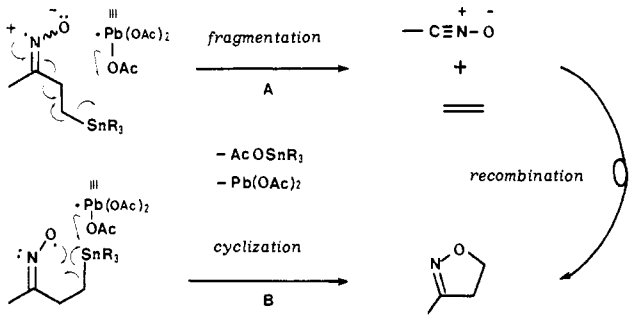
direct C–O bond-forming cyclization route (path B).



Our findings provide a new approach to Δ^2-isoxazolines, which supplement recent studies by other authors to show their versatility in synthesis.[11]

Supplementary Material Available: Details of the preparation and spectral data on the oximes and products (6 pages). Ordering information is given on any current masthead page.

Symmetry-Assisted Synthesis of Triepoxide Stereoisomers of (*E*,*Z*,*E*)-Dodeca-2,6,10-triene-1,12-diol and Their Cascade Reactions to 2,5-Linked Bistetrahydrofurans

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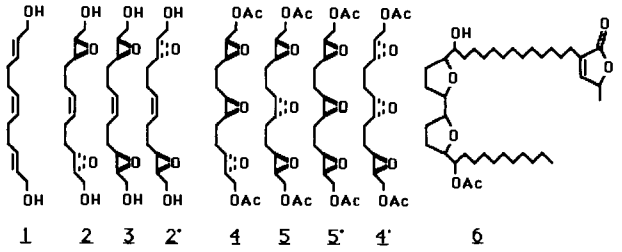
Internal nucleophilic ring opening of oligoepoxides formally derived from oligo-1,5-dienes to generate 2,5-linked oligotetrahydrofurans has emerged as a useful concept in polymer,[1] biosynthetic,[2,3] and synthetic[4] studies. Since the stereochemical details of this process are unknown, we have prepared configurationally defined triepoxides from (*E*,*Z*,*E*)-dodeca-2,6,10-triene-1,12-diol (**1**) and investigated the stereochemical consequences of their cascade reactions to generate 2,5-bistetrahydrofurandiyls.

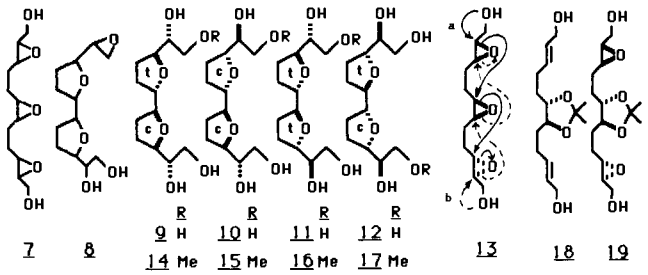
One strategy for controlled generation of a relative stereorelationship is to establish two independent stereogenic centers, each in an absolute sense. In the present case triene **1**[5a] of C_{2v} symmetry (prepared from (*Z*)-oct-4-enedial by a double Horner–Emmons reaction and DIBALH reduction) was epoxidized by the chiral Sharpless procedure[6] to give a mixture of *d,l*- and *meso*-diepoxides **2**/**2′** and **3** of C_2 and C_s symmetries, respectively. We found no way to measure the relative amounts of these stereoisomers but could predict them by first assuming a typical value, say 19:1 (90% ee), for the enantiofacial selectivity of a single Sharpless reaction and then applying the following generally applicable observation: *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* $(A_1 + B_1)(A_2 + B_2).....(A_n + B_n)$ *where* A_i:B_i *is the ratio of major/minor isomers for the i th process. The mathematical consequences of such an expansion are that the ratio of antipodal isomers (i.e.,* $A_1A_2...A_n$:$B_1B_2...B_n$) is large. Thus, assuming no end effects (i.e., $A_1/B_1 = A_2/B_2$) in this double Sharpless reaction, a reasonable expection for the **2**:**3**:**2′** ratio was (19 + 1)(19 + 1) or 361:38:1. That is, the optical purity (ee) of the chiral diepoxide should be 99.45%. Also, the **2**:**3** ratio of 9.5:1 should be half of the inherent enantiofacial selectivity since the symmetry of the triene **1** provides two paths to the meso compound **3** (initial *re* then *si* attack, or vice versa). Regardless of the absolute accuracy of this analysis, it was assured that the ratio of the *d,l*-pair **2**:**2′** was significantly enhanced compared with that arising from a single epoxidation.



1 **2** **3** **2′** **4** **5** **5′** **4′** **6**

The mixture of **2**/**3**/**2′** was acetylated (Ac_2O/py) and then epoxidized with MCPBA. The olefin faces in the chiral diepoxide **2** (or **2′**) are interconverted by 180° rotation about the C_2 axis; therefore, only a single triepoxide **4** (or **4′**) was formed. The faces in the meso isomer **3** are not interchanged by reflection through the mirror plane; thus, two new *meso*-triepoxides **5** and **5′** were generated. We were again unable to separate this mixture[5a] of diastereomers, but their ratios could be deduced by careful analysis of ^{13}C NMR data and were consistent with our expectations.

The importance of the ability to efficiently desymmetrize synthetic intermediates that have been prepared by symmetry-assisted approaches has been demonstrated by us previously.[7] Our current needs are no different since we ultimately hope to use this chemistry in a synthetic approach to the interesting natural material uvaricin (**6**),[8] an unsymmetrical target. Stereochemistry aside, an attractive desymmetrization operation appeared to be



7 **8** **9** R = H **14** R = Me **10** R = H **15** R = Me **11** R = H **16** R = Me **12** R = H **17** R = Me **13** **18** **19**

the cascade of triepoxide diols **7** to the bistetrahydrofuran monoepoxide diols **8**. This crucial process was effected by exposure of the **4**/**5**/**5′**/**4′** mixture to aqueous sodium hydroxide (1 N, 50 °C) which resulted in rapid saponification (the mixture of primary diols **7** was isolable) and a slower, Payne-rearrangement-initiated series of S_N2 reactions. However, the terminal epoxides **8** did not accumulate; they presumably were rapidly opened by hydroxide ion under the reaction conditions to give the bistetrahydrofurantetrols **9**–**12** which were also best isolated (≈80% from **4**/**5**/**5′**/**4′**) and characterized as their tetraacetate derivatives[5b] (the ratio of **9**/**12**:**10**:**11** was 19.8:1.15:1 (cgc) which is entirely consistent with the expectations delineated above). The failure of this scheme to differentiate the termini in **9**–**12** was accompanied by a second disappointing but most surprising event. The high level of optical purity introduced in the double Sharpless reaction is nearly completely lost since *cascades of the major, chiral diol triepoxide* ***13*** *from the "top-down" (a) and from the "bottom-up" (b)—although diasteromeric operations—give the enantiomeric tetrols* ***9*** *and* ***12*** *in nearly equal proportion. This "racemization" process is unusual since no symmetry element is present at any point along the reaction coordinate.* Both of the above counterproductive events were eliminated by a simple modification; the medium for the cascade reaction was changed

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from water to methanol. The intermediate terminal epoxides **8** were now opened by methoxide ion to give the end-differentiated monoether triols **14–17**.[5b] These are HPLC separable. Each of the diastereomers **14** and **17** arising from the two modes of cascade in the major triepoxide **13** retains the high level of optical purity of their common precursor.

During the cascade process the *meso*-triepoxides **5** and **5′** each gave a racemic mixture of the C_2-tetrols **10** and **11** which were easily distinguished by ^1H NMR from their unsymmetrical partners **9** and **12**. However, there was no basis for assigning which of the two C_2 samples had a pair of cis- (i.e., **10**) and which had a pair of trans-disubstituted (i.e., **11**) THF rings. This issue was settled by an alternative synthesis that used an "inside-out" process. Thus, L-(2*R*,3*R*)-(+)-diethyl tartrate was processed in eight steps to the (4*S*,5*S*)-dioxolane **18**. The chiral Sharpless reaction of **18** using L-(+)-diethyl tartrate provided **19** which underwent deprotection and acid-catalyzed opening to give *cis-cis*-**10**, but not its enantiomer. This "inside-out" process therefore complements the "end-to-end" cascade of the *meso*-triepoxides since the latter gives racemates, but by the proper combination of L- and D-diethyl tartrate as starting material and Sharpless catalyst, any of the individual tetrols (**10**, **11**, or their enantiomers) is available optically pure from the former scheme.

We are currently applying many of the above reactions and ideas to three other isomers of dodeca-2,6,10-triene-1,12-diol and will report later on those efforts.

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Synthesis of 1,1-Dilithio-2,2,3,3-tetramethylcyclopropane

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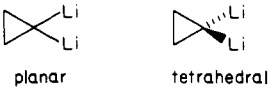
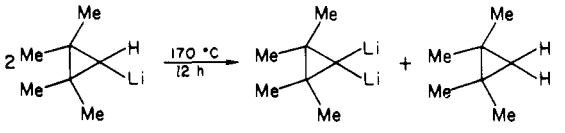
Since the prediction by Schleyer, Pople, and co-workers that 1,1-*gem*-dilithiocyclopropane monomers[1] were prime candidate molecules for observation of planar tetracoordinate carbon, these species have become intriguing synthetic target molecules and work directed toward their synthesis has proceeded in several laboratories. They are interesting species as reagents for further synthetic work whether they prove to be planar or tetrahedral. Schleyer



planar tetrahedral

and Pople have predicted higher stability for the planar form by at least 7 kcal/mol. Our laboratory has developed a very facile synthesis for such species. The method involves pyrolysis of 1-lithio-2,2,3,3-tetramethylcyclopropane and produces a dilithio compound in higher yield over a 10–12-h time period:



We have not yet been successful in applying this reaction technique directly to cyclopropyllithium for there is a problem with elimination of lithium hydride. The starting material 1-lithio-2,2,3,3-tetramethylcyclopropane was prepared by the reaction of 1-bromo-2,2,3,3-tetramethylcyclopropane and lithium in diethyl ether[2] but is contaminated with lithium bromide. This compound, 1-lithio-2,2,3,3-tetramethylcyclopropane, has excellent thermal stability and sublimes at 140 °C under high vacuum (10^{-5} torr). Sublimation of this crude material (~2-g scale) at 140 °C for 12 h usually gives about 50% yield of crystalline 1-lithio-2,2,3,3-tetramethylcyclopropane, leaving a slightly yellowish residual solid. The residual solid (mainly lithium bromide) was found also to contain 1,1-dilithio-2,2,3,3-tetramethylcyclopropane, and this was confirmed by the hydrolysis with D_2O.

Typically, 1.04 g (10 mmol) of 1-lithio-2,2,3,3-tetramethylcyclopropane was placed in a round-bottom flask coupled with a small distillation apparatus and heated to 170 °C under dry and oxygen-free argon for 10 h. Rapid stirring of the powdered sample with a magnetic stirring bar is required when larger quantities are desired. The 1,1,2,2-tetramethylcyclopropane generated was collected in a receiver cooled with an ice bath. The system was then evacuated and 1,1,2,2-tetramethylcyclopropane (0.46 g; 94%) was isoalted, using a vacuum line. The residual solid was carefully hydrolyzed by introducing an excess of D_2O. Through the vacuum line, the products were fractionated through a −45 °C bath (to trap excess D_2O) and a −196 °C bath. A mixture of 1,1-dideuterio-2,2,3,3-tetramethylcyclopropane (94%), dideuterioacetylene (4%), and tetradeuteriopropyne (2%) was obtained from the −196 °C bath.[3] The yield of 1,1-dideuterio-2,2,3,3-tetramethylcyclopropane (0.45 g) was calculated to be 90% based on the starting monolithio compound used. When the pyrolysis was performed at 210 °C, followed by the deuterolysis, a mixture of 1,1-dideuterio-2,2,3,3-tetramethylcyclopropane (41%), dideuterioacetylene (45%), and tetradeuteriopropyne (14%) was obtained. Pyrolysis at 240 °C for 15 min resulted in $(C_2D_2)_n$ (75%) and $(C_3D_4)_n$ (25%) after the deuterolysis. As indicated by the above experiments, 1,1-dilithio-2,2,3,3-tetramethylcyclopropane decomposed into C_2Li_2 and C_6Li_4 as did dilithiomethane[4] and 1,1-dilithioneopentane.[5]

In addition, pure 1,1-dilithio-2,2,3,3-tetramethylcyclopropane was obtained when 1-lithio-2,2,3,3-tetramethylcyclopropane was pyrolyzed under an inert atmosphere at 170 °C (yield 40%). At this temperature, the reaction proceeded slowly and 8–10 h were required for completion.

The ^1H NMR spectrum of 1-lithio-2,2,3,3-tetramethylcyclopropane in hexadeuteriobenzene consisted of singlets at δ 1.28 and 1.40 due to the methyl groups and a singlet at δ −2.59 due to the ring proton, while the ^1H NMR of 1,1-dilithio-2,2,3,3-tetramethylcyclopropane in hexadeuteriobenzene contained only a singlet at δ 1.13 from the methyl groups. (The equivalence of the four methyl groups indicates a symmetrical structure of the dilithio compound.) Absence of the peak at δ −2.59 is good evidence for geminal lithium substitution on the cyclopropane ring. The methyl-substituted cyclopropane ring enhanced the solubility of the compound in organic solvents, compared with dilithiomethane which is only very slightly soluble in most organic solvents.

Mass spectral analysis of the lithiated cyclopropane after deuterolysis showed a molecular ion at *m/e* 100 and a base peak at *m/e* 85, corresponding to $C_7H_{12}D_2$ and $C_6H_9D_2$, respectively. ^1H NMR of this compound contained only a singlet at δ 1.21, due to the methyl groups, indicating deuteration at two sites on the cyclopropane ring. Elemental analysis for $C_7H_{12}Li_2$. Calcd: C, 76.36%; H, 10.91%. Found: C, 76.18%; H, 10.87%.

Flash vaporization mass spectroscopy of the new *gem*-dilithiotetramethylcyclopropane shows that only monomers and dimers are present in the gas phase. Thus, the bulky methyl groups and cyclopropyl ring prevent extensive polymerization such as exists in dilithiomethane.[6] The structure of the dimer (and the

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