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C-6 Allylated Pyranosides for the Synthesis of Complex Oxygenated Tetrahydrofurans

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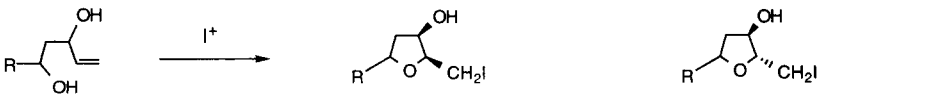
Abstract: The iodoetherification of C6 allylated D-pyranosides containing an allylic benzyloxy substituent, and their acyclic 5-hexen-,1,2,4-triol analogs were performed. Pyranosides of R configuration at the allylic ether gave exclusively a *syn,syn*-2,5-dialkyl-3-oxy-tetrahydrofuran which is primed for elaboration into several classes of naturally occurring THF's. By comparison, the stereoselectivity for the non-pyranoside derivative was much lower. In the S series, the bias was opposite for the pyranoside vs. the non-pyranoside substrates, but the selectivity in both cases was low.

The synthesis of 2,5-dialkyl-3-oxygenated-tetrahydrofurans (THF's) has received considerable attention because of their occurrence in several groups of natural products and their utility as precursors to highly substituted THF's.[1,2] Methodologies based on the electrophilic cyclization of 4-penten-1,3-diol precursors are attractive because the allylic alcohol can function as a stereocontrolling element.[1a,b,3-5] Stereoselectivity is however very dependent on the structure of the substrate. High stereoselectivity is usually obtained for simple terminal alkene derivatives, in which case the *cis*-2-iodomethyl-3-hydroxy-THF is the major product. Anomalous results are often obtained in more substituted systems.[1a,b]

Scheme 1



syn or *anti* 4-alken-1,3-diols

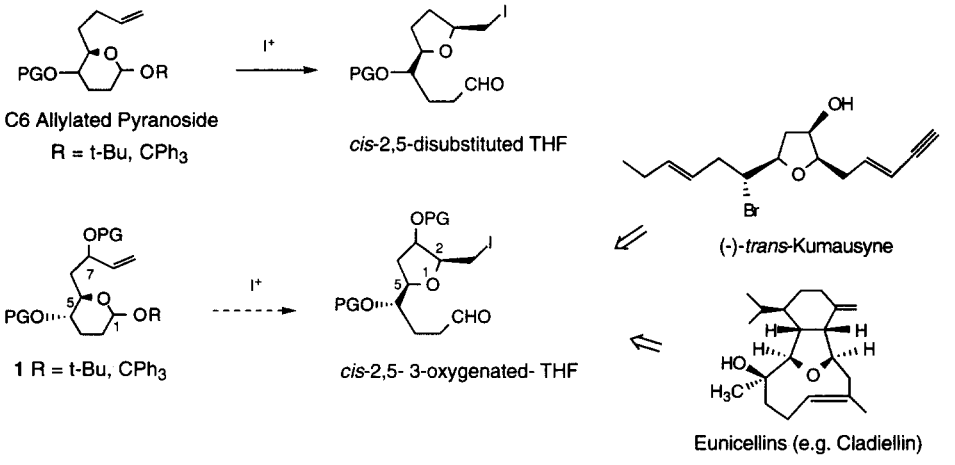
cis-3-hydroxy-2-iodomethyl THF

trans-3-hydroxy-2-iodomethyl THF

In connection with the synthesis of complex THF's, we have shown that C6 allylated pyranosides with bulky aglycones are reliable iodocyclization templates for the synthesis of *cis*-2,5-disubstituted THF's.[6] The stereoselectivity varied from modest to high in going from the t-butyl to the trityl glycosides. Interest in the

synthesis of 2,5-dialkyl-3-oxy-THF's led to the examination of the iodocyclization of R and S allylic alcohol pyranosides of the type **1.** The *cis*-2,5-dialkyl-3-oxygenated-THF products are versatile building blocks for the complex structures found in the kumausyne[7,8] and eunicellin[9,10] families, and other groups of natural products. The results of this study are discussed herein (Scheme 2).

Scheme 2



The test compounds were prepared from the known pyranoside diol **2.**[11] Selective tosylation of the primary alcohol gave **3** which was converted to its benzyl ether, thence the C6-allylated pyranoside **4.**[6,12] Selenium dioxide oxidation of **4** gave an almost 1:1 mixture of allylic alcohols **5** and **6**. Each was individually converted to the respective benzyl ether **7** or **8**. The trityl pyranoside derivatives **9**α/β and **10**α/β were obtained by acid hydrolysis of **7** and **8**, followed by silver mediated tritylation of the resulting lactols. The α/β mixtures of trityl glycosides were used without separation in the subsequent iodocyclization, since they were chromatographically inseparable, and because previous studies suggested that both anomers should exhibit high *cis*-2,5 stereoselectivity (Scheme 3).[6]

The configuration at the allylic alcohol center in **5** and **6** was assigned from ^{1}HNMR analysis of the respective (R)- and (S)-MTPA esters. [13] Thus, the upfield shift of the vinyl protons for the 5-(S)-MTPA ester [δ 5.13 (m, 2H) and 5.70 (m, 1H)] compared to the 5-(R)-MTPA derivative [δ 5.20, 5.32 (both dd, 1H ea.) and 5.84 (m, 1H)] indicated the R configuration. Similarly, application of the Mosher paradigm to the (R)- and (S)-MTPA esters of **6** led to the independent assignment of the S allylic alcohol epimer (Fig. 1).

Scheme 3

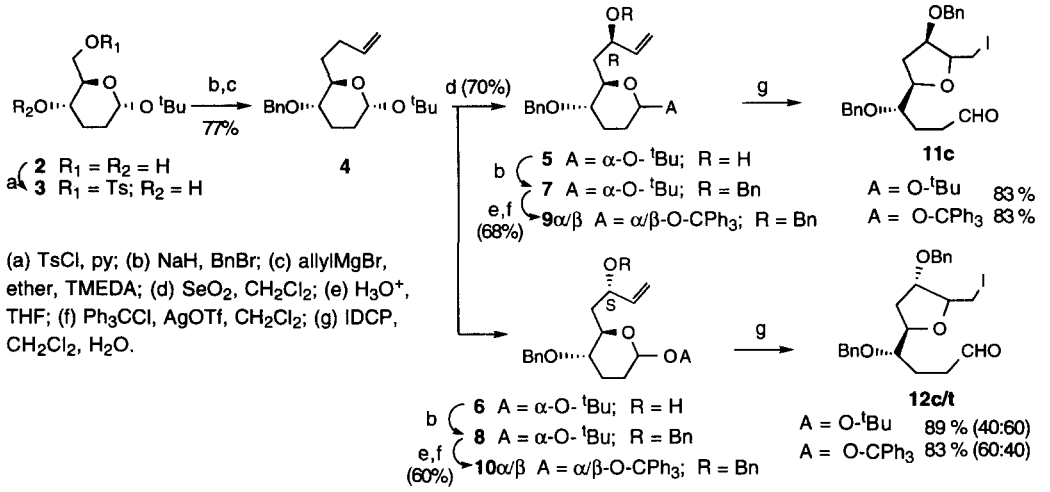
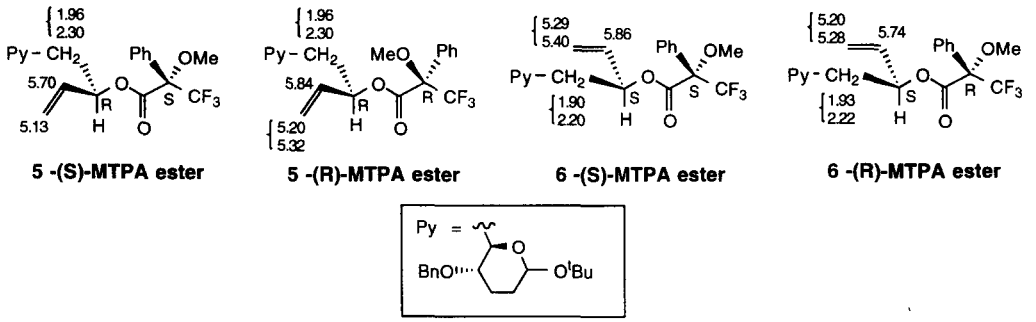


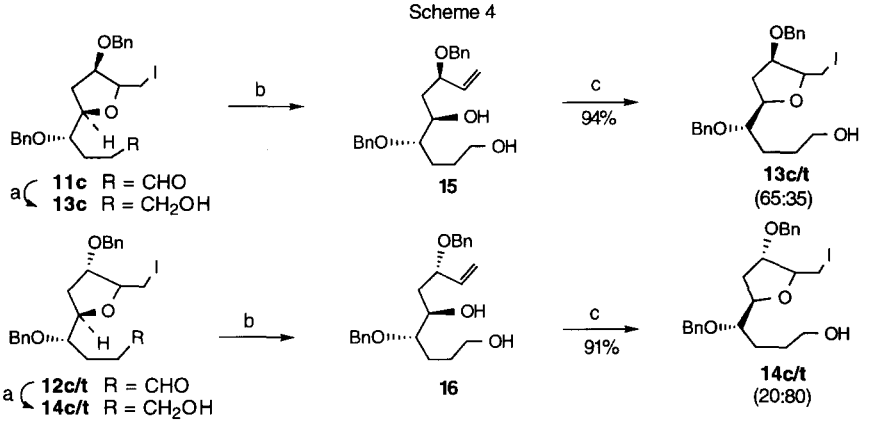
Fig. 1



The iodocyclization reactions were carried out using iodonium dicollidine perchlorate (IDCP)[14] in wet dichloromethane (Scheme 3). Both the t-butyl and trityl R allylic alcohol pyranosides **7** and **9**α/β, yielded exclusively, within the limits of ^{1}H NMR detection, the *cis*-2,5-THF **11c**.[15] The corresponding S substrates **8** and **9**α/β gave *cis/trans* mixtures **12c/t**. A moderate preference for the *trans*-2,5-THF **12t** was observed for the t-butyl pyranoside (*c:t* 40:60). The stereoselectivity was reversed for the trityl derivative (*c:t* 60:40).

In order to assess the importance of the pyranoside framework, on the stereoselectivity of the iodocyclization, the acyclic 5-hexen-1,2,4-triol derivatives **15** and **16** were prepared. These were obtained by $NaBH_4$ reduction of the THF aldehydes **11c** and **12c/t**, followed by zinc mediated reductive elimination of the resulting primary alcohols **13c** and **14c/t**. Treatment of **15** and **16** under the standard iodocyclization conditions gave THF mixtures **13c/t** (65:35) and **14c/t** (20:80) respectively. This result was strikingly different from the high selectivity obtained with less substituted 4-penten-1,3-diol substrates (Scheme 4).[1a,b]

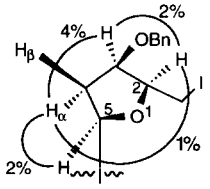
Scheme 4



(a) $NaBH_4$, EtOH; (b) Zn, 95% EtOH, reflux; (c) IDCP, CH_2Cl_2, H_2O.

The stereochemistry of the THF products was assigned by comparison of ^1H and ^{13}C NMR for cis/trans isomeric pairs with the data for known 2,5-dialkyl-3-oxy-THF's.[1a,b] In these systems the iodomethyl protons are more upfield for the *trans*-2,3-THF compared with the *cis*-2,3 isomer. The relative positions of the iodomethyl carbon resonances are opposite. These trends hold regardless of the configuration at C5. This analysis was carried out for C_6D_6 solutions rather than $CDCl_3$, because of higher signal resolution. This was especially important for determination of product ratios from the proton spectra. Thus, the *cis*-2,5-THF **12c** (i.e. *trans*-2,3-THF) was associated with signals at δ_H 2.80 and δ_C 8.0 ppm whereas the corresponding resonances of the *trans*-2,5 isomer **12t** (i.e. *cis*-2,3-THF) occurred at 3.17 and 3.4 ppm respectively. Since only a single THF isomer 11c was produced in the cyclization of the 7R pyranosides, the stereochemistry of the THF's in this series was determined by spectral analysis of the mixture of isomers **13c/t** produced from the reaction of the dihydroxyalkene **15**. Accordingly, **13c** (δ_H 3.19 and δ_C 2.7 ppm) and **13t** (δ_H 2.90 and δ_C 9.0 ppm) were assigned. These assignments meant that the THF-aldehyde **11c**, the $NaBH_4$ reduction precursor of **13c** was also *cis*.

Fig. 2



11c

The stereochemistry of **11c**, was substantiated by the NOESY spectrum (Fig. 2). First, H4α and H4β were distinguished on the basis of nOe effects between one of the H4 resonances (δ 2.20) and H3 (4%) and H5 (2%). The other H4 signal (δ 1.93) did not show a nOe with either of H3 or H5. The lowfield signal was therefore assigned as Hα. H4α and H4β could be also distinguished by the relative positions of their chemical shifts. In closely related *syn, syn*-2,5-dialkyl-3-oxy-THF's, the H4 proton *syn* to the protons at H3

and H5 resonates more downfield, relative to the *anti* proton.[16] Second, a 1% nOe between H4α and H2 indicated a *cis* relationship between these protons, and therefore that H5 and H2 were also *cis*. A 2% nOe between H2 and H3 was consistent with this stereochemical assignment.

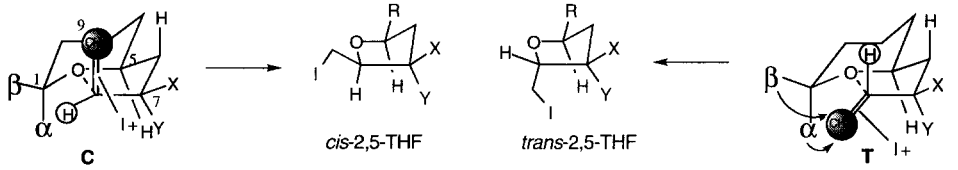
The different levels of THF stereoselectivity obtained for substrates in which the allylic alcohol residue is virtually identical (i.e. R substrates: **7**, **9**α/β, **15** or S systems: **8**, **10**α/β, **16**) substantiates the notion that THF stereoselectivity is not controlled solely by allylic stereocontrol in the initial halonium ion (or charge transfer) formation step, but also depends on the cyclization of the diastereomeric species to the THF-oxonium ions. The change in stereoselectivity is especially pronounced in going from the acyclic to the pyranoside templates, i.e. *cis*:*trans* from 65:35 to *cis* only for the R substrates and 20:80 to 60:40 for the S systems. Implicit in this argument is the generally held theory that the initial halonium ion or charge transfer formation step is reversible.[3]

The higher selectivities obtained for the R compared with the S allylic alcohol pyranoside templates might represent a case of matched and mismatched diatereoselection,[17] resulting from an interplay of two stereodirecting elements: allylic alcohol configuration, which induces the *cis*-2-iodomethyl-3-oxy product, and a bulky aglycone which favors the *cis*-2,5 disubstituted THF. These results appear to fit the chair-like transition state model which has previously been used to explain the stereoselectivity of these reactions. [3c,6] Accordingly, the *cis*-2,5-THF is formed from transition state **C** and the *trans*-2,5-THF from **T**. For the R pyranoside, the directing effects of the allylic alcohol and the aglycone act in the same sense. The transition state **C**, is favored over **T** because the alkoxy group adopts a stereoelectronically preferred, 'inside' (vs. 'outside')[4e] position relative to the alkene, and the 'olefin-up' (vs. 'olefin-down')[3c] orientation is less sterically congested relative to the bulky aglycone. For the S pyranoside substrates, these effects are opposed. **C** corresponds to the case of favored aglycone effect and disfavored allylic effect, and the reverse is the case for **T**. Thus for the S pyranoside **8**, the directing effect of allylic alcohol is apparently greater than that of the t-butyl aglycone, resulting in a predominance of the *trans*-2,5 disubstituted THF. In the trityl, S pyranoside **10**α/β, the aglycone effect is increased due to the increased steric demands of the trityl group, and this presumably outweighs the effect of the allylic alcohol.

These results illustrate once again the high degree of dependence of the stereoselectivity of the halocyclization reaction on substrate structure. The high stereoselectivity observed in the cyclization of 4-penten-1,3-diols derivatives to *cis*-2-iodomethyl-3-oxy-THF's, and expected on the basis of the configuration of the allylic alcohol, does not hold for the 5-hexen-1,2,4-triol substrates **15** and **16**. In the R allylic alcohol

substrate high stereoselectivity is restored on a conformationally restricted t-butyl or trityl pyranoside template. A similar device in the case of the S derivative, reverses, albeit in modest stereoselectivity, the preference normally expected by considering allylic alcohol configuration.

Scheme 5



smaller H-8 subst. closer to bulky aglycone: Fav

Matched - 7R : X = OBn, Y = H; Alkoxy 'inside': Fav

Mismatched - 7S : X = H, Y = OBn; Alkoxy 'outside': Disfav

larger C-9 subst. closer to bulky aglycone : Disfav

Matched - 7R : X = OBn, Y = H; Alkoxy 'outside': Disav

Mismatched - 7S : X = H, Y = OBn; Alkoxy 'inside': Fav

In conclusion, this study provides additional insight into the stereochemistry of the iodocyclization reaction of alkenols, and also expands on the synthetic utility of C6 allylated pyranosides. In particular, the halocyclization of R-allylic alcohol D-pyranosides such as **7** provides a highly stereoselective route to a versatile THF synthon. More efficient routes to these templates and their application to natural product synthesis are currently under investigation.

Experimental

TLC was carried out on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merck) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. ^{1}H and ^{13}C NMR spectra were obtained on GE-QE 300 and Varian UnityPlus 500 instruments. Unless otherwise noted, spectra were recorded at 300 and 75 MHz respectively. Optical rotations were determined on a Rudolph Research AUTOPOL III automatic polarimeter.

tert-Butyl 6-O-tosyl-2,3-dideoxy-α-D-*gluco*-pyranoside 3. p-Toluenesulfonyl chloride (5.95 g, 31.0 mmol) was added at 0 °C to a solution of of t-butyl 2,3-dideoxy-α-D-*gluco*-pyranoside **2** (5.27 g, 26.0 mmol) in dry pyridine (30 mL). The reaction mixture was warmed to rt and stirred for an additional 4 h, at which time methanol (1 mL) was added. Most of the solvent was removed *in vacuo* and the residue diluted with ether. The mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure. The crude product was purified by flash

chromatograpy to give **3** (7.38 g, 83%): R_f = 0.50 (20% EtOAc:P.E.); $[\alpha]^{23}_D$ 37° (c 0.25, $CHCl_3$); IR (neat) 3533, 2973, 1663, 1598, 1360, 1175, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.71-2.20 (m, 5H), 2.45 (s, 3H), 3.21 (m, 1H), 3.86 (d, 1H, J = 10.5 Hz), 4.05-4.43 (m, 2H), 5.56 (s, 1H), 7.32-7.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.7, 27.0, 28.5, 28.6, 28.8, 30.8, 65.9, 70.1, 71.4, 74.5, 90.7, 128.1, 129.9, 133.0, 144.9. Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 57.08; H, 7.35.

tert-Butyl 4-O-benzyl-2,3-dideoxy-α-D-*gluco*- non-8-enopyranoside 4 . To a solution of **3** (10.0 g, 28.0 mmol) in dry DMF (60 mL) at 0 °C was added NaH (1.34 g, 56.0 mmol), tetrabutylammonium iodide (0.52 g, 1.40 mmol), and benzyl bromide (3.67 mL, 30.8 mmol). The solution was warmed to rt and stirred for an additional 2 h. The reaction was then quenched by the addition of methanol (1 mL), and extracted with ether (3 x 100 mL). The ether extract was washed with brine, dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatograpy to give the 4-O-benzyl ether derivative (11.2 g, 90%): R_f = 0.8 (20% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.19 (s, 9H), 1.65 (m, 2H), 1.81 (m, 1H), 2.0 (m, 1H), 2.45 (s, 3H), 3.40 (m, 1H), 3.98 (m, 1H), 4.2 (d, 1H, J = 12.0 Hz), 4.3 (m, 1H), 4.47 (ABq, Δδ = 0.25 ppm, 2H, J = 11.8 Hz), 5.1 (s, 1H), 7.3 (m, 7H), 7.8 (d, 2H, J = 8.0 Hz).

Allylmagnesium bromide (90.0 mL of a 1M solution in ether, 90.0 mmol) was added under argon at rt, to a solution of the benyl ether-tosylate which was obtained in the previous step (8.0 g, 17.9 mmol), in a mixture of dry ether (90 mL) and TMEDA (0.90 mL). The reaction was stirred for 16 h, then carefully poured into saturated aqueous NH_4Cl (150 mL) at 0 °C. The resulting slurry was extracted with ether (3 x 100 mL), and the combined extract dried (Na_2SO_4), and filtered. The filtrate was concentrated in *vacuo* and the crude product purified by flash chromatography to give **4** (4.8 g, 85%): R_f = 0.8 (10% EtOAc:P.E.); $[\alpha]^{25}_D$ 140° (c 2.6, EtOH); IR (neat) 1640, 910, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.45 (m, 2H), 1.60 (m, 2H), 1.80 (m, 1H), 1.92 (m, 2H), 1.97 (m, 2H), 3.03 (m, 1H), 3.74 (m, 1H), 4.50 (ABq, Δδ = 0.19 ppm, 2H, J = 11.5 Hz), 4.97 (s, 1H), 4.90 (m, 2H), 5.76 (m, 1H), 7.20 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.8, 28.9, 30.0, 31.0, 32.0, 70.8, 70.9, 74.0, 78.0, 90.5, 114.3, 127.7, 127.9, 128.5, 138.7, 139.3. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.56; H, 9.29.

t-Butyl Pyranoside- 7R Alcohol 5 and 7S Alcohol 6. A 250 mL flask was charged with SeO_2 (0.261 g, 2.35 mmol), 90% TBHP (0.69 mL, 6.28 mmol) and CH_2Cl_2 (15 mL). After the mixture had been stirred for 0.5 h at rt, a solution of alkene **4** (1.00 g, 3.14 mmol) in CH_2Cl_2 (4 mL) was added over several minutes, and stirring continued for an additional 72 h. At that time 1M NaOMe in MeOH was added to pH 7, and the

mixture diluted with water (50 mL), and extracted with ether (3 x 15 mL). The ether extract was washed with saturated aqueous $NaHCO_3$ (2 x 15 mL) and brine (2 x 15 mL), then dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the crude residue purified by flash chromatography to yield allylic alcohols **5** (402 mg, 39%) and **6** (329 mg, 31%).

For **5**: R_f = 0.60 (15% EtOAc;P.E.); ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 9H), 1.6 (m, 2H), 1.8 (m, 2H), 1.95 (m, 2H) 3.18 (m; 2H), 3.25 (m, 1H), 4.1 (m, 1H), 4.25 (bm, 6H), 4.50 (ABq, Δδ = 0.30 ppm, 2H, J = 11.8 Hz), 5.0 (t, 1H), 5.1 (s, 1H), 5.25 (d, 1H, J = 15.5 Hz), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 28.6, 30.8, 38.5, 69.6, 70.3, 74.2, 76.3, 77.5, 90.3, 113.6, 127.6, 127.8, 128.2, 128.3, 138.2, 141.3. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.81; H, 9.04. Found: C, 71.43; H, 8.92.

For **6**: R_f = 0.55 (15% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9H), 1.5 (m, 2H), 1.75 (m, 3H), 2.2 (m, 1H), 3.70 (s, 1H), 4.10 (m, 1H), 4.45 (ABq, Δδ = 0.3 ppm, 2H, J = 11.8 Hz), 5.00 (s, 1H), 5.10 (s, 1H), 5.25 (d, 1H, J = 15.5 Hz), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1, 28.6, 30.6, 39.5, 70.6, 72.0, 72.2, 77.8, 90.2, 113.6, 127.6, 127.7, 128.3, 138.2, 141.7.

5-(S)-MTPA ester. To a stirred solution of allylic alcohol **5** (5.0 mg, 0.015 mmol) in CH_2Cl_2 (1.5 mL) at rt, was added anhydrous pyridine (0.8 mL, 10 mmol), 4-(dimethylamino)pyridine (7 mg, 0.06 mmol) and R-MTPA-Cl (0.06 mL, 0.15 mmol). The solution was stirred at this temperature for 3 h, then diluted with saturated aqueous $NaHCO_3$ and ether (4 mL) and stirring continued for 30 min. The organic phase was then seperated and the aqueous layer extracted with ether (3 x 10 mL). The organic phase was washed with 5% aqueous $NaHSO_4$ (3 x 3 mL) and brine (10 mL), dried ($MgSO_4$) and filtered. Evaporation of the filtrate was concentrated under reduced pressure and flash chromatography of the residual oil gave **5-(S)-MTPA ester** (7.2 mg, 88%): R_f = 0.75 (10% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.55 (m, 4H), 1.96 (m, 1H), 2.30 (m, 1H), 3.10 (m, 1H), 3.56 (s, 3H), 3.85 (m, 1H), 4.49 (ABq, Δδ = 0.21 ppm, 2H, J = 11.8 Hz), 4.97 (m, 1H), 5.13 (m, 2H), 5.64 (m, 1H), 5.70 (m, 1H), 7.30 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2619.

5-(R)-MTPA ester. R_f = 0.75 (10% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 1.60 (m, 4H), 1.96 (m, 1H), 2.30 (m, 1H), 3.1 (m, 1H), 3.51 (s, 3H), 3.82 (m, 1H), 4.48 (ABq, Δδ = 0.19 ppm, 2H, J = 11.8 Hz) 4.98 (m, 1H), 5.20 (dd, 1H, J = 10.4, 2.0 Hz), 5.32 (dd, 1H, J = 17.1, 2.0 Hz), 5.65 (m, 1H), 5.84 (m, 1H), 7.30 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2623.

6-(S)-MTPA ester. R_f = 0.70 (10% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.70 (m, 4H), 1.90 (m, 1H), 2.20 (m, 1H), 3.09 (m, 1H), 3.50 (s, 3H), 3.79 (m, 1H), 4.43 (ABq, Δδ = 0.19 ppm, 2H, J = 11.6 Hz), 4.96 (m, 1H), 5.29 (dd, 1H, J = 10.5, 2.0 Hz), 5.40 (dd, 1H, J = 17.2, 2.0 Hz), 5.66 (m, 1H), 5.86 (m, 1H), 7.40 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2616.

6-(R)-MTPA ester. R_f = 0.70 (10% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.70 (m, 4H), 1.93 (m, 1H), 2.22 (m, 1H), 3.09 (m, 1H), 3.51 (s, 3H), 3.81 (m, 1H), 4.48 (ABq, Δδ = 0.19 ppm, 2H, J = 11.7 Hz), 4.98 (m, 1H), 5.20 (dd, 1H, J = 10.7, 2.0 Hz), 5.28 (dd, 1H, J = 16.7, 2.0 Hz), 5.64 (m, 1H), 5.74 (m, 1H), 7.38 (m, 10H). HRMS (CI-CH_4) calcd for $C_{30}H_{38}O_6F_3$ $(M+H)^+$ 551.2621, found 551.2621.

t-Butyl Pyranoside-7R Benzyl Ether 7. NaH (45 mg, 1.1 mmol, 60% suspension in mineral oil) and nBu_4NI (17 mg, 0.05 mmol) was added at 0 °C to a solution of alcohol **5** (150 mg, 0.45 mmol) in anhydrous DMF (4 mL). The suspension was stirred at this temperature for 15 min at which time benzyl bromide (0.12 mL, 1.0 mmol) was added. The reaction was warmed to rt, stirred for an additional 16 h, then recooled to 0 °C and quenched by addition of MeOH (0.1 mL). Water (25 mL) was added and the mixture extracted with ether (4 x 20 mL). The ether extract was washed with $NaHCO_3$, and brine, dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure and the crude brown residue purified by flash chromatography to give **7** (162 mg, 84%): R_f = 0.60 (5% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 1.5 (m, 1H), 1.75 (m, 3H), 2.0 (m, 2H), 2.39 (m, 1H), 3.16 (m, 1H), 4.20 (m, 2H), 4.49 (ABq, Δδ = 0.29 ppm, 2H, J = 11.7 Hz), 4.6(ABq, Δδ = 0.18 ppm, 2H, J = 11.7 Hz), 4.63 (s, 1H), 5.11 (t, 1H), 5.3 (m, 2H), 5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) 21.5, 26.6, 29.0, 37.6, 30.6, 65.8, 67.8, 68.4, 71.9, 75.2, 76.2, 88.3, 114.5, 125.1, 125.3, 125.4, 125.6, 126.1, 126.2, 126.3, 136.7,137.0, 137.8. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.54; H, 8.81.

t-Butyl Pyranoside-7S Benzyl Ether 8. Benzylation of **6** (100 mg, 0.30 mmol) under the conditions described for the preparation of **7**, gave **8** (113 mg, 92%): R_f = 0.55 (5% EtOAc:P.E.); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.60 (m, 2H), 1.80 (m, 3H), 1.90 (m, 1H), 2.15 (m, 1H), 3.20 (m, 1H), 3.82 (m, 1H), 4.03 (m, 1H), 4.42 (ABq, Δδ = 0.25 ppm, 2H, J = 10.3 Hz), 4.48 (ABq, Δδ = 0.23 ppm, 2H, J = 14.0 Hz), 4.95 (t, 1H), 5.15 (m, 2H), 5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5 26.6, 28.8, 36.7, 66.4, 68.0, 68.6, 71.8, 75.7 75.8, 88.2, 115.9, 125.2, 125.3, 125.4, 125.6, 125.8, 126.1, 126.2, 136.5, 136.7. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.01; H, 8.34.

Trityl Pyranoside-7R Benzyl Ether 9α/β. A solution of **7** (100 mg, 0.30 mmol) in a mixture of THF (7 mL)

and 0.5 N HCl (2 mL) was stirred at rt for 20 h. The mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with ether (4 x 15 mL). The ether extract was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. Purification of the residue by flash chromatography (R_f = 0.10; 5% EtOAc:P.E.) gave the presumed lactol derivative (87.2 mg, 80%) which was dried under high vacuum and used directly in the next step.

Freshly activated, powdered 4A molecular sieves (100 mg) was added to a solution of the material obtained in the previous step (85 mg, 0.23 mmol), 2,4,6-collidine (0.07 mL, 0.506 mmol) and trityl chloride (141 mg, 0.51) in CH_2Cl_2 (3 mL). The mixture was stirred for 15 min, at which time AgOTf (118 mg, 0.46 mmol) was added. After stirring for an additional 15 min, the solution was diluted with 10% aqueous $Na_2S_2O_3$, (10 ml) and extracted with ether (4 x 10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and filtered. Evaporation of the filtrate under reduced pressure and flash chromatography of the residue gave **9**α/β (119 mg, 85%): R_f = 0.60 (5% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.40-2.20 (m, 6H), 3.15 (m, 1H), 3.40 (m, 1H), 3.45 (m, 1H), 4.10 (d, J = 10.3 Hz, 1H), 4.50, 5.15 (both m, 6H), 5.7 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 27.8, 31.1, 39.8, 69.8, 71.0, 74.4, 77.5, 79.0, 87.9, 97.2, 116.7, 126.5-129.6 (several lines), 138.6, 139.6, 139.9, 144.8; (minor isomer, selected peaks) 23.8, 29.9, 39.5, 87.9, 92.6, 116.7, 138.6, 139.6, 139.9, 145.0. HRMS (CI-NH_4) calcd for $C_{42}H_{43}O_4$ $(M+H)^+$ 611.3161, found 611.3162.

Trityl Pyranoside-7S Benzyl Ether 10α/β . Application of the identical two-step procedure described for the preparation of **9**α/β, to the t-butyl pyranoside **8** (100 mg, 0.30 mmol) afforded the trityl glycoside 10α/β (110 mg, 60%): R_f = 0.60 (5% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.4-2.1 (m, 6H), 2.9, 3.6, 3.8, 4.0 (all m, 2H), 3.2 (m, 1H), 4.2-4.6, 4.9-5.2 (both m, 7H), 5.6 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 28.1, 31.3, 38.1, 70.4, 71.3, 75.4, 76.7, 77.1, 77.4, 88.1, 97.5, 117.6, 127.0-129.0 (several lines), 138.7, 139.0, 139.1, 145.1; (minor isomer, selected peaks) 24.3, 31.1, 38.3, 87.8, 92.6, 117.7, 127.0-129.0 (several lines), 138.7, 139.1, 139.2, 144.9. HRMS (CI-NH_4) calcd for $C_{42}H_{43}O_4$ $(M+H)^+$ 611.3161, found 611.3162.

***cis*-2,5-THF-aldehyde 11c.** IDCP (132 mg, 2.82 mmol) was added to a solution of alkene **7** (100 mg, 0.24 mmol) in CH_2Cl_2:H_2O (20:1, 5 mL). The solution was stirred at rt for 5 min, then diluted with 10% aqueous $Na_2S_2O_3$ (10 mL) and extracted with ether (4 x 20 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography yielded aldehyde **11c** (96 mg, 83%): R_f = 0.30 (10% EtOAc:P.E.); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.82 (m, 1H), 1.93 (m, 1H),

2.20 (m, 2H), 2.78 (m, 2H), 3.31 (dd, 1H, J = 6.3, 10 Hz), 3.38 (dd, 1H, J = 7.9, 10 Hz), 3.64 (m, 1H), 4.02 (m, 1H), 4.10 (m, 1H), 4.18 (m, 1H), 4.51 (ABq, $\Delta\delta$ = 0.23 ppm, 2H, J = 10 Hz), 4.53 (m, 2H), 7.25 (m, 10H), 9.7 (s, 1H); ^{1}H NMR (C_6D_6) δ 1.6 (m, 3H), 2.0 (m, 3H), 3.1 (dd, 1H, J = 6.4, 9.5 Hz), 3.22 (dd, 1H, J = 7.7, 9.5 Hz), 3.35 (q, 1H, J = 5.3 Hz), 3.6 (m, 2H), 3.65 (m, 1H), 4.07 (ABq, $\Delta\delta$ = 0.16 ppm, 2H, J = 11.1 Hz), 4.39 (ABq, $\Delta\delta$ = 0.18 ppm, 2H, J = 12.1 Hz), 7.1 (m, 10H), 9.35 (s, 1H); ^{13}C NMR (C_6D_6) δ 2.6 (CH_2I-*cis*-2,5), 24.6, 33.3, 40.1, 71.8, 73.0, 79.2, 79.5, 81.5, 83.6, 128.1, 128.4, 128.8, 129.0, 138.9, 139.7, 201.0. MS (CI) m/z 512 (M+NH_4^+), 495 (M+H^+). Anal. Calcd for $C_{23}H_{27}O_4I$: C, 55.88; H, 5.51. Found: C, 55.70; H, 5.50.

Application of the above procedure to trityl pyranoside **9**α/β (139 mg, 0.228 mmol) afforded aldehyde **11c** (94 mg, 83%).

***cis/trans* -2,5-THF-aldehyde 12c/t.** Application of the standard iodoetherification procedure individually, to t-butyl pyranoside **8** (100 mg, 0.236 mmol) and trityl pyranoside **10**α/β (80 mg, 0.13 mmol) afforded *cis/trans* -2,5-THF-aldehydes **12c/t** as inseparable mixtures in yields of (104 mg, 89%) and (54 mg, 83%) respectively. The *c:t* ratios as determined by the integration of the ^{1}H NMR signals at δ 2.80 and 3.17 were 40:60 and 60:40. For **12c/t**: R_f = 0.30 (10% EtOAc:P.E.); ^{1}H NMR (C_6D_6) δ 1.40-2.20 (m, 6H), 2.80 (CH_2I-*cis*-2,5), 3.17 (CH_2I-*trans*-2,5), 3.34, 3.75, and 4.18, (all m, 6H), 4.20-4.60 (m, 4H), 7.20 (m, 10H), 9.25 (s, 1H); ^{13}C NMR (C_6D_6) δ 3.4 (CH_2I-*trans*-2,5), 8.0 (CH_2I-*cis*-2,5), 24.7, 24.8, 33.1, 33.6, 40.3, 40.5, 71.6, 72.3, 73.7, 73.8, 79.4, 80.0, 80.1, 82.1, 82.6, 83.6, 84.4, 121.4, 127.9, 128.4, 128.6, 128.8, 129.0, 139.0, 139.8, 200.8. HRMS (CI-NH_4) calcd for $C_{23}H_{28}O_4I$ (M+H)$^+$ 495.1032, found 495.1021.

***cis*--2,5-THF-alcohol 13c.** $NaBH_4$ (15 mg, 0.40 mmol) was added to a solution of the aldehyde **11c** (100 mg, 0.202 mmol) in ethanol (5 mL), under an atmosphere of argon at rt. The solution was stirred at this temperature for 10 min, then cooled to 0 °C and quenched by addition of 10% methanolic HCl to pH 7. The mixture was then filtered through a bed of celite and the filtrate concentrated under reduced pressure. Flash chromatography of the residue afforded THF-alcohol **13c** (95 mg, 95%): R_f = 0.65 (15% EtOAc:P.E.); ^{1}HNMR (C_6D_6) δ 1.5 (m, 5H), 2.05 (m, 1H), 3.18 (dd, 1H, J = 6.5, 9.5 Hz, CH_2I-*cis*-2,5), 3.3 (m, 3H), 3.50 (m, 1H), 3.70 (m, 3H), 4.1 (ABq, $\Delta\delta$ = 0.17 ppm, 2H, J = 11.6 Hz), 4.5 (ABq, $\Delta\delta$ = 0.17 ppm, 2H, J = 11.5 Hz), 7.2 (m, 10H); ^{13}C NMR (C_6D_6) 2.7 (CH_2I-*cis*-2,5), 28.7, 29.1, 33.3, 63.1, 71.8, 73.2, 79.3, 80.3, 81.8, 83.5, 128.5-129.2 (several lines), 138.7, 140.0. MS (CI) m/z 514 (M+NH_4^+), 497 (M+H^+). Anal. Calcd for $C_{23}H_{29}O_4I$: C, 55.65; H, 5.89. Found: C, 55.59; H, 5.91.

***cis/trans*-2,5-THF-alcohol 14c/t.** Treatment of aldehyde **12c/t** (100mg, 0.202 mmol), which was obtained from the iodoetherification of t-butyl pyranoside **8**α/β, under the $NaBH_4$ reduction procedure described for the preparation of **13c**, gave **14c/t** (93 mg, 93%). A *c:t* ratio of 40:60 was determined from the relative integrals of the signals at δ 2.9 and 3.22 ppm. For **12c/t**: R_f = 0.65 (15% EtOAc:P.E.); ^1H NMR (C_6D_6) δ 1.5 (m, 4H), 1.85 (m, 2H), 2.79 (CH_2I-*cis*-2,5), 2.90 (CH_2I-*cis*-2,5), 3.22 (CH_2I-*trans*-2,5-) and 3.30 (dd, J = 6.9, 9.8 Hz, dd, J = 5.2, 9.8 Hz, dd, J = 6.9, 9.3 Hz, and m, resp., 4H), 3.50 (m, 1H), 3.69 (m, 1H), 4.2 (m, 4H), 4.60 (m, 2H), 7.20 (m, 10H). ^{13}C NMR (C_6D_6) δ 3.5 (CH_2I-*trans*-2,5), 8.1 (CH_2I-*cis*-2,5), 28.7, 29.0, 29.4, 29.5, 32.8, 33.2, 63.0, 71.6, 72.3, 73.8, 73.9, 80.1, 80.9, 82.5, 83.0, 83.5, 83.7, 84.4, 128.1-129.2 (several lines), 139.1, 140.0. MS (CI) m/z 514 ($M+NH_4^+$), 497 ($M+H^+$). Anal. (mixture) Calcd for $C_{23}H_{29}O_4I$: C, 55.65; H, 5.89. Found: C, 55.59; H, 5.82.

Dihydroxyalkene 15. A mixture of **13c** (45mg, 0.091 mmol), freshly activated zinc dust (100 mg) and 95% ethanol (2 mL) was heated at reflux for 1 h. The mixture was cooled to rt, diluted with ether and filtered through a bed of celite. Evaporation of the filtrate under reduced pressure, followed by purification of the residue by flash chromatography afforded **15** (31 mg, 93): R_f = 0.40 (30% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.58-1.90 (m, 6H), 2.81 (d, 1H, J = 3.6 Hz), 3.40 (m, 1H), 3.60 (m, 1H), 4.1 (m, 1H), 4.5 (ABq, Δδ = 0.27 ppm, 2H, J = 11.7 Hz), 4.6 (m, 2H), 5.3 (m, 2H), 5.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 28.5, 37.7, 62.8, 68.9, 70.5, 71.9, 77.8, 81.8, 117.1, 127.6, 127.8, 128.4, 138.1, 138.2; HRMS (CI-NH_4) calcd for $C_{23}H_{31}O_4$ $(M+H)^+$ 371.2222, found 371.2208.

Dihydroxyalkene 16. Treatment of alcohol **14c/t** (50 mg, 0.10 mmol) under the conditions described for the preparation of **15**, afforded **16** (32 mg, 80%): R_f = 0.38 (30% EtOAc:P.E.); ^1H NMR ($CDCl_3$) δ 1.40-2.00 (m, 6H), 3.30 (q, 1H, J = 4.8 Hz), 3.55 (d, 2H, J = 5.1 Hz), 3.8 (q, 1H, J = 6.3 Hz), 3.98 (q, 1H, J = 6.6 Hz), 4.43 (ABq, Δδ = 0.27 ppm, 2H, J = 11.6 Hz), 4.53 (ABq, Δδ = 0.08 ppm, 2H, J = 11.5 Hz), 5.3 (m, 2H), 5.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.9, 27.0, 36.8, 64.2, 70.4, 72.8, 73.5, 80.0 80.7, 119.4, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 135.9, 136.5, 136.7; HRMS (CI-NH_4) calcd for $C_{23}H_{31}O_4$ $(M+H)^+$ 371.2222, found 371.2223.

Iodoetherification of Dihydroxyalkene 15. Application of the standard iodoetherification procedure to diol alkene **15** (31 mg, 0.084 mmol) afforded **13c/t** as an inseparable mixture (39 mg, 94%). The major component was identical to previously obtained **13c** (TLC, ^1H and ^{13}C NMR). A *cis:trans* -2,5 ratio of 65:35 was determined from comparison of the proton integrals at δ 3.19 and 2.90 ppm respectively. For **13c/t**: R_f = 0.65

(30% EtOAc:P.E.); ^{1}H NMR (C_6D_6) δ 1.50 (m, 4H), 1.90 (m, 1H), 2.05 (m, 1H), 2.90 (CH_2I-*trans*-2,5) and 3.19 (CH_2I-*cis*-2,5) and 3.30 (ABq, Δδ = 0.02 ppm, J = 10.1 Hz, dd, 6.5, 9.5 Hz and m, resp., 4H), 3.55, 3.70, 3.95 (all m, 4H), 4.20 (m, 2H), 4.55 (m, 2H), 7.2 (m, 10H); ^{13}C NMR (C_6D_6) δ 2.7 (CH_2I-*cis*-2,5), 9.0 (CH_2I-*trans*-2,5), 28.5, 28.7, 29.1, 29.2, 33.3, 33.9, 63.1, 71.8, 72.2, 73.2, 73.4, 79.3, 80.3, 80.7, 81.7, 81.8, 82.7, 83.5, 83.7, 127.5-129.6 (several lines), 138.7, 140.0. MS (CI) m/z 514 ($M+NH_4^+$), 497 ($M+H^+$).

Iodoetherification of Dihydroxyalkene 16. Application of the standard iodoetherification procedure to diol alkene **16** (30 mg, 0.081 mmol) afforded **14c/t** as an inseparable mixture (37 mg, 91%). The mixture showed identical TLC, ^{1}H and ^{13}CNMR to previously obtained **14c/t**. A *cis*:*trans*-2,5 ratio of 80:20 was determined by comparisons of the proton integrals at δ 2.90 and 3.22 ppm respectively.

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