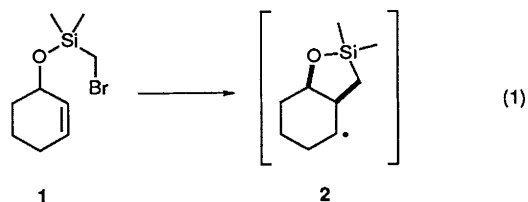# Stereoselective Reductive Hydroxymethylation of an Annulated Sugar Derivative *via* Radical Cyclisation

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Addition of a silylmethylene and hydride radical to the carbon–carbon double of two allylic silyl ethers derived from annulated carbohydrates has been shown to occur in an *anti* fashion.

The study and application of radical cyclisations in synthesis is currently a field of organic chemistry that is receiving substantial attention.[1] A very attractive protocol involves the intramolecular reaction of an alkene with a radical species. Such an approach has been elegantly pioneered independently by Stork[2] and Nishiyama,[3] and used by others,[4] by cyclisation of an allylic (bromomethyl)silyl ether in a 5-*exo* sense to form a five-membered siloxane, as in the reaction 1 ⟶ 2 [eqn. (1)]. Consequent oxidation, by a silyl Bayer–Villiger reaction, to



(1)

**1**        **2**

a diol formally constitutes a reductive hydroxymethylation as the overall transformation, a procedure that is sometimes difficult to achieve by more established strategies—*e.g.*, aldol reaction with formaldehyde followed by reduction.

We needed to carry out such a transformation on an annulated carbohydrate derivative where it was very important to us that the process be highly stereoselective, to be of use in a synthetic programme underway in our laboratory. We recently detailed our results in a preliminary communication,[5] and now report our findings in full.

## Results and Discussion

Silylation of the alcohol **3**[6] with (bromomethyl)chloro-dimethylsilane gave the silyl ether **4**, which upon treatment with tributylstannane and catalytic azoisobutyronitrile (AIBN) in refluxing benzene furnished the tetracyclic siloxane **5** in 82% yield. The same cyclisation can also be achieved (in 60% yield) by treatment of the silyl ether **4** (0.05 mol dm$^{-3}$ in *t*-butyl alcohol) with tributylchlorostannane (cat),[7] sodium cyanoboro-hydride (2 mol equiv.), and AIBN (cat) (reflux, 6 h): a protocol that avoids the use of syringe pumps and the tedious removal of tin residues. The nuclear Overhauser effects (NOE) observed in the $^1$H NMR spectrum were consistent with our structural assignment of compound **5**. The most important interaction is between 10-H and 11-H, indicating the silylmethylene and hydride radicals have been added in a *trans* fashion to the alkene group. That the 5-membered-ring siloxane is *cis*-fused—there being an NOE of 3.6% between 10-H and 15-H—is not surprising and in agreement with previous examples of such cyclisations.[2–4] Treatment of compound **5** with potassium fluoride and hydrogen peroxide gave the diol **6** (82%), a useful intermediate in our taxane synthesis, to affect the overall process of hydroxymethylation (Scheme 1).
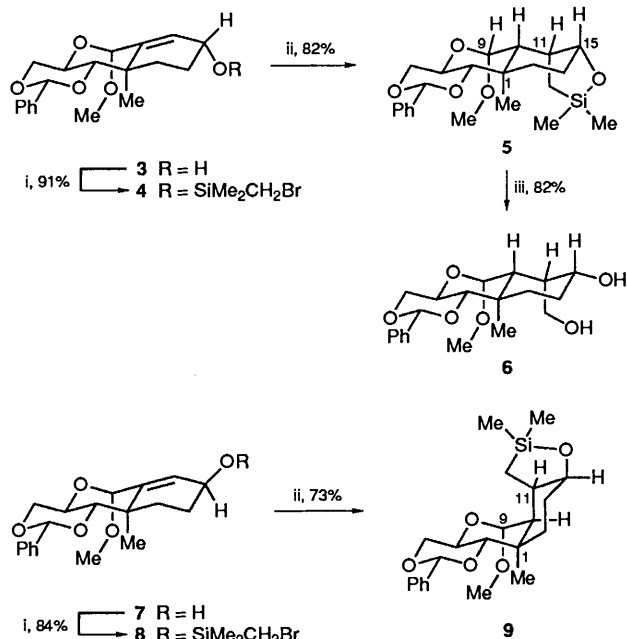


**Scheme 1** *Reagents:* i, ClSiMe$_2$CH$_2$Br, Et$_3$N; ii, azoisobutyronitrile (AIBN); iii, H$_2$O$_2$, KF

The isomer of opposite stereochemical configuration at C-11 would be of even greater benefit to our synthesis. To this end the silyl ether **8** was made in the same way from the allyl alcohol **7**. Radical cyclisation occurred upon treatment with tributyl-stannane to produce the tetracyclic siloxane **9**, where the silylmethylene radical and hydrogen species have again added *trans*, despite the fact that this results in the formation of two *cis*-fused ring junctions. In this case the structure of compound **9** was confirmed unambiguously by X-ray crystal-structure determination.

The *trans* stereochemistry of compound **5** would be expected from steric arguments, since approach of a hydrogen species, probably a bulky tributylstannane molecule, to the species **2** derived from siloxane **4** will be blocked by the C-9 methoxy, C-1 methyl, and C-11 silylmethyl groups. On the other hand the approach of a hydrogen species to the radical species **2** derived from siloxane **8** will involve, in part, a play-off between the steric effects of the methoxy and methyl group against the silylmethyl group. Unfortunately, whatever the reason for this stereocontrol, the *cis* relationship between the C-1 methyl group and the C-10 hydrogen is of little use in our taxane synthesis. It is, however, very interesting to note that there is only one reported example[2c] of a *cis* addition to a radical of type **2**, *i.e.* the cyclisation of siloxane **10** to the *cis*-hydrindane **11** [equation (2)]. The factors controlling this stereochemistry obviously require further study.

(2)
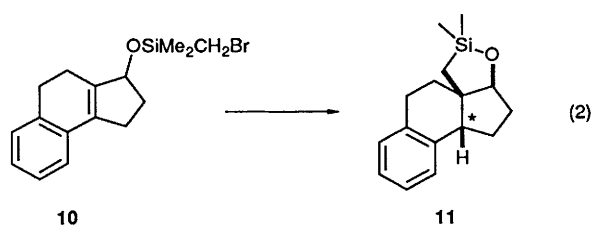
3:7 mix of diastereoisomers at C* with *cis*-isomer as the major product.

## Experimental

90 MHz $^1$H NMR spectra were recorded on a Varian EM-390 spectrometer. Highfield $^1$H NMR (400 7Hz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Brucker AM-400 spectrometer in the highfield NMR service at the University of Warwick. J Values are given in Hz. Mass spectra were recorded on a V.G. micromass 16B spectrometer and accurate mass determination was carried out by the SERC mass spectrometry service at the University College of Swansea. Elemental analysis was carried out by CHN Analysis, Wigston, Leicester. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. M.p.s were determined on a Kofler hot-stage and are uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*,[8] using silica gel manufactured by Merck and Co., Kiesel 60, 230–400 mesh (ASTM). TLC was conducted on precoated aluminium sheets (60–254) with 0.2 mm layer thickness, manufactured by Merck and Co.

Light petroleum refers to the 40–60 °C fraction; both light petroleum and ethyl acetate were distilled prior to use. Tetrahydrofuran (THF) and toluene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether which was distilled from LiAlH$_4$.

Unless specified as otherwise, standard aqueous work-up involved addition of buffered aq. ammonium chloride (pH 8), and extraction with ether ( × 3). The extracts were dried (Na$_2$SO$_4$), and evaporated under reduced pressure.

(1R,2S,4R,7R,9S,12R)-12-[(*Bromomethyl*)*dimethylsiloxy*]-9-*methoxy-1-methyl-4-phenyl*-3,5,8-*trioxatricyclo*[8.4.0.0$^{2,7}$]-*tetradec*-10-*ene* 4.—To a solution of the allylic alcohol 3[6] (1.87 g, 5.62 mmol), 4-(dimethylamino)pyridine (DMAP) (0.095 g, 0.78 mmol), and triethylamine (8 cm$^3$) in dry dichloromethane (15 cm$^3$) was added (bromomethyl)chlorodimethylsilane (1.06 g, 5.63 mmol) dropwise during 5 min and the mixture was then stirred for 1.5 h. Standard aqueous work-up and chromatography (SiO$_2$; ether) gave the siloxane 4 (2.48 g, 91%) as an oil; $R_f$ 0.75 (ether); $[\alpha]_D^{20}$ +4.5° (c 10.0, MeOH); $\nu_{max}$(film)/cm$^{-1}$ 2900s, 1450m, 1375m, 1250m, 1100s, 850s and 700m; $\delta_H$(300 MHz; CDCl$_3$) 0.35 (6 H, SiMe$_2$), 1.46 (3 H, s, Me) overlapping with 1.48 (1 H, br m, CH$_a$H$_b$CHOSi), 1.74 (1 H, br m, CH$_a$H$_b$CHOSi), 1.97 (2 H, br m, CH$_2$CMe), 2.47 (2 H, s, CH$_2$Br), 3.30 (1 H, d, J 10.0, PhCHOCH), 3.45 (3 H, s, OMe), 3.72 (1 H, t, J 10.1, PhCHOCH$_{ax}$H$_{eq}$), 4.15 (1 H, dt, J 10.1 and 5.1, PhCHOCH$_2$CH), 4.35 (1 H, dd, J 10.1 and 5.1, PhCHOCH$_{ax}$H$_{eq}$) overlapping with 4.45 (1 H, ddd, J 9.3, 8.1 and 3.5, CHOSi), 4.80 (1 H, s, OCHOMe), 5.57 (1 H, s, CHPh), 5.69 (1 H, br s, C=CH) and 7.40–7.60 (5 H, m, Ph); $\delta_C$(75 MHz; CDCl$_3$) −2.42 (q), 16.21 (t), 18.87 (q), 28.13 (t), 34.38 (q), 37.18 (s), 54.86 (q), 60.33 (d), 68.56 (d), 69.59 (t), 86.83 (d), 101.48 (d), 103.28 (d), 126.10 (d), 128.11 (d), 128.83 (d), 131.86 (d), 137.77 (s) and 138.75 (s) [Found: (M$^+$ − H), 481.1088. C$_{22}$H$_{30}$($^{79}$Br)O$_5$Si requires (M$^+$ − H), 481.1073]; m/z 481, 482 (M$^+$, 20%), 430 (50), 380 (75), 330 (95), 318 (65), 280 (100), 157 (75) and 92 (70).

(1R,2S,4R,7R,9S,10R,11S,15R)-9-*Methoxy*-1,13,13-*trimethyl*-4-*phenyl*-3,5,8,14-*tetraoxa*-13-*silatetracyclo*[8.7.0.0$^{2,7}$0$^{11,15}$]-*heptadecane* 5.—To a solution of the siloxane 4 (1.49 g, 3.07 mmol) and AIBN (0.025 g, 0.075 mmol) in dry benzene (20 cm$^3$) heated under reflux was added dropwise, during 30 min, a solution of tributylstannane (1.34 g, 4.61 mmol) in benzene (10 cm$^3$). After 2 h the benzene was removed under reduced pressure. Light petroleum was added and the solution was left at 4 °C for 24 h. The crystals were filtered off to give the *cyclic siloxane* 5 (1.01 g, 82%), m.p. 155–157 °C; $[\alpha]_D^{20}$ +15.2° (c 6.3, MeOH) (Found: C, 65.2; H, 8.0; N, 0.0. C$_{22}$H$_{32}$O$_5$Si requires C, 65.31; H, 7.97; N, 0.0%); $\nu_{max}$(CH$_2$Cl$_2$)/cm$^{-1}$ 2950s, 1450w, 1375m, 1200w, 1130m, 1050s and 850s; $\delta_H$(300 MHz; CDCl$_3$), 0.21 (3 H, s, SiMe$_a$Me$_b$), 0.33 (3 H, s, SiMe$_a$Me$_b$), 0.96 (1 H, dd, J 15.2 and 7.8, SiCH$_a$H$_b$), 1.14 (1 H, t, J 15.2, SiCH$_a$H$_b$), 1.16 (1 H, br dm, SiOCHCH$_2$CH$_a$H), 1.45 (3 H, s, Me), 1.47 (1 H, m, SiOCHCH$_a$H$_b$), 1.86 (3 H, m, OCHOMeCH, SiOCHCH$_a$H$_b$ and SiOCH$_2$CH$_a$H$_b$), 2.39 (1 H, m, SiCH$_2$CH), 3.21 (1 H, d, J 9.4, PhCHOCH), 3.44 (3 H, s, OMe), 3.72 (1 H, t, J 10.2, PhCHOCH$_{ax}$H$_{eq}$), 4.05 (1 H, m, SiOCH) overlapping with 4.07 (1 H, dt, J 9.6 and 5.0, PhCHOCH$_2$CH), 4.29 (1 H, dd, J 10.2 and 5.0, PhCHOCH$_{ax}$H$_{eq}$), 4.51 (1 H, d, J 3.0, OCHOMe), 5.56 (1 H, s, CHPh) and 7.35–7.53 (5 H, m, Ph); signal at $\delta$ 1.80 (10-H) shows an NOE to those at $\delta$ 4.50 (9-H, 5.2%), 4.00 (15-H, 3.6%); signal at $\delta$ 2.35 (11-H) shows an NOE to those at $\delta$ 4.00 (15-H, 3.1%), 4.5 (9-H, 5.2%); signal at $\delta$ 4.00 (15-H) shows an NOE to those at $\delta$ 2.35 (11-H, 3.1%), 1.8 (10-H, 3.6%); signal at $\delta$ 4.50 (9-H) shows an NOE to those at $\delta$ 1.8 (10-H, 5.2%) and 2.35 (11-H, 5.2%); $\delta_C$(75 MHz; CDCl$_3$) 0.22 (q), 1.51 (q), 13.47 (t), 15.83 (q), 27.41 (t), 35.84 (t), 36.12 (s), 39.90 (d), 47.18 (d), 55.15 (q), 60.73 (d), 69.77 (t), 79.29 (d), 87.93 (d), 101.28 (d), 103.08 (d), 126.11 (d), 128.11 (d), 128.77 (s) and 137.97 (s); m/z 404 (M$^+$, 13%), 256 (84), 224 (56), 195 (34), 149 (72), 121 (85) and 105 (100).

(1R,2S,4R,7R,9S,10R,11R,12R)-11-*Hydroxymethyl-9-methoxy-1-methyl-4-phenyl*-3,5,8-*trioxatricyclo*[8.4.0.0$^{2,7}$]-*tetradecan*-12-*ol* 6.—To a mixture of the siloxane 5 (1.03 g, 2.54 mmol) and potassium fluoride (0.44 g, 7.62 mmol) in dimethylformamide (30 cm$^3$) was added dropwise hydrogen peroxide (2.5 cm$^3$ of a 30% aq. solution). The mixture was stirred for room temp. for 24 h, after which standard, aq. work-up and chromatography (SiO$_2$; ethyl acetate) and recrystallisation (light petroleum–ethyl acetate) gave the *diol* 6 (0.64 g, 69%) as a solid; m.p. 146–148 °C; $R_f$ 0.34 (ethyl acetate); $[\alpha]_D^{20}$ +26° (c 0.8, MeOH) (Found: C, 65.6; H, 7.75; N, 0.0. C$_{20}$H$_{28}$O$_6$ requires C, 65.91; H, 7.74; N, 0.00%); $\nu_{max}$(CH$_2$Cl$_2$) 3450s (OH), 2900s, 1450m, 1350s, 1125m, 1100s and 1025s; $\delta_H$(300 MHz; CDCl$_3$) 1.50 (1 H, br t, J 10.1 and 5.1, MeCCH$_a$H$_b$) overlapping with 1.20 (3 H, s, Me), 1.69 (3 H, br m, CH$_2$CHOH, and CHCHOMe), 1.87 (1 H, dt, J 13.3 and 6.7, MeCCH$_a$H$_b$), 2.31 (1 H, br m, CHCH$_2$OH), 3.15 (1 H, d, J 9.5, PhCHOCH), 3.35 (3 H, s, OMe), 3.49 (2 H, br s, OH), 3.65 (1 H, t, J 10, PhCHOCH$_{ax}$H$_{eq}$), 3.85 (1 H, br m, CHOH), 3.95 (1 H, dt, J 10.0 and 5.2, CHOCHOMe), 4.02 (1 H, br t, J 9.8, CH$_a$H$_b$OH), 4.20 (1 H, dd, J 10.0 and 5.2, PhCHOCH$_{ax}$H$_{eq}$) overlapping with 4.19 (1 H, br m, CH$_a$H$_b$OH), 4.6 (1 H, d, J 4.5, CHOMe), 5.50 (1 H, s, CHPh) and 7.30–7.50 (5 H, m, Ph); $\delta_C$(75 MHz; CDCl$_3$) 15.64 (q), 26.65 (t), 35.71 (s), 36.76 (t), 44.90 (d), 47.75 (d), 55.06 (q), 60.19 (t), 60.28 (d), 69.53 (t), 74.57 (d), 87.69 (d), 101.31 (d), 102.57 (d), 126.07 (d), 128.10 (d), 128.82 (d) and 137.76 (s); m/z 364 (M$^+$, 5%), 185 (18), 165 (64), 159 (48), 119 (36) and 105 (100).

(1R,2S,4R,7R,9S,12S)-12-[(*Bromomethyl*)*dimethylsiloxy*]-9-*methoxy-1-methyl-4-phenyl*-3,5,8-*trioxatricyclo*[8.4.0.0$^{2,7}$]-*tetradec*-10-*ene* 8.—In a manner similar to the synthesis of the siloxane 4, the allylic alcohol 7[6] (0.58 g, 1.75 mmol), (bromomethyl)chlorodimethylsilane (0.36 g, 1.75 mmol), and

DMAP (0.04 g, 0.36 mmol) gave the *siloxane* **8** (0.71 g, 84%) as an oil; $R_f$ 0.75 (ether); $[\alpha]_D^{20}$ +6° (*c* 6.0, $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2900s, 1450m, 1380m, 1100s and 850s; $\delta_H$(300 MHz; $CDCl_3$) 0.32 (6 H, $SiMe_2$), 1.34 (3 H, s, Me), 1.70–1.90 (4 H, br m, $CH_2CH_2$CHOSi), 2.52 (2 H, s, $CH_2$Br), 3.41 (3 H, s, OMe), overlapping with 3.41 (1 H, d, *J* 9.5, PhCOCH*H*), 3.72 (1 H, t, *J* 10.1, PhCHOCH$_{ax}$H$_{eq}$), 4.12 (1 H, dt, *J* 10.1 and 5.0, Ph-CHOCH$_2$C*H*), 4.27 (1 H, br m, CHOSi) overlapping with 4.32 (1 H, dd, *J* 10.1 and 5.0, PhCHOCH$_{ax}$*H*$_{eq}$), 4.83 (1 H, s, OC*H*OMe), 5.56 (1 H, s, C*H*Ph), 5.77 (1 H, d, *J* 4.6, CH=C) and 7.30–7.55 (5 H, m, Ph); $\delta_C$(75 MHz; $CDCl_3$) − 2.38 (q), 16.31 (t), 18.00 (q), 27.92 (t), 30.08 (t), 37.20 (s), 54.89 (q), 60.30 (d), 64.58 (d), 69.58 (t), 85.94 (d), 101.50 (d), 103.36 (d), 126.13 (d), 128.14 (d), 128.84 (d), 129.35 (d), 137.85 (s) and 140.30 (s) [Found: ($M^+$ − H), 483.0928. $C_{22}H_{30}(^{81}Br)O_5Si$ requires ($M^+$ − H), 483.0926]; *m/z* 484 ($M^+$, 5%), 453 (27), 452 (37), 149 (30), 115 (21), 107 (20) and 105 (61).

(1R,2S,4R,7R,9S,10S,11R,15S)-9-*Methoxy*-1,13,13-*trimethyl*-4-*phenyl*-3,5,8,14-*tetraoxa*-13-*silatetracyclo*[8.7.0.0$^{2,7}$0$^{11,15}$]-*heptadecane* **9**.—In a manner similar to the synthesis of the siloxane **5**, the siloxane **8** (0.25 g, 0.51 mmol), AIBN (0.01 g, 0.061 mmol), and tributylstanne (0.17 cm$^3$, 0.64 mmol) gave the siloxane **9** (0.15 g, 73%) as a crystalline solid; m.p. 142–145 °C; $R_f$ 0.32 [ether–light petroleum (1:1 v/v)]; $[\alpha]_D^{20}$ +7.6° (*c* 5.0, MeOH) (Found: C, 65.3; H, 8.0; N, 0.0. $C_{22}H_{32}O_5Si$ requires C, 65.31; H, 7.97; N, 0.00%); $\nu_{max}$($CH_2Cl_2$)/$cm^{-1}$ 3080s, 2950s, 1440s, 1255s, 1075m, 1025m, and 900m; $\delta_H$(300 MHz; $CDCl_3$) 0.02 (3 H, s, Si*Me*$_a$Me$_b$), 0.06 (3 H, s, SiMe$_a$*Me*$_b$), 0.90 (2 H, br m, SiCH$_2$), 1.10 (1 H, br dt, *J* 10.1 and 5.0, SiOCHCH$_2$C*H*$_a$H$_b$), 1.37 (1 H, br m, SiOCHCH$_2$CH$_a$*H*$_b$) overlapping with 1.32 (3 H, s, Me), 1.65 (1 H, br m, SiOCHC*H*$_a$H$_b$), 2.05 (1 H, dt, *J* 13.4 and 3.5, SiOCHCH$_a$*H*$_b$), 2.07 (1 H, br s, MeOCHC*H*), 2.40 (1 H, br m, SiCH$_2$C*H*), 3.41 (3 H, s, OMe), 3.77 (1 H, 5, *J* 10.1, PhCHOC*H*$_{ax}$H$_{eq}$), 3.88 (1 H, d, *J* 10.0, PhCHOC*H*), 4.00 (1 H, dt, *J* 10.1 and 5.0, C*H*OCHOMe) overlapping with 4.05 (1 H, m, CHOSi), 4.30 (1 H, dd, *J* 10.1 and 5.1, PhCHOCH$_{ax}$*H*$_{eq}$), 4.55 (1 H, s, OC*H*OMe), 5.59 (1 H, s, C*H*Ph) and 7.30–7.50 (5 H, m, Ph); $\delta_C$(75 MHz; $CDCl_3$) 0.01 (q), 1.30 (q), 15.06 (t), 24.87 (q), 26.38 (q), 32.21 (t), 34.61 (s), 41.09 (d), 47.93 (d), 54.95 (q), 60.34 (d), 70.01 (t), 78.12 (d), 78.91 (d), 101.98 (d), 103.21 (d), 126.01 (d), 128.21 (d), 129.00 (d) and 138.08 (s); *m/z* 404 ($M^+$, 5%), 373

(15), 372 (17), 313 (18), 256 (31), 255 (100), 223 (34), 195 (17) and 149 (35).

A crystal which was suitable for X-ray analysis was obtained and the data have been deposited at the Cambridge Crystallographic Data Centre.

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