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Studies of intramolecular alkylidene carbene reactions; an approach to heterocyclic nucleoside bases

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Abstract—A series of investigations into the applications of intramolecular cyclisations of alkylidene carbenes are described. The insertion reaction of the carbene generated from 1,4-di(*tert*-butyldimethylsilyloxy)-3-benzyloxy-butane-2-one to the benzylic position proceeded in good yield and a diastereoselectivity of 3.6:1. The corresponding insertion process of 1,4-di(*tert*-butyldimethylsilyloxy)-3-methyloxy-methyl-butane-2-one gave a mixture of products, including one resulting from a competitive trapping of the carbene by the oxygen atom of a silyloxy group.

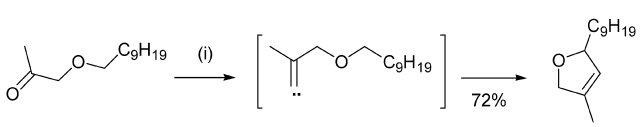
1. Introduction

Alkylidene carbenes undergo intramolecular insertion reactions into 1,5-CH bonds to form cyclopentenes.[1,2] Where heteroatoms are incorporated, heterocycles such as 2,5-dihydrofurans are formed in good yields (Scheme 1).[1,3–8,11,12] A number of methods have been developed for the generation of alkylidene carbenes. These include; retro-1,2-shifts in alkynes,[9,10] Li/Br exchange in 1,1-dihaloalkenes,[7,11,12] and base induced α-elimination from terminal vinylbromides.[1,2]

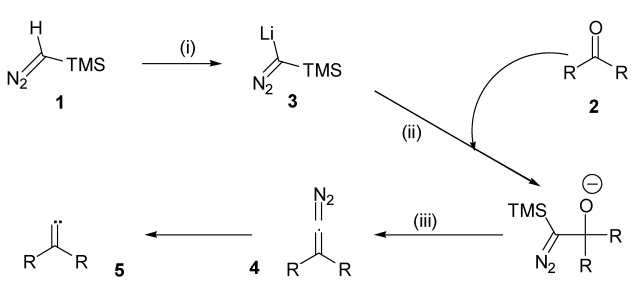
Alkenyl(phenyl)-iodonium tetrafluoroborates and enol triflates have also been used to good effect via addition of soft nucleophiles to the acetylene bond.[13–16,17]

Diazoalkenes extrude nitrogen with formation of an unsaturated carbene. In 1973 Colvin reported the one step conversion of carbonyl compounds to acetylenes using lithiated trimethylsilyldiazomethane (TMSDM) or dimethyl-diazomethane-phosphonate.[18,19] Mechanistically, formation of the carbene by TMSDM (**1**) is thought to proceed via addition to the ketone (**2**), of lithiated anion (**3**) generated from the action of *n*-butyllithium upon the TMSDM (Scheme 2). This then undergoes a Peterson elimination to give **4** which is subject to diazo decomposition producing the unsaturated carbene **5**.[4,20] The base promoted action of dimethyl-diazomethanephosphonate or diethyl-diazomethanephosphonate (DAMP) upon a ketone is thought to proceed in a similar manner.[21,22]

TMSDM was first used by Ohira to promote 1,5-CH insertion reactions[4] and its use was extended by Taber and Meagley.[23] When an alkylidene carbene undergoes a 1,5-insertion reaction into a C–H bond at a chiral centre, retention of the configuration about that centre is observed.[24–27] In 1994 Taber and Meagley reported the first case of diastereoselectivity in an alkylidene carbene 1,5-CH insertion (Scheme 3).[23] Having established 1,3 diastereoselective induction Taber and Yu went on to demonstrate 1,2 induction of relative stereochemistry in the synthesis of α-necrodol.[28,29] A pseudo chair-like transition



Scheme 1. *Reagents and conditions*: (i) TMSDMLi, DME/hexane, −78°C→rt.



Scheme 2. *Reagents and conditions*: (i) *n*-butyllithium, hexane, −78°C→rt; (ii) **2**, −78°C; (iii) warm to rt.

Keywords: carbene; alkylidene; insertion; ketone; stereoselective; cyclisation.

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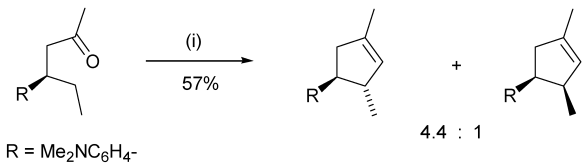


Scheme 3. *Reagents and conditions*: (i) LiTMSDM, DME, Et_2O, −60°C→rt.

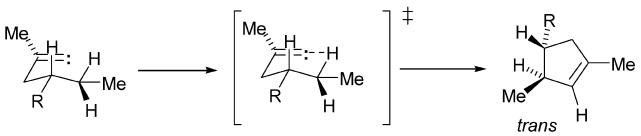


Figure 1. Proposed transition state model for diastereoselective 1,5-CH insertion.

state was assumed, the phenyl group adopting an equatorial orientation in the proposed model (Fig. 1). The experimental results obtained were in accordance with this analysis.

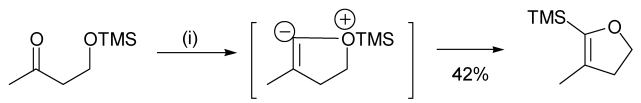
In 1994, Shiori et al. reported the formal insertion of an alkylidene carbene into a 1,5-OSi bond to yield 5-trimethylsilyl-2,3-dihydrofurans.[30] These products could however have been the result of a ylide intermediate followed by TMS group migration as was suggested at the time (Scheme 4). In previously reported work in this group we extended 2,5-dihydrofuran formation via alkylidene carbenes to the synthesis of a model of the zaragozic acid core structure.[5,6,31]

The extension of vinylidene carbene insertions to the construction of the pentose moiety of a functionalised nucleoside model was therefore considered appealing.[32–34]

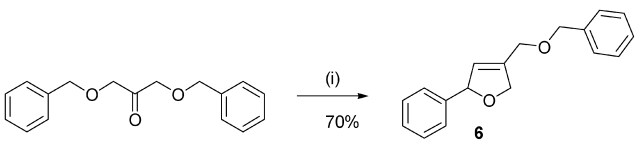
2. Results and discussion

The methodology was first applied to the synthesis of a model system (Scheme 5). In this example the carbene inserted cleanly into the methylene CH bond of a benzyl protecting group to generate dihydrofuran **6**. In order to investigate diastereoselective variations on this reaction substrate **7** was selected for study and its synthesis was undertaken (Scheme 6).

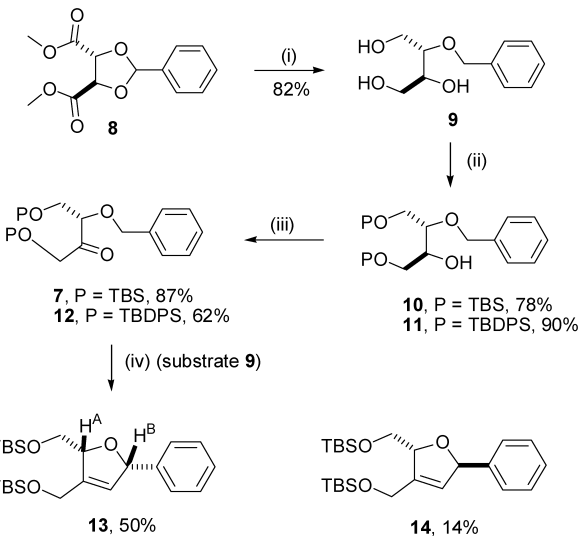
Dimethyl (L)-tartrate was condensed with the dimethoxyacetal of benzaldehyde in the presence of catalyst *p*-TSA, to protect the 1,2-diol functionality, giving product **8**, in 89%



Scheme 4. *Reagents and conditions*: (i) LiTMSDM, THF/hexane, −78°C.

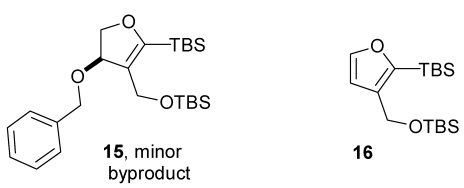


Scheme 5. *Reagents and conditions*: (i) TMSDMLi, DME/hexane, −78°C→rt.



Scheme 6. *Reagents and conditions*: (i) $LiAlH_4$, $AlCl_3$, DCM/Et_2O; (ii) TBSCl, imidazole, DMF, or TBDPS, pyridine, DMAP, DCM; (iii) TPAP, NMO, DCM; (iv) LiTMSDM, DME/hexane, −78°C→rt.

yield. The esters were reduced and the [1,3]dioxolane ring system cleaved in one pot by reduction with lithium aluminium hydride and aluminium chloride in DCM/ether, to give the triol **9**, in 82% yield. The primary alcohols in **9** were then protected with TBS groups (TBSCl, imidazole, DMF) to give the TBS protected alcohol **10** in 78% yield, or with TBDPS groups (TBDPSCl, pyridine, DMAP, DCM) to give the TBDPS protected alcohol **11** in 90% yield. In both of these compounds the secondary alcohols were oxidised to the ketones using TPAP and NMO in DCM, furnishing **7** in 87% and **12** in 62% yields. With these substrates in hand an investigation of the diastereoselectivity in the insertion process was initiated. When ketone **12** was subjected to the standard conditions used for the generation of alkylidene carbenes, only the starting material was recovered from the crude products upon workup. This was attributed to the TBDPSO groups in **12** being too bulky to allow attack of the LiTMSDM nucleophile on the ketone carbon. On the other hand, when the TBS protected ketone **7** was subjected to equivalent conditions reaction proceeded smoothly to give a (major **13** (*cis*) 3.6: 1 minor **14** (*trans*)) ratio of diastereoisomers. The minor diasteroisomer was inseparable from a small amount of a third compound and its yield was calculated from its NMR integrals in this mixture.



This third component, **15**, from examination of its NMR spectrum, was thought to be the product of an insertion into the 1,5-OSi bond and is not without precedent (Scheme 4).[35,30] Upon standing this third product was found to rearrange to the furan **16** and benzyl alcohol. Assignment of the configuration of the two diastereoisomers, **13** and **14**, was made using nuclear Overhauser enhancement spectroscopy (NOESY), there being a significant nuclear Overhauser effect (nOe) between protons A and B for **13**, the

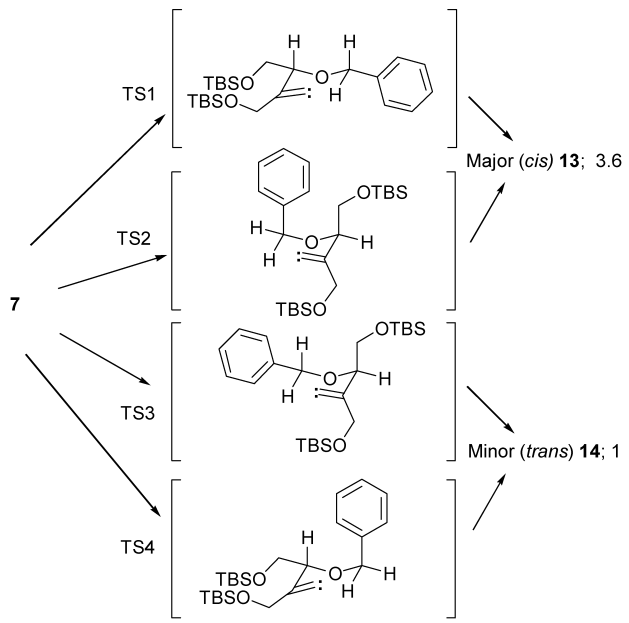
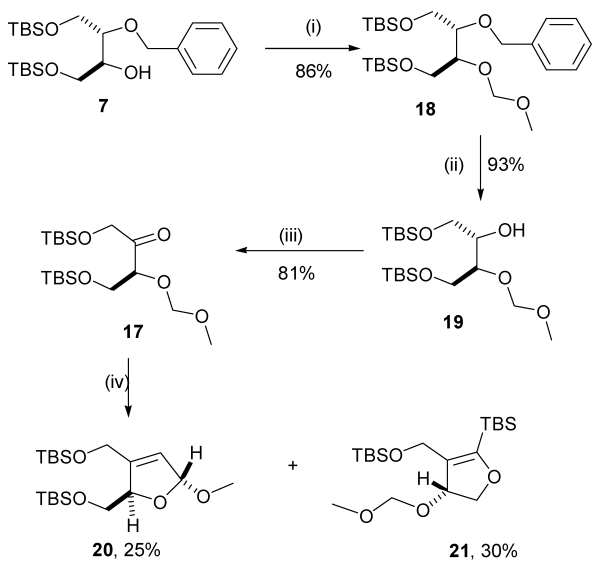


Figure 2. Possible transition states in the alkylidene carbene 1,5-CH insertion reaction on **7**.

major product, showing that these protons are in close proximity and therefore *cis*. This effect is not observed in **14** and thus confirms it as the *trans* product.

It is thought that free alkylidene carbenes adopt a pseudo chair-like transition state to bring the carbene centre into appropriate proximity with the relevant hydrogen atom, then to undergo a 1,5-CH insertion reaction in a concerted manner. In the case of substrate **7**, this could give four possible transition states (Fig. 2) labelled TS1–TS4. In this experiment it was thought that most of the reactant molecules react via TS1. This was assumed to be the lowest energy conformation because both the phenyl group and $-CH_2-OTBS$ groups are in equatorial orientations in the pseudo chair-like transition state. As the experimental results suggest this model is substantiated to some extent and is in accordance with similar findings of Taber et al. (Scheme 3, Fig. 1).[28,29]



Scheme 7. *Reagents and conditions*: (i) MOMCl, diisopropyl-ethylamine; (ii) 5% Pd/C, EtOH, H_2; (iii) TPAP, NMO, DCM; (iv) LiTMSDM, −78°C→rt.

The insertion process into the methylene CH of a methoxymethyl (MOM) protecting group in substrate **19** (Scheme 7) was next selected for study, as this would furnish **20**, a nucleoside precursor.

We reasoned that, already having multigram quantities of the secondary alcohol **7** from the previous synthesis, a reliable route to the substrate might be to protect this secondary alcohol with a MOM group, then remove the benzyl protecting group and oxidise the deprotected alcohol to the ketone **17**. Synthesis of the ketone substrate **17** was achieved via, MOM protection of the secondary alcohol in **7** with MOMCl and diisopropylethylamine, to give the MOM protected alcohol **18** in 86% yield. Removal of the benzyl protecting group using 5% Pd on carbon in ethanol under hydrogen, gave **19** in 93% yield. Subsequent oxidation of this secondary alcohol with TPAP and NMO in DCM gave the ketone **17** in 81% yield (Scheme 7).

With this substrate an alkylidene carbene 1,5-CH insertion reaction was then performed using lithiated TMSDM under the standard conditions that had been developed. When the reaction was complete, TLC of the crude reaction mixture showed the clean formation of two products which were separated by column chromatography yielding 25% of **20**, and 30% of **21**. In this case, the major product **21** appeared to be the result of an insertion into the 1,5-OSi bond in the substrate. Why this should form preferentially in this case is perhaps because insertion into a MOM methylene CH is a less favourable process and therefore insertion into an alternative site is permitted kinetically. Insertions into O–Si bonds have been reported by other groups.[35,30]

The reason for any MOM methylene deactivation could be due to there now being an oxygen atom within the substrate bearing a 1,6-relationship to the carbene centre which could coordinate to the carbene to form an internal oxonium ylide thus deactivating 1,5-CH insertion. Evidence for and against reversible oxonium ylide formation in ethereal solvents has

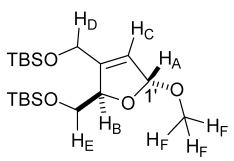


Figure 3. Proton assignments for nOe of dihydrofuran **20**.

Table 1. Summary of nOe effects for dihydrofuran **20**

Proton irr	Proton (nOe, %)	Proton irr	Proton (nOe)%
A	B, 2.03	D	C, 1.31
A	E, 3.41	D	B, 1.49
A	F, 1.55	E	B, 5.18
A	D, 4.87	E	F, 1.29
B	F, 2.31	F	A, 2.55
C	A. 1.41	F	B. 0.80

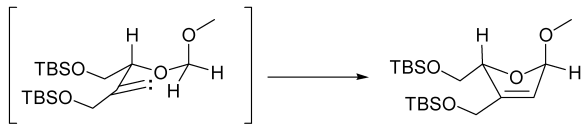


Figure 4. Pseudo chair-like transition state in the reaction of ketone **17**.

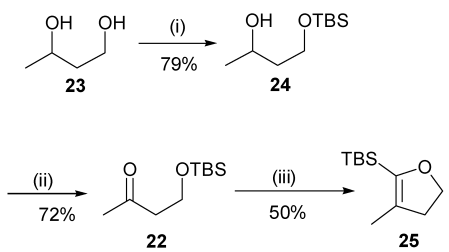
been published by Ochiai et al.[36] and separately by Gilbert et al.[37]

The minor product **20**, although formed in a disappointing yield, is interesting as it was formed as a single diastereoisomer. The relative configuration was confirmed by nOe spectroscopy (Fig. 3 and Table 1). These results show no nOe between protons A and B and significant nOes between protons B and F, A and E, thus confirming it as the *trans* diastereoisomer. In rationalising this observed diastereoselectivity it is believed that the reaction proceeds via a similar transition state to that proposed in the previous section, i.e. a pseudo chair-like transition state (Fig. 4). However in this case the diastereoselectivity proposed is a result of preference for an axial orientation of the methoxy in the transition state due to anomeric stereoelectronic effects.

From the previous two alkylidene carbene reactions an order of insertion site preference was emerging: the alkylidene carbene appears to prefer to insert into 5,6-bonds in the following order; benzyl methylene CH≫O–TBS>MOM methylene CH.

To demonstrate that TBS protecting group migration to the carbene centre is a facile process and therefore, the likely origin of the products **15** and **21**, a simple experiment was designed and executed. It was reasoned that to demonstrate 1,5-insertion into OTBS bonds would require the synthesis of a substrate **22** (Scheme 8) in which competing reactions would not be possible, or very slow. In this ketone there is no available 1,5-CH insertion site and the possibility of a 1,2-migration to give an alkyne is discouraged by the low migratory aptitude of the alkyl groups.

The primary alcohol of diol **23** was first protected with a TBS group by treatment with TBSCl and imidazole in DMF affording the TBS protected alcohol **24** in 79% yield. This was treated with TPAP and NMO in DCM to give the ketone **22** in 72% yield. Exposure of **22** to LiTMSDM under the standard set of conditions employed gave a 50% yield of the insertion product **25**. In this way it was demonstrated that, in the absence of more favourable reaction pathways, insertion into OTBS bonds is a facile process and that this kind of



Scheme 8. *Reagents and conditions*: (i) TBSCl, imidazole, DMF; (ii) TPAP, NMO, DCM; (iii) LiTMSDM, DME/hexane, −78°C→rt.

insertion accounts for some of the observed reaction products.

In conclusion, we have demonstrated that intramolecular alkylidene carbene C–H insertion reactions exhibit a complex pattern of reactivity. In certain cases the insertion is clean and diastereoselective whereas, in contrast, the presence of oxygen atoms proximal to the insertion position can result in competing trapping by the heteroatom. Trapping by the oxygen atom can lead to a synthetically useful synthesis of dihydrofurans.

3. Experimental

3.1. General

All reactions were carried out in oven or vacuum-flame dried glassware under nitrogen. All reagents were obtained from commercial sources and used without purification unless stated. THF was distilled from sodium using benzophenone as an indicator under nitrogen. DME was distilled from calcium hydride under nitrogen. DCM and methanol were supplied from Romil as Hi-Dry™ solvents, DMF from Aldrich as anhydrous in Sure/Seal™ bottles. All other solvents were from commercial sources and used without further preparation unless otherwise stated. Petrol refers to that fraction of petrol ether which boils in the range 40–60°C.

Thin layer chromatography (tlc) was performed on aluminium backed silica gel 60 (F_{254}) plates supplied by Merck and visualised by UV_{254}, 2,4-dinitrophenylhydrazine solution, phosphomolybdic acid solution, iodine (adsorbed onto silica) or potassium permanganate solution. Column chromatography was carried out on silica gel 40-63U 60A supplied by Fluorochem Limited. Organic solvents were removed on a Buchi Rotary Evaporator and then a static oil pump (2 mm Hg).

Melting points were determined using a Stuart Scientific SMP1 instrument and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1310 FTIR spectrometer on sodium chloride plates. Optical rotations were measured using a Perkin–Elmer 241 polarimeter (sodium D line) at rt with a 10 cm rotation cell and are reported in 10^{-1} deg cm^2 g^{-1}. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker AC 250 MHz, Bruker ARX-400, Bruker 300 MHz or Bruker 500 MHz spectrometers. Chemical shift values are quoted in ppm and are relative to the internal standard tetramethylsilane (TMS) for ^{1}H NMR, or the middle of the chloroform triplet δ 77 for ^{13}C NMR. Multiplicities are quoted as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m) and coupling constants (J) are quoted in Hz. Mass Spectra (MS) were recorded on a Kratos analytical MS80 RFAO spectrometer, except some high resolution mass determinations (HRMS) which were obtained from the Swansea EPSRC Mass Spectrometry Service. Elemental analysis were obtained using a Carlo Erba 1160 elemental analyser.

3.1.1. 1,1-Bis(benzyloxymethyl)-ethylene. Sodium hydride (4 g, 60% dispersion in mineral oil, 100 mmol)

was dispersed in DMF (200 mL) at 0°C. To this benzyl alcohol (10.4 mL, 10.87 g, 100 mmol) was added via syringe pump over 1 h. After addition was complete the mixture was stirred for a further 20 min at 0°C then 1 h at rt. 3-Chloro-2-chloromethyl-1-propene (4.8 mL, 5.18 g, 41 mmol) was then added and the reaction left for 12 h, after which tlc (1:19, ethyl acetate/petrol) revealed substantial product formation. The products were poured into saturated NH_4Cl solution (150 mL), and the organics were extracted into ethyl acetate (4×200 mL). The combined extracts were washed with water (5×200 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding the alkene as a colourless oil (9.40 g, 35 mmol, 88%).[6,31] The spectroscopic data matched that described in the literature.

3.1.2. 1,3-Bis(benzyloxy)-2-propanone. 1,1-Bis(benzyloxymethyl)-ethylene (2.84 g, 10.60 mmol) was dissolved in DCM (10 mL) and cooled to −78°C. Ozone was then bubbled through this until the reaction mixture adopted a persistent pale blue coloration. Oxygen was bubbled through for 10 min and then nitrogen for 30 min. Triphenylphosphine (5.24 g, 20 mmol) was added, the cooling bath removed and the mixture left for 12 h at rt. The crude products were adsorbed directly onto silica and the product purified by column chromatography (1:5 v/v, ethyl acetate/petrol) yielding the ketone **5** as a colourless oil which solidifies upon storage (2.36 g, 8.74 mmol, 82%).[6,31] The spectroscopic data matched that described in the literature.

3.1.3. 4-Benzyloxymethyl-2-phenyl-2,5-dihydro-furan 6. A mixture of TMSDM (1.0 mL, 2 mmol, 2.0 M in hexane) and DME (1 mL) were cooled to −78°C. To this was added slowly, *n*-BuLi (0.84 mL, 2.1 mmol, 2.5 M in hexane), to give a solution which was stirred for 20 min and then allowed to warm to rt. The reaction mixture was again cooled to −78°C and 1,3-bis(benzyloxy-2-propanone (0.21 g, 0.77 mmol) was added, in a little DME (1 mL). The reaction was allowed to warm to rt over 4 h and quenched by the addition of water (5 mL) and extracted into diethyl ether (3×10 mL). The organic extracts were combined, dried (anhydrous $MgSO_4$) and the solvent was removed yielding a crude brown oil. The crude products were adsorbed onto silica and the product purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding **6** as an orange oil (0.15 g, 0.56 mmol, 73%).[6,31] The spectroscopic data matched that described in the literature.

3.1.4. (2*R*,3*R*)-(−)-Dimethyl-2,3-*O*-benzylidene-L-tartrate 8. Dimethyl-(L)-tartrate (3.56 g, 20 mmol), benzaldehyde–dimethylacetal (15 g, 99 mmol) and *p*-TSA (0.38 g, 2 mmol, 10 mol%) were mixed and stirred under reduced pressure for 8 h, after which time tlc (1:5 v/v, ethyl acetate/petrol) revealed complete consumption of the starting material. The acid catalyst was neutralised with $NaHCO_3$ (1 g), DCM (50 mL) added, and the mixture stirred a further 1 h. The mixture was then diluted with DCM (70 mL), washed with water (50 mL), then dried (anhydrous $MgSO_4$) and the solvent removed under reduced pressure. Any benzaldehyde or benzaldehyde–dimethylacetal were removed by reduced pressure distillation (40°C at 2 mm Hg). The crude product was then recrystallised from EtOH, washed with EtOH and then hexane yielding **8** as white crystals (4.76 g, 17.90 mmol, 89%). The ^{1}H NMR spectrum was identical to authentic product.[38] The spectroscopic data matched that described in the literature.

3.1.5. (2*S*,3*S*)-(+)-2-Benzyloxy-1,3,4-butanetriol 9. Aluminium trichloride (10.64 g, 80.6 mmol) was dissolved in diethyl ether (40 mL) at −20°C and to this was added $LiAlH_4$ (3.73 g, 80 mmol) in diethyl ether (60 mL) at −20°C. This mixture was then diluted with DCM (80 mL) and whilst maintained at −20°C, (−)-dimethyl-2,3-*O*-benzylidene-L-tartrate **8** (3.65 g, 13.72 mmol) in DCM (80 mL) was added. The reaction mixture was allowed to warm to rt and then refluxed at 50°C for 4 h. After this the reaction was cooled to −10°C, then diluted with THF (240 mL) and $Na_2SO_4{\cdot}10H_2O$ (38 g) was added. This was then stirred at −10°C for 2 h, allowed to warm to rt and left for 16 h. The products were filtered through a pad of celite. After removal of the solvent under reduced pressure the product was purified by recrystallisation from ethyl acetate and washed with hexane yielding **9** as fine white crystals (2.37 g, 11.18 mmol, 81.5%). The ^{1}H NMR spectrum was identical to authentic product.[39]

3.1.6. (2*S*,3*S*)-(+)-3-Benzyloxy-1,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-ol 10. (2*S*,3*S*)-(+)-2-Benzyloxy-1,3,4-butanetriol **9** (0.50 g, 2.36 mmol), *tert*-butyl-dimethyl-chlorosilane (0.78 g, 5.00 mmol), imidazole (0.80 g, 11.80 mmol) and DMF (10 mL) were mixed at −20°C, allowed to warm to rt, then stirred for 24 h. After this time tlc (1:9 v/v, ethyl acetate/petrol) revealed consumption of the starting materials. The mixture was poured into water (50 mL) and extracted into diethyl ether (5×50 mL). The combined organic fractions were dried (anhydrous $MgSO_4$) and the solvent removed under reduced pressure. The product was then purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding **9** as a clear oil (0.81 g, 1.84 mmol, 78%);[40] CHN requires C 62.68%, H 10.06%, found C 62.93%, H 10.09%; $[\alpha]^D$=+14.30 (*c* 1.00, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2954, 2471, 1256, 1100, 833, 776; δ_H (250 MHz, $CDCl_3$) 7.35–7.24 (5H, m, Ph*H*), 4.77 (1H, d, J_{AB}=12 Hz, Ph–CH_2–O–), 4.60 (1H, d, J_{AB}=12 Hz, Ph–CH_2–O–C), 3.87–3.58 (6H, m, Ph–CH_2–O–C*H*(R)CH_2–O–Si and HO–C*H*(R)–CH_2–O–Si), 2.56 (1H, d, *J*=6 Hz, *H*O), 0.90 and 0.89 (18H, 2×s, Si(CH_3)$_2$–C(CH_3)$_3$), 0.06 and 0.05 (12H, 2×s, Si(CH_3)$_2$–C(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 138.9 (*C*^{ipso}), 128.7 (Ph*C*H), 128.3 (Ph*C*H), 128.10 (Ph*C*H), 78.8 (Ph–CH_2–O–*C*H(R)CH_2–O), 73.7 (Ph–*C*H_2–O–C), 72.1 (HO–*C*H(R)–CH_2–O–), 64.1 and 63.5 (Ph–CH_2–O–CH(R)*C*H_2–O–Si and HO–CH(R)–*C*H_2–O–Si), 26.3 (Si(CH_3)$_2$–C(*C*H_3)$_3$) 18.6 (Si(CH_3)$_2$–*C*(CH_3)$_3$), −4.9 and −4.0 (2×Si(*C*H_3)$_2$–C(CH_3)$_3$); *m/z* (CI) 441 [M+H]$^+$, 383, 309, 108; HRMS (CI) [M+H ($C_{23}H_{45}O_4Si_2$)]$^+$ calculated 441.2856, found 441.2854.

3.1.7. (3*R*)-(−)-3-Benzyloxy-1,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-one 7. *N*-Methylmorpholine oxide (NMO) (2 g, 14.81 mmol) was dissolved in DCM (100 mL), dried (anhydrous $MgSO_4$) and filtered. Of this solution a portion (17 mL) was taken and to it was added (2*S*,3*S*)-(+)-3-benzyloxy-1,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-ol **10** (0.456 g, 1.06 mmol) and some 2 Å

molecular sieves (1 g). This mixture was stirred gently for 20 min and then tetrapropylammonium perruthenate (TPAP) (0.018 g, 0.05 mmol, 5 mol%) was added. The reaction was monitored by tlc (1:19 v/v, ethyl acetate/petrol) and after 16 h was complete, therefore, the crude products were adsorbed directly onto silica and the product purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding **7** as a yellow oil (0.403 g, 0.92 mmol, 87%);[40] $[\alpha]^{D}=-16.50$ (*c* 0.996, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2930, 1738, 1471, 1255, 1130, 837; δ_H (250 MHz, $CDCl_3$) 7.37–7.29 (5H, m, Ph*H*), 4.62 (2H, s, Ph–CH_2–O), 4.58 (1H, d, J_{AB}=19 Hz, O=C(R)–CH_2–O), 4.48 (1H, d, J_{AB}=19 Hz, O=C(R)–CH_2–O–Si), 4.07 (1H, dd, J_{AX}=4 Hz, J_{BX}=5 Hz, Ph–CH_2–O–C*H*(R)–CH_2–O–Si), 3.93 (1H, dd, J_{AX}=4 Hz, J_{AB}=11 Hz, Ph–CH_2–O–CH(R)–CH_2–O–Si), 3.87 (1H, dd, J_{BX}=5 Hz, J_{AB}=11 Hz, Ph–CH_2–O–CH(R)–CH_2–O–Si), 0.90 and 0.88 (18H, 2×s, O–Si(CH_3)$_2$–C(CH_3)$_3$), 0.07 and 0.06 (12H, 2×s, Si(CH_3)$_2$–C(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 208.5 (O=*C*), 137.5 (*C*^{ipso}), 128.5 (Ph*C*H), 127.9 (Ph*C*H), 127.8 (Ph*C*H), 83.6 (Ph–CH_2–O–*C*H(R)CH_2–O–Si), 72.6 (Ph–*C*H_2–O), 68.8 (O=C(R)–*C*H_2–O–Si), 63.8 (Ph–CH_2–O–CH(R)*C*H_2–O–Si), 25.8 and 25.8 (2×Si(CH_3)$_2$–C(*C*H_3)$_3$), 18.4 and 18.3 (2×Si(CH_3)$_2$–*C*(CH_3)$_3$), −5.3 and −5.5 (2×Si(*C*H_3)$_2$–C(CH_3)$_3$); *m/z* (CI) 456 $[M+NH_4]^+$, 391, 331, 273; HRMS (CI) $[M+NH_4, (C_{23}H_{46}O_4Si_2N)]^+$ calculated 456.2965, found 456.2965.

3.1.8. (2*S*,3*S*)-3-Benzyloxy-1,4-bis-(*tert*-butyl-diphenyl-silanyloxy)-butan-2-ol 11. (2*S*,3*S*)-2-Benzyloxy-1,3,4-butanetriol **9** (0.100 g, 0.472 mmol), *tert*-butyl-diphenyl-chlorosilane (0.283 g, 1.030 mmol), dimethylamino pyridine (DMAP) (0.003 g, 0.025 mmol, 5 mol%), pyridine (1.5 mL) and DCM (2 mL) were mixed at 0°C and stirred, with monitoring by tlc (1:19 v/v, ethyl acetate/petrol). After 24 h the reaction had reached completion and the mixture was adsorbed directly onto silica and purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding **11** as a yellow oil (0.294 g, 0.427 mmol, 90%); ν_{max} (NaCl)/cm^{-1} 3448, 2931, 1471, 1113, 823, 701; δ_H (250 MHz, $CDCl_3$) 7.71–7.18 (25H, m, Ph*H*), 4.65 (1H, d, J_{AB}=11 Hz, Ph–CH_2–O), 4.44 (1H, d, J_{AB}=11 Hz, Ph–CH_2–O), 3.94–3.71 (6H, m, Ph–CH_2–O–C*H*(R)CH_2–O–Si and HO–C*H*(R)–CH_2–O–Si), 2.50 (1H, br s, *H*O), 1.05 (18H, s, Si(Ph)$_2$–C(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 138.7 (*C*^{ipso}), 133.8 (*C*^{ipso}), 133.7 (*C*^{ipso}), 136.1–128.1 (Ph*C*H's), 78.7 (Ph–CH_2–O–*C*H(R)CH_2–O–Si or HO–*C*H(R)–CH_2–O–Si), 73.5 (Ph–*C*H_2–O–CH(R)CH_2–O–Si), 72.0 (Ph–CH_2–O–*C*H(R)CH_2–O–Si or HO–*C*H(R)–CH_2–O–Si), 64.7 and 63.7 (Ph–CH_2–O–CH(R)*C*H_2–O–Si and HO–CH(R)–*C*H_2–O–Si), 27.3 (Si(Ph)$_2$–C(*C*H_3)$_3$), 19.6 (Si(Ph)$_2$–*C*(CH_3)$_3$); *m/z* (CI) 706 $[M+NH_4]^+$, 365, 129; HRMS (CI) $[M+NH_4 (C_{43}H_{56}O_4NSi_2)]^+$ calculated 706.3748, found 706.3737.

3.1.9. (3*R*)-3-Benzyloxy-1,4-bis-(*tert*-butyl-diphenyl-silanyloxy)-butan-2-one 12. NMO (2 g, 14.81 mmol) was dissolved in DCM (100 mL), dried (anhydrous $MgSO_4$) and filtered. A portion of this solution (10 mL) was taken and to it was added (2*S*,3*S*)-(+)-3-benzyloxy-1,4-bis-(*tert*-butyl-diphenyl-silanyloxy)-butan-2-ol **11** (0.254 g, 0.37 mmol) and 2 Å molecular sieves (0.5 g). This mixture was stirred gently for 20 min and then TPAP (0.007 g, 0.02 mmol, 5 mol%) was added. The reaction was monitored by tlc (1:19 v/v, ethyl acetate/petrol) and after 48 h was complete, therefore, the crude products were adsorbed directly onto silica and the product purified by column chromatography (1:19 v/v, ethyl acetate/petrol) yielding **12** as a pale green oil (0.155 g, 0.23 mmol, 62%); ν_{max} (NaCl)/cm^{-1} 3071, 2931, 1739, 1472, 1113, 707; δ_H (300 MHz, $CDCl_3$) 7.76–7.11 (25H, m, Ph*H*), 4.61 (1H, d, J_{AB}=19 Hz, Ph–CH_2–O), 4.54 (1H, d, J_{AB}=19 Hz, Ph–CH_2–O), 4.43 (1H, d, J_{AB}=12 Hz, O=C(R)–CH_2–O–Si), 4.39 (1H, d, J_{AB}=12 Hz, O=C(R)–CH_2–O–Si), 4.03 (1H, t, J_{AX}=4 Hz, J_{BX}=4 Hz, Ph–CH_2–O–C*H*(R)–CH_2–O–Si), 3.85 (1H, dd, J_{AB}=11 Hz, J_{BX}=4 Hz, Ph–CH_2–O–CH(R)–CH_2–O–Si), 3.80 (1H, dd, J_{AB}=11 Hz, J_{AX}=4 Hz, Ph–CH_2–O–CH(R)–CH_2–O–Si), 1.08 (9H, s, Si(Ph)$_2$–C(CH_3)$_3$), 1.00 (9H, s, Si(Ph)$_2$–C(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 208.0 (O=*C*), 137.7 (*C*^{ipso}), 136.1 (Ph*C*H), 136.01 (Ph*C*H), 135.98 (Ph*C*H), 133.32 (Si*C*^{ipso}), 130.26 (Ph*C*H), 130.2 (Ph*C*H), 130.2 (Ph*C*H), 128.8 (Ph*C*H), 128.1 (Ph*C*H), 128.0 (Ph*C*H), 84.1 (Ph–CH_2–O–*C*H), 72.7 (O=C(R)–*C*H_2–O–Si), 69.4 (Ph–*C*H_2–O), 64.7 (Ph–CH_2–O–CH(R)–*C*H_2–O–Si), 27.1 (Si(Ph)$_2$–C(*C*H_3)$_3$), 19.7 and 19.6 (Si(Ph)$_2$–*C*(CH_3)$_3$); *m/z* (CI) 704 $[M+NH_4]^+$, 501, 450, 433, 391; HRMS (CI) $[M+NH_4, (C_{43}H_{54}O_4NSi_2)]^+$ calculated 704.3591, found 704.3591.

3.1.10. (2*R*,5*S*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-phenyl-2,5-dihydro-furan 13, (2*R*,5*R*)-2,3-bis-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-phenyl-2,5-dihydro-furan 14–16. A mixture of TMSDM (1.3 mL, 2.6 mmol, 2.0 M in hexane) and DME (1.3 mL) were cooled to −78°C. To this mixture was added slowly, *n*-BuLi (1.04 mL, 2.6 mmol, 2.5 M in hexane), which was stirred for 20 min and then allowed to warm to rt. The reaction mixture was again cooled to −78°C and a solution of (3*R*)-(−)-3-benzyloxy-1,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-one **7** (0.548 g, 1.25 mmol) dissolved in DME (1.3 mL) was added dropwise. The reaction was allowed to warm to rt over 4 h and quenched by the addition of water (20 mL) to give a mixture which was extracted with ethyl acetate (3×30 mL). The organic extracts were combined, dried (anhydrous $MgSO_4$) and the solvent was removed under reduced pressure. The crude products were then purified by column chromatography (1:49 v/v, ethyl acetate/petrol) yielding: **13** the major *cis* diastereoisomer as a clear oil (0.273 g, 0.63 mmol, 50%); and **14** the minor *trans* diastereoisomer as a clear oil (0.078 g, 0.18 mmol, 14%).

Compound **13** $[\alpha]^{D}=-1.86$ (*c* 1.62, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2929, 2857, 1471, 1255, 1093, 838; δ_H (300 MHz, $CDCl_3$) 7.37–7.25 (5H, m, Ph*H*), 5.77 (1H, m, C*H*=C), 5.74 (1H, m, Ph–C*H*(R)–OR), 4.81 (1H, m, Ph–CH(R)–O–C*H*(R)–CH_2–OTBS), 4.43 (1H, d, *J*=15 Hz, CH=C(R)–CH_2–OTBS), 4.26 (1H, d, *J*=15 Hz, CH=C(R)–CH_2–OTBS), 3.83 (1H, dd, J_{AX}=3 Hz, J_{AB}=10 Hz, O–CH(R)–CH_2–OTBS), 3.75 (1H, dd, J_{BX}=6 Hz, J_{AB}=10 Hz, O–CH(R)–CH_2–OTBS), 0.91 (9H, s, R–O–Si(CH_3)$_2$–C(CH_3)$_3$), 0.90 (9H, s, R–O–Si(CH_3)$_2$–C(CH_3)$_3$), 0.08, 0.08, 0.06 and 0.05 (12H, 4×s, 4×R–O–Si(CH_3)$_2$–C(CH_3)$_3$); ^{1}H-NOESY (500 MHz, $CDCl_3$). Irradiation at 5.80 ppm; 7.40 ppm (nOe=2.45), 4.40 ppm (nOe=1.42); irradiation at 5.75 ppm; 7.40 ppm (nOe=5.83), 4.86 ppm (nOe=1.35); irradiation at 4.85 ppm;

5.75 ppm (nOe=1.71), 4.30 ppm (nOe=1.48), 3.85 ppm (nOe=5.77); δ_C (300 MHz, $CDCl_3$) 143.3 (*C ipso*), 142.4 (Ph–CH(OR)–CH=*C*(R)–CH_2–OTBS), 128.7 (Ph*C*H), 128.2 (Ph*C*H), 127.4 (Ph*C*H), 125.0 (Ph–CH(OR)–*C*H=C(R)–CH_2–OTBS), 87.5 (Ph–*C*H(OR)–C), 86.6 (Ph–CH(R)–O–*C*H(R)–CH_2–OTBS), 66.0 (O–CH(R)–*C*H_2–OTBS), 60.0 (CH=C(R)–*C*H_2–OTBS), 30.1 (Si$(CH_3)_2$–*C*$(CH_3)_3$), 26.3 (Si$(CH_3)_2$–C(*C*$H_3)_3$), −5.0 (Si(*C*$H_3)_2$–C$(CH_3)_3$); *m/z* (CI) 452 $[M+NH_4]^+$, 435 $[M+H]^+$, 417, 301; HRMS (CI) $[M+NH_4(C_{24}H_{46}O_3NSi_2)]^+$ calculated 452.3016, found 452.3009.

Compound **14** $[\alpha]^D$=+15.7 (*c* 0.23, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2955, 2857, 1471, 1255, 1087, 836; δ_H (250 MHz, $CDCl_3$) 7.37–7.24 (5H, m, Ph*H*), 5.78 (2H, m, C*H*=C and Ph–C*H*(R)–OR), 4.94 (1H, m, O–C*H*(R)–CH_2–OTBS), 4.41 (1H, d, *J*=15 Hz, CH=C(R)–CH_2–OTBS), 4.28 (1H, d, *J*=15 Hz, CH=C(R)–CH_2–OTBS), 3.81 (1H, dd, J_{AX}=4 Hz, J_{AB}=11 Hz, O–CH(R)–CH_2–OTBS), 3.75 (1H, dd, J_{BX}=6 Hz, J_{AB}=11 Hz, O–CH(R)–CH_2–OTBS), 0.91 (18H, s, O–Si$(CH_3)_2$–C(C$H_3)_3$), 0.08, 0.07 and 0.06 (12H, 3×s, 3×Si(C$H_3)_2$–C$(CH_3)_3$); ^{1}H-NOESY (500 MHz, $CDCl_3$). Irradiation at 5.80 ppm; 7.40 ppm (nOe=4.08); irradiation at 5.75 ppm; 7.40 ppm (nOe=5.83), 4.86 ppm (nOe=1.35); irradiation at 4.95 ppm; 7.4 ppm (nOe=1.87), 4.30 ppm (nOe=1.88), 3.85 ppm (nOe=5.87); δ_C (300 MHz, $CDCl_3$) 142.9 (*C ipso*), 142.4 (CH=*C*(R)), 128.8 (Ph*C*H), 128.1 (Ph*C*H), 127.4 (Ph*C*H), 125.0 (*C*H=C(R)), 87.9 (Ph–*C*H(OR)–CH=C), 86.7 (Ph–CH(R)–O–*C*H(R)–CH_2–OTBS), 65.6 (Ph–CH(R)–O–CH(R)–*C*H_2–OTBS), 60.0 (Ph–CH(OR)–CH=C(R)–*C*H_2–OTBS), 31.4 (Si$(CH_3)_2$–*C*$(CH_3)_3$), 26.3 (Si$(CH_3)_2$–C(*C*$H_3)_3$), −4.9 (Si(*C*$H_3)_2$–C$(CH_3)_3$); *m/z* (CI) 452 $[M+NH_4]^+$, 435 $[M+H]^+$, 417, 327, 195; HRMS (CI) [M+H $(C_{24}H_{43}O_3Si_2)]^+$ calculated 435.2751, found 435.2750.

The yield of minor *trans* product is calculated from ^{1}H NMR integrals, it being inseparable from a third product by column chromatography. The third product **15** rearranges upon leaving to the furan **16** plus benzyl alcohol (a 1:1 mixture). The presence of the benzyl alcohol was confirmed by spiking the ^{1}H NMR sample with benzyl alcohol and observing an increase in the integrals for the peaks attributed to the benzyl alcohol within the mixture.

Compound **15** δ_H (250 MHz, $CDCl_3$) 7.32–7.27 (5H, m, Ph*H*), 4.92 (1H, dd, J_{AX}=2 Hz, J_{BX}=7 Hz, Bn–O–C*H*), 4.52 (1H, d, *J*=12 Hz, Ph–CH_2–O), 4.46 (1H, d, *J*=12 Hz, Ph–CH_2–O), 4.32 (2H, s, C=C(R)–CH_2–OTBS), 4.28 (1H, dd, J_{AX}=2 Hz, J_{AB}=11 Hz, O–CH_2–CH(OBn)), 4.10 (1H, dd, J_{BX}=7 Hz, J_{AB}=11 Hz, O–CH_2–CH(OBn)), 0.93 and 0.90 (18H, 2×s, 2×Si–$(CH_3)_2$–C(C$H_3)_3$), 0.17 and 0.18 (12H, 2×s, 2×Si–(C$H_3)_2$–C$(CH_3)_3$).

Compound **16** δ_H (250 MHz, $CDCl_3$) 7.56 (1H, d, *J*=2 Hz, O–C*H*=CH), 6.44 (1H, d, *J*=2 Hz, O–CH=C*H*), 4.61 (2H, s, CH_2–OTBS), 0.91 and 0.89 (18H, 2×s, 2×Si–$(CH_3)_2$–C(C$H_3)_3$), 0.26 and 0.08 (12H, 2×s, 2×Si–(C$H_3)_2$–C$(CH_3)_3$).

3.1.11. (2*S*,3*S*)-[3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxy)-2-methoxymethoxy-propoxymethyl]-benzene 18. (2*S*,3*S*)-(+)-3-Benzyloxy-1,4-bis-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-ol **7** (0.602 g, 1.37 mmol), di-isopropylethylamine (3 mL, 2.23 g, 16 mmol) and chloromethyl methyl ether (1 mL, 1.06 g, 13 mmol) were mixed and stirred at 0°C for 1 h, then at rt for 29 h. The mixture was poured into ethyl acetate (50 mL), washed with water (3×30 mL), brine (30 mL), dried (anhydrous $MgSO_4$) and the ethyl acetate removed under reduced pressure. The crude product was purified by column chromatography (1:32 v/v, ethyl acetate/petrol) yielding **18** as a clear oil (0.573 g, 1.18 mmol, 86%); $[\alpha]^D$=+1.30 (*c* 1.02, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2929, 1471, 1255, 1101, 1036, 837; δ_H (300 MHz, $CDCl_3$) 7.37–7.25 (5H, m, Ph*H*), 4.75 (1H, d, *J*=7 Hz, CH_3–O–CH_2–O–CH), 4.71 (1H, d, *J*=11 Hz, Ph–CH_2–O), 4.68 (1H, d, *J*=7 Hz, CH_3–O–CH_2–O–CH), 4.64 (1H, d, *J*=11 Hz, Ph–CH_2–O), 3.80–3.64 (6H, m, MOMO–C*H*(R)–CH_2–OTBS and BnO–C*H*(R)–CH_2–OTBS), 3.36 (3H, s, CH_3–O–CH_2–O), 0.89 and 0.88 (18H, 2×s, 2×O–Si$(CH_3)_2$–C(C$H_3)_3$), 0.05 and 0.02 (12H, 2×s, 2×O–Si(C$H_3)_2$–C$(CH_3)_3$); δ_C (300 MHz, $CDCl_3$) 139.2 (*C ipso*), 128.6 (Ph*C*H), 128.5 (Ph*C*H), 127.9 (Ph*C*H), 97.6 (CH_3–O–*C*H_2–O), 79.3 and 78.0 (MOMO–*C*H(R)–CH_2–OTBS and BnO–*C*H(R)–CH_2–OTBS), 74.0 (Ph–*C*H_2–O), 62.7 and 62.7 (MOMO–CH(R)–*C*H_2–OTBS and BnO–CH(R)–*C*H_2–OTBS), 56.0 (*C*H_3–O–CH_2–O), 26.7 (O–Si$(CH_3)_2$–C(*C*$H_3)_3$), 18.6 (O–Si$(CH_3)_2$–*C*$(CH_3)_3$), −5.0 (O–Si$(CH_3)_2$–C(*C*$H_3)_3$); *m/z* (CI) 502 $[M+NH_4]^+$, 485 $[M+H]^+$, 453, 380, 361; HRMS (CI) $[M+NH_4(C_{25}H_{52}O_5Si_2N)]^+$ calculated 502.3384, found 502.3386.

3.1.12. (2*S*,3*S*)-1,4-Bis(*tert*-butyl-dimethyl-silanyloxy)-3-methoxymethoxy-butan-2-ol 19. (2*S*,3*S*)-[3-(*tert*-Butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxy)-2-methoxymethoxy-propoxymethyl]-benzene **18** (0.316 g, 0.65 mmol), ethanol (2 mL) and 5% palladium on carbon (0.05 g, 0.02 mmol, 3 mol%) were mixed and stirred vigorously under hydrogen (1 atm) for 3 h. After this time tlc (1:9 v/v, ethyl acetate/petrol) showed complete consumption of the starting material, so the products were filtered through celite. After removal of the solvents and toluene under reduced pressure, **19** was obtained as a colourless oil (0.239 g, 0.61 mmol, 93%); CHN requires C 54.77%, H 10.73%, found C 54.76%, H 10.69%; $[\alpha]^D$=+9.60 (*c* 1.09, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 3466, 2954, 1471, 1255, 1101, 1036; δ_H (250 MHz, $CDCl_3$) 4.78 (1H, d, *J*=7 Hz, CH_3–O–CH_2–O), 4.71 (1H, d, *J*=7 Hz, CH_3–O–CH_2–O), 3.89–3.66 (6H, m, MOMO–C*H*(R)–CH_2–OTBS and HO–C*H*(R)–CH_2–OTBS), 3.40 (3H, s, CH_3–O–CH_2–O), 2.76 (1H, d, *J*=5 Hz, *H*O), 0.90 (18H, s, O–Si$(CH_3)_2$–C(C$H_3)_3$), 0.07 (12H, s, O–Si(C$H_3)_2$–C$(CH_3)_3$); δ_C (300 MHz, $CDCl_3$) 97.4 (CH_3–O–*C*H_2–O), 77.9 (MOMO–*C*H(R)–CH_2–OTBS or HO–*C*H(R)–CH_2–OTBS), 72.3 (MOMO–*C*H(R)–CH_2–OTBS or HO–*C*H(R)–CH_2–OTBS), 64.0 and 63.8 (MOMO–CH(R)–*C*H_2–OTBS and HO–CH(R)–*C*H_2–OTBS), 56.1 (*C*H_3–O–CH_2–O), 26.2 (O–Si$(CH_3)_2$–C(*C*$H_3)_3$), 18.6 (O–Si$(CH_3)_2$–*C*$(CH_3)_3$), −5.0 and −5.1 (2×O–Si(*C*$H_3)_2$–C$(CH_3)_3$); *m/z* (CI) 412 $[M+NH_4]^+$, 395 $[M+H]^+$, 380, 363, 132.

3.1.13. (3*S*)-1,4-Bis(*tert*-butyl-dimethyl-silanyloxy)-3-methoxymethoxy-butan-2-one 17. NMO (2 g,

14.81 mmol) was dissolved in DCM (100 mL). This was dried (anhydrous $MgSO_4$) and then filtered. Of this solution a portion (14 mL) was taken and to it added (2*S*,3*S*)-1,4-bis(*tert*-butyl-dimethyl-silanyloxy)-3-methoxymethoxy-butan-2-ol **19** (0.221 g, 0.561 mmol) and 2 Å molecular sieves (0.5 g). This mixture was stirred gently for 20 min and then TPAP (0.020 g, 0.06 mmol, 11 mol%) was added. The reaction was monitored by tlc (1:19 v/v, ethyl acetate/petrol) and after 2 h was complete. The mixture was diluted with DCM (50 mL), filtered, washed with sodium sulphite solution (20 mL), brine (20 mL), dried (anhydrous $MgSO_4$), filtered again and the solvent removed under reduced pressure. The crude product was purified by column chromatography (1:9 v/v, ethyl acetate/petrol) yielding **17** as an colourless oil (0.179 g, 0.457 mmol, 81%); CHN requires C 55.06%, H 10.27%, found C 55.18%, H 10.38%; $[\alpha]^D=-0.51$ (*c* 1.24, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2953, 1738, 1472, 1255, 1123, 1036; δ_H (250 MHz, $CDCl_3$) 4.74 (1H, d, *J*=7 Hz, CH_3-O-CH_2-O), 4.65 (1H, d, *J*=7 Hz, CH_3-O-CH_2-O), 4.56 (1H, d, *J*=19 Hz, $C(=O)-CH_2-$OTBS), 4.45 (1H, d, *J*=19 Hz, $C(=O)-CH_2-$OTBS), 4.27 (1H, t, *J*=4 Hz, MOMO$-CH(R)-CH_2-$OTBS), 3.89 (2H, d, *J*=4 Hz, MOMO$-CH(R)-CH_2-$OTBS), 3.37 (3H, s, CH_3-O-CH_2-O), 0.92 and 0.87 (18H, 2×s, $2\times O-Si(CH_3)_2-C(CH_3)_3$), 0.09 and 0.08 (6H, 2×s, $2\times O-Si(CH_3)_2-C(CH_3)_3$), 0.05 and 0.04 (6H, 2×s, $2\times O-Si(CH_3)_2-C(CH_3)_3$); δ_C (300 MHz, CDCl3) 208.3 ($C(=O)$), 96.8 (CH_3-O-CH_2-O), 81.5 (MOMO$-CH(R)-CH_2-$OTBS), 69.2 ($R-C(=O)-CH_2-$OTBS), 64.2 (MOMO$-CH(R)-CH_2-$OTBS), 56.3 (CH_3-O-CH_2-O), 26.2 ($O-Si(CH_3)_2-C(CH_3)_3$), 18.8 ($O-Si(CH_3)_2-C(CH_3)_3$), −5.0 ($O-Si(CH_3)_2-C(CH_3)_3$); *m*/*z* (CI) 410 $[M+NH_4]^+$, 395, 280, 220, 148; HRMS (CI) $[M+NH_4\ (C_{18}H_{44}O_5Si_2N)]^+$ calculated 410.2758, found 410.2762.

3.1.14. (1*R*,5*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silanyloxy-methyl)-5-methoxy-2,5-dihydro-furan 20 and 5-(*tert*-butyl-dimethyl-silanyl)-4-(*tert*-butyl-dimethyl-silanyl-oxy-methyl)-3-methoxymethoxy-2,3-dihydro-furan 21. A mixture of TMSDM (0.4 mL, 0.08 mmol, 2.0 M in hexane) and DME (0.4 mL) were cooled to −78°C. To this was added slowly, *n*-BuLi (0.32 mL, 0.8 mmol, 2.5 M in hexane), which was stirred for 20 min and then allowed to warm to rt. The reaction mixture was again cooled to −78°C and (3*S*)-1,4-bis(*tert*-butyl-dimethyl-silanyloxy)-3-methoxy-methoxy-butan-2-one **17** (0.157 g, 0.40 mmol) dissolved in DME (0.4 mL) was added dropwise. The reaction was allowed to warm to rt over 4 h and quenched by the addition of water (5 mL), to give a mixture which was extracted into ethyl acetate (5×5 mL). The organic extracts were combined, dried (anhydrous $MgSO_4$) and the solvent was removed under reduced pressure. The crude products were then purified by column chromatography (3:97 v/v, ethyl acetate/petrol) yielding: **20** as a pale yellow oil (0.046 g, 0.12 mmol, 30%); and **21** as a pale yellow oil (0.038 g, 0.10 mmol, 25%).

Compound **21** $[\alpha]^D=-17.43$ (*c* 1.635, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2953, 1625, 1472, 1362, 1253, 1032, 837; δ_H (250 MHz, $CDCl_3$) 4.92 (1H, dd, J_{AX}=3 Hz, J_{BX}=7 Hz, $O-CH_2-CH$(OMOM)), 4.71 (1H, d, *J*=7 Hz, CH_3-O-CH_2-O), 4.66 (1H, d, *J*=7 Hz, CH_3-O-CH_2-O), 4.33 (1H, d, *J*=12 Hz, CH_2-OTBS), 4.27 (1H, d, *J*=12 Hz, CH_2-OTBS), 4.24 (1H, dd, J_{AX}=3 Hz, J_{AB}=11 Hz, $O-CH_2-CH$(MOMO)), 4.16 (1H, dd, J_{BX}=7 Hz, J_{AB}=11 Hz, $O-CH_2-CH$(MOMO)), 3.38 (3H, s, CH_3-O-CH_2-O), 0.91 and 0.89 (18H, 2×s, $2\times O-Si(CH_3)_2-C(CH_3)_3$), 0.18 and 0.17 (6H, 2×s, $2\times Si(CH_3)_2-C(CH_3)_3$), 0.07 and 0.05 (6H, 2×s, $2\times Si(CH_3)_2-C(CH_3)_3$); δ_C (300 MHz, $CDCl_3$) 154.0 (TBS−*C*), 96.7 (CH_3-O-CH_2-O), 81.6 (*C*H(MOMO)), 76.0 ($O-CH_2-CH$(MOMO)), 56.7 (CH_2-OTBS), 56.1 (CH_3-O-CH_2-O), 27.0 and 26.6 ($2\times O-Si(CH_3)_2-C(CH_3)_3$), 18.7 and 17.5 ($2\times O-Si(CH_3)_2-C(CH_3)_3$), −4.6 ($Si(CH_3)_2-C(CH_3)_3$); *m*/*z* (EI) 387, 322, 280, 147, 73; HRMS (EI) $[M\ (C_{19}H_{40}O_4Si_2)]^+$ calculated 388.2465, found 388.2446.

Compound **20** $[\alpha]^D=+14.95$ (*c* 1.03, Abs. EtOH); ν_{max} (NaCl)/cm^{-1} 2995, 2858, 1472, 1102, 963; δ_H (250 MHz, $CDCl_3$) 5.73 (1H, m, $CH(O-CH_3)$), 5.68 (1H, m, $C=CH$), 4.80 (1H, m, $O-C(R)H-CH_2-$OTBS), 4.39 (1H, d, J_{AB}=16 Hz, TBSO$-CH_2-C(R)=CH$), 4.23 (1H, d, J_{AB}=16 Hz, TBSO$-CH_2-C(R)=CH$), 3.76 (1H, dd, J_{AB}=11 Hz, J_{AX}=4 Hz, $O-CH(R)-CH_2-$OTBS), 3.61 (1H, dd, J_{AB}=11 Hz, J_{BX}=6 Hz, $O-CH(R)-CH_2-$OTBS), 3.37 (3H, s, $O-CH_3$), 0.90 and 0.87 (18H, 2×s, $2\times Si(CH_3)_2-C(CH_3)_3$), 0.06 and 0.05 (12H, 2×s, $2\times Si(CH_3)_2-C(CH_3)_3$); ^{1}H-NOESY (500 MHz, $CDCl_3$). Irradiation at 5.76 ppm; 3.40 ppm (nOe=4.87); irradiation at 5.71 ppm; 4.33 ppm (nOe=1.07), 3.40 ppm (nOe=1.42); irradiation at 4.83 ppm; 4.27 ppm (nOe=1.55), 3.78 ppm (nOe=3.41), 3.64 ppm (nOe=2.04), 3.40 ppm (nOe=2.31); irradiation at 4.33 ppm; 5.71 ppm (nOe=1.31), 4.83 ppm (nOe=1.49); irradiation at 3.72 ppm; 4.83 ppm (nOe=5.18), 3.40 ppm (nOe=1.30); irradiation at 3.40 ppm; 5.76 ppm (nOe=2.55), 4.83 ppm (nOe=0.80); δ_C (300 MHz, CDCl3) 149.3 (TBSO$-CH_2-C(R)=CH$), 120.7 (TBSO$-CH_2-C(R)=CH-CH(O-CH_3)$), 109.2 ($C=CH-CH(O-CH_3)$), 85.4 (TBSO$-CH_2-CH(R)-O$), 65.3 ($O-CH(R)-CH_2-$OTBS), 59.7 (TBSO$-CH_2-C(R)=CH$), 54.2 ($O-CH_3$), 26.2 ($Si(CH_3)_2-C(CH_3)_3$), 18.8 ($Si(CH_3)_2-C(CH_3)_3$), −5.0 ($Si(CH_3)_2-C(CH_3)_3$); *m*/*z* (EI) 387, 357, 299, 225, 82; HRMS (EI) $[M\ (C_{19}H_{40}O_4Si_2)]^+$ calculated 388.2465, found 388.2448.

3.1.15. 4-(*tert*-Butyl-dimethyl-silanyloxy)-butan-2-ol 24. 1,3-Butanediol **23** (1 mL, 1.01 g, 11.2 mmol) was dissolved in DMF (20 mL) and cooled to −20°C. To this was added *tert*-butyl-dimethylchlorosilane (2.00 g, 13.4 mmol), imidazole (1.76 g, 26.0 mmol) and the resulting mixture was stirred at −20°C for 20 min, then at rt for 12 h. The mixture was then poured into water (100 mL) and the organic components extracted into diethyl ether (5×50 mL). The combined organic extracts were dried (anhydrous $MgSO_4$) and the solvent removed under reduced pressure. The crude product was then purified by column chromatography (1:9 v/v, ethyl acetate/petrol) yielding **24** as a pale yellow oil (1.82 g, 8.9 mmol, 79%); ν_{max} (NaCl)/cm^{-1} 3383, 2929, 1466, 1257, 1097, 834; δ_H (300 MHz, $CDCl_3$) 4.05–3.99 (1H, m, TBSO$-CH_2-CH_2-CH(OH)-CH_3$), 3.93–3.77 (2H, m, TBSO$-CH_2-CH_2-CH(OH)-CH_3$), 3.45 (1H, br s, TBSO$-CH_2-CH_2-CH(OH)-CH_3$), 1.72–1.60 (2H, m, TBSO$-CH_2-CH_2-CH(OH)-CH_3$), 1.19 (3H, d, *J*=6 Hz, TBSO$-CH_2-CH_2-CH(OH)-CH_3$), 0.91 (9H, s, $Si(CH_3)_2-C(CH_3)_3$), 0.08 (6H, s, $Si(CH_3)_2-C(CH_3)_3$); δ_C (300 MHz,

$CDCl_3$) 68.8 (TBSO–CH_2–CH_2–*C*H(OH)–CH_3), 63.2 (TBSO–*C*H_2–CH_2–CH(OH)–CH_3), 40.3 (TBSO–CH_2–*C*H_2–CH(OH)–CH_3), 26.2 (Si(CH_3)$_2$–C(*C*H_3)$_3$), 23.7 (TBSO–CH_2–CH_2–CH(OH)–*C*H_3), 18.5 (Si(CH_3)$_2$–*C*(CH_3)$_3$), −5.2 and −5.2 (Si(*C*H_3)$_2$–C(CH_3)$_3$); *m/z* (CI) 222 $[M+NH_4]^+$, 205 $[M+H]^+$; HRMS (CI) [M+H ($C_{10}H_{25}O_2Si$)]$^+$ calculated 205.1624, found 205.1625.

3.1.16. 4-(*tert*-Butyl-dimethyl-silanyloxy)-butan-2-one 22. NMO (2 g, 14.81 mmol) was dissolved in DCM (100 mL). This was dried over anhydrous $MgSO_4$ and then filtered. To this solution was added 4-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-ol **24** (1.12 g, 5.49 mmol) and some 2 Å molecular sieves (2.0 g). This mixture was stirred gently for 20 min and then TPAP (0.050 g, 0.15 mmol, 3 mol%) was added. The reaction was monitored by tlc (1:9 v/v, ethyl acetate/petrol) and after 14 h was complete. The mixture was diluted with DCM (50 mL), filtered, washed with sodium sulphite solution (100 mL), brine (100 mL), saturated copper sulphate solution (100 mL), dried (anhydrous $MgSO_4$), filtered again and the solvent removed under reduced pressure. The crude product was purified by column chromatography (1:9 v/v, ethyl acetate/petrol) yielding **22** as a clear oil (0.807 g, 3.96 mmol, 72%); CHN requires C 59.35%, H 10.96%, found C 59.15%, H 10.96%; ν_{max} (NaCl)/cm^{-1} 2955, 2857, 1716, 1472, 1255, 1103; δ_H (250 MHz, $CDCl_3$) 3.88 (2H, t, *J*=6 Hz, TBSO–C*H*$_2$–CH_2–C(=O)–CH_3), 2.62 (2H, t, *J*=6 Hz, TBSO–CH_2–C*H*$_2$–C(=O)–CH_3), 2.19 (3H, s, TBSO–CH_2–CH_2–C(=O)–C*H*$_3$), 0.88 (9H, s, Si(CH_3)$_2$–C(C*H*$_3$)$_3$), 0.05 (6H, s, Si(C*H*$_3$)$_2$–C(CH_3)$_3$); δ_C (300 MHz, $CDCl_3$) 208.6 (TBSO–CH_2–CH_2–*C*(=O)–CH_3), 59.2 (TBSO–*C*H_2–CH_2–C(=O)–CH_3), 46.9 (TBSO–CH_2–*C*H_2–C(=O)–CH_3), 31.3 (TBSO–CH_2–CH_2–C(=O)–*C*H_3), 26.2 (Si(CH_3)$_2$–C(*C*H_3)$_3$), 18.6 (Si(CH_3)$_2$–*C*(CH_3)$_3$), −5.1 (Si(*C*H_3)$_2$–C(CH_3)$_3$); *m/z* (CI) 220 $[M+NH_4]^+$, 203 $[M+H]^+$, 182, 145.

3.1.17. *tert*-Butyl-dimethyl-(3-methyl-4,5-dihydro-furan-2-yl)-silane 25. TMSDM (3.5 mL, 7.0 mmol, 2.0 M in hexane) and DME (3.5 mL) were cooled to −78°C. To this was added slowly, *n*-BuLi (2.8 mL, 7.0 mmol, 2.5 M in hexane), which was stirred for 20 min and then allowed to warm to rt. The reaction mixture was again cooled to −78°C and a solution of 4-(*tert*-butyl-dimethyl-silanyloxy)-butan-2-one **22** (0.705 g, 3.49 mmol) dissolved in DME (3.5 mL) was added dropwise. The reaction was allowed to warm to rt over 4 h and quenched by the addition of water (20 mL), to give a solution which was extracted into ethyl acetate (4×20 mL). The organic extracts were combined, dried (anhydrous $MgSO_4$) and the solvent removed under reduced pressure. The crude products were then purified by column chromatography (100% petrol) yielding **25** as a colourless oil (0.348 g, 1.76 mmol, 50%); ν_{max} (NaCl)/cm^{-1} 2952, 2855, 1470, 1249, 1085, 773; δ_H (250 MHz, $CDCl_3$) 4.17 (2H, t, *J*=9 Hz, O–C*H*$_2$–CH_2–C(CH_3)), 2.54 (2H, t q, *J*=9, 1 Hz, O–CH_2–C*H*$_2$–C(CH_3)), 1.74 (3H, t, *J*=1 Hz, C–C*H*$_3$), 0.91 (9H, s, (C*H*$_3$)$_3$C–Si), 0.15 (6H, s, (C*H*$_3$)$_2$Si); δ_C (300 MHz, $CDCl_3$) 151.9 ((CH$_3$)$_3$C–Si(CH_3)$_2$–*C*=), 123.0 (O–CH_2–CH_2–*C*(=)(CH_3)), 69.4 (O–*C*H_2–CH_2–C), 37.8 (O–CH_2–*C*H_2–C), 26.8 ((*C*H$_3$)$_3$C–Si(CH_3)$_2$), 17.7 ((CH$_3$)$_3$*C*–Si(CH_3)$_2$), 13.1 (C(=)–O–CH_2–CH_2–C(=)–*C*H_3), −5.3 ((CH$_3$)$_3$C–Si(*C*H$_3$)$_2$–C); *m/z* (EI) 215 $[M-H+NH_4]^+$, 197 $[M-H]^+$; HRMS (EI) [M ($C_{11}H_{22}OSi$)]$^+$ calculated 198.1440, found 198.1429.

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