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# Highly functionalized *trans*-2,5-disubstituted tetrahydrofurans from ribofuranoside templates: precursors to linked polycyclic ethers☆

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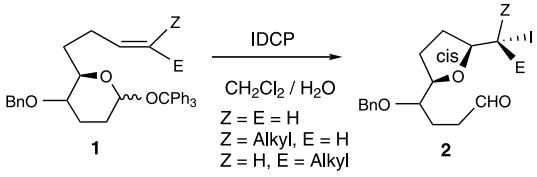
**Abstract**—Iodoetherification of C5 allylated ribo-furanosides leads to *trans*-2,5-disubstituted tetrahydrofurans with high selectivity. The application of this reaction to the synthesis of complex polycyclic ethers is illustrated in the preparation of a truncated, tricyclic analog of monensin A.


The easy accessibility and chemical constitution of simple carbohydrate derivatives make them attractive starting materials for the synthesis of highly oxygenated structures.[1] In this vein, we have shown that the iodoetherification of C6 allylated pyranosides **1** lead to *cis*-2,5-disubstituted tetrahydrofurans (THFs) **2**, with functionalized branches, in high yields and stereoselectivity (Scheme 1).[2,3]




**Scheme 1.**

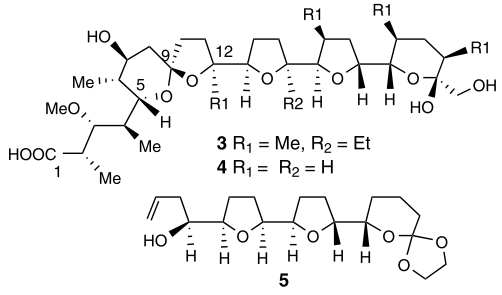



**Figure 1.**

Screening of templates for the analogous *trans*-THF frameworks revealed high stereoselectivity C5 allylated 2,3-*O*-isopropylidene-ribofuranosides.[4] The iodoetherification reaction was also found to be compatible with polyene monosaccharide substrates, a result of relevance to more complex syntheses. These findings are illustrated herein, in the synthesis of **5**, an advanced precursor to an analog (i.e. **4**), of the polyether antibiotic monensin A, **3**.[5,6] Less substituted structures like **4** are relevant to a clear understanding of substituent effects on the kinetics and thermodynamics of cation binding and transport (Fig. 1).[7]

Preliminary experiments with methyl 2,3-*O*-ribofuranoside **6** displayed high *trans*-THF selectivity, but also indicated a significant amount of iodohydrin products **8**. The formation of this side product could be reduced by using more bulky aglycones. The isopropyl derivative **9** was found to be the most practical in terms of its synthesis and the efficiency of the iodoetherification. We envisaged that a triene derivative like **10** could lead to the product **11** which is primed for elaboration to linked polycyclic ether frameworks.[8] However, major concerns were the chemoselectivity of the key iodoetherification reaction with respect to the triene

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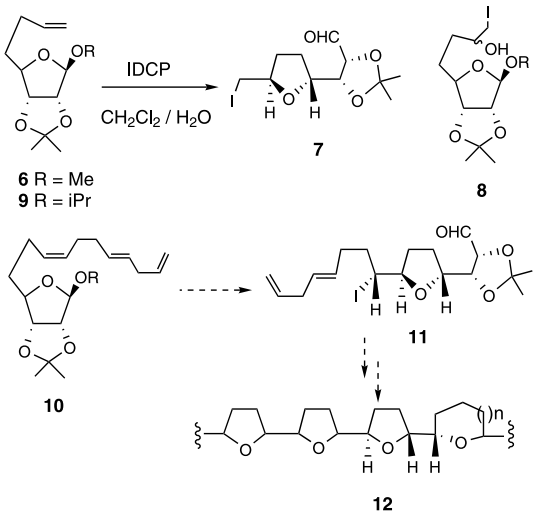
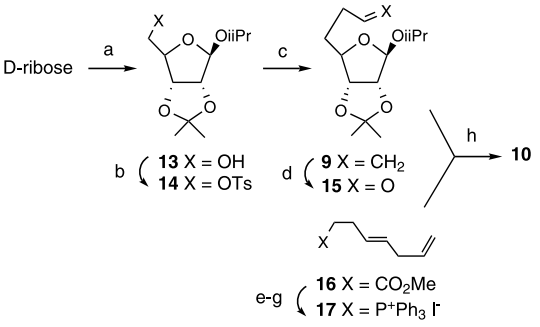



**Scheme 2.**




**Scheme 3.** *Reagents and conditions*: (a) acetone, *i*PrOH, $CuSO_4$, $H_2SO_4$, 64%; (b) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, (99%); (c) AllylMgBr, TMEDA, $Et_2O$, (80%); (d) $O_3$, MeOH, $CH_2Cl_2$, −78°C then $Ph_3P$; (e) DIBALH, $CH_2Cl_2$, −78°C; (f) $Ph_3P$, $I_2$, imidazole, $CH_2Cl_2$, 78% two steps; (g) $Ph_3P$, $(iPr)_2NEt$, $CH_3CN$, toluene, reflux, 87%; (h) **17**, $NaN(SiMe_3)_2$, toluene, −78°C, then **15**, (75%).

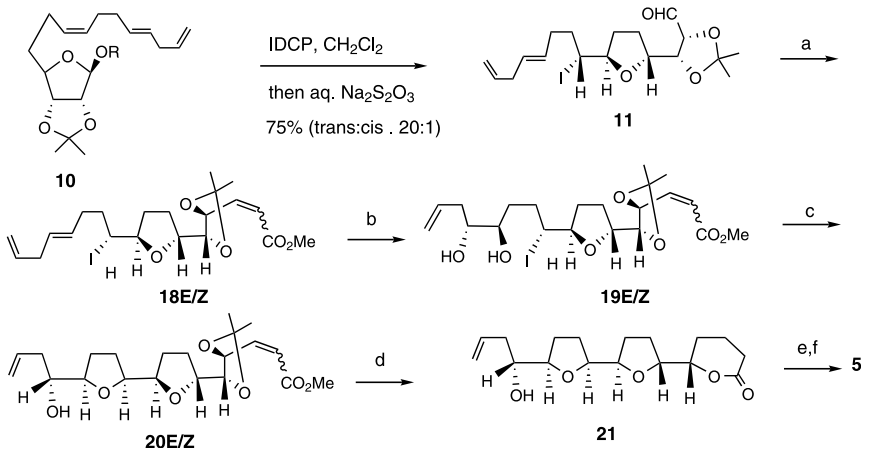
residue, and the development of concise routes from **11** to the desired targets. These issues were examined within the context of the truncated monensin A analog **5** (Scheme 2).

Furanoside triene **10** was obtained in a straightforward fashion.[9] Thus, D-ribose was transformed in a single step to isopropyl 2,3-*O*-isopropylidene-D-ribo-furanoside **13** via a known procedure.[10] Treatment of the derived tosylate **14** with allylmagnesium bromide provided the C5 allylated furanoside **9**. Ozonolysis of **9** gave aldehyde **15**. Wittig reaction of **15** and the phosphorane obtained from phosphonium salt **17** led to the desired triene in 75% yield with a *Z*/*E* selectivity of greater than 95%, as determined from NMR analysis. The phosphonium salt **17** was prepared from *E*-methyl 1,4-octadienoate via standard procedures (Scheme 3).[11]

The iodocyclization of **10** was initially performed by addition of iodonium dicollidine perchlorate (IDCP) to a solution of **10** in a mixture of dichloromethane and water. This led to the desired product **11**, but was accompanied by an appreciable amount of products that appeared to be arising from electrophilic attack on the other alkenes. Optimal results were obtained by pouring a premixed solution of **10** and IDCP into a saturated solution of aqueous sodium thiosulfate. These conditions afforded a 75% yield of **11** (based on 60% conversion of **10**, for reactions on up to 20 g scale), with a *trans*:*cis* selectivity of greater than 20:1.[12] The stereochemistry of the THF isomers was assigned on the basis of the results obtained in the cyclization of a very closely related furanoside alkene substrate,[13] and the accepted mechanism of anti-addition in the iodoetherification of alkenes (Scheme 4).[14]

The first step in transformation of **11** to **5** was the olefination of aldehyde **11**, under standard stabilized ylide conditions. The *E*/*Z* (10/1) mixture of unsaturated esters **18E/Z** was next treated with AD-mix-β to provide a mixture **19E/Z** as a single vicinal diol diastereomer in 55% yield, as determined by $^{13}C$ and $^{1}H$ NMR analysis. The stereochemistry of the vicinal diol was based on the high stereoselectivity that has been observed for 'AD-mixes' and *E*-disubstituted alkenes that are remote from resident stereogenic centers.[15] That the reaction of **18E** with AD-mix α gave a single, diastereomeric diol product that was different from **19E**, supports this argument. The moderate yield of **19E/Z** was due to side products that arose from competing dihydroxylation of the terminal alkene. Optimization of the synthesis by utilization of these side products is conceivable. Formation of the second THF ring was effected by the reaction of dihydroxyiodide **19E/Z** with dibutyltin oxide in benzene.[16] These conditions were found to be superior to base mediated procedures, which led to side products resulting from dehydroiodination. Dissolving metal reduction (Mg, methanol) of bis-THF **20E/Z**,[17] followed by exposure of the crude product to acidic conditions (CSA, molecular sieves) provided lactone **21** in 60% overall yield from **20E/Z**.[18] Thus the transformation of **11** to the tricyclic skeleton of target compound **5** was accomplished in five simple operations. Protection of the lactone **21** as the orthoester, followed by configurational inversion of the homoallylic alcohol via the Mitsonobu procedure,[19] provided **5**. The gross structure of **5** was confirmed by NMR and HRMS analysis, and the stereochemistry assigned on the basis of the well documented stereoselectivity and specificity of the reactions involved in the synthesis.[20]

In summary, the application of readily available isopropyl 2,3-*O*-isopropylidene ribofuranoside as a precursor to highly functionalized *trans*-2,5-disubstituted THFs has been demonstrated. The observation that the key iodocyclization reaction is compatible with polyene substrates suggests that it should be possible to access polyether systems of varying stereochemistry and degrees of oxygenation, by altering the polyene residue. As illustrated in the synthesis of **5**, the methodology appears to be especially well suited to linked polycyclic ether frameworks found in the polyether antibiotics,[21] and to the related motifs in the acetogenin group of




**Scheme 4.** *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Me$, $CH_3CN$, reflux (95%); (b) AD-mix β, $MeSO_2NH_2$, *t*-BuOH, $H_2O$, –3°C (55%); (c) $Bu_2SnO$, PhH, Dean–Stark, reflux (86%); (d) (i) Mg, MeOH, reflux; (ii) CSA, $CH_2Cl_2$, 4 Å MS, reflux, 60% two steps; (e) ethylene glycol, CSA, Dowex 50WX8-400, PhH, $MgSO_4$, reflux (89%); (f) (i) $PPh_3$, DEAD, *p*-$NO_2$-$C_6H_4COOH$, toluene; (ii) 3N aq. NaOH, EtOH, reflux 50% two steps.

natural products.[22] Further investigations in these directions are in progress.

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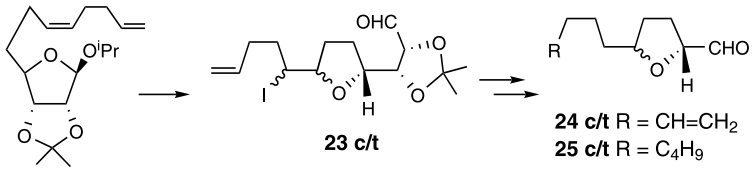
(s, 3H), 1.68 (m, 1H), 1.77 (m, 2H), 1.89 (m, 1H), 2.06–2.18 (m, 3H), 2.26 (m, 1H), 2.72 (t, $J=8$ Hz, 2H), 3.72 (m, 1H), 3.99 (m, 1H), 4.17 (m, 1H), 4.30 (t, $J=8.0$ Hz, 1H), 4.49 (dd, $J=2.0$, 8.0 Hz, 1H), 4.97 (dd, $J=15$, 8 Hz, 2H), 5.37 (m, 1H), 5.48 (m, 1H), 5.78 (m, 1H), 9.66 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 25.5, 27.4, 30.2, 31.3, 32.5, 36.2, 36.6, 41.4, 78.2, 81.1, 81.6, 82.8, 110.8, 114.9, 129.3, 129.3, 136.9, 198.0. FABHRMS calcd for $C_{18}H_{28}O_4I$ $(M+H)^+$ 435.1032, found 435.1032.

13. The iodocyclization of furanoside diene **22** led to a mixture **23 c/t** (*cis*/*trans*, ca. 20/1). The stereochemistry of the products was assigned by conversion to aldehydes **24 c/t**, and comparison of the NMR data for these derivatives with the known compounds **25 c/t** (Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S.; Singh, M.; Gupta, Y. K.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175–1184).




**22** **23 c/t**

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18. Physical data for **21**: $R_f=0.22$ (50% EtOAc/petroleum ether); IR ($CHCl_3$ film) 3452, 1737, 1641 cm$^{-1}$; $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 1.04 (m, 2H), 1.14 (m, 1H), 1.28 (m, 1H), 1.50–1.80 (m, 8H), 1.93 (m, 1H), 2.02 (m, 1H), 2.34 (m, 1H), 2.42 (m, 1H), 2.97 (d, $J=6.0$ Hz, 1H, OH), 3.42 (m, 1H), 3.61 (q, $J=7.0$ Hz, 1H), 3.65 (m, 1H), 3.74 (m, 1H), 3.81 (m, 1H), 4.01 (m, 1H), 5.10 (dd, $J=15$, 8 Hz, 2H), 6.04 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) $\delta$ 18.8, 25.7, 27.7, 28.6, 28.9, 29.0, 30.3, 40.2, 74.5, 81.8, 82.0, 82.2, 82.4, 82.4, 116.9, 136.4, 169.8. FABHRMS calcd for $C_{17}H_{27}O_5$ $(M+H)^+$ 311.1858, found 311.1857.
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20. Physical data for **5**: $R_f=0.41$ (40% EtOAc/petroleum ether); $[\alpha]_D^{25}=-4.3$ (*c* 0.91, $C_6H_6$); $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 1.15 (m, 1H), 1.32 (m, 1H), 1.56 (m, 2H), 1.70 (m, 3H), 1.83 (m, 6H), 1.98 (m, 1H), 2.13 (m, 1H), 2.31 (m, 1H), 3.21 (br s, 1H, OH), 3.53 (m, 2H), 3.72 (m, 2H), 3.84 (m, 4H), 4.01 (m, 1H), 4.13 (m, 1H), 5.03 (dd, $J=16.0$, 10.0 Hz, 2H), 5.91 (m, 1H); $^{13}$C NMR (75 MHz, $C_6D_6$) $\delta$ 21.9, 25.7, 27.7, 28.3, 28.9, 29.3, 32.4, 39.0, 63.7, 65.0, 73.2, 77.4, 82.2, 82.4, 82.8, 83.2, 117.0, 120.2, 136.1. FABHRMS calcd for $C_{19}H_{30}O_6$ $(M+Na)^+$ 377.1940, found 377.1939.
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