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Direct synthesis of substituted tetrahydrofurans via regioselective dehydrative polyol cyclization cascades

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Abstract—A one-pot procedure for the conversion of 1,2,4,5-tetraols into substituted tetrahydrofuran moieties has been developed. This involves the regioselective sulfonylation of the terminal hydroxyl of the polyol array followed by sequential oxirane and oxolane formation under basic conditions. A survey of reaction conditions has defined the use of *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole as sulfonylation reagent, potassium *tert*-butoxide as base, and *tert*-butanol as solvent to be optimal. Under these conditions, 8-*O*-benzyl-octan-1,2,4,5,8-pentaol was converted stereospecifically into tetrahydrofurans in 62% yield. Polyol substrates were derived from Sharpless asymmetric dihydroxylation of 1,4-dienes. Hence, substituted tetrahydrofurans could be obtained stereospecifically from diene substrates in two operations.

1. Introduction

Substituted cyclic ethers occur widely among various classes of natural products.[1–3] A common biogenetic mechanism postulated for the formation of both oxolane and oxane ring systems in compounds such as the emergent marine toxin azaspiracid (**1**),[4] the bis-THF acetogenin motrilin (**2**),[5,6] the ionophoric antibiotic monensin (**3**),[1] and the squalenoid polyether thyrsiferol[2] (**4**, Fig. 1) is the isomerization of the precursor hydroxy epoxides.[7] Hydroxy epoxide intermediates, in turn, may be derived from the enzymatic incorporation of molecular oxygen into polyene systems.[8,9] These tenets of cyclic ether biosynthesis, combined with the widespread occurrence and potent biological activities of cyclic ether containing natural products have prompted the development of a variety of laboratory methods for their synthesis.[3,10–14] A conventional strategy toward tetrahydrofuran construction involves the isomerization of γ-hydroxy epoxides via acid-catalyzed 5-*exo*-trig opening (Scheme 1), as suggested by biogenetic considerations.[15] In the seminal polyether total synthesis of lasalocid A, Kishi demonstrated the stereoselective hydroxyl-directed epoxidation of bishomoallylic alcohols using $VO(acac)_2$ to access γ-hydroxy epoxides, which could be cyclized in situ under acidic conditions to generate the corresponding THF rings.[16] We considered that the same type of hydroxy epoxide intermediates could be obtained via the direct regioselective dehydration of a polyol array, but under basic conditions that could also promote in situ epoxide opening to provide substituted cyclic ethers.[17] Reported here are the details of a direct synthesis of highly functionalized tetrahydrofurans that employs a novel dehydrative cyclization cascade of polyols that may avoid the necessity of isolation or handling of activated alcohol or epoxide intermediates.

The envisioned conversion of a polyol into a substituted cyclic ether would involve selective sulfonylation of the kinetically more reactive hydroxyl group, followed by base-induced epoxide formation and intramolecular *trans*-etherification in an *exo*-mode (Scheme 2). Sharpless asymmetric dihydroxylation (SAD)[18,19] of the corresponding polyene precursors would provide a facile entry to the polyol cyclization precursors. Thus, the proposed cyclic ether synthesis could be achieved in only two operations from readily accessible polyenes. The use of SAD to access the polyol systems would dictate both the enantio and diastereoselectivity of the process.[18] In principle, either *cis* or *trans* substituted cyclic ether products may be obtained by dihydroxylation of (*E*)- or (*Z*)-alkenes. To establish directionality of the dehydrative polyol cyclization cascade, steric differentiation of the individual hydroxyl groups may be exploited using a sterically discriminating activating reagent. Hence, *N*-arylsulfonyl imidazole reagents were selected for this purpose. *N*-*p*-(Toluenesulfonyl)imidazole (*N*-TsIm)[20] and *N*-(2,4,6-triisopropylbenzenesulfonyl)-imidazole (*N*-TrisIm)[21] have been used previously for the in situ conversion of vicinal diols into the corresponding epoxides in several cases.

Rather than relying upon sequential protecting or functional group manipulations, the regioselective formation of the

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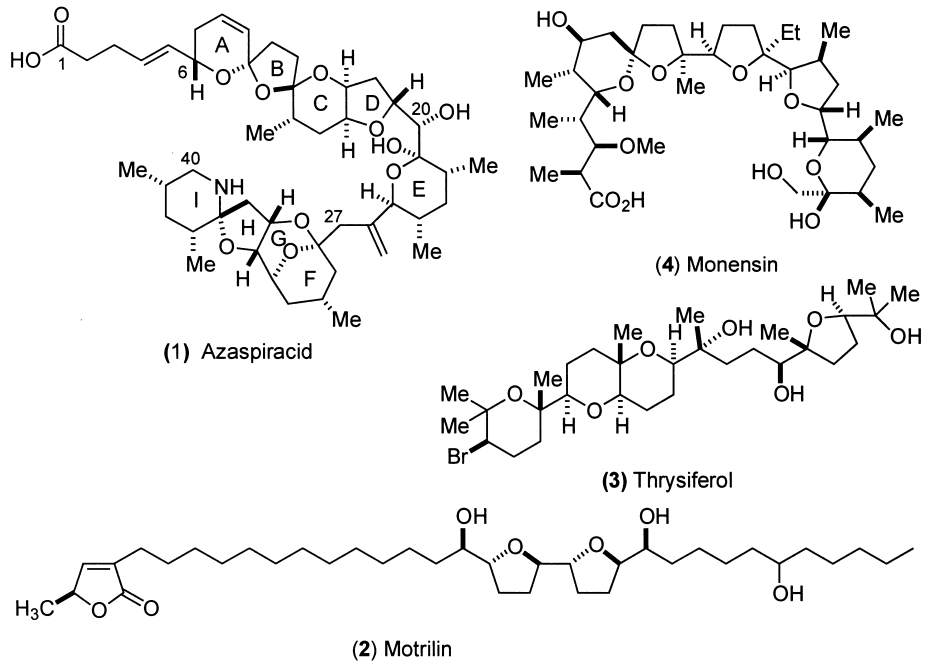
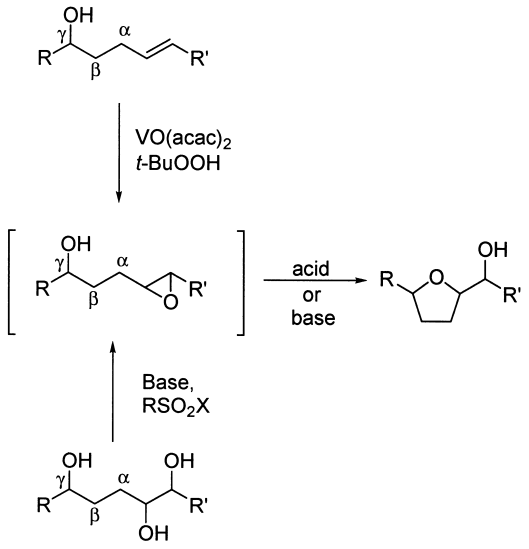


Figure 1. Representative tetrahydrofuran-containing natural products.

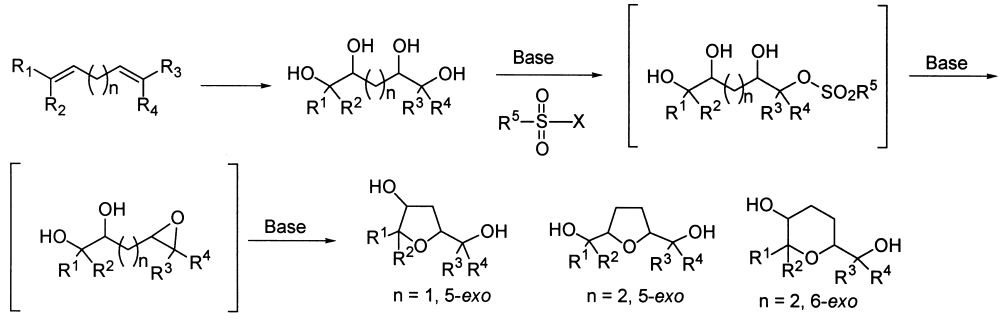


Scheme 1. In situ generation and transetherification of γ-hydroxy-epoxides.

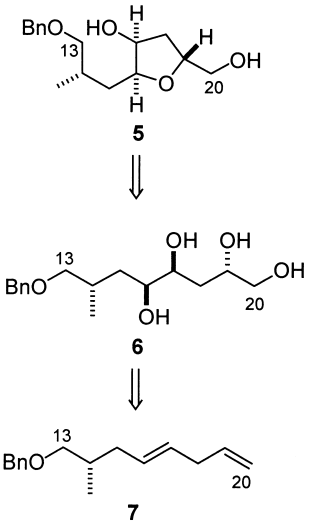
requisite hydroxy epoxides would be determined by the relative reactivity of the individual alcohols in polyol substrates. In addition to the inherent steric discrimination of the sulfonyl imidazole reagents, the by-products of epoxide formation (arylsulfonate and imidazolide salts) may be innocuous to subsequent transformations.[22]

2. Results and discussion

The direct conversion of a polyene to a cyclic ether via a polyol intermediate was originally explored in the context of tetraols derived from 1,4-dienes. Rapid synthetic access to the D-ring tetrahydrofuran of azaspiracid (**1**, Fig. 1)[4] was specifically targeted via this approach (Scheme 3). Here, a hydroxyl group at the 3-position and a hydroxymethyl group at the 5-position of the THF ring **5** were required for subsequent elaboration. This oxygenation pattern resident in tetraol **6** would derive from bis-dihydroxylation of 1,4-diene **7**.



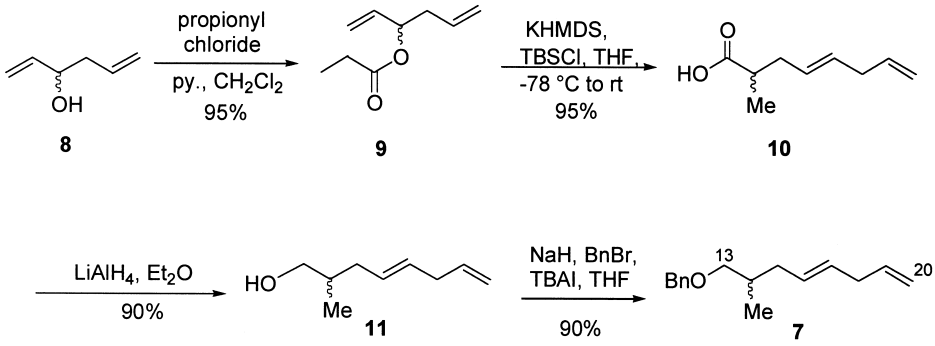
Scheme 2. Proposed synthesis of substituted cyclic ethers from dienes via one-pot conversion of a tetraol into a tetrahydrofuran.



Scheme 3. Retrosynthesis of the azaspiracid D-ring.

chloride provided ester **9** (Scheme 4). Treatment of **9** with KHMDS followed by TBSCl in THF at −78°C gave the *t*-butyldimethylsilyl ketene acetal, which underwent Ireland–Claisen rearrangement to provide the α-methyl silyl ester in nearly quantitative yield upon warming to room temperature.[24] The silyl ester was then hydrolyzed using an acidic workup to give carboxylic acid **10**. Treatment of **10** with lithium aluminum hydride provided the primary alcohol **11**. Benzylation of alcohol **11** under standard conditions provided diene **7**,[25] which would serve as the scaffold for examining the bis-dihydroxylation/dehydrative cyclization cascade en route to the azaspiracid D-ring.

Treatment of (±)-**7** under standard SAD conditions consistently provided a ~1.5:1 mixture of chromatographically separable tetraols that were epimeric not only at the C14 methyl-bearing carbon (azaspiracid carbon numbering), but also at the C19 carbinol center (Scheme 5).[26]

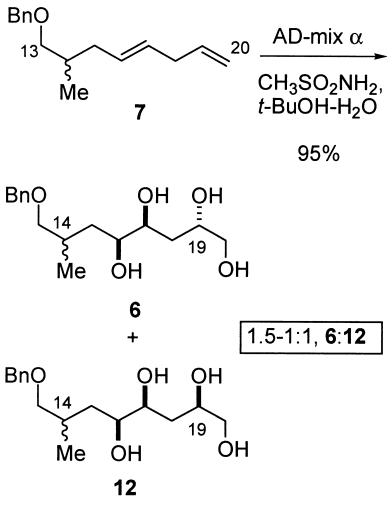


Scheme 4. Synthesis of C13–C20 diene.

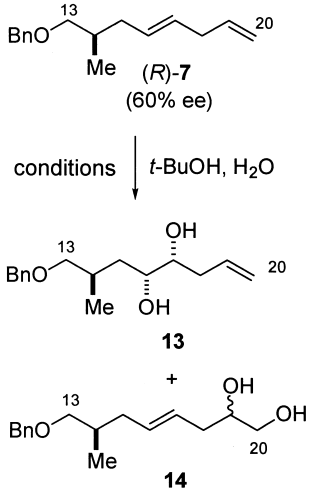
2.1. Two-step approach to cyclic ethers from dienes (diene to tetrahydrofuran)

2.1.1. Diene synthesis and hydroxylation. The synthesis of **7** began with the readily available allylic alcohol (±)-1,5-hexadien-3-ol ((±)-**8**).[23] Acylation of **8** with propionyl

To investigate the unexpectedly low level of diastereoselectivity of the bis-dihydroxylation reaction, enantiomerically enriched (*R*)-**7** was subjected to a series of experiments (Scheme 6). Diene **7** was first oxidized using 3 equiv. of AD-mix-β to the regioisomeric diols **13** and **14**. Analysis of the diols by ^{1}H NMR spectroscopy allowed for



Scheme 5. Bis-dihydroxylation of diene **7**.



Scheme 6. Attempts to enhance the diastereoselectivity of diene **7** dihydroxylation.

Table 1. Ligand effects in diene to tetraol transformation according to Scheme 6

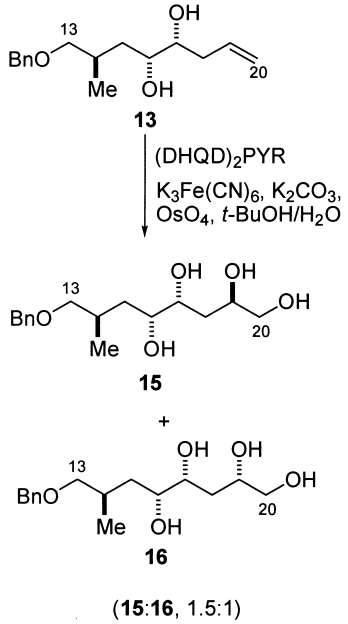
Ligand	dr **13**	dr **14**
$(DHQD)_2PHAL$ (AD-mix β)	>95:5	~1.5:1
$(DHQD)_2PYR^*$	>95:5	~1.5:1
$(DHQD)_2AQN^*$	>95:5	~2:1

Ligand was premixed with OsO_4, $K_3Fe(CN)_6$, and K_2CO_3 in *t*-BuOH/H_2O prior to addition of **7**. Note: tetraols were also formed to a minor degree under the reaction conditions; therefore, the diastereomeric ratios are only approximate.

determination that **13** was a single diastereomer, and **14** was a ~1.5:1 mixture of diastereomers. This result demonstrated that the configuration at the C14 methyl-bearing center had little effect on dihydroxylation diastereoselectivity. Furthermore, this indicated that the previously observed low levels of diastereoselectivity in the bis-dihydroxylation were not a result of intramolecular directing effects during the conversion of the diol to the tetraol, because the low level of stereocontrol is already evident during the dihydroxylation to **14**.

The modest stereoselectivity achieved with oxidation of the terminal olefin of **7** with AD-mix led to the examination of other ligands for the SAD that might provide higher levels of diastereoselectivity (Scheme 6, Table 1). However, neither the $(DHQD)_2PYR$ ligand system, which was optimized by Sharpless and co-workers specifically for problematic terminal olefins,[27] nor the $(DHQD)_2AQN$ system[28] provided any significant improvement in diastereoselectivity for dihydroxylation of the terminal olefin of **7**.

To verify that the observations for the conversion of diene **7** to diols **13** and **14** were consistent with results for the synthesis of the tetraols, diol **13** was further oxidized using the $(DHQD)_2PYR$ ligand under Sharpless conditions (Scheme 7). Once again, as in the one-pot bis-dihydroxylation, a 1.5:1 mixture of **15** and **16** was obtained.

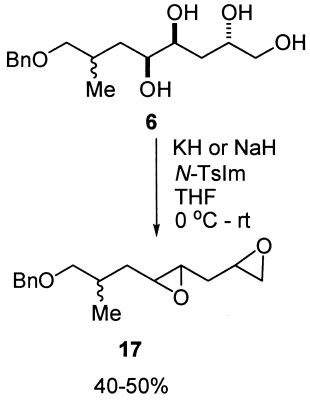


Scheme 7. Stepwise conversion to tetraols.

Despite significant efforts to optimize the SAD of diene **7**, no conditions were identified under which bis-dihydroxylation could be achieved with a high level of diastereoselectivity at the terminal olefin. Nevertheless, the C19-epimeric tetraols could be chromatographically separated and the high overall yield and brevity of this approach allowed for facile synthetic access to tetraol **6** in five steps from the known 1,4-hexadien-3-ol.[29]

2.1.2. One-pot tetraol to THF transformation. Initial attempts toward the conversion of tetraol **6** to tetrahydrofuran **5** (Scheme 8) involved treatment of **6** with excess KH or NaH in THF, followed by addition of 0.95 equiv. of *N*-TsIm. However, these conditions led only to bis-epoxide **17**, which resulted from non-selective sulfonylation of the tetraol. Treatment of **6** with excess KH or NaH in THF followed by addition of 1.0 equiv. of the bulkier sulfonylation reagent *N*-TrisIm also resulted in formation of **17** as the major product (Table 2, entries 1 and 2). Under the NaH conditions, a small amount (~5–10%) of the THF product (**5**) was generated, but none was observed under the KH conditions.

To thoroughly examine the one-pot tetraol etherification cascade, simplified desmethyl cyclization precursors (**19** and **20**) were synthesized following the previous route toward tetraol **6** with the exception that the initial acylation of 1,5-hexadien-3-ol was accomplished with acetic anhydride rather than propionyl chloride. The cyclization reactions of tetraols **6** and **12** and **19** and **20** were examined using a series of bases and solvents.[30] The preliminary experiments with KH and NaH had suggested that control of the base stoichiometry might be required for selective sulfonylation of the primary alcohol of **6**. To control this parameter more easily, commercially available solutions of KHMDS in toluene were used. After extensive experimentation, it was found that treatment of tetraols **6** and **12** with 1 equiv. of KHMDS followed by slow addition of 1.0–1.1 equiv. of *N*-TrisIm allowed for selective sulfonylation of the primary alcohol, which underwent rapid conversion to the diol-epoxide intermediate. Subsequent base-induced tetrahydrofuran formation was effected by gradually adding an additional ~2.5 equiv. of KHMDS to the reaction mixture over the course of 3–4 h and allowing the reaction to continue at room temperature for 12 h. This one-pot protocol allowed for conversion of tetraols **6** and **12** to



Scheme 8. Initial attempts at one-pot conversion of tetraol to tetrahydrofuran.

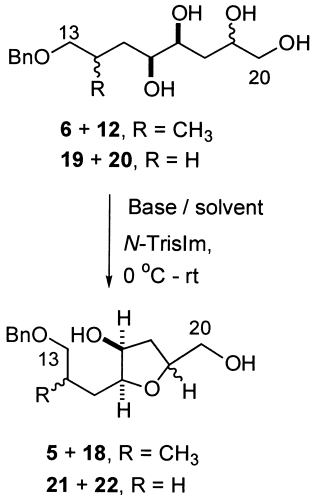
substituted tetrahydrofuran **5** and **14** in 50% combined yield (entry 3). Reaction of the desmethyl tetraols (**19**+**20**) under the same conditions provided the corresponding tetrahydrofurans in comparable yield (47–53%, entry 4). The bis-epoxide by-product formed under these reaction conditions was isolated in 22% yield.[31] The use of NaHMDS in the cyclization rather than KHMDS led to reduced yields of the tetrahydrofuran (19%, entry 7) due to increased formation of the bis-epoxide by-product. A variety of other bases were surveyed for this reaction in THF, including Triton-B, *i*-PrMgBr, CsOH, K_2CO_3, and BrMgHMDS, but none provided any improvement in conversion to tetrahydrofuran products.

The tetraols **19** and **20** were also used in a brief study of solvent effects in the cyclization cascade (Table 2, Scheme 9). To test the role of solvent polarity, solid KHMDS was used instead of commercially available toluene solutions. With KHMDS, the yield of tetrahydrofurans (**21**+**22**) was lower in THF solvent alone (entry 5), due to the formation of slightly more bis-epoxide by-product. When the reaction was performed in DMF (entry 6), the tetrahydrofurans were isolated in yields comparable to those achieved in THF/toluene. However, the major by-product formed in DMF was the alternative tetrahydrofuran regioisomer resulting from intramolecular 5-*exo* displacement of the primary sulfonate. Less of the bis-epoxide was apparent (TLC) when the reaction was performed in DMF.

Table 2. Base and solvent effects in one-pot tetraol to tetrahydrofuran transformation

Entry	R	Base	Solvent	Time (h)	Yield (%)
1	Me	NaH	THF	2–3	5–10[a]
2	Me	KH	THF	2–3	0[a]
3	Me	KHMDS	THF/toluene	8–22	50
4	H	KHMDS	THF/toluene	8–22	47–53
5	H	KHMDS	THF	6–22	28
6	H	KHMDS	DMF	22	39
7	H	NaHMDS	THF	8	19
8	H	KO*t*-Bu	*t*-BuOH	16	**62**

[a] Bis-epoxide **17** is formed rapidly under these reaction conditions.



Scheme 9. Survey of cyclization conditions summarized in Table 2.

Optimal results for the one-pot tetraol to THF conversion were achieved using potassium *tert*-butoxide in *tert*-butanol (entry 8, Table 2). Under these conditions, a mixture of tetraols **19** and **20** were converted into the corresponding tetrahydrofurans **21** and **22** in 62% combined, isolated yield. Only a minor amount of bis-epoxide byproducts (ca. 8%) were formed under these reaction conditions. Best results were obtained using solutions of potassium *tert*-butoxide that were freshly prepared from solid KH and *tert*-butanol.

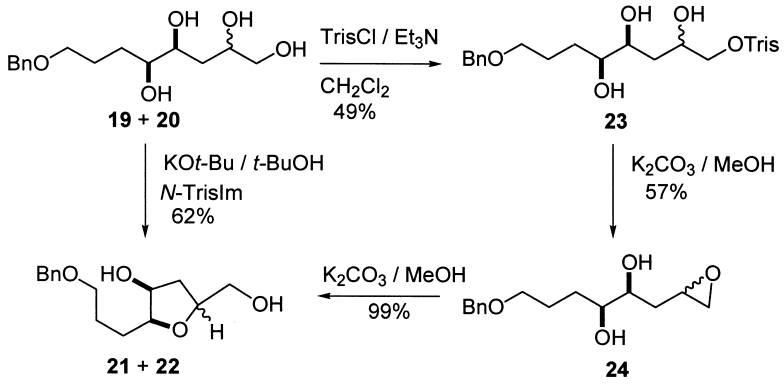
The use of the polar, protic solvent *tert*-butanol in conjunction with the portion-wise addition of potassium *tert*-butoxide (see Section 4) reduced the formation of bis-epoxide resulting from over sulfonylation of the polylol substrates. In an effort to further enhance the selectivity of primary sulfonylation, the mixture of tetraols (**19** and **20**) were treated with 1 equiv. each of KHMDS and *N*-TrisIm at −40°C, and the reaction was maintained at this temperature. However, the sulfonylation was extremely slow at this temperature, and virtually only starting material remained after several hours at −40°C. Hence, a step-wise sulfonylation–etherification cascade process was examined to determine whether enhanced regioselectivity via a discrete sulfonylation step would translate into higher overall efficiency.

2.2. Step-wise sulfonylation–dehydrative cyclization cascade

Examination of a discrete step-wise approach to the dehydrative polyol cyclization cascade began with the selective mono-sulfonylation of the primary alcohol of tetraols **19** and **20** (Scheme 10). 2,4,6-Triisopropylbenzenesulfonyl chloride (TrisCl) has previously been employed under standard conditions (pyridine, 0°C, 24 h)[32] and lengthy reaction times for such a purpose. Here, it was found that **19** and **20** could be converted into the corresponding sulfonates **23** using TrisCl and Et_3N in CH_2Cl_2 at rt. In contrast to the one pot sulfonylation–cyclization cascade, the pre-formed primary sulfonate could be converted into the tetrahydrofurans in very high yield upon treatment with K_2CO_3 in methanol at room temperature (ca. 3 h). However, **23** was very sensitive to purification and handling, being obtained in 49% after flash chromatography. That THF formation may proceed through the in situ generation of epoxide **24** was demonstrated in separate experiments by the isolation and characterization of **24** followed by its resubmission to the K_2CO_3/methanol reaction conditions to yield the cyclic ethers **21** and **22**. Again, **24** was quite unstable. In this step-wise approach, side reactions resulting from sulfonylation of secondary alcohols were clearly avoided. However, difficulties associated with the handling of sulfonate and epoxide intermediates diminish the utility of this sequence compared to the optimized one-pot procedure (entry 8, Table 2).

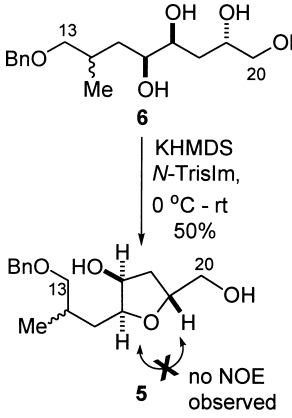
2.3. Stereochemical assignment of tetraols and tetrahydrofurans

To assign the relative configurations of the tetraols **6** and **12** and the resulting tetrahydrofuran products (**5** and **18**) of the cyclization reactions, further studies of the one-pot tetraol to tetrahydrofuran conversion were conducted using **6**, which had been chromatographically separated from its C19

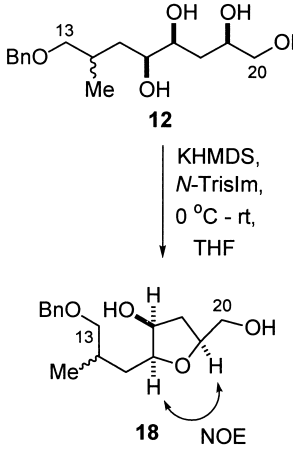


Scheme 10. Step-wise vs. one-pot sulfonylation–dehydrative cyclization cascade.

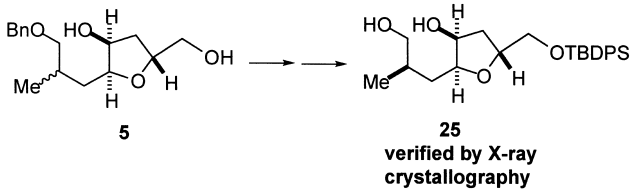
epimer (**12**) using MPLC.[29] The C19 configurations of **6** and **12** were initially assigned on the basis of the Sharpless mnemonic.[19] NOE experiments on the cyclization products of **6** and **12** supported the initial C19 stereochemical assignments. No NOE enhancement was observed between the C16 and C19 protons of **5**, suggesting that this was the *trans*-substituted tetrahydrofuran expected to arise from cyclization of **6** (Scheme 11).[33] Likewise, NOE enhancement was observed between the C16 and C19 protons of tetrahydrofuran **18**, as expected for a *cis*-substituted tetrahydrofuran (Scheme 12). These experiments provided further support for the initial stereochemical assignments of tetraols **6** and **12** and allowed the tentative assignments of relative configurations of tetrahydrofurans **5** and **18**. Ultimately, these stereochemical assignments were verified via X-ray crystallography. THF **5** was converted into diol 25 via lactone B (Scheme 13) which was subjected to X-ray crystallography to provide relative configurational assignments for all of the stereocenters in this system.



Scheme 11. Cyclization of tetraol **6** to tetrahydrofuran **5**.



Scheme 12. Tentative assignment of C19 stereochemistry based on observed NOE enhancement.



Scheme 13. Assignment of relative stereochemistry based on derivatization and X-ray crystallography.

3. Conclusions

The one-pot conversion of polyols to substituted tetrahydrofurans under the conditions defined here represents a remarkably convenient and relatively efficient method for construction of highly substituted cyclic ethers. Although the overall yield for this transformation is moderate, several reactions that might typically be accomplished in multiple steps are taking place in this one-pot procedure. In contrast, the step-wise alternative involving the isolation of sensitive sulfonate and epoxide intermediates provides considerably lower yields of tetrahydrofuran products. The dehydrative polyol etherification cascade couples with the ready accessibility of stereochemically enriched polyol arrays from the corresponding dienes via SAD methodology[18,19,27,28] to provide a two-operation conversion of dienes to cyclic ethers. This methodology compares favorably in yield and absolute stereocontrol with direct metal-mediated oxidative cyclizations of 1,4- and 1,5-dienes leading to substituted cyclic ethers.[14a] Applications of this methodology to the total synthesis of polyether natural products, including the azaspiracids[4,17] and bis-THF acetogenins,[5,6] will be reported in due course.

4. Experimental

4.1. General

Unless otherwise noted, all reactions were carried out under an Ar or N_2 atmosphere using oven dried glassware and standard syringe, cannula, and septa techniques. Diethyl ether, THF, and benzene were distilled from Na/benzophenone under N_2. Toluene was distilled from Na under N_2. CH_2Cl_2, CH_3CN, Et_3N, *i*-Pr_2NH, and $BF_3{\cdot}OEt_2$ were distilled from CaH_2 under N_2. AD-mix-α [$K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL, K_3FeCN_6, K_2CO_3][19] and β [$K_2OsO_2(OH)_4$, $(DHQD)_2$-PHAL, K_3FeCN_6, K_2CO_3],[19] solutions of KHMDS in toluene, and solid KHMDS were obtained from Aldrich Chemical Company. A 0.78 M solution of KHMDS in toluene was purchased from Lancaster Chemical Company. Flash chromatography was performed using ICN silica gel 32–63 and the solvent systems indicated. Analytical TLC was performed with 0.25 or 0.50 mm EM silica gel 60 F_{254} plates that were analyzed by fluorescence upon 254 nm irradiation or by staining upon heating with anisaldehyde reagent (450 mL 95% EtOH, 25 mL conc. H_2SO_4, 15 mL acetic acid, and 25 mL anisaldehyde). High resolution mass spectrometric data were obtained by the University of Minnesota Mass Spectrometry Laboratory using CI, FAB, and MALDI techniques. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

4.1.1. (±)-3-Propanoyl-1,4-pentadiene ((±)-9). To a stirred 0°C solution of (±)-1,5-hexadien-3-ol (10.0 g, 102 mmol) in CH_2Cl_2 (500 mL) under Ar was added pyridine (10.7 mL, 133 mmol), followed by freshly distilled propionyl chloride (11.7 mL, 133 mmol). After 1.5 h, saturated aqueous $NaHCO_3$ (150 mL) was added. The organic layer was separated and washed again with saturated aqueous $NaHCO_3$ (150 mL). The separated organic layer was washed with 5% aqueous HCl (2×100 mL) and saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. The solution was filtered, concentrated, and purified by silica gel column chromatography (hexanes/ethyl acetate, 12:1→8:1, v/v) to provide (±)-**9** (15.0 g, 97.4 mmol, 95%) as a clear, colorless oil: R_f 0.60 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 2978, 1706, 1464, 1417, 1241, 971, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.84–5.66 (m, 2H), 5.33–5.04 (m, 5H), 2.37 (m, 2H), 2.32 (q, *J*=7.5 Hz, 2H), 1.12 (t, *J*=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 136.0, 133.2, 117.9, 116.6, 73.4, 38.8, 27.8, 9.1; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; Found: C, 70.28; H, 8.96; HRCIMS Calcd for $C_9H_{15}O_2$ $[M+H]^+$ 155.1072, found 155.1088.

4.1.2. (±)-(*E*)-2-Methyl-4,7-octadienoic acid ((±)-10). To a stirred −78°C solution of **9** (4.0 g, 26 mmol) in THF (200 mL) under Ar, KHMDS (53 mL of a 0.78 M solution in toluene, 42 mmol) was added via syringe over a 15 min period. After an additional 20 min, a solution of TBSCl (6.3 g, 42 mmol) in THF (60 mL) was added via cannula. After an additional 30 min, the cooling bath was removed, allowing the reaction to gradually warm to rt. The reaction mixture was maintained at this temperature for 1.5 h. The mixture was then cooled to 0°C, and H_2O (25 mL) and 10% aqueous HCl (100 mL) were added. The mixture was stirred vigorously at rt for 1 h to ensure complete hydrolysis of the silyl ester intermediate, as indicated by TLC analysis. Aqueous NaOH (15%) was added to adjust the aqueous phase to pH 10. The aqueous layer was separated and acidified to pH 2 with aqueous HCl (10%), then washed with CH_2Cl_2 (8×75 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated to provide (±)-**10** (3.8 g, 25 mmol, 95%) as a pale yellow oil: R_f 0.11 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 2978, 1708, 1638, 1463, 1417, 1241, 970, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 11.2 (br. s, 1H), 5.81 (dddd, *J*=16.5, 10.0, 6.0, 6.0 Hz, 1H), 5.52 (ddd, *J*=15.5, 6.5, 6.5 Hz, 1H), 5.42 (ddd, *J*=15.0, 7.5, 7.5 Hz, 1H), 5.04–4.98 (m, 2H), 2.76 (dd, *J*=6.0, 6.0 Hz, 2H), 2.52 (dddd, *J*=14.0, 7.0, 7.0, 7.0 Hz, 1H), 2.41 (ddd, *J*=13.5, 6.5, 5.5 Hz, 1H), 2.18 (ddd, *J*=14.5, 8.0, 6.5 Hz, 1H), 1.18 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.8, 136.9, 130.7, 127.7, 115.1, 39.5, 36.6, 36.3, 16.3; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; Found: C, 70.19; H, 9.09; HRCIMS Calcd for $C_9H_{18}NO_2$ $[M+NH_4]^+$ 172.1336, found 172.1338.

4.1.3. (±)-(*E*)-2-Methyl-4,7-octadien-1-ol ((±)-11). To a stirred 0°C suspension of lithium aluminum hydride (1.6 g, 42 mmol) in diethylether (175 mL) under Ar was added a solution of (±)-**10** (3.85 g, 25 mmol) in diethylether (75 mL) via cannula. After 30 min, H_2O (1.6 mL) was added, followed by 15% aqueous NaOH (1.6 mL), and an additional portion of H_2O (3.2 mL). The mixture was stirred for 15 min, and then the white solid was removed by vacuum filtration and washed with diethylether (2×20 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated to provide (±)-**11** (3.2 g, 23 mmol, 90%) as a clear, colorless oil: R_f 0.28 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 3338, 3079, 2957, 2913, 1638, 1456, 1037, 970, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.82 (dddd, *J*=16.5, 10.0, 6.5, 6.5 Hz, 1H), 5.46 (m, 2H), 5.05–4.97 (m, 2H), 3.52 (dd, *J*=10.5, 6.0 Hz, 1H), 3.44 (dd, *J*=10.5, 6.0 Hz, 1H), 2.76 (m, 2H), 2.12 (m, 1H), 1.92 (m, 1H), 1.70 (dddd, *J*=13.5, 6.5, 6.5, 6.5 Hz, 1H), 1.41 (s, 1H), 0.91 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.2, 129.5, 129.4, 114.9, 68.0, 36.7, 36.5, 35.9, 16.4; HRCIMS Calcd for $C_9H_{20}NO$ $[M+NH_4]^+$ 158.1544, found 158.1549.

4.1.4. (±)-(*E*)-1-Benzyloxy-2-methyl-4,7-octadiene ((±)-7). To a stirred 0°C solution of (±)-**11** (10.7 g, 76 mmol) in THF (500 mL) under Ar was added NaH (6.1 g of a 60% dispersion in mineral oil, 0.15 mol). The reaction mixture was allowed to warm to rt over a 1 h period. The mixture was recooled to 0°C and benzyl bromide (13.1 mL, 107 mmol) and *tetra-n*-butylammonium iodide (8.4 g, 24 mmol) were added. After stirring at rt for 15 h, the mixture was cooled to 0°C and anhydrous methanol (13 mL) was added. The solution was allowed to warm to rt, and after 1 h, saturated NH_4Cl (150 mL) was added. The mixture was diluted with ethyl acetate (200 mL), and the aqueous phase was extracted with ethyl acetate (3×150 mL). The combined organic extracts were washed with saturated NaCl (200 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (pentane/diethylether, 1:0→50:1→40:1, v/v) provided (±)-**7**

(15.7 g, 68 mmol, 90%) as a clear, colorless oil: R_f 0.80 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 3063, 3029, 2956, 2903, 1637, 1453, 1363, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.25 (m, 5H), 5.83 (dddd, J=16.5, 10.2, 6.3, 6.3 Hz, 1H), 5.44 (m, 2H), 5.07–4.97 (m, 2H), 4.51 (s, 2H), 3.34 (dd, J=9.0, 6.0 Hz, 1H), 3.27 (dd, J=9.0, 6.3 Hz, 1H), 2.76 (m, 1H), 2.19 (m, 1H), 1.95–1.79 (m, 2H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 137.4, 129.5, 129.3, 128.3, 127.6, 127.5, 114.8, 75.3, 73.0, 36.8, 36.7, 33.7, 16.9; Anal. Calcd for $C_{16}H_{22}O$: C, 83.42; H, 9.63; Found: C, 83.58; H, 9.80; HRCIMS Calcd for $C_{16}H_{23}O$ $[M+H]^+$ 231.1749, found 231.1743.

4.1.5. (2*S*,3*S*,5*R*)-2-[(*R*,*S*)-3-(1-Benzyloxy-2-methyl)]propyl-3-hydroxy-5-(hydroxy)methyltetrahydrofuran (5) and (2*S*,3*S*,5*S*)-2-[(*R*,*S*)-3-(1-benzyloxy-2-methyl)]propyl-3-hydroxy-5-(hydroxy)methyltetrahydrofuran (18). A rt mixture of AD-mix-α (50 g) in *tert*-butanol (240 mL) and H_2O (240 mL) was stirred until both phases became clear. Methanesulfonamide (2.27 g, 23.9 mmol) was added, and the mixture was cooled to 0°C. A solution of (±)-**7** (5.5 g, 24 mmol) in *tert*-butanol (10 mL) was added, and the reaction mixture was stirred vigorously at 0°C for 13 h. Sodium sulfite (~50 g) was added, and the mixture was warmed to rt and stirred for 30 min. The mixture was diluted with ethyl acetate (200 mL) and H_2O (100 mL), and the separated aqueous phase was extracted with ethyl acetate (8×50 mL). The combined organic fractions were washed with 20% aqueous KOH and saturated aqueous NaCl (150 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (ethyl acetate/methanol, 1:0⟶20:1, v/v) to provide a ca. 1.5–1.0:1.0 mixture of *(2S,4S,5S,7R,S)-8-O-benzyl-7-methyl-octan-1,2,4,5,8-pentaol* (**6**) and *(2R,4S,5S,7R,S)-8-O-benzyl-7-methyl-octan-1,2,4,5,8-pentaol* (**12**), respectively (6.5 g combined, 23 mmol, 96%), as an oil. A portion of this was used directly in the subsequent reaction. To a 0°C solution of a mixture of **6** and **12** (1.6 g, 5.4 mmol) in THF (90 mL) under Ar was added KHMDS (11.8 mL of a 0.50 M solution in toluene, 5.9 mmol). After 15 min, the cooling bath was removed, and the reaction mixture was maintained at rt for 20 min. The reaction was cooled to 0°C, and *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (2.16 g, 6.44 mmol) in THF (10 mL) was added slowly via syringe over 1 h. The cooling bath was removed, and the mixture was stirred at rt for an additional 1.3 h. The mixture was cooled to 0°C, and KHMDS (5.0 mL of a 0.50 M solution in toluene, 2.5 mmol) was added. The reaction mixture was gradually warmed to rt, and after an additional 1.6 h, it was again cooled to 0°C and another portion of KHMDS (5.0 mL of a 0.5 M solution in toluene, 2.5 mmol) was added. The reaction mixture was gradually warmed to rt, and after an additional 1.6 h, it was cooled to 0°C and another aliquot of KHMDS (12 mL of a 0.5 M solution in toluene, 5.9 mmol) was added. The cooling bath was removed, and the mixture was stirred at rt for an additional 14 h. Saturated aqueous NH_4Cl (15 mL) and ethyl acetate (50 mL) were added, and the separated aqueous phase was washed with ethyl acetate (3×50 mL). The combined organic fractions were washed with H_2O and saturated aqueous NaCl (75 mL ea), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/methanol, 1:1:0⟶0:1:0⟶0:20:1, v/v) to provide **5** (455 mg, 1.6 mmol, 30%) and **18** (300 mg, 1.1 mmol, 20%) as colorless oils. **5**: R_f 0.45 (ethyl acetate/methanol, 5:1, v/v); IR (neat): 3425, 2925, 2850, 1500, 1435, 1180, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.26 (m, 5H), 4.52 (s, 1H), 4.50 (s, 1H), 4.33 (m, 0.5H), 4.29 (m, 0.5H), 4.25 (s, 0.5H), 4.21 (s, 0.5H), 3.89 (m, 1H), 3.65 (m, 1H), 3.44 (m, 1H), 3.35 (m, 1H), 3.26 (t, J=7.5 Hz, 0.5H), 3.12 (s, 0.5H), 2.54 (d, J=5.0 Hz, 0.5H), 2.41 (br s, 0.5H), 2.06–1.95 (m, 1.5H), 1.91–1.84 (m, 1.5H), 1.77 (m, 1H), 1.52 (m, 1H), 0.98 (d, J=6.0 Hz, 1.5H), 0.97 (d, J=6.0 Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 137.8, 128.5, 128.4, 127.8, 127.6, 127.5, 81.8, 80.2, 77.7, 77.2, 75.8, 75.7, 73.6, 73.4, 73.0, 72.6, 64.5, 36.9, 36.2, 32.9, 32.6, 30.8, 30.6, 18.4, 17.2; HRCIMS Calcd for $C_{16}H_{25}O_4$ $[M+H]^+$ 281.1753, found 281.1741. **18**: R_f 0.55 (ethyl acetate/methanol, 5:1, v/v); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 4.51 (s, 1H), 4.50 (s, 1H), 4.14–3.71 (m, 4H), 3.31–3.31 (m, 3H), 2.30 (m, 1H), 2.03–1.80 (m, 3H), 1.55 (m, 1H), 1.00 (d, J=6.6 Hz, 1.5H), 0.98 (d, J=6.6 Hz, 1.5H).

4.1.6. (2*S*,4*S*,5*S*)-8-*O*-Benzyl-octan-1,2,4,5,8-pentaol (19) and (2*R*,4*S*,5*S*)-8-*O*-benzyl-octan-1,2,4,5,8-pentaol (20). A rt mixture of AD-mix-α (29.2 g) in *tert*-butanol (80 mL) and H_2O (90 mL) was stirred until both phases became clear. Methanesulfonamide (2.0 g, 21 mmol) was added, and the mixture was cooled to 0°C. A solution of (*E*)-8-benzyloxy-1,4-octadiene (2.3 g, 10.6 mmol) in *tert*-butanol (10 mL) was added, and the reaction mixture was stirred vigorously at 0°C for 7.5 h. Sodium sulfite (~50 g) was added, and the mixture was warmed to rt and stirred for 30 min. The mixture was diluted with ethyl acetate (100 mL) and H_2O (25 mL), and the separated aqueous phase was washed with ethyl acetate (8×50 mL). The combined organic fractions were washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (ethyl acetate/methanol, 1:0⟶10:1, v/v) to provide a mixture of tetraols **19** and **20** (ca. 1.5:1.0, **19/20**, 2.7 g, 9.5 mmol, 90%) as a white amorphous solid which was used directly in the subsequent reaction.

4.1.7. (2*S*,3*S*,5*R*)-2-[3-(1-Benzyloxy)]propyl-3-hydroxy-5-(hydroxy)methyltetrahydrofuran (21) and (2*S*,3*S*,5*S*)-2-[3-(1-benzyloxy)]propyl-3-hydroxy-5-(hydroxy)methyltetrahydrofuran (22) using KHMDS and *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole. To a 0°C solution of a mixture of **19** and **20** (ca. 1.5:1.0, 19:20, 450 mg, 1.58 mmol) in THF (50 mL) under Ar was added KHMDS (3.4 mL of a 0.50 M solution in toluene, 1.7 mmol). After 15 min, the cooling bath was removed, and the reaction mixture was maintained at rt for 20 min. The mixture was cooled to 0°C, and a solution of *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (584 mg, 1.74 mmol) in THF (4 mL) was added slowly via syringe over 1.5 h. The cooling bath was removed, and the mixture was stirred at rt for an additional 1.3 h. The mixture was re-cooled to 0°C, and KHMDS (3.4 mL of a 0.50 M solution in toluene, 1.7 mmol) was added. The reaction mixture was gradually warmed to rt, and after an additional 2 h, it was again cooled to 0°C and

another portion of KHMDS (3.4 mL of a 0.5 M solution in toluene, 1.7 mmol) was added. The cooling bath was removed, and the mixture was stirred at rt for an additional 3 h. Saturated aqueous NH_4Cl (20 mL) and ethyl acetate (50 mL) were added, and the separated aqueous phase was washed with ethyl acetate (3×50 mL). The combined organic fractions were washed with H_2O and saturated aqueous NaCl (75 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate/methanol, 2:1:0→0:1:0→0:10:1, v/v) to provide **21** (109 mg, 0.41 mmol, 26%) and **22** (87 mg, 0.33 mmol, 21%) as colorless oils in 47% combined yield. **21**: R_f 0.38 (methanol/CH_2Cl_2, 1:9, v/v), R_f 0.22 (ethyl acetate/methanol, 10:1, v/v); $[\alpha]_D^{25}$=+1.4 (*c* 3.4, $CHCl_3$); IR (neat): 3401, 2930, 2863, 1495, 1453, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.26 (m, 5H), 4.50 (s, 2H), 4.32 (m, 1H), 4.25 (t, *J*=3.5 Hz, 1H), 3.79 (ddd, *J*=7.5, 7.5, 3.0 Hz, 1H), 3.65 (dd, *J*=12.0, 3.5 Hz, 1H), 3.56–3.44 (m, 3H), 2.50 (br s, 1H), 2.27 (br s, 1H), 1.98 (ddd, *J*=13.5, 6.5, 1.0 Hz, 1H), 1.90 (ddd, *J*=13.5, 9.0, 4.0 Hz, 1H), 1.78 (m, 3H), 1.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 128.6, 127.9, 127.8, 82.9, 77.7, 73.2, 73.0, 70.2, 65.0, 36.8, 26.2, 25.6; HRCIMS Calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1612. **22**: R_f 0.47 (methanol/CH_2Cl_2, 1:9, v/v); $[\alpha]_D^{25}$=+22.2 (*c* 1.65, $CHCl_3$); IR (thin film): 3374, 2864, 1452, 1454, 1363, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.28 (m, 5H), 4.52 (s, 2H), 4.16 (dddd, *J*=9.5, 3.0, 2.5, 2.5 Hz, 1H), 4.07 (dd, *J*=5.0, 2.5 Hz, 1H), 3.83 (dd, *J*=12.0, 2.5 Hz, 1H), 3.67 (ddd, *J*=7.0, 6.5, 3.0 Hz, 1H), 3.53 (t, *J*=6.0 Hz, 2H), 3.50 (dd, *J*=11.5, 2.0 Hz, 1H), 2.76 (br s, 2H), 2.36 (ddd, *J*=14.5, 9.5, 5.0 Hz, 1H), 1.89 (dd *J*=14.5, 3.5 Hz, 1H), 1.83–1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.5, 127.8, 127.7, 84.3, 77.2, 71.5, 70.4, 64.3, 37.2, 26.4, 25.6; HRFABMS Calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1612.

4.1.8. Tetrahydrofurans 21 and 22 using potassium *t*-butoxide and *N*-(2,4,6-triisopropylbenzenesulfonyl)-imidazole. To a solution of tetraols **19** and **20** (ca. 1.5:1, **19/20**, 142 mg, 500 μmol) in THF (14 mL) was added 1.1 mL of a 0.50 M solution of potassium *tert*-butoxide in *tert*-butanol/THF (0.55 mmol, 1:1, v/v) that was freshly prepared using KH and *tert*-butanol. The resulting solution was stirred at rt for 1 h. The solution was cooled to 0°C and a solution of *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (184 mg, 0.55 mmol) in THF (2 mL) was added dropwise over 1 h. After warming to rt and stirring for 1.5 h, the mixture was re-cooled to 0°C and an additional 1.1 mL of 0.50 M potassium *tert*-butoxide in *tert*-butanol/THF (0.55 mmol, 1:1, v/v) was added. The reaction mixture was allowed to warm to rt and stir for 1 h before being re-cooled to 0°C. A third aliquot (1.1 mL of 0.50 M solution, 0.55 mmol) of potassium *tert*-butoxide in *tert*-butanol/THF (1:1, v/v) was added and the reaction mixture allowed to warm to rt and stir for 16 h. At this time, some amount of **19** and **20**, as well as the corresponding primary sulfonates remained in the reaction mixture (TLC). The mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3×50 mL). The combined organic fraction was washed with saturated aqueous NaCl (75 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate →CH_2Cl_2/methanol, 19:1, v/v) to provide **21** (51 mg, 0.19 mmol, 38%) and **22** (32 mg, 0.12 mmol, 24%) in 62% combined yield, and the corresponding 1,2,4,5-bis-epoxides (10 mg, 40 μmol, 8%).

4.1.9. (2*R*/*S*,4*S*,5*S*)-8-*O*-Benzyl-octan-1,2,4,5,8-pentaol-1-(2,4,6-triisopropylbenzenesulfonate (23). To a stirred solution of tetraols **19** and **20** (101 mg, 0.356 mmol) in CH_2Cl_2 (5.0 mL) at rt was added triethylamine (198 μL, 1.42 mmol), and 2,4,6-triisopropylbenzenesulfonylchloride (431 mg, 1.42 mmol). After 12 h, further triethylamine (198 μL, 1.42 mmol) was added. After an additional 12 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (3×15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexanes, 1:1, v/v) provided **23** as a diastereomeric mixture (96 mg, 49%). R_f 0.26 (ethyl acetate/hexanes, 1:1, v/v); IR (thin film): 3404, 2959, 2869, 1600, 1563, 1496, 1454, 1425, 1364, 1346, 1274, 1178, 1103, 1010 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.28 (m, 5H), 7.20 (s, 2H), 4.53 (s, 2H), 4.25–4.05 (m, 4H), 4.03 (m, 1H), 3.82–3.66 (m, 1H), 3.58–3.50 (m, 1H), 3.49–3.39 (m, 1H), 3.13 (br s, 3H), 2.93 (septet, *J*=6.9 Hz, 1H), 1.84–1.46 (m, 6H), 1.27 (d, *J*=6.6 Hz, 1H); HRFABMS Calcd for $C_{30}H_{47}O_7S$ $[M+H]^+$ 551.3043, found 551.3036.

4.1.10. Epoxide 24. To a stirred solution of sulfonate **23** (72 mg, 0.13 mmol) in methanol (2.0 mL) was added K_2CO_3 (91 mg, 0.66 mmol) at 0°C. After 30 min at rt, the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (4×20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/hexanes, 3:1, v/v) gave epoxide **24** (20 mg, 57%). R_f 0.41 (ethyl acetate); IR (thin film): 3422, 3030, 2922, 2862, 1654, 1601, 1560, 1496, 1453, 1410, 1364, 1276, 1206, 1099, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.29 (m, 5H), 4.54 (s, 2H), 3.76–3.63 (m, 1H), 3.60–3.44 (m, 3H), 3.22 (br s, 1H), 3.21–3.11 (m_{obs}, 1H), 2.86 (dd, *J*=4.8, 4.2 Hz, 0.5H), 2.82 (dd, *J*=4.8, 4.2 Hz, 0.5H), 2.74 (br s, 0.5H), 2.67 (br s, 0.5H), 2.61 (dd, *J*=4.8, 2.7 Hz, 0.5H), 2.54 (dd, *J*=4.8, 2.7 Hz, 0.5H), 2.02–1.87 (m, 1H), 1.85–1.51 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.0, 128.6, 127.9 (2C), 74.0, 73.2, 72.1, 70.5, 50.3, 47.4, 36.3, 31.0, 26.2; HRFABMS Calcd for $C_{15}H_{23}O_4$ $[M+H]^+$ 267.1596, found 267.1610.

4.1.11. Tetrahydrofurans 21 and 22 using epoxide 24. To a stirred solution of epoxide **24** (44 mg, 0.165 mmol) in methanol (2.0 mL) was added K_2CO_3 (228 mg, 1.65 mmol) at 0°C. After 2.5 h at rt, the mixture was diluted with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (3×15 mL). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (ethyl acetate/methanol/CH_2Cl_2, 1:0:0→0:1:19, v/v) gave a mixture of tetrahydrofurans **21** and **22** (43 mg, 99%).

4.1.12. Tetrahydrofurans 21 and 22 using 2,4,6-triisopropylbenzenesulfonate 23. To a stirred solution of sulfonate **23**. (67 mg, 0.12 mmol) in methanol (1.5 mL) was added K_2CO_3 (169 mg, 1.22 mmol) at 0°C. After 3 h

at rt, the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (4×15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (methanol/CH_2Cl_2, 1:32→1:19, v/v) provided **21** (20 mg, 62%) and **22** (12 mg, 37%).

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25. Racemic **7** was used because, in this case, the stereochemistry would be established at later stage via equilibration (see Ref. 17). For the synthesis of non-racemic diene, enantioenriched allylic alcohol **8** could also be converted to enantioenriched carboxylic acid via Ireland–Claisen rearrangement with moderate stereochemical control.
26. The carbinol epimers were chromatographically separable by MPLC (SiO_2), and each showed a distinctive doubling of the C13 (azaspiracid numbering) methyl doublet in the ^1H NMR spectrum.
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29. Due to the difficulty in separating the C14 epimers of **6** and **12**, the mixture of C14 epimers was used throughout the studies described herein.
30. To avoid tedious MPLC purification, the mixtures of tetraols (**6**+**12**) and (**19**+**20**) were used directly in the preliminary cyclization studies.
31. Unreacted starting material accounted for approximately 10% of the remaining mass balance. A by-product tentatively assigned as the regioisomeric tetrahydrofuran resulting from intramolecular displacement of the C20 (azaspiracid numbering) sulfonate by the C17 alkoxide was formed in <10% yield under these conditions.
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33. The expected diol–epoxide has been isolated as an intermediate in this reaction, and epoxide openings are known to proceed with inversion of configuration under basic conditions. Therefore, the configurational assignments of the tetrahydrofuran products also allow for deduction of the configurational assignments of the tetraol starting materials.