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Substituted Diether Diols by Ring-Opening of Carbocyclic and Stannylene Acetals

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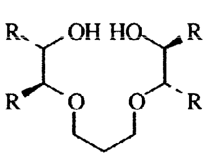
Abstract : Reduction of malonaldehyde bis(ethylene and propylene acetals) with borane or monochloroborane produces diether diols **1** and **2** in high yield. Similar reduction of glyoxal bis(ethylene acetals) has only limited utility for the preparation of tetrasubstituted triethylene glycols **3**. Organotin chemistry is complementary: stannylene acetals prepared from disubstituted vicinal diols can be alkylated with half an equivalent of 1,2-dibromoethane to produce tetrasubstituted triethylene glycols **3**, or with two equivalents of 2-chloroethanol to produce disubstituted triethylene glycols **4**. © 1998 Elsevier Science Ltd. All rights reserved.

Crown ethers bearing alkyl, aryl, and functional group substituents have been used as enzyme mimics, receptor site models, and selective ionophores.[1-3] Our interest in highly substituted crown ethers prompted the development of methodology for the preparation of substituted polyether diols **1-4** useful as acyclic precursors to these. Disubstituted triethylene glycols **4** have been prepared by others by dialkylation of disubstituted ethylene glycols with (for example) ethyl diazoacetate/$BF_3 \cdot Et_2O$, with subsequent reduction of the resulting diester to the diol.[4] Where substituents are sensitive to reduction, the dialkylation has been accomplished with protected haloalcohols and base.[5] The preparation of tetrasubstituted dietherdiols **1-3** is less direct. Synthesis has required the extensive use of protective groups; the protection/deprotection steps frequently outnumber those which construct the polyetherdiol backbone.[1,5] We report here the synthesis of diether diols **1-4** by more direct procedures.[6]



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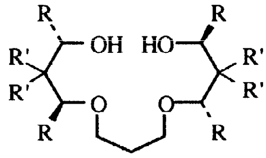
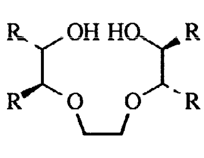


2a R= substituent, R'= H
2b R= H, R'= substituent



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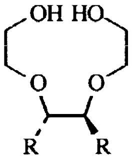

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Tetrasubstituted Dietherdiols 1 and 2 By Reduction of Malonaldehyde Bis(acetals)

Our approach to the preparation of tetrasubstituted dietherdiols **1** and **2** is conceptually simple: they would result from the reductive cleavage of one C-O bond in each 1,3-dioxolane (or 1,3-dioxane) ring in bis(acetals) **5**. These could, in turn, be prepared from malonaldehyde (or a synthetic

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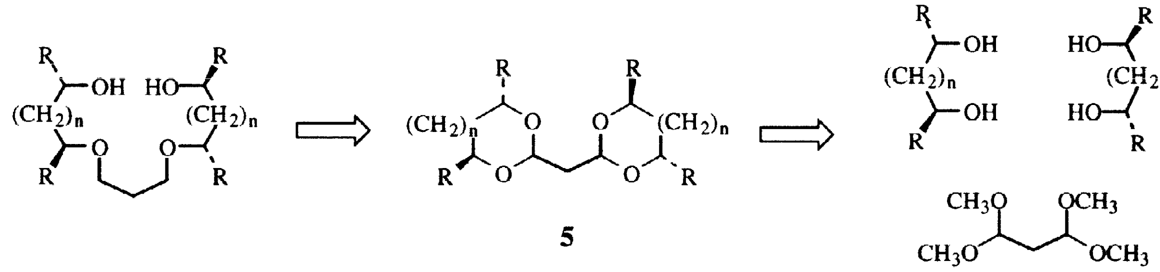
equivalent) and two equivalents of an appropriately substituted 1,2- or 1,3-diol.[7]



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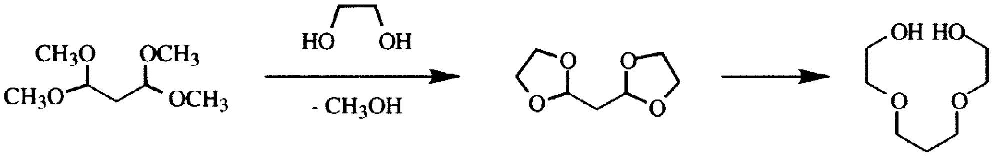
Unsubstituted bis(ethylene acetal) **6** was prepared in 95% yield by the acid catalyzed reaction of malonaldehyde bis(dimethyl acetal) and ethylene glycol, with azeotropic removal of methanol.[7] The selective reduction of **6** to 3,7-dioxa-1,9-nonanediol (**7**) was initially attempted with $LiAlH_4/AlCl_3$ mixtures in diethyl ether solvent.[8a] However, only 8-11% yields of diether diol **7** were obtained and no starting material was recovered. Manipulation of reaction conditions and isolation procedures failed to significantly increase yields. The aqueous workup required to remove aluminum salts was unacceptable, since most of the product was not recovered, possibly due to its great water solubility and/or its being intractably associated with the aluminum salts.

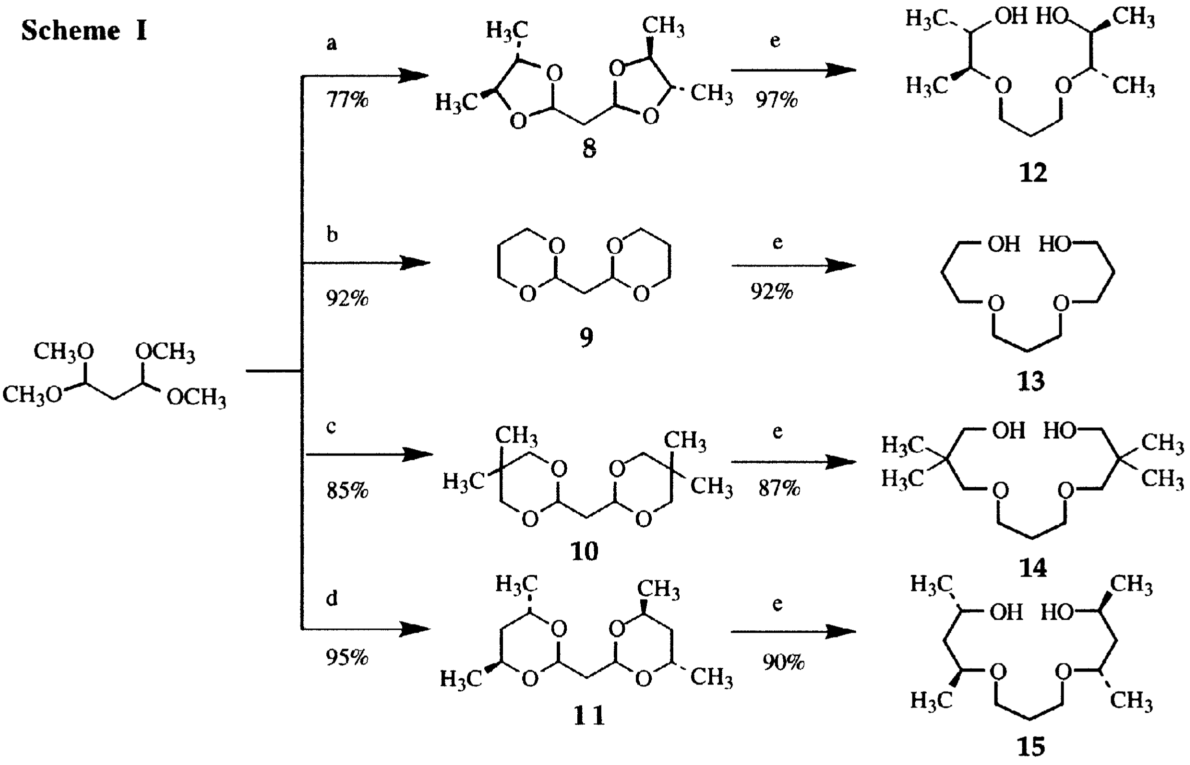


6 **7**

Reduction was finally achieved in high yield with 2.5 equivalents of borane-tetrahydrofuran (BH_3-THF) complex in refluxing THF for 48 h. A modification of the procedure used by Fleming and Bolker to reduce monoacetals allowed us to easily produce and isolate **7** in good yields.[8b] Instead of an aqueous workup, intermediate borate esters and remaining hydride were decomposed with excess methanol. The residue after removal of the THF, methanol, and volatile trimethylborate at reduced pressure was a 98% yield of essentially pure **7**, which could be made analytically pure by chromatography. The use of the more electrophilic monochloroborane-dimethylsulfide[8c] (BH_2Cl-SMe_2) in diethyl ether solvent afforded the identical product in under 12 h at room temperature. THF is attacked by BH_2Cl-SMe_2 to produce (after workup) 4-chlorobutanol, a result consistent with the observation that cyclic ethers are cleaved by haloboranes.[9]

We also prepared bis(acetals) **8**-**11**[7] and reduced them in good yield to the alkyl substituted diether diols **12**-**15** (**Scheme I**). These bis(acetals) have either a symmetry plane (**6**, **9**, and **10**) or a C_2 axis (**8** and **11**), and consequently reduction is unambiguous: cleavage of either geminal C-O bond produces the same diether diol. Chiral diols (2*S*,3*S*)-2,3-butanediol and (2*S*,4*S*)-2,4-pentanediol were used to prepare the bis(1,3-heterocycles) **8** and **11**; diether diol products **12** and **15** resulting from reduction incorporate that chirality.

Scheme I

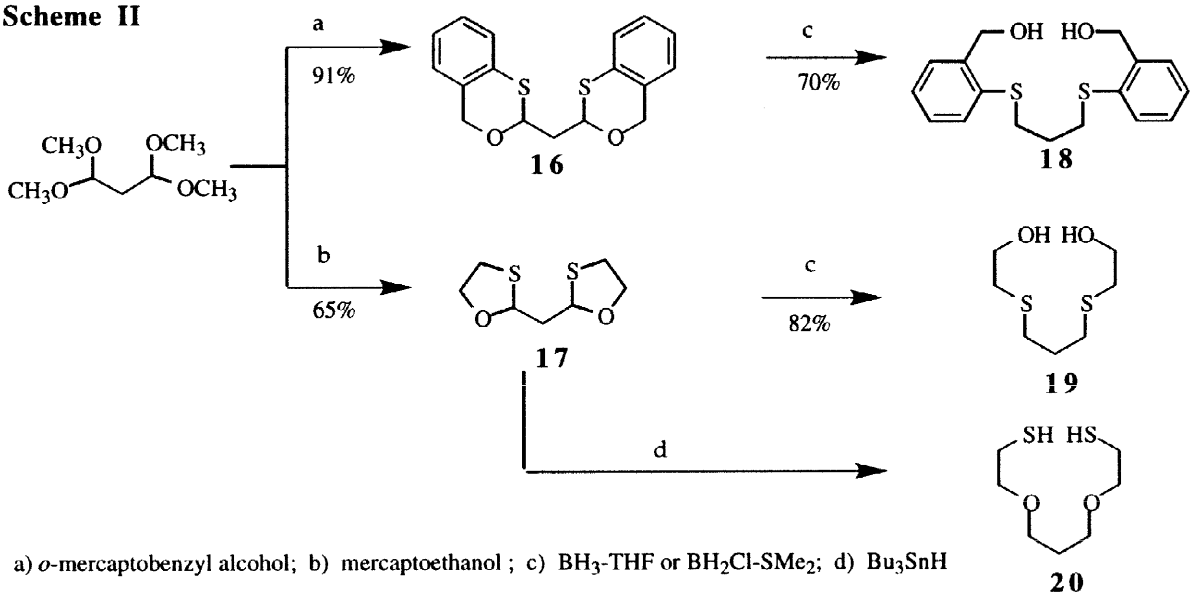


a) (2*S*,3*S*)-2,3-butanediol; b) 1,3-propanediol; c) 2,2-dimethyl-1,3-propanediol; d) (2*S*,4*S*)-2,4-pentanediol; e) BH_3-THF or BH_2Cl-SMe_2

Reduction of Bis(hemithioacetals)

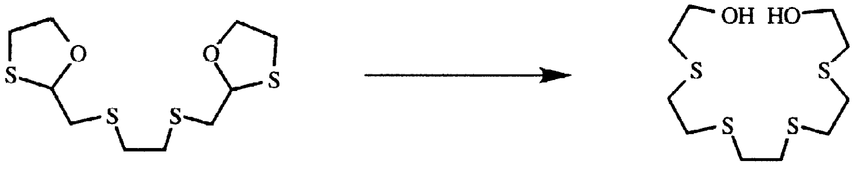
We also found that bis(hemithioacetals) **16** and **17** are reduced to the dithioether diols **18** and **19** in good yields (**Scheme II**). Under no circumstances did we see the cleavage of a C-S bond in these reductions. This procedure is complementary to other work[10, 11] in our laboratories wherein the C-S bonds are reduced by tributyltin hydride (TBTH) to the isomeric diether dimercaptan **20**.

Scheme II



a) *o*-mercaptobenzyl alcohol; b) mercaptoethanol ; c) BH_3-THF or BH_2Cl-SMe_2; d) Bu_3SnH

Bis(ethylene hemithioacetal) **21**[11] was reduced by BH_2Cl-SMe_2 to tetrathiatetraundecanediol **22** in 69% yield. Hemithioacetals **16**, **17** and **21** are produced as mixtures of diastereomers; destruction of the chiral centers by reduction produced **18**, **19** and **22** each as a single compound.



21 **22**

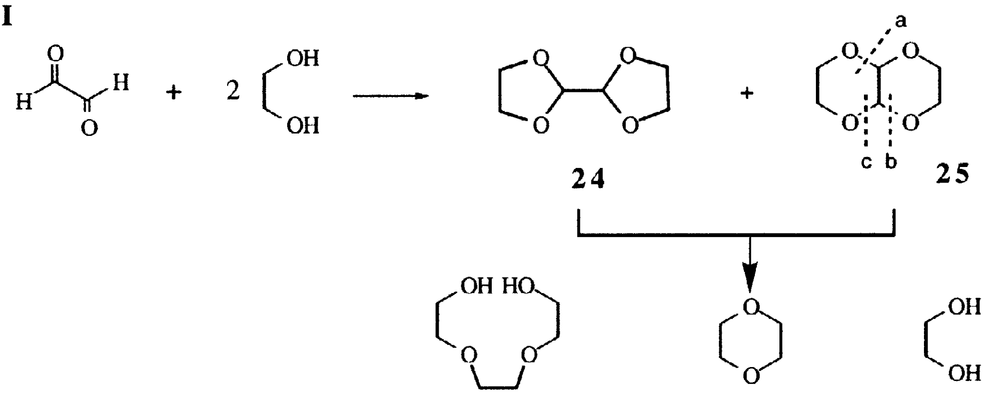
Diether Diols 3 By Reduction of Glyoxal Bis(acetals)

It was anticipated that reduction of a bi-1,3-dioxolane of type **23** would produce tetrasubstituted triethylene glycols **3**, which we required as precursors to substituted 18-crown-6 derivatives.

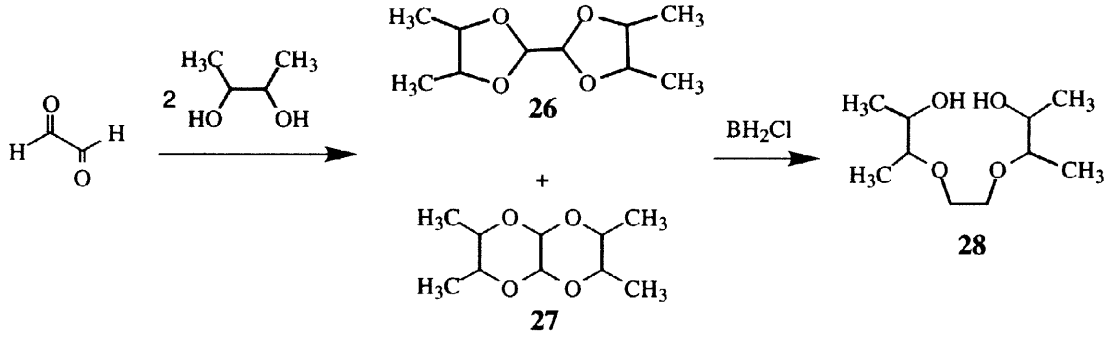
23 **3**

However, the chemistry of glyoxal is more complicated than that of malonaldehyde. The reaction between glyoxal and ethylene glycol produced not only unsubstituted parent bidioxolane **24** but also tetraoxadecalin isomer **25** as a 7:3 mixture (Scheme III).[6, 12, 13] Reduction of this mixture with either BH_3-THF or BH_2Cl-SMe_2 was complicated by the presence of **25**: the bidioxolane **24** reduced cleanly to triethylene glycol (confirmed by the reduction of a pure sample of **24** obtained by fractional recrystallization). However the tetraoxadecalin **25** can yield triethylene glycol if bonds labeled "a" and "b" are cleaved; but also dioxane and ethylene glycol if bonds "a" and "c" are reduced. The latter appears to be the more favored mode.

Scheme III



Sprung and Guenther[12] have reported the preparation of acetals from glyoxal and several diols (including 2,3-butanediol), but the analysis of the bidioxolane and tetraoxadecalin products was complicated by the formation of polymers. We reacted one equivalent of 40% aqueous glyoxal with two of a mixture of racemic and meso 2,3-butanediol and isolated a 75% yield of a 1:1 mixture of tetramethylbidioxolane **26** and tetramethyltetraoxadecalin **27** [in subsequent sections we describe work with (2*S*,3*S*)-2,3-butanediol]. Reduction of this mixture of isomers was slower than of the unsubstituted parents **22** and **23**, or of the acetals derived from butanediol and malonaldehyde (within 24 h by BH_3-THF at THF reflux, or within 5 h by BH_2Cl-SMe_2 at ambient temperature in diethyl ether). By comparison, no reduction of isomers **26** and **27** was observed in BH_3-THF after eight days at THF reflux. BH_2Cl-SMe_2 at diethyl ether reflux effected reduction, with isomer **26** reacting faster than **27**: after 48 h the ^1H NMR spectrum of the reaction mixture indicated the disappearance of the bidioxolane **26** acetal methine singlet at δ 4.74 ppm, the appearance of signals corresponding to product triethyleneglycols **28**, and the persistence of tetraoxadecalin **27**. The reaction resulted in the isolation, however, of only a 27% yield of diastereomeric products **28**.



Lithium Ion-Assisted Formation of Bidioxolanes

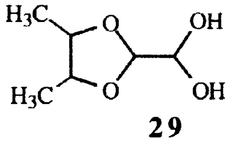
Chastrette[7] observed that alkali and alkaline earth perchlorates selectively complex glyoxal bidioxolane acetals, and used this to separate a mixture of unsubstituted bisacetals **24** and **25**. Our attempts to separate tetramethyl bisacetals **26** and **27** by this method were only modestly successful (we were able to separate only 20% of **26** contained in the 1:1 mixture). We, however, found useful result in controlling the bidioxolane:tetraoxadecalin ratio by running the acetalization reactions of glyoxal and 1,2-diols in the presence of lithium perchlorate. Chastrette reports that their attempts led to "considerable resinification", yet we found that lithium perchlorate increased the amount of bidioxolane **26** at the expense of tetraoxadecalin **27**. However, increasing the amount of perchlorate salt beyond one equivalent decreased the total yield of monomeric products, and also the ratio of bidioxolane to tetraoxadecalin products. Entries 1-4 in the **Table** summarize these results. The use of magnesium or sodium perchlorate led to lower yields.

A large excess of glyoxal in the acetal-forming reaction, whose stoichiometry requires a 2:1 ratio of diol to glyoxal, also gave useful results. The reaction of 2 equivalents of 2,3-butanediol with up to 2.5 of glyoxal (a 150% molar excess beyond that required by stoichiometry), gave us a 74% yield of a 9:1 mixture of **26**:**27**. It appears that the excess glyoxal allows for easier equilibration of the reaction mixture, and that the complex of **26** (or an intermediate leading to **26**) with $LiClO_4$, is the more stable product in the reaction mixture. Increasing the amount of glyoxal further did not increase the relative amount of **26** nor result in a greater yield of product (cf. **Table**, entries 5-7).

Table. Reaction of 2,3-butanediol with glyoxal to produce bis(acetals) **26** and **27**

Entry	Equivalents of Starting Materials			Products		
	Diol	Glyoxal	$LiClO_4$	Combined % Yield	Ratio of Bidioxolane **26**:	Tetraoxadecalin **27**
1	2	1	0	86	1	1
2	2	1	0.5	64	7	3
3	2	1	1.0	73	8	2
4	2	1	2.0	31	6	4
5	2	2.5	1.0	74	9	1
6	2	3.1	1.0	70	9	1
7	2	4.0	1.0	46	9	1
8	2	2.5	0	----	0	0
9	2	2.5	0.3	75	9	1
10	2	2.5	0.5	83	9	1
11	2	2.5	0.8	79	9	1
12	2	2.5	1.0	74	9	1
13	2	2.5	1.2	64	9	1

The effect of lithium perchlorate on the course of the reaction of diol with 2.5 equivalents of glyoxal is profound (**Table**, entries 8-13). In the absence of lithium perchlorate, the reaction produced no bidioxolane **26** nor tetraoxadecalin **27** but rather a mixture consistent with the presence of glyoxal monoacetals **29** and **30**. As the equivalents of lithium perchlorate were increased from 0 to 0.5, the ratio of **26**:**27** increased to 9:1 and the combined yield of **26** and **27** increased from 0 to 83%. As lithium perchlorate was increased beyond 0.5 equivalent, the 9:1 ratio of isomers **26** and **27** persisted, but the total amount of monomeric products decreased; consistent with Chasterette's observation that [excess] perchlorate salts promote polymerization.[7]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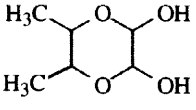
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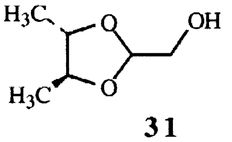
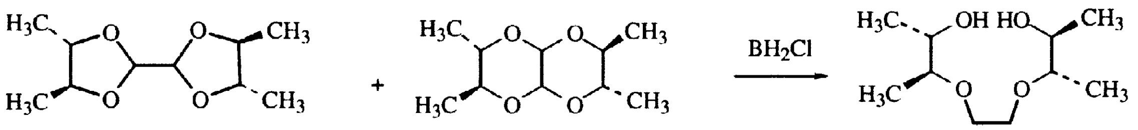

31

It may be likely that bidioxolane **26**, or an intermediate leading to it, forms a 2:1 complex with $LiClO_4$. Models indicate that bidioxolane **26** can serve as a tridentate ligand to lithium cation: two equivalents of **26** may provide a hexacoordinate environment for the cation. The same effect may be observed with the possible intermediates: 1,2-dioxolane-2-carboxaldehyde or its hydrate **29**.[14] Tetraoxadecalin **27** cannot readily complex lithium. Models of the rigid trans and the more flexible cis isomer of **27** imply that at best it could be a bidentate ligand, as only two oxygen atoms are geometrically situated for such coordination. The ^1H NMR signal corresponding to the methine proton of bidioxolane **26** shifts upfield from 5.02 to 4.96 ppm (5.4 Hz) when $LiClO_4$ is added to a mixture of the bisacetals in toluene solvent. We prepared 4,5-dimethyl-2-hydroxymethyl-1,3-dioxolane (**31**) from glycolaldehyde dimer and butanediol as a model for the putative intermediate **29**. It exhibits a similar ^1H NMR peak shift of the methine proton from 5.00 ppm to 4.96 ppm, consistent with the assumption that intermediates leading to bidioxolane **26** may form a complex with lithium perchlorate. We observed no corresponding shift in the tetraoxadecalin **27** methine signal.

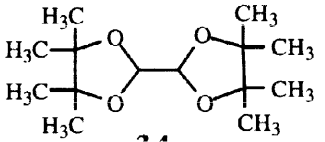
The synthesis of chiral **3a** (the *S,S,S,S*-diastereomer of **28**) by the present methodology requires chiral bidioxolane **32** as substrate for reduction. Surprisingly, when we used (2*S*,3*S*)-2,3-butanediol to produce **32** and tetraoxadecalin **33**, the acid catalyzed reaction of two equivalents of the chiral diol and one of glyoxal gave a 20:80 mixture of bidioxolane **32** and tetraoxadecalin **33**. This low production of **32** was quite surprising, since the racemic/meso mixture of 2,3-butanediols reacted with glyoxal to yield a 50:50 mixture of the isomers **26** and **27** in the absence of lithium perchlorate (cf. the **Table**). The *trans*-fused isomer of tetramethyltetraoxadecalin **33** bears two methyl groups in obligate axial positions. This made us anticipate an increase in the relative amount of **32**. We observed the opposite, implying that (2*S*,3*S*,6*S*,7*S*)-2,3,6,7-tetramethyl-1,4,5,8-tetraoxadecalin (**33**) may be *cis*-fused. This isomer has all methyl substituents in equatorial positions, and is possibly less disfavored (relative to the corresponding carbocyclic *cis*-decalin) because of anomeric effects.[15] As before, the composition of the reaction mixture was manipulated by the use of 0.5 equivalents $LiClO_4$ and 2.5 of glyoxal to generate (4*S*,4'*S*,5*S*,5'*S*)-4,4',5,5'-tetramethyl-2,2'-bi-1,3-dioxolane (**32**) as the major product: these conditions produced a 74% yield of an 83:17 mixture of **32**:**33**.[13]



32 **33** **3a**

That chiral butanediol forms less bi-1,3-dioxolane than does a mixture of diastereomeric (racemic and meso) 2,3-butanediols may be a consequence of the presence of the meso diastereomer. Its incorporation appears to destabilize the tetraoxadecalin isomers **27**, resulting in the relative increase in the amount of bidioxolane **26**: the various *cis*- and *trans*-fused tetraoxadecalins **27** which incorporate one or two meso diol units result in structures which have one or two axial methyl groups. The tetraoxadecalins formed from glyoxal and one each *R,R*- and *S,S*- enantiomeric diols results in three isomers: one has all four methyl groups in axial position; one all equatorial; and the third has one methyl in an axial position. The reaction of two equivalents of the same diol enantiomer and glyoxal forms a trans isomer with two axial methyls, but the cis isomer has all of them in equatorial positions. The overall effect when racemic and meso diols are used is the general increase in the relative amount of **26** and concomitant decrease in **27**.

We took as corroboration of the assumption that axial substituents destabilize tetraoxadecalins relative to bidioxolanes the observation that the acid catalyzed reaction of 2,3-dimethyl-2,3-butanediol with glyoxal produces an 80% yield of a 72:28 mixture of **34** and **35**.[13] Here axial methyl groups are obligatory in both tetraoxadecalin isomers **35**. The use of $LiClO_4$ and excess glyoxal resulted in a yield (74%) slightly lower than in the salt-free case, but with a more favorable 88:12 ratio of bidioxolane **34** to tetraoxadecalin **35**.



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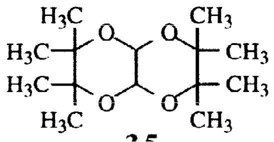

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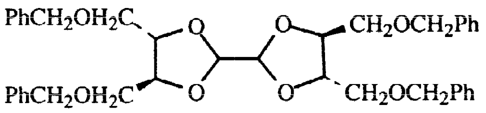

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Reduction of the tetramethyl bidioxolane-rich mixture of chiral **32** and **33** (83:17) with BH_2Cl-SMe_2 complex produced (2*S*,3*S*,8*S*,9*S*)-3,8-dimethyl-4,7-dioxa-2,9-decanediol (**3a**)[16] in 63% isolated yield. As noted before, the bidioxolane **32** reduced faster than its isomer **33**. Thus after the reduction of **32** was completed, the reaction was stopped and the mixture of diether diol **3a** and unreacted **33** was separated by column chromatography.

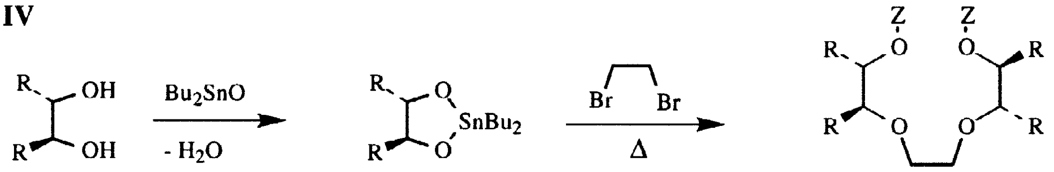
Unfortunately, this approach was not, in our hands, general for the preparation of tetrasubstituted triethyleneglycols **3**. While reasonable yields were obtained in the reduction of **32** to the dietherdiol, **3a**, BH_2Cl-SMe_2 was unsuccessful in reducing more hindered bidioxolanes **34** and **36**.

Tetra- and Disubstituted Triethylene Glycols 3 and 4 From Stannylene Acetal Precursors

We have found that tetrasubstituted triethylene glycols **3** and disubstituted **4** may be prepared from organotin derivatives of substituted ethylene glycols. Organotin alkoxides are useful synthetic intermediates in that the oxygen is more nucleophilic and less basic than in the parent alcohol.[17] Stannylene acetals have been used primarily in carbohydrate chemistry to effect selective alkylation of particular hydroxyls in molecules wherein several are present.[18] Also, it has been reported that while acylation of both Sn-O bonds is common,[19] alkylation is generally limited to mono-, and then only with activated alkyl (benzyl, allyl, methyl) halides.[17, 20]

We have observed monoalkylation of 2,2-dibutyl-2-stanna-1,3-dioxolanes **37** with 1,2-dibromoethane to acyclic products **38**, which are subsequently destannylated to the tetrasubstituted triethylene glycols **3**, **Scheme IV**. For example, heating a neat mix of two equivalents of **37b** (R= CH_2OCH_2Ph) and one equivalent of ethylene bromide at 110° resulted in the alkylation of one Sn-O in each stannylene acetal to produce the bis(dibutylbromostannyl) dialkoxide **38b** (Z= $SnBu_2Br$).[21] This was destannylated by passage through a column of silica gel to produce tetrabenzyloxymethyl triethylene glycol **3b** in good yield. The destannylation can be accomplished alternatively by reaction of the intermediate bis(dibutylhalotin alkoxides) **38** with oxalic acid.[22]

Scheme IV

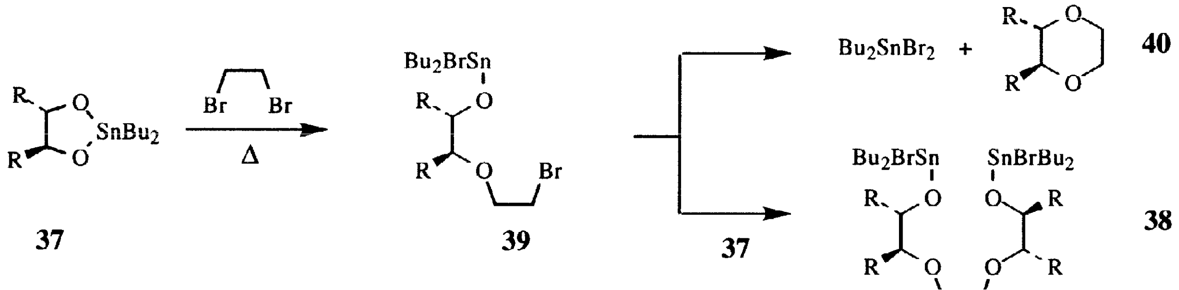


			38	Z= $SnBu_2Br$	
R= CH_3	**37a**	92%	**3a**	Z= H	5%
R= CH_2OCH_2Ph	**37b**	90%	**3b**	Z= H	71%
R= CO_2CH_3	**37c**	95%	**3c**	Z= H	82%

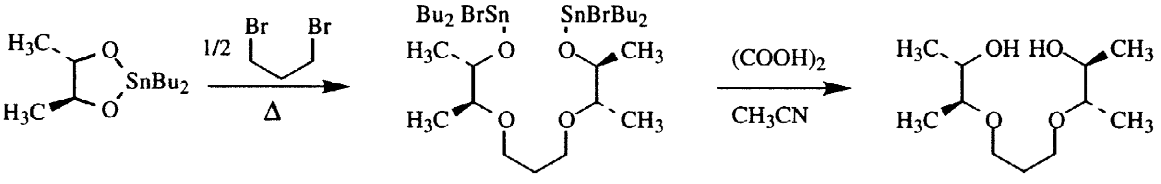
Noteworthy is the preparation of tetra(carboxymethyl)triethylene glycol **3c** from (*R*,*R*) dimethyl tartrate in an overall 78% yield. While the preparation of triethylene glycols having a similar substitution pattern has been reported, the present method avoids the many protection/deprotection steps, and the use of toxic thallium alkoxides to effect alkylation.[5a] Indeed, our organotin approach avoids the use of any external base.

Surprisingly, the reaction of dimethyl stannylene acetal **37a** and 1,2-dibromoethane produced 2,3-dimethyl-1,4-dioxane[23] as the major product, and after destannylation of the non-volatile residue, only a 5% yield of (2*S*,3*S*,8*S*,9*S*)-3,8-dimethyl-4,7-dioxadecane-2,9-diol (**3a**), identical to the sample prepared by the $BH_2Cl\text{-}SMe_2$ reduction of **32**, the glyoxal bis(acetal) of (2*S*,3*S*)-2,3-butanediol. The reactions appear to follow the outline in **Scheme V**, with the product composition determined by the competition for intermediate **39** by either the second equivalent of **37** to produce **38**; or by internal alkylation to produce dioxanes **40**. While monoalkylation of **37** is generally observed, internal dialkylation to produce the dioxane **40** is possible and appears dependent on the nature of the substituents R.

Scheme V

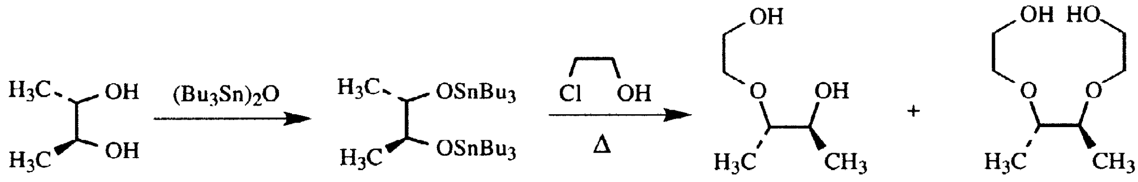


Dialkylation of the stannylene acetals **37** may also be limited to the formation of six-membered rings. The use of 1,3-dibromopropane resulted only in monoalkylation of two equivalents of stannylene acetal **37a** to produce (2*S*,3*S*,9*S*,10*S*)-3,9-dimethyl-4,8-dioxaundecane-2,10-diol (**12**) (after destannylation of intermediate **41** with oxalic acid), identical to the product from $BH_2Cl\text{-}SMe_2$ reduction of malonaldehyde bis(acetal) **11** (cf. **Scheme I**). We detected no corresponding 2,3-dimethyl-1,4-dioxacycloheptane.



37a **41** **12**

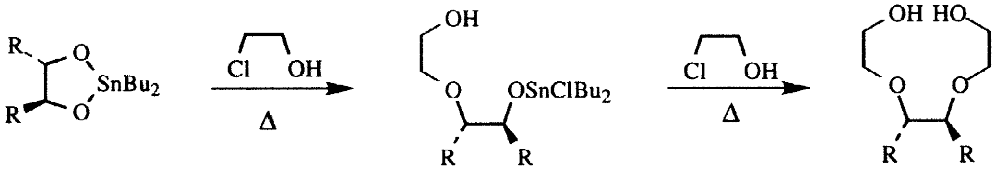
The use of organotin intermediates also suggested an alternative synthesis of disubstituted triethylene glycols **4**. Bistributylstannyl ether **42**[23b] was prepared with the intent of dialkylation with two equivalents of 2-chloroethanol to produce dimethyltriethyleneglycol **4a** (R= CH_3). However, the reaction product consisted of a 42% yield of a mixture of **4a** and (4*S*,5*S*)-4-methyl-3-oxa-1,5-hexanediol (**43**), the product of monoalkylation. The remainder of the chloroethanol was presumably lost as ethylene oxide by a competing process which requires initial exchange of a tributylstannyl group from **42** to chloroethanol, and subsequent internal alkylation[24] of that intermediate to generate the epoxide and tributyltin chloride. This result was not unexpected in that tributyltin ethers are prone to exchange among oxygen nucleophiles, and also to slow hydrolysis with atmospheric moisture.



42 **43** **4a**

However, stannylene acetals **37** can be sequentially dialkylated[25] with 2-chloroethanol without solvent, **Scheme VI**. For example, at 140 °C we observed clean monoalkylation, even with excess chloroethanol, of **37a** (R= CH_3) to (4*S*,5*S*)-4-methyl-3-oxa-1,5-hexanediol (**43**) in 93% yield after destannylation of the intermediate chlorodibutyltin alkoxide (**44a,** R=CH_3) on silica gel. However, at 170 °C we observed dialkylation of **37a** to (4*S*,5*S*)-4,5-dimethyl-3,6-dioxa-1,8-octanediol (**4a**) in 84% yield. While the diacylation of stannylene acetals is well documented,[19] this report shows that dialkylation with monohalogen compounds is also possible, and synthetically useful. The second Sn-O bond of stannylene acetals is not inert towards alkylation, but considerably less reactive than the first. Earlier reports describe the solution chemistry of stannylene acetals, and the sequential dialkylation of Sn-O bonds in stannylene acetals with monohalides is rarely observed, possibly because the reaction temperature was limited by the solvent.[26]

Scheme VI



37a R= CH_3
37b R= CH_2OCH_2Ph
37c R= CO_2CH_3

44

4a 84%
4b 80%
4c 78%

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Experimental

Melting points are reported uncorrected. Solvents were dried by standard methods and used after distillation. Glassware was dried overnight in a 140 °C oven. Reactions were stirred magnetically and run in a dry nitrogen atmosphere, except where noted. Chromatographic separations were performed on silica gel by flash chromatography[27] or radially accelerated thin layer chromatography.[28] Nuclear magnetic resonance spectra were recorded at 90 MHz (Varian EM-390) or 300 MHz (Brucker 300). Chemical shifts are reported in δ values (ppm) relative to tetramethylsilane internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR; only selected absorptions are reported. Since many reactions are similar, only representative examples are presented.

Preparation of bis(acetals). Malonaldehyde bis(acetals) **6**, and **8-11**, and -bis(hemithioacetals) **16** and **17** were all prepared as illustrated below for **8**. Glyoxal bis(acetals) were prepared as in the example below for **32** and **33**. Bis(acetals) **6**, **9**, **24** and **25** and bis(hemithioacetals) **17** and **21** have been previously reported; our samples exhibited consistent physical properties.[7,11] Analytical data are provided only for new compounds. The yields were presented in the **Schemes**.

Malonaldehyde bis[(*S*,*S*)-1,2-dimethylethylene] acetal (8). A solution of 0.135 g (0.82 mmol) malonaldehyde bis(dimethyl acetal), 0.129 g (1.43 mmol) of (2*S*,3*S*)-2,3-butanediol, and .02 g of *p*-toluenesulfonic acid in 25 mL of toluene was heated, and the toluene-methanol azeotrope (64 °C) removed by distillation. After the head temperature rose to the boiling point of toluene, the reaction mixture was cooled; diluted with 20 mL dry diethyl ether; the acid catalyst neutralized by addition of solid $NaHCO_3$; and filtered. The solvent was removed at reduced pressure and the residue chromatographed on silica gel to give 0.120 g (77%) of **8** as an oil: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.30 (d, 12H), 1.95 (t, 2H), 3.50 (m, 4H), 5.10 (t, 2H). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.01; H, 9.45.

Malonaldehyde bis(2,2-dimethylpropylene) acetal (10). ^1H NMR ($CDCl_3$, 90 MHz) δ 0.70 (s, 6H), 1.20 (s, 6H), 2.00 (t, 2H), 3.45 (m, 8H), 4.50 (t, 2H). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.76; H, 10.15.

Malonaldehyde bis[(*S*,*S*)-1,3-dimethylpropylene] acetal (11). ^1H NMR ($CDCl_3$, 90 MHz) δ 1.15 (d, 6H), 1.30 (d, 6H), 1.70 (m, 6H), 4.10 (m, 4H), 4.75 (t, 2H). Anal. $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.68; H, 9.78.

Di[2-(5,6-benzo-1,3-oxathianyl)]methane (16). ^1H NMR ($CDCl_3$, 90 MHz) δ 2.38 (br t, 2H), 4.87 (s, 4H), 5.48 (m, 2H), 6.7-7.2 (m, 8H). Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.5; H, 5.10. Found: C, 64.18; H, 5.29.

(*4S*,*5S*)-4,5-dimethyl-2-hydroxymethyl-1,3-dioxolane (31). A solution of 0.925 g (10.3 mmol) of (*S*,*S*)-2,3-butanediol and 0.678 g (5.65 mmol) of glycolaldehyde dimer in pentane, and a catalytic amount of *p*-toluenesulfonic acid was refluxed with azeotropic removal of 0.16 mL water (Dean-Stark trap). Solid sodium bicarbonate was added to the reaction mixture, stirred 5 min. and then filtered. The solvent was removed by distillation to give 1.273 g (94%) of **31** as an oil: ^1H NMR (CCl_4, 90 MHz) δ 4.95 (t, 1H, J=2.7 Hz), 3.52 (q, 2H, J=5.2 Hz), 3.42 (d, 2H, J=4.5 Hz), 3.00 (s, 1H), 1.22 (t, 6H, J=4.5 Hz); IR (neat) 3467 cm^{-1}. Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.72; H, 9.24.

(4*S*,4'*S*,5*S*,5'*S*)-4,4',5,5'-Tetramethyl-2,2'-bi-1,3-dioxolane (32), and (2*S*,3*S*,6*S*,7*S*)-2,3,6,7-tetramethyl-1,4,5,8-tetraoxadecalin (33). A mixture of 2.934 g (32.6 mmol) (*S*,*S*)(+)-2,3-butanediol, 6.274 g (43.2 mmol) of glyoxal (40% in water), 40 mL of toluene, 0.866 g (0.0081 mol) of lithium perchlorate, and catalytic amount of *p*-toluenesulfonic acid was heated azeotropic removal of water for 2 h, by which time 4.05 mL of water had collected in a Dean Stark trap. The solution was cooled, then neutralized by stirring 15 min with solid $NaHCO_3$. The solids were removed by filtration, and evaporation of solvent and chromatography on silica gel gave 2.430 g (74% yield) of isomeric **32** and **33** in a ratio (by NMR) of 83:17. ^1H NMR ($CDCl_3$, 90 MHz) δ 1.17 (m, 12H), 3.60 (m, 4H), 4.65 (s, 0.34H, **33**), 4.85 (s, 1.66H, **32**). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.57; H, 9.28.

4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3-dioxolane (34), and 2,2,3,3,6,6,7,7-octamethyl-1,4,5,8-tetraoxadecalin (35). ^1H NMR (CCl_4, 90 MHz): δ 1.06-1.20 (m, 24H), 4.11 (s, 0.24H), 4.55 (s, 1.76H). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 65.33; H, 9.92.

Reduction of bisacetals with borane reagents. Examples are presented for the reduction of **8** to **12** with BH_3-THF, and of the **32** and **33** mixture to **3a** with BH_2Cl-SMe_2. Only the analytical data is given for other products, except **19**[29] and **21**[11] which are known compounds.

(2*S*,3*S*,9*S*,10*S*)-3,9-Dimethyl-4,8-dioxaundecan-2,10-diol (12). A solution of 0.120 g (0.55 mmol) of tetramethyl malonaldehyde bis(ethylene acetal) **8** in 10 mL dry THF was cooled to 0 °C. Five mL of 1M BH_3-THF complex (Aldrich Chemical Co.) were added dropwise. The mixture was stirred 10 min, allowed to warm to room temperature, and then refluxed 96 h. The mixture was cooled to 0 °C, and 2 mL of methanol were added dropwise. Volatiles were evaporated at reduced pressure to give 0.119 g (97%) of essentially pure product as a colorless oil. An analytical sample was prepared by radially accelerated thin layer chromatography: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.05 (d, 12H), 1.55 (br s, 2H, OH), 1.80 (t, 2H), 3.40 (m, 8H); IR (neat) 3500 cm^{-1}. Anal. Calcd for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 59.63; H, 11.21.

2,2,10,10-Tetramethyl-4,8-dioxaundecan-1,11-diol (14). ^1H NMR ($CDCl_3$, 90 MHz) δ 0.83 (s, 12H), 1.75 (m, 2H), 2.70 (br s, OH, 2H), 3.11 (s, 4H), 3.22 (s, 4H), 3.44 (t, 4H); IR (neat) 3300 cm^{-1}. Anal. Calcd for $C_{13}H_{28}O_4$: C, 62.87; H, 11.36. Found: C, 62. 68; H, 11.57.

(2*S*, 4*S*, 10*S*, 12*S*)-4,10-Dimethyl-5,9-dioxatriundecan-2,12-diol (15). ^{1}H NMR (CDCl$_3$, 90 MHz) δ 1.05 (d, 12H), 1.65 (m, 6H), 3.1- 3.9 (m, 10H, including 2 OH); IR (neat) 3475 cm^{-1}. Anal. Calcd for $C_{13}H_{28}O_4$: C, 62.87; H, 11.36. Found: C, 62.59; H, 11.48.

1,5-Di(*o*-hydroxymethylphenyl)-1,5-dithiapentane (18). ^{1}H NMR (CDCl$_3$, 90 MHz) δ 1.92 (p, 2H), 2.14 (br s, OH, 2H), 3.03 (t, 4H), 4.70 (s, 4H), 6.9-7.4 (m, 8H); IR (neat) 3340 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_2S_2$: C, 63.80 H, 6.29. Found: C, 63.52 H, 6.47.

(2*S*,3*S*,8*S*,9*S*)-3,8-dimethyl-4,7-dioxadecan-2,9-diol (3a). A solution of 0.385 g (0.0019 mol) of a 83:17 mixture of isomer tetramethyldioxolane **32** and tetramethyltetraoxadecalin **33** in 10 mL of dry diethyl ether was cooled in an ice bath. Dropwise addition of 3.13 mL (0.0304 mol) of 95% BH$_2$Cl-SMe$_2$.(Aldrich Chemical Co.) was followed by 24 h reflux. The reaction mixture was cooled in an ice bath, and 6 mL methanol were added dropwise. Volatiles were evaporated at reduced pressure, and the residue chromatographed on silica gel to give 0.247 g (63% yield) of diether diol **3a**: ^{1}H NMR (CCl$_4$, 90 MHz): δ 1.07 (d, 12H, J = 4.45 Hz), 3.03-4.00 (m, 10H); IR (neat) 3420 cm^{-1}. Anal. Calcd for $C_{10}H_{22}O_4$: C, 58.23; H, 10.75. Found: C, 58.29; H, 10.58.

Preparation of stannylene acetals 37. Stannylene acetals **37a**[30] and **37c**[31] have been previously reported. **(4*S*,5*S*)-2,2-Dibutyl-4,5-(dibenzyloxymethyl)-1,3-dioxa-2-stannolane (37b)** was prepared as follows: A mixture of 6.35 g dibutyltin oxide (25.1 mmol) and 7.54 g (25.1 mmol) (*S*,*S*)-1,2-(dibenzyloxymethyl)ethane-1,2-diol[32] was reacted at toluene reflux 12 h with azeotropic removal of water. Cooling to room temp precipitated **37a** as a colorless crystal. Recrystallization from hot toluene gave 11.98 g (90%): mp 93.5-95.0 °C; ^{1}H NMR (CDCl$_3$, 90 MHz) 0.68-1.60 (m, 18H), 2.86-3.86 (m, 6H), 4.40-4.58 (m, 4H), 7.15-7.31 (m, 10H). Anal. Calcd for $C_{26}H_{38}O_4Sn$: C, 58.56; H, 7.18. Found: C, 58.70; H, 7.01.

(2*S*, 3*S*, 8*S*,9*S*)-1,9-di(benzyloxy)-3,8-di(benzyloxymethyl)-4,7-dioxadecane-2,9-diol (3b). A neat mixture of 0.800 g (1.50 mmol) of **37b** and 0.141 g (0.75 mmol)o of ethylene bromide was heated at 110° for 12 h. The mixture was cooled and the residue passed through a column of silica gel to give 0.336 g (71%) of **3b**. ^{1}H NMR (CDCl$_3$, 90 MHz) δ 3.2-3.9 (m, 18H), 4.42 (m, 8H), 7.20 (s, 20H); IR (neat) 3566, 3450 cm^{-1}. Anal. Calcd for $C_{38}H_{46}O_8$: C, 72.36; H, 7.35. Found: C, 72.64; H, 7.51.

Dimethyl (2*R*,3*R*,8*R*,9*R*)-3,8-di(carbomethoxy)-2,9-dihydroxy-4,7-dioxadecanedicarboxylate (3c). Produced at 175 °C in a wax bath. ^{1}H NMR (CD$_3$CN, 300 MHz) δ 3.75 (overlapping singlets, 16H), 4.55 (s, 4H), 4.51 (s, 2H); IR (neat) 3488, 1752 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_{12}$: C, 43.98; H, 5.80. Found: C, 43.87; H, 5.98.

(2*S*,3*S*)-4-methyl-3-oxa-1,5-hexanediol (43). A mixture of 2.500 g of **37a** (7.79 mmol) and 1.249 g chloroethanol were heated at 140° for 12 h. Volatiles were removed at reduced pressure and the residue column chromatographed on silica gel to give 0.972 g (93%) of **43** as an oil: ^{1}H NMR (CDCl$_3$, 90 MHz) δ 1.03 (d, J = 6 Hz), 3.0-3.8 (m, 6H), 4.3 (br s, 2H)]; IR (neat) 3456 cm^{-1}. Anal. Calcd for: $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.99; H, 10.87.

(4*S*,5*S*)-4,5-dimethyl-3,6-dioxa-1,8-octanediol (4a). A mixture of 2.001 g (6.23 mmol) of **37a** and 1.505 g (18.69 mmol) chloroethanol were heated at 170° for 12 h. Chromatography of the residue gave 0.702 g (84%) of **4a** as an oil, identical with an authentic sample[4]: ^{1}H NMR (CDCl$_3$, 90 MHz) δ 1.06 (d, 6H, J=6 Hz), 3.65 (m, 10H), 3.96 (s, 2H); IR (neat) 3435 cm^{-1}.

(4*S*,5*S*)-4,5-di(benzyloxymethyl)-3,6-dioxa-1,8-octanediol (4b). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.60 (broad m, 16H), 4.47 (d, 4H), 7.25 (s, 10H); IR (neat) 3436 cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.91; H, 7.50.

(4*R*,5*R*)-4,5-di(carbomethoxy)-3,6-dioxa-1,8-octanediol (4c). Produced at 140 °C. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.3-5.0 (m including br s at 3.65, 18H). IR (neat) 3490, 1752 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_8$: C, 45.11; H, 6.81. Found: C, 45.27; H, 6.97.

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   In bidioxolane **24** they absorb at δ 4.72 ppm; those on the tetraoxadecalin **25** at δ 4.41 ppm. We found that this trend towards lower field for the dioxolane acetal methine protons relative to the dioxane acetal methine protons was consistent with the shifts (in $CDCl_3$) observed in unambiguous compounds: **6** (4.95 ppm) and **9** (4.45 ppm); **8** (5.15 ppm) and **11** (4.85 ppm). Extending this, we assigned the absorbance at 4.74 ppm to the acetal methine protons in tetramethylbidioxolane **32**, and the resonance at 4.43 to those on tetramethyltetraoxadecalin **33**; and 4.55 ppm for octamethylbidioxolane **34** and 4.11 ppm for the octamethyltetraoxadecalin **35**.

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