# Stereocontrolled syntheses of 2,5-disubstituted tetrahydrofurans using remote asymmetric induction

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**Dedicated to Professor T. R. Govindachari on the occasion of his 85th birthday**

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**Abstract**

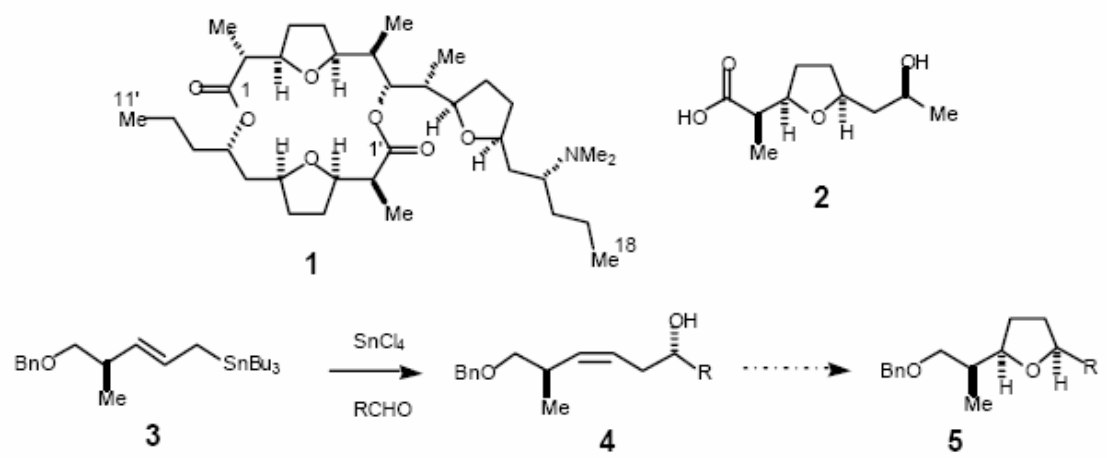
Stereocontrolled syntheses of *cis*- and *trans*-2,5-disubstituted tetrahydrofurans with a 1-methyl-2-benzyloxyethyl group at C(2) are described. The starting material for this work was prepared by the tin(IV) chloride promoted reaction of a 4-methyl-5-benzyloxypent-2-enylstannane with an aldehyde which proceeds with excellent 1,5-induction.

**Keywords :** Tetrahydrofuran, stereoselective, cyclization, homoallylic alcohol, allylstannanes

## Introduction

Several biologically active natural products are characterized by the presence of *cis*-2,5-disubstituted tetrahydrofurans which have an α-methyl bearing stereogenic centre in the 2-substituent. Examples include the pamamycins, e.g. pamamycin 607 **1**[1] and nonactic acid **2**.[2] During recent studies on the reactions of allylstannanes with aldehydes, it was found that the 4-methyl-5-benzyloxypent-2-enylstannane **3** was transmetallated stereoselectively to give an allyltin trichloride which reacted with aldehydes with excellent 1,5-stereocontrol to give the (*Z*)-1,5-*anti*-alkenols **4**.[3] If procedures could be developed for the stereoselective cyclisation of these alkenols to 2,5-*cis*-disubstituted tetrahydrofurans **5**, then it may be possible to develop this strategy to provide total syntheses of nonactic acid and pamamycin 607.

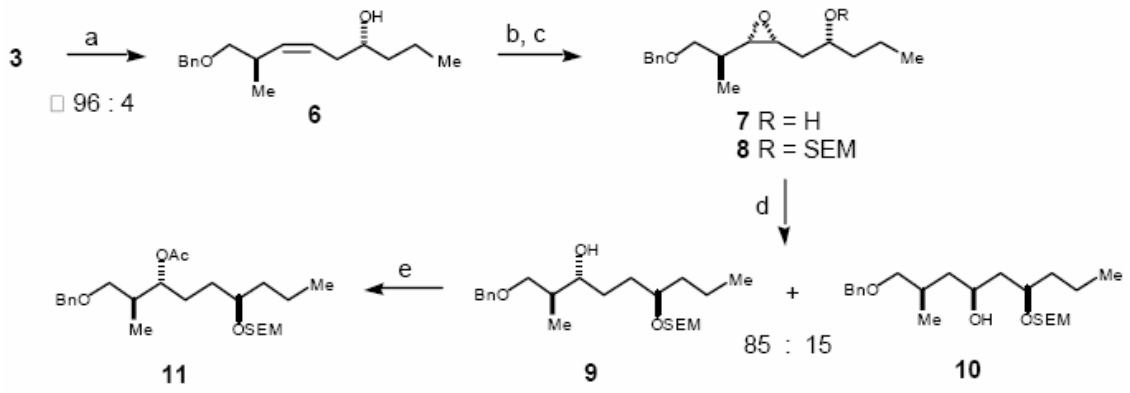
 




Early studies into the preparation of the tetrahydrofurans **5** from the alkenols **4**, were based on dehydration/cyclisation of hydroxyselenides prepared by epoxidation of the alkenols followed by epoxide ring opening using sodium phenylselenide.[4,5] However, this chemistry was successful only with relatively simple systems. With more complex substrates, the dehydration/cyclisation step was accompanied by loss of phenylselenenic acid giving the returned alkenol as the major product.[6] It transpired that direct cyclisation using either phenylselenenyl chloride[7] or phthalimide[8] in the presence of 20 mol% of tin(IV) chloride was more successful and led to the completion of syntheses of the methyl ester of nonactic acid **2** and pamamycin 607 **1**.[9] During the course of this work it was necessary to prepare a sample of a *cis*-2,5-disubstituted tetrahydrofuran by a stereochemically unambiguous route. The results of this study are described herein together with procedures for the synthesis of the diastereoisomeric 2,5-*trans*-isomers.

## Results and Discussion

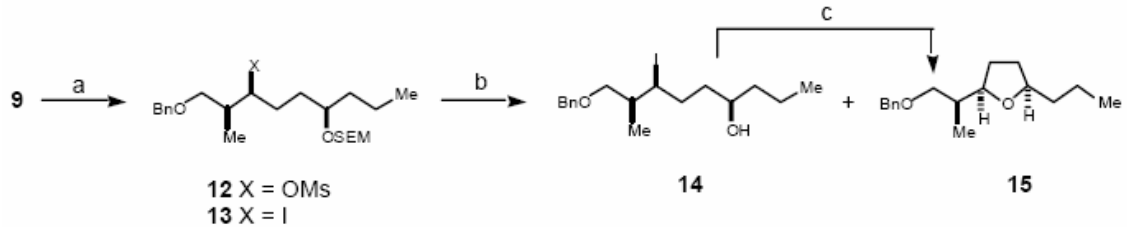
The reaction between butanal and the allyltin trichloride generated from the 4-methyl-5-benzyloxypent-2-enylstannane **3** gave the (*Z*)-1,5-*anti*-alkenol **6** with excellent stereocontrol, 1,5-*anti* : 1,5-*syn* ≥ 96 : 4, with no (*E*)-alkenols being detected (Scheme 1).[3] It was decided that one strategy for tetrahydrofuran formation would be to effect regio- and stereoselective hydration of the double-bond and so the alkenol **6** was converted into the *syn*-epoxide **7** using the well-precedented vanadyl catalysed *syn*epoxidation procedure.[10] This epoxidation was highly stereoselective with only the one stereoisomer being detected (≥95 : 5) in the crude reaction mixture by high field $^1$H NMR. Since this stereoselectivity is higher than that usually observed in this kind of epoxidation (more typically 85 : 15 in favour of the *syn*-diastereoisomer), it may well be that both of the stereogenic centres in the alkenol contribute to this stereocontrol.




**Scheme 1.** (a) $SnCl_4$, -78 °C, 5 min, *n*-PrCHO (78%); (b) $VO(acac)_2$, *t*-BuOOH (80%); (c) SEMCl, *i*-$Pr_2NEt$ (80%); (d) Red-Al, 15 h (52%); (e) $Ac_2O$, $Et_3N$, DMAP (48%).

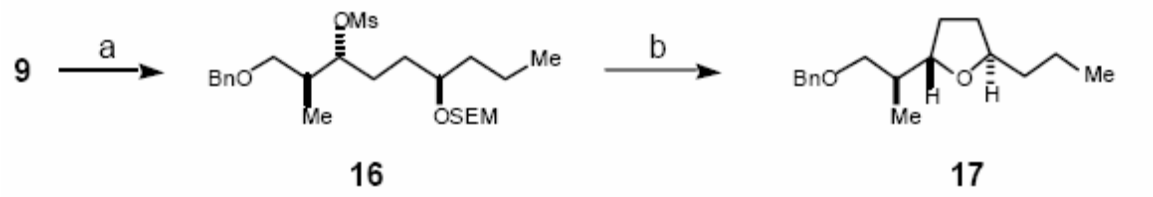
The next step was to reduce the epoxide regioselectively to give a 1,4-difunctionalised intermediate as the precursor of the tetrahydrofuran ring. To avoid problems of having to differentiate between two secondary hydroxyl groups later in the synthesis, the hydroxy-epoxide **7** was first converted into its SEM-ether **8**. Reduction of this epoxyether by Red-Al was found to be usefully regioselective and gave the required alcohol **9** together with its regioisomer **10** in a ratio of *ca*. 85 : 15. The regioselectivity of this reduction was established by a COSY $^1H$ NMR study of the acetate **11** of the major reduction product **9** and may be due to reduced steric hindrance to attack at C(4) and preferred co-odination by the OSEM substituent.

It now remained to convert the hydroxyl group of the alcohol **9** into a good leaving group with inversion of configuration. Preliminary studies into the preparation of its inverted mesylate **12** using a Mitsunobu reaction were not promising since only low conversion into product was observed at room temperature and extensive decomposition took place in toluene heated under reflux (Scheme 2). However, reaction with iodine, imidazole and triphenylphosphine gave the inverted iodide **13** in a reasonable, non-optimized yield of 64%. Removal of the SEM-protecting group using dilute aqueous hydrogen fluoride gave mainly the iodo-alcohol **14** together with a small amount of the tetrahydrofuran **15**. Conversion of the remainder of the iodo-alcohol into the tetrahydrofuran was accomplished by treatment with sodium hydride in THF as solvent and gave the 2,5-*cis*-disubstituted tetrahydrofuran **15** in a 65%yield.




**Scheme 2.** (a) $I_2$, $Ph_3P$, imid. (64%) (b) 40% HF, acetonitrile (**14**, 57%; **15**, 18%); (c) NaH, THF (65%).

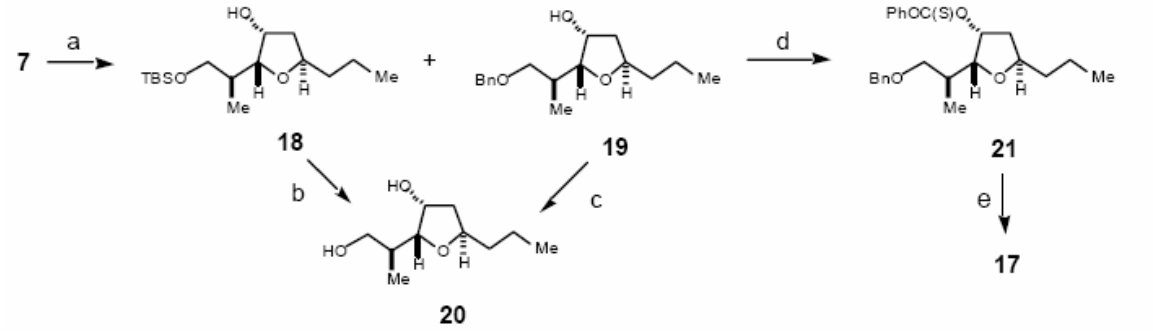
The 1,5-*cis*-configuration assigned to the tetrahydrofuran **15** follows from its method of synthesis and was confirmed by the synthesis of the racemic 1,5-*trans*-isomer **17** (Scheme 3). Thus deprotection of the mesylate **16** prepared from the racemic alcohol **9** was accompanied by cyclisation and gave the 2,5-*trans*-disubstituted tetrahydrofuran **17** directly. The 2,5-*cis*- and 2,5–*trans*-disubstituted tetrahydrofurans **15** and **17** could be distinguished spectroscopically. These syntheses of the tetrahydrofurans **15** and **17** were found to be highly stereoselective with little, if any (≤5%), contamination by the other stereoisomer being observed.




**Scheme 3.** (a) MsCl, $Et_3N$, (61%); (b) 40% HF, acetonitrile (31%).

A second synthesis of the racemic 2,5-*trans*-isomer **17** from the hydroxyepoxide **7** was also developed. Thus treatment of the hydroxyepoxide with *tert*-butyldimethylsilyl triflate and trimethylaluminium gave a mixture of the hydroxytetrahydrofurans **18** and **19**.[11] The stereochemical homology between these two compounds was proved by their deprotection which gave the same diol **20**. Removal of the hydroxyl group from **19** was accomplished by conversion into the thionocarbonate **21** which, on reduction using tributyltin hydride, gave the 2,5-*trans*-disubstituted terahydrofuran **17** identical to a sample prepared by the earlier procedure (Scheme 4).

This work shows how the alkenols prepared with 1,5-stereocontrol using the allylstannane **3** can be incorporated into stereoselective syntheses of either 2,5-*cis*- or *trans*-disubstituted tetrahydrofurans. The synthesis of natural products using this and related chemistry is underway.[9]




**Scheme 4.** (a) TBSOTf, Me3Al (**18**, 22%; **19**, 63%); (b) TBAF (89%); (c) $H_2$, Pd/C (91%); PhOC(S)Cl, py (83%); (e) Bu3SnH, AIBN (53%).

## Experimental Section

**General Procedures.** $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker AC 300, Varian Inova 300 and Varian Gemini 200 spectrometers in chloroform-$d_1$. Mass spectra were recorded on Kratos Concept 1S and Fisons VG Trio 2000 mass spectrometers using electron impact (EI) or chemical ionisation (CI) modes. IR spectra were recorded on an ATI Mattson Genesis FTIR spectrometer as evaporated films on sodium chloride plates unless otherwise stated. Flash column chromatography was carried out using Merck silica gel 60H (40-60μ, 230-300 mesh) as the stationary phase. Optical rotations were measured on an Optical Activity AA-100 polarimeter operating at 589 nm. Light petroleum refers to the fraction with b.p. 40° C – 60°C and was redistilled before use. Ether refers to diethyl ether. All solvents were distilled and purified by standard procedures. All products were obtained as colourless oils after chromatography.

**(4*R*,8*R*,6*Z*)-9-(Benzyloxy)-8-methyl-6-nonen-4-ol (6).** A cooled solution, -78 $^{o}$C, of tin(IV) chloride (2.1 cm$^3$, 2.1 mmol) in dichloromethane was added to a stirred solution of the stannane **3** (1.0 g, 2.08 mmol) in dichloromethane (20 cm$^3$) at –78 $^{o}$C. After 5 min, a cooled solution of butanal ( 2.5 cm$^3$, 2.5 mmol) in dichloromethane was added and the mixture was stirred at –78 $^{o}$C for 45 min. Saturated aqueous sodium bicarbonate (20 cm$^3$) was added and the mixture was allowed to warm to room temperature. The mixture was partitioned between dichloromethane (60 cm$^3$) and water (60 cm$^3$) and the organic phase washed with water (40 cm$^3$), brine (40 cm$^3$) and dried ($MgSO_4$). After concentration under reduced pressure, flash chromatography of the residue using light petroleum : ether, (3 : 1) and triethylamine (1%) as eluant gave the *title compound*, **6** (0.426 g, 78%), as a colourless oil, $[\alpha]D^{22}$ -7.6 (*c* 0.91, $CHCl_3$); (Found: $M^+$+H, 263.2013. $C_{17}H_{27}O_2$ requires *M*, 263.2010); $\upsilon_{max}$ / cm$^{-1}$ 3429, 1454, 1364, 1094, 1024, 738 and 698; $\delta_H$ 0.85 (6 H, m, 1-$H_3$, 8-$CH_3$), 1.37 (4 H, m, 2-$H_2$ and 3-$H_2$), 2.02 - 2.26 (2 H, m, 5-$H_2$), 2.72 (1 H, d, *J* 3, O*H*), 2.80 (1 H, m, 8-H), 3.10 (1 H, t, *J* 8, 9-H), 3.25 (1 H, dd, *J* 8 and 5, 9-H), 3.51 (1 H, m, 4-H), 4.41 and 4.47 (each 1 H, d, *J* 12, PhC$H_2$O), 5.25 (1 H, t, *J* 10, 7-H), 5.41 (1 H, m, 6-H) and 7.18 - 7.30 (5 H, m, Ph-*H*); δC 14.0, 17.2, 18.8, 32.2, 35.7, 39.4, 70.5, 72.9, 74.6, 126.3, 127.4, 127.6, 128.2, 136.1 and 138.0; *m/z* (C.I.) 280 ($M^+$+18, 19%), 263 ($M^+$+1, 100) and 245 (14).

**(2*R*)-1-{(2*R*,3*S*)-3-[(1*S*)-2-(Benzyloxy)-1-methylethyl]oxiran-2-yl}pentan-2-ol (7).** Vanadyl ac-etoacetonate (4 mg, 2 mol%, 0.016 mmol) and *tert*-butyl hydroperoxide (0.24 cm$^3$, 5 M solution in nonane, 1.20 mmol) were added to a solution of the alkene **6** (0.21 g, 0.801 mmol) in dichloromethane (7 cm$^3$) at 0 $^{o}$C. After 10 min, the solution was allowed to warm to room temperature and stirred for a further 20 h. Saturated aqueous sodium thiosulfate (5 cm$^3$) was added and the mixture extracted with ether (3 x 10 cm$^3$). The combined organic phase was washed with water (10 cm$^3$), brine (10 cm$^3$), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue using light petroleum : ether, (2 : 1) as eluant gave the *title compound*, **7** (0.178 g, 80%), as a colourless oil, $[\alpha]D^{21}$ -10.3 (*c* 0.96, $CHCl_3$); (Found: $M^+$+NH4, 296.2221. $C_{17}H_{30}NO_3$ requires *M*, 296.2225); $\upsilon_{max}$ / cm$^{-1}$ 3436, 1453, 1360, 1095,

1072, 1026, 737 and 697; $\delta_H$ 0.98 (3 H, t, *J* 7, 5-$H_3$), 1.08 (3 H, d, *J* 7, 1″-$CH_3$), 1.34 - 1.78 (6 H, m, 1-H, 3-H2, 4-$H_2$ and 1″-H), 1.91 (1 H, dt, *J* 7 and 3, 1-H), 2.27 (1 H, brs, O*H*), 2.86 (1 H, dd, *J* 9 and 4, 3′H), 3.20 (1 H, m, 2′-H), 3.53 (1 H, dd, *J* 9 and 6, 2″-H), 3.64 (1 H, dd, *J* 9 and 4, 2″-H), 3.98 (1 H, m, 2-H), 4.58 (2 H, s, PhC$H_2$O) and 7.30 - 7.40 (5 H, m, Ph-*H*); $\delta_C$ 13.5, 13.9, 18.6, 33.2, 34.6, 39.5, 54.8, 57.8, 70.6, 73.1, 127.4, 128.2 and 138.4; *m/z* (C.I.) 296 ($M^+$+18, 100%), 279 ($M^+$+1, 60) and 207 (19).

**[2-({[(1*R*)-1-({(2*R*,3*S*)-3-[(1*S*)-2-(Benzyloxy)-1-methylethyl]oxiran-2-yl}methyl)butyl]oxy}-methoxy)ethyl](trimethyl)silane (8).** DIPEA (1.64 $cm^3$, 9.39 mmol) was added to a solution of epoxide **7** (0.87 g, 3.12 mmol) in dichloromethane (5 $cm^3$) at 0 °C. After 20 min SEM-Cl (0.83 $cm^3$, 4.69 mmol) was added and the resultant solution was stirred at room temperature overnight. The reaction was quenched by the addition of water (3 $cm^3$). The organic phase was separated and washed with water (3 $cm^3$), brine (3 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure to leave an oil which was purified by flash chromatography using light petroleum : ether, (4 : 1), as eluant. The *title compound*, **8** (1.03 g, 80%), was obtained as a colourless oil, $[\alpha]_D^{22}$ -7.5 (*c* 1.05, $CHCl_3$); (Found: $M^+$+$NH_4$, 426.3044. $C_{23}H_{40}NO_4Si$ requires *M*, 426.3039); $\upsilon_{max}$ / $cm^{-1}$ 1455, 1362, 1248, 1194, 1099, 1052, 1032, 859, 836, 738 and 696; $\delta_H$ 0.00 (9 H, s, (C$H_3$)$_3$Si), 0.92 (5 H, m, 4-H3 and C$H_2$Si), 1.05 (3 H, d, *J* 7, 1″-$CH_3$), 1.20 - 1.90 (7 H, m, 2-$H_2$, 3-$H_2$, 1′-$H_2$, and 1″-H), 2.76 (1 H, dd, *J* 9 and 4, 3′-H), 3.09 (1 H, m, 2′-H), 3.48 (1 H, dd, *J* 9 and 7, 2″-H), 3.62 (3 H, m, 2″-H and OC$H_2$CH2Si), 3.78 (1 H, m, 1-H), 4.54 (2 H, s, PhC$H_2$O), 4.71 (2 H, s, $OCH_2O$) and 7.24 - 7.36 (5 H, m, Ph-*H*); δC -1.5, 13.7, 14.0, 18.0, 18.5, 32.5, 33.2, 36.6, 53.4, 57.9, 65.0, 73.1, 73.3, 75.2, 93.4, 127.3, 127.4, 128.2 and 138.4; *m/z* (C.I.) 426 ($M^+$+18, 100%), 261 (15) and 90 (12).

**(2*S*,3*R*,6*R*)-1-(Benzyloxy)-2-methyl-6-{[2-(1,1,1-trimethylsilyl)ethoxy]methoxy}-nonane-3-ol (9).** Red-Al (0.23 $cm^3$, 65% *w/v* in toluene, 0.764 mmol) was added to a solution of epoxide **8** (0.104 g, 0.254 mmol) in tetrahydrofuran (2 $cm^3$) at 0 °C. The solution was then heated under reflux for 15 h. The reaction mixture was cooled to room temperature and saturated aqueous ammonium chloride (2 $cm^3$) was added. The precipitate was removed by filtration and the filtrate was extracted with ether (3 x 3 $cm^3$). The organic phase was washed with water (3 $cm^3$), brine (3 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue using light petroleum : ether, (2 : 1) yielded *the title compound*, **9** (54 mg, 52%), as a colourless oil, $[\alpha]_D^{22}$ -3.69 (*c* 0.976, $CHCl_3$); (Found: $M^+$+H, 411.2936. $C_{23}H_{43}O_4Si$ requires *M*, 411.2930); $\upsilon_{max}$ / $cm^{-1}$ 3460, 1454, 1369, 1249, 1098, 1053, 1029, 926, 859, 836, 739 and 697; $\delta_H$ 0.00 (9 H, s, (C$H_3$)$_3$Si), 0.91 (8 H, m, 2-$CH_3$, 9-$H_3$ and $CH_2$Si), 1.23 - 2.06 (9 H, m, 2-H, 4-H2, 5-$H_2$, 7-$H_2$ and 8-$H_2$), 3.38 -3.68 (6 H, m, 1-$H_2$, 3-H, 6-H and OC$H_2$$CH_2$Si), 4.50 (2 H, s, PhC$H_2$O), 4.68 (2 H, s, OC$H_2$O) and 7.25 - 7.37 (5 H, m, Ph-*H*); δC -1.5, 13.9, 14.1, 18.0, 18.4, 30.1, 30.4, 36.5, 38.5, 65.0, 65.2, 73.3, 74.9, 76.0, 76.5, 93.3, 126.8, 127.5, 128.3, 128.4 and 137.7; *m/z* (C.I.) 411 ($M^+$+1, 12%), 310 (11), 293 (100) and 90 (15).

**(1*R*,4*R*)-1-[(1*S*)-2-(Benzyloxy)-1-methylethyl]-4-{[2-(1,1,1-rimethylsilyl)ethoxy]methoxy}-heptyl) acetate (11).** Acetic anhydride (8 µl, 0.091 mmol) was added to a solution of alcohol **9**, (30 mg, 0.073 mmol), triethylamine (20 µl, 0.146 mmol) and DMAP (1 mg, cat.) in

dichloromethane (1 $cm^3$) at 0 °C. The resultant solution was stirred at room temperature for 4 h. Water (1 $cm^3$) was added and the mixture was extracted with dichloromethane (3 x 2 $cm^3$). The combined organic phase was washed with saturated aqueous sodium hydrogen carbonate (3 $cm^3$), brine (3 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography using light petroleum : ether, (3 : 1) afforded the *title compound*, **11** (16 mg, 48%) as a colourless oil, (Found: $M^+$+$NH_4$, 470.3297. $C_{25}H_{48}NO_5$ requires *M*, 470.3301); $\upsilon_{max}$ / $cm^{-1}$ 1736, 1454, 1371, 1243, 1099, 1052, 1030, 835 and 696; $\delta_H$ 0.00 (9 H, ($CH_3$)$_3$Si), 0.93 (8 H, m, 1′-$CH_3$, 7-$H_3$, and $CH_2$Si), 1.20 - 1.90 (8 H, m, 2-$H_2$, 3-$H_2$, 5-$H_2$ and 6-$H_2$), 1.99 (3 H, s, C$H_3$CO), 2.06 (1 H, m, 1′-H), 3.26 (1 H, dd, *J* 9 and 7, 2′-H), 3.44 (1 H, dd, *J* 9 and 5, 2′-H), 3.48 - 3.68 (3 H, m, 4-H and OC$H_2$C$H_2$Si), 4.46 (2 H, m, PhC$H_2$O), 4.65 (2 H, s, OC$H_2$O), 4.90 (1 H, m, 1-H) and 7.30 (5 H, m, Ph-*H*); δC -1.5, 13.4, 14.1, 18.0, 18.4, 21.0, 26.5, 29.8, 36.3, 36.8, 65.0, 72.0, 72.9, 75.6, 76.6, 93.3, 127.3, 127.5, 128.2, 138.3 and 170.5; *m/z* (C.I.) 470 ($M^+$+18, 100%), 263 (34), 185 (24) and 90 (22).

**[2-({[(1*R*,4*S*,5*S*)-6-(Benzyloxy)-4-iodo-5-methyl-1-propylhexyl]oxy}methoxy)-ethyl] (trimethyl)-silane (13).** Imidazole (86 mg, 1.26 mmol), triphenylphosphine (200 mg, 0.761 mmol) and iodine (193 mg, 0.761 mmol) were added to a solution of alcohol **9** (260 mg, 0.634 mmol) in THF (1 $cm^3$) at room temperature. The resultant suspension was stirred at room temperature for 15 h. Saturated sodium hydrogen carbonate solution (2 $cm^3$) was added and the mixture stirred for 10 mins. Iodine was then added until the organic layer remained iodine coloured. After a further 10 mins stirring saturated sodium thiosulfate solution (5 $cm^3$) was added. The two layers were separated and the aqueous layer was extracted with ether (3 x 5 $cm^3$). The combined organic layers were washed with brine (5 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was preabsorbed onto silica and purified by flash chromatography using light petroleum : ether, (4 : 1) as eluant to afford the *title compound*, **13** (210 mg, 64%), as a colourless oil, (Found: $M^+$+$NH_4$, 538.2217. $C_{23}H_{45}NO_3SiI$ requires *M*, 538.2215); $\upsilon_{max}$ / $cm^{-1}$ 1454, 1375, 1248, 1099, 1052, 1031, 858, 835 and 696; $\delta_H$ 0.00 (9 H, s, ($CH_3$)$_3$Si), 0.90 (8 H, m, 5-$CH_3$, C$H_3$C$H_2$C$H_2$ and C$H_2$Si), 1.10 - 2.20 (9 H, m, 2-$H_2$, 3-$H_2$, 5-H and C$H_2$C$H_2$C$H_3$), 3.20 - 3.70 (5 H, m, 4-H, 6-$H_2$ and OC$H_2$C$H_2$Si), 4.49 (3 H, m, 1-H and PhC$H_2$O), 4.66 (2 H, s, OC$H_2$O) and 7.26 - 7.36 (5 H, m, Ph-*H*); δC -1.4, 14.1, 14.2, 18.0, 18.5, 34.3, 36.4, 39.4, 46.6, 65.1, 73.2, 75.6, 76.0, 93.4, 127.5, 127.6, 128.2 and 138.2; *m/z* (C.I.) 538 ($M^+$+18, 100%), 410 (58), 263 (61) and 90 (63).

**(4*R*,7*S*,8*S*)-9-(Benzyloxy)-7-iodo-8-methylnonan-4-ol (14) and (2*R*,5*R*)-2-[(1*S*)-2-(Benzyloxy-1-methylethyl]-5-propyltetrahydrofuran (15).** Hydrogen fluoride (0.30 $cm^3$, 40% solution in water) was added to a solution of iodide **13** (154 mg, 0.296 mmol) in acetonitrile (1 $cm^3$). The resultant solution was stirred at room temperature for 15 h. Saturated sodium hydrogen carbonate solution (2 $cm^3$) was added. The aqueous phase was extracted with ether (3 x 3 $cm^3$) and the combined organic phase was washed with brine (3 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue using light petroleum : ether, (4 : 1) gave *title compound* **14**, (65 mg, 57%), as a colourless oil and *title compound* **15**, (14 mg, 18%), as a colourless oil.

**14.** (Found: $M^+$+H, 391.1139. $C_{17}H_{28}O_2I$ requires *M*, 391.1135); $\upsilon_{max}$ / $cm^{-1}$ 3422, 1453, 1375, 1364, 1329, 1204, 1098, 1026, 738 and 697; $\delta_H$ 0.96 (6 H, m, 1-$H_3$ and 8$CH_3$), 1.20 - 2.20 (9 H, m, 2-$H_2$, 3-$H_2$, 5-$H_2$, 6-$H_2$ and 8-H), 3.31 -3.80 (3 H, m, 7-H and 9-$H_2$), 4.55 (3 H, m, 4-H and PhC$H_2$O) and 7.38 (5 H, m, Ph-*H*); δC 13.9, 14.3, 18.7, 34.6, 37.4, 39.5, 39.7, 46.4, 70.6, 73.2, 75.4, 127.5, 127.6, 128.3 and 138.2; *m/z* (C.I.) 408 ($M^+$+18, 40%), 391 ($M^+$+1, 29), 263 (100) and 106 (72).

**15.** (Found: $M^+$+H, 263.2015. $C_{17}H_{27}O_2$ requires *M*, 263.2010); $\upsilon_{max}$ / $cm^{-1}$ 1455, 1366, 1100, 1074, 735 and 697; δH 0.86 (6 H, m, 1'-$CH_3$ and C$H_3$C$H_2$C$H_2$), 1.20 - 1.90 (9H, m, 1'-H, 3-$H_2$, 4-$H_2$ and C$H_2$C$H_2$C$H_3$), 3.29 (1 H, m, 2'-H), 3.54 (1 H, dd, *J* 4 and 9, 2'-H), 3.62 (1 H, m, 2-H), 3.73 (1 H, m, 5-H), 4.42 (2 H, s, PhC$H_2$O) and 7.26 (5 H, m, Ph-*H*); δC 13.4, 14.1, 19.3, 28.4, 30.8, 38.2, 38.8, 72.9, 73.2, 78.9, 80.6, 127.2, 127.3, 128.1 and 138.8; *m/z* (C.I.) 280 (2%), 263 (100) and 173 (5).

Alcohol (**14).** (62 mg, 0.159 mmol) in THF (0.5 $cm^3$) was added to a suspension of sodium hydride (8 mg, 60% dispersion in mineral oil, 0.206 mmol) in THF (0.5 $cm^3$) at 0 °C. The resultant suspension was stirred at room temperature for 3 h. Water (1 $cm^3$) was added and the aqueous phase was extracted with ether (3 x 3 $cm^3$). The combined organic phase was washed with brine (4 $cm^3$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue using light petroleum : ethyl acetate, (20 : 1) yielded the *title compound*, **15** (27 mg, 65%), as a colourless oil, (Found: $M^+$+H, 263.2015. $C_{17}H_{27}O_2$ requires *M*, 263.2010); $\upsilon_{max}$ / $cm^{-1}$ 1455, 1365, 1100, 1074, 735 and 697. The $^1H$ and $^{13}C$ spectroscopic data were identical to that for the tetrahydrofuran obtained directly from the deprotection.

**(±)-1-Benzyloxy-3-mesyloxy-2-methyl-6-(2-trimethylsilylethoxy)methoxynonane (16).** To a stirred solution of the alcohol **9** (201 mg, 0.49 mmol) and triethylamine (204 μL, 1.47 mmol) in DCM (5 $cm^3$) at 0 $^0$C, methanesulphonyl chloride (114 μL, 1.47 mmol) was added dropwise. The mixture was stirred at 0 $^0$C for 1 h, then saturated aqueous $NaHCO_3$ (5 $cm^3$) was added and the mixture allowed to warm to ambient temperature. The reaction mixture was partitioned between dichloromethane (10 $cm^3$) and water (10 $cm^3$). The aqueous layer was extracted with dichloromethane (2 x 10 $cm^3$) and the combined organic phase was washed with brine (2 x 15 $cm^3$), dried ($MgSO_4$) and the solvent removed under reduced pressure to give an oil. Flash chromatography using petrol : ether (20:1) as eluent gave the *title compound*, **16** (145 mg, 61%), (Found: 506.2979. $C_{24}H_{44}O_6SSi$ requires 506.2971); $\upsilon_{max}$/$cm^{-1}$ 2934, 1455, 1354, 1333, 1175, 1099, 1029, 907, 736 and 699; $\delta_H$ 0.00 (9 H, s, $SiMe_3$), 0.90 (5 H, m, 9-$CH_3$, $SiCH_2$), 0.99 (3 H, d, *J* = 7.01 Hz, 2-$CH_3$), 1.26 - 1.52 (4 H, m, 7-$CH_2$, 8-$CH_2$), 1.56 -1.75 (4 H, m, 4-$CH_2$, 5-$CH_2$), 2.28 (1 H, m, 2-CH), 2.97 (3 H, s, SO2CH3), 3.40 (2 H, m, 1-CH2), 3.58 (3 H, m, 6-H, O$CH_2$$CH_2$$SiMe_3$), 4.44 and 4.52 (each 1 H, d, *J* = 11.95 Hz, $OCH_2Ar$), 4.66 (2 H, s, O-$CH_2$-O), 4.81 (1 H, m, 3-H) and 7.22 - 7.44 (5 H, m, ArH); δC -1.5, 12.6, 14.1, 18.0, 18.5, 26.1, 29.3, 36.3, 37.2, 38.4, 65.1, 71.4, 73.0, 73.3, 85.3, 93.4, 127.5, 127.7, 128.3 and 137.2; m/z (C.I.) 506 (20%), 404 (20) and 263 (100).

**2,5-*trans*-3-Hydroxy-5-propyl-2-[(1′-methyl-2-*tert*-butyldimethylsilyloxy)ethyl]tetrahydrofuran (18) and 2,5-*trans*-3-Hydroxy-5-propyl-2-[(1′-methyl-2-benzyloxy)ethyl]tetrahydrofuran (19).** To a stirred solution of epoxide **7** (189 mg, 0.679 mmol) in dichloromethane (5 $cm^3$), *tert*-butyl dimethylsilyl trifluoromethanesulphonate (155 μL, 0.679 mmol) and trimethylaluminium (679 μL, 1.0 M in hexane, 0.679 mmol) were added at 0 $^0$C. The reaction mixture was stirred at room temperature for 16 h, then a mixture of acetic acid and water (3 $cm^3$:1.5 $cm^3$) was added at 0 $^0$C. The mixture was allowed to stir at room temperature for a further 16 h. Water (15 $cm^3$) was added and the mixture partitioned between dichloromethane (10 $cm^3$) and water. The aqueous layer was extracted with dichloromethane (2 x 5 $cm^3$) and the combined organic phase washed with water (2 x 20 $cm^3$), brine (2 x 20 $cm^3$) and dried ($MgSO_4$). After concentration under reduced pressure, flash chromatography of the residue using petrol : ether (10:1) as eluent afforded the *title compound* **18** (45 mg, 22%). Further elution using petrol : ether (5:2) as eluent afforded the *title compound* **19** (119 mg, 63%).

**18.** (Found: $(M+1)^+$, 303.2355. $C_{16}H_{35}O_3Si$ requires *M*, 303.2355); $\upsilon_{max}/cm^{-1}$ 3473, 2930, 1463, 1254, 1099, 836, 776 and 696; $\delta_H$ 0.00 (6 H, s, $SiMe_2$), 0.85 (12 H, m, $CH_3$, $CMe_3$), 0.92 (3 H, d, *J* = 6.87 Hz, 1′-$CH_3$), 1.35 (5 H, m, 4-H, 2 x $CH_2$), 1.62 (1 H, dt, *J* = 2.33 Hz & 14.01 Hz, 4-H′), 1.77 (1 H, br s, OH), 2.16 (1 H, m, 1-CH), 3.46 (1 H, t, *J* = 8.51 Hz, 5-H), 3.68 (1 H, s, 2′-H), 3.75 (1 H, dd, *J* = 3.29 Hz & 5.63 Hz, 2-H), 3.84 (1 H, dt, *J* = 2.89 Hz & 11.12 Hz, 3-H) and 3.93 (1 H, t, *J* = 9.89 Hz, 2′-H); δC 4.7, 10.6, 14.0, 18.0, 18.5, 25.7, 37.4, 39.6, 40.2, 71.3, 73.4, 78.8 and 86.8; m/z (C.I.) 320 (2%) and 303 (100).

**19.** (Found: $(M+1)^+$, 279.1954. $C_{17}H_{27}O_3$ requires *M*, 279.1960); $\upsilon_{max}/cm^{-1}$ 3468, 2931, 1454, 1357, 1308, 1095, 736 and 698; $\delta_H$ 0.86 (3 H, t, *J* = 6.18 Hz, $CH_3$), 1.02 (3 H, d, *J* = 6.87 Hz, 1′-$CH_3$), 1.37 (5 H, m, 4-H, 2 x $CH_2$), 1.58 (1 H, dt, *J* = 2.85 Hz & 14.15 Hz, 4-H′), 2.29 (1 H, m, 1-CH), 3.49 (1 H, m, 5-H), 3.55 (1 H, dd, *J* = 3.98 Hz & 6.32 Hz, 2′-H), 3.74 (1 H, m, 3-H), 3.95 (1 H, dd, *J* = 7.96 Hz & 15.24 Hz, 2-H), 4.03 (1H, dt, *J* = 3.70 Hz & 9.57 Hz, 2-H′), 4.48 (2 H, s, $OCH_2Ar$) and 7.00 -7.38 (5 H, m, ArH); δC 10.7, 14.0, 18.5, 36.2, 39.6, 40.8, 71.1, 71.8, 73.6, 83.2, 85.0, 127.5, 127.7, 128.4 and 138.0; m/z (C.I.) 296 (8%) and 279 (100).

**2,5-*trans*-3-Hydroxy-5-propyl-2-[(1′-methyl-2-hydroxy)ethyl]tetrahydrofuran (20)**

Method A : By debenzylation of **19** : Palladium on charcoal (10%, 10 mg) and 5 drops of acetic acid were added to a solution of tetrahydrofuran, **19** (46 mg, 0.165 mmol) in absolute ethanol (3 $cm^3$). The flask was evacuated and flushed with hydrogen four times, and then the reaction mixture was allowed to stir under an atmosphere of hydrogen for 72 h. The mixture was filtered through Celite and the residue washed with ethanol (2 x 5 $cm^3$). The filtrate was extracted with dichloromethane (2 x 5 $cm^3$) and the organic phase washed with water (2 x 10 $cm^3$), brine (2 x 10 $cm^3$) then dried ($MgSO_4$). Concentration under reduced pressure gave an oil which on flash chromatography using petrol : ether (1:1) as eluent gave the *title compound*, **20** (85 mg, 91%), (Found: $(M+1)^+$,189.1489. $C_{10}H_{21}O_3$ requires *M*, 189.1490); $\upsilon_{max}/cm^{-1}$ 3399, 3366, 2960, 1459, 1127, 1054, 996 and 815; $\delta_H$ 0.86 (3 H, t, *J* = 6.73 Hz, $CH_3$), 0.97 (3 H, d, *J* = 7.01 Hz, 1′-$CH_3$), 1.36 (5 H, m, 4-H, 2 x $CH_2$), 1.68 (1 H, m, 4-H), 1.92 (1 H, d, *J* = 4.39 Hz, 3OH), 2.24 (1 H, m, 1′-CH), 3.44 (2 H, m, 5-H, 2-OH), 3.81 (2 H, m, 2-H, 2-H), 3.91 (1H, dt, *J* = 3.71 Hz & 10.03

Hz, 3-H) and 3.97 (1 H, t, *J* = 7.97 Hz, 2′-H); δC 9.9, 14.0, 18.6, 37.2, 40.2, 71.1, 73.1, 78.1 and 86.3; m/z (C.I.) 206 (15%) and 189 (100).

Method B : By deprotection of **18** : TBAF (645 μL, 0.645 mmol) was added to a solution of the silyl ether, **18** (65 mg, 0.215 mmol) in THF (2 $cm^3$) at 0 $^0$C. After 5 h at room temperature, water (5 $cm^3$) was added. The reaction mixture was extracted with ether (2 x 10 $cm^3$) the organic phase washed with brine (2 x 10 $cm^3$) then dried ($MgSO_4$).

Concentration under reduced pressure gave an oil which on flash chromatography using petrol : ether (1:1) as eluent gave the diol **20** (36 mg, 89%).

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**2,5-*trans*-3-*O*-Phenoxythiocarbonyl-5-propyl-2-[(1′-methyl-2-benzyloxy)ethyl]-tetrahydrofuran (21)**. To a stirred solution of tetrahydrofuran **19** (37 mg, 0.133 mmol) in dichloromethane (2 $cm^3$) was added pyridine (43 μL, 0.532 mmol) and phenoxythiocarbonyl chloride (20 μL, 0.146 mmol). After 3 h, water (3 $cm^3$) was added and the mixture partitioned between water (5 $cm^3$) and dichloromethane (5 $cm^3$). The organic phase was washed with brine (2 x 5 $cm^3$) dried ($MgSO_4$) and concentrated under reduced pressure to afford an oil which on flash chromatography using petrol : ether (10:1) gave the *title compound*, **21** (46 mg, 83%); (Found: $(M+18)^+$, 432.1997.$C_{24}H_{34}NO_4S$ requires *M*, 432.1993); $\upsilon_{max}/cm^{-1}$ 2960, 1593, 1494, 1455, 1256, 1210, 1093, 777, 734 and 698; $\delta_H$ 0.90 (3 H, t, *J* = 7.14 Hz, $CH_3$), 1.04 (3 H, d, *J* = 6.87 Hz, 1′-$CH_3$), 1.38 (2 H, t, *J* = 7.14 Hz, $CH_2$), 1.52 (1 H, m), 1.62 (1 H, m), 1.75 (1 H, dd, *J* = 5.35 Hz & 10.43 Hz, 4-H), 1.78 (1 H, m, 4-H′), 2.28 (1 H, m, 1-CH), 3.48 (1 H, t, *J* = 8.37 Hz, 5-H), 3.59 (1 H, dd, *J* = 7.05 Hz & 10.03 Hz, 2-H), 3.98 (2 H, m, 2′-H, 2-H), 4.50 (2 H, s, $OCH_2Ar$), 4.92 (1 H, m, 3-H) and 7.04-7.38 (10 H, m, ArH); δC 1.0, 10.7, 14.1, 18.6, 36.3, 39.6, 40.8, 71.1, 71.8, 73.6, 83.2, 85.0, 121.8, 126.7, 127.6, 127.7, 128.4, 129.4, 129.6 and 153.5; m/z (C.I.) 432 (80%), 414 (50), 398 (100) and 261 (20).

**2,5-*trans*-5-Propyl-2-[(1′-methyl-2-benzyloxy)ethyl]tetrahydrofuran (17).** To a stirred solution of tetrahydrofuran **21** (42 mg, 0.101 mmol) in toluene (1.5 $cm^3$) was added tri-*n*-butyltin hydride (27 μL, 0.101 mmol) and AIBN (5mg). The solution was heated under reflux under a nitrogen atmosphere for 2 h then concentrated under reduced pressure. Flash chromatography of the residue using petrol : ether (20:1) as eluent gave the *title compound*, **17** (14 mg, 53%), as a colourless oil, (Found: $(M+18)^+$, 280.2270. $C_{17}H_{30}NO_2$ requires *M*, 280.2276); $\upsilon_{max}/cm^{-1}$ 2929, 1495, 1455, 1257, 1095, 784 and 697; $\delta_H$ 0.81 (1 H, t, *J* = 6.45 Hz, $CH_3$), 1.01 (1 H, d, *J* = 6.86 Hz, 1′-$CH_3$), 1.22 (6 H, m, 3-H, 4-H, 2 x $CH_2$), 1.36 (2 H, m, 3-H′, 4-H), 2.23 (1 H, m, 1-CH), 3.44 (1 H, q, *J* = 8.38 Hz, 2-H), 3.51 (1 H, dd, *J* = 6.04 Hz & 9.47 Hz, 2′-H), 3.82 (1 H, q, *J* = 6.86 Hz, 5-H), 3.90 (1 H, dd, *J* = 7.14 Hz & 8.10 Hz, 2′-H), 4.43 and 4.47 (each 1 H, d, *J* = 11.94 Hz, $OCH_2Ar$) and 7.15-7.35 (5 H, m, ArH); δC 10.4, 14.0, 22.5, 25.7, 31.8, 34.6, 37.0, 71.5, 73.2, 83.4, 84.5, 127.5, 127.6, 128.3 and 138.4; m/z (C.I.) 280 (100%) and 263 (85).

Aqueous hydrogen fluoride (40%, 8 $cm^3$) and acetonitrile (5 drops) were added to the SEM-ether **16** (97 mg, 0.2 mmol), and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched by the addition of water (5 $cm^3$) and extracted with ether (2 x 10 $cm^3$). The organic phase was washed with brine (2 x 10 $cm^3$), dried ($MgSO_4$) and

concentrated under reduced pressure to give an oil. Flash chromatography using petrol : ether (20:1) as eluent gave the tetrahydrofuran **17** identical to a sample prepared from the thionocarbonate **21** (16.1 mg, 31%).

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