH4 was used as the reducing agent, and alcohol S13 was obtained in 91% yield. Conversion of this alcohol to the corresponding bromide using NBS/PPh3 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) NaIO4, NaHCO3, MeOH, H2O, 0 °C to rt; (ii) EtO2CCH2BrPO(OEt)2, K2CO3, H2O, 0 °C to rt; 96% (two steps); (iii) DIBAL, CH2Cl2, −78 °C, 77%; (iv) NBS, PPh3, CH2Cl2, 0 °C to rt, 93%; (v) AcOH, H2O, 98%; (vi) TBSCI, imidazole, CH2Cl2, 77%; (vii) DIBAL, CH2Cl2, hexane, −78 °C, 93%; (viii) NBS, PPh3, CH2Cl2, 0 °C to rt, 71%; (ix) EtO2CCH=PH3, MeOH, H2O, −60 °C to 0 °C, 81% (two steps); (x) DIBAL, CH2Cl2, −78 °C, 89%; (xi) NBS, PPh3, CH2Cl2, 0 °C to rt, 72%.

**Scheme S2** Reagents and conditions: (i) NaIO4, NaHCO3, H2O, 0 °C to rt; (ii) EtO2CCHBrPO(OEt)2, K2CO3, H2O, 0 °C to rt; (iii) DIBAL, CH2Cl2, −78 °C, 41% 18b + 25% S9 (three steps); (iv) NBS, PPh3, CH2Cl2, 0 °C to rt, 67% 18b, 54% 20b; (v) AcOH, H2O, 35% S10 + 54% S11; (vi) TBSCI, imidazole, CH2Cl2, 87%; (vii) LiAlH4, THF, Et2O, 0 °C 91%; (viii) TsCl, Et3N, DMAP, CH2Cl2, 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 periodate6 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, H2O, 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.

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(PPh3)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.
Experimental Section

General Experimental Procedures

All non-aqueous reactions were carried out under argon with dry solvents. Dry THF, MeCN and CH₂Cl₂ were obtained by passage through activated alumina columns under nitrogen; pyridine, Et₃N and DMF were distilled from CaH₂ 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 F₂₅₄, which were visualised either by UV light (254 nm), aq KMnO₄ 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. 1H and 13C NMR spectra were recorded as CDCl₃ 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 (1H 7.26 ppm and 13C 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 given in g/100 mL.

Diacetonide S1, esters S2b and S6, bromide 18a, triethyl bromophosphonoacetate and 1-benzylpyrrolidine-2-thione 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 S2b (1.00 g, 5.0 mmol) in 3:2 AcOH/H₂O (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: Rf = 0.16 (petrol/EtOAc 1:1); [α]D⁺ +8.0 (c 1.03, CHCl₃) [lit.10 [α]D = −5.0 (c 0.5, CHCl₃)]; νmax/cm⁻¹ (film) 3398br (OH), 2937 (CH), 1715 (C=O), 1659 (C=C); 1H NMR (CDCl₃, 300 MHz) δ 1.29 (3H, t, J 7.2 Hz, CH₂), 2.34–2.89 (2H, br s, CH₂), 3.55 (1H, dd, J 11.2, 6.9 Hz) and 3.77 (1H, dd, J 15.5, 3.8 Hz, HOCH₂); 13C NMR (CDCl₃, 75 MHz) δ 14.2 (CH₃), 25.8 and 26.0 (2 × Si(CH₃)₂), 43.4 (1H, br, s, CH₂O), 61.0 (CH₂), 65.5 (CH₂OH), 71.7 (CH₂O), 120.9 (OCH₂CH₂), 146.2 (OCH₂CH₂CH₂), 166.6 (C=O); m/z (EI) 161 (MH⁺, 51%), 143 (MH⁺–H₂O, 55), 115 (52), 97 (100); HRMS found 161.0803, C₇H₁₀O₄ (MH⁺) requires 161.0808.

Ethyl (S,E)-4,5-di(tert-butyl)methylsilanyloxy)pent-2-enoate (S4)

To a solution of diol S3 (5.00 g, 31.2 mmol) and imidazole (8.50 g, 125 mmol) in CH₂Cl₂ (80 mL) at 0 °C was added tert-butylchloromethylsilane (10.4 g, 68.7 mmol) and the mixture stirred at room temperature for 4 h. The solution was diluted with H₂O (250 mL), the organic material extracted with CH₂Cl₂ (3 × 150 mL), washed with brine (200 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (SiO₂; petrol/EtOAc 98:2) afforded ester S4 (9.35 g, 77%) as a colourless oil: Rf = 0.45 (petrol/EtOAc 19:1); [α]D⁻ −16.8 (c 0.63, CHCl₃); νmax/cm⁻¹ (film) 3332br (OH), 2929 (CH); 1H NMR (CDCl₃, 300 MHz) δ 0.04 (6H, s), 0.06 (3H, s) and 0.07 (3H, s, 2 × Si(CH₃)₂), 0.87 (9H, s) and 0.89 (9H, s, 2 × Si(CH₃)₂), 1.27 (3H, t, J 7.1 Hz, CH₃CH₂), 3.48 (1H, dd, J 9.9, 6.5 Hz) and 3.58 (1H, dd, J 9.9, 6.3 Hz, TBSOCH₂), 4.19 (2H, q, J 7.1 Hz, CH₂CH₂), 4.33 (1H, m, TBSOCH₂), 6.04 (1H, dd, J 15.6, 1.8 Hz, EtOOC=CH=CH), 7.01 (1H, dd, J 15.6, 4.2 Hz, EtOOC=CH=CH); 13C NMR (CDCl₃, 75 MHz) δ −5.5, −5.3, −4.9 and −4.8 (2 × Si(CH₃)₂), 14.2 (CH₂), 18.2 and 18.3 (2 × CH₃), 25.8 and 25.9 (2 × CH₃), 60.3 (CH₂CH₂), 67.2 (TBSOCH₂), 72.7 (TBSOCH₂), 120.8 (EtOOC=CH=CH), 148.5 (EtOOC=CH=CH), 166.6 (O=CH); m/z (ESI) 411 (MNa⁺, 100%), 389 (MH⁺, 50), 257 (64); HRMS found 389.2556, C₁₀H₁₄O₃Si₂ (MH⁺) requires 389.2538.

Ethyl (S,E)-4,5-di(tert-butyl)methylsilanyloxy)pent-2-en-1-ol (S5)

To a solution of ester S4 (600 mg, 1.5 mmol) in CH₂Cl₂ (5 mL) at −78 °C was added DIBAL (1.0 M in hexane, 3.9 mL, 9.3 mmol) dropwise, and the resulting mixture stirred for 4 h at −78 °C. After warming the reaction mixture to room temperature, MeOH (5 mL), Et₂O (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 H₂O (250 mL) and the organic material extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (SiO₂; petrol/EtOAc 19:1) provided alcohol S5 (500 mg, 93%) as a colourless oil: Rf = 0.23 (petrol/EtOAc 9:1); [α]D⁻ −16.8 (c 0.63, CHCl₃); νmax/cm⁻¹ (film) 3332br (OH), 2929 (CH); 1H NMR (CDCl₃, 300 MHz) δ 0.04 (6H, s), 0.05 (3H, s) and 0.07 (3H, s, 2 × Si(CH₃)₂), 0.88 (9H, s) and 0.89 (9H, s, 2 × Si(CH₃)₂), 1.41 (1H, br, s, CH), 3.44 (1H, dd, J 10.0, 5.9 Hz) and 3.53 (1H, dd, J 10.0, 6.5 Hz, TBSOCH₂), 4.14–4.21 (3H, m, TBSOCH₂ and CH₂OH), 5.72 (1H, dd, J 15.5, 3.8 Hz, HOCH₂CH=CH)=CH₂) 5.87 (1H, dt, J 15.5, 5.2 Hz, HOCH₂CH=CH)=CH₂; 13C NMR (CDCl₃, 75 MHz) δ −5.4, −5.2 and −4.6 (2 × Si(CH₃)₂), 18.3 and 18.4 (2 × CH₃), 25.9 and 26.0 (2 × CH₃), 63.2 (CH₂OH), 68.0 (TBSOCH₂), 73.4 (TBSOCH₂), 129.6 (HOCH₂CH=CH), 132.3 (HOCH₂CH=CH); m/z (ESI) 369 (MNa⁺, 100%), 215 (17); HRMS found 369.2268, C₁₇H₂₃O₄Si₂Na (MNa⁺) requires 369.2252.

Ethyl (S,E)-1-Bromo-4,5-di(tert-butyl)methylsilanyloxy)pent-2-en-1-ol (S9a)

To a stirred solution of alcohol S5 (2.85 g, 8.2 mmol) in CH₂Cl₂ (80 mL) at 0 °C, triphenylphosphine (2.37 g, 9.0 mmol) was added, followed by N-bromosuccinimide (1.54 g, 8.6 mmol) portionwise over several minutes. The solution was stirred at room temperature for 3 h, then quenched with H₂O (100 mL). The organic material was extracted with CH₂Cl₂ (3 × 100 mL) and the combined organic extracts...
To a solution of ester S6b (2.46 g, 12.3 mmol) in CH₂Cl₂ (40 mL) at −78 °C was added DIBAL (1.2 M in toluene, 25.5 mL, 30.6 mmol) dropwise, and the solution stirred for 2 h at −78 °C. After warming the reaction mixture to room temperature, MeOH (80 mL), Et₂O (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 H₂O (60 mL) and the organic material extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄) and the solvent removed in vacuo to give a cloudy liquid. Purification by flash chromatography (SiO₂, petrol/EtOAc 8:2−7:3) afforded azadiene (S,Z)-4-(3-bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (20a).

With the presence of washed with brine (170 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (SiO₂, petrol/EtOAc 9:6:4) afforded bromide 19a (2.37 g, 71%) as a colourless oil. Rf = 0.71 (petrol/EtOAc 19:1); [α]D²⁰ = −18.7 (c 0.73, CHCl₃); νmax/cm⁻¹ (film) 2929 (C=H); ¹H NMR (CDCl₃, 300 MHz) δ 0.06 (3H, s), 0.07 (6H, s) and 0.08 (3H, s, 2 × S(C₂H₅)); 0.89 (OH, s) and 0.90 (OH, s, 2 × C(PhH₃)); 3.42 (1H, dd, J 9.9, 6.2 Hz) and 3.54 (1H, dd, J 9.9, 6.2 Hz, TBSOCH₃); 3.96 (2H, d, J 7.2 Hz, BrCH₂); 4.19 (1H, m, TBSOCH₃); 5.75 (1H, dd, J 15.3, 5.0 Hz, BrCH₂=CH₂); 5.91 (1H, m, BrCH₂=CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ −5.3−, −5.3−, −4.7 and −4.6 (2 × S(PhH₃)); 18.3 and 18.4 (2 × C(PhH₃)); 25.9 and 26.0 (2 × C(PhH₃)); 32.5 (BrCH₂); 67.7 (TBSOCH₃); 73.0 (TBSOCH₃); 126.7 (BrCH₂=CH₂); 136.0 (BrCH₂=CH₂); m/z (EI) 431/433 (M⁺/2, 12%), 351/353 (40/40), 330 (38), 329 (84), 307 (45), 197 (56), 189 (61), 177 (81), 176 (100); HRMS found 431.1418, C₇H₇BrO₂Si₃Na (M⁺/Na⁺) requires 431.1413.

To a solution of ester S6b (2.46 g, 12.3 mmol) in CH₂Cl₂ (40 mL) at −78 °C was added DIBAL (1.2 M in toluene, 25.5 mL, 30.6 mmol) dropwise, and the solution stirred for 2 h at −78 °C. After warming the reaction mixture to room temperature, MeOH (80 mL), Et₂O (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 H₂O (60 mL) and the organic material extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄) and the solvent removed in vacuo to give a cloudy liquid. Purification by flash chromatography (SiO₂, petrol/EtOAc 8:2−7:3) afforded azadiene (S,Z)-4-(3-bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (20a)

With the presence of washed with brine (170 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (SiO₂, petrol/EtOAc 9:6:4) afforded bromide 19a (2.37 g, 71%) as a colourless oil. Rf = 0.71 (petrol/EtOAc 19:1); [α]D²⁰ = −18.7 (c 0.73, CHCl₃); νmax/cm⁻¹ (film) 2929 (C=H); ¹H NMR (CDCl₃, 300 MHz) δ 0.06 (3H, s), 0.07 (6H, s) and 0.08 (3H, s, 2 × S(C₂H₅)); 0.89 (OH, s) and 0.90 (OH, s, 2 × C(PhH₃)); 3.42 (1H, dd, J 9.9, 6.2 Hz) and 3.54 (1H, dd, J 9.9, 6.2 Hz, TBSOCH₃); 3.96 (2H, d, J 7.2 Hz, BrCH₂); 4.19 (1H, m, TBSOCH₃); 5.75 (1H, dd, J 15.3, 5.0 Hz, BrCH₂=CH₂); 5.91 (1H, m, BrCH₂=CH₂); ¹³C NMR (CDCl₃, 75 MHz) δ −5.3−, −5.3−, −4.7 and −4.6 (2 × S(PhH₃)); 18.3 and 18.4 (2 × C(PhH₃)); 25.9 and 26.0 (2 × C(PhH₃)); 32.5 (BrCH₂); 67.7 (TBSOCH₃); 73.0 (TBSOCH₃); 126.7 (BrCH₂=CH₂); 136.0 (BrCH₂=CH₂); m/z (EI) 431/433 (M⁺/2, 12%), 351/353 (40/40), 330 (38), 329 (84), 307 (45), 197 (56), 189 (61), 177 (81), 176 (100); HRMS found 431.1418, C₇H₇BrO₂Si₃Na (M⁺/Na⁺) requires 431.1413.

To a solution of ester S6b (2.46 g, 12.3 mmol) in CH₂Cl₂ (40 mL) at −78 °C was added DIBAL (1.2 M in toluene, 25.5 mL, 30.6 mmol) dropwise, and the solution stirred for 2 h at −78 °C. After warming the reaction mixture to room temperature, MeOH (80 mL), Et₂O (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 H₂O (60 mL) and the organic material extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄) and the solvent removed in vacuo to give a cloudy liquid. Purification by flash chromatography (SiO₂, petrol/EtOAc 8:2−7:3) afforded azadiene (S,Z)-4-(3-bromoprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (20a).
To a solution of alcohol S8 (0.95 g, 4.0 mmol) in CH₂Cl₂ (35 mL) at 0°C it was added triphenylphosphine (1.16 g, 4.4 mmol), followed by N-bromosuccinimide (0.75 g, 4.2 mmol) portionwise over a few minutes. The solution was stirred at room temperature for 3 h. The reaction was quenched with H₂O (50 mL) and the organic material extracted with CH₂Cl₂ (3 × 50 mL), washed with brine (0.1 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (SiO₂, petrol/EtOAc 92:8) afforded bromide 18b (0.80 g, 67%) as a yellow oil: Rₙ = 0.47 (petrol/EtOAc 9:1); [α]D⁺ = +22.5 (c 1.2, CHCl₃) vₖₑₒₚ = 1780 cm⁻¹ (CHCl₃) cast) 2986, 2932 (CH₃), 1647 (C=C); ¹H NMR (CDCl₃, 500 MHz) δ 1.40 (3H, s) and 1.45 (3H, s, C(CH₃)₂), 3.67 (1H, dd, J = 8.4, 6.8 Hz, OCH₃), 4.21 (1H, d, J = 11.7 Hz) and 4.24 (1H, d, J = 11.7 Hz, CH₂Br), 4.25 (1H, dd, J = 8.4, 6.4 Hz, OCH₂), 4.86 (1H, q, J = 6.9 Hz, OCH₂), 6.29 (1H, d, J = 7.1 Hz, C(Cr)=CH), ¹³C NMR (CDCl₃, 125 MHz) δ 25.6 and 26.6 (C(CH₂)), 64.6 (CH₂Br), 68.4 (OCH₂), 75.7 (OCH), 110.0 (C(Me₃)), 124.2 (CBr), 132.7 (C(Br)=CH); m/z (CI²) 299/301/303 (MH⁺, 28/52/22%), 241/243/245 ([MH–MeCO⁺]², 25/73/23), 219/221 ([MH–HBr]⁺, 27/27), 189/191 (50/50), 161/163 (100/99); HRMS found 298.9289, C₇H₇Br₂O₂ (MH⁺) requires 298.9282.

To a solution of alcohol S9 (0.43 g, 1.8 mmol) in CH₂Cl₂ (20 mL) at 0°C it 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 H₂O (30 mL) and the organic material extracted with CH₂Cl₂ (3 × 30 mL), washed with brine (0.5 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (SiO₂, petrol/EtOAc 97:3) afforded bromide 20b (0.29 g, 54%) as a colourless oil: Rₙ = 0.33 (petrol/EtOAc 7:3); [α]D²⁰ = +40.0 (c 0.43, CHCl₃) vₖₑₒₚ = 1750 cm⁻¹ (CHCl₃) cast) 2986, 2933, 2873 (CH₃), 1683 (C≡C); ¹H NMR (CDCl₃, 500 MHz) δ 1.41 (3H, s) and 1.44 (3H, s, C(CH₃)₂), 3.69 (1H, dd, J = 8.5, 7.0 Hz) and 4.18 (1H, dd, J = 8.5, 6.2 Hz, OCH₂), 4.23 (1H, d, J = 11.3 Hz) and 4.46 (1H, d, J = 11.3 Hz, CH₂Br), 4.75 (1H, dd, J = 8.3, 7.0, 6.2 Hz, OCH₂) 6.08 (1H, d, J = 8.3 Hz, C(Br)=CH); ¹³C NMR (CDCl₃, 125 MHz) δ 25.7 and 26.6 (C(CH₂)), 32.2 (CH₂Br), 68.5 (OCH₂), 72.7 (OCH), 110.1 (C(Me₃)), 124.2 (C(Br)=CH) 134.8 (C(Br)=CH); m/z (CI²) 299/301/303 (MH⁺, 17/27/15%), 283/285/287 (26/64/25), 214/243/245 ([MH–MeCO⁺]², 25/73/23), 219/221 ([MH–HBr]⁺, 27/27), 189/191 (50/50), 161/163 (100/99); HRMS found 298.9279, C₇H₇Br₂O₂ (MH⁺) requires 298.9282.

**Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry**

[Page S6]
To a solution of acrolein S13 (120 mg, 0.3 mmol), triethylamine (120 μL, 0.8 mmol) and DMAP (5.2 mg, 0 μmol) in CH₂Cl₂ (3 mL) at 0 °C was added TscI (64 mg, 0.3 mmol), and the solution stirred for 5 h at rt. The solution was diluted with CH₂Cl₂ (10 mL), washed successively with HCl (1M, 5 mL), sat. aq. NaHCO₃ (5 mL) and brine (2 × 5 mL), dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (SiO₂; petrol/EtOAc 99:1) afforded (S,Z)-2-bromo-4,5-di(tert-butylmethylsilyloxy)-pent-2-ene (82 mg, 60%) as a colourless oil: Rf = 0.73 (petrol/EtOAc 9:1); [α]D²⁰ −12.5 (c 0.42, CHCl₃); νmax/cm⁻¹ (CDCl₃) 2954, 2929, 2857 (CH₃), 1599 (C=O), 1H NMR (CDCl₃, 400 MHz) δ 0.03 (3H), 0.04 (6H), 0.06 (3H), 0.08 (9H, s) and 0.88 (9H, s) 2 × Si(CH₃)₃); 0.89 (9H, s) and 0.90 (9H, s, 2 × C(Si(CH₃)₃)) 3.54 (1H, d, J 10.3 Hz) and 3.60 (1H, dd, J 7.9, 6.2 Hz, OCH₂) 4.20 (1H, d, J 11.3 Hz) and 4.24 (1H, d, J 11.3 Hz, CH₂Br) 4.50 (1H, d, J 7.9, 6.2 Hz, OCH₂) 6.06 (1H, d, J 7.9 Hz, C(Br)=C) 13C NMR (CDCl₃, 125 MHz) δ −5.4, −5.3, −4.7 and −4.5 (2 × Si(CH₃)₃) 18.1 and 18.4 (2 × C(Si(CH₃)₃)) 25.8 and 25.9 (2 × C(CH₃)₃) 66.0 (TBSO) 73.2 (CH₃)OS) 117.8 (C(Br)), 128.0 and 129.9 (aromatic CH), 132.8 (aromatic C), 135.9 (C(Br)=C) 145.1 (aromatic C); m/z (CI⁺) 579/581 (M⁺, 8/8%), 449 (100), 447 (66), 409 (76), 407 (58), 345 (45), 277 (75); HRMS found 579.1647, C₂H₉Br₂Si₃O₂ (M⁺) 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, the residue was added and the organic material extracted with EtOAc (2 × 50 mL). The combined extracts were dried (MgSO₄) and the solvent removed in vacuo to yield bromide 19b (250 mg, 60%) as a colourless oil: Rf = 0.50 ((petrol/EtOAc 19:1); [α]D⁰ +38.4 (c 0.85, CHCl₃); νmax/cm⁻¹ (CDCl₃) 2954, 2929, 2857 (CH₃); 1H NMR (CDCl₃, 500 MHz) δ 0.06 (3H, s), 0.07 (3H, s, 0.08 (3H, s) and 0.10 (3H, s, 2 × Si(CH₃)₂); 0.89 (9H, s) and 0.90 (9H, s, 2 × C(Si(CH₃)₃)); 3.54 (1H, d, J 10.3 Hz) and 3.60 (1H, d, J 10.3 Hz, OCH₂) 4.20 (1H, d, J 11.3 Hz) and 4.24 (1H, d, J 11.3 Hz, CH₂Br) 4.50 (1H, d, J 7.9, 6.2 Hz, OCH₂) 6.06 (1H, d, J 7.9 Hz, C(Br)=C) 13C NMR (CDCl₃, 125 MHz) δ −5.4, −5.3, −4.7 and −4.5 (2 × Si(CH₃)₃) 18.1 and 18.4 (2 × C(Si(CH₃)₃)) 25.8 and 25.9 (2 × C(CH₃)₃) 38.1 (CH₂Br) 66.4 (OCH₂) 73.9 (OCH) 122.2 (C(Br)) 135.3 (C(Br)=C); m/z (EI) 429/431/433 (M⁺–Bu⁺, 6/6/6%), 207 (22), 205 (17), 189 (30), 148 (15), 147 (100); HRMS found 428.9903, C₁₅H₂₇Br₂O₂Si₂ (M⁺–Bu⁺) requires 428.9916.

Assignment of Stereochemistry of Thia-Claissen products

(3S,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 acid. 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 azotropically by concentrating successively from EtOH (3 × 15 mL) and toluene (3 × 15 mL) to give diol 166 (232 mg, 98%) as a pale yellow oil: Rf = 0.20 ((petrol/EtOAc 1:1); [α]D²⁰ +159.3 (c 1.1, CHCl₃); νmax/cm⁻¹ (CDCl₃ cast) 3362br (OH), 2969, 2930, 2282, 2878 (CH₃), 1637 (C=O), 1510, 1452, 1310 (C=O); 1H NMR (CDCl₃, 500 MHz) δ 2.02 (4H, ddt, J 13.0, 8.9, 6.7 Hz, NCH₂CH₂H) 2.11 (1H, br s, OH) 2.24 (1H, dt, J 13.0, 9.0, 5.1 Hz, NCH₂CH₂H) 2.60 (1H, d, J 9.8, 2.8 Hz, CH₂=CHCH₂) 3.31 (1H, m, C=CH₂) 3.45 (1H, d, J 11.1, 8.7, 6.7 Hz) and 3.56 (1H, d, J 11.1, 9.0, 5.2 Hz, NCH₂CH₂H) 3.62 (2H, m, CH₂OH) 3.95 (1H, d, J 2.8 Hz, OCH₂) 4.14 (1H, t, J 5.7, 2.8 Hz, CH₂OH) 4.94 (1H, d, J 14.3 Hz) and 5.08 (1H, d, J 14.3 Hz, NCH₂Ph) 5.15–5.22 (2H, m, CH₂=CH₂) 5.99 (1H, d, J 16.9, 10.1 Hz, CH₂=CH₂) 7.31–7.38 (5H, m, ArH); 13C NMR (CDCl₃, 125 MHz) δ 24.7 (NCH₂CH₂H) 50.0 (C=CH₂CH₂) 52.1 (NCH₂Ph) 52.7 (NCH₂CH₂H) 58.4 (C=CH₂) 72.8 (CHOH) 119.7 (CH₂=CH₂) 128.1, 128.3, 128.8 (aromatic CH) 134.2 (CH₂=CH₂) 134.7 (aromatic C); 202.1 (C=O); m/z (CI⁺) 292 (M⁺, 25%), 274 (10), 230 (32), 191 (78), 91 (100); HRMS found 292.1364, C₁₅H₂₇NO₂S (M⁺) requires 292.1371.

Depletion 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 was separated and concentrated in vacuo. The residue was dried by azetroping 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.
(3S,1'R)-1-Benzyl-3-(1-hydroxymethylallyl)pyrroldine-2-thione (S18)

To a solution of NaIO₄ (2.57 g, 12.0 mmol) in H₂O (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. To a suspension of this silica-supported NaIO₄ powder (0.32 g, ca. 0.31 mmol) in CH₂Cl₂ (2 mL) was added a solution of diol S16 (102 mg, 0.3 mmol) in CH₂Cl₂ (2 mL). The mixture was stirred for 1 h at room temperature. After removal of the solid by filtration, and removal of CH₂Cl₂ in vacuo, the intermediate aldehyde was dissolved in EtOH/THF (2:1 v/v, 6 mL), and NaBH₄ (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 (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (SiO₂, petrol:EtOAc 70:30) afforded alcohol S18 (46 mg, 51%) as a pale yellow oil: Rf (0.3 mg, 0.004 mmol) in THF (0.2 mL) was added a solution of bromide 22b (60 mg, 0.1 mmol), PPh₃ (3.1 mg, 0.01 mmol), NEt₃ (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 reflux overnight. The mixture was cooled to room temperature, and the reaction mixture was diluted with brine (10 mL) and the organic material extracted with Et₂O (2 × 10 mL). The combined organic extracts were dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (SiO₂, petrol:EtOAc 95:5) afforded thiolaclam 22a (17 mg, 35%) and 23a (10 mg, 21%) as colourless oils.

References

10. M. D. Swift and A. Sutherland, Tetrahedron 2008, 64, 9521.