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1,2-*O*-Isopropylidene-5-alkene templates for the synthesis of oligo-tetrahydrofurans

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Abstract—The highly functionalized THF **4** was prepared in eight steps from 2,5-cyclooctadiene. The key step in this synthesis was a novel desymmetrization reaction involving the iodoetherification of the C2 symmetric bis-isopropylidene alkene **6** to THF **4**. The versatility of **4** was demonstrated by its conversion to bis-THF **3**, a known precursor for trilobacin, and to the tris-THF-lactone **5**, a potential relay compound for cyclic polyether analogues.

1. Introduction

2,5-Disubstituted tetrahydrofurans (THFs) are subunits of several groups of bioactive natural products. Prominent examples are the acetogenins and the polyether antibiotics which are noted for their potent and wide ranging pharmacological properties.[1,2] Both groups have attracted considerable synthetic attention.[3–6] We have been interested in applying the halocyclization reaction of 5-alkoxyalkenes towards the synthesis THFs, with a focus on templates which allow for efficient access to adjacently linked bis-THF motifs. The electrophilic cyclization of 5-alkoxyalkenes has been extensively used for stereoselective THF synthesis but stereoselectivity is highly dependant on substrate substitution.[7] Based on the notion that the reaction of conformationally rigid templates should be more stereoselective than more flexible systems, we have explored C6-allylated pyranosides and 1,2-*O*-isopropylidene-5-alkenes as precursors to complex *cis*-2,5- and *trans*-2,5-disubstituted THFs, respectively.[8,9] Herein we describe the synthesis of the synthetically versatile, highly functionalized THF **4**, via our *trans*-THF methodology. The utility of **4** as a precursor to adjacently, linked oligo-THFs is illustrated by its conversion to the bis-THF **3** and the tetracyclic lactone **5**. Bis-THF **3** is a known precursor[4e,f] to the acetogenin trilobacin **1**.[10] Trilobacin has been shown to be over 1 billion times more cytotoxic against human solid tumor lines than adriamycin. Compound **5** is a potential relay intermediate for less substituted analogues of kijimicin, a polyether which has shown promising anti-HIV activity.[11] Less substituted polyethers have attracted interest as podands in computational and mechanistic studies on ion transport.[12]

2. Discussion

Bis-acetonide THF **4**, by virtue of its alcohol substitution pattern and different acetal protecting groups is primed for transformation to oligo-THFs containing up to four adjacently linked rings. Compound **4** could be obtained by iodocyclization of bis-*O*-isopropylidene alkene **6** under aqueous conditions, and acetonation of the product. However, we were mindful of the possibility that iodoetherification of **6** under anhydrous conditions could lead directly to **4**. The C2 symmetry of bis-isopropylidene alkene **6** suggested a two directional type synthesis starting from (*Z*)-4-octenedial **7** (Scheme 1).

Selective oxidative cleavage of 2,5-cyclooctadiene via the reported procedure[13] provided crude **7**, which was stabilized by the addition of a crystal of 1,4-dihydroquinone, and treated with vinylmagnesium bromide at 0°C. The overall yield of the bisallylic alcohol **8** from 2,5-cyclooctadiene was 40%. Claisen–Johnson rearrangement[14] on **8** followed by DIBALH reduction of the resulting diester provided the *E*,*Z*,*E*-triene-diol **9** in 60% overall yield. Double dihydroxylation of **9** using AD mix-β[15] at −3°C for 20 h led primarily to the product resulting from double dihydroxylation (55%) and a lesser amount of mono dihydroxylation product (34%). The composition of the product from double dihydroxylation was determined after isopropylidination. NMR analysis indicated a 5:1 ratio of bis-*O*-isopropylidene-*Z*-alkene **6** and another compound presumed to be the *E*-isomer **10**. The overall yield of the desired product **6** was 43% over two steps. A longer reaction time (ca. 40 h) in the dihydroxylation reaction led to essentially pure **6**, but in lower yield (30% over two steps). The correlation of longer reaction time with an increased proportion of the desired *Z*-hexitol (cf. **6**) vs the *E*-regioisomer (cf. **10**) in the product of the double dihydroxylation, is likely a result of the more rapid conversion of the latter to the

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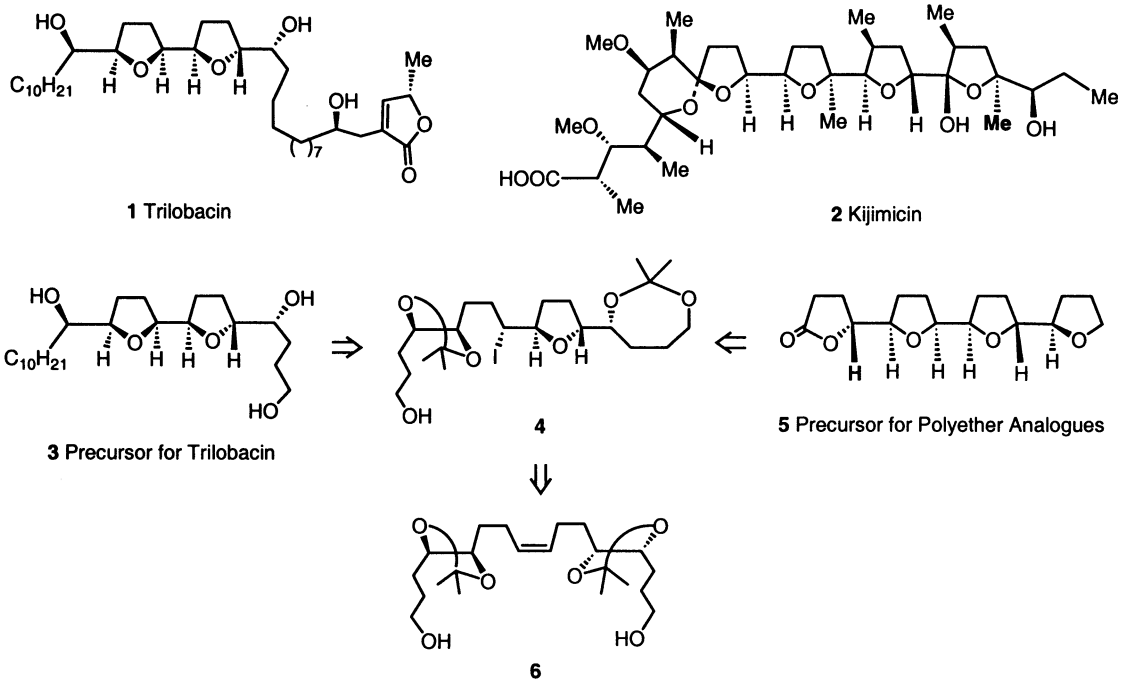
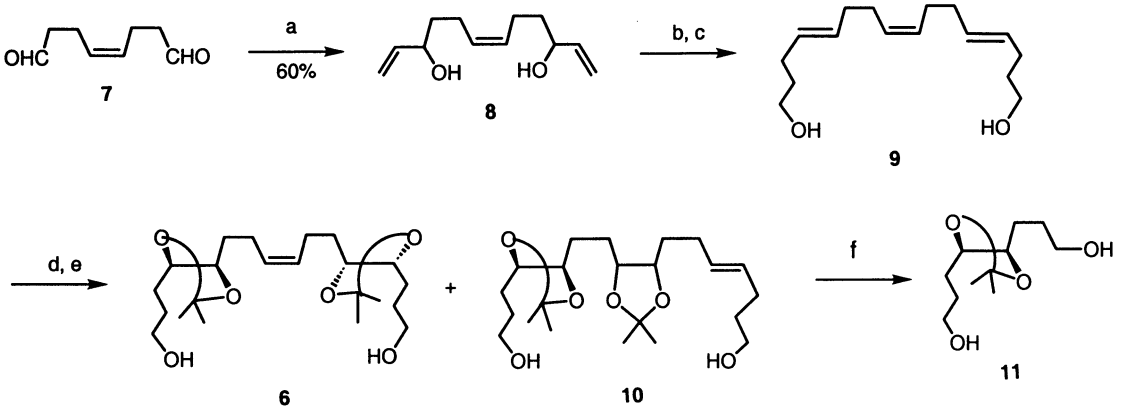


Scheme 1.

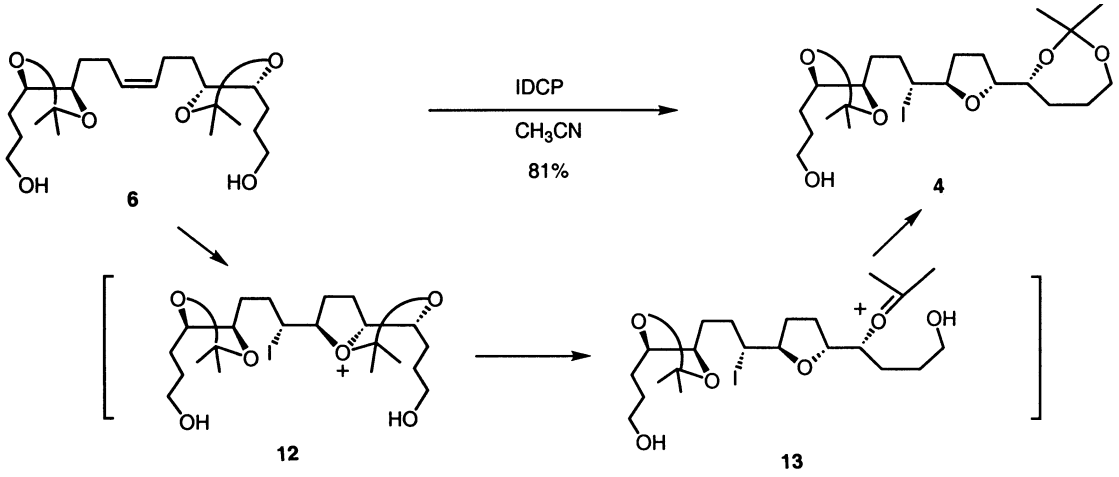
completely hydroxylated product.[15] Variations in the scale of the reaction, catalyst concentration, and temperature led to no significant improvement. Operationally, best overall yields of **6** (ca. 40–45% from **9**) were obtained by using a shorter reaction time for the dihydroxylation step, and separating the material derived from **10** at a later stage (i.e. compounds **15** or **18** vide infra). The optical purity of **6** was determined to be greater than 97% ee by conversion of **5** to the known diol **11** (Scheme 2).[16]

Treatment of an anhydrous solution of **6** with iodonium dicollidine perchlorate (IDCP) led to the iodo-THF **4** in 81% yield, with no evidence of the *cis* isomer. The stereochemistry of the THF ring **4** was tentatively assigned on the basis of the observed *trans* selectivity in the iodocyclization of related isopropylidene alkenes.[9] We have previously suggested that the high stereoselectivity observed in the reactions of these isopropylidene alkene systems may be due to the formation of a THF-oxonium ion intermediate which has a *cis* fused [5.5.0] oxahydrindane type geometry.[9a] The configuration at the iodinated carbon was deduced from the established *anti* addition in the electrophilic addition to the alkene.[17] The assignment was confirmed by conversion to the known compound **3**[4e,f] (vide infra). The high yield of the seven membered isopropylidene is consistent with the intramolecular attack of the proximal alcohol on the oxocarbenium ion in the intermediate **13** (Scheme 3).

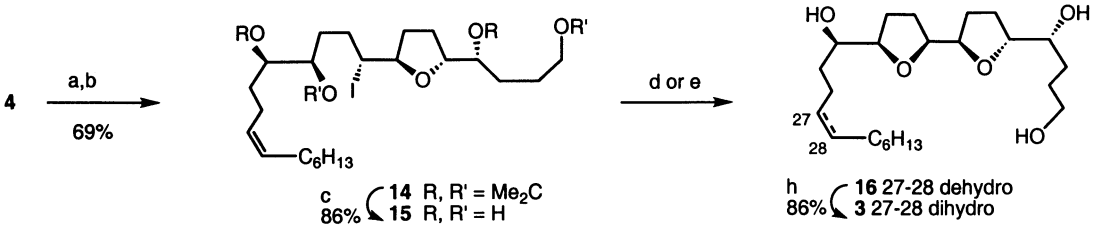
Compound **4** was next transformed through a straightforward series of reactions (Swern oxidation, Wittig reaction and acetal hydrolysis) to the tetrahydroxyiodide **15**. The formation of the second THF ring was carried out by heating **15** in pyridine. The bis-THF product **16** was obtained together with side products resulting from dehydroiodination. This reaction was somewhat capricious and resulted in lower yields of the bis-THF product when the tempera-



Scheme 2. (a) Vinylmagnesium bromide, THF; (b) $CH_3C(OEt)_3$, CH_3CH_2COOH, 138–140°C; (c) DIBALH, CH_2Cl_2, −78°C; (d) AD mix-β, *t*-BuOh-H_2O, $MeSONH_2$, −3°C; (e) $Me_2C(OMe)_2$, CSA, DMF; (f) (i) O_3, CH_2Cl_2, MeOH then Ph_3P; (ii) $NaBH_4$, EtOH.



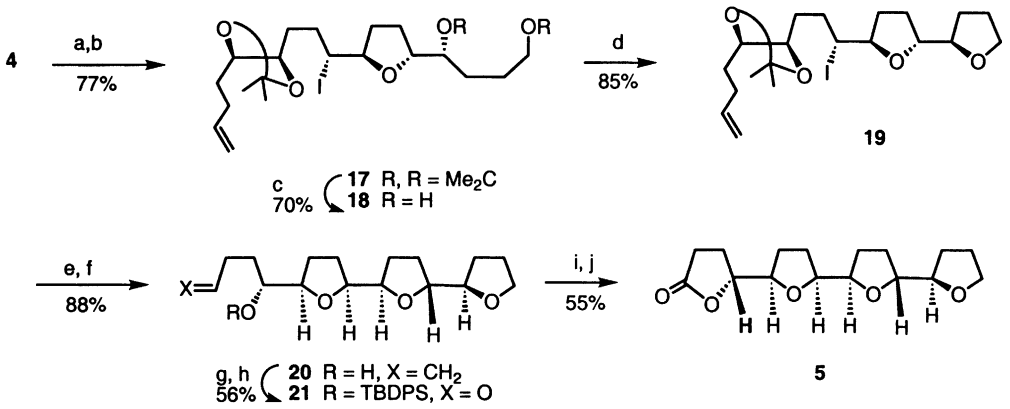
Scheme 3.



Scheme 4. (a) Swern's Ox; (b) $C_6H_{13}CH{=}PPh_3$, toluene; (c) HCl, H_2SO_4; (d) py, 100°C (67%); (e) Bu_2SnO, toluene, reflux (71%); (h) H_2/Pd/C, EtOAc (92%).

ture was not carefully controlled. The treatment of **15** with dibutyltin oxide in toluene at reflux, was a more reliable procedure,[18] providing **16** in 71% yield, with no indication of dehydroiodination products. Hydrogenation of **16** gave the target compound **3**, for which the ^1H and ^{13}C NMR data were essentially identical to that recorded for the previously prepared material.[4e,f,19] The authencity of **3** confirms the initial stereochemical assignment of the iodocyclization product **4** (Scheme 4).

The conversion of **4** to precursors which could be used for the preparation of analogues of the pentacyclic spiroketal-polyether frameworks found in many polyether antibiotics, was next undertaken. Specifically, aldehyde **21** and lactone **5** were viewed as attractive relay compounds. The primary alcohol in **4** was first transformed in two straightforward operations (Swern oxidation and Wittig methylenation) to a terminal alkene residue, which was to serve as a masked carbonyl group (Scheme 5). Selective acetal hydrolysis of the resulting THF-alkene **17** furnished THF-diol **18**. Reaction of **18** under Mitsonobu type conditions led to a single bis-THF product **19**. Previous examples of this etherification reaction supports the product resulting from activation of the primary alcohol and retention of configuration at the secondary alcohol carbon.[20] Treatment of **19** according to the identical two-step sequence (acetonide hydrolysis and dibutyltin oxide etherification), that was used on mono-THF **15**, gave tris-THF **20** in 89% overall yield from **19**. Silylation of **20** followed by ozonolysis of the product provided aldehyde **21**. $NaClO_2$ oxidation of **21**, and



Scheme 5. (a) Swern's Ox; (b) $CH_2{=}PPh_3$, toluene; (c) PPTS, EtOH; (d) Ph_3P, DEAD, CH_2Cl_2; (e) BF_3OEt_2, THF-H_2O; (f) Bu_2SnO, toluene, reflux; (g) TBDPSCl, imidazole, DMF; (h) O_3, then Ph_3P; (i) $NaClO_2$, CH_3CN; (j) 6N HCl-THF.

subsequent treatment of the resulting acid under acidic conditions provided lactone **5**. This three step sequence from **20** to **5** has not been optimized. The gross structure of **5** was assigned on the basis HRMS, ^{1}H and ^{13}C NMR analysis. The stereochemistry of **5** follows from the authenticity of precursor **4**, the stereospecificity of the Mitsonobu type etherification (**18→19**),[20] and the similarity of the dibutyltin oxide mediated etherification (**19→20**) to the corresponding reaction in the synthesis of **3** (i.e. **15→16**).

In summary, the elaboration of **6** to **3** and **5**, illustrates the use of bis-1,2-*O*-isopropylidene-alkenes as precursors to complex oligo-THFs. Key aspects of the methodology are the easy accessibility of the isopropylidene alkene precursors, the efficiency of the pivotal iodoetherification reaction, and the versatility of the iodo-THF product of this reaction. The preparation of the trilobacin precursor **3** (11 steps from 2,5-cyclooctadiene, ca. 5% overall yield) indicates that the methodology is of comparable efficiency to other strategies for the adjacently linked bis-THF segments of the acetogenins. It is anticipated that application of similar chemistry to stereoisomers of **6** would lead to a variety of analogues of **3** and **5**.

3. Experimental

3.1. 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, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions, with $CHCl_3$ as internal standard. Elemental analysis was performed in Schwarzkopf Microanalysis Laboratory. High resolution mass spectroscopy was carried out at the Mass Spectrometry Facility at the University of Illinois at Urbana-Champaign.

3.1.1. (*Z*)-1,6,11-Dodecatriene-3,10-diol 8. CH_3COOOH (39 mL, 0.2 mol) was slowly added, at rt, to a rapidly stirred suspension of 1,5-cyclooctadiene (24.5 g, 0.2 mol) and NaOAc (16.4 g, 0.2 mol) in $CHCl_3$ (750 mL). After stirring for 1 h, the reaction mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. To the crude residue was added a solution of periodic acid (45.6 g, 0.2 mol) in H_2O (700 mL). The mixture was stirred for 1 h at 40°C, then cooled to 0°C, neutralized with aqueous $NaHCO_3$, diluted with brine and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and filtered. The filtrate was stabilized by addition of hydroquinone (10 mg) and concentrated to give crude **7** (19.9 g, ca. 71%). ^{1}H NMR δ 2.30 (m, 4H), 2.44 (m, 4H), 5.28 (m, 2H), 9.68 (s, 2H). ^{13}C NMR δ 20.0, 43.5, 128.9, 201.8.

A solution of **7** (19.9 g, 142 mmol) in dry THF (150 mL) was added, dropwise, to a solution of vinylmagnesium bromide (300 mL, 1 M) in dry THF (440 mL) at 0°C. The reaction was stirred at this temperature for 1 h, diluted with 1 M aqueous HCl and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and then concentrated. FCC of the residue provided **8** (21.5 g, 77%): R_f=0.28 (30% EtOAc/petroleum ether); IR (neat) 3356, 1644 cm^{-1}; ^{1}H NMR δ 1.58 (m, 4H), 2.16 (m, 4H), 2.58 (s, 2H, D_2O ex.), 4.12 (m, 2H), 5.15 (m, 4H), 5.40 (m, 2H), 5.87 (m, 2H). ^{13}C NMR δ 23.2, 37.0, 72.3, 114.6, 129.9, 141.3. FABHRMS calcd for $C_{12}H_{21}O_2$ (M+H) 197.1542, found 197.1539.

3.1.2. (4*E*,8*Z*,12*E*)-Hexadecatriene-1,16-diol 9. A 100 mL, one-necked round-bottomed flask containing a magnetic stirring bar was fitted with a Claisen adaptor, two thermometers and a receiving flask. The flask was charged with ethyl orthoacetate (160 mL), **8** (17.8 g, 90 mmol) and propionic acid (0.8 mL). Ethanol was distilled from the reaction mixture, and heating was continued between 138 and 142°C, for additional 2 h. The reaction mixture was then cooled to rt and excess ethyl orthoacetate and propionic acid were removed by distillation under reduced pressure, to give the crude triene ester. IR (neat) 1727 cm^{-1}; ^{1}H NMR δ 1.24 (t, J=6.6 Hz, 6H), 2.03 (m, 8H), 2.33 (m, 8H), 4.16 (q, J=6.6 Hz, 4H), 5.34 (m, 2H), 5.46 (m, 4H). ^{13}C NMR δ 14.5, 27.4, 28.1, 32.7, 34.6, 60.4, 128.6, 129.5, 131.2, 173.4. FABHRMS calcd for $C_{20}H_{33}O_4$ (M+H) 337.2379, found 337.2380.

A solution of DIBAL (347 mL, 347 mmol, 1 M in heptane) was added, dropwise, under argon, to a stirred solution of above diester (30.3 g, 90 mmol) in dry CH_2Cl_2 (300 mL) at −78°C. The mixture was stirred for 1 h at this temperature, then warmed to rt, and poured into an ice cold solution of saturated aqueous $KNaC_4H_4O_6$ (500 mL). The mixture was warmed to rt, and stirred until all the solid was dissolved. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. FCC of the residue afforded **9** (16.15 g, 71% from **7**): R_f=0.55 (EtOAc); IR (neat) 3329, 1657 cm^{-1}; ^{1}H NMR δ 1.59 (m, 4H), 2.03 (m, 12H), 2.43 (s, 2H, D_2O ex.), 3.59 (t, J=4.5 Hz, 4H), 5.33 (m, 2H), 5.41 (m, 4H). ^{13}C NMR δ 27.4, 29.0, 32.46, 36.8, 62.4, 129.6, 130.0, 130.5. FABHRMS calcd for $C_{16}H_{29}O_2$ (M+H) 253.2167, found 253.2167.

3.1.3. (8*Z*,4*R*,5*R*,12*R*,13*R*)-Hexadecaene-4,5:12,13-diisopropylidenedioxy-1,16-diol 6. A mixture of *t*-butyl alcohol (60 mL), H_2O (60 mL), AD-mix-β (15.9 g), and $MeSO_2NH_2$ (1.08 g, 11.3 mmol) was stirred at rt until both phases were clear, and then cooled to −3°C, whereupon the inorganic salts partially precipitated. At this point, triene diol **9** (1.60 g, 12.6 mmol) was added, and the heterogeneous slurry was stirred vigorously at −3°C for 20 h. The reaction was then quenched by addition of sodium sulfite (17 g), warmed to rt and stirred for an additional 1 h. The organic layer was separated and the aqueous layer was extracted with *t*-butyl alcohol (1×) and EtOAc (4×). The combined organic phase was washed with 2N KOH, dried (Na_2SO_4) and concentrated in vacuo. FCC of the residue gave two fractions: (0.60 g, 34%, R_f=0.55, 20% MeOH/EtOAc) and (1.13 g, 55%, R_f=0.30, 20% MeOH/EtOAc). For major component in the more polar fraction: ^{1}H NMR (CD_3OD) δ 1.58 (m, 12H), 2.20 (m, 4H), 3.40 (m, 4H), 3.58

(m, 4H), 5.40 (bt, J=4.4 Hz, 2H). ^{13}C NMR (CD_3OD) δ 24.8, 30.3, 30.6, 34.2, 63.2, 74.9, 75.3, 131.0. FABHRMS calcd for $C_{16}H_{33}O_6$ (M+H) 321.2277, found 321.2276.

2,2-Dimethoxypropane (0.86 mL, 7.0 mmol) and camphorsulfonic acid (487 mg, 4.35 mmol) were added to a solution of the more polar material (1.13 g, 3.5 mmol) in anhydrous DMF (40 mL) at 0°C. The reaction mixture was warmed to rt, stirred for 30 min at this temperature, poured into saturated aqueous $NaHCO_3$ and extracted with ether (3×) and EtOAc (1×). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. FCC of the crude material provided an inseperable mixture of **6** and another compound presumed to be **10** (3.28 g, 94%). For **6**: R_f=0.50 (EtOAc); IR (neat) 3419, 1448 cm^{-1}; ^{1}H NMR δ 1.32 (s, 12H), 1.58 (m, 12H), 2.14 (m, 4H), 3.58 (m, 8H), 3.82 (bs, 2H, D_2O ex.), 5.35 (m, 2H). ^{13}C NMR δ 24.1, 27.6, 27.7, 29.9 (2 carbons), 33.2, 62.9, 80.7, 81.1, 108.3, 129.8. FABHRMS calcd for $C_{22}H_{40}O_6$ (M+H) 401.2903, found 401.2903. Selected data for **10**: ^{1}H NMR δ 5.42 (m). ^{13}C NMR δ 62.8, 78.5, 81.4, 81.5, 108.4, 130.4. The approximate ratio of **6/10** based on the integration of the signals at δ 5.35 and 5.42, respectively, was 5:1.

3.1.4. (4*R*,5*R*)-4,5-(Isopropylidenedioxy)-1,8-octanediol 11. A solution of **6** (40 mg, 0.1 mmol) in 4:1 CH_2Cl_2/MeOH (2 mL) was cooled to −78°C. A stream of O_3 in O_2 was bubbled through the solution until **5** was not detectable by TLC (10% EtOAc/PE). The mixture was flushed with N_2 and then triphenylphosphine (40 mg, 0.15 mmol) was added. The solution was warmed to rt, stirred for 2 h, and concentrated in vacuo to give a slurry, which was dissolved in EtOH (5 mL) and treated with $NaBH_4$ (5 mg, 0.13 mmol) at rt. The reaction mixture was stirred for 1 h, and then diluted with 10% HCl in MeOH until the pH was **8**. The ethanol was removed under reduced pressure. FCC of the residue afforded **11** (25 mg, 57%): R_f:0.38 (10% MeOH/EtOAc); $[\alpha]_D^{26}$=29.8° (*c* 0.52, $CHCl_3$); Lit: $[\alpha]_D^{26}$=29.2° (*c* 0.51, $CHCl_3$); ^{1}H NMR δ 1.39 (s, 6H), 1.50–1.90 (m, 8H), 2.42 (s, 2H, D_2O ex.), 3.67 (m, 6H). ^{13}C NMR δ 27.5, 29.6, 29.7, 62.8, 81.1, 108.4. FABHRMS calcd for $C_{11}H_{23}O_4$ (M+H) 219.1596, found 219.1583.

3.1.5. THF iodide 4. To a solution of **6** (563 mg, 1.4 mmol) in dry CH_3CN (50 mL) was added IDCP (985 mg, 2.1 mmol). The mixture was stirred at rt for 10 min, then poured into saturated, aqueous $Na_2S_2O_3$, and extracted with ether. The combined organic phase was dried (Na_2SO_4), filtered and evaporated in vacuo. FCC of the crude residue gave **4** (616 mg, 83%): R_f=0.50 (EtOAc); IR (neat) 3455 cm^{-1}; ^{1}H NMR δ 1.31, 1.32 (both s, 6H), 1.36 (s, 6H), 1.65 (m, 12H), 1.95, 2.05 (both m, 4H), 2.40 (bs, 1H, D_2O ex.), 3.60 (m, 7H), 3.85 (m, 1H), 4.01 (m, 2H). ^{13}C NMR δ 25.4, 27.5, 28.5, 29.4, 29.7, 30.6, 31.2, 32.1, 33.0, 41.9, 62.1, 62.8, 74.3, 80.0, 80.9, 82.6, 82.8, 100.8, 108.5. FABHRMS calcd for $C_{22}H_{40}O_6I$ (M+H) 527.1870, found 527.1869.

3.1.6. THF alkene 14. A 50 mL, round-bottomed flask, equipped with a magnetic stirring bar, was charged with oxalyl chloride (0.336 mL, 3.78 mmol) and CH_2Cl_2 (10 mL). The set up was purged with argon and cooled to −78°C. DMSO (0.54 mL, 7.55 mmol) was added, dropwise, and stirring continued for 20 min. Then a solution of THF iodide **4** (795 mg, 1.51 mmol) in $CH_2Cl_2$was slowly introduced. The reaction mixture was stirred for 25 min at −78°C, at which time Et_3N (1.47 mL, 10.57 mmol) was added. After warming to rt, the mixture was stirred for additional 10 min, diluted with ether, washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo. FCC of the residue gave the aldehyde derivative of **4** (710 mg, 90%): R_f=0.60 (60% EtOAc/petroleum ether); IR (neat) 1723 cm^{-1}; ^{1}H NMR δ 1.26, 1.30 (both s, 6H), 1.33 (s, 6H), 1.20–2.22 (m, 14H), 2.64 (m, 2H), 3.62 (m, 5H), 3.90 (m, 1H), 4.05 (m, 2H), 9.78 (s, 1H). ^{13}C NMR δ 25.1, 25.4, 25.4, 27.4, 28.5, 29.3, 30.6, 31.2, 32.1, 33.0, 40.5, 41.9, 62.1, 74.2, 79.7, 79.8, 82.6, 82.7, 100.7, 108.6, 201.7. FABHRMS calcd for $C_{22}H_{38}O_6I$ (M+H) 525.1713, found 525.1716.

To a solution of heptyl triphenylphosphonium iodide (988 mg, 2.02 mmol) in dry toluene (50 mL) was added a 1 M solution of sodium bis(trimethylsilyl) amide (1.89 mL, 1.89 mmol) in toluene, under an argon atmosphere. The yellow–orange suspension was stirred for 1 h at rt then cooled to −78°C. A solution of the aldehyde prepared in previous step (710 mg, 1.35 mmol) in dry toluene (30 mL), was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, then diluted with ether (100 mL). The mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by FCC to afford **14** (708 mg, 77%): R_f=0.35 (20% EtOAc/petroleum ether); IR (neat) 1651 cm^{-1}; ^{1}H NMR δ 0.84 (t, J=6.6 Hz, 3H), 1.28, 1.30 (both s, 6H), 1.35 (s, 6H), 1.20–2.22 (m, 26H), 3.63 (m, 5H), 3.90 (m, 1H), 4.06 (m, 2H), 5.35 (m, 2H). ^{13}C NMR δ 14.3, 22.8, 23.9, 25.4, 25.4, 27.4, 27.5, 28.5, 29.1, 29.4, 29.8, 30.5, 31.2, 31.9, 32.2, 33.1, 33.2, 42.0, 62.1, 74.2, 79.9, 80.4, 82.6, 82.7, 100.7, 108.2, 128.8, 131.1. MS (ES, *m*/*z*) 624.3 (M+NH_4).

3.1.7. THF-tetraol 15. To a stirred solution of **14** (400 mg, 0.66 mmol) in MeOH (20 mL) at rt, was added H_2SO_4 (100 mL). After 14 h, the reaction mixture was neutralized with 1 M NaOMe in MeOH and the solvent was removed in vacuo. The residue was diluted with brine and extracted with ether. The organic phase was dried (Na_2SO_4), and evaporated under reduced pressure. FCC of the residue afforded **15** (307 mg, 88%): R_f=0.60 (EtOAc); IR (neat) 3395 cm^{-1}; ^{1}H NMR δ 0.87 (t, J=6.6 Hz, 3H), 1.00–2.31 (m, 26H), 2.57 (s, 1H, D_2O ex.), 3.05 (s, 1H, D_2O ex.), 3.25–3.80 (m, 7H, partial D_2O ex.), 3.92 (m, 2H), 4.37 (m, 1H), 5.37 (m, 2H). ^{13}C NMR δ 14.3, 22.8, 23.6, 27.5, 28.9, 29.2, 29.9, 30.5, 31.5, 31.8, 32.0, 33.4, 33.6, 41.24, 62.9, 73.2, 74.3, 82.6, 83.9, 129.0, 131.1. FABHRMS calcd for $C_{23}H_{44}O_5I$ (M+H) 527.2234, found 527.2234.

3.1.8. Bis-THF alkene 16. A mixture of **15** (61 mg, 0.116 mmol) and pyridine (4 mL) was heated at 100°C for 1 h. After cooling to rt, the excess pyridine was removed in vacuo. FCC of the residue afforded the bis-THF alkene **16** (31 mg, 67%): R_f=0.35 (EtOAc); IR (neat) 3411, 1638 cm^{-1}; ^{1}H NMR δ 0.86 (t, J=6.6 Hz, 3H), 1.28 (m, 8H), 1.55 (m, 4H), 1.70 (m, 5H), 1.90 (m, 1H), 1.98 (m, 6H), 2.15 (m, 2H), 3.01 (bs, 3H, D_2O ex.), 3.41 (m, 2H), 3.64 (t, J=5.7 Hz, 2H), 3.83 (m, 2H), 3.97 (m, 1H), 4.06 (m, 1H), 5.34 (m, 2H). ^{13}C NMR δ 14.3, 22.8, 23.7, 26.9, 27.4, 28.3,

28.4, 29.0, 29.2, 29.4, 29.9, 30.8, 32.0, 34.5, 62.9, 74.0, 74.1, 81.1, 81.8, 82.7, 83.3, 129.3, 130.8. FABHRMS calcd for $C_{23}H_{43}O_5$ (M+H) 399.3111, found 399.3114.

In an alternative procedure, a mixture of **15** (85 mg, 0.16 mmol) and Bu_2SnO (46 mg, 0.18 mmol) in benzene (20 mL) was heated at reflux for 17 h, with the azeotropic removal of water. The solution was concentrated in vacuo, and the residue was processed by FCC to afford **16** (46 mg, 71%).

3.1.9. Bis-THF 3. A suspension of **16** (24 mg, 0.065 mmol) and 10% w Pd/C in EtOAc (4 mL) was stirred for 16 h under hydrogen (balloon). The suspension was filtered through a short plug of Celite and concentrated in vacuo to give **3** (22 mg, 92%): R_f=0.35 (EtOAc); $[\alpha]_D^{23}$=+1.4° (*c* 0.38, $CHCl_3$), ^{1}H NMR (400 MHz) δ 0.86 (t, *J*=6.7 Hz, 3H), 1.26 (m, 15H), 1.42–2.05 (m, 13H), 2.90 (bd, 3H, D_2O ex.), 3.39 (m, 2H), 3.43 (m, 2H), 3.65 (apparent t, *J*= 5.6 Hz, 2H), 3.83 (m, 2H), 3.97 (m, 1H), 4.06 (m, 1H). ^{13}C NMR (100 MHz) δ 14.3, 22.9, 26.0, 26.9, 28.4, 29.0, 29.4, 29.5, 29.8, 29.9, 30.8, 32.1, 34.5, 62.9, 74.0, 74.7, 81.1, 81.8, 82.7, 83.2. FABHRMS calcd for $C_{23}H_{45}O_5$ (M+H) 401.3267, found 401.3266.

3.1.10. THF-alkene 17. To a solution of methyl triphenylphosphonium iodide (4.73 g, 11.8 mmol) in dry toluene (200 mL) was added a 0.6 M solution of sodium bis(trimethylsilyl) amide (19.5 mL, 11.8 mmol) in toluene, under an argon atmosphere. The yellow orange suspension was stirred for 1 h at rt then cooled to −78°C. A solution of the aldehyde derivative of **4** (4.08 g, 7.79 mmol, see synthesis of **14**) in dry toluene (50 mL), was added dropwise over 30 min. After an additional 15 min, the reaction mixture was warmed to rt, then diluted with ether (200 mL). The mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by FCC to afford THF-alkene **17** (3.49 g, 86%): R_f=0.7 (20% EtOAc/petroleum ether); IR (neat) 1641 cm^{-1}; ^{1}H NMR δ 1.20, 1.25 (both s, 6H), 1.30 (s, 6H), 1.35–2.25 (m, 16H), 3.60 (m, 5H), 3.85 (m, 1H), 4.00 (m, 2H), 4.95 (m, 2H), 5.75 (m, 1H). ^{13}C NMR δ 25.3, 25.4, 27.4, 27.5, 28.4, 29.3, 30.2, 30.5, 31.2, 32.2, 33.1, 41.9, 62.0, 74.1, 79.7, 80.1, 82.4, 82.6, 100.5, 108.1, 114.9, 137.9. FABHRMS calcd for $C_{23}H_{40}O_5I$ (M+H) 523.1921, found 523.1926.

3.1.11. THF-diol 18. The bis-*O*-isopropylidene derivative **17** (2.02 g, 3.87 mmol) was dissolved in EtOH (25 mL). PPTS (586 mg, 2.33 mmol) was then added and stirred for 3 h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ether (3×50 mL). The ethereal extract was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by FCC to yield THF-diol **18** (1.31 g, 70%): R_f=0.10 (10% EtOAc/petroleum ether); IR (neat) 3420, 1640 cm^{-1}; ^{1}H NMR δ 1.35 (s, 6H), 1.40–2.30 (m, 16H), 3.05 (br s, 2H), 3.40 (m, 1H), 3.60 (m, 4H), 3.90 (m, 2H), 4.05 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H). ^{13}C NMR δ 27.4, 27.5, 28.8, 29.3, 30.2, 30.4, 31.6, 32.2, 32.4, 33.1, 41.6, 62.7, 74.1, 79.7, 80.2, 82.5, 83.6, 108.2, 114.9, 137.9. FABHRMS calcd for $C_{20}H_{36}O_5I$ (M+H) 483.1607, found 483.1612.

3.1.12. Bis-THF 19. Diol **18** (1.34 g, 2.77 mmol) and triphenylphosphine (1.45 g, 5.54 mmol) were dissolved in dry CH_2Cl_2 (50 mL). DEAD (0.9 mL, 5.54 mmol) was then added and the reaction mixture was stirred for 2 h. Removal of the solvent under reduced pressure and FCC of the residue gave bis-THF **19** (1.09 g, 85%): R_f=0.80 (10% EtOAc/petroleum ether); IR (neat) 1640 cm^{-1}; ^{1}H NMR δ 1.35 (s, 6H), 1.60 (m, 3H), 1.70–2.30 (m, 13H), 3.65(m, 2H), 3.75 (m, 2H), 3.85 (m, 1H), 4.00 (m, 2H), 4.10 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H). ^{13}C NMR δ 26.7, 28.1, 28.1, 28.9, 29.6, 30.9, 31.4, 32.4, 32.8, 34.0, 41.9, 69.3, 80.9, 82.5, 83.5, 108.8, 115.6, 138.1. FABHRMS calcd for $C_{22}H_{34}O_4I$ (M+H) 465.1502, found 465.1507.

3.1.13. Tris-THF-alkene 20. BF_3 EtO_2 (3.5 mL) was added to a solution of **19** (1.42 g, 3.06 mmol) in THF (40 mL) and H_2O (6 mL) at room temperature. The reaction mixture was stirred for 2 d. The solution was neutralized to pH 7 by the addition of saturated aqueous sodium bicarbonate. The mixture was then concentrated under reduced pressure, diluted with water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by FCC to afford recovered **19** (112 mg) and the dihydroxy-iodide derivative (1.11 g, 93% based on recovered **19**): R_f=0.30 (10% acetone/$CHCl_3$, double elution); ^{1}H NMR δ 1.50–2.35 (m, 16H), 2.75 (s, 2H), 3.40 (m, 2H), 3.80 (m, 3H), 4.00 (m, 2H), 4.15 (m, 2H), 4.95 (m, 2H), 5.80 (m, 1H). ^{13}C NMR δ 26.2, 28.3, 29.1, 30.2, 30.8, 31.4, 32.9, 33.8, 41.1, 68.7, 73.4, 74.1, 82.0, 83.1, 83.2, 115.1, 138.5. FABHRMS calcd for $C_{17}H_{30}O_4I$ (M+H) 425.1189, found 425.1188.

A mixture of dihydroxy-iodide from the previous step (839 mg, 1.98 mmol) and Bu_2SnO (493 mg, 1.98 mmol) in benzene (30 mL) was heated at reflux for 17 h using a Dean–Stark set-up for the azeotropic removal of water. Removal of the solvent in vacuo, and FCC of the residue provided tris-THF-alkene **20**: (563 mg, 96%): R_f=0.70 (10% acetone/$CHCl_3$, double elution); ^{1}H NMR δ 1.30–2.30 (m, 16H), 2.90 (d, *J*=6.0 Hz, 1H), 3.30 (m, 1H), 3.65–3.95 (m, 6H), 4.00 (m, 1H), 4.95 (m, 2H), 5.80 (m, 1H). ^{13}C NMR δ 26.1, 27.4, 28.3, 28.5, 28.8, 30.1, 33.6, 68.7, 74.1, 81.3, 81.4, 81.9, 82.2, 82.6, 114.6, 138.6. FABHRMS calcd for $C_{17}H_{29}O_4$ (M+H) 297.2066, found 297.2064.

3.1.14. Tris-THF-aldehyde 21. A solution of **20** (90 mg, 0.30 mmol), TBDPSCl (0.25 mL, 0.9 mmol) and imidazole (61.3 mg, 0.9 mmol) in anhydrous DMF (2 mL) was stirred at 50°C for 3 h. The reaction mixture was then diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by FCC to give the silyl ether derivative (105 mg, 66%) as a colorless oil; R_f=0.8 (20% EtOAc/petroleum ether); ^{1}H NMR δ 1.05 (s, 9H), 1.30–2.05 (m, 16H), 3.60–3.95 (m, 8H), 4.80 (m, 2H), 5.50 (m, 1H), 7.35 (m, 6H), 7.70 (m, 4H); ^{13}C NMR δ 19.8, 26.1, 26.7, 27.4, 28.41, 28.7, 28.9, 29.3, 29.8,32.5, 68.7, 75.0, 81.6, 81.8, 81.9, 114.2, 127.4, 129.4, 134.2, 134.6, 136.0, 138.7. FABHRMS calcd for $C_{33}H_{45}O_4Si$ (M−H) 533.3087, found 533.3087.

A solution of the material from the previous step (105 mg,

0.20 mmol) in 4:1 CH_2Cl_2/MeOH (5 mL) was cooled to −78°C. A stream of O_3 in O_2 was bubbled through the solution until the starting material was not detectable by TLC. The mixture was flushed with N_2 and then triphenylphosphine (55 mg, 0.21 mmol) was added. The solution was warmed to rt, stirred for 1 h and concentrated in vacuo. The resulting slurry was purified by FCC to afford **21** (89 mg, 85%) as a colorless oil; R_f=0.55 (20% EtOAc/petroleum ether); ^{1}H NMR δ 1.05 (s, 9H), 1.50–2.00 (m, 14H), 2.30 (m, 2H), 3.65–3.90 (m, 8H), 7.30 (m, 6H), 7.75 (m, 4H), 9.55 (s, 1H); ^{13}C NMR δ 19.7, 25.4, 26.0, 26.5, 27.2, 28.3, 28.6, 28.8, 28.9, 40.1, 68.5, 74.2, 81.5, 81.6, 81.7, 81.7, 81.9, 127.4, 127.5, 129.6, 133.8, 134.2, 135.9, 135.9, 201.9. FABHRMS calcd for $C_{32}H_{43}O_5Si$ (M−H) 535.2880, found 535.2882.

3.1.15. Tris-THF-lactone 21. To a mixture of **21** (89 mg, 0.17 mmol) and $NaH_2PO_4{\cdot}H_2O$ (234.6 mg, 1.7 mmol) in CH_3CN–H_2O (5:1 mL) were successively added 30% aqueous H_2O_2 (6 mL, 0.2 mmol) aqueous $NaClO_2$ (18.5 mg, 0.2 mmol) in water (1.5 mL) at 0–5°C. The reaction mixture was warmed to rt, stirred for an additional 1 h, then quenched by addition of Na_2SO_3 (100 mg). The mixture was extracted with EtOAc (3×10 mL). The organic extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by FCC to yield the acid derivative (82 mg, 89%) as a colorless oil; R_f=0.90 (60% EtOAc/petroleum ether); ^{1}H NMR δ 1.05 (s, 9H), 1.45–2.00 (m, 14H), 2.30 (m, 2H), 3.55–3.90 (m, 8H), 7.35 (m, 6H), 7.75 (m, 4H); ^{13}C NMR δ 19.8, 26.1, 26.49, 27.3, 28.1, 28.3, 28.6, 28.9, 28.9, 30.2, 68.6, 74.1, 81.5, 81.7, 81.8, 81.9, 127.4, 127.5, 129.5, 129.61, 134.0, 134.1, 136.0, 178.8. FABHRMS calcd for $C_{32}H_{43}O_6Si$ (M−H) 551.2829, found 551.2831.

To a solution of the acid obtained in the previous step (24.7 mg, 0.045 mmol) in THF (2 mL) was added an aqueous solution of 6N HCl (2 mL) and stirred for 2 d. The solution was then extracted with EtOAc (3×5 mL), and the organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by FCC to afford **5** (8.1 mg, 61%) as a colorless oil; R_f=0.3 (60% EtOAc/petroleum ether); IR ($CHCl_3$ film) 1772 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 1.34 (m, 2H), 1.46–1.72 (m, 10H), 1.83 (m, 2H), 2.07 (m, 1H), 2.30 (m, 1H), 3.36 (m, 1H), 3.61 (m, 1H), 3.68–3.78 (m, 4H), 3.89 (m, 1H), 3.96 (m, 1H); ^{13}C NMR (C_6D_6) δ 25.0, 26.9, 27.6, 28.6, 28.7, 29.0, 29.3, 29.9, 68.9, 81.1, 81.8, 81.9, 82.3, 83.3, 176.3. FABHRMS calcd for $C_{16}H_{25}O_5$ (M+H) 297.1702, found 297.1703.

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