# Towards the Total Synthesis of Ambruticin: Preparation of the Fully Functionalised Right-Hand Portion Using the Intramolecular Silyl-Modified Sakurai (ISMS) Annulation

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Dedicated fondly to Dr. Alan H. Davidson

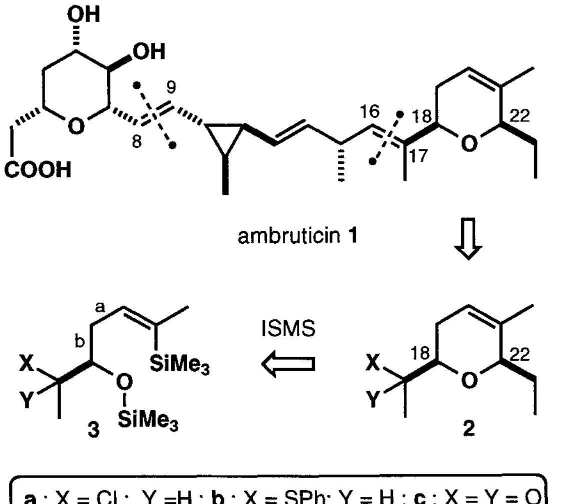
The concise synthesis of the fully functionalised right-hand dihydropyran subunit of the antifungal antibiotic ambruticin (1), using the ISMS annulation as the key-step, is described.

Ambruticin (**1**), isolated from fermentation of the Myxobacterium *Polyangium cellulosum var. fulvum* by the Warner–Lambert team in the late 1970s, not only displays unique biological activities as an antifungal antibiotic but also possesses a challenging architectural framework.[2] The structure elucidation of ambruticin (**1**), including the determination of its absolute stereochemistry, was achieved by an elegant combination of spectroscopic and degradation studies.[3] The complexity of ambruticin (**1**) coupled with its intriguing biological properties have elicited considerable interest in the synthetic community, resulting in the preparations of several portions of the natural product.[4] However, only one total synthesis of ambruticin (**1**), by the group of Kende, has been repeated to date.[5]

As part of a programme aimed at the efficient and versatile total synthesis of natural products using, as the key-step, the Intramolecular Silyl-Modified Sakurai (ISMS) reaction,[6] we became interested in the preparation of ambruticin (**1**) as well as analogues, for further modulation of its biological activities. We already reported an expedient entry into the left-hand portion of the antifungal antibiotic, using a cascade process involving the combination ene reaction/ISMS condensation,[7] as well as the study of a model for the right-hand subunit of **1**.[8] In this article, we describe our results on the total synthesis of the fully functionalised eastern fragment **2**.

With a view of imparting flexibility and convergency to the total synthesis, we selected to disconnect ambruticin (**1**) into three fragments by cleavage of the $C_8$-$C_9$ and $C_{16}$-$C_{17}$ double bonds (Scheme 1) and decided to construct the trisubstituted $C_{16}$-$C_{17}$ double bond by using our recent modification[9] of the Julia–Lythgoe olefination reaction.[10] Two options are therefore possible; either condensing a primary sulfone with ketone **2c** (X = Y = O) or reacting a $\beta,\gamma$-unsaturated aldehyde with secondary sulfone **2** (X = H, Y = $SO_2Ph$). Both intermediates could be readily available from the corresponding sulfide **2b** (X = H, Y = SPh) or chloride **2a** (Scheme 1).

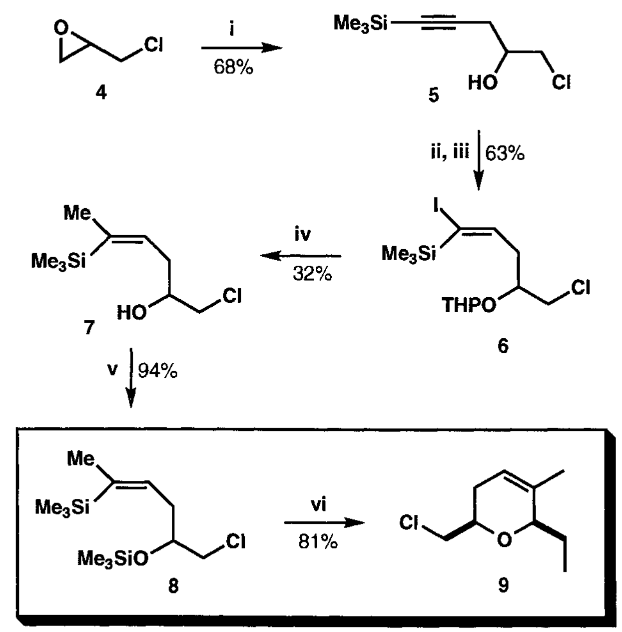
Further antithetic analysis of subunit **2**, using the ISMS retron, suggests the condensation of propionaldehyde with the annulating agent **3**, which could be assembled either by opening of an epoxide with a vinyl metal species (bond a) or by addition of a propargylic anion onto a suitable aldehydic partner (bond b).[11] In view of the ready availability of epichlorohydrin (**4**), both in racemic and optically pure forms, we decided to direct our initial efforts towards the preparation of annulating agent **3a** and hence subunit **2a**.



**Scheme 1**

Epichlorohydrin (**4**) was reacted with the lithio anion of (trimethylsilyl)acetylene, in the presence of $BF_3 \cdot OEt_2$ in THF at −78 °C, affording in good yield the corresponding homopropargylic alcohol **5** (Scheme 2).[12] Protection of the hydroxy function [3,4-dihydro-2*H*-pyran (DHP), pyridinium *p*-toluenesulfonate (PPTS)], followed by regioselective hydroalumination with diisobutylaluminum hydride (DIBAL) and iodine quench of the resulting vinylalane, generated the sterochemically pure, trisubstituted vinylsilane **6**.[13] According to the procedure of Ashby,[14] addition of one equivalent of MeLi to vinyl iodide **6**, in THF at room temperature, resulted in transmetallation to the vinyllithium species which was alkylated by the in situ generated methyl iodide leading to the trisubstituted alkene **7** after acidic workup. This sequence proved to be highly stereoselective and only the *Z*-olefin was produced. Silylation then led to the desired annulating agent **8**.

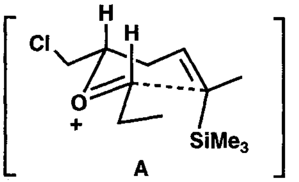
With ready access to large amounts of **8**, we then turned our attention to the crucial ISMS cyclisation. Addition of a catalytic amount of trimethylsilyl triflate (TMSOTf) to a dichloromethane solution of **8** and propionaldehyde



i = $Me_3SiC{\equiv}CH$, nBuLi, $BF_3.Et_2O$, THF, -78°C; ii = DHP, PPTS, $CH_2Cl_2$, 20°C, iii = Dibal, $Et_2O$, 20°C then $I_2$; iv = MeLi, THF, 20°C then PPTS, EtOH, $H_2O$, 60°C; v = $Me_3SiCl$, $Et_3N$, $CH_2Cl_2$, 20°C, vi = $CH_3CH_2CHO$, $Me_3SiOTf$ cat, $CH_2Cl_2$, -78°C to 20°C.

Scheme 2

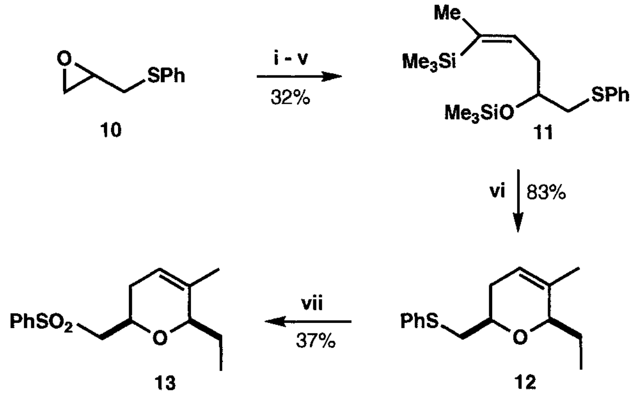
smoothly afforded the desired 5,6-dihydro-2*H*-pyran derivative **9** in excellent yield. Interestingly only the isomer possessing the *cis*-stereochemical relationship between the substituents present at carbon centres $C_{18}$ and $C_{22}$ (ambruticin numbering) was formed implying a condensation reaction proceeding through the cyclic transition state **A**. In this six-membered transition state, both the ethyl and chloromethyl substituents occupy equatorial positions. The trimethylsilyl moiety is locked in the axial position due to the olefin geometry.



**A**

Unfortunately, every subsequent attempt at substituting the chlorine atom by either iodide, thiophenyl or tosylate failed.[15] Similarly, experiments aimed at oxidising the primary chloride into an aldehyde function, by a variety of techniques, proved fruitless.[16]

These failures prompted us to reinvestigate our approach towards the ambruticin right-hand fragment and it was decided to incorporate the phenylthio group from the beginning, thus ensuring that the two original options for formation of the $C_{16}$-$C_{17}$ double bond (*vide supra*) could still remain available. Epichlorohydrin (**4**) was therefore transformed into the corresponding thioether **10** and the previous sequence was repeated (Scheme 3).



i = $Me_3SiC{\equiv}CH$, nBuLi, $BF_3.Et_2O$, THF, -78°C; ii = DHP, PPTS, $CH_2Cl_2$, 20°C, iii = Dibal, $Et_2O$, 20°C then $I_2$; iv = MeLi, THF, 20°C then PPTS, EtOH, $H_2O$, 60°C; v = $Me_3SiCl$, $Et_3N$, $CH_2Cl_2$, 20°C, vi = $CH_3CH_2CHO$, $Me_3SiOTf$ cat, $CH_2Cl_2$, -78°C to 20°C; vii = mCPBA, $CH_2Cl_2$, -78°C to 20°C.

Scheme 3

The key-ISMS cyclisation of annulating agent **11** proceeded efficiently and, once again, only the *cis*-2,6-disubstituted 5,6-dihydro-2*H*-pyran **12** was produced. Addition of the missing $C_{17}$-methyl substituent was attempted after chemoselective oxidation of adduct **12** into sulfone **13**. Disappointingly, this seemingly trivial transformation could not be performed successfully under a variety of experimental conditions and the starting material was consistently recovered.[17]

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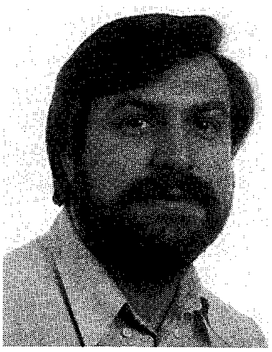
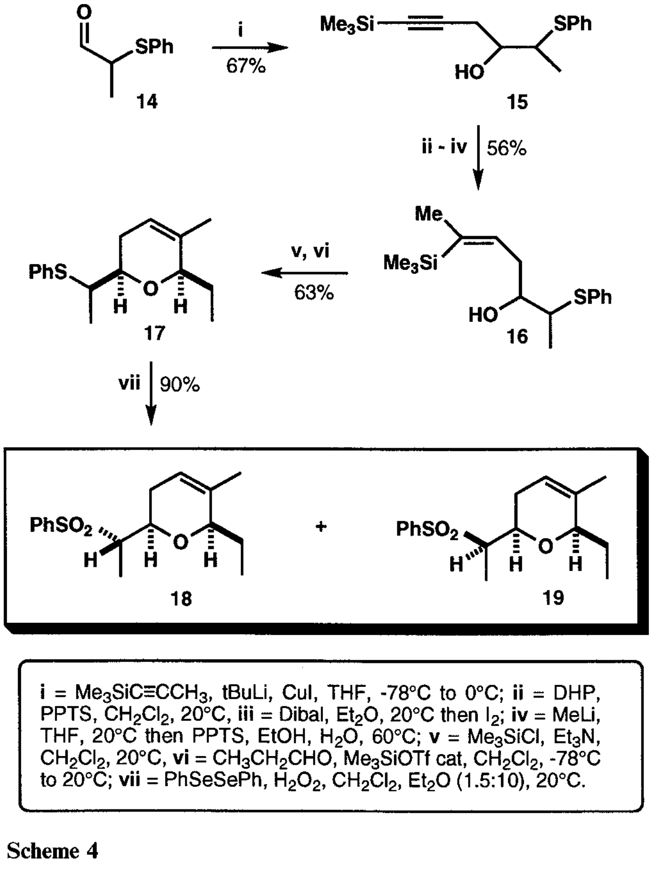
## Biographical Sketch



**István Marko** was born in Pápa, Hungary in 1956. He received his Ph. D. from Louvain University, Belgium in 1983 working with Prof. L. Ghosez. Between 1985–1988 he worked in the United States as a post-doctoral associate first with Prof. M.E. Kuehne and then with Prof. K.B. Sharpless. In 1988 he joined the University of Sheffield and spent 5 years there as lecturer. In 1993 he was appointed Professor at the University of Louvain in Belgium. He is currently Chairman of the newly formed European Chemical Society. His main areas of research are the total synthesis of natural products, development of new methodologies based on multiple bonds and ring formation, asymmetric catalysis with and without metals, and new organometallic reagents.

The necessity to incorporate the methyl group at $C_{17}$ of ambruticin by a circuitous and inelegant manner[18] from adduct **12** prompted us to reshape our strategy and a third, this time successful, approach was devised (Scheme 4).

The readily available aldehyde **14**[19] was thus reacted with the lithium anion of (1-trimethylsilyl)prop-1-yne, in the presence of CuI,[20] affording the homopropargylic alcohol **15** in good yield. Protection of the free hydroxyl function, followed by hydroalumination, iodination and methylation generated, after aqueous acidic treatment, trisubstituted alkene **16** in good overall yield and high stereochemical purity. Silylation followed by ISMS cyclisation produced the requisite 5,6-dihydro-2*H*-pyran derivative **17** as a 1 : 1 mixture of diastereoisomers at $C_{17}$ (Scheme 4).



i = $Me_3SiC{\equiv}CCH_3$, tBuLi, CuI, THF, -78°C to 0°C; ii = DHP, PPTS, $CH_2Cl_2$, 20°C, iii = Dibal, $Et_2O$, 20°C then $I_2$; iv = MeLi, THF, 20°C then PPTS, EtOH, $H_2O$, 60°C; v = $Me_3SiCl$, $Et_3N$, $CH_2Cl_2$, 20°C, vi = $CH_3CH_2CHO$, $Me_3SiOTf$ cat, $CH_2Cl_2$, -78°C to 20°C; vii = PhSeSePh, $H_2O_2$, $CH_2Cl_2$, $Et_2O$ (1.5:10), 20°C.

**Scheme 4**

Finally, the sulfides **17** were oxidised into the sulfones **18** and **19** using PhSeSePh/$H_2O_2$, this time in excellent yield.[21] At this stage, the two epimers could be easily separated by crystallisation. The presence of two epimers at $C_{17}$ is of no consequence for the rest of the total synthesis since this chiral centre will be lost at a later stage, either by transformation into the sulfone anion or by generation of a ketone function from **17**. Nevertheless, simple derivatisation of the solid sulfone isomer **18** produced suitable crystals for X-ray diffraction analysis (Figure).[22]

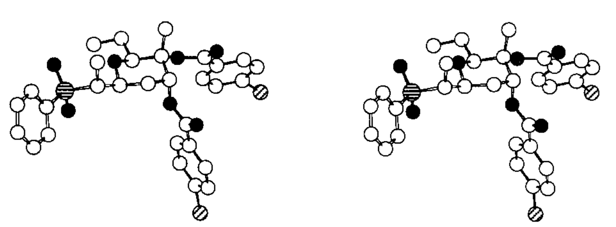


**Figure.** Cross-Eyed Stereoscopic View of Compound **20**

This analysis demonstrates unambiguously the *cis*-relationship between the two substituents attached at carbon centres $C_{18}$ and $C_{22}$. It also establishes the structure of adduct **19** and allows the assignment of the stereochemistry at $C_{17}$ of both sulfone epimers as depicted in Scheme 4.

In summary, using the ISMS condensation as a key-step, we have achieved the efficient (7 steps, 21 % overall yield) synthesis of the fully functionalised eastern-portion of the antifungal antibiotic ambruticin (**1**). Further work aimed at the coupling of this unit with the western part of the natural product and at the completion of the total synthesis of ambruticin (**1**) is currently under active investigation in our laboratory. The results of these studies will be reported in due course.

All the reactions were carried out under anhydrous conditions under an atmosphere of Ar, unless otherwise stated. Routine NMR spectra were recorded on Bruker Aspect 250 ($^1H$ 250 and $^{13}C$ 62.9 MHz), Varian Gemini-200 ($^1H$ 200 MHz and $^{13}C$ 50.29 MHz), Varian Gemini-300 ($^1H$ 300 and $^{13}C$ 75.5 MHz) and Bruker WH 400 ($^1H$ 400 and $^{13}C$ 100 MHz) spectrometers. $^1H$ NMR chemical shifts are reported in ppm downfield from internal TMS or calibrated from $CHCl_3$ in the case of silyl-containing compounds. $^{13}C$ NMR spectra were recorded using $CDCl_3$ as the internal standard, unless otherwise stated. Low resolution mass spectral data were collected on a Kratos MS25 or a Varian MATT 445 instrument using chemical ionisation or electron impact (70 eV). HRMS were recorded using a Kratos MS80 system. Microanalyses were performed at The University of Sheffield using a Perkin-Elmer 2400 CHN analyser, or at the University College, London. IR spectra were recorded using a Perkin-Elmer 684 or a Nicolet 205 instrument. Melting points were determined on a Kofler hot-stage micro melting point apparatus and are uncorrected. TLC was performed on Merck 0.2 mm, aluminum-backed plates, visualised using UV light, or developed using $I_2$ or alkaline $KMnO_4$ solution. Column chromatography was performed using Merck silica gel 60 (230–400 mesh) under pressure with the stated solvents. Anhydrous solvents were distilled from $CaH_2$; THF and $Et_2O$ were dried using the Na/benzophenone ketyl method and collected just prior to use. Petroleum ether, bp 40–60 °C fraction was used.

### 1-Chloro-5-trimethylsilylpent-4-yn-2-ol (5):

To a cold (– 78 °C) solution of (trimethylsilyl)acetylene (1.2 equiv, 8.3 g, 0.085 mol) in THF (120 mL) was added a 2.5 M hexane solution of BuLi (1.2 equiv, 34 mL, 0.085 mol). The solution was stirred at this temperature for 30 min, then epoxide **4** (1.0 equiv, 7.12 g, 0.077 mol) was added followed by $BF_3 \cdot OEt_2$ (1.2 equiv, 10.5 mL, 0.085 mol) at such a rate so as to maintain the internal temperature below – 65 °C. The resulting solution was stirred at – 78 °C for 1 h, and poured onto sat. aq $NH_4Cl$ (200 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to leave a brown oil. Purification by flash column chromatography (silica gel, hexane/EtOAc, 5:1) afforded the title compound **5** (11.1 g, 68 %) as a colourless oil.

IR (neat): $\nu = 3400, 2955, 2870, 2170, 1430, 1250, 1035, 845\ \mathrm{cm}^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 3.93$–$4.03$ (1 H, m), 3.72 (1 H, $ABX_1$, $J = 11.1, 4.5$ Hz), 3.63 (1 H, $ABX_1$, $J = 11.1, 6.1$ Hz), 2.62 (1 H, $ABX_2$, $J = 17.0, 5.8$ Hz), 2.55 (1 H, $ABX_2$, $J = 17.0, 6.6$ Hz), 2.44 (1 H, d, $J = 5.9$ Hz), 0.16 (9 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 101.15, 88.24, 69.55, 48.23, 25.69, -0.08$.

MS (EI): $m/z = 192$ ($M^+$ [$^{37}$Cl], 4%), 190 ($M^+$ [$^{35}$Cl], 7%), 177, 175, 153, 151, 112, 95, 93, 73.

HRMS: Calc. mass for $C_7H_{12}ClOSi$: 175.0346. Found: 175.0370.

Anal. calc. for $C_8H_{15}ClOS$: C, 50.38; H, 7.93. Found: C, 50.04; H, 7.81.

**1-Chloro-5-trimethylsilyl-2-(2-tetrahyropyranyloxy)pent-4-yne:**
A mixture of **5** (1.0 equiv, 6.3 g, 0.033 mol), 3,4-dihydro-2*H*-pyran (1.2 equiv, 4.2 g, 0.050 mol) and PPTS (0.1 equiv, 0.83 g, 3.32 mmol) in $CH_2Cl_2$ (45 mL) was stirred at r.t. for 24 h. The solution was diluted with $Et_2O$ (100 mL) and the white precipitate formed was filtered. The filtrate was evaporated in vacuo to leave a pale yellow oil. Purification by distillation (bp 150 °C/1.5 Torr) furnished the title compound (1:1 mixture of diastereoisomers, 8.8 g, 97%) as a colourless oil.

IR (neat): $\nu = 2950, 2170, 1255, 1035, 845\ \mathrm{cm}^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 4.76$–$4.83$ (1 H, m), 3.89–4.03 (2 H, m), 3.45–3.78 (3 H, m), 2.45–2.72 (2 H, m), 1.47–1.85 (6 H, m), 0.14 (9 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 102.40, 102.36, 98.48, 98.07, 86.95, 74.74, 74.39, 62.49, 62.27, 46.45, 45.35, 30.48, 30.36, 25.25, 24.71, 23.27, 19.27, 19.06, -0.11$.

MS (EI): $m/z = 275$ ($M^+$, 100%), 191, 171, 139, 91.

Anal. calc. for $C_{13}H_{23}ClO_2Si$: C, 56.81; H, 8.43. Found: C, 56.80; H, 8.51.

**(*E*)-1-Iodo-5-chloro-1-trimethylsilyl-4-(2-tetrahydropyranyloxy)-pent-4-ene (6):**
To an ice cold solution of 1-chloro-5-trimethylsilyl-2-(2-tetrahydropyranyloxy)pent-4-yne (1.0 equiv, 8.8 g, 0.032 mmol) in $Et_2O$ (42 mL) was added a 1.0 M hexane solution of DIBAL (2.0 equiv, 64 mL, 0.064 mol). The resulting mixture was treated with a solution of $I_2$ (2.1 equiv, 17.3 g, 0.067 mol) in $Et_2O$ (42 mL) at such a rate so as to maintain the internal temperature below − 65 °C. The black solution was allowed to reach 0 °C over 3 h, poured onto ammonia (200 mL) and stirred vigorously for 30 min. The slurry was filtered through a pad of Celite, washed with $Et_2O$ (3 × 80 mL), the phases separated and the aqueous layer extracted with $Et_2O$ (3 × 80 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Purification by flash column chromatography (silica gel, hexane/EtOAc/$Et_3N$, 30:1:1) furnished the title compound **6** (1:1 mixture of diastereoisomers, 8.36 g, 65%) as a colourless oil.

IR (neat): $\nu = 2945, 1590, 1255, 1125, 1035, 845\ \mathrm{cm}^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.21$ (1 H, t, $J = 7.6$ Hz), 7.13 (1 H, t, $J = 7.6$ Hz), 4.75 (1 H, t, $J = 3.6$ Hz), 4.64 (1 H, t, $J = 3.6$ Hz), 3.40–3.95 (10 H, m), 2.30–2.55 (4 H, m), 1.43–1.85 (12 H, m), 0.25 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 152.29, 150.82, 110.24, 110.03, 99.54, 97.34, 76.41, 74.15, 62.87, 62.29, 46.45, 45.22, 38.31, 37.23, 30.77, 30.50, 25.37, 25.29, 19.56, 19.13, 1.10$.

MS (EI): $m/z = 402$ [$M^+$ ($^{35}$Cl), 4%], 311, 300, 185, 173, 85.

Anal. calc. for $C_{13}H_{24}ClIO_2Si$: C, 30.15; H, 5.06. Found: C, 30.41; H, 4.92.

**(*Z*)-1-Chloro-5-trimethylsilylhex-4-en-2-ol (7):**
To a cold (− 78 °C) solution of **6** (1.0 equiv), 8.44 g, 0.021 mol) in THF (70 mL) was added a 1.6 M $Et_2O$ solution of MeLi (1.5 equiv, 20 mL, 0.031 mol). The resulting mixture was allowed to reach r.t. and was stirred for another 20 h before pouring onto aq ammonia (140 mL). The aqueous layer was extracted with $Et_2O$ (3 × 100 mL) and the combined organic layers were concentrated in vacuo to give a brown oil which was taken up in EtOH/$H_2O$ (9:1, 70 mL). This solution was treated with PPTS (0.1 equiv, 0.56 g, 2.06 mmol) and heated at 65 °C for 12 h. The cold (0 °C) mixture was poured onto sat. aq $NaHCO_3$ (140 mL), the aqueous phase separated and extracted with $Et_2O$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed in vacuo to leave a brown oil which was purified by flash column chromatography (silica gel, hexane/EtOAc, 20:1) to afford the title compound **7** (1.47 g, 34%) as a colourless oil.

IR (neat): $\nu = 3380, 2945, 2880, 1615, 1255, 1060, 840\ \mathrm{cm}^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 5.93$ (1 H, tq, $J = 7.5, 1.6$ Hz), 3.77–3.87 (1 H, m), 3.62 (1 H, ABX, $J = 11.1, 3.6$ Hz), 3.48 (1 H, ABX, $J = 11.1, 6.8$ Hz), 2.28–2.45 (2 H, m), 2.18 (1 H, d, $J = 4.6$ Hz), 1.77 (3 H, s), 0.12 (9 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 139.39, 135.78, 71.36, 49.54, 36.40, 24.85, -0.26$.

MS (EI): $m/z = 206$ [$M^+$ ($^{35}$Cl), 3%], 193, 191, 95, 93, 81, 75, 73.

HRMS: Calc. mass for $C_9H_{19}ClOSi$: 206.0894. Found: 206.0891.

**(*Z*)-1-Chloro-5-trimethylsilyl-2-trimethylsilyloxyhex-4-ene (8):**
To a cold (0 °C) solution of **7** (1.0 equiv, 1.44 g, 7.05 mmol) and $Me_3SiCl$ (1.1 equiv, 0.9 g, 8.46 mmol) was added $Et_3N$ (1.2 equiv, 0.93 g, 9.17 mmol). The mixture was stirred overnight at r.t. and then poured onto sat. aq $NaHCO_3$ (45 mL). The aqueous phase was separated and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to leave a brown oil. Purification by distillation (bp 125 °C/0.1 Torr) furnished the title compound **8** (1.85 g, 94%) as a colourless oil.

IR (neat): $\nu = 2970, 2940, 2845, 1595, 1480, 1440, 1120, 1055, 735\ \mathrm{cm}^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 5.92$ (1 H, tq, $J = 7.4, 1.5$ Hz), 3.76–3.84 (1 H, m), 3.43 (1 H, ABX, $J = 11.0, 5.3$ Hz), 3.40 (1 H, ABX, $J = 11.0, 6.1$ Hz), 2.35–2.46 (1 H, m), 2.19–2.31 (1 H, m), 1.77 (3 H, q, $J = 1.5$ Hz), 0.13 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 137.13, 137.02, 73.00, 48.66, 37.35, 24.83, 0.31, -0.14$.

MS (EI): $m/z = 278$ ($M^+$ [$^{35}$Cl], 3%), 229, 153, 151, 81, 73.

***cis*-2-Chloromethyl-2-ethyl-5,6-dihydro-3-methyl-2*H*-pyran (9):**
To a cold (− 78 °C) solution of propionaldehyde (1.0 equiv, 0.35 g, 5.91 mmol) and **8** (1.0 equiv, 1.64 g, 5.91 mmol) in $CH_2Cl_2$ (25 mL) was added $Me_3SiOTf$ (0.2 equiv, 0.26 g, 1.18 mmol). The mixture was allowed to warm to 0 °C over 2 h, before pouring onto sat. aq $NaHCO_3$ (30 mL). The aqueous layer was separated and extracted with $CH_2Cl_2$ (3 × 30 mL). The organic phases were combined and dried ($K_2CO_3$). The solvent was removed in vacuo to afford the crude product. Purification by distillation (bp 150 °C/15 Torr) afforded the title compound **9** (1.03 g, 81%) as a colourless oil.

IR (neat): $\nu = 2970, 2940, 1680, 1435, 1105, 1050\ \mathrm{cm}^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 5.52$–$5.57$ (1 H, m), 4.08–4.13 (1 H, m), 3.65–3.78 (1 H, m), 3.58 (1 H, ABX, $J = 11.0, 6.0$ Hz), 3.49 (1 H, ABX, $J = 11.0, 5.4$ Hz), 2.01–2.05 (2 H, m), 1.70–1.85 (1 H, m), 1.60 (3 H, s), 1.45–1.60 (1 H, m), 0.89 (3 H, t, $J = 7.3$ Hz).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 135.36, 119.63, 78.35, 73.18, 47.00, 28.95, 25.46, 18.80, 8.21$.

MS (EI): $m/z = 176$ [$M^+$ ($^{37}$Cl), 27%], 174, 161, 159, 145, 97, 81, 57.

HRMS: Calc. mass for $C_9H_{15}ClO$: 174.0811. Found: 174.0972.

**1-Thiophenyl-5-trimethylsilylpent-4-yn-2-ol**
To a cold (− 78 °C) solution of (trimethylsilyl)acetylene (1.2 equiv, 8.5 g, 0.087 mol) in THF (120 mL) was added a 2.5 M hexane solution of BuLi (1.2 equiv, 35 mL, 0.087 mol). The solution was stirred at this temperature for 30 min, then epoxide **10** (1.0 equiv, 12.0 g, 0.072 mol) was added followed by $BF_3 \cdot OEt_2$ (1.2 equiv, 10.7 mL, 0.087 mol) at such a rate so as to maintain the internal temperature below − 65 °C. The resulting solution was stirred at − 78 °C for 1 h and poured onto sat. aq $NH_4Cl$ (200 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to leave a brown oil which was

distilled at reduced pressure (bp 136–138 °C/0.06 Torr) to give the title compound (17.3 g, 91 %) as a clear oil.

IR (neat): $\nu$ = 3400, 2955, 2180, 1580, 1480, 1250, 1120, 845 cm$^{-1}$.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 7.15–7.45 (5 H, m), 3.74–3.92 (1 H, m), 3.29 (1 H, ABX, $J$ = 13.9, 4.4 Hz), 2.98 (1 H, ABX, $J$ = 13.9, 7.9 Hz), 2.44–2.66 (3 H, m), 0.15 (9 H, s).

$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 135.20, 129.42, 129.00, 126.39, 102.16, 87.92, 68.01, 39.90, 27.18, –0.02.

MS (EI): $m/z$ = 264 ($M^+$, 48 %), 246, 173, 157, 135, 123, 109, 73.

HRMS: Calc. mass for $C_{14}H_{20}OSSi$: 264.1004. Found: 264.1013.

### 1-Thiophenyl-5-trimethylsilyl-2-(2-tetrahydropyranyloxy)pent-4-yne

A mixture of 1-thiophenyl-5-trimethylsilylpent-4-yn-2-ol (1.0 equiv, 2.0 g, 7.58 mmol), 3,4-dihydro-2*H*-pyran (1.2 equiv, 0.76 g, 9.09 mmol) and PPTS (0.1 equiv, 0.19 g, 0.76 mmol) in $CH_2Cl_2$ (10 mL) was stirred at r. t. for 24 h. The solution was diluted with $Et_2O$ (100 mL) and the white precipitate formed was filtered. The filtrate was evaporated in vacuo to leave a pale yellow oil which was purified by flash column chromatography (hexane/EtOAc/$Et_3N$, 20 : 1 : 1) to give the title compound (2.4 g, 92 %) as a colourless oil.

IR (neat): $\nu$ = 2950, 2160, 1575, 1440, 1250, 1025, 840 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.13–7.40 (10 H, m), 4.81 (1 H, t, $J$ = 3.6 Hz), 4.67 (1 H, t, $J$ = 3.6 Hz), 3.90–4.05 (4 H, m), 3.41–3.53 (2 H, m), 3.37 (1 H, ABX, $J$ = 14.7, 4.2 Hz), 3.29 (1 H, ABX, $J$ = 13.5, 5.4 Hz), 3.17 (1 H, ABX, $J$ = 13.5, 6.6 Hz), 3.06 (1 H, ABX, $J$ = 14.7, 7.2 Hz), 2.76 (1 H, ABX, $J$ = 16.2, 5.1 Hz), 2.44–2.66 (3 H,m), 1.45–1.86 (12 H, m), 0.17 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 136.53, 128.79, 128.69, 128.49, 125.74, 125.62, 103.32, 103.12, 99.13, 97.83, 86.86, 86.69, 74.94, 73.71, 62.35, 37.82, 37.31, 30.50, 30.44, 26.51, 25.31, 24.48, 19.29, –0.03.

MS (EI): $m/z$ = 349 ($M^+$ + H, 6 %), 246, 173, 123, 109, 85.

### (*E*)-1-Iodo-5-thiophenyl-1-trimethylsilyl-4-(2-tetrahydropyranyloxy)pent-4-ene

To an ice cold solution of 1-thiophenyl-5-trimethylsilyl-2-(2-tetrahydropyranyloxy)pent-4-yne (1.0 equiv, 1.34 g, 3.85 mmol) in $Et_2O$ (5 mL) was added a 1.0 M hexane solution of DIBAL (2.0 equiv, 7.7 mL, 7.7 mmol). The resulting mixture was treated with a solution of $I_2$ (2.1 equiv, 2.1 g, 8.1 mmol) in $Et_2O$ (5 mL) at such a rate so as to maintain the internal temperature below –65 °C. The black solution was allowed to reach 0 °C over 3 h, poured onto aq ammonia (25 mL) and stirred vigorously for 30 min. The slurry was filtered through a pad of Celite, washed with $Et_2O$ (3 × 10 mL), the phases separated and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Purification by flash column chromatography (silica gel, hexane/EtOAc/$Et_3N$, 30 : 1 : 1) yielded the title compound (1.49 g, 81 %) as a colourless oil.

IR (neat): $\nu$ = 2945, 1595, 1440, 1245, 1025, 845 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.10–7.40 (12 H, m), 4.73 (1 H, t, $J$ = 3.3 Hz), 4.62 (1 H, t, $J$ = 3.3 Hz), 3.73–4.0 (4 H, m), 3.42–3.55 (2 H, m), 3.39 (1 H, ABX, $J$ = 13.7, 3.8 Hz), 2.96–3.10 (2 H, m), 2.94 (1 H, ABX, $J$ = 13.7, 8.4 Hz), 2.30–2.55 (4 H, m), 1.44–1.80 (12 H, m), 0.27 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 152.04, 151.51, 136.22, 128.95, 128.86, 128.33, 126.03, 125.67, 109.58, 109.42, 99.25, 97.53, 75.53, 74.01, 62.84, 62.19, 39.82, 38.38, 37.59, 37.29, 30.74, 30.48, 25.28, 25.13, 19.65, 19.19, 1.09.

MS (EI): $m/z$ = 402 ($M^+$ – $Me_3SiH$, 9 %), 300, 226, 185, 173, 85.

### (*Z*)-1-Thiophenyl-5-trimethylsilylhex-4-en-2-ol

To a cold (– 78 °C) solution of (*E*)-1-iodo-5-thiophenyl-1-trimethylsilyl-4-(2-tetrahydropyranyloxy)pent-4-ene (1.0 equiv, 1.47 g, 3.09 mmol) in THF (10 mL) was added a 1.6 M $Et_2O$ solution of MeLi (1.5 equiv, 2.9 mL, 4.63 mmol). The resulting mixture was allowed to reach r. t. and was stirred for another 20 h before pouring onto aq ammonia (20 mL). The aqueous layer was extracted with $Et_2O$ (3 × 15 mL) and the combined organic layers were concentrated in vacuo to give a brown oil which was taken up in EtOH/$H_2O$ (9 : 1, 10 mL). This solution was treated with PPTS (0.1 equiv, 0.08 g, 0.31 mmol) and heated at 65 °C for 12 h. The cold (0 °C) reaction mixture was poured onto sat. aq $NaHCO_3$ (20 mL) the aqueous phase separated and extracted with $Et_2O$ (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvents removed in vacuo to leave a brown oil which was purified by flash column chromatography (silica gel, hexane/EtOAc, 20 : 1) to afford the title compound (0.49 g, 57 %) as a colourless oil (bp 125 °C/at 0.003 Torr).

IR (neat): $\nu$ = 3420, 2955, 1615, 1575, 1435, 1245, 840 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.05–7.28 (5 H, m), 5.85 (1 H, tq, $J$ = 7.4, 1.7 Hz), 3.55–3.65 (1 H, m), 3.03 (1 H, ABX, $J$ = 13.7, 3.8 Hz), 2.76 (1 H, ABX, $J$ = 13.7, 8.4 Hz), 2.21–2.30 (3 H, m), 1.66 (3 H, s), 0.00 (9 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 138.88, 136.64, 135.27, 129.70, 128.96, 126.40, 69.48, 41.22, 38.11, 24.89, –0.17.

MS (EI): $m/z$ = 280 ($M^+$, 16 %), 262, 153, 135, 123, 109, 73.

HRMS: Calc. mass for $C_{15}H_{24}OSSi$: 281.1395. Found: 281.1332.

### (*Z*)-1-Thiophenyl-5-trimethylsilyl-2-trimethylsilyloxyhex-4-ene (11):

Following the procedure described for the preparation of **8**, (*Z*)-1-thiophenyl-5-trimethylsilylhex-4-en-2-ol (0.49 g, 1.75 mmol) was treated with $Me_3SiCl$ (0.228 mg, 2.10 mmol) and $Et_3N$ (0.231 mg, 2.28 mmol) in $CH_2Cl_2$ (10 mL). Aqueous workup and purification by distillation (bp 150 °C/0.05 Torr) furnished the title compound **11** (0.56 g, 91 %) as a colourless oil.

IR (neat): $\nu$ = 2975, 2905, 1630, 1590, 1255, 1090, 840 cm$^{-1}$.

$^1$NMR (300 MHz, $CDCl_3$): $\delta$ = 7.13–7.37 (5 H, m), 5.96 (1 H, t, $J$ = 6.4 Hz), 3.77–3.88 (1 H, m), 3.00 (2 H, d, $J$ = 5.8 Hz), 2.42–2.53 (1 H, m), 2.24–2.38 (1 H, m), 1.78 (3 H, s), 0.14 (9 H, s), 0.10 (9 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.87, 137.23, 137.11, 128.79, 125.67, 71.87, 40.65, 38.83, 24.86, 0.33, –0.14.

MS (EI): $m/z$ = 352 ($M^+$, 5 %), 337, 262, 225, 147, 135, 73.

### *cis*-2-Ethyl-5,6-dihydro-3-methyl-6-(thiophenyl)methyl-2*H*-pyran (12):

Following the procedure described for the preparation of **9**, propionaldehyde (51 mg, 0.88 mmol) was treated with vinylsilane **11** (310 mg, 0.88 mmol) in the presence of $Me_3SiOTf$ (40 mg, 0.18 mmol). Aqueous workup and purification by flash column chromatography (silica gel, hexane/EtOAc, 25 : 1) afforded the title compound **12** (0.18 g, 83 %) as a colourless oil.

IR (neat): $\nu$ = 2950, 2895, 1625, 1255, 1100, 840 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.12–7.39 (5 H, m), 5.50–5.55 (1 H, m), 4.02–4.08 (1 H, m), 3.61–3.69 (1 H, m), 3.18 (1 H, ABX, $J$ = 13.2, 6.4 Hz), 2.96 (1 H, ABX, $J$ = 13.2, 6.2 Hz), 1.92–2.15 (2 H, m), 1.68–1.80 (1 H, m), 1.58 (3 H, s), 1.43–1.58 (1 H, m), 0.89 (3 H, t, $J$ = 7.3 Hz).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 137.05, 135.45, 128.96, 128.70, 125.67, 120.08, 78.41, 72.43, 39.00, 30.72, 25.51, 18.82, 8.39.

MS (EI): $m/z$ = 248 (85 %), 162, 125, 124, 109, 81, 57.

HRMS: Calc. mass for $C_{15}H_{20}OS$: 248.1235. Found: 248.1211.

### *cis*-2-Ethyl-5,6-dihydro-3-methyl-6-(phenylsulfonyl)methyl-2*H*-pyran (13):

To a cold (– 78 °C) solution of sulfide **12** (1.0 equiv, 0.177 g, 0.714 mmol) in $CH_2Cl_2$ (5 mL) was added a solution of *m*-CPBA (2.0 equiv, 1.43 mmol) in $CH_2Cl_2$ (5 mL). The mixture was allowed to warm to 0 °C over 90 min and was stirred at this temperature for a further 90 min before pouring onto sat. aq $NaHCO_3$ (30 mL). The aqueous phase was separated and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic extracts were dried ($K_2CO_3$) and the solvent removed in vacuo to leave a colourless oil. Purification by flash column chromatography (silica gel, hexane/EtOAc, 5 : 1) gave the title compound **13** (74 mg, 37 %) as a white solid (mp 96–97 °C).

IR (KBr): $\nu$ = 2980, 2925, 1580, 1445, 1280, 1145, 745 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90–7.95 (2 H, m), 7.51–7.67 (3 H, m), 5.46–5.50 (1 H, m), 3.95–4.04 (1 H, m), 3.78–3.85 (1 H, m), 3.46 (1 H, ABX, $J = 14.6$, 8.0 Hz), 3.21 (1 H, ABX, $J = 14.6$, 3.5 Hz), 1.97–2.04 (2 H, m), 1.53 (3 H, m), 1.20–1.46 (2 H, m), 0.56 (3 H, t, $J = 7.3$ Hz).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 140.28$, 135.41, 133.32, 128.87, 128.00, 119.36, 78.08, 68.27, 61.63, 30.82, 25.20, 18.74, 8.16.

MS (EI): $m/z = 280$ ($M^+$, 100 %), 251, 139, 125, 121, 109, 95, 81, 77.

Anal. calc. for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 63.83; H, 7.60.

**1-Trimethylsilyl-4-hydroxy-5-thiophenylhex-1-yne (15):**

To a cooled (– 78 °C) solution of 1-trimethylsilylprop-1-yne (2.0 equiv, 9.46 g, 0.0845 mol) in THF (150 mL) was added a 1.3 M hexane solution of *t*-BuLi (2.0 equiv, 65 mL, 0.0845 mol). The bright yellow solution was stirred at – 78 °C for 2.5 h and CuI (1.0 equiv, 8.02 g, 0.0422 mol) added. The temperature was raised to 0 °C and the solution stirred for 30 min. After recooling the mixture to – 78 °C, aldehyde **14** (0.82 equiv, 5.73 g, 0.0345 mol) was added and stirring was continued at this temperature for 20 min. The solution was poured onto sat. aq $NaHCO_3$ (500 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with sat. aq $NH_4Cl$ (300 mL) and dried ($MgSO_4$). The volatiles were removed at reduced pressure to leave a brown oil. Purification by flash column chromatography (silica gel, hexane/EtOAc, 20 : 1) furnished the title product (6.41 g, 67 %) as a colourless oil and as a mixture of diastereoisomers.

IR (neat): $\nu = 3415$, 2960, 2880, 2185, 1580, 1250, 1025, 845.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.23$–7.50 (5 H, m), 7.35–3.85 (2 H, m), 2.38–2.72 (3 H, m), 1.32 (3 H, t, $J = 7.2$ Hz), 0.15 (9 H, s).

$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 134.21$, 133.91, 132.52, 131.64, 129.03, 128.95, 127.32, 127.11, 102.66, 102.54, 87.65, 72.36, 70.70, 49.15, 47.43, 25.50, 25.23, 17.96, 13.91, 0.03.

MS (EI): $m/z = 278$ ($M^+$, 41 %), 260, 167, 151, 137, 109, 73.

Anal. calc. for $C_{15}H_{22}OSSi$: C, 64.69; H, 7.96. Found: C, 64.52; H, 7.88.

**(*Z*)-2-Thiophenyl-6-trimethylsilylhept-5-en-3-ol (16):**

Following the procedure described for the transformation of alkyne **5**, alcohol **15** (1.0 equiv, 6.31 g, 0.0227 mol) was protected as its THP ether using 3,5-dihydro-2*H*-pyran (1.3 equiv, 2.48 g, 0.0295 mol) and PPTS (0.1 equiv, 0.57 g, 2.27 mmol) in $CH_2Cl_2$ (25 mL). Without purification of the THP ether, the alkyne was treated with DIBAL (2.0 equiv, 0.0454 mol) in $Et_2O$ (45 mL) and quenched with $I_2$ (2.1 equiv, 12.11 g, 0.0477 mol) in $Et_2O$ (60 mL) to provide the corresponding vinyl chloride (7.82 g, 70 %). Exposure to a 1.6 M $Et_2O$ solution of MeLi (1.5 equiv, 14.9 mL, 0.0239 mol) in THF (25 mL) effected the metallation/alkylation reaction. Aqueous acidic workup with wet EtOH (25 mL) and PPTS (0.1 equiv, 0.40 g, 1.59 mmol) followed by purification by flash column chromatography (silica gel, hexane/EtOAc, 20 : 1) furnished the title product **16** (3.73 g, 80 %) as a colourless oil and as a mixture of diastereoisomers.

IR (neat): $\nu = 3450$, 2960, 1620, 1580, 1445, 1250, 1025, 835 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–7.47 (10 H, m), 6.02 (1 H, t, $J = 7.0$ Hz), 5.95 (1 H, tq, $J = 7.4$, 1.7 Hz), 3.53–3.68 (2 H, m), 3.36 (1 H, dq, $J = 7.0$, 3.2 Hz), 3.23 (1 H, quintet, $J = 7.0$ Hz), 2.20–2.50 (6 H, m), 1.78 (3 H, br, H-1), 1.79 (3 H, s), 1.31 (3 H, d, $J = 7.0$ Hz), 1.29 (3 H, d, $J = 7.4$ Hz), 0.11 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 138.73$, 138.25, 137.62, 134.20, 132.52, 132.07, 128.95, 128.87), 128.70, 128.65, 127.19, 127.14, 73.74, 72.25, 49.99, 49.28, 35.72, 35.69, 24.86, 24.83, 14.30, 14.20, – 0.20, – 0.17.

MS (EI): $m/z = 294$ ($M^+$, 25 %), 276, 183, 167, 157, 149, 137, 95, 85, 73.

Anal. calc. for $C_{16}H_{26}OSSi$: C, 65.25; H, 8.90. Found: C, 65.17; H, 8.94.

**(*Z*)-2-Thiophenyl-3-trimethylsilyloxy-6-trimethylsilylhept-5-ene**

Following the procedure described for the preparation of silyl ether **8**, alcohol **16** (1.0 equiv, 2.50 g, 8.50 mmol) was reacted with $Me_3SiCl$ (1.2 equiv, 1.11 g, 1.30 mL, 0.010 mol) and $Et_3N$ (1.3 equiv, 1.12 g, 1.54 mL, 0.011 mol) in $CH_2Cl_2$ (15 mL). Aqueous workup and distillation (bp 175 °C/0.2 Torr) provided the title product (2.77 g, 89 %) as a colourless oil.

IR (neat): $\nu = 2950$, 2905, 1615, 1580, 1250, 1025, 840 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.55 (5 H, m), 6.00–6.06 (1 H, m), 3.83–3.95 (1 H, m), 3.32–3.42 (1 H, m), 2.35–2.50 (2 H, m), 1.87 (3 H, s), 1.35–1.42 (3 H, m), 0.10 (18 H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 139.21$, 138.54, 136.97, 136.41, 136.15, 131.79, 131.64, 131.03, 128.77, 126.61, 126.29, 75.53, 74.95, 49.21, 48.64, 37.47, 34.52, 24.83, 15.10, 15.85, 0.62, 0.52, 0.39, – 0.12.

MS (EI): $m/z = 366$ ($M^+$, 3 %), 294, 276, 239, 167, 149, 95, 73.

***cis*-2-Ethyl-5,6-dihydro-3-methyl-6-(1-thiophenylethyl)-2*H*-pyran (17):**

Following the procedure described for the preparation of **9**, propionaldehyde (1.1 equiv, 0.48 g, 0.60 mL, 8.27 mmol) was reacted with (*Z*)-2-thiophenyl-3-trimethylsilyloxy-6-trimethylsilylhept-5-ene (1.0 equiv, 2.75 g, 7.51 mmol) in the presence of $Me_3SiOTf$ (0.2 equiv, 0.33 g, 0.29 mL, 1.50 mmol). Aqueous workup and purification by flash column chromatography (silica gel, hexane/EtOAc, 50 : 1) afforded the title compound **17** (1.35 g, 69 %) as a colourless oil.

IR neat): $\nu = 2970$, 2940, 1670, 1585, 1480, 1445, 1380, 1055, 1025 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$–7.45 (2 H, m), 7.17–7.30 (3 H, m), 5.50–5.55 (1 H, m), 3.96–4.05 (1 H, m), 3.34–3.57 (1 H, m), 3.24 (1 H, quintet, $J = 6.8$ Hz), 1.95–2.20 (2 H, m), 1.68–1.80 (1 H, m), 1.58 (3 H, s), 1.40–1.53 (1 H, m), 1.36 (3 H, d, $J = 7.0$ Hz), 0.90 (3 H, t, $J = 7.4$ Hz).

$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta = 135.98$, 135.36, 131.84, 131.45, 128.00, 126.54, 126.38, 120.34, 78.66, 78.37, 76.37, 75.46, 47.92, 47.10, 29.20, 27.05, 25.68, 25.54, 18.77, 17.42, 16.60, 8.72, 8.35.

MS (EI): $m/z = 262$ ($M^+$, 50 %), 176, 153, 137, 125, 109, 95.

***cis*-2-Ethyl-5,6-dihydro-3-methyl-5-(1-phenylsulfonyethyl)-2*H*-pyrans (18/19):**

To a cold (0 °C) mixture of sulfide **17** (1.0 equiv, 1.17 g, 4.47 mmol) and $(PhSe)_2$ (1.0 equiv, 1.39 g, 4.47 mmol) in $CH_2Cl_2/Et_2O$ (3 mL, 20 mL) was added a 30 % aq solution of $H_2O_2$ (2.6 mL). After stirring at this temperature for 30 min a second portion of $H_2O_2$ (2.6 mL) was added. The resulting mixture was stirred at r. t. for 6 h and poured onto sat. aq $NaHCO_3$ (30 mL). The layers were separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with sat. aq $NaHSO_3$ (25 mL) and dried ($MgSO_4$). The volatiles were removed in vacuo and the residue purified by flash column chromatography (silica gel, hexane/EtOAc, 3 : 1) to provide the title products (1.18 g, 90 %) as a colourless oil. Trituration with hexane effected precipitation of one of the diastereoisomers which was characterised as follows; mp 110–112 °C.

IR (KBr): $\nu = 2960$, 2940, 1640, 1580, 1450, 1145.

$^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.85$–7.92 (2 H, m), 5.48–5.54 (1 H, m), 4.19 (1 H, dt, $J = 10.3$, 2.9 Hz), 3.77–3.86 (1 H, m), 3.10 (1 H, qd, $J = 7.2$, 2.9 Hz), 1.80–2.18 (2 H, m), 1.52 (3 H, s), 1.20–1.46 (2 H, m), 1.36 (3 H, d, $J = 7.2$ Hz), 0.56 (3 H, t, $J = 7.3$ Hz).

$^{13}$C NMR (50 MHz, $CDCl_3$): $\delta = 138.30$, 135.24, 133.29, 129.26, 128.60, 119.77, 77.71 69.70, 65.28, 28.97, 25.23, 18.67, 8.75, 8.06.

MS (EI): $m/z = 294$ ($M^+$, 33 %), 265, 153, 137, 123, 95.

***cis*-4-(4-Bromobenzoyloxy)-5,6-dihydro-3-hydroxy-3-methyl-6-(1-phenylsulfonylethyl)-2*H*-pyran (22):**

To a solution of olefin **18** (1.0 equiv, 0.440 g, 1.50 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 2.0 equiv, 0.35 g, 3.0 mmol) in acetone/$H_2O$ (5 mL : 2.5 mL) was added a 0.1 M toluene solution of $OsO_4$ (0.05 equiv, 0.75 mL) and the solution stirred at r. t. for 20 h. The mixture was then diluted with $CH_2Cl_2$ (20 mL) and solid $Na_2S_2O_3$ (1.0 g) added. After stirring vigorously for 30 min, the solution was dried ($K_2CO_3$) and the solvents removed at reduced pressure. Purification by flash column chromatography (silica gel, hexane/EtOAc, 1 : 2) gave diol **21** (0.33 g, 67 %) as a colourless oil. None of the other diastereoisomer, resulting from dihydroxylation from the other face, could be isolated from the chromatography. The diol could not be solidified. It was therefore immediately derivatised using *p*-bromobenzoyl chloride (1.5 equiv, 0.332 g, 1.52 mmol), $Et_3N$ (1.5 equiv, 0.154 g, 0.21 mL, 1.52 mmol) and DMAP (0.1 equiv, 0.012 g, 0.101 mmol) in $CH_2Cl_2$ (10 mL). The solution was stirred at r.t. for 20 h and then poured onto sat. aq $NaHCO_3$ (15 mL). The aqueous phase was separated and extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic extracts were dried ($K_2CO_3$) and the volatiles removed in vacuo. Purification by flash column chromatography (silica gel, hexane/EtOAc, 4 : 1) furnished the monobenzoate **22**, as a white solid (mp 162–163 °C) along with a small amount of the dibenzoate **20**, also as a white solid (mp 215–216 °C). Recrystallisation of **20** from $CH_2Cl_2/Et_2O$ gave crystals suitable for X-ray analysis.

**22:**

IR (film): $\nu$ = 3140, 3050, 2985, 1720, 1580, 1425, 1270, 1150, 900 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.82–7.87 (4 H, m), 7.48–7.65 (5 H, m), 5.16 (1 H, t, *J* = 3.0 Hz), 4.27 (1 H, dt, *J* = 9.9, 3.9 Hz), 3.45 (1 H, dd, *J* = 9.9, 1.9 Hz), 3.06 (1 H, qd, *J* = 7.1, 3.9 Hz), 2.11 (1 H, s), 1.95–2.05 (2 H, m), 1.59–1.71 (1 H, m), 1.37 (3 H, d, *J* = 7.1 Hz), 1.21–1.35 (1 H, m), 1.21 (3 H, s), 0.93 (3 H, t, *J* = 7.4 Hz).

$^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 165.33, 138.18, 133.51, 131.86, 131.12, 128.97, 128.81, 128.62, 128.54, 80.85, 76.00, 70.04, 69.63, 63.84, 32.65, 21.27, 19.37, 11.03, 9.01.

MS (EI): $m/z$ = 512 [$M^+ + H$ ($^{81}Br$), 2 %], 510 [$M^+ + H$ ($^{79}Br$), 2 %], 313, 311, 252, 202, 200, 185, 183.

Dibenzoate **20**:

IR (KBr): $\nu$ = 3040, 2990, 1730, 1585, 1420, 1275, 1155, 905 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.55–7.97 (13 H, m), 6.27 (1 H, t, *J* = 2.9 Hz), 4.48–4.55 (1 H, m), 3.95 (1 H, dd, *J* = 9.9, 2.0 Hz), 3.15 (1 H, qd, *J* = 7.1, 3.1 Hz), 2.12–2.18 (2 H, m), 1.79–1.89 (1 H, m), 1.76 (3 H, s), 1.50–1.60 (1 H, m), 1.49 (3 H, d, *J* = 7.1 Hz), 1.16 (3 H, t, *J* = 7.4 Hz).

$^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 164.30, 164.17, 138.28, 133.59, 131.74, 131.62, 131.20, 131.09, 130.90, 130.77, 130.37, 130.29, 129.30, 128.51, 128.35, 128.08, 129.05, 128.80, 79.56, 78.99, 71.79, 69.61, 63.60, 31.89, 21.85, 16.98, 10.98, 8.85.

MS (EI): $m/z$ = 294 (40 %), 292, 252, 209, 183.

Anal. calc. for $C_{30}H_{30}Br_2O_7S$: C, 51.88; H, 4.35. Found: C, 51.91; H, 4.34.

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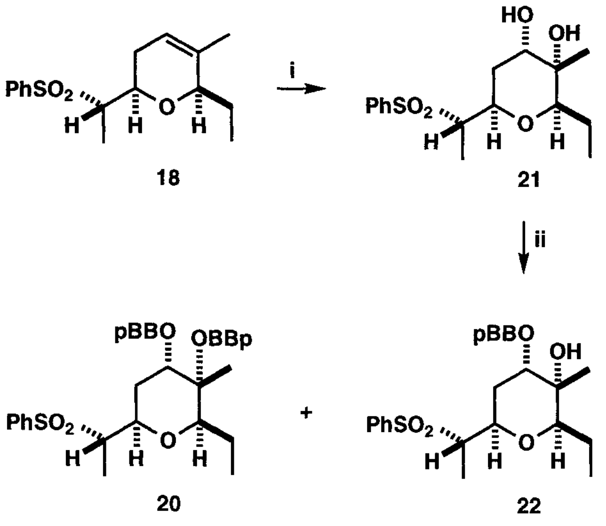

**i** = $OsO_4$ cat., NMO, $H_2O$, acetone (1:10), 20°C; **ii** = pBBCl, $Et_3N$, $CH_2Cl_2$, 4-DMAP cat., 20°C. **pBBCl** = *p*$BrC_6H_4COCl$.

Scheme 6

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Benzoylation of **21**, using *p*-bromobenzoyl chloride (pBBCl) in the presence of catalytic quantities of 4-dimethylamino pyridine, resulted in the preferential formation of the monobenzoylated material **22** accompanied by minor amounts of the bis-benzoylated compound **20**. Although crystalline, **22** proved unsuitable for X-Ray analysis, the minor bis-benzoyl derivative **20** gave good quality X-Ray crystals.