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PYRANOSIDE ALKENE TEMPLATES FOR THE SYNTHESIS OF *CIS*-2,5-DISUBSTITUTED TETRAHYDROFURAN SUBUNITS OF THE ACETOGENINS

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ABSTRACT

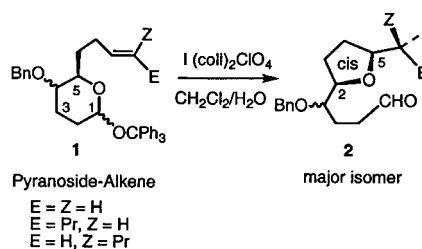
The iodoetherification reaction of *t*-butyl and trityl glycosides of C6 allylated-2,3-dideoxy-D-*erythro*- and D-*threo*-pyranosides was examined as part of a model study aimed at the synthesis of the 2,5-disubstituted tetrahydrofuran subunits found in the acetogenin group of natural products. In general, the *t*-butyl glycosides gave moderate, and the trityl derivatives, excellent stereoselectivity for the *cis* THF product.

Key Words: 2,5-disubstituted tetrahydrofuran; Iodoetherification; Acetogenins

INTRODUCTION

The broad spectrum pharmacological activity of the tetrahydrofuran (THF) containing acetogenins^[1–4] has resulted in considerable interest in their synthesis.^[5–18] We have reported that C6 allylated pyranosides (e.g., **1**) are practical templates for *cis*-2,5-disubstituted THF motifs (e.g., **2**) found in the acetogenins^[19–22] (Scheme 1). The

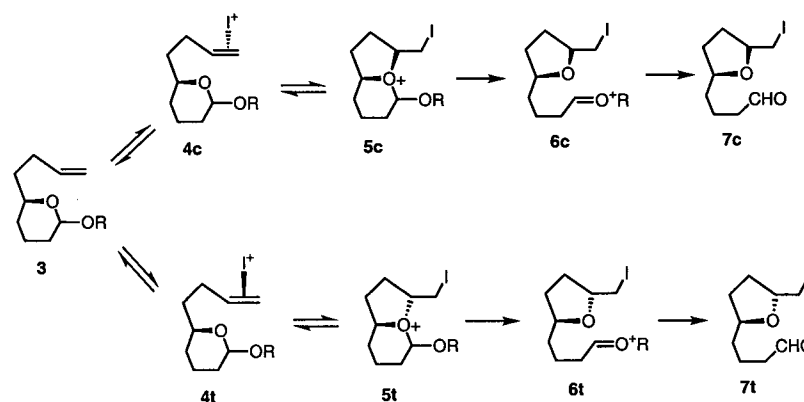
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Scheme 1. Iodoetherification of C6 allylated pyranosides.

key reaction in this methodology is an iodoetherification involving the ring oxygen of the pyranoside on the pendant alkene. It was found that the structure of the aglycone substituent affected the *cis/trans* selectivity, with optimal results being obtained for trityl glycosides. Herein, we describe the details of this investigation.

This methodology derives from the well known electrophilic etherification of 4-hydroxyalkenes.^[23,24] This reaction has been widely used for rapid entry into a variety of complex THF frameworks. However, a drawback is the uncertainty of the stereochemical outcome in highly substituted systems. We speculated that it should be possible to control stereoselectivity by performing the reaction on conformationally restrained templates. Saccharide alkenes are attractive because of their easy availability and the highly functionalized nature of the reaction products. Early experiments indicated that a variety of allylated furanosides and pyranosides were converted to iodo-THF-aldehydes in high yield, but with a variable degree of THF stereoselectivity.^[25] Our working mechanistic model (Scheme 2) presumes initial reaction of the saccharide alkene **3** with iodonium ion to generate diastereomeric iodonium ions or charge transfer complexes **4c/t**, which are attacked by the ring oxygen to give THF-oxonium ions **5c/t**.^[26–30] Fragmentation of **5c/t** leads to oxocarbenium ions **6c/t**, which in the presence of water, leads to aldehydes **7c/t**. We surmised that variation of the size of the aglycone should alter the stereoselectivity and in order to test this hypothesis, evaluated substrates that could be used as precursors for the THF containing acetogenins.



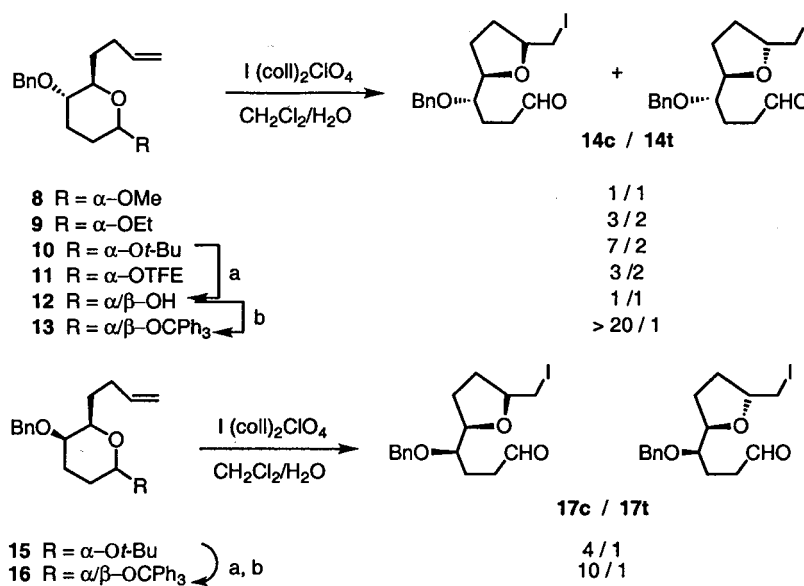
Scheme 2. Proposed mechanism for iodoetherification of C6 allylated pyranosides.

RESULTS AND DISCUSSION

Alkene Synthesis and Iodoetherification Reactions

The iodoetherification reactions of 2,3-dideoxy-D-8-enopyranosides of *erythro* or *threo* configuration (corresponding to the stereochemical motifs in the acetogenins), with terminal, *E* or *Z* alkenes, were examined. The reactions of a set of *erythro*-terminal alkene templates containing different aglycones were first investigated in order to identify any general trends between aglycone structure and THF stereo-selectivity. Pyranoside alkenes **8–11** (R = OMe, OEt, O-*t*-Bu, O-TFE) were obtained by treatment of the corresponding 6-*O*-tosylate precursor with allylmagnesium bromide.^[22] (Scheme 3). The tosylates were prepared via a straightforward sequence of reactions on the 2,3-eno-pyranoside derived from the Ferrier reaction of tri-*O*-acetyl-D-glucal and the requisite alcohol.^[31,32] The trityl glycoside mixture **13** was prepared as an inseparable mixture of anomers (ca. $\alpha/\beta = 3/7$). This material was obtained by acid hydrolysis of the *t*-butyl derivative **10**, followed by silver triflate mediated tritylation of the resulting lactol **12**.

Iodoetherification reactions were performed in wet dichloromethane with iodonium dicollidine perchlorate (IDCP).^[33] The *cis* and *trans* THF products were separated by chromatography^[34] and their stereochemistry assigned by analysis of the ¹³C NMR (vide infra). There was a noticeable increase in the level of *cis* selectivity as the size of the aglycone was increased. Highest selectivity was obtained with the α/β mixture of trityl glycosides **13**. The iodoetherification of lactol **12** was also examined in order to



(a) aq HCl:THF; (b) Ph₃CCl, AgOTf, collidine, CH₂Cl₂, MS

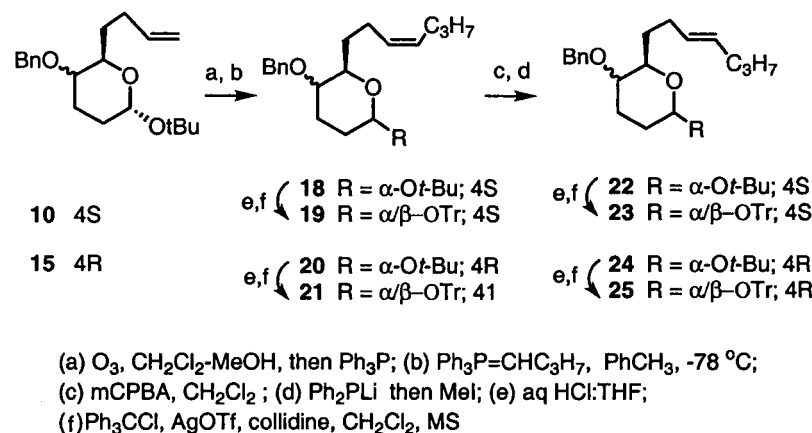
Scheme 3. Iodoetherification of terminal alkenes.

address the possibility that the THF product from **13** might be arising through **12** as a result of initial hydrolysis of the labile trityl group. The lack of any selectivity observed for **12** indicates that the intermediate formation of **12** was not a major factor in the iodoetherification of **13**. It is also of interest to note that increasing the electronegativity of the aglycone (cf. **11**) decreased reactivity, but had no noticeable effect on stereoselectivity.

The reactions of the *t*-butyl and trityl glycosides **15** and **16** in the *threo* series were next examined, in order to determine whether the apparent *cis*-directing effect of bulky aglycones is affected by changing the configuration at the C4 position of the pyranoside template. Compound **15** was obtained by Mitsunobu inversion at the C4 position of a precursor in the *erythro* series.^[22] Indeed, a similar trend was observed, the mixture of trityl glycosides **16** showing an appreciable increase in the level of *cis* stereoselectivity over the *t*-butyl derivative **15**.

The effect of alkene substitution was next assessed by evaluating the reactions of *Z* and *E* disubstituted alkenes of *t*-butyl- and trityl-2,3-dideoxypyranosides in the *erythro* and *threo* series. The *t*-butyl-*Z*-alkenes **18** and **20** were obtained from the Wittig reaction of butylidenetriphenylphosphorane and the aldehydes derived from the ozonolysis of terminal alkenes **10** and **15**, respectively (Scheme 4). The corresponding *E* isomers **22** and **24** were obtained from the *Z* derivatives **18** and **20** through the Vedejs isomerization protocol.^[35] The isomer purity of the *Z* and *E* compounds was determined to be greater than 95% as judged from NMR. The stereochemistry of the *Z* and *E* alkenes was established by comparison of the ¹³C chemical shifts. The allylic carbons for the *Z* isomer resonate upfield relative to those of the *E* isomer (e.g. **18**: δ 31.8 and 33.9; **22**: δ 33.8 and 35.6).^[36,37]

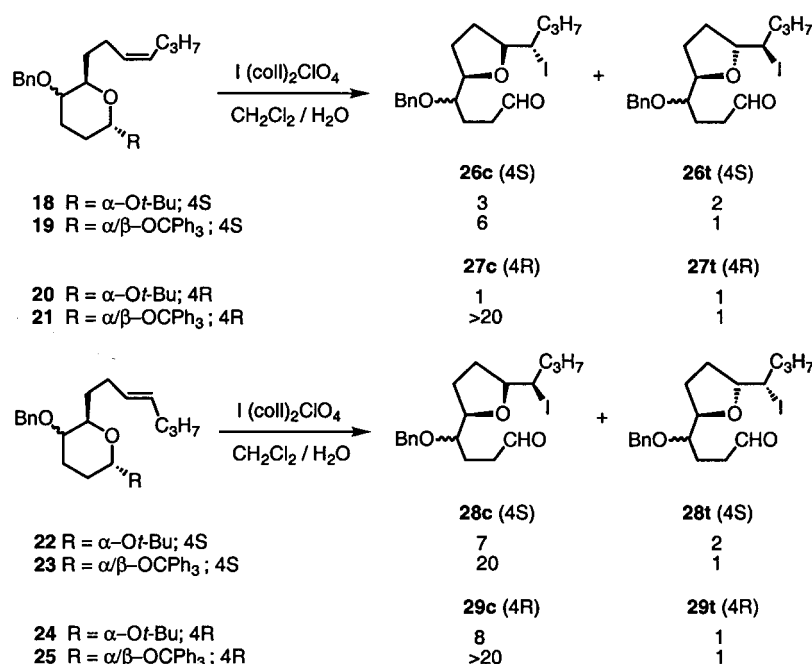
The trityl glycoside mixtures **19**, **21**, **23** and **25** were prepared from the respective *t*-butyl precursors as described earlier. Treatment of alkenes **18**–**25** under the standard iodoetherification conditions led to similar results as observed for the terminal alkenes, with the *t*-butyl systems showing low to moderate *cis* selectivity, and the trityl cases giving appreciably higher selectivity ranging from 6:1 to greater than 20:1 (Scheme 5).



Scheme 4. Synthesis of Z- and E-alkenes.

PYRANOSIDE ALKENE TEMPLATES

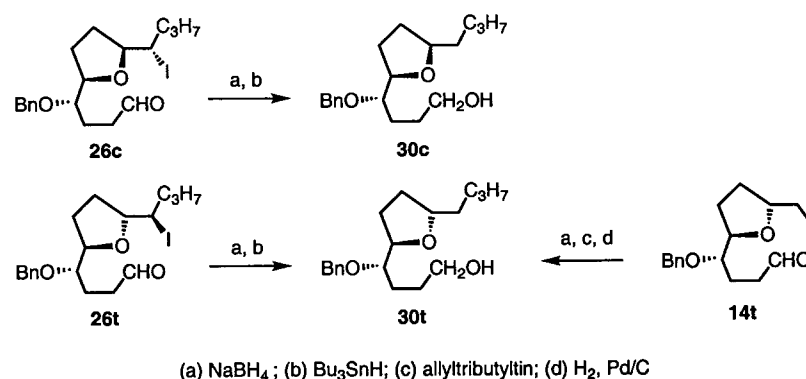
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Scheme 5. Iodoetherification Z- and E-alkenes.

Stereochemical Assignment

In the absence of any helpful NOE data, the stereochemistry of the THF products was deduced by comparison of the ¹³C resonances of the methylene carbons of the THF ring for corresponding pairs of *cis* and *trans* isomers. These carbons were assigned through HSQC experiments and by comparison with data for related THFs.^[38,39] We had previously shown for pairs of primary iodo-THFs analogous to **14c/t**, that the methylene carbons in the *trans* isomer are downfield relative to those of the *cis* derivative.^[25] This assignment was confirmed by conversion of the isomers to known THFs. We have also observed this trend for secondary iodo THFs related to **26c/t–29c/t**.^[40–42] In these cases, stereochemistry was independently assigned on the basis of NOE data and conversion to known compounds. This correlation between chemical shift and stereochemistry appears to be general for other classes of 2,5-disubstituted THFs.^[38,39] Additional support for our stereochemical assignments came from the correlation of the so assigned primary and secondary iodides **14t** and **26t** through a central THF derivative **30t** (Scheme 6). Iodide **26t** was transformed to **30t** via Bu₃SnH reduction of the derived alcohol. For comparison of NMR data, **30c** was obtained in a similar fashion from **24c**. Compound **14t** was converted to **30t** via a three step sequence involving NaBH₄ reduction of the aldehyde, radical allylation of the iodide and hydrogenation of the resulting alkene. The relative configuration at the iodidated carbon was inferred from the established *anti* addition in the haloetherification of alkenes.



Scheme 6. Stereochemical correlations for more substituted THFs.

Our tentative transition state model for the high *cis* stereoselectivity that is observed for both α - and β -trityl pyranosides, assumes that the pyranose ring adopts a chair-like conformation^[43] with a preferred pseudoequatorial (vs.pseudoaxial) approach of the iodonium ion onto the ring oxygen (Figure 1). A half-chair like orientation is assumed for the five atoms of the forming THF ring.^[29,30] Two diastereomeric structures of types **A** and **B** corresponding to an “alkene up” or “alkene down” orientation, are possible. The relative stabilities of **A** and **B** are also likely to be highly dependent on the conformation with respect to the aglyconic bond. An interesting speculation is that the reactive conformation for both α and β glycosides is a rotamer which is stabilized by the exo-anomeric effect,^[44] e.g., **A- α /B- α** , and **A- β /B- β** . These rotamers are also expected to make the major contribution to the basicity of the ring oxygen.^[45–47] For both anomers transition state **B** places the iodinated branch of the THF closer to the aglycone substituent, and this leads to an appreciable destabilizing interaction for sterically demanding aglycones such as trityl, resulting in a preference for **A**, and consequently the *cis* THF.

It is also possible that the results obtained with the trityl glycosides represent a higher degree of kinetic control. It is likely, due to steric crowding, that the bulky aglycone induces an increased rate of fragmentation of the THF-oxonium ions **5c** and **5t** to THF products (relative to their equilibration). Alternatively, it is conceivable that the THF oxonium ion intermediate **5** could be more rapidly transformed to the THF-aldehyde **7** via a mechanism involving formation of an incipient trityl cation.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Flash column chromatography (FCC) was performed using Kieselgel 60 (230–400 mesh, E. Merck) and employed a stepwise solvent polarity gradient, correlated with TLC mobility. Unless otherwise stated, ¹H and ¹³C NMR spectra were recorded at 300 and 75.5 MHz respectively. Assignments for selected nuclei were determined from ¹HCOSY and

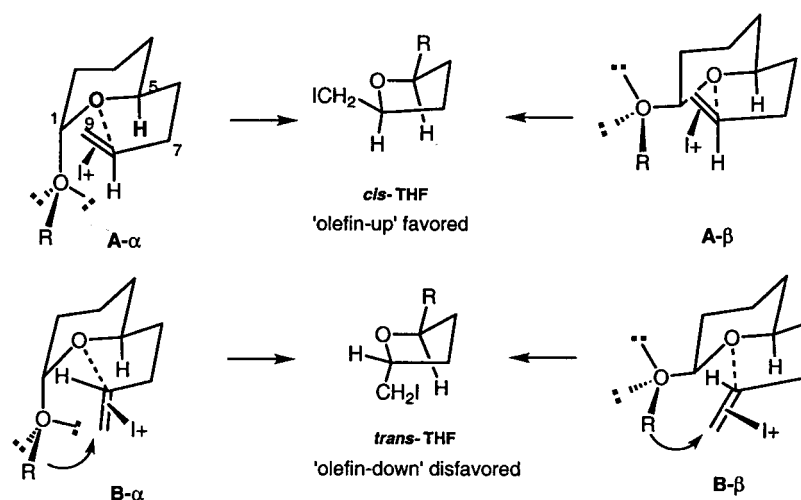


Figure 1. Model for stereochemistry of THF formation.

HSQC experiments, and by spectral correlation for analogous compounds (Tables 1–4). Elemental analysis were performed by Schwarzkopf Microanalysis Laboratory. High resolution mass spectroscopy (HRMS) was carried out at the mass spectrometry facility of the University of Illinois at Urbana-Champaign. The general procedure for preparation of the C6-allylated monosaccharides from tri-*O*-acetyl-D-glucal, and the synthesis of **15**, has been previously described.^[22]

Terminal Alkenes

Methyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α -D-erythro-non-8-enopyranoside (8). $R_f=0.20$ (5% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 1.40–2.40 (m, 8H), 3.20 (m, 1H), 3.40 (s, 3H), 3.62 (t, $J=7.2$ Hz, 1H), 4.50–4.80 (m, 3H), 5.06 (m, 2H), 5.92 (m, 1H), 7.40 (m, 5H).

Ethyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α -D-erythro-non-8-enopyranoside (9). $R_f=0.20$ (5% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 1.25 (t, $J=7.2$ Hz, 3H), 1.40–2.40 (m, 8H), 3.20 (m, 1H), 3.45 (m, 1H), 3.74 (m, 2H), 4.58 (ABq, $\Delta\delta=0.19$ ppm, $J=12$ Hz, 2H), 4.80 (d, $J=2.5$ Hz, 1H), 5.06 (m, 2H), 5.90 (m, 1H), 7.40 (m, 5H).

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α -D-erythro-non-8-enopyranoside (10).** $R_f=0.40$ (5% EtOAc:petroleum ether); $[\alpha]_D^{25}$ 140° (c 2.6, EtOH); IR (neat) 1640, 910, 735 cm^{-1} ; ^1H NMR (C_6D_6) δ 1.15 (s, 9H), 1.45–2.60 (m, 8H), 3.07 (ddd, $J=4.6, 9.4, 11.6$ Hz, 1H), 4.05 (dt, $J=1.9, 9.0$ Hz, 1H), 4.36 (ABq, $\Delta\delta=0.28$ ppm, 2H, $J=11.5$ Hz), 5.02 (bs, 1H), 5.06 (m, 2H), 5.84 (m, 1H), 7.00–7.30 (m, 5H); ^{13}C NMR (C_6D_6) δ 25.0, 28.9, 31.2, 32.2, 33.4, 71.1, 71.9, 74.5, 78.7, 91.5, 115.3, 128.7, 128.8, 128.9, 140.5.

Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.50. Found: C, 75.56; H, 9.29.

Table 1. Selected ^1H NMR Data for *t*-Butyl and Trityl Pyranoside Alkenes

Pyranoside Alkene	H1	H4, H5
<i>t</i> -Butyl-erythro 10	5.02 (bs, H1)	4.05 (dt, 1.9, 9.0, H5), 3.07 (ddd, 4.6, 9.4, 11.6, H4)
Trityl-erythro 13α/β	5.25 (bs, H1 α), 4.45 (dd, 1.8, 8.9, H1 β)	4.18 (bt, 10.0, 5 α), 3.02 (m, H4 α / β , H5 β)
<i>t</i> -Butyl-threo 15	5.14 (bs, H1)	3.95 (bt, 9.0, H5), 3.10 (bs, H4)
Trityl-threo 16α/β	5.35 (bs, H1 α), 4.56 (dd, 1.9, 9.3, H1 β)	4.03 (m, H5 α), 3.18 (bs, H4 α), 2.86 (m, H5 β), 2.78 (bs, H4 β)
<i>t</i> -Butyl- <i>Z</i> -erythro 18	5.08 (bs, H1)	4.17 (bt, 9.1, H5), 3.18 (dt, 4.0, 9.0, H4)
Trityl- <i>Z</i> -erythro 19α/β	5.18 (bs, H1 α), 4.36 (dd, 2.1, 9.1, H1 β)	4.16 (dt, 2.0, 10.0, 5 α), 3.00 (m, H4 α / β , H5 β)
<i>t</i> -Butyl- <i>Z</i> -threo 20	5.21 (bs, H1)	4.07 (bt, 9.1, H5), 3.21 (bs, H4)
Trityl- <i>Z</i> -threo 21α/β	5.28 (bs, H1 α), 4.42 (dd, 1.9, 9.5, H1 β)	4.00 (t, 6.5, H5 α), 3.16 (bs, H4 α), 2.82 (t, 5.6, H5 β), 2.75 (bs, H4 β)
<i>t</i> -Butyl- <i>E</i> -erythro 22	5.10 (bs, H1)	4.13 (bt, 10.0, H5), 3.15 (dt, 5.0, 10.0, H4)
Trityl- <i>E</i> -erythro 23α/β	5.18 (bs, H1 α), 4.36 (dd, 2.1, 9.1, H1 β)	4.16 (dt, 2.0, 10.0, 5 α), 3.00 (m, H4 α / β , H5 β)
<i>t</i> -Butyl- <i>E</i> -threo 24	5.21 (bs, H1)	4.05 (bt, 9.0, H5), 3.22 (bs, H4)
Trityl- <i>E</i> -threo 25α/β	5.28 (bs, H1 α), 4.42 (dd, 1.9, 9.5, H1 β)	4.00 (t, 6.5 H5 α), 3.16 (bs, H4 α), 2.82 (t, 5.6, H5 β), 2.75 (bs, H4 β)



PYRANOSIDE ALKENE TEMPLATES

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Table 2. Selected ^{13}C NMR Data for *t*-Butyl and Trityl Pyranoside Alkenes

Pyranoside Alkene	C1	CMe ₃ /CPh ₃	CH ₂ Ph, C4, C5 ^a
<i>t</i> -Butyl-terminal-erythro 10	91.5	74.5	71.1, 71.9, 78.7
Trityl-terminal-erythro 13 α	93.1	88.6	71.3, 73.1, 78.4
Trityl-terminal-erythro 13 β	98.1	88.8	71.4, 77.4, 78.5
<i>t</i> -Butyl-terminal-threo 15	91.8	74.0	70.5, 71.3, 74.2
Trityl-terminal-threo 16 α	93.8	88.3	71.4, 72.0, 73.8
Trityl-terminal-threo 16 β	98.7	88.8	71.6, 73.1, 78.0
<i>t</i> -Butyl-Z-erythro 18	91.2	74.2	71.1, 72.1, 78.7
Trityl-Z-erythro 19 α	92.9	88.2	71.1, 73.2, 78.2
Trityl-Z-erythro 19 β	98.1	88.5	71.1, 77.2, 78.7
<i>t</i> -Butyl-Z-threo 20	91.8	74.0	70.7, 71.2, 73.9
Trityl-Z-threo 21 α	94.0	88.8	71.5, 72.5, 73.9
Trityl-Z-threo 21 β	99.0	89.0	71.7, 73.1, 78.5
<i>t</i> -Butyl-E-erythro 22	91.1	73.8	71.0, 71.8, 78.7
Trityl-E-erythro 23 α	93.2	88.6	71.3, 73.1, 78.5
Trityl-E-erythro 23 β	98.1	88.8	71.4, 77.5, 78.6
<i>t</i> -Butyl-E-threo 24	91.9	73.9	70.6, 71.2, 74.2
Trityl-E-threo 25 α	94.0	88.9	71.5, 72.2, 73.6
Trityl-E-threo 25 α	99.0	89.0	71.6, 73.1, 78.3

^aAssignments for CH₂Ph, C4, C5 may be interchanged.**Table 3.** Selected ^1H NMR Data for THF-Iodides

THF-Iodide	H1	H4, H5, H8, H9 ^a
14c	9.40 (s)	3.62 (m, 2H), 3.32 (q, 6.2, 1H), 2.88 (dd, 5.1, 9.9, 1H), 2.82 (dd, 6.2, 9.9, 1H)
14t	9.36 (bs)	3.82 (m, 1H), 3.74 (m, 1H), 3.30 (m, 1H), 2.89 (dd, 4.8, 9.9, 1H), 2.83 (dd, 6.6, 9.0, 1H)
17c	9.33 (s)	3.65 (m, 2H), 3.10 (m, 1H), 2.80 (m, 2H)
17t	9.33 (s)	3.85 (m, 1H), 3.72 (m, 1H), 3.05 (m, 1H), 2.80 (m, 2H)
26c	9.40 (bs)	3.88 (m, 1H), 3.68 (m, 1H), 3.46 (q, 6.2, 1H), 3.32 (m, 1H)
26t	9.37 (bs)	3.95 (m, 1H), 3.92 (m, 1H), 3.55 (m, 1H), 3.36 (dt, 4.8, 7.7, 1H)
27c	9.35 (s)	3.84 (m, 1H), 3.72 (m, 1H), 3.32 (m, 2H)
27t	9.35 (s)	3.98 (m, 1H), 3.60 (m, 1H), 3.30 (m, 1H), 3.09 (m, 1H)
28c	9.41 (bs)	4.04 (q, 5.7, 1H), 3.72 (q, 5.3, 1H), 3.55 (q, 6.6, 1H), 3.34 (q, 5.5, 1H),
28t	9.38 (s)	4.03 (m, 1H), 3.90 (m, 1H), 3.67 (m, 1H), 3.33 (m, 1H)
29c	9.32 (s)	3.99 (m, 1H), 3.74 (q, 7.5, 1H), 3.58 (q, 7.5, 1H), 3.15 (m, 1H)
29t	9.32 (s)	3.95 (m, 2H), 3.71 (m, 1H), 3.05 (m, 1H)

^aAssignments for H4, H5, H8, H9 may be interchanged.

Table 4. Selected ^{13}C NMR Data for THF-Iodides

THF-Iodide	C1	C4, C5, C8 ^a	PhCH ₂	C9	C6, C7
14c	200.7	83.0, 79.9, 79.2	73.4	10.6	27.3, 31.9
14t	200.7	82.8, 80.0, 79.0	73.4	11.5	28.0, 33.1
17c	200.9	84.1, 80.9, 79.3	73.5	10.9	28.2, 31.5
17t	200.9	84.1, 80.9, 79.2	73.4	11.2	29.2, 33.9
26c	200.9	82.9, 82.3, 79.8	73.2	42.5	27.8, 31.2
26t	200.7	83.2, 83.0, 80.0	73.4	43.5	28.0, 32.3
27c	200.9	83.9, 82.9, 81.0	73.7	43.0	28.5, 31.0
27t	200.9	83.6, 83.2, 81.0	73.4	43.2	29.3, 32.0
28c	200.5	83.3, 82.9, 80.1	73.2	42.9	27.3, 32.5
28t	200.3	83.1 (2C), 80.1	73.4	44.4	27.9, 33.8
29c	200.8	84.1, 83.3, 80.9	73.6	43.1	28.0, 32.2
29t	200.6	83.6, 83.3, 81.2	73.4	44.1	29.1, 33.8

^aAssignments for C4, C5 and C8 may be interchanged.

Trifluoroethyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α -D-erythro-non-8-enopyranoside (11). $R_f=0.40$ (5% EtOAc:petroleum ether); IR (neat) 1641 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.65 (m, 1H), 1.90 (m, 2H), 2.05–2.50 (m, 5H), 3.30 (dt, $J=5.5, 11.0\text{ Hz}$, 1H), 3.78 (dt, $J=2.7, 9.0\text{ Hz}$, 1H), 4.0 (m, 2H), 4.70 (ABq, $\Delta\delta=0.20\text{ ppm}$, $J=12.0\text{ Hz}$, 2H), 4.97 (bs, 1H), 5.15 (m, 2H), 5.98 (m, 1H), 7.50 (m, 5H). ^{13}C NMR (CDCl_3) δ 23.6, 28.7, 29.7, 31.2, 63.8 (q, $J_{\text{CCF}}=34.4\text{ Hz}$), 70.7, 71.8, 76.8, 96.7, 114.7, 124.3 (q, $J_{\text{CF}}=280\text{ Hz}$), 127.8, 127.9, 128.5, 138.4, 138.7.

Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{O}_3\text{F}_3$: C, 63.04; H, 7.02. Found: C, 62.78; H, 6.70.

4-*O*-Benzyl-2,3,6,7,8,9-hexadeoxy- α/β -D-erythro-non-8-enopyranose (12). To a solution of **10** (100 mg, 0.31 mmol) in THF (3 mL) was added 0.5N HCl (1 mL). The solution was stirred for 5 h at rt, then neutralized with NaHCO_3 , and concentrated *in vacuo*. FCC gave a mixture of pyranose anomers **12** (77 mg, 94%): $R_f=0.30$ (10% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 1.40–2.30 (m, 8H), 2.95 (bs, ca. 0.5H, OH), 3.16 (m, 1H), 3.35 (m, ca. 0.5H), 3.60 (bs, ca. 0.5H, OH), 3.88 (m, ca. 0.5H), 4.48 (m, 1H), 4.62 (m, 1H), 4.78 (m, ca. 0.5H, H1 β -anomer), 5.00 (m, 2H), 5.20 (bs, ca. 0.5H, H1 α -anomer), 5.90 (m, 1H), 7.15–7.40 (m, 5H); ^{13}C NMR (CDCl_3) δ 23.5, 27.7, 29.5, 29.8, 31.5, 31.6, 32.1, 70.8, 71.3, 76.6, 78.1, 91.0 (C1 α -anomer), 96.1 (C1 β -anomer), 114.6, 127.7, 127.8, 128.5, 138.7, 138.9.

Trityl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α/β -D-erythro-non-8-enopyranoside (13). Lactol **12** (50 mg, 0.19 mmol), anhydrous 2,4,6-collidine (0.7 mmol) and freshly activated 4 Å molecular sieves in dry CH_2Cl_2 (2 mL) was stirred for 15 min at rt. Trityl chloride (167 mg, 0.60 mmol) and silver trifluoromethane sulfonate (154 mg, 0.6 mmol) were then added. The solution was stirred for 10 min., then poured into 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with ether. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*. FCC of the residue provided **11** as a mixture of α/β anomers (73 mg, 76%, α/β ca. 3/7): $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 1.46–2.20 (m, 8H), 3.02 (m, ca. 1.7H), 4.18 (b t, $J=10\text{ Hz}$, ca. 0.3H), 4.25 (ABq,

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$\Delta\delta=0.20$ ppm, $J=11$ Hz, ca. 1.7H), 4.36 (ABq, $\Delta\delta=0.24$ ppm, $J=11$ Hz, ca. 0.6H), 4.45 (dd, $J=1.8, 8.9$ Hz, ca. 0.7H, H1 β -anomer), 5.00–5.18 (m, 2H), 5.25 (bs, ca. 0.3H, H1 α -anomer), 5.86 (m, 1H), 7.04–7.80 (m, 20H); ^{13}C NMR (C_6D_6), β anomer: δ 28.7, 30.2, 31.9, 32.7, 71.4, 77.4, 78.5, 88.8, 98.1 (C1), 114.7, 127.0–130.0 (several lines buried under C_6D_6 triplet), 139.7, 140.0, 145.9. Selected signals for α anomer: δ 71.3, 73.1, 78.4, 88.6, 93.1 (C1); HRMS(CI- CH_4) calcd for $\text{C}_{35}\text{H}_{37}\text{O}_3(\text{M}+\text{H})$ 505.2743, found 505.2741.

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy- α -D-threo-non-8-enopyranoside (15).**^[22] $R_f=0.40$ (5% EtOAc:petroleum ether); IR (neat) 1651 cm^{-1} ; ^1H NMR (C_6D_6) δ 1.21 (s, 9H), 1.50–2.30 (m, 8H), 3.10 (bs, 1H), 3.95 (m, 1H), 4.30 (ABq, $\Delta\delta=0.30$ ppm, $J=12$ Hz, 2H), 5.04 (m, 2H), 5.14 (bs, 1H), 5.82 (m, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (C_6D_6) δ 21.9, 26.9, 29.5, 31.1, 32.1, 70.5, 71.3, 74.0, 74.2, 91.8, 114.9, 127.9, 128.1, 128.6, 128.8, 139.7.

Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.62.

Trityl 4-*O*-benzyl-2,3-dideoxy- α/β -D-threo-non-8-enopyranoside (16) *t*-Butyl pyranoside **15** was subjected to the two-step hydrolysis-tritylation sequence that was used for **13**. An inseparable mixture of α/β trityl pyranosides **16** (65%, ca. ratio 1:1) was obtained: $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 1.15–2.25 (m, 8H), 2.78 (bs, ca. 0.5H), 2.86 (m, ca. 0.5H), 3.18 (bs, ca. 0.5H), 4.03 (m, ca. 0.5H), 4.13 (m, 1H), 4.48 (m, 1H), 4.56 (dd, $J=1.9, 9.3$ Hz, ca. 0.5H, H1 β -anomer), 5.08 (m, 2H), 5.35 (bs, ca. 0.5H, H1 α -anomer), 5.82 (m, 1H), 7.05–7.75 (m, 20H); ^{13}C NMR(C_6D_6), β anomer: δ 26.6, 27.7, 30.7, 31.8, 71.6, 73.1, 78.0, 88.8, 98.7 (C1), 114.7, 127.0–130.0 (several lines buried under C_6D_6 triplet), 139.8, 146.1; α anomer: δ 22.4, 26.2, 30.6, 31.6, 71.4, 72.0, 73.8, 88.3, 93.8 (C1), 114.7, 127.0–130.0 (several lines buried under C_6D_6 triplet), 139.7, 140.0, 146.1; HRMS(CI- CH_4) calcd for $\text{C}_{35}\text{H}_{37}\text{O}_3$ (M+H) 505.2743, found 505.2762.

Z and E Alkenes

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α -D-erythro-dodeca-8Z-enopyranoside (18).** Z-alkene **18** (49%) was prepared from terminal alkene **10**, according to the general procedure described for Z-alkene **20** (see later). $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.92 (t, $J=7.4$ Hz, 3H), 1.25 (s, 9H), 1.30–2.60 (m, 12H), 3.18 (dt, $J=4.0, 9.0$ Hz, 1H), 4.17 (bt, $J=9.1$ Hz, 1H), 4.45 (ABq, $\Delta\delta=0.27$ ppm, $J=11$.Hz, 2H), 5.08 (bs, 1H), 5.52 (m, 1H), 5.68 (m, 1H), 7.00–7.40 (m, 5H); ^{13}C NMR (C_6D_6) δ 14.4, 23.7, 24.5, 24.8, 29.4, 30.2, 31.8, 33.9, 71.1, 72.1, 74.2, 78.7, 91.2, 127.0–130.0 (several lines buried under C_6D_6 triplet), 130.2, 131.2, 140.2; MS (ES) m/z 378.3 (M+ NH_4).

Trityl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α/β -D-erythro-dodeca-8Z-enopyranoside (19). *t*-Butyl pyranoside **18** was subjected to the two-step hydrolysis-tritylation sequence that was used for **13**. An inseparable mixture of α/β trityl pyranosides **19** (68%, ca ratio 2:3) was obtained: $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.90, 0.92 (overlapping t, $J=7.0$ Hz, 3H), 1.25–2.20 (m,

12H), 3.00 (m, ca. 1.6H), 4.16 (dt, $J=2.0, 10.0$ Hz, ca. 0.4H), 4.18 (ABq, $\Delta\delta=0.19$ ppm, $J=11.0$ Hz, ca. 1.2H), 4.36 (ABq, $\Delta\delta=0.24$ ppm, $J=11.0$ Hz, ca. 0.8H), 4.36 (dd, $J=2.1, 9.1$ Hz, ca. 0.6H, H1 β -anomer), 5.18 (bs, ca. 0.4H, H1 α -anomer), 5.44 (m, 2H), 7.03–7.69 (m, 5H); ^{13}C NMR (C_6D_6), β anomer: δ 14.4, 23.6, 23.9, 28.5, 30.0, 31.7, 33.3, 71.1, 77.2, 78.7, 88.5, 98.1, 127.0–132.0 (several lines overlapped by C_6D_6 triplet), 139.5, 146.2; selected signals for α anomer: δ 71.1, 73.2, 78.2, 88.2, 92.9 (C1).

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α -D-*threo*-dodeca-8Z-enopyranoside (20).** The terminal alkene **15** (555 mg, 1.66 mmol) was dissolved in 5/1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10 mL) and cooled to -78°C . Ozone was bubbled through the solution and the reaction was monitored by TLC. Upon complete disappearance of the starting material, the solution was purged with argon and warmed to rt. MeOH (50 mL) and triphenylphosphine (652 mg, 2.49 mmol) were then added and stirring continued for 1 h. The solvent was removed under reduced pressure and the residue was purified by FCC to provide the aldehyde derivative (447 mg, 80%): $R_f=0.40$ (10% EtOAc:petroleum ether); $[\alpha]_D^{23}=+128^\circ$ (c 0.38, CH_2Cl_2); IR (neat) 2943, 1715 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.26 (s, 9H), 1.85 (m, 3H), 2.12 (m, 2H), 2.40 (m, 1H), 2.60 (t, $J=6.1$ Hz, 2H), 3.30 (m, 1H), 3.72 (dt, $J=2.6, 9.1$ Hz, 1H), 3.95 (m, 2H), 4.67 (ABq, $\Delta\delta=58.2$ Hz, $J=11.7$ Hz, 2H), 4.91 (s, 1H), 7.46 (m, 5H), 9.84 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.5, 24.9, 26.5, 29.51, 40.9, 70.0, 71.3, 73.5, 74.5, 91.9, 126.0–128.0 (several lines overlapped by C_6D_6 triplet), 139.1, 203.2.

Sodium bis(trimethylsilyl) amide (4.69 mmol, 4.69 mL of 1M solution in hexane) was added to a suspension of *n*-butyl triphenylphosphonium bromide (1.87 g, 4.69 mmol) in dry toluene (30 mL) at rt under an argon atmosphere. The yellow-orange suspension were stirred for 1 h at rt then cooled to -78°C . At that time, an anhydrous solution of the aldehyde from the previous step (500 mg, 1.56 mmol), in toluene (15 mL) was added dropwise to the solution of the ylide. The reaction was stirred at -78°C for 15 min, warmed to rt and diluted with ether. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by FCC to afford the Z-alkene **20**. (376 mg, 67%): $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.92 (t, $J=7.3$ Hz, 3H), 1.35–2.50 (m, 12H), 1.27 (s, 9H), 3.21 (bs, 1H), 4.07 (bt, $J=9.1$ Hz, 1H), 4.36 (ABq, $\Delta\delta=0.29$ ppm, $J=11.9$ Hz, 2H), 5.21 (s, 1H), 5.50 (m, 1H), 5.60 (m, 1H), 7.10–7.50 (m, 5H); ^{13}C NMR (C_6D_6) δ 14.3, 21.8, 23.6, 24.5, 26.8, 29.4, 30.1, 32.8, 70.7, 71.2, 73.9, 74.0, 91.8, 127.9, 128.8, 130.3, 130.8, 140.1.

Trityl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α/β -D-*threo*-dodeca-8Z-eno-pyranoside (21). *t*-Butyl pyranoside **20** was subjected to the two-step hydrolysis-tritylation sequence that was used for **13**. An inseparable mixture of α/β trityl pyranosides **21** (80%, ca. ratio 3:7) was obtained: $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.88, 0.90 (overlapping t, $J=7.2$ Hz, 3H), 1.24–2.30 (m, 12H), 2.75 (bs, ca. 0.7H), 2.82 (t, $J=5.6$ Hz, ca. 0.7H), 3.16 (bs, ca. 0.3H), 4.00 (t, $J=6.5$ Hz, ca. 0.3H), 4.08 (m, 1H), 4.36 (m, 1H), 4.42 (dd, $J=1.9, 9.5$ Hz, ca. 0.7H, H1 β -anomer), 5.28 (bs, ca. 0.3H, H1 α -anomer), 5.41 (m, 2H), 7.10–7.80 (m, 20H); ^{13}C NMR (C_6D_6), β anomer: δ 14.7, 23.9, 24.7, 26.6, 27.8, 30.3, 32.7, 71.7, 73.1, 78.5, 89.0, 99.0, 127.0–132.0 (several lines overlapped by C_6D_6 triplet), 139.5, 146.1; selected signals for α anomer: δ 71.5, 72.5, 73.9, 88.8, 94.0 (C1).

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α -D-erythro-dodeca-8*E*-enopyranoside (22).** *E*-alkene **22** (68%) was prepared from *Z* alkene **18**, according to the procedure described for *E*-alkene **24** (see later). $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.92 (t, $J=7.2\text{ Hz}$, 3H), 1.24 (s, 9H), 1.24–2.60 (m, 12H), 3.15 (dt, $J=5.0, 10.0\text{ Hz}$, 1H), 4.13 (bt, $J=10.0\text{ Hz}$, 1H), 4.45 (ABq, $\Delta\delta=0.28\text{ ppm}$, $J=11.0\text{ Hz}$), 5.10 (bs, 1H), 5.62 (m, 2H), 7.00–7.40 (m, 5H); ^{13}C NMR (C_6D_6) δ 14.3, 23.6, 24.7, 25.2, 29.5, 31.8, 33.8, 35.6, 71.0, 71.8, 73.8, 78.7, 91.1, 127.0–130.0 (several lines buried under C_6D_6 triplet), 130.6, 131.6, 140.0; MS (ES) m/z 378.4 ($\text{M}+\text{NH}_4$).

Trityl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α/β -D-erythro-dodeca-8*E*-enopyranoside (23). *t*-Butyl pyranoside **22** was subjected to the two-step hydrolysis-tritylation sequence that was used for **13**. An inseparable mixture of α/β trityl pyranosides **23** (63%, ca. ratio 2:3) was obtained: $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.90, 0.92 (overlapping t, $J=7.0\text{ Hz}$, 3H), 1.25–2.20 (m, 12H), 3.00 (m, ca. 1.6H), 4.16 (dt, $J=2.0, 10.0\text{ Hz}$, ca. 0.4H), 4.18 (ABq, $\Delta\delta=0.19\text{ ppm}$, $J=11.0\text{ Hz}$, ca. 1.2H), 4.36 (ABq, $\Delta\delta=0.24\text{ ppm}$, $J=11.0\text{ Hz}$, ca. 0.8H), 4.36 (dd, $J=2.1, 9.1\text{ Hz}$, ca. 0.6H, H1 β -anomer), 5.18 (bs, ca. 0.4H, H1 α -anomer), 5.44 (m, 2H), 7.03–7.69 (m, 5H); ^{13}C NMR (C_6D_6), β anomer: δ 14.3, 23.6, 28.7, 29.1, 31.9, 33.6, 35.6, 71.4, 77.5, 78.6, 88.8, 98.1, 127.0–132.0 (several lines overlapped by C_6D_6 triplet), 139.8, 145.9; selected signals for α -anomer: δ 71.3, 73.1, 78.5, 88.6, 93.2 (C1); MS (ES) m/z 569.3 ($\text{M}+\text{Na}$).

***Tert*-Butyl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α -D-threo-dodeca-8*E*-enopyranoside (24).** MCPBA (345 mg, ~50% w/w, 1.0 mmol) was suspended in a mixture of 4M $\text{NaH}_2\text{PO}_4/\text{Na}_2\text{HPO}_4$ buffer (18 mL) and CH_2Cl_2 (12 mL). The suspension was added to a solution of *Z*-alkene **20** (130 mg, 0.36 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at rt for 1 h. The organic layer was separated, washed with saturated aqueous solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$, and brine. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by FCC to afford a mixture of epoxide derivatives (120 mg, 92%): $R_f=0.20$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.83 (t, $J=7.0\text{ Hz}$, 3H), 1.20 (s, 9H), 1.28–2.18 (m, 12H), 2.67–2.83 (m, 2H), 3.09, 3.15 (both bs, 1H), 3.91 (m, ca. 0.5H), 4.04 (t, $J=5.8\text{ Hz}$, ca. 0.5H), 4.13–4.41 (m, 2H), 5.14 (bs, 1H), 7.26 (m, 5H).

A 0.5 M stock solution of Ph_2PLi was prepared by the addition of a hexane solution of *n*-butyllithium to a solution of Ph_2PH in dry THF at rt. under an argon atmosphere, followed by stirring for 1 h. An aliquot of the red solution of Ph_2PLi (2.5 mL, 1.25 mmol) was added to a solution of the above epoxide mixture (110 mg, 0.24 mmol) in dry THF (3 mL) at rt under an argon atmosphere, and stirring continued for 2 h. At that time freshly distilled MeI (0.15 mL, 2.4 mmol) was added. The mixture was stirred for an additional 1 h, and *n*-butyllithium (ca. 0.1 mL of a 1.6 M solution), was added until the red color persisted. The mixture was then diluted with ether, filtered through Celite and concentrated *in vacuo*. FCC of the residue gave *E*-alkene **24** (78.4 mg, 91%): $R_f=0.40$ (5% EtOAc:petroleum ether); ^1H NMR (C_6D_6) δ 0.94 (t, $J=7.4\text{ Hz}$, 3H), 1.35–2.60 (m, 12H), 1.28 (s, 9H), 3.22 (bs, 1H), 4.05 (bt, $J=9.0\text{ Hz}$, 1H), 4.35 (ABq, $\Delta\delta=0.29\text{ ppm}$, $J=11.9\text{ Hz}$, 2H), 5.21 (bs, 1H), 5.56 (m, 2H), 7.15–7.45 (m,



5H); ^{13}C NMR (C_6D_6) δ 14.2, 21.8, 23.5, 26.8, 29.4, 29.8, 32.8, 35.2, 70.6, 71.2, 73.9, 74.2, 91.9, 127.9, 128.9, 130.8, 131.4, 140.1.

Trityl 4-*O*-benzyl-2,3,6,7,8,9,10,11,12-nonadeoxy- α/β -D-threo-dodeca-8*E*-eno-pyranoside (25). *t*-Butyl pyranoside **24** was subjected to the two-step hydrolysis-tritylation sequence that was used for **13**. An inseparable mixture of α/β trityl pyranosides **25** (78%, ca. ratio 3:7) was obtained: $R_f=0.40$ (5% EtOAc:petroleum ether; ^1H NMR (C_6D_6) δ 0.88, 0.90 (overlapping t, $J=7.2$ Hz, 3H), 1.24–2.30 (m, 12H), 2.75 (bs, ca. 0.7H), 2.82 (t, $J=5.6$ Hz, ca. 0.7H), 3.16 (bs, ca. 0.3H), 4.00 (t, $J=6.5$ Hz, ca. 0.3H), 4.08 (m, 1H), 4.36 (m, 1H), 4.42 (dd, $J=1.9, 9.5$ Hz, ca. 0.7H, H1 β -anomer), 5.28 (bs, ca. 0.3H, H1 α -anomer), 5.41 (m, 2H), 7.10–7.80 (m, 20H); ^{13}C NMR (C_6D_6), β anomer: δ 14.5, 23.8, 26.6, 27.9, 29.9, 32.7, 35.8, 71.6, 73.1, 78.3, 89.0, 99.0, 93.6, 99.0, 103.4, 126.0–133.0 (several lines overlapped by C_6D_6 triplet), 139.0, 146.4; selected signals for α anomer: δ 71.5, 72.2, 73.6, 88.9, 94.0 (C1); HRMS(EI) calcd for $\text{C}_{38}\text{H}_{41}\text{O}_3$ (M-H) 545.3056, found 545.3064.

General Procedure for Iodoetherification Reactions

To a stirred solution of the alkene in CH_2Cl_2 (10 mL/mmol of alkene) and water (1% volume of CH_2Cl_2), was added iodonium dicollidine perchlorate (IDCP, 1.2 mmol/mmol of the alkene). The reaction mixture was stirred at rt for 10 min. The solution was then quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, and extracted with diethyl ether. The combined organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by FCC.

THF Aldehydes from Terminal Alkenes

cis-THF aldehyde (14c). $R_f=0.22$ (5% EtOAc:toluene); ^1H NMR(C_6D_6) δ 1.37 (m, 1H) 1.53 (m, 2H), 1.70 (m, 3H), 2.10 (m, 2H), 2.82 (dd, $J=6.2, 9.9$ Hz, 1H), 2.88 (dd, $J=5.1, 9.9$ Hz, 1H), 3.32 (apparent q, $J=6.2$ Hz, 1H), 3.62 (m, 2H), 4.47 (m, ABq, $\Delta\delta=0.12$ ppm, $J=11.7$ Hz, 2H), 7.05–7.40 (m, 5H), 9.40 (s, 1H); ^{13}C NMR (C_6D_6) δ 10.6, 24.8, 27.3, 31.9, 40.3, 73.4, 79.2, 79.9, 83.0, 128.0–129.0 (several lines buried under C_6D_6 triplet), 139.6, 200.7; HRMS(CI- CH_4) calcd for $\text{C}_{16}\text{H}_{22}\text{IO}_3$ (M+H) 389.0614, found 389.0610.

trans-THF aldehyde (14t). $R_f=0.26$ (5% EtOAc:toluene); ^1H NMR(C_6D_6) δ 1.28 (m, 1H) 1.50–1.80 (m, 5H), 2.10 (m, 2H), 2.83 (dd, $J=6.6, 9.0$ Hz, 1H), 2.89 (dd, $J=4.8, 9.9$ Hz, 1H), 3.30 (m, 1H), 3.74 (m, 1H), 3.82 (m, 1H), 4.47 (m, ABq, $\Delta\delta=0.13$ ppm, $J=11.7$ Hz, 2H), 7.05–7.50 (m, 5H), 9.36 (bs, 1H); ^{13}C NMR(C_6D_6) δ 11.5, 24.7, 28.0, 33.1, 40.5, 73.4, 79.0, 80.0, 82.8, 128.0–129.0 (several lines buried under C_6D_6 triplet), 139.7, 200.7; HRMS(FAB) calcd for $\text{C}_{16}\text{H}_{22}\text{IO}_3$ (M+H) 389.0614, found 389.0613.

cis-THF aldehyde (17c). $R_f=0.30$ (5% EtOAc:toluene); ^1H NMR (C_6D_6) δ 1.20–1.60 (m, 6H), 2.10 (m, 2H), 2.80 (m, 2H), 3.10 (m, 1H), 3.65 (m, 2H), 4.58 (ABq, $\Delta\delta=0.15$ ppm, $J=11.6$ Hz, 2H), 7.05–7.40 (m, 5H), 9.33 (s, 1H); ^{13}C NMR



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(C₆D₆) δ 10.9, 24.6, 28.2, 31.5, 40.6, 73.5, 79.3, 80.9, 84.1, 128.0–129.0 (several lines buried under C₆D₆ triplet), 138.4, 200.9; HRMS(CI-CH₄) calcd for C₁₆H₂₂IO₃ (M+H) 389.0614, found 389.0606.

trans-THF aldehyde (17t). R_f=0.35 (5% EtOAc:toluene); ¹H NMR(C₆D₆) δ 1.10–1.60 (m, 6H), 2.06 (m, 2H), 2.80 (m, 2H), 3.05 (m, 1H), 3.72 (m, 1H), 3.85 (m, 1H), 4.55 (ABq, $\Delta\delta$ =0.13 ppm, J=11.6Hz, 2H), 7.05–7.40 (m, 5H), 9.33 (s, 1H); ¹³C NMR (C₆D₆) δ 11.2, 24.2, 29.2, 33.9, 40.6, 73.4, 79.2, 80.9, 84.1, 128.0–129.0 (several lines buried under C₆D₆ triplet), 138.4, 200.9.

THF Aldehydes from Z Alkenes

cis-THF aldehyde (26c). R_f=0.20 (5% EtOAc:toluene); ¹H NMR (C₆D₆) δ 0.80 (t, J=7.1 Hz, 3H), 1.20–1.91 (m, 10H), 2.16 (m, 2H), 3.32 (m, 1H), 3.46 (q, J=6.2 Hz, 1H), 3.68 (m, 1H), 3.68 (m, 1H), 3.88 (m, 1H), 4.55 (ABq, $\Delta\delta$ =0.15 ppm, J=11.7 Hz, 2H), 7.05–7.50 (m, 5H), 9.40 (bs, 1H); ¹³C NMR (C₆D₆) δ 13.8, 23.8, 24.9, 27.8, 31.2, 39.6, 40.3, 42.5, 73.2, 79.8, 82.3, 82.9, 128.0–129.0 (several lines buried under C₆D₆ triplet), 139.7, 200.9; HRMS(FAB) calcd for C₁₉H₂₈IO₃(M+H) 431.1083, found 431.1084.

trans-THF aldehyde (26t). R_f=0.25 (5% EtOAc:toluene); ¹H NMR (C₆D₆) δ 0.82 (t, J=7.1 Hz, 3H), 1.20–1.90 (m, 10H), 2.15 (m, 2H), 3.36 (dt, J=4.8, 7.7 Hz, 1H), 3.55 (m, 1H), 3.92 (m, 1H), 3.95 (m, 1H), 4.53 (ABq, $\Delta\delta$ =0.14 ppm, J=11.7 Hz, 2H), 7.05–7.45 (m, 5H), 9.37 (bs, 1H); ¹³C NMR (C₆D₆) δ 13.9, 23.9, 24.8, 28.0, 32.3, 39.3, 40.6, 43.5, 73.4, 80.0, 83.0, 83.2, 128.0–129.0 (several lines buried under C₆D₆ triplet), 139.8, 200.7; HRMS(FAB) calcd for C₁₉H₂₈IO₃(M+H) 431.1083, found 431.1084.

cis-THF aldehyde (27c). R_f=0.50 (5% EtOAc:toluene); ¹H NMR (C₆D₆) δ 0.77 (t, J=7.1 Hz, 3H), 1.25–1.85 (m, 10H), 2.12 (m, 2H), 3.32 (m, 2H), 3.72 (m, 1H), 3.84 (m, 1H), 4.75 (ABq, $\Delta\delta$ =0.37 ppm, J=11.7 Hz, 2H), 7.10–7.45 (m, 5H), 9.35 (s, 1H); ¹³C NMR (C₆D₆) δ 13.8, 23.6, 24.8, 28.5, 31.0, 39.6, 40.7, 43.0, 73.7, 81.0, 82.9, 83.9, 128.0–129.0 (several lines buried under C₆D₆ triplet), 139.5, 200.9; HRMS(CI-CH₄) calcd for C₁₉H₂₈IO₃(M+H) 431.1083, found 431.1064.

trans-THF aldehyde (27t). R_f=0.55 (5% EtOAc:toluene); ¹H NMR (C₆D₆) δ 0.77 (t, J=7.1 Hz, 3H), 1.22–1.85 (m, 10H), 2.12 (m, 2H), 3.09 (m, 1H), 3.30 (m, 1H), 3.60 (m, 1H), 3.98 (m, 1H), 4.65 (ABq, $\Delta\delta$ =0.16 ppm, J=11.6 Hz, 2H), 7.10–7.40 (m, 5H), 9.35 (s, 1H); ¹³C NMR (C₆D₆) δ 13.8, 23.7, 24.2, 29.3, 32.0, 39.2, 40.6, 43.2, 73.4, 81.0, 83.2, 83.6, 128.0–129.0 (several lines buried under C₆D₆ triplet), 139.5, 200.9.

THF Aldehydes from E Alkenes

cis-THF aldehyde (28c). R_f=0.20 (5% EtOAc:toluene); ¹H NMR (C₆D₆) δ 0.82 (t, J=7.0 Hz, 3H), 1.20–1.80 (m, 10H), 2.15 (m, 2H), 3.34 (q, J=5.5 Hz, 1H), 3.55 (q,



$J=6.6$ Hz, 1H), 3.72 (q, $J=5.3$ Hz, 1H), 4.04 (q, $J=5.7$ Hz, 1H), 4.50 (ABq, $\Delta\delta=0.14$ ppm, $J=11.7$ Hz, 2H), 7.05–7.45 (m, 5H), 9.41 (bs, 1H); ^{13}C NMR (C_6D_6) δ 13.9, 23.5, 24.7, 27.3, 32.5, 39.5, 40.2, 42.9, 73.2, 80.1, 82.9, 83.3, 128.0–129.0 (several lines buried under C_6D_6 triplet), 139.7, 200.5; HRMS(FAB) calcd for $\text{C}_{19}\text{H}_{28}\text{IO}_3$ ($\text{M}+\text{H}$) 431.1083, found 431.1088.

trans-THF aldehyde (28t). $R_f=0.25$ (5% EtOAc:toluene); ^1H NMR (C_6D_6) δ 0.84 (t, $J=7.0$ Hz, 3H), 1.20–1.90 (m, 10H), 2.10 (m, 2H), 3.33 (m, 1H), 3.67 (m, 1H), 3.90 (m, 1H), 4.03 (m, 1H), 4.49 (ABq, $\Delta\delta=0.14$ ppm, $J=11.7$ Hz, 2H), 7.00–7.40 (m, 5H), 9.38 (s, 1H); ^{13}C NMR (C_6D_6) δ 13.9, 23.5, 24.7, 27.9, 33.8, 39.3, 40.5, 44.4, 73.4, 80.1, 83.1 (2 carbons), 128.0–129.0 (several lines buried under C_6D_6 triplet), 139.7, 200.3; HRMS(FAB) calcd for $\text{C}_{19}\text{H}_{28}\text{IO}_3$ ($\text{M}+\text{H}$) 431.1083, found 431.1088.

cis-THF aldehyde (29c). $R_f=0.50$ (5% EtOAc:toluene); ^1H NMR (C_6D_6) δ 0.80 (t, $J=7.1$ Hz, 3H), 1.30–1.73 (m, 10H), 2.06 (m, 2H), 3.15 (m, 1H), 3.58 (q, $J=7.5$ Hz, 1H), 3.74 (q, $J=7.5$ Hz, 1H), 3.99 (m, 1H, H_9), 4.60 (ABq, $\Delta\delta=0.25$ ppm, $J=11.7$ Hz, 2H), 7.05–7.40 (m, 5H), 9.32 (s, 1H); ^{13}C NMR (C_6D_6) δ 13.8, 23.2, 24.6, 28.0, 32.2, 39.3, 40.6, 43.1, 73.6, 80.9, 83.3, 84.1, 128.0–129.0 (several lines buried under C_6D_6 triplet), 138.7, 200.8; HRMS(CI- CH_4) calcd for $\text{C}_{19}\text{H}_{28}\text{IO}_3$ ($\text{M}+\text{H}$) 431.1083, found 431.1068.

trans-THF aldehyde (29t). $R_f=0.55$ (5% EtOAc:toluene); ^1H NMR (C_6D_6) δ 0.80 (t, $J=7.2$ Hz, 3H), 1.30–1.80 (m, 10H), 2.06 (m, 2H), 3.05 (m, 1H), 3.71 (m, 1H), 3.95 (m, 2H), 4.52 (ABq, $\Delta\delta=0.26$ ppm, $J=11.6$ Hz, 2H), 7.05–7.40 (m, 5H), 9.32 (s, 1H); ^{13}C NMR (C_6D_6) δ 13.9, 23.4, 24.3, 29.1, 33.8, 39.5, 40.7, 44.1, 73.4, 81.2, 83.3, 83.6, 128.0–129.0 (several lines buried under C_6D_6 triplet), 140.0, 200.6; MS(CI): m/z 448 ($\text{M}+\text{NH}_4$) for $\text{C}_{19}\text{H}_{27}\text{O}_3\text{I}$.

THF (30t), (from THF-iodide (14t)). The aldehyde 14t (500 mg, 1.29 mmol) was dissolved in EtOH (20 mL) and treated with NaBH_4 (60 mg, 1.6 mmol) at rt for 30 min. 10% HCl in MeOH was then added to the reaction mixture until the pH was 8. The volatiles were removed under reduced pressure. FCC of the residue afforded the derived alcohol (370 mg, 74%): R_f : 0.28 (30% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 1.40–1.90 (m, 6H), 2.00 (m, 2H), 2.20 (m, 1H), 3.25 (m, 2H), 3.52 (m, 3H), 4.06 (m, 1H), 4.17 (m, 1H), 4.70 (ABq, $\Delta\delta=0.17$ ppm, $J=11.0$ Hz, 2H), 7.20–7.50 (m, 5H). A solution of the product from the previous step (370 mg, 0.95 mmol), allyltributyltin (0.60 mL, 1.94 mmol) and AIBN (23 mg, 0.14 mmol) in benzene (5 mL) was purged with argon. The reaction mixture was then heated at reflux, under argon, for 18 h. The solvent was removed, and the residue dissolved in ether and stirred with a saturated, aqueous solution of KF for 0.5 h. The aqueous layer was extracted with ether and the organic extract dried (Na_2SO_4), and concentrated under reduced pressure. FCC of the residue provided the allylated derivative (65 mg, 23%): R_f : 0.60 (30% EtOAc:petroleum ether, double development); ^1H NMR (C_6D_6) δ 1.10–1.90 (m, 11H), 2.10 (m, 2H), 3.25 (m, 2H), 3.40 (m, 1H), 3.80 (m, 2H), 4.53 (ABq, $\Delta\delta=0.17$ ppm, $J=11.5$ Hz, 2H), 4.94 (m, 2H), 4.74 (m, 1H), 7.00–7.40 (m, 5H).

A mixture of the alkene from the previous step (35 mg, 0.12 mmol, 10% w Pd/C (5 mg) in EtOAc (5 mL) was stirred for 6 h under hydrogen (balloon). The suspension



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was filtered through a short plug of Celite and concentrated *in vacuo*. FCC of the residue provided **30t** (25 mg, 71%): $R_f=0.30$ (30% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 0.92 (t, $J=7.0$ Hz, 3H), 1.20–2.20 (m, 14H), 2.28 (m, 1H), 3.60 (m, 3H), 3.95 (m, 1H), 4.06 (m, 1H), 4.68 (ABq, $\Delta\delta=0.14$ ppm, $J=11.0$ Hz, 2H), 7.20–7.45 (m, 5H); ^{13}C NMR (CDCl_3) δ 14.3, 23.1, 27.7, 28.4, 28.7, 29.2, 32.5, 35.9, 63.2, 73.2, 79.8, 81.2, 81.4, 127.6, 128.0, 128.4, 139.2; HRMS(FAB) calcd for $\text{C}_{19}\text{H}_{31}\text{O}_3$ ($M+H$) 307.2273, found 307.2274.

THF (30t), (from THF-iodide (**26t**)). The aldehyde **26t** (50 mg, 0.12 mmol) was treated with NaBH_4 according to the procedure described in the previous experiment. FCC of the crude product provided the derived alcohol (50 mg, 96%): $R_f=0.20$ (5% EtOAc:toluene); ^1H NMR (C_6D_6) δ 0.75 (t, $J=7.2$ Hz, 3H), 1.15–1.90 (m, 13H), 3.26 (m, 2H), 3.52 (m, 1H), 3.79 (m, 1H), 3.94 (m, 1H), 4.52 (ABq, $\Delta\delta=0.14$ ppm, $J=11.8$ Hz, 2H), 7.00–7.40 (m, 5H).

A mixture of the above material (10 mg, 0.023 mmol), AIBN (5 mg, 0.03 mmol), Bu_3SnH (0.02 mL, 0.07 mmol) in toluene (5 mL) was purged with argon. The reaction mixture was then heated at reflux, under argon, for 3 h. Removal of the solvent under reduced pressure and FCC of the residue afforded **26t** (4 mg, 84 %), which was identical (TLC, NMR) with the material derived from **14t**.

THF (30c), (from THF-iodide (**26c**)). The aldehyde **26c** was transformed to THF **30c** following the procedure that was used for the conversion of **26t** to **30t**. For **30c**: $R_f=0.30$ (30% EtOAc:petroleum ether); ^1H NMR (CDCl_3) δ 0.92 (t, $J=7.0$ Hz, 3H), 1.25–2.10 (m, 15H), 3.52 (m, 1H), 3.62 (m, 2H), 3.80 (m, 1H), 3.91 (m, 1H), 4.66 (ABq, $\Delta\delta=0.16$ ppm, $J=11.0$ Hz, 2H), 7.20–7.45 (m, 5H); ^{13}C NMR (CDCl_3) δ 14.3, 23.1, 27.1, 28.5, 28.8, 29.2, 31.6, 36.0, 63.3, 73.1, 80.1, 80.8, 81.8, 127.6, 128.0, 128.4, 139.2; HRMS(FAB) calcd for $\text{C}_{19}\text{H}_{31}\text{O}_3$ ($M+H$) 307.2273, found 307.2274.

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REFERENCES

1. Rupprecht, J.K.; Hui, Y.-H.; McLaughlin, J.L. Annonaceous acetogenins: A review. *J. Nat. Prod.* **1990**, *53*, 237–278.
2. Fang, X.; Rieser, M.J.; Gu, Z.; Zhao, G.; McLaughlin, J.L. Annonaceous acetogenins: An updated review. *Phytochem. Anal.* **1993**, *4*, 27–48.
3. Zeng, L.; Ye, Q.; Oberlis, N.H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J.L. Recent advances in annonaceous acetogenins. *Nat. Prod. Rep.* **1996**, *13*, 275–306.
4. Alali, F.Q.; Liu, X.-X.; McLaughlin, J.L. Annonaceous acetogenins: Recent progress. *J. Nat. Prod.* **1999**, *62*, 504–540.



5. Figadère, B. Synthesis of acetogenins of annonaceae: A new class of bioactive polyketides. *Acc. Chem. Res.* **1995**, 28, 359–365, Recent reviews on synthesis of THF acetogenins, and Refs. [6–8].
6. Koert, U. Stereoselective synthesis of oligo-tetrahydrofurans. *Synthesis* **1995**, 115–132.
7. Hoppe, R.; Scharf, H.-D. Annonaceous acetogenins—Synthetic approaches towards a novel class of natural products. *Synthesis* **1995**, 1447–1464.
8. Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. Current advances in the chemistry synthesis of annonaceous acetogenins and relatives. *Chemtracts-Organic Chemistry* **1998**, 11, 803–827.
9. Hoye, T.R.; Hanson, P.R.; Kovelesky, A.C.; Ocain, T.D.; Zhang, Z. Synthesis of (+)-(15, 16, 19, 20, 23, 24)-*hexepi*-uvaricin: A bis(tetrahydrofuranyl) annonaceous acetogenin analogue. *J. Am. Chem. Soc.* **1991**, 113, 9369–9371, Representative syntheses of THF containing acetogenins, and Refs. [10–18].
10. Hoye, T.R.; Ye, Z. Highly efficient synthesis of the potent antitumor annonaceous acetogenin (+)-parviflorin. *J. Am. Chem. Soc.* **1996**, 118, 1801–1802.
11. Trost, B.M.; Shi, Z. A concise convergent strategy to acetogenins. (+)-Solamin and analogues. *J. Am. Chem. Soc.* **1994**, 116, 7459–7460.
12. Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. The first total synthesis of (+)-bullatacin, a potent antitumor annonaceous acetogenin, and (+)-(15, 24)-bisepi-bullatacin. *J. Org. Chem.* **1995**, 60, 4419–4427.
13. Sinha, S.C.; Sinha-Bagchi, A.; Keinan, E. Combined osmium-rhenium approach to synthesis of naturally occurring polyethers. *J. Am. Chem. Soc.* **1995**, 114, 1447–1448.
14. Sinha, S.C.; Sinha, A.; Yazbak, A.; Keinan, E. Toward chemical libraries of annonaceous acetogenins. Total synthesis of trilobacin. *J. Org. Chem.* **1996**, 61, 7640–7641.
15. Sinha, S.C.; Sinha, S.C.; Keinan, E. Total synthesis of squamotacin. *J. Org. Chem.* **1999**, 64, 7067–7073.
16. Marshall, J.A.; Jiang, H. Total synthesis of the cytotoxic *Threo*, *Trans*, *Erythro*, *Cis*, *Threo*, annonaceous acetogenin trilobin. *J. Org. Chem.* **1999**, 64, 971–975.
17. Emde, U.; Koert, U. Total synthesis of squamocin A and squamocin D, Bi-tetrahydrofuran acetogenins from annonaceae. *Eur. J. Org. Chem.* **2000**, 65, 1889–1904.
18. Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. Enantioselective syntheses of monotetrahydrofuran annonaceous acetogenins tonkinecin and annonacin starting from carbohydrates. *J. Org. Chem.* **2001**, 66, 853–861.
19. Zhang, H.; Wilson, P.; Shan, W.; Ruan, Z.; Mootoo, D.R. *Cis* 2,5-disubstituted tetrahydrofurans from pyranosides: A novel example of remote stereocontrol by the aglycone. *Tetrahedron Lett.* **1995**, 36, 649–652.
20. Ruan, Z.; Wilson, P.; Mootoo, D.R. Bis-pyranoside alkenes: Novel templates for the synthesis of adjacently linked tetrahydrofurans. *Tetrahedron Lett.* **1996**, 37, 3619–3622.
21. Seepersaud, M.; Mootoo, D.R. C-6 allylated pyranosides for the synthesis of complex oxygenated tetrahydrofurans. *Tetrahedron* **1997**, 53, 5711–5724.
22. Ruan, Z.; Dabideen, D.; Blumenstein, M.; Mootoo, D.R. A modular synthesis of the bis-tetrahydrofuran core of rolliniastatin from pyranoside precursors. *Tetrahedron* **2000**, 56, 9203–9211.



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23. Harmange, J.-C.; Figadère, B. Synthetic routes to 2,5-disubstituted tetrahydrofurans. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.
24. Cardillo, G.; Orena, M. Stereocontrolled cyclofunctionalization of double bonds through heterocyclic intermediates. *Tetrahedron* **1990**, *46*, 3321–3408.
25. Wilson, P.; Shan, W.; Mootoo, D.R. A novel strategy for the preparation of substituted tetrahydrofurans based on neighboring group participation by the ring oxygen of monosaccharides. *J. Carbohydr. Chem.* **1994**, *13*, 133–140.
26. Rychnovsky, S.D.; Bartlett, P.A. Stereocontrolled synthesis of *cis*-2,5-disubstituted tetrahydrofurans and *cis*- and *trans*-linalyl oxides. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964, For mechanistic discussions on the haloetherification of 5-hydroxyalkenes, and Refs. [27–30].
27. Chamberlin, A.R.; Mulholland, R.L., Jr.; Kahn, S.D.; Hehre, W.J. Modeling chemical reactivity. 7. The effect of a change in rate-limiting step on the stereoselectivity of electrophilic addition to allylic alcohols and related chiral alkenes. *J. Am. Chem. Soc.* **1987**, *109*, 672–677.
28. Reitz, A.B.; Nortey, S.O.; Maryanoff, B.E.; Liotta, D.; Monahan, R., III. Stereoselectivity of electrophile-promoted cyclizations of γ -hydroxyalkenes. An investigation of carbohydrate-derived and model substrates. *J. Org. Chem.* **1987**, *52*, 4191–4202.
29. Labelle, M.; Morton, H.E.; Guindon, Y.; Springer, J.P. Homoallylic chiral induction in the synthesis of 2,4-disubstituted THFs by iodoetherification. Synthetic scope and chiral induction mechanism. *J. Am. Chem. Soc.* **1988**, *110*, 4533–4540.
30. Labelle, M.; Guindon, Y. Diastereoselective synthesis of 2,3-disubstituted tetrahydrofuran synthons via the iodoetherification reaction. A transition state model based on the allylic asymmetric induction. *J. Am. Chem. Soc.* **1989**, *111*, 2204–2210.
31. Ferrier, R.J.; Prasad, N. Unsaturated carbohydrates. Part XI. Isomerization and dimerization of tri-*O*-acetyl-D-glucal. *J. Chem. Soc. C* **1969**, 581–586.
32. Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. Acyclic stereocontrol by heteroconjugate addition-4. Anti-diastereoselection by a β -chelation effect. *Tetrahedron* **1986**, *42*, 2863–2872.
33. Lemieux, R.U.; Morgan, A.R. The synthesis of β -D-glucopyranosyl-2-deoxy- α -D-arabino-hexopyranoside. *Can. J. Chem.* **1965**, *43*, 2190–2198.
34. With a developing solvent of 5% ethyl acetate:petroleum ether, the *cis* THF generally had a lower R_f than the *trans* isomer.
35. Vedejs, E.; Snoble, K.A.J.; Fuchs, P.L. Phosphorous betaines derived from cycloheptene and cyclooctene oxide. Inversion of cyclooctene oxide. *J. Org. Chem.* **1973**, *38*, 1178–1182.
36. Roy, R.; Dominique, R.; Das, S.K. Extended alkenyl glycosides by ruthenium-catalyzed cross-metathesis reaction and application toward novel C-linked pseudodisaccharides. *J. Org. Chem.* **1999**, *64*, 5408–5412.
37. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy, High Resolution Methods and Applications in Organic Chemistry*; VCH: New York, 1987; 192.
38. Sahai, M.; Singh, S.; Singh, M.; Gupta, Y.K.; Akashi, S.; Yuji, R.; Hirayama, K.; Asaki, H.; Araya, H.; Hara, N.; Eguchi, T.; Kakinuma, K.; Fujimoto, Y. Annonaceous acetogenin from the Seeds of *Annona squamosa*. Adjacent bis-tetrahydrofuranic acetogenins. *Chem. Pharm. Bull.* **1994**, *42*, 1163–1174.



39. Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y.K.; Sahai, M. Annonaceous acetogenins from the seeds of *Annona squamosa*. Non-adjacent bis-tetrahydrofuranic acetogenins. *Chem. Pharm. Bull.* **1994**, 42, 1175–1184.
40. Zhang, H.; Mootoo, D.R. Acetal templates for the synthesis of *trans* 2,5-disubstituted tetrahydrofurans. *J. Org. Chem.* **1995**, 60, 8134–8135.
41. Zhang, H.; Seepersaud, M.; Seepersaud, S.; Mootoo, D.R. The asymmetric dihydroxylation-haloetherification strategy for the synthesis of tetrahydrofuran containing acetogenins. *J. Org. Chem.* **1998**, 63, 2049–2052.
42. Ruan, Z.; Mootoo, D.R. A novel desymmetrization reaction of an acetogenin precursor: A formal synthesis of trilobacin and asimicin. *Tetrahedron Lett.* **1999**, 40, 49–52.
43. Although the alternative chair conformation for β -glycosides places the anomeric substituent in a stabilizing axial orientation, it appears unlikely that this would be a favorable reactive conformation, due to the high degree of congestion between the C4 and C1 axial substituents of the pyranoside and the substituent on the *cis*-THF ring that is being formed.
44. Lemieux, R.U.; Koto, S.; Voisin, D. Human blood groups and carbohydrate chemistry. *ACS Symp. Ser.* **1979**, 87, 17–62.
45. Delongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.
46. Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer Verlag: New York, 1983.
47. Guindon, Y.; Anderson, P.C. Stereoelectronic effects in the ring cleavage of methyl glycopyranosides using dimethylboron bromide. *Tetrahedron Lett.* **1987**, 28, 2485–2488.

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