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A Modular Synthesis of the Bis-Tetrahydrofuran Core of Rolliniastatin from Pyranoside Precursors

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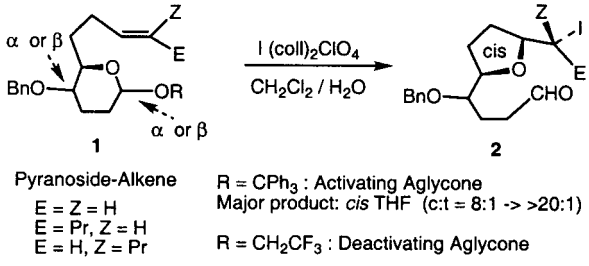
Abstract—The iodoetherification of C6 allyllated 2,3-dideoxypyranosides has been shown to give *cis*-2,5-disubstituted tetrahydrofurans in high stereoselectivity. This result is applied to a modular synthesis of the bis-THF core of the acetogenin, rolliniastatin.

Introduction

The tetrahydrofuran (THF) containing acetogenins have attracted attention because of their potent antitumor, immunosuppressive and pesticidal activities.[1] Their structures are characterized by the presence of 2,5-bishydroxyalkyl-THF or 2,2′-linked, 5-5′-bis(hydroxyalkyl)bis-THF subunits of variable stereochemistry. A number of total and formal syntheses have been reported. These procedures highlight methodologies for stereoselective THF formation, and strategies for enantioselective synthesis of THF precursors.[2–7] Among the more successful approaches for THF formation are the cyclization of hydroxy epoxides,[3] hydroxy alkenes[4] and variations of the Williamson ether synthesis.[5] Protocols based on Sharpless epoxidation and dihydroxylation,[2–4] addition of chiral allenyltin reagents to aldehydes,[5b] and elaboration of natural enantiopure materials,[6] have been employed for synthesis of the THF precursors. We have previously reported that C6 allylated pyranosides **1** are practical templates for *cis*-2,5-disubstituted THF's **2** (Scheme 1).[8] The application of this methodology to the adjacently linked bis-THF subunits of the acetogenins is illustrated herein,[6a] by the synthesis of the bis-THF core of rolliniastatin **3**.[9,10]



Scheme 1.

Our synthetic strategy was guided by observations on the rate- and stereo- controlling effects of the aglycone substituent in the iodoetherification reaction of C6 allylated 2,3-dideoxypyranosides. Substrates containing more electronegative aglycone substituents were less reactive than systems with less electronegative aglycones. Systems with sterically demanding aglycones showed a preference for the *cis*-2,5-disubstituted THF. In particular, trityl glycosides gave *cis*:*trans* stereoselectivities in the range of 8:1 to 20:1. These results were general with respect to the relative configuration of the vicinal carbinol centers (*erythro* or *threo*), and the substitution pattern of the alkene (terminal, and *Z* or *E* disubstituted alkenes). *t*-Butyl glycosides were less selective but also displayed selectivities as high as 8:1 (Scheme 1).

Accordingly we envisaged a modular approach to the *threo-cis-threo-cis-erythro* bis-THF subunit **4** of rolliniastatin. The bis-THF **4** could be related to a bis-pyranoside-*E*-alkene **5** or **6** in which one pyranoside contains a stereodirecting *t*-butyl or trityl aglycone and the other a deactivating trifluorethyl aglycone (Scheme 2). Regioselective halocyclization involving the ring oxygen of the more reactive, *t*-butyl or trityl pyranoside would give a *cis*-2,5-disubstituted THF iodide, and subsequent iodide displacement by the ring oxygen of the second pyranoside would lead to the bis-THF **4**. The key bis-pyranoside may be assembled in a convergent fashion from allylated pyranosides **7** and **8**. In principle pyranoside subunits of variable complexity and stereochemistry may be incorporated into the bis-pyranoside precursor, thereby leading to a variety of bis-THF systems. Furthermore, the stepwise liberation of the aldehydic carbons would allow for attachment of

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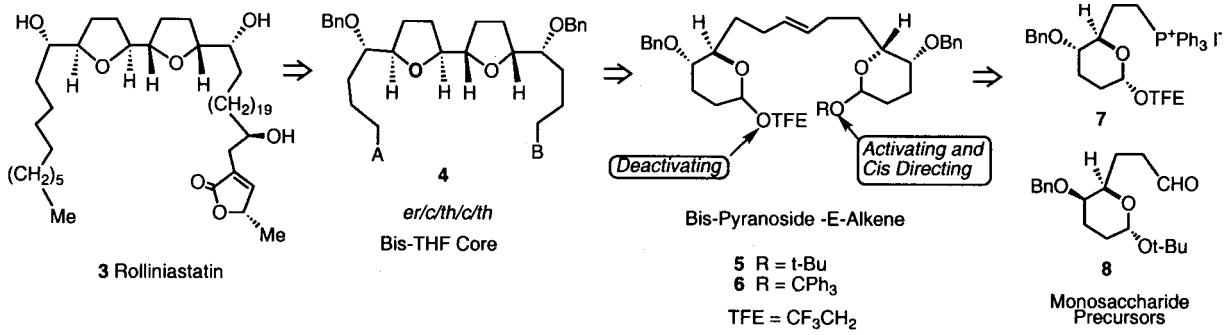


Scheme 2.

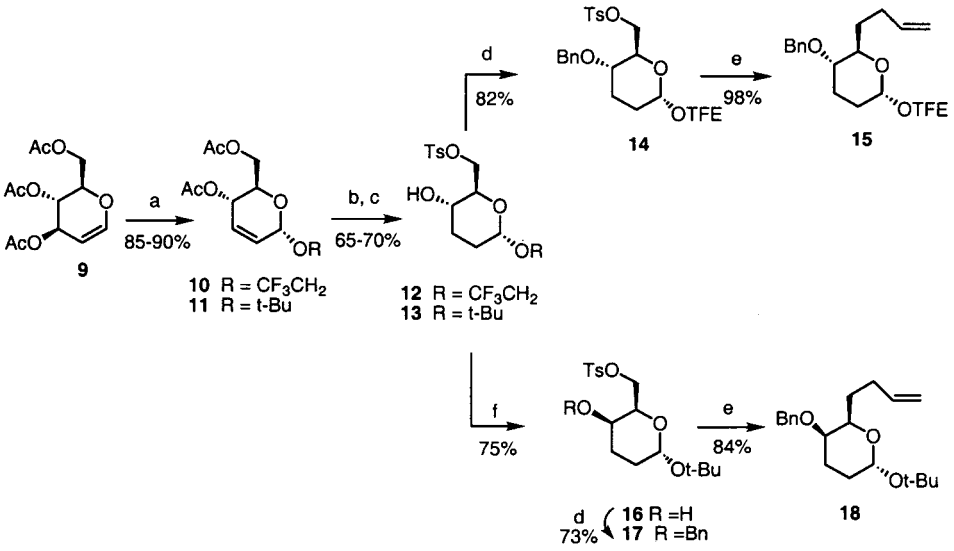
different side chains to the central bis-THF core, an attractive feature because of the structural diversity of these appendages.

Results and Discussion

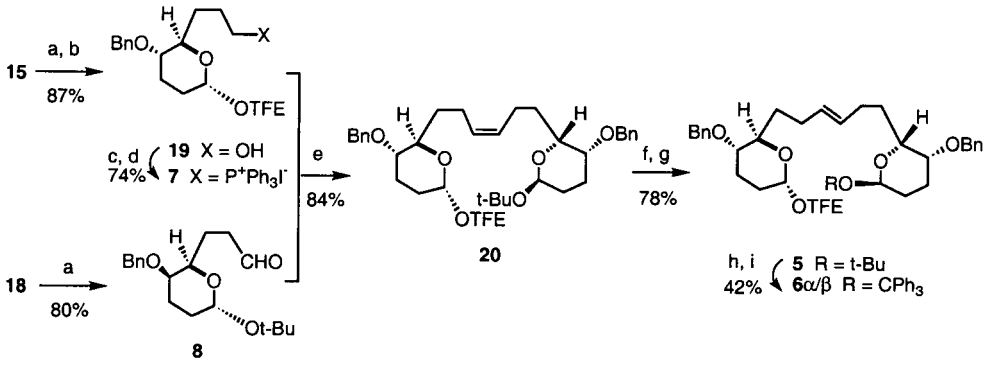
The synthesis of the pyranoside precursors started with the Ferrier reaction of tri-*O*-acetyl-D-glucal **9** and *t*-butanol or trifluoroethanol (Scheme 3).[11] The resulting 2,3-enopyranosides **10** and **11** were individually converted to the hydroxytosylate derivatives **12** and **13** over three straightforward operations: hydrogenation, acetate hydrolysis and selective tosylation of the resulting primary alcohols. Benzylation of **12** provided **14**, which led to alkene **15** on treatment with allylmagnesium bromide in diethyl ether containing 10% TMEDA. The *t*-butyl 2,3-dideoxygluco tosylate **13** was converted to its *galacto* epimer **16** via the Mitsunobu reaction on the alcohol and hydrolysis of the resulting benzoate.[12] Application of the two step benzylation-allylation sequence on **16** provided the *t*-butyl 2,3-dideoxy *galacto* alkene **18**.

Our initial plan for the synthesis of the key bis-pyranoside-E-alkenes **5** called for an *E*-selective coupling of Wittig partners. The aldehyde component **8** was obtained from the ozonolysis of the *t*-butyl alkene **18** (Scheme 4). The trifluoroethyl alkene **15** was converted to the phosphonium salt **7** over four straightforward steps: ozonolysis of the alkene, reduction of the aldehyde product, iodination of the resulting alcohol, and phosphonium salt formation. Unfortunately, the Schlosser variation which is reported to give high *E* selectivity with unstabilized ylides, led to poor *E*/*Z* ratios.[13] This problem was addressed by carrying out the conventional Wittig procedure on **7** and **8**, to produce the *Z* alkene **20** in greater than 95% selectivity (as determined by NMR analysis), and subsequently performing the two step Vedejs protocol for stereospecific alkene inversion.[14]The three step sequence from **7** and **8** to *E*-alkene **5** proceeded in 66% overall yield. The stereochemistry of the *Z* and *E* alkenes was established by comparison of the ^{13}C chemical shifts of the olefinic carbons. The carbons of the *Z* isomer are known to resonate upfield relative to those of the *E* isomer (δ: 129.5 and 130.1 vs. 130.0 and 130.7 ppm).[15] The trityl bispyranoside derivative was obtained as an inseparable mixture **6**α/β, via selective hydrolysis of the *t*-butyl glycoside in **5**, followed by silver triflate mediated tritylation of the resulting lactol.

Iodoetherification of the *t*-butyl-trifluoroethyl bispyranoside **5** in wet dichloromethane with iodonium dicollidine



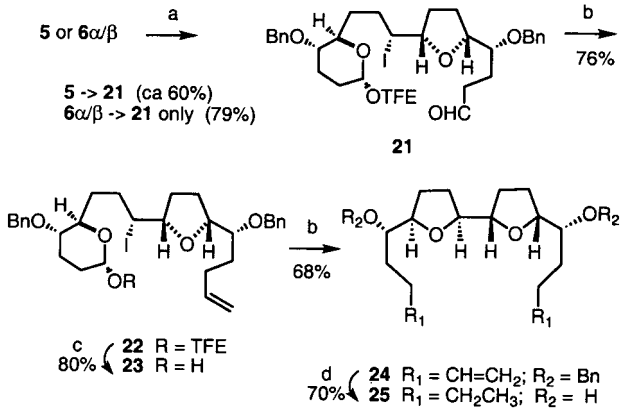
Scheme 3. (a) CF_3CH_2OH or *t*-BuOH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (b) (i) H_2, Pd/C. EtOAc; (ii) NaOMe, MeOH; (c) TsCl, py.; (d) BnBr, NaH, THF; Bu_4NI; (e) $CH_2{=}CHCH_2MgBr$, TMEDA, Et_2O; (f) (i) Ph_3P, DEAD, PhCOOH, $PhCH_3$; (ii) NaOMe, MeOH.



Scheme 4. (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*-Pr)$_2$NEt, 80°C; (e) **7**, Na(NSiMe$_3$)$_2$, $PhCH_3$, −78°C then **8**; (f) *m*-CPBA, 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.

perchlorate (IDCP) provided an inseparable mixture (ca 6:1) of the desired *cis* THF-iodide **21** and a minor product, which was not identifiable because of considerable overlap of NMR signals in the mixture (Scheme 5). By comparison the iodoetherification of the trityl derivatives **6**α/β led to **21** exclusively. In view of the relative stereoselectivities of *t*-butyl and trityl aglycone substituents in the iodoetherification of simpler pyranoside alkenes, it is probable that the side product in the reaction of **5** is the *trans* THF isomer of **21**. The *cis* stereochemistry of **21** was tentatively inferred from the aforementioned stereoselectivity trends, and subsequently corroborated by careful NMR analysis of the bis-THF system (vide infra).

Pyranoside-THF-iodoaldehydes like **21** are well suited for elaboration into adjacently linked bis-THF subunits with different appendages. In order to evaluate reactions which could be used towards this goal, the aldehyde **21** was converted to the alkene **22** by treatment with methylene triphenylphosphorane at low temperature. Acid hydrolysis of the glycosidic bond in **22** provided the lactol **23** in preparation for a second Wittig olefination. There was some concern that the acid hydrolysis conditions could lead, through an intermediate iodonium ion, to isomerization of the *cis* iodo-THF moiety to the *trans*-product. However, we have shown in experiments on closely related systems that no interconversion occurs when isomeric *cis* and *trans* iodo-THF's are subjected to the identical hydrolysis conditions.[8b] The lactol **23** was next treated with methylene triphenylphosphorane in THF at −78°C and the reaction mixture warmed to room temperature. To our pleasant surprise, these conditions resulted in both olefination of the aldehyde and THF formation, leading to the pseudo symmetrical bis-THF diene **24** in 68% overall yield. For the eventual synthesis of rolliniastatin, it would be necessary to use non-identical phosphoranes in order to access a non-symmetrical bis-THF intermediate. The bis-THF **24** was however important for stereochemical analysis. Thus **24** was transformed under standard hydrogenolysis conditions to the dibutylated bis-hydroxymethyl-bis-THF diol **25**.

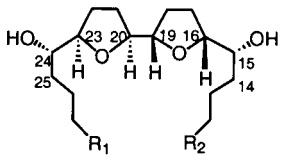


Scheme 5. (a) IDCP, CH_2Cl_2–H_2O; (b) $Ph_3P{=}CH_2$, THF; (c) $BF_3{\cdot}OEt_2$, THF-H_2O; 9d) H_2, Pd/C, MeOH, HCOOH.

Our stereochemical analysis assumes that the iodoetherification reaction proceeds with *anti* addition to the olefin,[16] and that formation of the second THF ring proceeds with configurational inversion at the iodinated carbon. Thus two possible bis-THF motifs are possible, *er/c/th/c/th* or *er/tr/th/tr/th* depending on whether the initial iodoetherifiction gave the *cis* or the *trans* THF. The *er/c/th/c/th* motif was verified by comparison of the ^{13}C chemical shifts of carbinol carbons of the diol **25**, and the corresponding carbons in rolliniastatin **3**[9] (*er/c/th/c/th*) and bullatacin **26**[17] (*er/tr/th/tr/th*) (Table 1). Specific assignments were based on ^1H–^1H COSY, HSQC and HMBC experiments and, or comparisons with previously assigned spectra.[18] Identification based on comparison of the proton data for **25-diacetate**, rolliniastatin triacetate (**3-triacetate**), and uvaracin diacetate (**27-diacetate**), was also attempted using the method of Hoye.[19] However this was not conclusive because of the similarity in the sums of the differences in chemical shifts ($\Sigma|\Delta\delta's|$) for the oxymethine protons in **25-diacetate** relative to the corresponding protons in **3-triacetate** and **27-diacetate** (0.09 and 0.16 respectively).

It was also possible to assign the methylene carbons in the THF rings of **25** by correlating the diagnostic methylenes of the THF rings (δ: 1.78, 1.9 ppm, both m, 4H ea.) to four carbon resonances at δ: 28.9, 28.6, 28.1 and 23.9 ppm. The most upfield of these signals does not fit the assignment in the original structural analysis of rolliniastatin. In this case the methylenes were matched with three resonances at δ: 28.7, 28.4 and 27.8 (two carbons) ppm.[9] However, it should be noted that these assignments were ambiguous. More recently, in studies involving both mono- and bis-THF

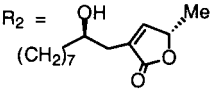
Table 1. NMR correlation of 25 and 25-diacetate with known bis-THF's. (superscripts a, b, c, d, e, and f-assignments in each pair may be interchanged)

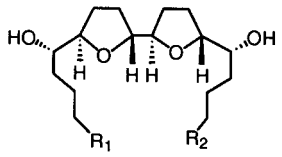


Rolliniastatin Core (er/c/th/c/th)

25 $R_1 = R_2 = CH_3$

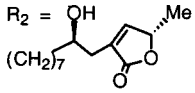
3 $R_1 = CH_3(CH_2)_6$; R_2 =



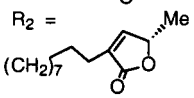


Bullatacin/Uvaricin Core (er/t/th/t/th)

26 $R_1 = CH_3(CH_2)_6$; R_2 =



27 $R_1 = CH_3(CH_2)_6$; R_2 =



Carbon	C NMR of alcohols			H NMR of acetate derivatives		
	25	**3**	**26**	**25-Diacetate**	**3-Triacetate**	**27-Diacetate**
14	34.1	34.1	33.3			
15	74.2	74.0	74.1	4.89[a]	4.88	4.86
16	83.1[e]	83.0	83.3	3.98[b]	3.96	3.98
19	81.3[f]	81.1	82.5	3.83[c]	3.81	3.89
20	81.2[f]	81.0	82.2	3.86[c]	3.85	3.89
23	83.3[e]	83.0	82.8	3.94[b]	3.92	3.98
24	72.0	71.8	71.3	4.92[a]	4.91	4.92
25	32.7	32.8	32.4			
					$\Sigma\|\Delta\delta\|=0.09$	$\Sigma\|\Delta\delta\|=0.16$

acetogenins, the methylene carbon which is proximal to a vicinal *erythro* dioxy subunit has been observed to consistently resonate at 3–4 ppm upfield compared to the situation in which a methylene is connected to a *threo* subunit.[18] This trend supports our assignment and suggests that the assignment of the C22 methylene in rolliniastatin should be reexamined.

Conclusion

In summary, the use of C6 allylated 2,3-dideoxypyranosides as precursors for the modular synthesis of the adjacently linked, bis-THF subunits of the acetogenins has been demonstrated. Features of this methodology are the convergent assembly of a bis-pyranoside-alkene THF precursor, and a highly stereoselective, four step conversion of this key intermediate to a bis-THF. A pivotal reaction in this sequence is the iodoetherification reaction of the bis-pyranoside-alkene to a highly functionalized *cis*-2,5-disubstituted THF. In principle, assembly of different bis-pyranoside alkenes from C6 allylated partners of varying constitution and complexity would lead to a variety of bis-THF systems.

Experimental

General

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 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 ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively, in $CDCl_3$ solutions, with $CHCl_3$ as internal standard. Elemental analysis were performed by Schwarzkopf Microanalysis Laboratory. High resolution mass spectroscopy was carried out at the Mass Spectral Facilities at PennState and the University of Illinois at Urbana-Champaign.

Trifluoroethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*gluco*-2-enopyranoside (10). To a solution of tri-*O*-acetyl-D-glucal **9** (15.0 g, 55.0 mmol) in dry CH_2Cl_2 (400 mL) was added CF_3CH_2OH (11.0 g, 110 mmol) and $BF_3{\cdot}Et_2O$ (0.93 mL, 7.3 mmol). The reaction was stirred at rt for 30 min. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the residue afforded **10** (15.1 g, 90%). R_f=0.76 (10% ethyl acetate/petroleum ether). ^1H NMR δ 2.15 (s, 6H), 4.00 (m, 2H), 4.13 (m, 1H), 4.24 (m, 2H), 5.15 (br s, 1H), 5.38 (dd, J=1.5, 8.5 Hz, 1H), 5.90 (dt, J=1.5, 8.5 Hz, 1H), 5.99 (bd, J=8.5 Hz, 1H). ^{13}C NMR: δ 21.1, 21.4, 63.2, 65.5 (q, J_{CCF}=34.0 Hz), 65.6, 68.2, 95.1, 124.4 (q, J_{CF}=276 Hz), 126.9, 130.9, 170.6, 170.1. MS (ES) *m/z* 330 ($M+NH_4^+$).

Trifluoroethyl 6-*O*-tosyl-2,3-dideoxy-α-D-*gluco*-pyranoside (12). A mixture of **10** (30.0 g, 0.100 mol) and 10% Pd/C in ethyl acetate (400 mL) was stirred under a hydrogen atmosphere (balloon) for 16 h. The suspension was then filtered through a short column of Celite and concentrated in vacuo to give a clear syrup (29.3 g). This material was dissolved in MeOH (200 mL) and treated with a solution of NaOMe in MeOH (ca 1 M, 20 mL) for 2 h at rt. The solution was then adjusted to pH 8 by dropwise addition of 10% HCl/MeOH, and concentrated under reduced pressure. The residue was partitioned between ether and saturated aqueous

$NaHCO_3$. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography of the resulting gum provided trifluoroethyl 2,3-dideoxy-α-D-*gluco*-pyranoside (18 g, 80%). R_f=0.20 (50% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.75–2.20 (m, 4H), 2.60 (br s, 1H, D_2O ex), 2.85 (br s, 1H, D_2O ex), 3.60 (m, 1H), 3.72 (m, 1H), 3.80–4.15 (m, 4H), 4.94 (br s, 1H).

To a stirred solution of material obtained from the previous step (7.45 g, 32.4 mmol) in dry pyridine (35 mL) was added p-toluenesulfonyl chloride (8.00 g, 42.1 mmol) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 2.5 h at rt. then quenched with MeOH. After concentration of the solution, the residue was dissolved in ether and washed with saturated aqueous $NaHCO_3$ and brine. The ethereal solution was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography to give product **12** (10.0 g, 84%). R_f=0.3 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+67° (*c*=0.72, $CHCl_3$). IR (neat) 3530 cm^{-1}. ^{1}H NMR: δ 1.68–1.95 (m, 4H), 2.43 (s, 3H), 2.70 (br s, 1H, D_2O ex), 3.62 (m, 2H), 3.81 (m, 2H), 4.19–4.36 (m, 2H), 4.79 (br s, 1H), 7.34 (d, *J*=8.0 Hz, 2H), 7.78 (d, *J*=8.0 Hz, 2H). ^{13}C NMR: δ 21.7, 26.7, 28.6, 64.0 (q, J_{CCF}=34.6 Hz), 65.3, 69.6, 72.3, 96.9, 123.8 (q, J_{CF}=280 Hz), 128.0, 130.0, 132.9, 145.1. Anal. Calcd for $C_{15}H_{19}O_{16}SF_3$: C, 46.87; H, 4.98. Found: C, 46.53; H, 5.10.

Trifluoroethyl 4-*O*-benzyl-6-*O*-tosyl-2,3-dideoxy-α-D-*gluco*-pyranoside (14). To a solution of **12** (8.90 g, 23.0 mmol) in dry THF (120 mL) at 0°C was added NaH (1.15 g, 60% in mineral oil, 28.8 mmol) and benzyl bromide (3.14 mL, 26.4 mmol), followed by tetrabutylammonium iodide (450 mg, 1.2 mmol). The solution was stirred for 2 h at rt under an argon atmosphere. The reaction was quenched with methanol (0.5 mL), and extracted with ether. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography to give **14** (9.3 g, 82%). R_f=0.20 (10% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+76.6° (*c*=2.74, $CHCl_3$). ^{1}H NMR: δ 1.84 (m, 2H), 2.05 (m, 1H), 2.18 (m, 1H), 2.54 (s, 3H), 3.52 (dt, *J*=4.6, 11.1 Hz, 1H), 3.85–4.00 (m, 3H), 4.33 (dd, *J*=2.1, 10.6 Hz, 1H), 4.42 (dd, *J*=4.7, 10.6 Hz, 1H), 4.58 (ABq, Δδ=63.5 Hz, *J*=11.3 Hz, 2H), 4.92 (br s, 1H), 7.34–7.52 (m, 7H), 7.90 (d, *J*=9.3 Hz, 1H). Anal. Calcd for $C_{22}H_{25}O_6SF_3$: C, 55.69; H, 5.31. Found: C, 55.64; H, 5.46.

Trifluoroethyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy-α-D-*gluco*-non-8-enopyranoside (15). Allylmagnesium bromide (90 mL of a 1 M solution in ether, 90 mmol) was added to a mixture of **14** (7.80 g, 16.5 mmol), TMEDA (0.85 mL) and dry ether (85 mL), at rt under an atmosphere of argon. The reaction was stirred for 8 h, then quenched with saturated aqueous NH_4Cl and extracted with ether. The organic extract was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Flash chromatography of the crude residue afforded **15** (5.50 g, 98%). R_f=0.30 (10% ethyl acetate/petroleum ether): IR (neat) 1641 cm^{-1}. ^{1}H NMR: δ 1.65 (m, 1H), 1.90 (m, 2H), 2.05–2.50 (m, 5H), 3.30 (dt, *J*=5.5, 11.0 Hz 1H), 3.78 (dt, *J*=2.7, 9.0 Hz, 1H), 4.0 (m, 2H), 4.70 (ABq, Δδ=0.20 ppm, *J*=12.0 Hz, 2H), 4.97 (br s, 1H), 5.15 (m, 2H), 5.98 (m, 1H), 7.50 (m, 5H). ^{13}C NMR: δ 23.6, 28.7, 29.7, 31.2, 63.8 (q, J_{CCF}=34.4 Hz), 70.7, 71.8, 76.8, 96.7, 114.7, 124.3 (q, J_{CF}=280 Hz), 127.8, 127.9, 128.5, 138.4, 138.7. Anal. Calcd for $C_{18}H_{23}O_3F_3$: C, 63.04; H, 7.02. Found: C, 62.78; H, 6.70.

***t*-Butyl 6-*O*-tosyl-2,3-dideoxy-α-D-*galacto*-pyranoside (16).** A solution of benzoic acid (3.68 g, 30 mmol) and DEAD (4.72 mL, 30.0 mmol) in dry toluene (120 mL) was slowly added, at −15°C, under an atmosphere of argon, to a mixture of tosylate **13**[20] (7.38 g, 20.6 mmol) and triphenylphosphine (6.61 g, 24.0 mmol) in dry toluene (120 mL). The reaction mixture was allowed to warm to rt and stirred for an additional 0.5 h at this temperature. The solution was then concentrated under reduced pressure, neutralized by addition of saturated aqueous $NaHCO_3$, and extracted with ether. The organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo. For characterization purposes, a small amount of the crude residue was purified by flash chromatography to give **16-benzoate**. R_f=0.45 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+16° (*c*=0.39, CH_2Cl_2). IR (neat) 1720 cm^{-1}. ^{1}H NMR: δ 1.23 (s, 9H), 1.40 (m, 1H), 1.80–2.15 (m, 3H), 2.25 (s, 3H), 3.94–4.07 (m, 2H), 4.41 (dt, *J*=0.9, 6.5 Hz, 1H), 5.06 (br s, 1H), 5.18 (br s, 1H), 7.12 (d, *J*=8.1 Hz, 2H), 7.38 (t, *J*=7.5 Hz, 2H), 7.53 (t, *J*=7.4 Hz, 1H), 7.66 (d, *J*=8.3 Hz, 2H), 7.92 (d, *J*=7.2 Hz, 2H). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.32; H, 6.54. Found: C, 62.04; H, 6.71.

1 M NaOMe in MeOH (20 mL) was added to a mixture of the crude material from the previous step in MeOH (200 mL). The solution was stirred at rt for 2 h, then adjusted to pH 8 by the dropwise addition of 10% HCl/MeOH, and concentrated under reduced pressure. The residue was diluted with brine and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Purification of the residue by flash chromatography provided **16** (5.4 g, 73% from **13**) as a light yellow oil. R_f=0.85 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+39° (*c*=0.29, CH_2Cl_2). IR (neat) 3533, 1598 cm^{-1}. ^{1}H NMR: δ 1.19 (s, 9H), 1.38 (m, 1H), 1.68 (m, 1H), 1.98 (d, *J*=8.0 Hz, D_2O ex), 2.10 (m, 2H), 2.44 (s, 3H), 3.92 (dd, *J*=6.8, 10.2 Hz, 1H), 4.11 (dd, *J*=5.9, 10.2 Hz, 1H), 4.20 (t, *J*=6.8 Hz, 1H), 5.08 (br s, 1H), 7.32 (d, *J*=8.1 Hz, 2H), 7.77 (d, *J*=8.1 Hz, 2H). ^{13}C NMR: δ 21.7, 25.2, 28.6, 28.8, 64.3, 67.9, 69.7, 74.6, 91.3, 128.1, 129.9, 132.9, 144.9. Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.96; H, 7.31. Found: C, 56.65; H, 7.42.

***t*-butyl 4-*O*-Benzyl-6-*O*-tosyl-2,3-dideoxy-α-D-*galacto*-pyranoside (17).** To a solution of **16** (5.39 g, 15.2 mmol) in dry THF (50 mL) at 0°C was added NaH (1.20 g, 60% in mineral oil, 30.0 mmol), tetrabutylammonium iodide (830 mg, 22.5 mmol), and benzyl bromide (2.8 mL, 26 mmol). The reaction mixture was warmed to rt, stirred for an additional 2 h, then quenched by the addition of methanol (1 mL), diluted with water and extracted with ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatograpy to give **17** (4.83 g, 71%). R_f=0.75 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+25° (*c*=0.32, $CHCl_3$). ^{1}H NMR: δ 1.32 (s, 9H), 1.45 (m, 1H), 1.90–2.15 (m, 3H), 2.52 (s, 3H), 3.59 (br s,

1H), 4.21 (m, 2H), 4.29 (br t, J=5.6 Hz, 1H), 4.54 (ABq, $\Delta\delta$=0.27 ppm, J=12.0 Hz, 2H), 5.22 (d, J=2.6 Hz, 1H), 7.38 (m, 7H), 7.85 (d, J=8.3 Hz, 2H). ^{13}C NMR: δ 20.4, 21.7, 25.7, 28.7, 68.1, 69.9, 70.7, 74.4, 91.3, 127.7, 127.8, 128.0, 128.4, 129.9, 133.0, 138.3, 144.8. Anal. Calcd for $C_{24}H_{32}O_6S$: C, 64.26; H, 7.19. Found: C, 64.32; H, 7.35.

***t*-Butyl 4-*O*-benzyl-2,3,6,7,8,9-hexadeoxy-α-D-*galacto*-non-8-enopyranoside (18).** Tosylate **17** (4.47 g, 9.98 mmol) was subjected to the allylation procedure used for the preparation of alkene **15**. Flash chromatography of the crude product provided alkene **18** (2.66 g, 84%). R_f=0.44 (10% ethyl acetate/petroleum ether). IR (neat) 1651 cm^{-1}. ^{1}H NMR: δ 1.24 (s, 9H), 1.20–2.20 (m, 8H), 3.34 (br s, 1H), 3.91(m, 1H), 4.55 (ABq, $\Delta\delta$=0.28 ppm, J=12.0 Hz, 2H), 4.94 (m, 2H), 5.16 (br s, 1H), 5.80 (m, 1H), 7.24–7.38 (m, 5H). ^{13}C NMR: δ 21.2, 26.1, 28.9, 30.0, 31.0, 69.8, 70.6, 72.7, 73.9, 91.2, 114.4, 127.5, 127.9, 128.4, 138.9, 139.0. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.04; H, 9.62.

Trifluoroethyl 4-*O*-Benzyl -2,3,6,7-tetradeoxy-α-D-*gluco*-octopyranoside (19). A stream of O_3 in O_2 was bubbled through a solution of alkene **15** (7.80 g, 22.7 mmol) in 4:1 CH_2Cl_2:MeOH (250 mL) at −78°C, until **15** was not detectable by tlc (10% ethyl acetate/petroleum ether). The mixture was flushed with N_2 and then triphenylphosphine (6.60 g, 25.0 mmol) was added. The solution was warmed to rt, stirred for 2 h, and concentrated in vacuo to give a slurry, which was used directly in the next step. For characterization purpose, a sample of the aldehyde product was purified by flash chromatography: R_f=0.33 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+128° (c=0.38, CH_2Cl_2); IR (neat) 2943, 1715 cm^{-1}. ^{1}H NMR: δ 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).

$NaBH_4$ (5.63 mmol, 213 mg) was added at rt to a solution of the crude mixture from the previous step in EtOH (100 mL). The reaction mixture was stirred for 1 h, carefully treated with 10% HCl in MeOH until the pH was 8, and evaporated under reduced pressure. Flash chromatography of the residue provided alcohol **19** (6.79 g, 87% from **15**). R_f=0.12 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+97° (c=0.34, CH_2Cl_2). IR (neat) 3401 cm^{-1}. ^{1}H NMR: δ 1.53–2.2 (m, 8H), 3.30 (dt, J=4.4, 9.7 Hz, 1H), 3.75 (m, 3H), 4.06 (m, 2H), 4.67 (ABq, $\Delta\delta$=55.9 Hz, J=11.4 Hz, 2H), 4.96 (s, 1H), 7.32–7.50 (m, 5H). ^{13}C NMR: δ 23.5, 28.3, 28.7, 63.0, 63.9 (q, J_{CCF}=34.7 Hz), 70.8, 72.3, 76.6, 96.8, 122.7 (q, J_{CF}=277 Hz), 127.8, 127.9, 128.5, 138.3. Anal. Calcd for $C_{17}H_{23}O_4F_3$: C, 58.61; H, 6.65. Found: C, 58.41; H, 6.79.

Trifluoroethyl pyranoside-phosphonium salt (7). Iodine (5.68 g, 22.4 mmol) was added to a mixture of alcohol **19** (6.75 g, 19.5 mmol), triphenylphosphine (7.65 g, 29.2 mmol) and imidazole (2.78 g, 40.8 mmol) in dry benzene (200 mL). The reaction mixture was heated at reflux for 1 h under an atmosphere of argon, then diluted with ether and washed with 10% aqueous $Na_2S_2O_3$, and brine. The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Flash chromatography of the residue afforded the iodide derivative (7.54 g, 85%). R_f=0.60 (20% ethyl acetate/petroleum ether). $[\alpha]_D^{23}$=+61° (c=0.68, CH_2Cl_2). ^{1}H NMR: δ 1.59–2.15 (m, 8H), 3.25 (m, 3H), 3.66 (m, 1H), 3.97 (m, 2H), 4.63 (m, 2H), 4.88 (br s, 1H), 7.30–7.50 (m, 5H). ^{13}C NMR δ 7.0, 23.5, 28.6, 29.6, 33.0, 63.9 (q, J_{CCF}=35.0 Hz), 70.7, 71.7, 76.4, 96.80, 122.6 (q, J_{CF}=278 Hz), 127.9, 128.5, 128.7, 138.3. HRMS calcd for $C_{17}H_{22}O_3F_3I$ 458.0589, found 458.0545.

Diisopropylethylamine (0.7 mL, 3.8 mmol) was added to a mixture of the iodide from the previous step (1.16 g, 2.53 mmol) and triphenylphosphine (1.33 g, 5.06 mmol) in anhydrous toluene (40 mL) and acetonitrile (20 mL). The reaction mixture was heated at reflux under an atmosphere of argon for 24 h, at which time most of the solvent was removed under reduced pressure. The resulting syrup was triturated with hexane (2×25 mL) and the residual gum was subjected to flash chromatography to give the phosphonium salt **7** (1.59 g, 87%) as a pale yellow gum. R_f=0.34 (10% MeOH/ethyl acetate). ^{1}H NMR: δ 1.40–2.20 (m, 8H), 3.25 (m, 1H), 3.45 (m, 2H), 3.63 (m, 2H), 4.55 (ABq, $\Delta\delta$=46.9 Hz, J=11.4 Hz, 2H), 4.79 (br s, 1H), 7.20–7.90 (m, 20H). ^{13}C NMR δ 19.2, 23.3, 23.4 (d, J_{CP}=50.5 Hz), 28.2, 32.4 (d, J_{CCP}=16.0 Hz), 64.2 (q, J_{CCF}=35.3 Hz), 70.7, 72.1, 76.3, 96.7, 118.1 (d, J_{CP}=86.4 Hz), 122.6 (q, J_{CF}=278 Hz, partially buried under aromatic carbons), 127.6, 127.9, 128.4, 130.5 (d, J_{CCP}=12.5 Hz), 133.6 (d, J_{CCCP}=9.9 Hz), 135.0. MS (FAB), m/z 593 [(M−I)$^+$, 100%].

***t*-Butyl pyranoside aldehyde (8).** Alkene **18** (555 mg, 1.75 mmol) was subjected to the ozonolysis procedure described in the preparation of **19**. Flash chromatography of the crude product provided aldehyde **8** (447 mg, 80%). R_f=0.51 (20% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.22 (s, 9H), 1.27 (m, 1H), 1.75 (m, 1H), 2.05 (m, 4H), 2.48 (m, 2H), 3.38 (br s, 1H), 3.97 (dd, J=5.2, 6.1 Hz, 1H), 4.55 (ABq, $\Delta\delta$=85.6 Hz, J=12.0 Hz, 2H), 5.19 (br s, 1H), 7.31–7.40 (m, 5H), 9.76 (s, 1H). ^{13}C NMR δ 21.5, 24.9, 26.5, 29.5, 40.9, 70.0, 71.3, 73.5, 74.5, 91.9, 128.3, 128.6, 129.0, 139.2, 203.2.

***t*-Butyl-trifluoroethyl bispyranoside *Z*-alkene (20).** Sodium bis(trimethylsilyl) amide (1.38 mL of a 1 M solution in toluene, 1.38 mmol) was added under an argon atmosphere, at 0°C, to solution of phosphonium salt **7** (1.18 g, 1.65 mmol) in dry toluene (25 mL). The yellow-orange suspension was stirred for 1 h at rt then cooled to −78°C, at which time a solution of aldehyde **8** (0.44 g, 1.38 mmol) in dry toluene (20 mL) was added dropwise, over 30 min. After an additional 15 min, the reaction mixture was warmed to rt and diluted with ether (100 mL). The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Flash chromatography of the residue afforded **20** (732 mg, 84%). R_f=0.55 (10% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.27 (s, 9H), 1.30–2.28 (m, 16H), 3.19 (dt, J=3.8, 9.6 Hz, 1H), 3.37 (br s, 1H), 3.63 (dt, J=1.3, 8.8 Hz, 1H), 3.75–4.00 (m, 3H), 4.58 (ABq, $\Delta\delta$=77.7 Hz, J=12.6 Hz, 2H), 4.60 (ABq, $\Delta\delta$=51.9 Hz, J=11.7 Hz, 2H), 4.67 (br s, 1H), 5.19 (br s, 1H), 5.42 (m, 2H), 7.28–7.42 (m, 10H). ^{13}C NMR: δ 21.2, 23.2, 23.7, 26.1, 28.7, 28.9, 31.6, 31.9, 63.7 (q, J_{CCF}=34.5 Hz), 69.9, 70.7, 70.8, 72.0, 72.9, 73.9, 76.8, 91.2, 96.6, 124.2 (q, J_{CF}=278 Hz), 127.5,

127.8, 128.1, 128.3, 128.5, 129.5, 130.1, 138.4, 139.0. Anal. Calcd for $C_{36}H_{49}O_6F_3$: C, 68.11; H, 7.78. Found: C, 67.85; H, 7.84.

***t*-Butyl-trifluoroethyl bispyranoside *E*-alkene (5).** *m*-CPBA (784 mg, 50% w/w, 2.5 mmol) was mixed with 4 M NaH_2PO_4/Na_2HPO_4 buffer (40 mL) and CH_2Cl_2 (20 mL). The suspension was added to a solution of **20** (635 mg, 0.998 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 1 h. The organic layer was separated, washed successively with saturated, aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography of the residue afforded the epoxide derivative (650 mg, 100%). R_f=0.45 (20% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.24 (s, 9H), 1.20–2.20 (m, 16H), 2.98 (m, 2H), 3.20 (m, 1H), 3.39 (br s, 1H), 3.60 (m, 1H), 3.79–4.07 (m, 3H), 4.40–4.75 (m, 4H), 4.86 (br s, 1H), 5.20 (br s, 1H), 7.28–7.42 (m, 10H).

A stock solution (ca 0.5 M) of Ph_2PLi was prepared by the addition of a hexane solution of *n*-butyllithium (10.2 mmol, 6.6 mL of a 1.55 M) to a solution of Ph_2PH (1.74 mL, 10.0 mmol) in dry THF (13.4 mL) at rt under an argon atmosphere. The solution was stirred for 1 h at which time an aliquot of the red solution of Ph_2PLi (6.0 mL, 3.0 mmol) was removed and added under an atmosphere of argon, to a THF (10 mL) solution of the product from the previous step (650 mg, 1.00 mmol). The reaction mixture was stirred for an additional 2 h and then treated with freshly distilled MeI (0.374 mL, 6.0 mmol). The mixture was stirred for another 1 h, and *n*-butyllithium (~0.1 mL) was added until a red color persisted. The reaction mixture was diluted with ether (30 mL), filtered through Celite. The filtrate was concentrated in vacuo and the residue was subjected to flash chromagraphy to give **5** (496 mg, 78%). R_f=0.54 (20% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.27 (s, 9H), 1.20–2.23 (m, 16H), 3.19 (dt, J=4.3, 9.9 Hz, 1H), 3.37 (br s, 1H), 3.63 (t, J=8.2 Hz, 1H), 3.75–4.00 (m, 3H), 4.58 (ABq, $\Delta\delta$=77.7 Hz, J=12.6 Hz, 2H), 4.60 (ABq, $\Delta\delta$=51.9 Hz, J=11.7 Hz, 2H), 4.67 (br s, 1H), 5.21 (br s, 1H), 5.39 (m, 2H), 7.28–7.42 (m, 10H). ^{13}C NMR δ 21.2, 23.6, 26.1, 28.6, 28.7, 28.9, 31.6, 32.0, 63.7 (q, J_{CCF}=35.6 Hz), 69.9, 70.7, 70.8, 71.9, 72.9, 73.9, 76.8, 91.2, 96.6, 124.0 (q, J_{CF}=278 Hz), 127.5, 127.8, 127.9, 128.3, 128.5, 130.0, 130.7, 138.4, 139.0. Anal. Calcd for $C_{36}H_{49}O_6F_3$: C, 68.11; H, 7.78. Found: C, 68.00; H, 7.78.

Trityl trifluoroethyl bispyranoside *E*-alkene (6α/β). A solution of *t*-butyl trifluoroethyl bispyranoside *E*-alkene **5** (140 mg, 0.22 mmol) in a 3:1 mixture of THF-0.5M HCl (12 mL) was stirred at rt for 4 h. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the residue afforded the trifluoroethyl- pyranose derivative (90 mg, 70%). R_f=0.15 (20% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.2–2.4 (m, 16H), 2.84 (br s, 1H, D_2O ex.), 3.24 (m, 1H), 3.37 (br s, ca 0.5H), 3.45 (br s, ca 0.5H), 3.56 (m, ca 0.5H), 3.65 (m, 1H), 3.80–4.32 (m, 2H), 4.22 (m, ca 0.5H), 4.56 (m, 2H), 4.78 (m, ca 2.5H), 4.96 (br s, 1H), 5.40 (br s, H_1 0.5H), 5.50 (br s, 2H), 7.08–7.52 (m, 10H). ^{13}C NMR δ 21.7, 24.0, 24.4, 24.6, 25.6, 26.5, 28.6, 29.7, 31.6, 32.3, 33.1, 33.4, 65.0 (q, J_{CCF}=34.0 Hz), 69.9, 71.8, 71.9, 73.0, 73.6, 74.4, 77.8, 92.6, 99.5, 97.8, 97.9, 128.6–131.40 (multiple signals), 139.4, 139.7, 146.2.

A portion of the mixture obtained in the previous step (137 mg, 0.236 mmol), trityl chloride (130 mg, 0.472 mmol), collidine (0.1 mL, 1 mmol), and freshly activated, powdered 4A molecular sieves (100 mg), in anhydrous CH_2Cl_2 (10 mL), was stirred at rt for 10 min. At that time $AgOCOCF_3$ (181 mg, 0.7 mmol) was added to the reaction mixture and stirring was continued for an additional 4 h. The reaction mixture was then poured into saturated aqueous $Na_2S_2O_3$, and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the residual gum afforded **6**α/β (116 mg, 60%) as an inseparable mixture of anomers. R_f=0.82 (20% ethyl acetate/petroleum ether). ^{1}H NMR: δ 1.00–2.40 (m, 16H,), 2.96 (m, ca 0.7H), 3.08 (br s, ca 0.7H), 3.22 (m, 1H), 3.42 (br s, ca 0.3H), 3.64 (m, 1H), 3.75–4.05 (m, ca 2.3H), 4.46 (m, ca 2.7H), 4.68 (m, 2H), 4.88 (br s, 1H) 5.24 (br s, ca 0.3H), 5.33 (br s, 2H), 7.20–7.67 (m, 25H); α/β:ca 3:7 (based on the relative ratio of H4 singlets at 3.42 and 3.08). ^{13}C NMR δ 22.6, 24.2, 24.7, 26.4, 26.9, 27. 9, 29.8, 30.8, 31.9, 64.8 (q, J_{CCF}=34.0 Hz), 71. 9, 72.1, 72.3, 73.1, 73.2, 77.9, 77.9, 78.3, 78.9, 88.3, 89.0, 94.0, 97.7, 99.3, 128.00–131.0 (multiple signals), 139.6, 139.9, 146.1. MS [CI(NH_3)] m/z: 838 $(M+NH_4)^+$, 821 $(M+H)^+$.

THF-iodide (21). A mixture of trityl-*E*-trifluororethyl alkenes **6**α/β (600 mg, 0.75 mmol), CH_2Cl_2 (20 mL), water (0.5 mL) and IDCP (540 mg, 1.15 mmol) was stirred at rt for 20 min. The mixture was then poured into saturated, aqueous $Na_2S_2O_3$, and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the residue afforded *cis*-THF-iodide **21** (406 mg, 79%). R_f=0.35 (2% ether/CH_2Cl_2). IR (neat) 1723 cm^{-1}. ^{1}H NMR (C_6D_6): δ 1.04–2.04 (m, 16H), 2.90 (m, 1H), 3.06 (m, 1H), 3.32 (m, 1H), 3.45–3.70 (m, 4H), 3.87 (m, 1H), 4.20–4.43 (m, 3H,), 4.38 (ABq, $\Delta\delta$=0.48 ppm, J=11.8 Hz, 2H), 6.95–7.40 (m, 10H), 9.25 (s, 1H). ^{13}C NMR (C_6D_6): δ 23.4, 23.9, 27.3, 28.3, 31.6, 31.7, 32.2, 39.8, 42.5, 63.6 (q, J_{CCF}=34.0 Hz), 70.2, 71.7, 72.8, 76.1, 80.2, 82.8, 83.6, 96.7, 127.0–129.0 (several signals buried under C_6D_6 triplet), 138.8, 139.2, 200.2. MS (FAB) m/z 703 $[(M-H)^+$, 30%], 605 $[(M-CF_3CH_2O)^+$, 45%], 577 $[(M-I)^+$, 15%], 497 $[(M-CF_3CH_2O-C_6H_5CH_2O)^+$, 100%). MS (ES) m/z 722 $(M+NH_4^+)$.

Iodocyclization of *t*-butyl-*E*-alkene (5). *t*-butyl alkene **5** (496 mg, 0.782 mmol) was subjected to the iodoetherification procedure that was described for the reaction of **6**α/β, using IDCP (549 mg, 1.17 mmol). Flash chromatography of the crude product afforded an inseparable mixture (406 mg) of *cis*-THF-iodide **21** and an unidentified minor component. The estimated ratio of products based on NMR signal ratio was 6:1.

Iodo-alkene (22). A solution of methylenetriphenyl phosphorane was prepared by addition of *n*-BuLi (1.23 mL of 1.55 M solution in hexane, 1.91 mmol) to a suspension of methyltriphenylphosphonium bromide (760 mg, 2.1 mmol)

in dry THF (5 mL), at 0°C, under an atmosphere of argon. The mixture was stirred at this temperature for 1 h, then cooled to −78°C, at which time a solution of **21** (270 mg, 0.383 mmol) in dry THF (5 mL) was slowly introduced. The solution was allowed to warm to rt, stirred for an additional 10 min, and then diluted with ether. The resulting suspension was filtered through a short column of Celite, and the filtrate was concentrated in vacuo. Flash chromatography of the residue gave **22** (205 mg, 76%). R_f=0.41 (10% ethyl acetate/petroleum ether). ^{1}H NMR (C_6D_6): δ 1.00–2.35 (m, 16H), 2.89 (m, 1H), 3.18 (m, 1H), 3.34 (m, 1H), 3.45–3.86 (m, 4H), 3.95 (m, 1H), 4.23 (ABq, $\Delta\delta$=0.22 ppm, J=11.7 Hz, 2H), 4.35 (br s, 1H), 4.58 (ABq, $\Delta\delta$=0.30 ppm, J=11.7 Hz, 2H), 4.94 (m, 2H), 5.70 (m, 1H), 6.80–7.70 (m, 10H). ^{13}C NMR (C_6D_6): δ 23.8, 27.7, 28.8, 30.3, 31.2, 32.1, 32.2, 32.7, 43.1, 63.9 (q, J_{CCF}=33.5 Hz), 70.6, 72.2, 73.3, 76.5, 81.1, 83.2, 84.1, 97.1, 115.0, 128.6, 128.7, 128.90, 139.1, 139.3.

***c/th/c* Bis-THF diene (24).** To a solution of alkene **22** (160 mg, 0.228 mmol) in a 10:1 mixture of THF/H_2O was added BF_3.Et_2O (120 μL). The mixture was stirred at rt for 5 h, at which time an additional portion of BF_3·Et_2O (120 μL) was introduced, and stirring continued for 2 d. The solution was then poured into saturated, aqueous $NaHCO_3$ and the mixture extracted with ether. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography of the residue afforded the lactol **23** (119 mg, 80%) as an α/β mixture of anomers: R_f=0.17 (20% ethyl acetate/petroleum ether). ^{1}H NMR (C_6D_6): δ 1.0–2.3 (m, 16H), 2.38 (br s, 1H, D_2O ex), 2.58 (br d, J=6.0 Hz, 1H, D_2O ex), 2.93 (m, 1H), 3.20 (m, 2H), 3.75 (m, 2H), 4.04 (m, 1H), 4.01–5.05 (m, 7H), 5.70 (m, 1H), 6.90–7.50 (m, 10H).

A solution of methylenetriphenylphosphorane was prepared by addition of *n*-BuLi (1.55 mL of 1.55 M solution in hexane, 2.40 mmol) to a suspension of methyltriphenylphosphonium bromide (942 mg, 2.64 mmol) in dry THF (10 mL) at 0°C, under an atmosphere of argon. The mixture was stirred at this temperature for 1 h, then cooled to −78°C, at which time a solution of **23** (155 mg, 0.24 mmol) in dry THF (5 mL) was slowly introduced. After 10 min, the solution was warmed to rt, stirred for an additional 1 h, and then diluted with ether. The resulting suspension was filtered through a short column of Celite, and the filtrate concentrated in vacuo. Flash chromatography of the residue gave **24** (83 mg, 68%). R_f=0.65 (20% ethyl acetate/petroleum ether). IR (neat) 1652 cm^{-1}. ^{1}H NMR (C_6D_6): δ 1.40–1.87 (m, 12H), 2.15–2.28 (m, 4H), 3.37 (q, J=6.0 Hz, 1H), 3.57 (m, 1H), 3.72–3.92 (m, 4H), 4.64 (ABq, $\Delta\delta$=0.20 ppm, J=12.0 Hz, 2H), 4.72 (ABq, $\Delta\delta$=0.30 ppm, J=12.0 Hz, 2H), 4.92–5.03 (m, 4H), 5.69–5.83 (m, 2H), 7.05–7.45 (m, 10H). ^{13}C NMR (C_6D_6): δ 26.7, 27.5, 27.6, 27.9, 29.8, 30.1, 30.8, 31.4, 72.8, 72.9, 79.8, 81.0, 82.2, 82.8, 114.50, 114.6, 127.2, 127.5, 127.6, 127.8, 127.9, 128.1, 128.2, 138.9, 139.8, 140.0. MS (Cl/NH_3) m/z 508 [$(M+NH_4)^+$, 100%], 491 [$(M+H)^+$, 2%], 399 [$(M-H)^+$, 6%], 293 [$(M-C_6H_5CH_2O)^+$, 4%].

***c/th/c* Bis-THF (25).** A solution of diene **24** (47 mg, 0.09 mmol), formic acid (20 μL) and 10% Pd/C (5 mg) in MeOH (4 mL) was stirred under hydrogen (balloon) for 16 h. The suspension was then filtered through Celite and the filtrate was evaporated in vacuo. Flash chromatography of the residue provided **25** (20 mg, 70%). R_f=0.25 (50% ethyl acetate/petroleum ether). ^{1}H NMR: δ 0.89 (t, J=7.5 Hz, 6H), 1.20–1.60 (m, 12H), 1.72–1.98 (m, 8H), 2.94 (br s, 2H, D_2O ex), 3.41 (m, 1H), 3.86 (m, 5H). ^{13}C NMR: δ 14.2, 22.9, 23.9, 28.1, 28.4, 28.6, 28.9, 32.7, 34.1, 72.0, 74.2, 81.2, 81.3, 83.1, 83.3. FABHRMS for $C_{18}H_{34}O_4$ 314.2506, found 314.2435.

25-Diacetate. A mixture of diol 24 (5 mg), Ac_2O (0.05 mL) and DMAP (2 mg) in ethyl acetate (2 mL) was stirred at rt for 20 min. Methanol (0.05 mL) was then added to the solution, and the mixture was concentrated under reduced presure. Flash chromatography of the residue provided **25-diacetate** (20 mg, 70%). R_f=0.40 (20% ethyl acetate/petroleum ether). ^{1}H NMR (500 MHz): 0.88 (t, J=7.5 Hz, 6H), 1.20–1.40 (m, 12H), 1.55–1.90 (m, 8H), 2.05, 2.07 (both s, 3H ea), 3.83 (m, 1H), 3.86 (q, J=6.5 Hz, 1H), 3.94 (q, J=6.0 Hz, 1H), 3.98 (dt, J=6.5 Hz, 1H), 4.89 (m, 1H), 4.92 (m, 1H).

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