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Stereoselective synthesis of the C13-C22 fragment of Callystatin A by a non-aldol approach

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Abstract. An efficient synthetic route to the C13-C22 subunit of callystatin A is reported. The key features include diastereoselective alkylation, using Myers auxiliary, for the preparation of the three carbon synthon **7**, stereo- and regioselective oxidative vicinal functionalization of an electron deficient trisubstituted (*Z*)-olefin using an intramolecular sulfinyl group as the nucleophile, diastereoselective radical debromination of a bromohydrin derivative using Guindon's protocol to prepare the C16-C18 *anti-anti* stereotriad, Lewis acid promoted crotylation following Keck's protocol to create C19, C20 stereocenters and use of Pummerer reaction to reveal an aldehyde for extension of two carbon by Wittig olefination.

Keywords.

Myer's auxiliary, sulfoxide, intramolecular oxidative functionalization, radical debromination, crotylation, Pummerer reaction.

Introduction

The leptomycin family[1] comprises a class of polyketides isolated over many years, which display potent anticancer activity[2] Fig. **1**. All compounds belonging to the leptomycin family display an α,β-unsaturated lactone and two diene systems separated by two sp^3-hybridized carbons, suggesting a common biosynthetic pathway. Callystatin A, **1** belonging to the leptomycin family, was isolated in 1997 from the marine sponge *Callyspongia truncata* which

was collected from the Goto Islands in the Nagasaki Prefecture of Japan by the Kobayashi group.[3] Since then its absolute configuration has been elucidated[4] and callystatin A was discovered to have anti-fungal and anti-tumor activities with tremendous potency against the human epidermoid carcinoma KB cells (IG50 = 10 pg/ml) and the mouse lymphocytic leukemia Ll210 cells (IG50 = 20 pg/ml).[5] The C17-carbonyl, the C19-hydroxyl and the three methyl groups at positions C16, C18 and C20, located in the β-hydroxyketone part of callystatin A all contribute to its remarkable cytotoxic activity. Due to its remarkable bioactivity combined with its complex structure, several total synthesis[6] and a few partial synthesis[7] of callystatin A have been reported.

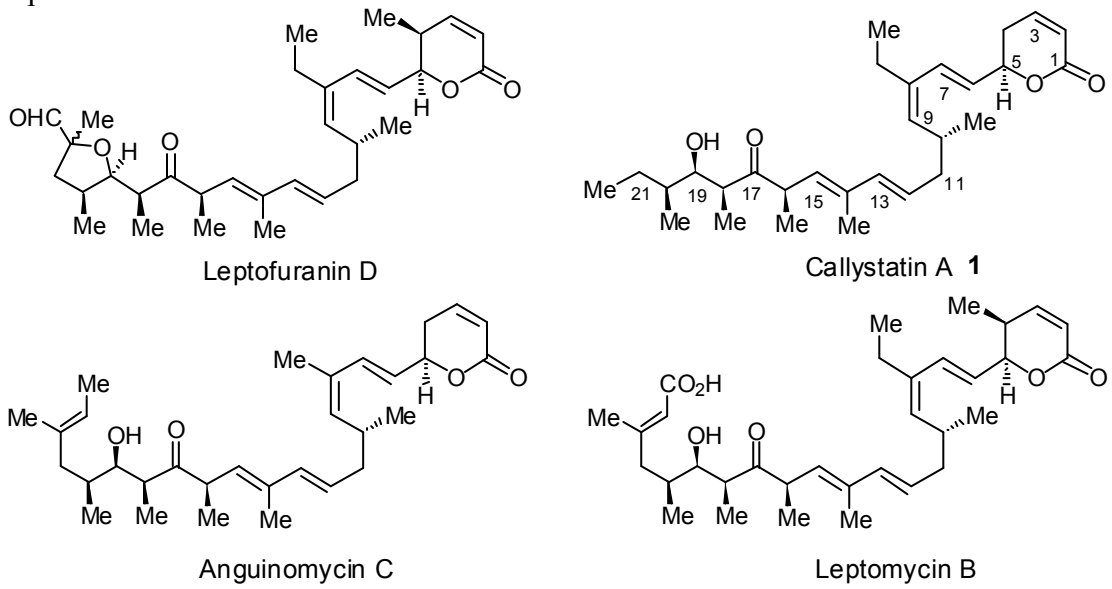
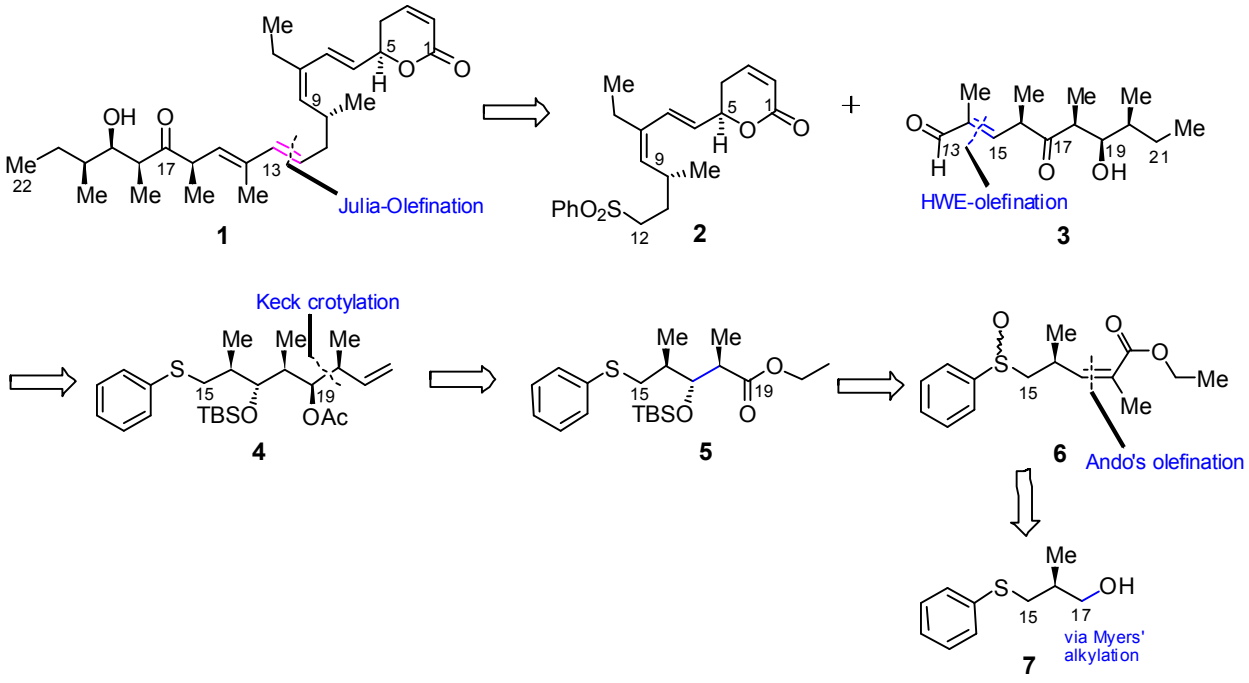


Figure 1. Leptomycin family of molecules.

Results and discussion

Here in we describe our efforts towards the stereoselective synthesis of the C13-C22 subunit **3** of callystatin A. By a retrosynthetic analysis, it was envisioned to synthesize callystatin A by a Julia-olefination between sulfone **2** and aldehyde **3**, Scheme **1**. The aldehyde **3** was

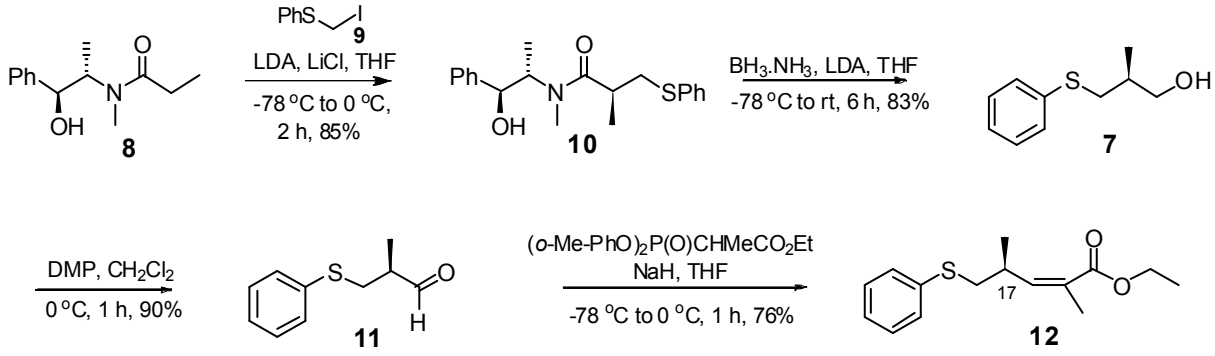
envisaged to be obtained from sulfide **4** which in turn can be obtained from the ester **5**. Compound **5** can be obtained from γ,δ-unsaturated sulfoxide **6**, by intramolecular oxidative functionalization employing the methodology developed in the group.[8] Unsaturated ester **6** can be traced to carbinol **7**.



Scheme 1. Retrosynthetic disconnection of callystatin A.

Alcohol **7**[9] was prepared following Myers' protocol[10] by a diastereoselective alkylation of the pseudoephedrine amide **8** with the unstable phenylthioiodo methane[11] **9**, Scheme **2**. The reaction proceeded with excellent stereocontrol affording sulfide **10** in good chemical yield. It is noteworthy that the reported alkylation of Evans oxazolidinone with **9** while reproducible, proceeding with excellent stereocontrol, afforded the product in poor chemical yield and over a long reaction period.[12] The poor yield is probably a consequence of the poor nucleophilicity of the oxazolidinone compounded by the instability of the iodide. Reductive removal of the auxiliary proceeded smoothly using lithium amidotrihydroborate[13] (LiH_2NBH_3) to furnish the

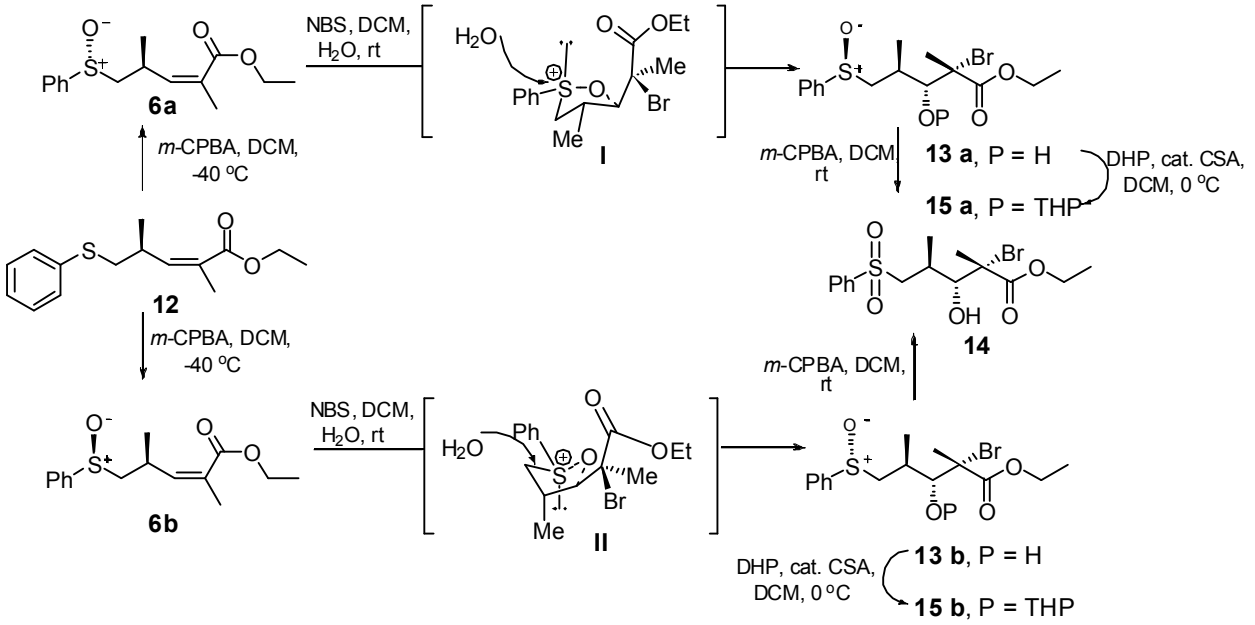
alcohol **7**, with the recovery of the pseudoephedrine. Conversion of the alcohol **7** to aldehyde **11**, by treatment with Dess-Martin periodinane **12**[14] followed by Horner–Wadsworth–Emmons homologation reaction employing Ando's protocol[15] furnished trisubstituted (*Z*)-α,β-unsaturated ester **12** (Z:E=95:05).[16]



Scheme 2. Synthesis of the unsaturated sulfide **12**.

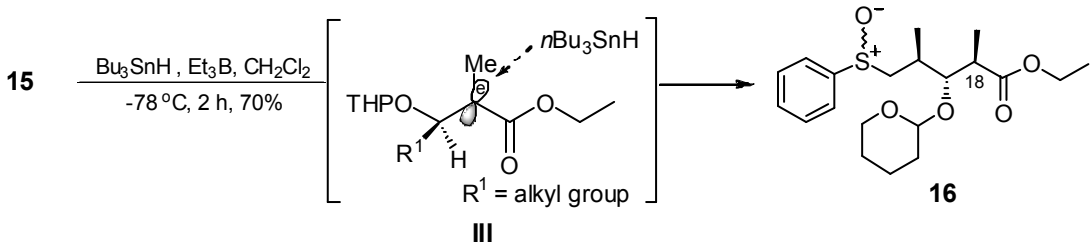
Chemoselective oxidation of sulfide **12** with *m*-CPBA at low temperature, yielded an equimolar, inseparable mixture of sulfoxides **6** (82% yield), Scheme **3**. Treatment of the sulfoxide **6** with *N*-bromosuccinimide[17] (NBS) in dichloromethane in the presence of water, afforded the bromohydrin **13** (80% yield) as an inseparable mixture. The epimeric nature of **13**, differing at sulfur, was confirmed by oxidation of **13** with *m*-CPBA to yield sulfone **14** (90% yield), which revealed a single set of signals in its ^{1}H NMR spectrum. In agreement with earlier results,[8] in this instance too, the methyl center alone influenced the stereochemical outcome of the reaction and sulfur chirality proved to be inconsequential. The stereochemical outcome of the reaction can be rationalized through the involvement of intermediates **I** and **II**. Thus a tetrasubstituted carbon could be created readily from a trisubstituted electron deficient alkene.[18] The hydroxyl group in **13** was protected as its THP ether **15** (80% yield). The C18 stereogenic center was introduced by radical debromination following Guindon's protocol.[19] Thus treatment of **15** with *n*-Bu_3SnH and Et_3B afforded **16** as a single diastereomer (excluding contribution due to sulfur and OTHP

chirality).[20] The stereochemical outcome of radical debromination can be rationalized by postulating intermediate **III** where in the dipole- dipole interactions between the ester and THP



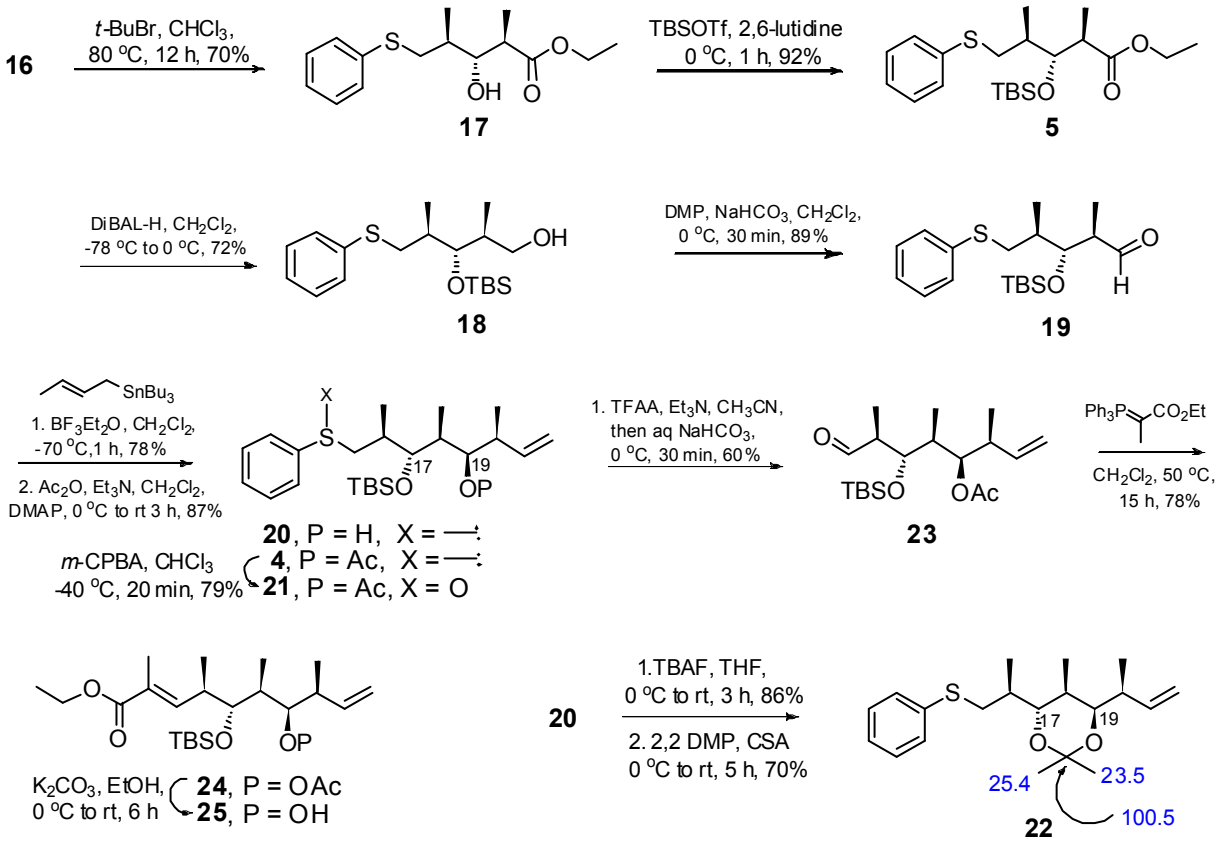
Scheme 3. Preparation of bromohydrin derivative **15**.

groups is minimized due to their are pointing away from each other and the hydrogen atom is abstracted from the side away from R^1 group. It is to be noted that the radical debromination of the corresponding sulfide proceeded with poorer stereoselection. It is probable that the sulfinyl group also points away from the OTHP group to avoid dipole-dipole interactions in intermediate **III** leading to the excellent stereocontrol, Scheme 4.



Scheme 4. Preparation of **16**.

Proceeding, reduction of sulfoxide **15** with *t*-butyl bromde,[21] afforded sulfide **17** by concomitant deprotection of the THP moiety. Protection of alcohol **17** as its TBS ether **5** and subsequent reduction with DIBAL-H furnished the alcohol **18**. Oxidation with DMP yielded the aldehyde **19**, which was subjected to crotylation following Keck's protocol[22] to furnish homoallyl alcohol **20** in good yield and excellent diastereoselectivity. The outcome of the reaction can be rationalized by a Felkin-Anh model and an open-transition state.



Scheme 5. Synthesis of compound C13-C22 subunit **24**.

The relative stereochemistry at C17 and C19 was confirmed by preparation of acetonide **22** from compound **20**. Acetonide methyl resonances in ^{13}C NMR spectrum at δ 23.5 and 25.4 ppm proved the *anti* disposition[23] of the hydroxy groups at C17 and C19. The protection of the

secondary hydroxyl in **20** as its acetate, followed by oxidation of sulfide with *m*-CPBA, afforded a mixture of epimeric sulfoxides **21.** Subjecting sulfoxide **21** to treatment with trifluoroacetic anhydride[24] and triethylamine in acetonitrile yielded the Pummerer intermediate that on hydrolysis with aq $NaHCO_3$ yielded aldehyde **23** in an one pot operation. Wittig olefination using the stable ylide furnished unsaturated ester **24** in 70% yield. Saponification using catalytic amount of anhydrous K_2CO_3 in ethanol yielded the alcohol **25**,[7f] a known compound comprising the C13-C22 subunit of callystatin A. The physical data of **25** were in good agreement with those reported in the literature.

Conclusions

In conclusion, we have synthesized the polypropionate C13-C22 subunit of callystatin A by using a non-aldol approach. Diastereoselective Myers' alkylation to prepare sulfide **7**, oxidative functionalization of the electron deficient trisubstituted olefin **6** using an intramolecular sulfinyl group as the nucleophile, diastereoselective radical debromination, Keck crotylation and Pummerer reactions are the key steps in the reaction sequence. The C16 Me stereocenter has been utilized to create all the other stereocenters by efficient substrate controlled 1,2-asymmetric induction. This strategy can be extended to synthesize other polypropionate natural products.

Experimental

General Information

All materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware, which was then cooled under nitrogen gas. Tetrahydrofuran (THF), toluene was distilled over Na/Ph_2CO under

nitrogen atmosphere. Dichloromethane (CH_2Cl_2), hexane, acetonitrile, triethylamine (TEA), 2,6-lutidine and diethyl ether (Et_2O) were dried over CaH_2 and distilled prior to use. Lithium Chloride were flame dried and then cooled under high vacuum prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates and analyzed with 254 nm UV light and/or anisaldehyde–sulfuric acid or potassium permanganate or PMA treatment. Silica gel for column chromatography was purchased from Acme (Silica Gel 60-120, 100-200 mesh). All 1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Gemini 200, Avance 300, Inova 400, Inova 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual $CHCl_3$ as an internal reference (1H: δ 7.26 ppm, 13C: δ 77.00 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded using Waters Mass spectrometer. HPLC spectra were recordedusing Waters 2998 spectrometer. High resolution mass (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometer and Thermo LTQ-Orbitrap mass spectrometer. All IR-spectra were recorded using Nexus 870-FT-IR Thermo Nicolet spectrometer.

(*S*)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethyl-3-(phenylthio)propanamde (10)

In a flame-dry round bottom flask containing dry lithium chloride (12.6 g, 300 mmol, 6 eq), anhydrous THF (100 mL) and diisopropylamine (14.2 mL, 110 mmol, 2.2 eq) were added. The resulting suspension was cooled to -78 °C and a solution of *n*-butyl lithium (42 mL, 2.5 M in hexane, 105 mmol, 2.1 eq) was added. The reaction mixture was warmed to 0 °C, stirred at this temperature for 30 min and then recooled to -78 °C. The solution of amide **8** (11.0 g, 50 mmol, 1 eq) in anhydrous THF (50 mL) was added to the reaction flask. The reaction mixture was stirred

at -78 °C for 1 h, at 0 °C for 15 min, at rt for 5 min and finally cooled to 0 °C, when freshly prepared iodide **9** (15.8 g, 60 mmol, 1.2 eq) was added. The mixture was stirred at 0 °C for 15 min and at rt for 2 h. The reaction was quenched by the addition of aq saturated ammonium chloride solution and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to afford the crude compound, which was purified by silica gel column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent to furnish amide **10** (15.2 g, 42.5 mmol) in 85% as a viscous oil. **TLC** $\mathbf{R}_f$ = 0.23 (50% EtOAc-hexanes). **IR** (neat): 3383, 3060, 2975, 2931, 2875, 1615, 1479, 1452, 1410, 1373, 1313, 1215, 1106, 1085, 1049, 1025, 920, 742, 699 cm^{-1}. **^{1}H NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 300 MHz, $CDCl_3$): δ7.45-7.08 (m,10H), 4.68-4.56 (m, 1H), 4.53- 4.3* (m, 1H) 4.21-4.06 (br, 1H), 3.96-3.85 (m, 1H), 3.46 (dd J = 13.4, 6.9 Hz, 1H), 3.27-3.16 (m, 1H), 3.06-2.78 (m, 1H), 2.91* (s, 3H), 2.73 (s, 3H), 2.42-2.29 (m, 1H), 1.24* (d, J = 6.9 Hz, 3H), 1.19 (d, J = 6.65 Hz, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.95* (d, J = 6.7 Hz, 3H). **^{13}C NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 75 MHz, $CDCl_3$): δ 176.3, 175.9*, 142.3, 141.4*, 136.6, 136.3*, 129.4, 129.0*, 128.8, 128.4*, 128.1, 128.0*, 127.4, 126.8, 126.4*, 126.0, 125.6*, 76.0, 74.8*, 58.1, 37.6, 37.1*, 36.6, 35.6*, 32.3, 26.9*, 17.4, 17.1*, 15.4, 14.2*. **MS (ESI)** 344 $[M+H]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{20}H_{26}O_2NS$ 344.16788; found 344.16815.

(*S*)-2-Methyl-3-(phenylthio) propan-1-ol (7)

A solution of *n*-butyl lithium (66.3 mL, 2.5 M in hexanes, 166 mmol, 3.9 eq) was added to a solution of diisopropylamine (23.1 mL, 178 mmol, 4.2 eq) in anhydrous THF (100 mL) at -78 °C. The resulting solution was stirred at -78 °C for 10 min, then warmed to 0 °C and held at that temperature for 10 min. Borane-ammonia complex (5.27 g, 170 mmol, 4 eq) was added in one portion and the suspension was stirred at 0 °C for 15 min and then warmed to rt. After 15 min,

the suspension was cooled to 0 °C. A solution of amide **10** (15.1 g, 42.5 mmol, 1eq) in anhydrous THF (60 mL) was added to the reaction mixture, warmed to rt and held at that temperature for 6 h. The reaction mixture was cooled to 0 °C and the excess hydride quenched by the slow addition of aq 3 N hydrochloric acid solution (120 mL). The mixture was stirred for 30 min at 0 °C and then extracted with ethyl acetate (120 mL). The combined organic extracts were washed with aq 3 N hydrochloric acid (40 mL), aq 2 N sodium hydroxide solution (40 mL) and brine (20 mL). The organic extracts were dried over sodium sulfate and concentrated. Purification of the crude residue by column chromatography using hexanes-EtOAc (8:2, v/v) as the eluent afforded alcohol **7** (6.4 g, 35.2 mmol) in 83% yield as a colorless liquid. **TLC** $\mathbf{R_f}$ = 0.12 (20% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 11.5 (*c* 1, CH_2Cl_2). **IR** (neat): 3390, 2959, 2876, 1583, 1478, 1030, 739, 691 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 2H), 7.31-7.22 (m, 2H), 7.20-7.12 (m, 1H), 3.64 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.59 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.07 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.84 (dd, *J* = 12.8, 6.7 Hz, 1H), 2.00-1.91 (m, 1H), 1.63 (bs), 1.04 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.6, 128.7, 125.6, 66.4, 37.1, 35.3, 16.3. **MS (ESI)** 205 $[M + Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{11}H_{14}O_2NaS$ 205.0663, found 205.0669.

HPLC: ee = 99.1% determined by chiral HPLC column, Eurocel; mobile phase: hexane/isopropanol 98/02, flow rate: 1 mL/min, temperature = 25 °C, detection: UV 220 nm, retention time (+)-isomer = 24.99 min, retention time (−)-isomer = 23.52 min. The title compound had physical characteristics in excellent agreement with the known literature compound.

(*S*)-2-Methyl-3-(phenylthio)propanal (11)

To a stirred solution of alcohol **7** (6.2 g, 34 mmol, 1 eq) in CH_2Cl_2 (100 mL), Dess–Martin periodinane (14.4 g, 34 mmol, 1 eq) was added at 0 ^oC. After completion of the reaction, the

reaction mixture was quenched with aq saturated sodium thiosulfate solution (50 mL) and aq saturated sodium bicarbonate solution (50 mL). The reaction mixture was extracted with dichloromethane (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the aldehyde **11** (5.5 g, 30.6 mmol) in 90% yield . This was used directly in the next step without further purification. **TLC** $\mathbf{R_f}$ = 0.21 (10% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 80.7 (*c* 1.4, $CHCl_3$). **IR** (neat): 2926, 2856, 2720, 1724, 1582, 1473, 1222, 1081, 771, 740, 691, 477 cm^{-1}. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 9.59 (d, *J* = 1.3 Hz, 1H), 7.30-7.10 (m, 5H), 3.22 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.82 (dd, *J* = 13.2, 7.1 Hz, 1H), 2.57-2.48 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H). ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 202.2, 130.1, 129.1, 128.2, 126.6, 45.9, 34.8, 13.5.

(*S,Z*)-Ethyl 2,4-dimethyl-5-(phenylthio)pent-2-enoate (12)

A solution of diaryl phosphonate (12.6 g, 33 mmol, 1.1 eq) in anhydrous THF (20 mL) was treated with NaH (1.34 g, 33 mmol, 60% dispersion in oil, 1 eq) in anhydrous THF (70 mL) at 0 °C for 20 min. The mixture was cooled to -78 °C and the solution of the aldehyde **11** (5.9 g, 30 mmol, 1eq) in anhydrous THF (20 mL) was added. After 30 min of stirring at the same temperature the reaction mixture was slowly warmed to 0 °C. The reaction was quenched with aq saturated ammonium chloride and the mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (2 x 50 mL), brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by chromatography using hexanes-EtOAc (9:1, v/v) as the eluent to afford compound **12** as a colorless oil (6.05 g, 22.8 mmol) in 76% yield. **TLC** $\mathbf{R_f}$ = 0.32 (10% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 28.5 (*c* 1, $CHCl_3$). **IR** (neat): 2976, 2927, 1711, 1477, 1239, 1188, 1111, 739, 691 cm^{-1} ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.29 (d, *J* = 6.7 Hz, 2H), 7.22 (t, *J* = 6.8 Hz, 1H), 7.11 (t, *J* = 6.8 Hz, 2H), 5.67(d, *J* = 7.8 Hz, 1H), 4.15-4.07 (m, 2H) 3.45-3.38 (m, 1H), 2.90 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.84 (dd, *J* = 12.6, 6.8 Hz, 1H), 1.87

(s, 3H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.3, 145.2, 136.8, 129.1, 128.6, 127.3, 125.6, 59.9, 40.6, 33.1, 20.7, 19.8, 14.1. **MS (ESI)**: 287 $[M + Na]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{15}H_{20}O_2NaS$ 287.1081, found 287.1091

(4*S*,*Z*)-Ethyl 2,4-dimethyl-5-(phenylsulfinyl)pent-2-enoate (6)

To a stirred solution of the sulfide **12** (5.8 g, 22 mmol, 1 eq), in dichloromethane (100 mL) cooled at -40 °C was added *m*-CPBA (70%, 5.4 g, 22 mmol, 1 eq) and the reaction progress was monitored by TLC. After 30 min the reaction mixture was diluted with DCM (20 mL) and washed successively with aq saturated Na_2SO_3, aq saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using hexanes-EtOAc (7:3, v/v) to afford an in-separable, epimeric mixture of sulfoxide **6** (5 g, 18 mmol) in 82% yield as a yellow color oil. Note: For characterization purposes a small sample of sulfoxide **6** was oxidized to the corresponding sulfone. The physical data presented is for the sulfone. **TLC** R_f = 0.1 (30% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 31.1 (*c* 1, $CHCl_3$). **IR** (neat): 2952, 2853, 1708, 1447, 1303, 1147, 1115, 1085, 748, 689, 532 cm^{-1} **^{1}H NMR**: (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 2H). 7.62 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 5.57 (d, *J* = 9.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H) 3.72-3.60 (m, 1H), 3.14 (dd, *J* = 13.9, 7.3 Hz, 1H), 3.06 (dd, *J* = 13.9, 6.2 Hz, 1H), 1.78 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.1, 143.2, 139.4, 133.4,129, 127.9, 119.6, 62, 60.3, 29.4, 20.4, 20.3, 14.1. **MS (ESI)**: 297 $[M + H]^+$. **HRMS (ESI)**: *m/z* calcd for $C_{15}H_{21}O_4S$ 297.1160, found 297.1173.

(2*S*,3*R*,4*S*)-Ethyl 2-bromo-3-hydroxy-2,4-dimethyl-5-(phenylsulfinyl) pentanoate (13)

To the solution of sulfoxide **6** (4.76 g, 17 mmol, 1 eq) in dichloromethane (80 mL) cooled at 0 ^oC in dark (covered with aluminium foil) was added water (0.5 mL, 25.5 mmol, 1.5 eq) followed

by a solution of NBS (3.3 g, 18.7 mmol, 1.1 eq) in dichloromethane (30 mL) through an addition funnel over a period of 1 h when TLC examination revealed the completion of the reaction. The reaction mixture was diluted with DCM (30 mL) and washed successively with aq saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using hexanes-EtOAc (6:4, v/v) as the eluent to yield bromohydrin **13** (5.1 g, 13.6 mmol) in 80% yield as a viscous oil. Note: For characterization purposes a small sample of sulfoxide **13** was oxidized to the corresponding sulfone. The physical data presented is for the sulfone. **TLC** $\mathbf{R_f}$ = 0.14 (40% EtOAc-hexanes). $[\alpha]_D^{25}$ = -19.5 (*c* 1.2, $CHCl_3$). **IR** (neat): 3339, 2926, 2857, 1727, 1452, 1300, 1143, 1076, 749, 689, 530 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.1 Hz, 2H). 7.63 (t, *J* = 7.1 Hz, 1H), 7.55 (t, *J* = 7.0 Hz, 2H), 4.25 (q, *J* = 7.1 Hz 2H), 3.98-3.91 (m, 1H), 3.61 (dd, *J* = 14.3, 0.9 Hz, 1H), 2.89 (dd, *J* = 14.5, 9.4 Hz, 1H), 2.36-2.22 (m, 1H), 1.8 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.2 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170, 140.4, 133.4, 129.2, 127.8, 77.1, 67.2, 62.2, 58.5, 31.1, 21, 19.4, 13.8. **MS (ESI)** 393 $[M + H]^+$ **HRMS (ESI)** *m/z* calcd for $C_{15}H_{22}O_5S$ Br 393.0371, found 393.0357.

(2*S*,3*R*,4*S*)-Ethyl2-bromo-2,4-dimethyl-5-(phenylsulfinyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)pentanoate (15)

To the solution of bromohydrin **13** (4.87 g, 13 mmol, 1 eq) in anhydrous dichloromethane (50 mL), dihydropyran (1.6 mL, 18.2 mmol, 1.4 eq) followed by camphor-10- sulfonic acid (CSA, 150 mg, 0.65 mmol, 0.05 eq) were added at 0 °C. The resulting mixture was warmed to rt and stirred for 1 h. An aq saturated solution of $NaHCO_3$ (20 mL) was added, the aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine, dried over on anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica

gel column chromatography using hexanes-EtOAc (7:3, v/v) as the eluent to afford the THP ether **15** (4.78 g, 10.4 mmol) in 80% yield as an oil. Note: For characterization purposes a small sample of sulfoxide **15** was oxidized to the corresponding sulfone. The physical data presented is for the sulfone. **TLC** $\mathbf{R_f}$ = 0.23 (30% EtOAc-hexanes). $[\alpha]_D^{25}$ = - 11.7 (*c* 2, $CHCl_3$). **IR** (neat): 2939, 2857, 1733, 1445, 1256, 1128, 1076, 1031, 750, 693, cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 6.7 Hz, 2H). 7.64 (t, *J* = 6.7 Hz, 1H), 7.56 (t, *J* = 6.7 Hz, 2H), 4.60-4.55 (m, 1H), 4.25 (q, *J* = 7.5 Hz, 2H) 3.98 (d, *J* = 2.2 Hz, 1H), 3.96-3.86 (m, 1H), 3.52-3.40 (m, 2H), 2.89 (dd, *J* = 14.3, 9.8 Hz, 1H), 2.07-1.95 (m, 1H), 1.88-1.77 (m, 2H), 1.68 (s, 3H), 1.56-1.42 (m, 4H), 1.34 (t, *J* = 6.7 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 169.6, 140.1, 133.4, 129.1, 128.1, 104.1, 86.0, 65.1, 62.1, 63.3 58.6, 31.5, 30.6, 25.1, 21.5, 21.1, 20.0, 13.9 **MS (ESI)** 499 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{20}H_{29}O_6NaSBr$ 499.0765, found 499.0751.

(2*S*,3*R*,4*S*)-ethyl2,4-dimethyl-5-(phenylsulfinyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)pentanoate (16)

To a stirred solution of THP ether **15** (2.3 g, 5 mmol, 1 eq) in anhydrous dichloromethane (25 mL) cooled at -78 °C was added drop wise *n*-Bu_3SnH (2.8 mL, 10 mmol, 2 eq) followed by Et_3B (3 mL, 3 mmol, 1 M soln in hexanes, 0.6 eq) in 1/3 portions every 15 min and the resulting mixture stirred for 2 h at the same temperature. The reaction was then quenched by the addition of water, extracted with dichloromethane (30 mL), washed with brine and dried over on Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography using hexanes-EtOAc (6:4, v/v) as the eluent to afford compound **16** as an oil (1.33 g, 3.5 mmol) in 70% yield. Note: For characterization purposes a small sample of sulfoxide **16** was oxidized to the corresponding sulfone. The physical data presented is for the sulfone. **TLC** $\mathbf{R_f}$ = 0.22 (40%

EtOAc-hexanes). $[\alpha]_D^{25}$ = - 16.8 (*c* 1, $CHCl_3$). **IR** (neat): 3063, 2975, 2940, 2879, 1727, 1585, 1447, 1379, 1302, 1181, 1144, 1073, 1028, 1004, 964, 868, 814, 749, 689 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.97-7.89 (m, 2H), 7.66-7.53 (m, 3H), 4.38 (dd, *J* = 6.1, 2.2 Hz, 1H), 4.12-4.03 (m, 2H), 3.88-3.80 (m, 1H) 3.61 (dd, *J* = 7.5, 3.1 Hz, 1H), 3.46-3.35 (m, 2H), 2.86 (dd, *J* = 14.3, 9.1 Hz, 1H), 2.52 (q, *J* = 6.7 Hz, 1H), 2.37-2.24 (m, 1H), 1.8-1.64 (m, 1H), 1.59-1.39 (m, 5H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.23 (t, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.1, 140.2, 133.1, 129.1, 127.8, 100.8, 84.1, 64.1, 60.1, 58.1, 43.2, 31.2, 30.1, 25.1, 20.7, 18.3, 14.1, 13.5. **MS (ESI)** 421 $[M + Na]^+$. **HRMS (ESI)** *m/z* calcd for $C_{20}H_{30}O_6NaS$ 421.1660, found 421.1651.

(2*R*,3*S*,4*S)*-Ethyl,3-hydroxy-2,4-dimethyl-5-(phenylthio)pentanoate (17)

t-Butyl bromide (2.2 mL, 20 mmol, 4 eq) was added to a solution of THP ether **16** (1.9 g, 5 mmol, 1 eq) in chloroform (25 mL) and the mixture heated at reflux overnight. After evaporation of the solvent, the residue was purified by column chromatography using hexanes-EtOAc (7:3, v/v) as the eluent to afford the compound **17** (0.98 g, 3.5 mmol) in 70% yield. **TLC** R_f = 0.13 (30% EtOAc-hexanes). $[\alpha]_D^{25}$ = +12.5 (*c* 1, $CHCl_3$). **IR** (neat): 3018, 2975, 2933, 1711, 1582, 1460, 1378, 1214, 1089, 984, 744, 667 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.33 (m, 2H), 7.29-7.25 (m, 2H), 7.18-7.14 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.48-3.43 (m, 1H), 3.38 (dd, *J* = 9.4, 3.3 Hz, 1H), 2.95 (d, *J* = 9.4 Hz, 1H), 2.76-2.71 (m, 2H), 1.87-1.81 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 136.9, 128.9, 128.7, 125.7, 77.1, 60.7, 41.7, 37.1, 36.5, 16.5, 15.1, 14.1. **MS (ESI)** 305 $[M + Na]^+$. **HRMS (ESI)** *m/z* calcd for $C_{15}H_{22}O_3Na\,S$ 305.11819, found 305.11813

(2*R*,3*S*,4*S)*-Ethyl3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethyl-5-(phenylthio)pentanoate (5)

To a solution of alcohol **17** (1.01 g, 3.5 mmol, 1 eq) in dichloromethane (20 mL) cooled at 0 ^{o}C was added 2,6-lutidine (0.81 mL, 7.0 mmol, 2 eq), followed by addition of TBSOTf (0.9 mL, 3.85 mmol, 1.1 eq). After 1 h, the reaction was quenched by addition of aq saturated $NaHCO_3$. The layers were separated and the layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine, dried and concentrated under reduced pressure. The crude product was purified by column chromatography chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to provide the product **5** (1.27 g, 3.2 mmol) in 92% yield as a bright yellow oil. **TLC** $\mathbf{R_f}$ = 0.2 (10% EtOAc-hexanes). $[\alpha]_D^{25}$ = + 2.2 (*c* 1, $CHCl_3$). **IR** (neat): 2932, 2883, 2857, 1726, 1692, 1439, 1258, 1214, 1025, 744, 667 cm^{-1}. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.28-7.24 (m, 2H), 7.17-7.13 (m, 1H), 4.15-4.07 (m, 2H), 3.95 (t, *J* = 5.9 Hz, 1H), 3.24 (dd, *J* = 9.4, 3.5 Hz, 1H), 2.7-2.64 (m, 1H), 2.62 (dd, *J* = 9.7, 3.1 Hz, 1H), 1.95-1.89 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H),0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 174.6, 137.1, 128.8, 128.7, 125.6, 77.1, 60.2, 44.9, 36.5, 36.3, 25.9, 18.1, 16.1, 14.1, 12.2, -4.3, -4.6. **MS (ESI)** 419 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{21}H_{37}O_3SSi$ 397.22272, found 397.22312

(2*S*,3*S*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-5-(phenylthio)pentan1-ol (18)

To a solution of compound **5** (1.2 g, 3.0 mmol, 1 eq) in anhydrous dichloromethane (18 mL) cooled at -78 °C, and maintained under atmosphere of N_2, was added DIBAL-H (1.4 M in toluene, 4.2 mL, 2 eq) over a period of 5 min. The reaction mixture was stirred at 0 °C for 30 min before being quenched with MeOH (2 mL). The mixture was allowed to warm to ambient temperature. An aq solution of Rochelle's salt was added (20 mL). The aqueous phase was extracted with DCM (3 x 10 mL), the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography on silica gel using hexanes-

EtOAc (8:2, v/v) as the eluent gave alcohol **18** (0.76 g, 2.1 mmol) in 72% as an oil. **TLC** $\mathbf{R}_f$ = 0.21(20% EtOAc-hexanes). $[\alpha]_D^{25}$ = -5.9 (*c* 1, $CHCl_3$). **IR** (neat): 3017, 2956, 2930, 2857, 1468, 1438, 1363, 1214, 1024, 749, 667 cm^{-1}. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.32 (m, 2H), 7.30-7.25 (m, 2H), 7.19-7.15 (m, 1H), 3.66 (t, *J* = 4.8 Hz, 1H), 3.63 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.59 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.13 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.69 (dd, *J* = 12.8, 9.0 Hz, 1H), 1.99-1.93 (m, 1H), 1.91-1.85 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 3H), 0.03 (s, 3H). ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 136.7, 129.2, 128.8, 125.9, 79.9, 65.7, 38.1, 37.2, 37.1, 26.1, 18.2, 16.2, 16.1, -4.1, -4.2. **MS (ESI)** 377 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{19}H_{35}O_2SSi$ 355.21215, found 355.21250.

(2*R*,3*S*,4*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-5-(phenylthio)pentanal (19)

To a stirred solution of alcohol **18** (0.7 g, 2.0 mmol, 1eq) in anhydrous dichloromethane (12 mL) was added solid $NaHCO_3$ (0.8 g, 10 mmol, 5 eq) followed by the Dess-Martin periodinane (1.0 g, 2.4 mmol, 1.2 eq). After stirring for 30 min, the reaction mixture was filtered through a pad of Celite. To the organic layer quenched by the aq saturated $Na_2S_2O_3$ (10 mL) and aq saturated $NaHCO_3$ (10 mL) were added and the biphasic mixture was stirred until both layers had cleared. The aq layer was extracted with CH_2Cl_2, the combine organic layers were washed with brine and dried over Na_2SO_4. The solution was filtered and concentrated under reduced pressure to provide **19** (0.55 g, 1.5 mmol) in 89% yield as a clear colorless oil which was used without further purification. **TLC** $\mathbf{R}_f$ = 0.22 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = -1.0 (*c* 1, $CHCl_3$). **IR** (neat): 2955, 2930, 2856, 1720, 1583, 1462, 1382, 1214, 1030, 748, 667 cm^{-1}. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 9.75 (d, *J* = 2.5 Hz, 1H), 7.34-7.31 (m, 2H), 7.29-7.25 (m, 2H), 7.19-7.15 (m, 1H), 3.94 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.1 (dd, *J* = 12.9, 5.3 Hz, 1H), 2.72 (dd, *J* = 13.1, 8.5 Hz, 1H), 2.56-2.49 (m, 1H), 2.01-1.93 (m, 1H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s,

3H), 0.02 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 203.7, 136.5, 129.1, 128.9, 125.9, 49.5, 38.1, 37.1, 25.9, 18.2, 15.7, 11.8, -4.1, -4.4. **MS (ESI)** 353 $[M + H]^+$. **HRMS (ESI)** *m/z* calcd for $C_{19}H_{33}O_2SSi$ 353.19650, found 353.19680.

(3*S*,4*S*,5*S*,6*S*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3,5,7-trimethyl-8-(phenylthio)oct-1-en-4-ol (20)

To the mixture the aldehyde **19** (0.52 g, 1.5 mmol, 1eq) and crotyl stannane (0.41 g, 1.8 mmol, 1.2 eq) in anhydrous dichloromethane (10 mL) cooled at -78 °C was added $BF_3.OEt_2$ (0.4 mL, 3.0 mmol, 2 eq). After 1 h, TLC examination indicated that all of the aldehyde had been consumed. The reaction was quenched with aq saturated $NaHCO_3$ solution. After warming to rt, the layers were separated and the aq layer extracted with dichloromethane (2 x 10 mL). The combined organic layers were separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude product. Purification by column chromatography on silica gel using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford the homoallylic alcohol **20** (0.4 g, 1.0 mmol) in 70% as a colorless oil. **TLC R_f** = 0.12 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = - 3.1 (*c* 1.1, $CHCl_3$). **IR** (neat): 3506, 2956, 2929, 2856, 1584, 1462, 1439, 1378, 1254, 1089, 1043, 1000, 834, 774, 690 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.14 (m, 5H), 5.61-5.41 (m, 1H), 5.05 (dd, *J* = 17.3, 1.5 Hz, 1H), 4.96 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.76-3.64 (m, 2H), 3.42-3.37 (bs, 1H), 3.16 (dd, *J* = 12.4, 8.1 Hz, 1H), 2.67 (dd, *J* = 12.4, 3.4 Hz, 1H), 2.33-2.19 (m, 1H), 1.91-1.80 (m, 1H), 1.72-1.59 (m, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.9 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.9, 136.7, 129.3, 128.9, 125.9, 114.7, 82.1, 74.6, 42.3, 38.1, 37.9, 35.6, 26.2, 18.3, 17.8, 16.3, 12.1, -3.7, -3.8. **MS (ESI)** 431 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{23}H_{40}O_2NaSSi$ 431.2415, found 431.24159.

(*4S,5S,6S)-4-((S)*-But-3-en-2-yl*)*-2,2,5-trimethyl-6-((*S*)-1-(phenylthio)propan-2-yl)-1,3-dioxane (22)

To a solution of **20** (41 mg, 0.1 mmol, 1 eq) in THF (3 mL) cooled at 0 °C was added TBAF (0.15 mL, 1M/THF, 0.15 mmol, 1.5 eq). The reaction mixture was stirred at ambient temperature for 3 h and then concentrated in vacuo. Purification by flash column chromatography on silica gel using hexanes-EtOAc (8:2, v/v) as the eluent furnished a diol (24 mg, 0.086 mmol) in 86% yield, which was used in the next step without characterization.

To a solution of the above diol in dichloromethane (3 mL) cooled at 0 °C was added, 2,2-dimethoxypropane (42 μL, 0.24 mmol, 3 eq) followed by CSA (2 mg, 0.008 mmol, 0.1 eq). The reaction mixture was stirred at room temperature for 3 h. An aq saturated solution of $NaHCO_3$ (2 mL) was added. The layers separated and aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford the acetonide **22** (19 mg, 0.06 mmol) in 70% yield as a colorless oil. **TLC** $\mathbf{R_f}$ = 0.12 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = -7.9 (*c* 1, $CHCl_3$). **IR (neat)**: 2981, 2962, 2929, 2874, 1641, 1583, 1457, 1377, 1224, 1158, 1065, 1000, 890, 737, 690 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.29-7.24 (m, 2H), 7.17-7.12 (m, 1H), 5.67-5.58 (m, 1H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.02 (dd, *J* = 10.3, 1.2 Hz, 1H), 3.42 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.27 (dd, *J* = 12.8, 3.3 Hz, 1H), 3.2 (t, *J* = 6.4 Hz, 1H), 2.69 (dd, *J* = 12.8, 9.1 Hz, 1H), 2.32-2.24 (m, 1H), 1.89-1.8 (m, 1H), 1.79-1.72 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.1, 137.5, 128.7, 128.6, 125.4, 115.2, 100.5, 78.1, 73.1, 38.2, 37.9, 36.6, 36.2, 25.3, 23.5, 17.9, 15.8, 12.8. **MS (ESI)** 373 $[M + Na]^+$ (sulfoxide) **HRMS (ESI)** *m/z* calcd for $C_{20}H_{30}O_3NaS$ 373.18079, found 373.18172.

(3*S*,4*S*,5*S*,6*S*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3,5,7-trimethyl-8-(phenylthio)oct-1-en-4-yl acetate (4)

To a solution of the alcohol **20** (0.32 g, 0.8 mmol, 1 eq) in dry dichloromethane (5 mL), cooled at 0 °C was added successively triethylamine (0.22 mL, 1.6 mmol, 2 eq), DMAP (10 mg, 0.08 mmol, 0.1 eq) and Ac_2O (0.14 mL, 1.2 mmol, 1.5 eq). The reaction mixture was stirred at rt for 3 h. An aq saturated solution of NH_4Cl (5 mL) was added. The layers separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford the title compound **4** (0.31 g, 0.7 mmol) in 87% as a colorless oil. **TLC** $\mathbf{R_f}$ = 0.3 (10% EtOAc- hexanes). $[\alpha]_D^{25}$ = -2.9 (*c* 1, $CHCl_3$). **IR** (neat): 2957, 2927, 2855, 1735, 1584, 1464, 1371, 1239, 1214, 1086, 1022, 920, 836, 751, 667 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.12 (m, 5H), 5.72-5.58 (m, 1H), 5.08-4.96 (m, 3H), 3.53 (dd, *J* = 5.4, 2.2 Hz, 1H), 3.2 (dd, *J* = 12.6, 9.4 Hz, 1H), 2.65 (dd, *J* = 12.8, 2.6 Hz, 1H), 2.48-2.34 (m, 1H), 2.06-1.93 (m, 1H), 2.01 (s, 3H), 1.92-1.8 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 7.1 Hz, 3H), 0.09 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.6, 140.4, 137.1, 129.3, 128.8, 125.8, 115.2, 78.3, 76.3, 41.1, 39.6, 36.8, 36.4, 26.2, 21.1, 18.4, 17.5, 15.8, 10.5, -3.7, -4.4. **MS (ESI)** 473 $[M + Na]^+$ **HRMS (ESI)**: *m/z* calcd for $C_{25}H_{42}O_3NaSSi$ 473.25161, found 473.25247.

(3*S*,4*S*,5*S*,6*S*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3,5,7-trimethyl-8-(phenylsulfinyl)oct-1-en-4-yl acetate (21)

To a stirred solution of compound **4** (270 mg, 0.6 mmol, 1 eq) in dichloromethane (4 mL) cooled at -40 °C was added *m*-CPBA (70%, 147 mg, 0.6 mmol, 1 eq). After 30 min the reaction mixture

was diluted with dichloromethane (10 mL) and washed successively with aq saturated Na_2SO_3, aq saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude product which was purified by column chromatography using hexanes-EtOAc (7:3, v/v) as the eluent to afford epimeric sulfoxides **21** (210 mg, 0.47 mmol) in 79% yield. **TLC** $\mathbf{R_f}$ = 0.12 (20% EtOAc-hexanes). **IR** (neat): 2956, 2929, 2886, 2856, 1736, 1463, 1443, 1371, 1238, 1214, 1086, 1025, 918, 836, 748, 667, 630 cm^{-1}. **^{1}H NMR** (1:1 ratio of diastereomers, asterisk denotes other diastereomer peaks, 300 MHz, $CDCl_3$): δ 7.67-7.64 (m, 2H), 7.63-7.59*(m, 2H), 7.55-7.48 (m, 6H), 5.66-5.56 (m, 2H), 5.04-4.97 (m, 4H), 4.96 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.90*(dd, *J* = 7.9, 5.1 Hz, 1H), 3.53 (dd, *J* = 6.4, 4.7 Hz, 1H), 3.42* (dd, *J* = 6.1, 3.9 Hz, 1H), 3.02 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.94 (dd, *J* = 13.2, 2.1 Hz, 1H), 2.77* (dd, *J* = 9.6, 3.5 Hz, 1H), 2.51-2.43* (m, 1H), 2.42-2.37 (m, 1H), 2.36-2.27 (m, 2H), 2.11 (s, 3H), 2.01* (s, 3H) 1.95-1.84 (m, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.10*(d, *J* = 7.1 Hz, 3H), 0.96-0.94 (m, 6H), 0.89 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.85*(s, 9H), 0.68* (d, *J* = 7.1 Hz, 3H), 0.1 (s, 3H), 0.08*(s, 3H), 0.06 (s, 3H), 0.02*(s, 3H). **^{13}C NMR** (1:1 ratio of diastereomers, asterisk denotes other diastereomer peaks, 75 MHz, $CDCl_3$): δ 171.1, 170.6*, 145.1, 144.3*, 140.2, 131.2, 130.7*, 129.3, 129.2*, 124.3, 123.8*, 115.5, 115.4*, 79.1, 78.6*, 76.4, 76.3*, 61.1, 60.7*, 41.2, 41.1*, 40.2, 39.8*, 31.9, 31.1*, 26.2, 26.1*, 21.1, 20.9*, 19.1, 18.5*, 18.4, 18.3*, 16.4, 16.1*, 10.1, 9.7*, -3.7, -3.8*, -4.3, -4.4*. **MS (ESI)** 489 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{25}H_{42}O_4NaSSi$ 489.24653, found 489.24549.

(3*S*,4*S*,5*S*,6*S*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3,5,7-trimethyl-8-oxooct-1-en-4-ylacetate (23)

To a solution of the alcohol of compound **21** (180 mg, 0.34 mmol, 1 eq) in dry acetonitrile (5 mL), cooled at 0 °C was added successively triethylamine (0.14 mL, 1.0 mmol, 3 eq) and

trifluoroacetic anhydride (0.15 mL, 1.0 mmol, 3 eq). After 10 min aq saturated $NaHCO_3$ (5 mL) was added at the same temperature and the mixture was allowed to warm to rt. The mixture was stirred for 30 min and diluted with water (10 mL) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford pure **23** (72 mg, 0.2 mmol) in 60% yield as an oil. **TLC R_f** = 0.2 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = -5.5 (*c* 1, $CHCl_3$). **IR** (neat): 2954, 2929, 2856, 1738, 1709, 1644, 1463, 1372, 1238, 1077, 1022, 917, 836, 774, 669 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.77 (d, *J* = 2.2 Hz, 1H), 5.69-5.61 (m, 1H), 5.08-5.02 (m, 2H), 4.96 (dd, *J* = 8.2, 5.5 Hz, 1H), 3.86 (dd, *J* = 5.6, 2.9 Hz, 1H), 2.5-2.38 (m, 2H), 2.08 (s, 3H), 2.07-2.01 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 204.1, 170.8, 140.1, 115.6, 76.8, 76.1, 49.7, 41.2, 40.1, 25.6, 21.1, 18.2, 16.2, 11.8, 9.5. -4.2, -4.7. **MS (ESI)** 379 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{19}H_{36}O_4NaSi$ 379.22751, found 379.22847

(*4R,5R,6S,7S,8S,E)*-Ethyl-7-acetoxy-*5*-((*tert*-butyldimethylsilyl)oxy)-2,4,6,8-tetramethyldeca-2,9-dienoate (24)

The solution of the aldehyde **23** (50 mg, 0.14 mmol, 1 eq) and (1-ethoxycarbonylethylidene) triphenylphosphorane (102 mg, 0.28 mmol, 2 eq) were in anhydrous dichloromethane (5 mL), was heated at reflux for 15 h. The reaction mixture was concentrated and the residue was purified by chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to yield unsaturated ester **24** (40 mg, 0.1 mmol) in 78% yield as a colorless oil. **TLC R_f** = 0.3 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = +8.2 (*c* 1, $CHCl_3$). **IR** (neat): 2984, 1731, 1443, 1374, 1246, 1215,

1096, 1045, 929, 847, 746, 667, 608 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.96 (d, *J* = 9.6 Hz, 1H), 5.74-5.59 (m, 1H), 5.09-4.99 (m, 2H), 4.96 (dd, *J* = 7.3, 3.7 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.59 (dd, *J* = 4.1, 3.1 Hz, 1H), 2.69-2.59 (m, 1H), 2.47-2.36 (m, 1H), 2.05 (s, 3H), 1.99-1.89 (m, 1H), 1.83 (s, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.6, 168.3, 144.7, 140.2, 128.8, 115.3, 78.3, 76.9, 60.2, 40.8, 40.3, 36.0, 26.1, 22.8, 21.1, 18.6, 15.4, 14.2, 12.4, 9.8, -3.7, -4.4. **MS (ESI)**: 463 $[M + Na]^+$ **HRMS (ESI)** *m/z* calcd for $C_{24}H_{44}O_5NaSi$ 463.28502, found 463.28435.

(*4R,5R,6S,7S,8S,E)*-Ethyl-5-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-2,4,6,8-tetramethyldeca-2,9-dienoate (25)

To a solution of ester **24** (25 mg, 0.05 mmol, 1 eq) in of EtOH (3 mL) was added K_2CO_3 (3 mg, 0.02 mmol, 0.4 eq) at 0 °C. The mixture was stirred at rt until complete conversion of the starting material (reaction followed by thin layer chromatography). The reaction was cooled down to 0 °C and quenched with cold aq saturated NH_4Cl solution. The aq layer was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4. The volatiles were removed in vacuo to give a yellow oil which was purified by chromatography using hexanes-EtOAc (9.5:0.5, v/v) as the eluent to afford the pure product **25** (13 mg, 0.04 mmol) in 76% yield. **TLC R_f** = 0.15 (5% EtOAc-hexanes). $[\alpha]_D^{25}$ = +32.5 (*c* 0.8, $CHCl_3$). Reported rotation $[\alpha]_D^{26}$ = +36.2 (*c* 1, $CHCl_3$). **IR (neat):** 3448, 2957, 2924, 2853, 1710,1643, 1462,1370, 1257, 1118, 755, 541 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.65 (q, *J* = 10.1 Hz, 1H), 5.61-5.53 (m, 1H), 5.07 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.98 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.24-4.16 (m, 2H), 3.71 (dd, *J* = 9.6, 1.3 Hz, 1H), 3.64 (dd, *J* = 7.9, 2.4 Hz, 1H), 3.48-3.34 (brs, 1H), 2.92-2.86 (m, 1H), 2.33-2.22 (m, 1H), 1.92-1.82 (m, 1H), 1.87 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 7.0

Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.1, 145.5, 140.8, 127.7, 114.8, 83.1, 74.4, 60.4, 42.2, 37.9, 35.8, 26.1, 18.2, 17.6, 17.2, 14.3, 12.7, 11.7, -3.3, -3.8. **MS (ESI)** 421 $[M + Na]^+$. **HRMS (ESI)** *m/z* calcd for C_{22} H_{42} O_4 Na Si = 421.27446, found 421.27346.

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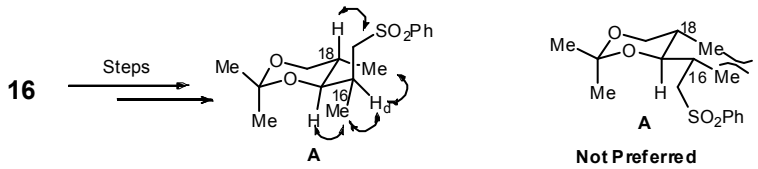

The NOE observed between C18 Me and H_d confirmed the *anti*-disposition of the C17-OH and C18-Me groups. So also, the NOE between CH_2SO_2Ph and C18-methine proton confirmed the *anti*-disposition of the C16-Me and C17-OH groups.

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Electronic Supplementary Information available.