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Bis-pyranoside Alkenes: Novel Templates for the Synthesis of Adjacently Linked Tetrahydrofurans

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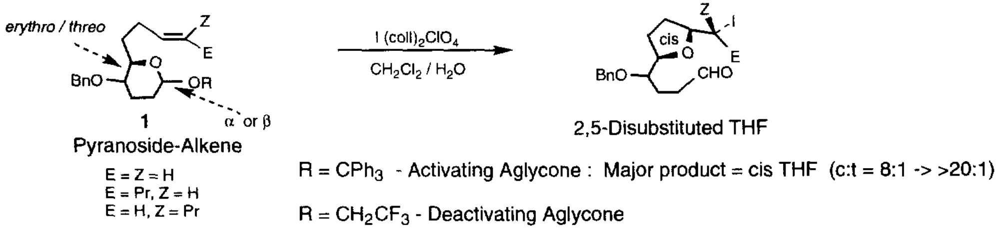
Abstract: Bis-pyranoside alkenes are used as templates for the convergent assembly of highly substituted, adjacently linked, tetrahydrofurans (THF's). The methodology centers on the stereoselective preparation of a bis-THF diol core structure. Copyright © 1996 Elsevier Science Ltd

Adjacently linked THF residues are found in several groups of important natural products. These structures are generally highly oxygenated and range in complexity from the bis-THF segments found in the acetogenins to the polyether-spiroketal frameworks of the ionophore antibiotics.[1,2] Carbohydrate based syntheses are appropriate because of the oxygenated nature of monosaccharides and their effectiveness as templates for multichiral, and non symmetrically substituted frameworks.[3,4]

Scheme 1



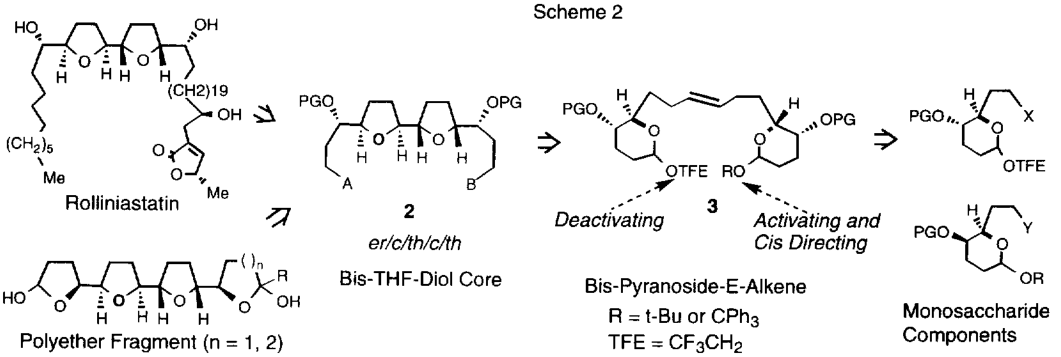
R = CPh$_3$ - Activating Aglycone : Major product = cis THF (c:t = 8:1 -> >20:1)

R = CH$_2$CF$_3$ - Deactivating Aglycone

We have been developing a strategy for the preparation of 2,5 disubstituted THF's based on the haloetherification reaction of alkenylated monosaccharides **1**[5,6] (Scheme 1). A noteworthy aspect is the obtention of a highly functionalized halo-THF-aldehyde in a single step from a monosaccharide alkene, with high stereoselectivity. Furthermore, the relative reactivity of different substrates could be modulated by varying the nature of the aglycone, a feature which is especially relevant to the synthesis of highly substituted systems, because it widens the scope of the cyclic acetal as a protecting group.[7] These principles coupled with the connectivity of the pyranoside framework allows for a novel, convergent strategy for the preparation of complex, contiguously linked polyethers. The plan centers around the initial construction of a bis-THF-diol core, which may be converted to bis-THF acetogenin or polyether subunits. Herein, we introduce the general aspects of this methodology by synthesis of the bis-THF core of the acetogenin, rolliniastatin.[8]

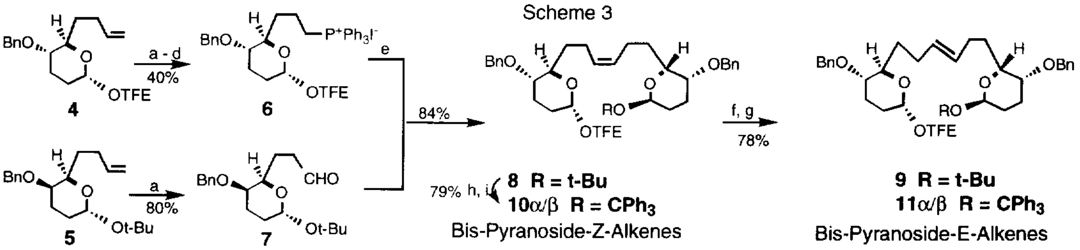
The target *er/c/th/c/th* bis-THF-diol **2** originates from a starting bis-pyranoside-E-alkene **3** which may be prepared by the coupling of two prefabricated monosaccharide components. One of the monosaccharide fragments is equipped with an activated *cis* directing aglycone (t-butyl or trityl) and the other with a deactivating aglycone (trifluoroethyl). The bis-THF is related to the bis-pyranoside alkene by sequential THF forming reactions: (i) an initial haloetherification involving the ring oxygen of the stereodetermining, activated pyranoside to give a halo-THF-trifluoroethyl pyranoside and, (ii) formation of the adjacent THF via displacement of the halide substituent by the ring oxygen of the deactivated pyranoside. The first step differentiates the two acetal residues, thereby facilitating desymmetrization of the bis-THF. The configuration of the bis-THF diol is determined by the stereochemistry of the starting monosaccharides, the geometry of the alkenic link, and the constitution of the aglycone in the activated pyranoside. The flanking chains of the bis-THF core may be more substituted and are primed for manipulation into additional cyclic ethers leading to more complex polyether fragments (Scheme 2).

Scheme 2



Accordingly, the monosaccharide synthons **6** and **7** were prepared from the respective allylated pyranosides **4** and **5** via straightforward carbohydrate based procedures.[6,9] The required t-butyl and trityl-E-trifluoroethyl bis-pyranoside alkenes **9** and **11**α/β were accessible by the stereospecific inversion of their respective Z-isomers **8** and **10**α/β.[10] Z-alkene **8** was obtained in greater than 95% stereoselectivity from the unstabilized Wittig reaction of the phosphorane derived from **6** and the aldehyde **7**.[11] The mixture of anomeric trityl derivatives **10**α/β was obtained from **8**, over two steps involving selective hydrolysis of the t-butyl glycoside, followed by silver trifluoroacetate promoted tritylation of the resulting lactol (Scheme 3).

Scheme 3

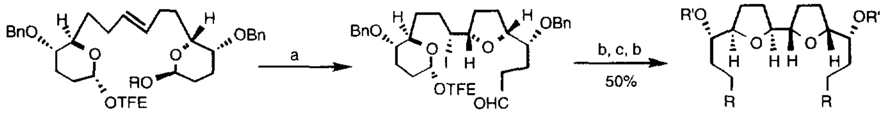


(a) O_3, CH_2Cl_2-MeOH, then Me_2S; (b) $NaBH_4$, MeOH; (c) Ph_3P, I_2, Imidazole, PhH; (d) Ph_3P, CH_3CN-$PhCH_3$, $(i\text{-}Pr)_2NEt$, 80°C; (e) $Na(NSiMe_3)_2$, $PhCH_3$, -78°C; (f) mCPBA, CH_2Cl_2, phosphate buffer; (g) Ph_2PLi then MeI; (h) THF-HCl (3:1); (i) Ph_3CCl, $AgOOCF_3$, collidine, CH_2Cl_2, MS

Treatment of **9** with iodonium dicollidine perchlorate[12] in wet dichloromethane afforded a 70% yield of a 9:1 mixture of the *cis* THF **12** and a side product which was presumed to be the *trans* isomer. No evidence of the THF arising from cyclization of the ring oxygen of the trifluoroethyl pyranoside was observed. As expected, the trityl bis-pyranoside alkene **11**α/β, under the identical conditions, led exclusively to the *cis* THF product in 79% yield. The transformations of both bis-pyranoside-E-alkenes to **12**, resulted in the formation of two new stereogenic centers with high stereoselectivity and concommitant differentiation of the two acetal carbons, thereby illustrating the potential of the methodology for the preparation of targets with complex substitution.

A protocol for conversion of the THF-iodo-pyranoside to the bis-THF was next devised. Thus, **12** was converted to the bis-THF **13** in 50% yield over three steps, which involved Wittig reaction on the aldehyde, followed by hydrolysis of the trifluoroethyl glycoside, and a second Wittig reaction on the derived lactol. Gratifyingly, both aldehyde elaboration and formation of the second THF ring was achieved in the second Wittig reaction (Scheme 4). For the synthesis of rolliniastatin, the bis-THF may be desymmetrized by using non-identical ylides in the Wittig reactions. The stereochemistry of the bis-THF core was assigned on the basis of the *cis* stereodirecting effect of trityl aglycones and the stereospecific nature of the reactions involved.[6,13] Furthermore the ^{13}CNMR resonances of the carbinol carbons in **14** showed excellent correlation with the corresponding signals for the *er/c/th/c/th* bis-THF diol core of rolliniastatin, but not with those of the *er/t/th/t/th* core of bullatacin.[1]

Scheme 4



9 R = t-Bu (9:1 c:t THF's)
11α/β R = CPh$_3$ (cis THF only)

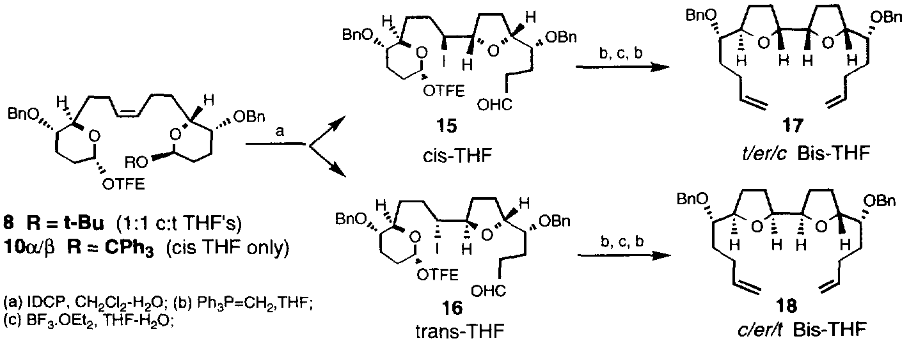
12
cis-THF

c/th/c Bis-THF
d **13 R = CH=CH$_2$; R' = Bn**
14 R = CH$_2$CH$_3$; R' = H

(a) IDCP, CH_2Cl_2-H_2O; (b) $Ph_3P=CH_2$, THF; (c) $BF_3.OEt_2$, THF-H_2O; (d) H_2,Pd/C, MeOH, HCOOH

The scope of the overall bis-THF forming strategy was of some concern, since it is likely that the stereoselectivity of the initial halocyclization, and the success of halide displacement step could be affected by the stereochemistry of the precursors for the respective reactions. Therefore, bis-pyranoside Z alkene substrates was next evaluated. Not suprisingly, based on the earlier observation that Z-alkenes are inherently less *cis*-selective, the t-butyl derivative **8** gave a 1:1 mixture of *cis* :*trans* THF iodides **15** and **16** (73%). However, as for the E series, the trityl analog **10**α/β, gave the *cis* THF exclusively. In order to evaluate the generality of the halide displacement step, mono THF-iodo-pyranosides **15** and **16** were treated under the identical 3-step sequence which was applied to **12**. The desired bis-THF's **17** and **18** were obtained in yields of 55 and 50% respectively (Scheme 5).

Scheme 5



8 R = t-Bu (1:1 c:t THF's)
10α/β R = CPh$_3$ (cis THF only)

(a) IDCP, CH_2Cl_2-H_2O; (b) $Ph_3P=CH_2$,THF;
(c) $BF_3.OEt_2$, THF-H_2O;

15
cis-THF

16
trans-THF

17
t/er/c Bis-THF

18
c/er/t Bis-THF

In summary this study illustrates a highly regio- and stereo- selective haloetherification reaction of complex, 1,8 diol-4-alkenes which are embedded in bis-pyranoside alkene frameworks. This selectivity derives from the 'fine-tuned' chemistry of C6 allylated pyranosides. Although related etherification reactions have been widely applied in simpler substrates, high stereoselectivity in more substituted cases, especially in a remote sense, is very substrate dependant, and generally less predictable.[13,14] The application of this methodology to the preparation of more complex polyethers is currently in progress and will be reported in due course.

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