Regiochemical Control in Intramolecular Cyclization of Methylene-interrupted Epoxydiols

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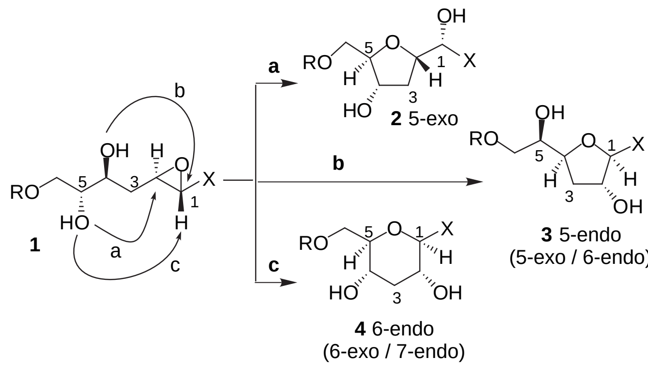
SUPPORTING INFORMATION

Experimental details and tabulated spectroscopic data for all new compounds **5a-h**, **6a**, **6d-g**, **7c**, **7f-g**, **8c**, **9**, and **13-15** (17 pages). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information.

A brief discussion on Baldwin's and Warren's terminology of endo and exo (hybrid terminology):

It is prudent to briefly discuss the nomenclature of epoxide opening in the context of Baldwin rules terminology with regards to the intramolecular ring opening of epoxides. Path a in Scheme 2 is clearly a 5-exo process, and is therefore considered favorable. Path b and c are somewhat more ambiguous, and are labeled 5-exo/6-endo and 6-exo/7-endo, respectively. This seemingly dual and yet opposing classification stems from viewing the ring formation from two different perspectives. This is illustrated in Figure 1 with the 5-exo/6-endo process, which follows Path b (Scheme 2). If one ignores the C4-O epoxide bond (Figure 1a), the attack of the hydroxyl onto C5, and the subsequent rupturing of the C5-O bond can be classified as 5-exo. However, disregarding the C4-C6 bond (Figure 1b), then the approach of the hydroxyl and breaking of the C6-O bond resembles a 6-endo process . Although this might seem to be a matter of semantics, it is important to realize that it could have profound consequences on the regiochemical choices available along the reaction pathway, i.e., since both *Path a* and *Path b* (Scheme 2) can be considered as 5-exo processes, is it possible to obtain regiochemical control? On the other hand, is the 5-exo/6-endo process less likely to occur from a Baldwin rules point of view since it has some elements of the unfavorable 6-endo attack?

Scheme 2. Possible modes of cyclization (see ref. 37 for hybrid definitions in parantheses)



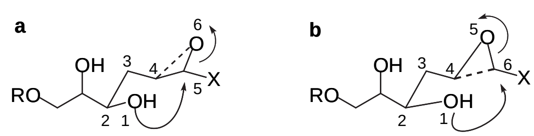
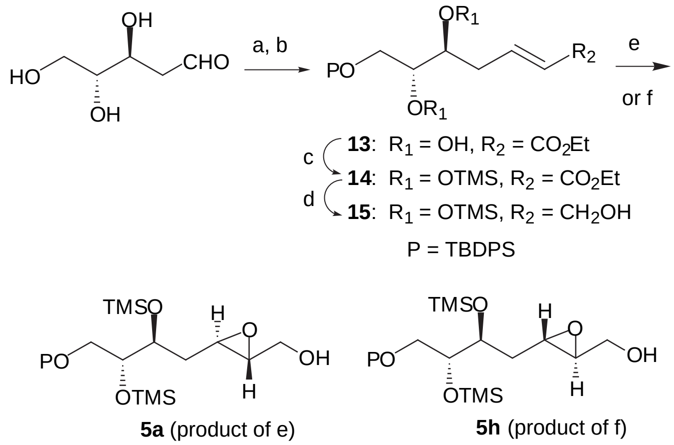


Figure 1. a) Attack of OH resembles a 5-exo system, disregarding the C4-O bond. b) On the other hand disregarding the C4-C6 bond suggests a 6-endo process.

Synthetic Schemes for Preparation of 5a-e

2-Deoxy-D-ribose was utilized as the entry point to obtain the common structural motif represented in **1**. Synthesis of **5a** with the hydroxyl pendant group was initiated by the Wittig olefination of 2-deoxy-D-ribose followed by selective silyl protection of the primary hydroxyl group to deliver **13** (Scheme 3). Both secondary hydroxyl groups in **13** were then protected as their corresponding trimethylsilyl ethers, and subsequent reduction of the ethyl ester group in **14** with DIBAL afforded the allylic alcohol **15** poised for Sharpless asymmetric epoxidation. Epoxides **5a** and **5h** were obtained in good yields with 99% and 92% de, respectively (GC analysis). Compound **5a** and its structural analogs serve as the epoxydiol precursor in which the diol functionality is liberated during ring closure. This strategy was adopted early on since the unprotected epoxydiols were found to be too reactive and were not stable to storage.

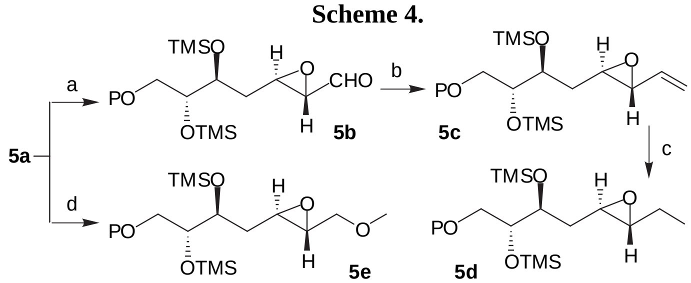
Scheme 3. Synthesis of epoxydiol



(a) $(Ph)_3PCHCO_2Et$, THF, 90 ˚C (92% 5/1:E/Z); (b) TBDPSCl, DMF, rt (72% E only); (c) TMSCl, Im, DMAP, THF, 45 ˚C, (75%); (d) DIBAL, Et_2O, 0 ˚C, (90%); (e) D (-) DET, $Ti(OiPr)_4$, tBuOOH, -20 ˚C to -30 ˚C, 4 Å mol. sieves, 73%, 99% de; (f) L (+) DET, $Ti(OiPr)_4$, tBuOOH, -20 ˚C to -30 ˚C, 4 Å mol. sieves, 55%, 92% de.

Other control elements in structure **1** were installed by routine modifications of **5a** (Scheme 4). Oxidation of **5a** with Dess-Martin Periodinane reagent yielded the desired epoxy aldehyde **5b**. Olefination of **5b** with methyl triphenylphosphonium bromide and *n*BuLi secured **5c**, which upon hydrogenation with H_2 Pd/C furnished the saturated alkyl substituent in **5d**. Attempted synthesis of **5e** with NaH and methyl iodide led to the deprotection of the TMS ether groups. However, treatment of **5a** with dimethylsulfate and LiHMDS led to the formation of **5e** in 75% isolated yield.

Scheme 4.

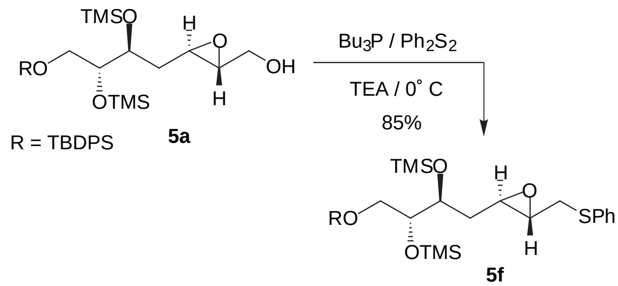


(a) DMP, Py, CH_2Cl_2, 90%; (b) CH_3PPh_3Br, nBuLi, Et_2O, 55%; (c) 10% Pd/C, H_2, EtOAc, 60%; (d) $(CH_3)_2SO_4$, LiHMDS, THF, 75%.

Synthetic Schemes for Preparation of 5f-g

The epoxysulfide **5f** was synthesized as shown in Scheme 5. Epxoyalcohol **5a** was secured as previously above. The conversion of the epoxyalcohol **5a** to **5f** was best achieved using Hata's Reagent. An alternative method comprising of the conversion of epoxyalcohol to the tosylate followed by treatment with sodium thiophenoxide resulted in decomposition of the epoxyalcohol. Epoxysulfide **5g** was synthesized in an analogous fashion in 85% yield.

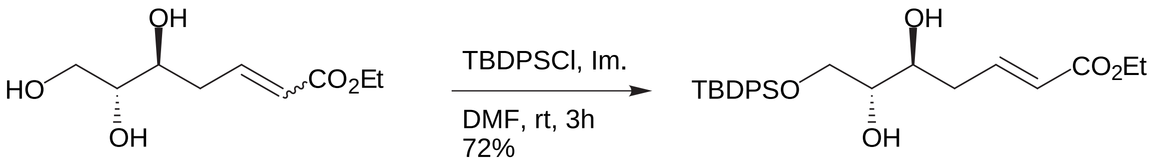
Scheme 5



General Procedures:

Diethyl ether and THF were dried over sodium/benzophenone under nitrogen. Dichloromethane was dried over calcium hydride. TMSCl was dried and distilled over sodium hydride. All the other commercially available reagents were used without further purification. All the air and water sensitive reaction were done in flame dried apparatus under nitrogen atmosphere. ^{1}H, ^{13}C, 2D-COSY and NOE spectra were recorded on 500 MHz NMR spectrometer (VARIAN 500 MHz) in $CDCl_3$. IR spectra were recorded on Nicolet IR/42 spectrometer using NaCl cells. Optical rotations were measured using Perkin-Elmer (model 341) polarimeter. Column chromatography was performed using Silicycle (40-60 μm) silica gel. Analytical TLC was done using pre-coated silica gel 60 F_{254} plates. GC analysis was performed using HP (6890 series) GC system (Column AltechSE-54, 30 m x 320 μm x 0.25 μm).

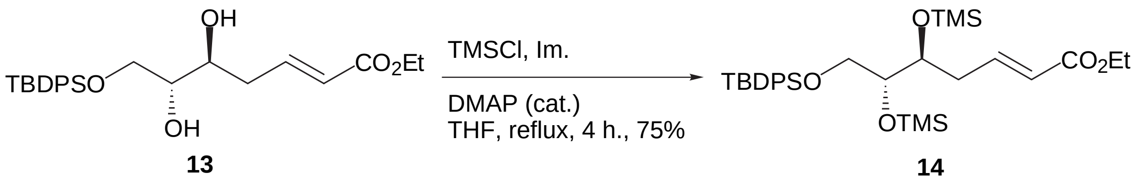
13:



12 (E/Z = 5/1) **13**

To a solution of **12** (8.2 g, 0.04 mol) in DMF (30 mL), imidazole (3.0 g, 0.044 mol) and t-butylchlorodiphenylsilane (12 g, 0.044 mol) were added at room temperature. The mixture was stirred at room temperature for 3 h, after which time the reaction was quenched by adding H_2O and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x100 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The E and Z isomers were separated by flash column chromatography (ethyl acetate / hexanes = 20 / 80). The purified E isomer **13** was obtained as a yellow oil (72% yield). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.65-7.63 (m, 4 H), 7.45-7.37 (m, 6 H), 6.99-6.92 (m, 1 H), 5.87 (dt, J = 15.7, 1.4 Hz, 1 H), 4.17 (q, J = 7.07 Hz, 1 H), 3.80-3.79 (m, 3 H), 3.60-3.58 (m, 1 H), 2.60 (br-s, 1 H), 2.47-2.43 (m, 1 H), 2.37-2.32 (m, 1 H), 2.15 (br-s, 1 H), 1.27 (t, J = 7.07, 3 H), 1.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.1, 135.7, 132.9, 130.3, 128.1, 124.2, 73.5, 71.6, 64.8, 60.5, 36.1, 27.1, 19.4, 14.5; IR (neat, thin film), 3461, 3973, 2932, 2859, 1968, 1899, 1830, 1719, 1655, 1472, 1428, 1393, 1370, 1267, 1167, 1113, 1044, 824, 741, 702 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{34}O_5Si$, 460.2519 m/z $(M+ NH_4)^+$; observed, 460.2550 m/z.

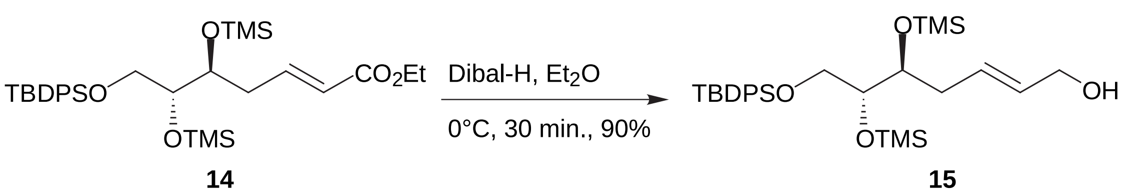
14:



To a solution of **13** (0.5 g, 1.13 mmol) in THF (5 mL), imidazole (308 mg, 4.52 mmol), chlorotrimethylsilane (0.57 mL, 4.52 mmol) and cat. dimethylaminopyridine were added and the mixture was refluxed for 4 h. The reaction was cooled to room temperature, diluted with ethyl acetate and filtered. The precipitate was washed with ethyl acetate (200 mL). The filtrate was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. Th crude product was purified by flash column chromatography (ethyl acetate / hexane = 5/95) to isolate **14** as a colorless oil (75% yield).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.67-7.65 (m, 4 H), 7.43-7.35 (m, 6 H), 6.99-6.93 (m, 1 H), 5.81 (d, J = 14.2, 1 H), 4.18 (q, J = 7.1, 2 H), 3.90-3.87 (m, 1 H), 3.75-3.72 (m, 1 H), 3.62-3.52 (m, 2 H), 2.41-2.26 (m, 2 H), 1.28 (t, J = 7.1, 3 H), 1.05 (s, 9 H), 0.07 (s, 9 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 147.3, 135.9, 133.6, 130.0, 128.0, 123.3, 72.7, 65.7, 60.2, 35.1, 27.1, 19.4, 14.5, 0.6, 0.5; IR (neat, thin film) 3086, 2957, 2896, 2859, 1982, 1893, 1824, 1722, 1657, 1474, 1429, 1368, 1318, 1252, 1113, 982, 841, 745, 702 cm^{-1}; HRMS (CI) calcd for $C_{31}H_{50}O_5Si_3$, 587.3044 m/z (M+ H)$^+$; observed, 587.3030 m/z.

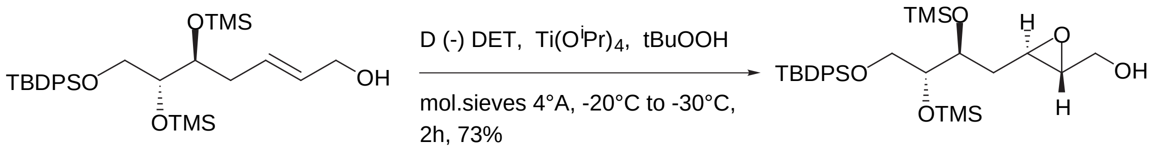
15:



A solution of **14** (2 g, 3.4 mmol) in Et_2O (15 mL) was cooled to 0°C. To this, a solution of DIBAL-H (1.0 M in hexane, 13.6 mL) was added. The reaction was continued at 0˚C and it was complete after 30 min. The reaction was quenched by adding saturated aqueous solution of Na-K tartrate (25 mL) and diluted with ether (50 mL). To this biphasic mixture, glycerol (0.7 mL) was added and the mixture was stirred vigorously for 8 h. The layers were separated and the aqueous layer was extracted with ether (2x50 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. Purification after flash column chromatography lead to **15** (90% yield) as a colorless oil.

^{1}H NMR (500MHz, $CDCl_3$) δ 7.67-7.64 (m, 4 H), 7.41-7.34 (m, 6 H), 5.66-5.64 (m, 2 H), 4.07 (d, J = 4.6 Hz, 2 H), 3.76-3.71 (m, 2 H), 3.64 (dd, J = 10.6, 5.7 Hz, 1 H), 3.52 (dd, J = 10.4, 6.1 Hz, 1 H), 2.22-2.19 (m, 2 H), 1.04 (s, 9 H), 0.08 (s, 9 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.7, 131.3, 130.6, 129.8, 127.9, 73.8, 65.9, 64.1, 35.3, 27.1, 19.4, 0.7, 0.6; IR (neat, thin film) 3349, 3073, 2957, 2859, 1962, 1900, 1824, 1474, 1429, 1250, 1113, 972, 841, 702 cm^{-1}; HRMS (CI) calcd for $C_{29}H_{48}O_4Si_3$, 545.2939 m/z (M+ H)$^+$; observed, 545.2927 m/z.

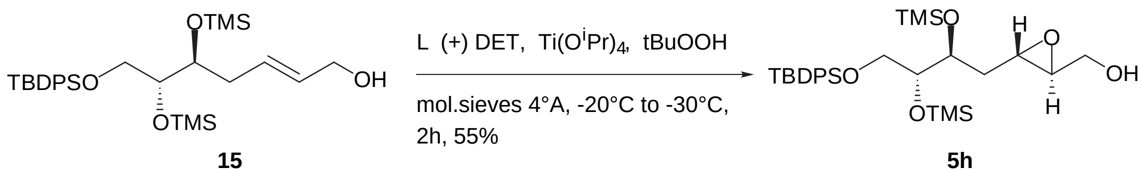
5a:



To a round bottom flask charged with powdered, preactivated mol. sieves (50 mg), CH_2Cl_2 (2 mL) was added and cooled to -30˚C. To this, Ti(O^{i}Pr)$_4$ (0.4 mL, 0.132 mmol) was added followed by addition of D (-) DET (0.32 mL, 0.184 mmol in 1 mL CH_2Cl_2). This mixture was stirred at -30˚C, under N_2 for 30 min after which time a solution of the allylic alcohol **15** (0.2 g, 0.368 mmol in 2 mL CH_2Cl_2) was added dropwise (over 30 min) to the reaction. This mixture was held for 45 min. at -20˚C and t-BuOOH (0.50 mL, 0.184 mmol) was added to the reaction. Stirring was continued at -20˚C for 2 h and quenched by adding satd. solutions of Na_2SO_4 (0.32 mL) and Na_2SO_3 (0.6 mL) and diluted with 10 mL ether. The mixture was stirred vigorously at room temperature for 3 h (yellow paste was formed in the reaction) and refrigerated overnight. The paste was diluted with anhydrous Et_2O (200 mL) and celite was added to it. This mixture was filtered on a celite pad using a sintered funnel. The yellow residue was further washed with anhydrous ether (200 mL) when it turned granular. The filtrate was concentrated and the crude product was purified by column chromatography (ethyl acetate / hexanes = 10 / 90). The epoxide **5a** was obtained as a colorless oil (73% yield).

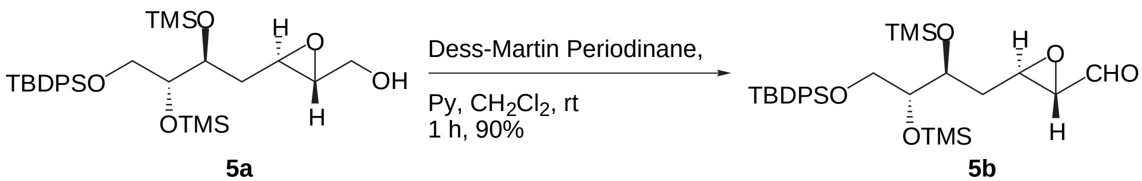
$[\alpha]_D^{20.2}$ + 35.6 (c 1.0, $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.65-7.63 (m, 4 H), 7.42-7.35 (m, 6 H), 3.96-3.93 (m, 1 H), 3.88-3.86 (m, 1 H), 3.78-3.74 (m, 1 H), 3.60-3.55 (m, 2 H), 3.52-3.49 (m, 1 H), 3.05 (dt, J = 5.9, 2.2 Hz, 1 H), 2.84-2.82 (m, 1 H), 1.96-1.90 (m, 1 H), 1.57-1.48 (m, 2 H), 1.04 (s, 9 H), 0.06 (s, 9 H), 0.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 133.6, 129.9, 127.9, 71.7, 65.7, 61.9, 58.4, 54.2, 34.6, 27.1, 19.4, 1.2, 0.4 IR (neat, thin film) 3418, 3071, 2957, 2864, 1962, 1893, 1824, 1590, 1472, 1428, 1252, 1111, 841, 747, 702 cm^{-1}; HRMS (CI) calcd for $C_{29}H_{48}O_5Si_3$, 561.2888 m/z $(M+ H)^+$; observed, 561.2881 m/z.

5h:



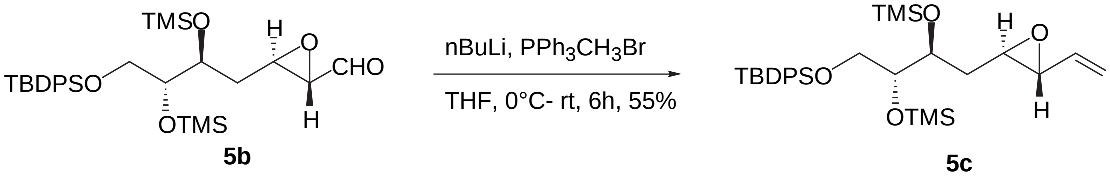
The same procedure as the one for **5a** was used for **5h** with L (+) diethyl tartrate.
$[\alpha]_D^{20.2}$ -21.8 (c 0.73 $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.66-7.65 (m, 4 H), 7.42-7.35 (m, 6 H), 4.06-4.04 (m, 1 H), 3.90-3.88 (m, 1 H), 3.78 (dt, J = 6.4, 2.2 Hz, 1 H), 3.61-3.57 (m, 1 H), 3.51 (d, J = 2.7, 1 H), 3.49 (d, J = 2.3 Hz, 1 H), 3.06-3.03 (m, 1 H), 2.89 (m, 1 H), 1.85-1.80 (m, 1 H), 1.67 (s (br), 1 H), 1.43 (ddd, J = 14.4, 7.2, 2.6 Hz, 1 H), 1.04 (s, 9 H), 0.1 (s, 9 H), 0.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 133.5, 129.9, 127.9, 71.1, 65.3, 62.0, 59.4, 54.0, 34.1, 27.1, 19.3, 0.5, 0.4 IR (neat, thin film) 3430, 3073, 2957, 2859, 1967, 1900, 1821, 1590, 1474, 1429, 1252, 1113, 841, 743, cm^{-1}; HRMS (CI) calcd for $C_{29}H_{48}O_5Si_3$, 561.2888 m/z (M+ H)$^+$; observed, 561.2872 m/z.

5b:



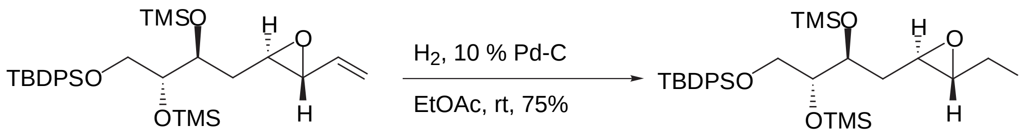
Pyridine (50 μL) was added to a mixture of Dess-Martin Periodinane (45 mg, 0.09 mmol) in CH_2Cl_2 (1.5 mL). To this, a solution of **5a** (45 mg, 0.08 mmol) in 1.5 mL CH_2Cl_2 was added and the reaction was stirred at room temperature for 1 h after which time it was diluted with ether (15 mL). The reaction was quenched by adding satd. $NaHCO_3$ (5 mL) containing $Na_2S_2O_3$ (2.5 g) and the mixture was stirred for 5 min after which ether (15 mL) was added and the layers were separated. The ether layer was washed with H_2O (15 mL), dried over Na_2SO_4, filtered and concentrated. The product was purified by column chromatography (ethyl acetate / hexanes = 5 / 95) to furnish the aldehyde **5b** as a colorless oil (90% yield).
^{1}H NMR (500MHz, $CDCl_3$) δ 8.96 (d, J = 6.4 Hz, 1 H), 7.65-7.35 (m, 10 H), 3.99-3.96 (m, 1 H), 3.75 (dt, J = 6.3, 3.3 Hz, 1 H), 3.56 (dd, J = 10.6, 6.6 Hz, 1 H), 3.51 (dd, J = 10.6, 6.0 Hz, 1 H), 3.32 (dt, J = 5.8, 1.8 Hz, 1 H), 3.04 (dd, J = 6.3, 1.8 Hz, 1 H), 2.02-1.96 (m, 1 H), 1.57-1.53 (m, 1 H), 1.04 (s, 9 H), 0.05 (s, 9 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 135.8, 133.5, 130.0, 127.9, 76.7, 71.2, 65.6, 59.2, 55.1, 34.0, 27.1, 19.4, 0.5, 0.4; IR (neat, thin film) 3073, 2959, 2932, 2859, 1968, 1893, 1824, 1732, 1474, 1429, 1390, 1252, 1113, 843, 743, 702 cm^{-1}; HRMS (CI) calcd for $C_{29}H_{46}O_5Si_3$, 559.2731 m/z (M+ H)$^+$; observed, 559.2721 m/z.

5c:



A mixture of methyltriphenylphosphonium bromide (206 mg, 0.58mmol) in THF (2 mL) was cooled to 0˚C. To this, n-butyllithium (0.48mmol, 0.13 mL of 0.25M solution in hexanes) was added and stirred for 30 min. during which time the solution turned yellow and clearer. This ylide solution was added to a precooled (0˚C) solution of **5b** (90 mg, 0.16 mmol) in THF (2 mL). The reaction was warmed to rt and stirred for 6 h and quenched by adding H_2O (10 mL) and diluted with ethyl acetate (20 mL). The organic layer was washed with NH_4Cl (10 mL). The aqueous layer was extracted with ethyl acetate (2x20 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (ethyl acetate / hexanes = 1/99) to yield the vinyl epoxide **5c** (55% yield).
^{1}H NMR (500MHz, $CDCl_3$) δ 7.65-7.63 (m, 4 H), 7.45-7.34 (m, 6 H), 5.58-5.51 (m, 1 H), 5.42 (dd, J = 17.4, 1.5, 1 H), 5.28-5.22 (m, 1 H), 3.97-3.94 (m, 1 H), 3.75 (dt, J = 6.3, 3.4, 1 H), 3.58 (dd, J = 10.5, 6.3 Hz, 1 H), 3.52 (dd, J = 10.6, 6.2 Hz, 1 H), 3.03 (dd, J = 7.6, 2.1 Hz, 1 H), 2.95-2.92 (m, 1 H), 1.99-1.93 (m, 1 H), 1.50-1.45 (m, 1 H), 1.04 (s, 9 H), 0.06 (s, 9 H), 0.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.8, 133.6, 129.8, 127.8, 119.1, 71.8, 65.7, 58.8, 35.0, 27.1, 19.4, 1.2, 0.5; IR (neat, thin film) 3073, 2959, 2859, 1962, 1887, 1818, 1591, 1429, 1252, 1113, 841, 741, 702 cm^{-1}; HRMS (CI) calcd for $C_{30}H_{48}O_4Si_3$, 557.2939 m/z $(M+ H)^+$; observed, 557.2934 m/z.

5d:

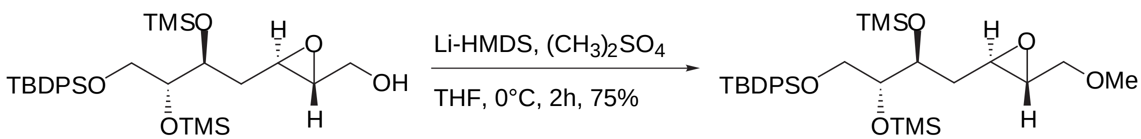


5c **5d**

10 % Pd-C (4 mg) was added to a solution of **5c** (40 mg, 0.072 mmol) in ethyl acetate (2 mL) and the mixture was stirred under H_2 atmosphere at room temperature for 1.5 h. The reaction was filtered through a celite pad and the residue was washed with ethyl acetate. The filtrate was concentrated and the crude product was purified by flash column chromatography (ethyl acetate / hexanes = 1/99) to furnish alkyl epoxide **5d** (75% yield).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.68-7.66 (m, 4 H), 7.44-7.36 (m, 6 H), 3.96-3.93 (m, 1 H), 3.78 (dt, J = 5.8, 3.5 Hz, 1 H), 3.63 (dd, J = 6.2, 10.4 Hz, 1 H), 3.53 (dd, J = 6.2, 10.6 Hz, 1 H), 2.83-2.80 (m, 1 H), 2.60 (dt, J = 5.5, 2.2 Hz, 1 H), 1.92 (ddd, J = 14.2, 7.5, 5.3 Hz, 1 H), 1.62-1.45 (m, 3 H), 1.06 (s, 9 H), 0.99 (t, J = 7.5 Hz, 2 H), 0.09 (s, 9 H), 0.07 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 133.4, 129.7, 127.7, 71.8, 65.5, 59.9, 56.4, 35.1, 26.9, 25.1, 19.2, 9.9, 0.4, 0.3; IR (neat, thin film) 3076, 3961, 1736, 1429, 1250, 113, 841, 742, 702 cm^{-1}.

5e:

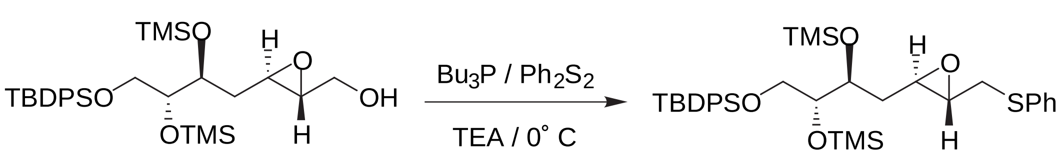


5a **5e**

A solution of **5a** (51 mg, 0.09 mmol) in THF (0.7 mL) was cooled to 0 ˚C. To this solution $(CH_3)_2SO_4$ (50 µL, 0.52 mmol) and LiHMDS (140 µL of 1.0 M solution in THF) were added. The reaction was complete in 2 h. The reaction was diluted with ethyl acetate (20 mL) and washed with H_2O (2x15 mL). The aqueous layer was extracted with ethyl acetate (2x20 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The product **5e** was purified by flash column chromatography (ethyl acetate / hexanes = 5 / 95) as a colorless oil (75% yield).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.66-7.63 (m, 4 H), 7.42-7.34 (m, 6 H), 3.94-3.91 (m, 1 H), 3.77-3.73 (m, 2 H), 3.61-3.48 (m, 3 H), 2.93 (dt, J = 5.9, 1.9 Hz, 1 H), 2.79-2.77 (m, 1 H), 1.93-1.87 (m, 1 H), 1.53-1.49 (m, 1 H), 1.51 (s, 3 H), 1.04 (s, 9 H), 0.11 (s, 9 H), 0.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 133.6, 129.8, 127.8, 71.9, 65.8, 63.3, 58.6, 54.5, 34.9, 27.1, 19.4, 0.6, 0.5; IR (neat, thin film) 3073, 2957, 2859, 192, 1893, 1824, 1589, 1474, 1429, 1252, 1113, 843, 747, 702 cm^{-1}.

5f:

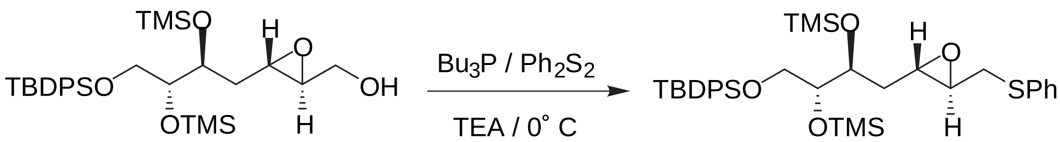


5a **5f**

To a solution of diphenyl disulphide (60 mg, 0.275 mmol) in triethyl amine (0.2 ml), tributyl phosphine (63 μL, 0.275 mmol) was added, stirred for 5 min. and cooled to 0˚ C. To this, a solution of the epoxyalcohol **5a** (50 mg, 0.09 mmol) in triethyl amine (0.2 ml) cooled to 0˚ C was added dropwise. The reaction was allowed to warm to room temperature and stirred for 4 h. The reaction was diluted with ether (20 mL) and washed with H_2O (2x15 mL). The aqueous layer was extracted with ether (2x20 mL). **5f** was purified by flash column chromatography (ethyl acetate / hexanes = 5 / 95) as a yellow oil (yield = 85%).

^{1}H NMR (500MHz, $CDCl_3$) δ 7.66-7.63 (m, 4 H), 7.42-7.33 (m, 8 H), 7.27-7.23 (m, 2H), 7.18-7.15 (m, 1H), 3.89-3.86 (dt, J = 7.6, 4.2 Hz, 1 H), 3.75-3.72 (dt, J = 6.0, 3.6 Hz 1 H), 3.57 (dd, J = 10.6, 6.0 Hz, !H), 3.48 (dd, J = 10.6, 6.2 Hz, 1 H), 3.07 (dd, 13.8, 5.2 Hz, 1 H), 2.95 (dd, 13.9, 5.3 Hz, 1 H), 2.87-2.83 (m, 2H),1.82-1.77 (m, 1 H), 1.52-1.47 (m, 1H), 1.03 (s, 9 H), 0.06 (s, 9 H), 0.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.6, 130.3, 129.9, 129.2, 127.9, 126.8, 71.7, 65.8, 57.5, 57.1, 36.7, 34.9, 27.1, 19.4, 0.6, 0. IR (neat, thin film) 3073, 2957, 2859, 1856, 1831, 1712, 1574, 1473, 1427, 1391, 1113, 941, 841, 741,cm^{-1}; HRMS (CI) calcd for $C_{35}H_{52}O_4SSi_3$, 653.2972 m/z $(M+H)^+$; observed, 653.2969 m/z.

5g:



5a

5g

5g was synthesized in an identical fashion to **5f**.

[1]H NMR (500MHz, $CDCl_3$) δ 7.65-7.62 (m, 4 H), 7.42-7.32 (m, 8 H), 7.28-7.25 (m, 2H), 7.20-7.17 (m, 1H), 3.98 (dt, J = 5.0, 2.5 Hz, 1 H), 3.73 (dt, J = 6.3, 2.4 Hz, 1 H), 3.47-3.45 (.m, !H), 3.07 (dd, 13.9, 5.3 Hz, 1 H), 2.97 (dd, 13.9, 5.8 Hz, 1 H), 2.88 (dt, 2.0, 5.5 Hz, 1H),1.82-1.77 (m, 1 H), 1.21 (ddd, 18.3, 7.9, 2.9 Hz, 1H), 1.02 (s, 9 H), 0.08 (s, 9 H), 0.07 (s, 9H); [13]C NMR (125 MHz, $CDCl_3$) δ 135.9, 133.6, 129.8, 129.2, 127.9, 126.9, 71.7, 65.3, 57.9, 57.2, 36.9, 34.3, 27.1, 19.3, 0.6, 0.5. IR (neat, thin film) 3176, 2957, 2859, 1956, 1831, 1587, 1474, 1429, 1250, 1113, 943, 841, 741,cm^{-1}; HRMS (CI) calcd for $C_{35}H_{52}O_4SSi_3$, 653.2972 m/z $(M+ H)^+$; observed, 653.2965 m/z.

General Procedure for the BF_3•Et_2O Mediated Epoxide Opening Reactions:
A solution of the epoxide (0.088 mmol) in anhydrous Et_2O (1 mL) was cooled to 0 ˚C. BF_3•Et_2O (0.616 mmol) was added to this solution at 0 ˚C. The reaction was allowed to warm to the room temperature for 1 h. The reaction was quenched by adding H_2O. The mixture was diluted with ethyl acetate (10 mL) and washed with $NaHCO_3$ (satd., 5 mL). The aqueous layer was extracted with ethyl acetate (2x10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to acetylation without purification.

General Procedure for the Acetic acid Mediated Epoxide Opening Reactions:
A solution of the epoxide (0.1 mmol) in THF (0.5 mL) was cooled to 0 ˚C. Aqueous acetic acid (AcOH:H_2O:THF (6:3:1), 3 mL) was added to the THF solution at 0 ˚C and the reaction was allowed to warm to room temperature for 3 h, after which time the reaction was diluted with ethyl acetate and neutralized by adding satd. $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate (2x15 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to acetylation without purification.

General Procedure for the Acetylation Reaction:
The crude cyclization product (0.11 mmol) was dissolved in pyridine (0.5 mL). Acetic anhydride (0.66 mmol) was added to the solution and the mixture was stirred at 60 ˚C for 4 h. The reaction was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed

5a

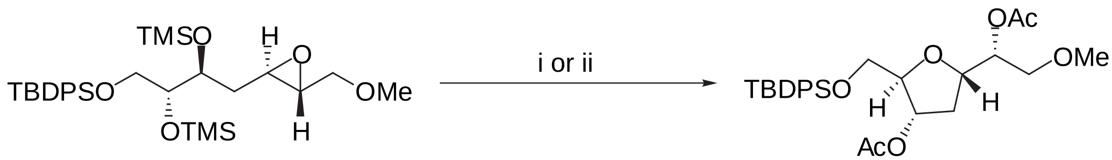
6a

with 10% HCl (2x10 mL). The aqueous layers were combined and extracted with ethyl acetate (2x15 mL). The organic layers were combined, dried over Na2$_S$O4, filtered and concentrated. The crude product was purified by flash column chromatography (hexanes/ethyl acetate).

6a:

$[\alpha]_D^{20.2}$ +46.9 (c 1.7, $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.43-7.35 (m, 6H), 5.34 (dt, J = 4.5, 2.1 Hz, 1 H), 5.15-5.11 (m, 1 H), 4.6 (dd, J = 12.1, 2.7 Hz, 1H), 4.31 (dt, J = 7.8, 4.5 Hz, 1H), 4.15-4.10 (m, 2 H), 3.72 (dd, J = 11.0, 3.3 Hz, 1 H), 3.68 (dd, J = 11.1, 4.2 Hz, 1H), 2.50-2.44 (m, 1 H), 2.05 (s, 6 H), 2.02 (s, 3 H), 1.91 (ddd, J = 13.7, 4.4, 2.9 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.3, 135.8, 133.3, 130.1, 128.0, 85.1, 76.3, 72.7, 64.9, 63.2, 34.9, 27.0, 21.3, 21.2, 21.0, 19.4; IR (neat, thin film) 3070, 2932, 2859, 1984, 1903, 1744, 1429, 1370, 1237, 1113, 824, 743, 704 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{39}O_8Si$, 543.2415 m/z $(M+H)^+$; observed, 543.2390 m/z.

6e:

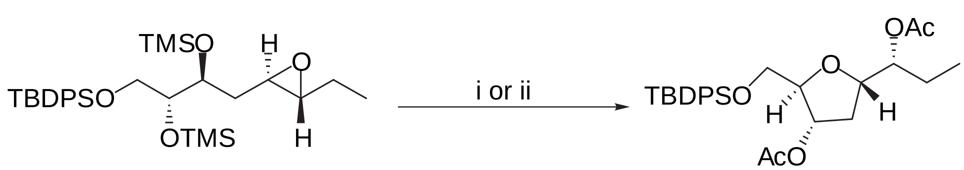


5e **6e**

i (a) BF_3•Et_2O, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 75%)
ii (a) AcOH:H_2O:THF (6:3:1), 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 80%)

$[\alpha]_D^{20.2}$ +31.8 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4 H), 7.42-7.35 (m, 6 H), 5.31 (dt, J = 6.4, 2.7 Hz, 1 H), 5.09 (m, 1 H), 4.32 (dt, J = 7.9, 4.7 Hz, 1 H), 4.09 (m, 1 H), 3.72 (dd, J = 11.0, 3.6 Hz, 1 H), 3.66 (dd, J = 11.0, 4.4 Hz, 1 H), 3.61 (dd, J = 10.9, 3.2 Hz, 1 H), 3.56 (dd, J = 10.9, 5.6 Hz, 1 H), 3.35 (s, 3 H), 2.45-2.40 (m, 1 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 1.90 (ddd, J = 13.9, 4.7, 3.0 Hz, 1 H), 1.03 (s, 9 H); ^{13}C NMR (125MHz) $CDCl_3$ δ 170.9, 170.5, 135.8, 133.4, 130.0, 128.0, 84.8, 76.3, 73.6, 71.8, 64.9, 59.5, 34.6, 27.0, 21.3, 19. 4; IR (neat, thin film) 3073, 3017, 2932, 2859, 1968, 1900, 1736, 1590, 1471, 1429, 1372, 1235, 1113, 1055, 762, 704 cm^{-1}; HRMS (CI) calcd for $C_{28}H_{38}O_7Si$, 513.2309 m/z $(M-H)^-$; observed , 513.2306 m/z.

6d:

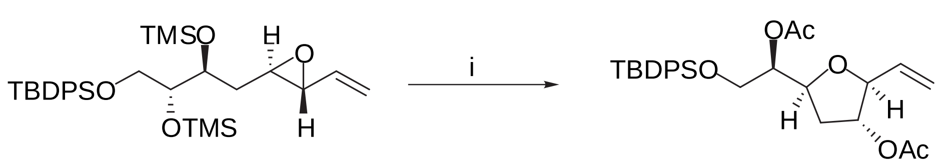


5d **6d**

i (a) BF_3•Et_2O, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 80%)
ii (a) AcOH:H_2O:THF (6:3:1), 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 78%)

$[\alpha]_D^{20.2}$ +21.9 (c 0.3, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.67 7.62 (m, 4 H), 7.42-7.34 (m, 6 H), 5.32-5.30 (m, 1 H), 4.95 (ddd, J = 8.3, 6.6, 4.0 Hz, 1 H), 4.18-4.14 (m, 1 H), 3.72 (dd, J = 11.1, 3.5 Hz, 1 H), 3.68 (dd, J = 11.0, 4.3 Hz, 1 H), 2.45-2.39 (m, 1 H), 2.05 (s, 6 H), 1.86 (ddd, J = 13.7, 5.7, 3.5 Hz, 1 H), 1.73 (ddd, J = 14.3, 7.5, 3.9 Hz, 1 H), 1.58-1.54 (m, 1 H), 1.03 (s, 9 H), 0.89 (t, J = 7.5 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.7, 135.8, 133.4, 130.0, 128.0, 84.4, 80.0, 76.3, 76.0, 65.0, 34.6, 30.0, 27.0, 24.3, 21.3, 19.4, 9.6; IR (neat, thin film) 3071, 2928, 2857, 1975, 1887, 1740, 1590, 1462, 1429, 1370, 1242, 1113, 1020, 801, 741, 702 cm^{-1}.

7c:

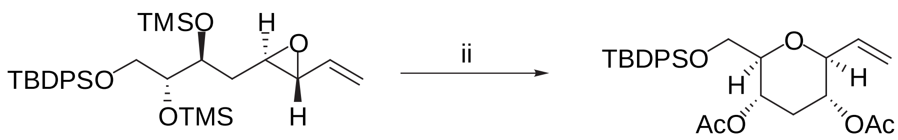


5c **7c**

i (a) BF_3•Et_2O, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 82%)

$[\alpha]_D^{20.2}$ –12.0 (c 0.3, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.65–7.63 (m, 4 H), 7.42-7.34 (m, 6 H), 5.82-5.75 (m, 1 H), 5.27-5.23 (m, 1 H), 5.20-5.16 (m, 1 H), 5.13-5.10 (m, 1 H), 4.96 (m, 1 H), 4.34-4.30 (m, 1 H), 3.81 (d J=5.3 Hz, 1 H), 2.07-2.03 (m, 1 H), 2.05, (s, 3 H), 2.02 (s, 3 H), 1.95-1.91, (m, 1 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.3, 136.0,135.8, 133.5, 130.0, 127.9, 116.5, 84.8, 78.8, 74.8, 63.3, 33.4, 27.0, 21.3, 21.2, 19.4; IR (neat, thin film) 3072, 2932, 2858, 1746, 1590, 1474, 1429, 1374, 1235, 1113, 860, 823, 734, 704 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{36}O_6Si$, 535.1918 m/z $(M+K)^+$; observed, 535.1912 m/z.

8c:

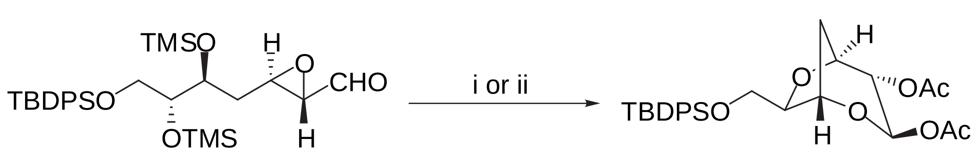


5c **8c**

ii (a) AcOH:H_2O:THF (6:3:1), 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over t wo steps =80%)

$[\alpha]_D^{20.2}$ –12.0 (c 0.3, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.69-7.63 (m, 4 H), 7.41-7.32 (m, 6 H), 5.81-5.75 (m, 1 H), 5.35-5.32 (m, 1 H), 5.23-5.20 (m, 1 H), 4.70 (ddd, J = 11.2, 9.5, 4.8 Hz, 1 H), 3.79-3.71 (m, 3 H), 3.43 (ddd, J = 9.7, 4.5, 2.2 Hz, 1 H), 2.58 (dt = 9.7, 4.5, 2.2 Hz, 1 H), 1.99 (s, 3 H), 1.93 (s, 3 H), 1.56-1.50 (m, 1 H), 1.02 (s, 9 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.6, 135.9, 134.9, 133.8, 129.8, 127.8, 118.2, 80.5, 79.9, 69.9, 66.6, 63.4, 35.1, 26.9, 21.2, 21.1, 19.5; IR (neat, thin film) 3037, 2959, 2932, 2859, 1744, 1474, 1428, 1374, 1235, 1115, 995, 825, 798, 740, 706 cm^{-1}; HRMS (CI) calcd for $C_{28}H_{36}O_6Si$, 497.2359 m/z $(M+H)^+$; observed, 497.2377 m/z.

9:



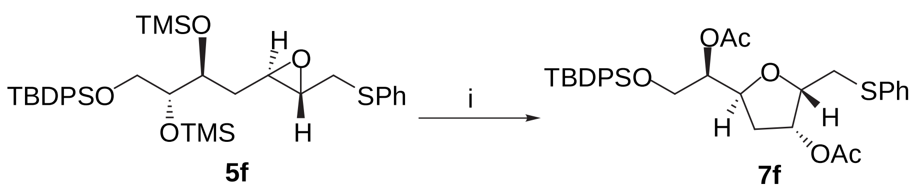
5b **9**

i (a) BF_3•Et_2O, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 17%)

ii (a) AcOH:H_2O:THF (6:3:1), 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 20%)

$[\alpha]_D^{20.2}$ +45.6 (c 0.9, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.62–7.59 (m, 4 H), 7.43-7.34 (m, 6 H), 6.00 (d, J = 6.8 Hz, 1 H), 4.66 (dd, J = 6.8, 1.6 Hz, 1 H), 4.57 (m, 1 H), 4.52-4.50 (m, 1 H), 4.34 (m,1 H), 3.68 (dd, J = 11.2, 3.8 Hz, 1 H), 3.43 (dd, J = 11.2, 6.6 Hz, 1 H), 2.08 (s, 6 H), 2.06-2.11 (m, 2 H),1.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 170.3, 169.6, 135.7, 133.1, 130.1, 128.0, 92.2, 82.3, 76.2, 74.2, 64.3, 33.9, 27.0, 21.7, 19.4; IR (neat, thin film) 3070, 2932, 2859, 1968, 1896, 1744, 1429, 1370, 1235, 1113, 897, 824, 758, 704 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{34}O_7Si$, 537.1711 m/z $(M+K)^+$; observed, 537.1732 m/z.

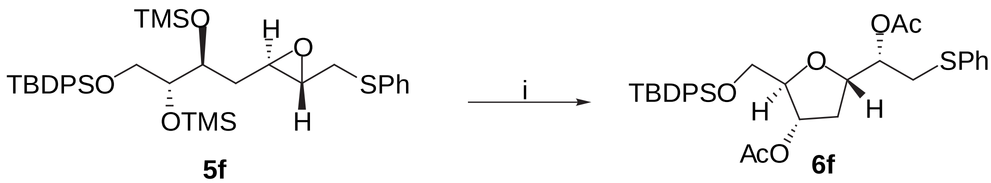
7f:



i (a) $BF_3{\bullet}Et_2O$, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 65%)

$[\alpha]_D^{20.2}$ - 37.5 (c 0.8, $CHCl_3$); ^{1}H NMR (500MHz, $CDCl_3$) δ 7.63-7.61 (m, 4 H), 7.43-7.33 (m, 8 H), 7.26-7.23 (m, 2 H), 7.19-7.15 (m, 1 H), 5.33-5.31 (m, 1 H), 5.10-5.07 (m, 1 H), 4.37 (dt, J = 9.0, 5.8 Hz, 1 H), 4.05-4.02 (m, 1 H). 3.77-3.72 (m, 2 H), 3.13 (dd, J = 13.5, 5.7 Hz, 1 H), 2.17-2.12 (m, 1 H), 2.05-2.00 (m, 3 H), 1.99 (s, 3 H), 1.95 (s, 3 H), 1.02 (s, 9 H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 170.0, 135.5, 133.1, 130.1, 129.8, 129.0, 127.7, 126.6, 80.3, 76.4, 74.9, 74.4, 62.7, 34.9, 32.8, 26.7, 21.0; IR (neat, thin film) 3073, 2932, 2859, 1956, 1900, 1744, 1588, 1474, 1429, 1373, 1230, 1113, 951, 823, 741, 704 cm^{-1}; HRMS (CI) calcd for $C_{33}H_{40}O_6SSi$, 593.2393 m/z $(M+H)^+$; observed, 593.2383 m/z.

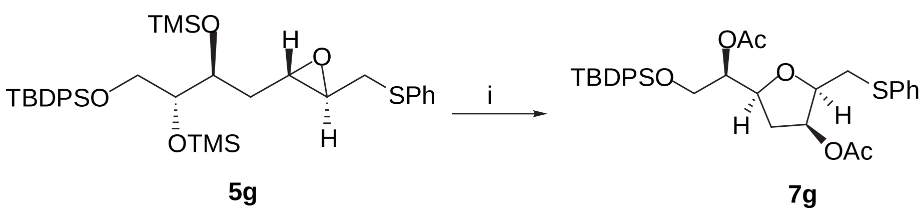
6f:



i (a) 1.5N HCl:THF (9:1), 0 °C to rt (b) Ac_2O, Py, 60 °C, overall yield over t wo steps = 74%

$[\alpha]_D^{20.2}$ - 37.5 (c 0.8, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.66-7.60 (m, 4 H), 7.42-7.33 (m, 8 H), 7.27-7.23 (m, 2 H), 7.18-7.14 (m, 1 H), 5.29 (dt, J = 6.8, 2.5 Hz, 1 H), 5.12 (dt, J = 7.6, 3.4 Hz, 1 H), 4.32 (dt J = 7.8, 4.5 Hz, 1 H), 4.06 (m, 1 H), 3.70 (dd, J = 11.0, 3.6 Hz, 1 H), 3.65 (dd, J = 11.1, 4.2 Hz, 1 H), 3.38 (dd, J = 14.3, 3.4 Hz, 1 H), 3.07 (dd, J = 14.3, 7.5 Hz 1 H), 2.45-2.39 (m, 1 H), 2.00 (s, 3 H), 1.88 (s, 3 H), 1.85-1.84 (m, 1 H), 1.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.3, 136.3, 135.8, 133.3, 130.2, 130.0, 129.1, 128.0, 126.5, 84.9, 79.2, 73.8, 64.9, 35.6, 34.7, 27.0, 21.3; IR (neat, thin film) 3073, 2932, 2859, 1962, 1891, 1742, 1588, 1472, 1428, 1370, 1239, 1113, 1026, 823, 740, 702 cm^{-1}; HRMS (CI) calcd for $C_{33}H_{40}O_6SSi$, 621.2706 m/z $(M+ C_2H_5)^+$; observed, 621.2702 m/z.

7g :



i (a) BF_3•Et_2O, Et_2O, 0 °C to rt (b) Ac_2O, Py, 60 °C (yield over two steps = 70%)

$[\alpha]_D^{20.2}$ + 35.6 (c 1.0, $CHCl_3$); ^1H NMR (500MHz, $CDCl_3$) δ 7.66-7.65 (m, 4 H), 7.44-7.35 (m, 8 H), 7.27-7.16 (m, 3 H), 5.25-5.22 (m, 1 H), 5.07 (dt, J = 7.0, 4.5 Hz, 1 H), 4.13 (dt, J = 7.7, 4.9 Hz, 1 H), 3.95 (ddd, J = 8.0, 5.8, 3.9 Hz, 1 H), 3.81 (d, J = 4.4 1 H), 3.12 (dd, J = 13.7, 5.8 Hz, 1 H), 3.02 (dd, J = 13.7, 8.0 Hz, 1 H), 2.33-2.27 (m, 1 H), 2.01, (s, 3 H), 1.96 (s, 3 H), 1.89-1.85 (m, 1 H), 1.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 170.4, 136.0, 135.8, 133.6, 130.1, 129.9, 129.2, 127.9, 126.7; IR (neat, thin film) 3074, 2932, 2859, 1962, 1900, 1742, 1588, 1473, 1428, 1373, 1242, 1113, 953, 823, 741, 702 cm^{-1}; HRMS (CI) calcd for $C_{33}H_{40}O_6SSi$, 593.2393 m/z $(M+ H)^+$; observed, 593.2377 m/z.