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STEREOCONTROLLED SYNTHESIS OF 2,5-LINKED BISTETRAHYDROFURANS VIA THE TRIEPOXIDE CASCADE REACTION

THOMAS R. HOYE* and JOSEPH C. SUHADOLNIK
Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, U.S.A.

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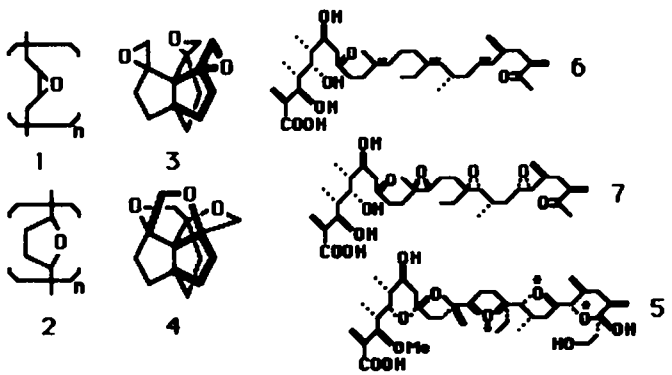
Abstract—A complementary set of stereochemically controlled approaches to the preparation of twelve diastereomers of the bistetrahydrofurans **11** is described. The key transformation involves a series of nucleophilic displacement reactions within triepoxides **19**—the "end-to-end" triepoxide cascade reaction—which leads, presumably via **22** and **23**, after acetylation to bistetrahydrofuran tetraacetates **24**. The "inside-out" cyclization of **30** exemplifies a useful variation with significant stereochemical consequences. The role of symmetry in these approaches is discussed. A general mathematical analysis for conceptualizing isomer distribution within multistep sequences is presented.

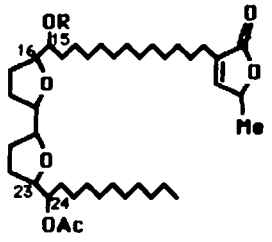
INTRODUCTION

The rearrangement of oligoepoxides formally derived from oligo-1,5-dienes (i.e. **1**), via a series of internal nucleophilic displacement reactions, into oligo-2,5-linked tetrahydrofurans (**2**) is a transformation receiving increased attention. In 1980, Smith and co-workers at 3M described[1] a fascinating series of heterocyclic polymers [e.g. 2,5-poly(tetrahydrofuran)diyl; **2**, where *n* is large] derived by nucleophile-induced isomerization of polyepoxides [e.g. poly(butadiene epoxide); **1** where *n* is large]. The ramifications of their observation that the materials derived from all-*cis* vs all-*trans* polybutadiene possess significantly different metal ion binding abilities may be far-reaching. The following year, Simmons and Maggio[2] and Paquette and Vazeux[3] reported a related transannular rearrangement of the rigid triepoxide **3** to the topologically unique tris-tetrahydrofuran **4**. Cane *et al.* have advanced the hypothesis[4] that intramolecular opening of di- and triepoxides is involved in the biosynthesis of many polyether antibiotics and ionophores. Experimental support for this idea in the specific case of monensin (**5**) was found in the Cane laboratory,[5] with the observation that labeled molecular oxygen was incorporated at the starred positions in **5**. This is consistent with the intermediacies of triene **6** and triepoxide **7** in nature's pathway, an idea natural materials uvaricin (**8**)[7] and teurilene (**9**).[8] It is intriguing that the latter compound might arise from an *internal* squalene tetraepoxide by a process that is conceptually reminiscent of the *terminal* squalene oxide to sterol conversion. Finally, Dolle and Nicolaou recently described[9] the "zip-type" reaction of a stereorandom mixture of triepoxides **10** to give bistetrahydrofurans.

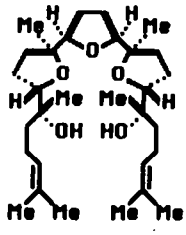
Confronted with the facts that the stereospecificity of this cascade reaction had/has not been systematically probed and that the stereochemistry of uvaricin (**8**) was/is not known, we set out to prepare twelve of the twenty possible diastereomers of the bistetrahydrofuran diacetates **11**. It was hoped that we could simultaneously probe the stereochemical features of the cascade and related transformations as well as ultimately assign the stereostructure of uvaricin by spectroscopic correlations among the natural material **8**, its acetate derivative **12**, and the analogs **11a–l** in whose structures we could be confident because of their mode of synthesis. The specific twelve isomers of **11** targeted were those formally available from the four 2,6,10-dodecatriene-1,12-diols **13** having higher symmetry than C_s (i.e. *E,Z,E*-**13** and *Z,Z,Z*-**13**, both of C_{2v} symmetry, and *E,E,E*-**13** and *Z,E,Z*-**13**, both of C_{2h} symmetry). Each of these trienes should give three diastereomers of **11** if converted to a stereorandom mixture of triepoxides with peracid and then sub-



now more testable with the availability of synthetic **6** as described by Sih and co-workers.[6] It is logical to entertain similar ideas to explain the origin of the jected to a cascade reaction which proceeds strictly with inversions of configuration. A useful way to differentiate the diastereomers **11a–l** is to assign a



8 R = H
12 R = Ac



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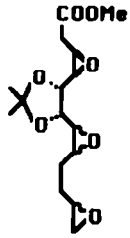

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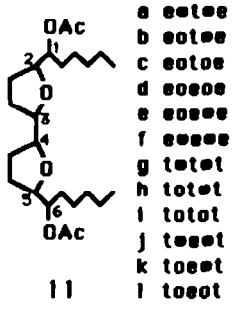
stereochemical descriptor to each successive pair of configurational relationships starting, arbitrarily, with the topmost of the six chirotopic atoms. The relationships between pairs of centers 1/2, 3/4 and 5/6 are then described as *erythro* (e) or *threo* (t) and those between centers 2/3 and 4/5 as *cis* (●) or *trans* (○).

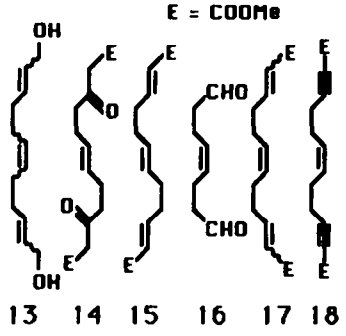
DISCUSSION

Since in actual practice (*vide infra*) we have found it more expedient to use one of the olefin isomers as a precursor to two different sets of three of the diastereomeric bis-tetrahydrofurans **11**, only three of the triene isomers **13** have been prepared. The all-*trans* compound arose from alkylation of the Weiler dianion[10] with one-half of an equivalent of *E*-1,4-dibromo-2-butene. The *β*-ketoesters in the resulting **14** were reduced with sodium borohydride to diols which were dehydrated by the action of methanesulfonyl chloride and triethylamine. The triendioate **15** was reduced to *E,E,E*-**13** with diisobutylaluminum hydride. The *trans-cis-trans* and all-*cis* isomers were generated from the common precursor, *Z*-4-octendial (**16**).[11] Horner–Emmons reaction of **16** with 2 equiv of methyl diisopropylphosphonoacetate[12] and reduction (DIBALH) gave *E,Z,E*-**13** via the diester *E,Z,E*-**17**. The all-*cis* triene was made by sequential reaction of **16** with dibromomethylene triphenylphosphorane,[13] 4 equiv of n-butyllithium, and methyl chloroformate to give the endiynoate **18**. DIBALH and Lindlar reductions provided *Z,Z,Z*-**13**.



a eetee
b eotee
c eotoe
d eoeoe
e eoeee
f eeeee
g tetet
h totet
i totot
j teeet
k toeet
l toeot

11



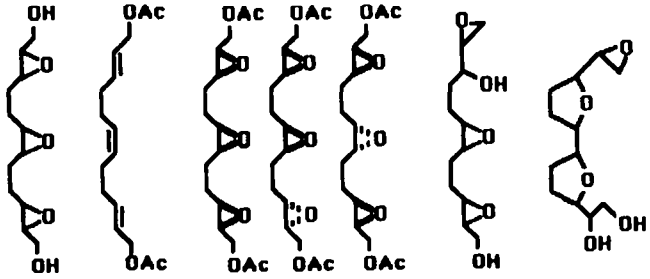
E = COOMe

13 14 15 16 17 18

Careful examination of the material arising from the bis-Horner–Emmons reaction of **16** revealed that the major product, *E,Z,E*-**17**, was contaminated by one part in sixty of the *E,Z,Z*-isomer (capillary GC analysis). However, none of the *Z,Z,Z*-isomer of **17** could be detected, even under conditions where one part in five-hundred should have been observable. Reflection upon these facts led us to the following statement which formalizes in a general and useful way the intuitive feeling which many have regarding this type of problem. *The distribution of isomers which results from a series of n sequential chemical processes, each of which can occur with generation of two possible isomers, can be represented as the expansion of the polynomial*: $(A_1+B_1)(A_2+B_2)\ \ldots\ (A_n+B_n)$, *where* $A_i:B_i$ *is the ratio of major and minor isomers A and B for the ith process. The mathematical consequences of such an expansion are that the ratio of antipodal isomers* (*i.e.* $A_1A_2\ldots A_n:B_1B_2\ldots B_n$) *is large.* Thus, in the case of the double olefination operation on **16**, if one assumes that the *trans* (*t*) : *cis* (*c*) ratios of the first and second Horner–Emmons reactions are identical (i.e. $t_1/c_1 = t_2/c_2$), then, because of the symmetry in **16**, the binomial $t_1t_2+t_1c_2+t_2c_1+c_1c_2$ simplifies to $tt:2tc:cc$ (where *tt*, *tc* = *ct*, and *cc* represent *E,Z,E*-**17**, *E,Z,Z*-**17** and *Z,Z,Z*-**17**, respectively). The experimental observation is that $tt/2ct = 60$. Thus, $t/2c = 60$ or $t/c = 120$. In other words, the *E,Z,E*-**17**(*tt*) : *E,Z,Z*-**17**(*tc*) : *Z,Z,Z*-**17**(*cc*) ratio was $(120+1)^2$ or 14,400:280:1. Notice that the *tt* : *cc* ratio is the square of the inherent *t*/*c* selectivity and the *tt* : *tc* ratio, because there are two distinct pathways (first *trans* then *cis* olefination or vice versa) to the latter isomer, is half of the inherent *t*/*c* selectivity. The above treatment is general and can provide systematic insight into a number of conceptually difficult ideas such as double diastereoselection, classical or kinetic resolution, and enhanced levels of enantiomeric purities arising from either sequential

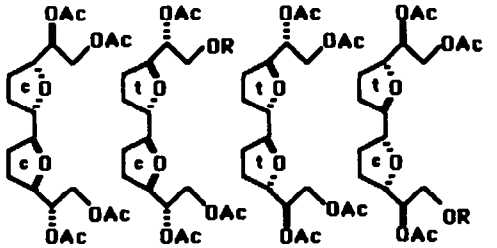
asymmetric reactions [*in vitro* (*vide infra*) or *in vivo*†] or syntheses which involve coupling of chiral fragments.[14]

The first series of triepoxides made was that derived from *E,Z,E*-**13**.[15] Since the triepoxydiols **19** are so polar as to be difficult to handle, *E,Z,E*-**13** was first acetylated and the resulting **20** was then epoxidized with MCPBA to provide the three diastereomeric triepoxides **21*ss***, **21*sa*** and **21*aa*** containing *syn/syn*, *syn/anti* and *anti/anti* relationships, respectively, among the pairs of "top"/"middle" and "middle"/"bottom" epoxides on the carbon skeleton as drawn. The *ss* and *aa*-isomers are *meso*-compounds and the *as*-isomer is racemic. We found no way to separate these, so the mixture was treated with aqueous sodium hydroxide at 50°. Rapid double saponification (the diols of constitution **19** could be isolated, although with low mass recoveries) was followed by a rate-limiting Payne rearrangement. Neither the isomeric triepoxides like **22** nor the bistetrahydrofuran epoxides like **23** could be detected as intermediates, which suggests that the ensuing cascade reaction of **22** and the bimolecular ring opening of **23** by hydroxide ion are fast.[16] The crude product



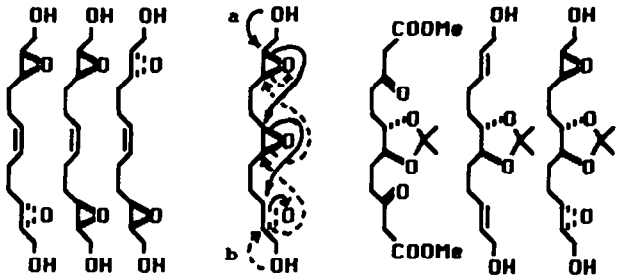
mixture was acetylated and separated by combination of medium- and high-pressure liquid chromatography. Three isomeric, racemic bistetrahydrofuran diacetates (**24*a*–c**) were isolated in a ~1:2:1 ratio. Structure assignment for the major isomer (**24b**) rests on the assumption that all steps in the cascade proceed with inversion of stereochemistry and on the fact that it is the only unsymmetrical product (as seen by both ^{1}H- and ^{13}C-NMR) in the set. That this assumption is valid is supported by the isolation of only three diastereomers of **24**. Final conversion to the bisbutylated model compounds **11a–c** was achieved by saponification of each pure isomer of **24** to the corresponding tetrol, selective tosylation of the primary alcohols in each, and reaction of the bistosylates with $(n\text{-Bu})_2\text{CuLi}$.

It was possible to improve substantially upon the more or less stereorandom synthesis of **24a–c** just described. The triendiol *E,Z,E*-**13** was subjected to an asymmetric bis-Sharpless reaction[17] with natural (2*R*,3*R*)-(+)-diisopropyl L-tartrate. The crude product was acetylated, but once again the ratio of isomeric diepoxides (**25*a* (all *S*):25*s*:25*a* (all *R*)**) could not be determined. Under the assumption that the asymmetric Sharpless epoxidation proceeds with 19:1 enantiofacial selectivity (95% ee) at both allylic alcohols in *E,Z,E*-**13**, we expected the above ratio to be $(19+1)^2$ or 361:38:1. Notice that once again the ratio of antipodal species **25*a*** (**all *S***) and **25*a*** (**all *R***)



(enantiomers in this case) is the square of the inherent selectivity and that the **25*a*:25*s*** (or *d,l*:*meso*) ratio is one half of the inherent selectivity. Thus, we were confident that the level of optical purity of **25*a*** was very high (99.45% ee expected under the above assumption). The mixture of **25** was treated with MCPBA and acetylated. In **25*a*** the two faces of the olefin are interconverted by rotation about the molecular C_2-axis; thus only one diastereomer, **21*sa***, arose from epoxidation of **25*a***. The *meso*-compound **25*s*** presumably gave a mixture of the *meso*-triepoxides **21*ss*** and **21*aa***. Cyclization of this optically active mixture of **21**, as with the inactive mixture, gave **24*a*–c**. A disappointing although relatively unique stereochemical event occurred in the reaction of the optically pure diol **26** derived from **25*a*** (**all *S***) with $^-$OH/H_2O.

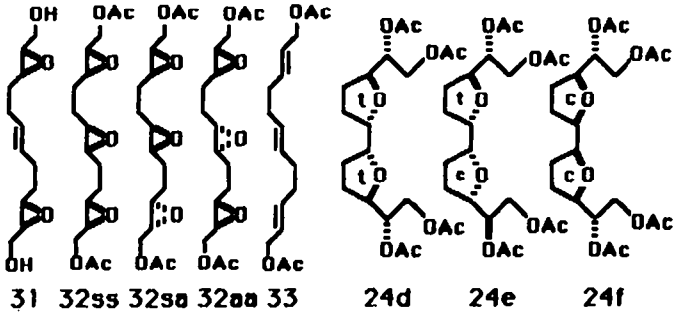
† An amusing application provides an answer to the hypothetical question of whether natural D-glucose contains any of its enantiomer, L-glucose. If one assumes that the average "specificity" for each of the nine steps at which selection can occur in gluconeogenesis (i.e. those converting phosphoenolpyruvate into glucose) is 1000:1, then one would have to examine over 1000 mol of natural (and artificially uncontaminated) D-glucose to find a single molecule of L-glucose (i.e. $(10^3:1)^9 = 10^{27}:1$ of D- and L-antipodes)! It is important to recognize that stereoselection can occur even in processes which do not establish or destroy any stereochemistry; in the present instance, some of the nine steps presumably involve acceptance of the proper stereoisomer as a substrate by the enzyme while other isomers are not processed further. In chemical terms this amounts to kinetic selection among diastereoisomers, a concept perhaps too infrequently used to achieve stereocontrol.



Cascade from the "top-down" (see a) and from the "bottom-up" (see b)—although diastereomeric operations—give the *enantiomeric* tetrols **24b** and **24b*** in what should be nearly equal amounts. *This "racemization" is unique in that at no point along the reaction coordinate is a symmetrical geometry transcended.* This undesirable event could be avoided simply by changing the reaction medium from water/hydroxide to alcohol/alkoxide (methanol, benzyl alcohol and crotyl alcohol all work) which produced the diastereomeric, but optically pure, pair of HPLC-separable monoethers **27** and **27***. An added benefit of the availability of **27** is that the terminal functionality in each molecule is now different; this will be useful in further work on the synthesis of the unsymmetrical uvaricin (**8**). Finally, the ratio of **24a : 24b/24b* : 24c** (1.15 : 19.8 : 1) allowed for the extrapolation of both the enantiofacial selectivity for the Sharpless epoxidation of any one olefin in *E,Z,E*-**13** (~18 : 1) and the diastereofacial selectivity for the peracid epoxidation of **25s** (1.15 : 1).

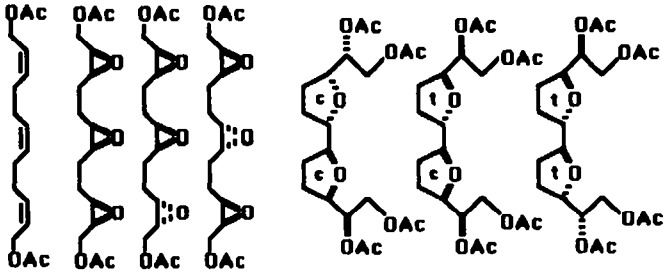
The preparations of the symmetrical (C_2) bistetrahydrofurans **24a** and **24c** described thus far were less than ideal because they proceeded via the *meso*-triepoxides **21ss** and **21aa**, which are the minor isomers and which cascade from the "top-down" and "bottom-up" with equal ease to generate racemic **24a** and **24c**. Moreover, it was not yet possible to assign which of the two C_2-products contained the pair of *cis*-substituted (i.e. **24a**) and which contained the pair of *trans*-substituted THF-rings (i.e. **24c**). All of these situations were simultaneously solved by adopting a complementary "inside-out" approach to their preparation. Natural (2*R*,3*R*)-(+)-diethyl L-tartrate was converted via its acetonide, 1,4-diol, 1,4-ditosylate,[18] and 1,4-diiodide[18] to the bis-β-ketoester **28**. This was in turn transformed to the *E,E*-bisallylic alcohol **29** as with **14** → **15**. Asymmetric Sharpless bis-epoxidation of **29** with natural tartrate gave **30**, which under the conditions of acetonide removal (H^+/THF/H_2O) suffered subsequent and rapid epoxide ring opening. The major product of this sequence upon acetylation was confidently assigned as the single enantiomer **24a**. The "inside-out" process therefore complements the "end-to-end" cascade of *meso*-triepoxides since the latter gives racemates but, by judicious combination of L- and D-dialkyl tartrates as starting material and Sharpless catalyst, any of the four bistetrahydrofurans—**24a**, **24c** or their enantiomers—can be individually accessed by the former scheme.

The next substrate was the all-*trans* triene, *E,E,E*-**13**. Stereochemical analysis showed that the major product expected from the asymmetric bis-Sharpless reaction would have been the C_2-diepoxide **31**, which, since its C_2-axis is perpendicular to the plane of the olefin, would have given rise to two diastereomeric C_2-

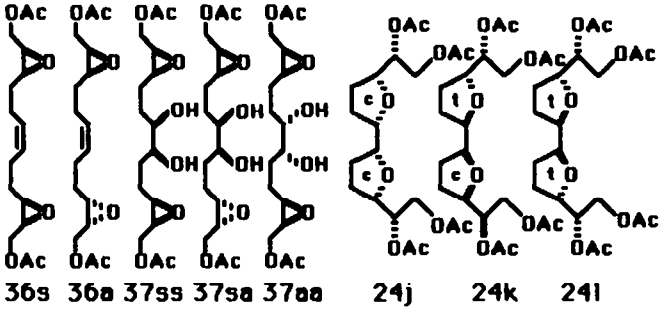


triepoxides **32ss** and **32aa** upon exposure to MCPBA. It is ironic that each of these, which would have possessed high optical purity, would have given the optically inactive *meso*-compounds **24d** and **24f** upon cascade (notice that the identical product arises from "top-down" and "bottom-up" operations in each but that the chirality could presumably have been preserved by again performing the cascade in alcohol instead of water). In view of this situation, only the stereorandom epoxidation was performed; that is, the all-*trans* triene diacetate **33** was treated with an excess of MCPBA to generate the mixture **32ss**, **32sa** and **32aa**. Processing these with $^-OH/H_2O$ and then acetic anhydride as in the previous series led smoothly to the separable bistetrahydrofurans **24d–f**. Selective tosylation of the derived tetrols and coupling with $(n\text{-BuLi})_2CuLi$ provided the targets **11d–f**. It is of interest that, if necessary for further uvaricin synthetic efforts, the individual enantiomers of **24e** should be available using the "inside-out" strategy, although in this case the central four-carbon unit would originate with *meso*-tartaric acid.

Attention was next turned to the all-*cis* triene, *Z,Z,Z*-**13**, which was converted to the diacetate **34** and epoxidized with excess MCPBA to provide the mixture of triepoxides **35ss**, **35*sa*** and **35*aa***. Once again, saponification and cascade with $^-OH/H_2O$ followed by reacetylation led to a separable mixture of the bistetrahydrofurans **24g–i**. Since the symmetries in the triepoxides **35** derived from *Z,Z,Z*-**13** are identical to those of **21** derived from *E,Z,E*-**13** [recall that both of these precursor trienes are of the same (C_{2v}) symmetry], the same analyses apply to the present series of cascades. Namely, the unsymmetrical triepoxide **35*sa*** gave a pair of enantiomeric bistetrahydrofurans (**24h** and its mirror image) upon cascade from one end or the other; and the *meso*-triepoxides **35ss** and **35*aa*** gave rise to the racemic products **24g** and **i**. The tetraacetates **24g–i** were each converted to the bisbutylated model materials **11g–i**.



The preparation of the final set of three model bistetrahydrofurans (**11j–l**) is in progress and proceeds by a route that is once again complementary to those described above since it commences with one of the same triendiols (*Z,Z,Z*-**13**) already used. Thus, a stereorandom bis-Sharpless epoxidation with $VO(acac)_2$ and t-BuOOH[19] gives a mixture of diepoxides **36*s*** and **36*a***. *cis*-Hydroxylation with OsO_4 should give **37ss**, **37*sa*** and **37*aa***, which are projected substrates for another "inside-out" closure, and conversion to **11j–l** via **24j–l**.



With the entire set of twelve diastereomers of **11** in hand, we will be in a position to address the correlation of NMR spectroscopic data from this set with analogous data from the uvaricin molecule itself. Indication that our endeavors along these lines may be fruitful is found in the ^1H chemical shift trends for the acetate methyl groups. In the nine compounds **11a–i** every 1/2 and 5/6 *erythro* relationship leads to a δ of 2.051 ± 0.007 whereas every *threo* arrangement gives rise to a δ of 2.075 ± 0.008. In uvaricin (**8**) the acetate is seen at δ 2.049 while in uvaricin acetate (**12**) the two acetates are found at δ 2.049 and 2.074. This single correlation suggests an *erythro* relationship between C(23) and C(24) and a *threo* relationship between C(15) and C(16) in **8**. Detailed analysis of the spectroscopic data will be presented when warranted.

EXPERIMENTAL

General. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. IR spectra were recorded on a Perkin–Elmer 297 spectrophotometer. ^1H-NMR spectra were obtained on a Varian HFT-80 or Nicolet NT-300 spectrometer. MPLC refers to chromatography done at 10–50 psi with glass columns dry-packed with LiChroprep Si60 (40–63 μm). HPLC was performed on various manufacturers' SiO_2 support. Virtually all reactions were run under an atmosphere of N_2.

5,5′-*Di*(1-*acetoxyhexyl*)*octahydro*-2,2′-*bifurans* (**11a–c**). A mixture of tetraacetates **24a** and **b** (342 mg, 0.8 mmol) was dissolved in 3 ml of MeOH and ~25 mg of K_2CO_3 was added. After 2 h at room temp the mixture was concentrated, C_6H_6 was added, and the mixture reconcentrated. This crude mixture was dissolved in 1.5 ml of pyridine, cooled to 0°, and treated with *p*-TsCl (267 mg, 1.4 mmol). After 6 h at 0° the mixture was partitioned between CH_2Cl_2 and 10% HCl. Ordinary processing of the organic layer and purification by MPLC on SiO_2 (1:3 hexane–EtOAc) gave 5,5′-di(1-hydroxy-2-tosyloxyethyl)octahydro-2,2′-bifurans (236 mg, 0.41 mmol, 50%). To a stirred suspension of CuI (666 mg, 3.5 mmol) in 14 ml of dry Et_2O at −40° was added n-BuLi (2.6 ml of 2.7 M in hexane, 7 mmol). This mixture was stirred for 30 min at −20°, and a soln of the ditosylates (200 mg, 0.35 mmol) in 4 ml of CH_2Cl_2 was added. After 2 h at −20°, sat NH_4Cl and Et_2O were added. The slurry was washed with NaCN aq until two homogeneous layers resulted. Standard processing left a crude diol (84 mg, 0.27 mmol, 78%) which was dissolved in equal volumes of excess pyridine and Ac_2O. After 16 h the usual workup and MPLC (6:1 hexane–EtOAc) left a mixture of pure **11a** and **b** (38 mg, 0.09 mmol, 25%). Final separation was achieved by HPLC (6:1 hexane–EtOAc). **11a**: ^1H-NMR ($CDCl_3$, 300 MHz) δ 4.90 (ddd, J = 8.3, 5.6 and 4.4 Hz), 3.94

(ddd, J = 7.3, 5.6 and 5.6 Hz), 3.81 (2H, m), 2.045 (s, OAc), 1.49–1.92 (m), 1.28 (br m), 0.87 (br t). **11b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.91 (2H, m), 4.01 (ddd, J ≈ 6.1, 6.1 and 6.1 Hz), 3.93 (ddd, J = 7.2, 5.5 and 5.5 Hz), 3.92–3.76 (2H, m), 2.053 and 2.048 (OAc's), 1.5–2.0 (m's), 1.28 (br m), 0.87 (br t). IR ($CDCl_3$) 1730, 1375, 1255, 1060, 1030. (Found: C, 67.79; H, 9.89. Calc for $C_{24}H_{42}O_6$: C, 67.57; H, 9.92%.) In a separate but entirely analogous experiment **24c** (104 mg, 0.24 mmol) gave the analogous ditosylate (54 mg, 39% after MPLC), 40 mg of which was converted into **11c** (14.5 mg, 48% after MPLC). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.91 (ddd, J = 9.0, 4.5 and 4.5 Hz), 3.98 (ddd, J ≈ 6.4, 6.4 and 6.4 Hz), 3.88 (2H, ddd, J ≈ 5 Hz), 2.045 (s, OAc), 1.95 (2H, m), 1.72 (2H, m), ~1.5 (m), 1.28 (br m), 0.87 (br t).

E,Z,E-Dodeca-2,6,10-trien-1,12-diol (*E,Z,E*-**13**). By the procedure described for the preparation of *E,E,E*-**13**, diester **17** was reduced to give *E,Z,E*-**13** as a colorless oil after MPLC (1:1.1 hexane–EtOAc) in 64% yield (42% from cycloocta-1,5-diene monoepoxide). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.68 (pair of AB dd's, H(2,3,10,11)), 5.38 (br t, J = 4 Hz), 4.09 (br d, J = 3.8 Hz, H(6,7)), 2.12 (br m, H(4,5,8,9)). IR ($CDCl_3$) 3620, 3010, 1670, 1385, 1085, and 970. (Found: C, 73.54; H, 10.46. Calc for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.)

E,E,E - Dodeca - 2,6,10 - trien - 1,12 - diol (*E,E,E* - **13**). The diester **15** (2.8 g, 11.2 mmol) in 100 ml of dry Et_2O was added dropwise to DIBALH (80 ml, 1 M in hexane, 80 mmol) at 0°. After 30 min the reaction was warmed to room temp for 30 min and quenched by the addition of H_2O and sat $NaHSO_4$. The aq layer was saturated with solid NaCl and extracted with Et_2O. Ordinary processing yielded 2.2 g of crude oil which after MPLC (1:1.5 hexane–EtOAc) gave diol *E,E,E*-**13** (1.6 g, 8.16 mmol, 73%) as a white solid, m.p. 37.5–38.5°. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.66 (pair of AB dd's, H(2,3,10,11)), 5.42 (tt, J = 3.5 and 1.5 Hz, H(6,7)), 4.08 (d, J = 4.5 Hz, H(1,12)), 2.1 (br m, H(4,5,8,9)), 1.47 (br s, OH). IR ($CDCl_3$) 3625, 3020, 1670, 1385, 1090, 970, and 860 cm^{-1}. (Found: C, 73.24; H, 9.96. Calc for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.)

Z,Z,Z - Dodeca - 2,6,10 - trien - 1,12 - diol (*Z,Z,Z*-**13**). The diyne **18** (780 mg, 3.1 mmol) was reduced by a procedure identical to that described in the preparation of *E,E,E*-**13** to give a diynediol (520 mg, 2.7 mmol, 87%) after MPLC (1:1 hexane–EtOAc). This diol (1.5 g, 7.8 mmol) was dissolved in 10 ml of MeOH and 1.5 ml of quinoline. Pd on $BaSO_4$ (100 mg) was added, and the mixture was exposed to 1 atm of H_2 at room temp for 20 h. The mixture was filtered through a bed of Celite and concentrated to leave *Z,Z,Z*-**13** (1.2 g, 6.1 mmol, 78%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.64 (dt, J = 10.9 and 6.6 Hz, H(2,11)), 5.54 (m, H(3,10)), 5.40 (br t, J = 4.4 Hz, H(6,7)), 4.16 (d, J = 6.6 Hz, H(1,12)), 2.12 (m, H(4,5,8,9)), 1.68 (br s, OH). IR ($CDCl_3$) 3610, 3015, 2260, 1020 cm^{-1}.

E-Dimethyl 3,10-dioxodec-6-endioate (**14**). To diisopropylamine (3.75 g, 37 mmol) in 37 ml of dry THF at 0° was added n-BuLi (14.2 ml, 2.6 M in hexane, 37 mmol) over 5 min. After 10 additional min at 0°, methyl acetoacetate (2 ml, 18.5 mmol) was added, and the soln was stirred for 40 min and then cooled to −78°. A soln of *E*-1,4-dibromobut-2-ene (1.98 g, 9.27 mmol) in 2 ml of THF was added. The reaction was stirred at −78° for 40 min, warmed to 0° for 40 min, and quenched with 10% HCl. Ordinary workup left 2.11 g of orange oil which after MPLC (2:1 hexane–EtOAc) gave a 57% yield of pure **7**. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.43 (tt, J = 3.4 and 1.5 Hz, HC=CH), 3.74 (s, OCH_3), 3.44 (s, CH_2CO_2), 2.59 (t, J = 7.2 Hz, CH_2CH_2CO), 2.27 (m, =CHCH$_2$). IR ($CDCl_3$) 1750, 1720, 1660, 1630, 1440, 1410, 1320, 860 cm^{-1}. (Found: C, 58.80; H, 6.74. Calc for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09%.)

E,E,E - Dimethyl dodeca - 2,6,10 - triendioate (**15**). The diketone **14** (530 mg, 1.87 mmol) in 6 ml of MeOH at 0° was treated with $NaBH_4$ (70 mg, 1.84 mmol) for 15 min. After warming to room temp over 20 min, the mixture was acidified with formic acid. An ordinary workup was followed by azeotropic removal of residual formic acid with C_6H_6 to leave 445 mg of a thick oil. A portion of these diols was purified for analysis by MPLC (1:2 hexane–EtOAc). (Found: C, 58.14; H, 8.30. Calc for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39%.) The remaining oil was dissolved in 7 ml of CH_2Cl_2 and treated at 0° with Et_3N (1.94 ml, 14 mmol) and CH_3SO_2Cl (0.265 ml, 3.4 mmol). After 30 min the reaction was warmed to room temp and stirred for 14 h. An ordinary workup and MPLC (9:1 hexane–EtOAc) yielded **15** (208 mg, 0.83 mmol, 44% from **14**) as a white solid, m.p. 33.5–34° along with 10.8 mg of the *E,E,Z*-isomer of **15**. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.95 (dt, J = 15.7 and 6.6 Hz, HC=CHCO), 5.82 (dt, J = 15.6 and 1.5 Hz, =CHCO), 5.44 (tt, J = 3.4 and 1.5 Hz, $H_2CHC{=}CHCH_2$), 2.25 (br t, J = 7.7 Hz, H(4)), 2.2 (m, H(5)). IR ($CDCl_3$) 3040, 3010, 1720, 1665, 1440, 1280, 1210, 1045, 975, 860 cm^{-1}. (Found: C, 66.76; H, 7.93. Calc for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%.)

E,Z,E - Dimethyl dodeca - 2,6,10 - triendioate (**17**). To cycloocta-1,5-diene monoxide[11] (10 g, 80 mmol) was added a soln of periodic acid (18.4 g, 81 mmol) in 500 ml of H_2O. The mixture was stirred for 2 h at 45°, cooled to 0°, and neutralized with sat $NaHCO_3$ aq. The mixture was saturated with NaCl and extracted with CH_2Cl_2. The extracts were dried (Na_2SO_4) and concentrated to ~20 ml; a 70% yield of *Z*-4-octendial (**16**)[11] was assumed. To a stirred suspension of NaH (6.24 g as a 50% dispersion in mineral oil, 130 mmol) in 500 ml of dry Et_2O at 0° was added dropwise methyl diisopropylphosphonoacetate[12] (27.5 g, 115 mmol). The mixture was cooled to −78°, and the soln of crude **16** was added. The mixture was allowed to warm to room temp and quenched with H_2O. An ordinary workup gave crude **17** (13.1 g, 70% from the cyclic epoxide) which was used directly in the next step. A small portion was purified by MPLC (9:1 hexane–EtOAc) for analysis (52% extrapolated yield of pure material). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.95 (dt, J = 15.7 and 6.6 Hz, HC=CHCO), 5.83 (dt, J = 15.7 and 0.5 Hz, HC=CHCO), 5.40 (br t, J ≈ 4.5 Hz, $H_2CHC{=}CHCH_2$), 3.75 (s, OCH_3), 2.23 (m, CH_2CH_2). IR ($CDCl_3$) 3010, 2960, 1720, 1660, 1435, 1280, 1210, 1050, 975, 860 cm^{-1}. (Found: C, 66.62; H, 7.98. Calc for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%.)

E - Dimethyl dodec - 6 - en - 2,10 - diyndioate (**18**). Carbon tetrabromide (100 g, 0.3 mol) was added to a slurry of triphenylphosphine (79 g, 0.3 mol) in 600 ml of CH_2Cl_2 and Zn dust (19.6 g, 0.3 mol) at 0°. This mixture was allowed to warm slowly to room temp and stirred for 24 h. A soln of *Z*-4-octendial in CH_2Cl_2 was prepared from 1,5-cyclooctadiene monoepoxide (10.5 g, 0.085 mol) as described above in the preparation of *E,Z,E*-**17**. This crude dialdehyde in 40 ml of CH_2Cl_2 was added to the above slurry. The mixture was stirred for 2 h and hexane was added to precipitate inorganic salts. Filtration, concentration, reconstitution in CH_2Cl_2, and reprecipitation with hexane was repeated twice to leave crude *Z*-1,1,12,12-tetrabromodeca-1,5,9-triene (24 g, 62% from the cyclic epoxide). This crude material was dissolved in 250 ml of dry THF and cooled to −78°, and n-BuLi (88 ml, 2.4 M in hexane, 0.212 mol) was added. This mixture was stirred for 40 min at −78°, warmed to 0° and stirred for 1 h, and recooled to −78°. Methyl chloroformate (20 g, 0.212 mol) was added, and after 15 min the mixture was allowed to warm to 0° and was quenched with H_2O. Ordinary workup left a black liquid (14 g, ~100%), a portion of which was purified by MPLC to provide **18** (30% based on the cyclic epoxide) as a colorless liquid. ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 5.55 (br t, J = 4.5 Hz, HC=CH), 3.78 (s, OMe), 2.40 (br m, H(4,5,8,9)). IR (neat) 3010, 2260, 1705, 1430, 1260, 1070 cm^{-1}. (Found: C, 67.86; H, 6.72. Calc for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50%.)

E,Z,E - 1,2 - Diacetoxydodeca - 2,6,10 - triene (**20**). Diol *E,Z,E*-**13** (1 g, 5.1 mmol) was dissolved in 2 ml of pyridine and 1.5 ml of Ac_2O. After 2 h the mixture was partitioned between Et_2O and H_2O; and the Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated to leave crude **20** as an orange oil (1.22 g, 4.36 mmol, 85%). ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 5.68 (m, H(2,3,10,11)), 5.40 (br t, J = 5 Hz, H(6,7)), 4.45 (br d, J = 6 Hz, H(1,12)), 2.09 (br m, H(4,5,8,9)), 2.07 (s, OAc). IR ($CDCl_3$) 3015, 1740, 1385, 1370, 1250, 1025, 970 cm^{-1}.

1,12 - Diacetoxydodeca - 2,6,10 - triene trioxides (**21**). To the crude diacetate **20** (1.22 g, 4.36 mmol) in 20 ml of CH_2Cl_2 was added MCPBA (2.8 g, 80% pure, 13 mmol). After 20 h at room

temp the mixture was taken up into Et_2O; washed with sat Na_2SO_3 aq, sat $NaHCO_3$ aq, and brine; dried (Na_2SO_4); filtered; and concentrated to leave a light orange oil (1.4 g) which was purified by MPLC (1 : 1 hexane–EtOAc) to give the mixture of **21** as a colorless oil (1 g, 3.05 mmol, 70%). ^{1}H-NMR (C_6D_6, 300 MHz) δ 4.22–4.23 (pair of dd's, J = 13 and 3 Hz, CHHOAc), 3.77 (pair of dd's, J = 13 and 6, CHHOAc), 2.77, 2.68, 2.60 (m's, epoxide CH's), 1.74 (s, OAc), 1.3–1.6 (br m, H(4,5,8,9)). IR ($CDCl_3$) 1740, 1385, 1370, 1235, 1040 cm^{-1}. (Found: C, 58.87; H, 7.32. Calc for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37%.)

(2*S*,3*S*,6*R*,7*S*,10*S*,11*S*) - 1,12 - *Diacetoxydodeca* - 2,6,10 - *triene trioxide* (**21*sa***). To the diacetate derivative of diepoxide **25*a*** (135 mg, 0.43 mmol) in 2 ml of CH_2Cl_2 was added MCPBA (91 mg, 0.52 mmol) at 0°. This mixture was stirred at room temp for 2 h and then quenched by the addition of sat Na_2SO_3 and CH_2Cl_2. The organic layer was washed with sat $NaHCO_3$ aq and brine and processed to provide **21*sa*** (130 mg, 92%) which gave ^{1}H-NMR and capillary GC data which were indistinguishable from those from the diastereomeric, racemic mixture of **21*ss***, **21*sa*** and **21*aa***. The unpurified material was used directly in the cascade reaction.

5,5' - *Bis*(1,2 - *diacetoxyethyl*)*octahydro* - 2,2' - *bifurans* (**24*a*–c**). The triepoxides **21** (136 mg, 0.41 mmol) in 1 ml of 1 N NaOH were stirred at 50° for 3 h. The mixture was cooled to room temp, acidified with excess HOAc, and concentrated to dryness under high vacuum. Pyridine (1 ml) and Ac_2O (0.8 ml) were added and the mixture was allowed to stand for 16 h. Et_2O (15 ml) and the minimum quantity of H_2O (~1 ml) necessary to dissolve the NaOAc were added. The H_2O layer was saturated with solid NaCl; and the Et_2O layer was dried (Na_2SO_4), filtered, concentrated, and purified by MPLC (2 : 1 hexane–EtOAc) to afford the less polar *trans-trans* isomer **24*c*** and a mixture of the more polar *trans-cis* and *cis-cis* isomers (total recovery of 147 mg, 0.342 mmol, 83%). The latter were then separated by HPLC (3 : 1 hexane–EtOAc), with **24*b*** eluting before **24*a***. **24*a***: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.00 (ddd, J = 6.7, 6.6 and 2.9 Hz), 4.45 (dd, J = 12.1 and 2.9 Hz), 4.15 (dd, J = 12.1 and 6.3 Hz), 4.05 (ddd, J = 7.2, 7.2 and 5.4 Hz), 3.85 (2H, m), 2.065 and 2.050 (OAc's), 1.6–2.1 (m's). **24*b***: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.03 (ddd, J = 6.8, 6.8 and 2.9 Hz), 5.01 (ddd, J = 6.7, 6.7 and 2.9 Hz), 4.437 and 4.432 (dd, J = 12.1 and 2.9 Hz), 4.12 (two dd's, J = 12.1 and 6.5 Hz), 4.10 (ddd, J ≈ 7.2, 7.2 and 7.2 Hz), 4.07 (ddd, J ≈ 7.0, 7.0 and 5.1 Hz), 3.92 (ddd, J ≈ 7.5, 7.1 and 4.5 Hz), 3.85 (ddd, J ≈ 4.4, 6.5 and 7.0 Hz), 2.074 and 2.050 (OAc's), 1.7–2.1 (m's). IR ($CDCl_3$) 1740, 1370, 1230, 1050 cm^{-1}. (Found: C, 55.91; H, 7.09. Calc for $C_{20}H_{30}O_{10}$: C, 55.81; H, 7.03%.) **24*c***: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.02 (ddd, J = 6.6, 6.6 and 2.9 Hz), 4.42 (dd, J = 12.0 and 2.9 Hz), 4.13 (dd, J = 12.0 and 6.5 Hz), 4.09 (ddd, J ≈ 6.6, 6.6 and 6.6 Hz), 3.91 (2H, m), 2.071 and 2.053 (OAc's), 1.9–2.1 (m), 1.66–1.85 (m's).

(2*S*,2'*S*,5*R*,5'*R*) - 5,5' - *Bis*(1(*S*),2 - *diacetoxyethyl*)*octahydro* - 2,2' - *bifuran* (**24*a***). The acetonide diol **30** (20 mg) was dissolved in 0.5 ml of moist THF and stirred over Amberlite H^+ resin for 16 h. The THF was decanted, and excess pyridine and Ac_2O were added. After 16 h concentration left an oil whose capillary GC, HPLC and ^{1}H-NMR data showed it to contain a 10 : 1 ratio of **24*a*** : **24*b***.

Z - (2*S*,3*S*,10*S*,11*S*) - 1,12 - *Dihydroxydodeca* - 2,6,10 - *triene* 2(3),10(11) - *dioxide* (**25*a***). To 25 ml of CH_2Cl_2 at −20° was added Ti(i-PrO)$_4$ (4.25 ml, 14.3 mmol) and (+)-diisopropyl L-tartrate (3.6 ml, 17 mmol). After 10 min, *E,Z,E*-**13** (560 mg, 2.86 mmol) and t-BuOOH (3.8 M in CH_2Cl_2, 22 mmol) were sequentially added. The mixture was stirred until it became homogeneous and left standing at −15° for 18 h. Sat Na_2SO_4 (5 ml) and Et_2O (25 ml) were added, and the mixture was warmed to room temp and stirred for 3 h. Filtration through celite, drying (Na_2SO_4), concentration and MPLC (1 : 1 : 0.8 hexane–EtOAc–i-PrOH) provided the diepoxide **25*a*** (172 mg, 27%) as a white solid, m.p. 51–54°. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.43 (br t, J = 4.6 Hz, HC=CH), 3.87 (dd, J = 12.6 and 2.6 Hz, CHHOH), 3.63 (dd, J = 12.6 and 4.3 Hz), 2.92–3.00 (m, epoxide CH's), 2.6 (br s, OH), 2.23 (m, =CCH_2), 1.64 (m, CH_2CHO). IR ($CDCl_3$) 3600, 3440, 3010, 1445, 1075, 1020, 855 cm^{-1}. This material was converted to its diacetate derivative without incident. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.43 (br t, J = 4.6 Hz, HC=CH), 4.36 (dd, J = 12.2 and 3.2 Hz, CHHOAc), 3.91 (dd, J = 12.2 and 6.3 Hz, CHHOAc), 2.98 (ddd, J = ~2.5, ~3.0 and ~5.5 Hz, OCHCH_2OAc), 2.87 (ddd, J = 2.2, 5.0 and 6.7 Hz, CH_2CHO), 2.21 (m, =CHCH_2), 2.09 (s, OAc), 1.62 (m, CH_2CHO). IR ($CDCl_3$) 3010, 1745, 1370, 1240 1040 cm^{-1}. (Found: C, 61.52; H, 7.82. Calc for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%.)

E - 5 - (1,2 - *Diacetoxyethyl*) - 5' - (1 - *acetoxy* - 2 - (3' - *butenyloxy*)*ethyl*)*octahydro* - 2,2' - *bifurans* (**27** *and* **27***). The mixture of triepoxydiacetate **21*sa*** (58 mg, 0.177 mmol) in ml of MeOH was doped with ~20 mg of NaH and then warmed to 50° for 3 days. Sat NH_4Cl was added, and ordinary workup left a mixture of crude triols (33 mg). This material was treated directly with 1 ml each of pyridine and Ac_2O at room temp for 16 h. The usual workup and HPLC (3 : 1) gave **27** (R = Me) and **27*** (R = Me) in essentially equal amounts. Starting from the stereorandom mixture of triepoxides **21** and carrying out an analogous experiment in crotyl alcohol resulted in a 64% MPLC-purified yield of monocrotyl triacetates. **27/27*** (R = CH_2CH=$CHCH_3$): ^{1}H-NMR ($CDCl_3$, 300 MHz, of 1 : 1 mixture) δ 5.68 (dq, J = 15.3 and 6.4 Hz, CH_3HC=), 5.53 (dt, J = 15.4 and 5.6 Hz, CH_2HC=), 5.01 (m's, HC(C)$_2$OAc), 4.43 and 4.44 (two dd's, J = 12.1 and 2.8 Hz, CHHOAc), 4.13 and 4.12 (two dd's, J = 12.1 and 6.4 Hz, CHHOAc), ~4.07 (m's), 3.92 (br d, J = 6.2 Hz, OCH_2C=), 3.83 (m's), 3.63 and 3.62 (two dd's, J = 10.9 and 3.7 Hz, CHHOCH$_2$C=), 3.55 (dd, J = 10.9 and 5.8 Hz, CHHOCH$_2$C=), 3.54 (dd, J = 10.9 and 6.2 Hz, CHHOCH$_2$C=), 2.081, 2.078, 2.072 and 2.049 (OAc's), 1.6–2.1 (m's), 1.73 (d, J = 6.5 Hz, =CHCH_3). IR ($CDCl_3$) 1745, 1680, 1375, 1240, 1055 cm^{-1}. (Found: C, 59.93; H, 7.63. Calc for $C_{22}H_{34}O_9$: C, 59.71; H, 7.74%.)

(4*S*,5*S*) - 2,2 - *Dimethyl* - 4,5 - *di*(5 - *methoxy* - 3,5 - *dioxopentyl*) - 1,3 - *dioxolane* (**28**). (4*R*,5*R*) - 2,2 - Dimethyl - 4,5 - di(4 - methylphenyl)sulfononyloxymethyl - 1,3 - dioxolane[18] (1.58 g, 3.36 mmol) and NaI (2.4 g, 16 mmol) were dissolved in 33 ml of Me_2CO in a resealable tube and heated to 100° for 3 h. Concentration; dissolution in ether; washing with water, sat $Na_2S_2O_4$, water and brine; drying (Na_2SO_4); filtration; and concentration left the diiodide[18] as a pale yellow oil (1.18 g, 3.09 mmol, 92%). This material in 3 ml of dry THF was added at 0° to a soln of the dianion derived from methyl acetoacetate (887 mg, 7.65 mmol) and LDA, prepared as described in the preparation of **14**, which also contained HMPA (1.37 g, 7.65 mmol). After 4 h at 0° the mixture was quenched with 10% HCl. Ordinary workup and MPLC (2 : 1 hexane–EtOAc) left **28** as a slightly yellow oil (545 mg, 1.52 mmol, 49%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, OMe), 3.59 (m, OCH), 3.48 (s, O=CCH_2C=O), 2.76 (ddd, J = 18.1, 7.4 and 5.9 Hz, CH_2CHHC=O), 2.68 (ddd, J = 18.1, 7.9 and 6.7 Hz, CH_2CHHC=O), 1.94 (m, OCHCHH), 1.71 (m, OCHCHH), 1.34 (s, Me's). IR ($CDCl_3$) 1750, 1720, 1445, 1250, 1075 cm^{-1}. (Found: C, 56.64; H, 7.21. Calc for $C_{17}H_{26}O_8$: C, 56.97; H, 7.21%.)

E,E - (4*S*,5*S*) - 2,2 - *Dimethyl* - 4,5 - *di*(5 - *hydroxypent* - 3 - *enyl*) - 1,3 - *dioxolane* (**29**). The bis-β-ketoester **28** was reduced with $NaBH_4$, mesylated and eliminated with MsCl/Et_3N, and reduced with DIBALH by the procedures described in the preparations of **15** and *E,E,E*-**13** to provide **29** (30% after MPLC (1 : 1.5 hexane–EtOAc)). ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 5.73 (m, HC=CH), 4.10 (m, CH_2OH), 3.66 (m, OCHCH$_2$), 2.2 (br m, CH_2C=), 1.6 (br m, OCHCH$_2$), 1.45 (s, OH), 1.38 (s, Me's). IR ($CDCl_3$) 3650, 3200, 3000, 1665, 1380, 1090, 970 cm^{-1}.

(4*S*,5*S*) - 2,2 - *Dimethyl* - 4,5 - *di*(5 - *hydroxy* - 3(*S*),4(*S*) - *epoxypentyl*) - 1,3 - *dioxolane* (**30**). The bis-allylic alcohol **29** was epoxidized by the procedure described in the preparation of **25*a***. The diepoxy acetonide **30** was purified by filtration through SiO_2. ^{1}H-NMR ($CDCl_3$, 80 MHz) δ 3.75 (m, OCHCH$_2$), 3.62 (m, CH_2OH), 2.93 (m, epoxide CH's), 1.69 (m, CH_2CH_2), 1.36 (s, Me's).

Compounds **24*d*–*i***, **32**, **33**, **34** *and* **35** were prepared by

reactions entirely analogous to some of those already described and will not be detailed.

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