can be substantially facilitated by the ozonolysis of olefins on silica gel, presumably due to restricted migration of the adsorbed primary cleavage fragments.[4] However, application of this method to **1** also failed to produce ozonide **4**,[5] which, thus, has been unknown to now.

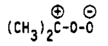
In the present investigation we have performed the ozonolysis of **1** adsorbed on powdered polyethylene (Microthene FN 500, spherical particles, maximum size 20 μm; supplier, Serva Feinbiochemica, Heidelberg, FRG). The adsorption of **1** (2.11 g on 60.0 g of polyethylene) was carried out at ambient temperatures and the ozone treatment at −78 °C for 4 h with 80 L of a gas stream containing 1.1 mmol of ozone per liter. The products were extracted with diethyl ether at ambient temperatures and the combined extracts were distilled at 15 torr and ambient temperatures. From the distillate, ether was largely removed by a second distillation step at normal pressure, using a 20-cm Vigreux column. The liquid distillation residue contained the ozonide **4** as the single major component, along with residual ether, unreacted **1**, and minor amounts of unidentified products. Separation of the residue by preparative gas chromatography (glass column 0.7 × 300 cm, 5% OV 101 on Chromosorb G; 80 °C) afforded the pure,[6] colorless liquid ozonide **4**: ^{1}H NMR ($CDCl_3$) δ 1.46 (s); ^{13}C NMR ($CDCl_3$) δ 24.60 (q, J = 127.6 Hz), 108.65 (s); IR no absorption in the carbonyl region; CI-MS, m/e (%) 133 (6) $(M + 1)^+$, 117 (5), 75 (100); yield 130.0 mg (3.9%).

$(CH_3)_2C{=}C(CH_3)_2$

1

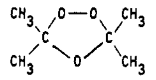
$(CH_3)_2C{=}O$

2



$(CH_3)_2\overset{\oplus}{C}{-}O{-}\overset{\ominus}{O}$

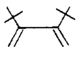
3



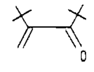
4

Ozonide **4** is unusually stable. Heating of **4** in $CDCl_3$ at 80 °C did not lead to a change in the ^{1}H NMR spectrum within 36 h. At ambient temperatures reduction of **4** occurred only slowly with sodium iodide in acetic acid and not at all within 3 days with dimethyl sulfide or with triphenylphosphine. At 80 °C **4** was slowly reduced by triphenylphosphine to give acetone (**2**).

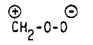
Trisubstituted and 1,1-disubstituted ethylenes are usually cleaved such that disubstituted carbonyl oxides and aldehydes are formed as primary fragments and hence ozonide formation is possible in most cases. Recently we have found, however, that diene **5** is cleaved in the opposite direction, providing **6** and **7** as the primary fragments.[7] In line with this, ozonolysis of **5** in pentane did not give the monoozonide **8**. Therefore, we have tried the ozonolysis of **5** on polyethylene under conditions similar to those described above for the ozonolysis of **1** (1.12 g of **5** on 44.2 g of polyethylene, ozone treatment at −78 °C for 2 h with 40 L of a gas stream containing 1.2 mmol of ozone per liter). The products were extracted from polyethylene with pentane and the pentane was distilled off. Column chromatographic separation of the residue on silica gel afforded among other products in ca. 30% yield the colorless, liquid ozonide **8**: ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.18 (s, 9 H), 5.00 (s, 1 H), 5.26 (s, 1 H), 5.28 (s, 1 H), 5.35 (s, 1 H); IR only a weak absorption in the carbonyl region due to partial decomposition; CI-MS, m/e (%) 215 (78) $(M + 1)^+$, 185 (94), 168 (43) $(M - CH_2O_2)^+$, 131 (100) $(M - C_6H_{11})^+$.



5

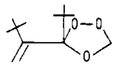


6

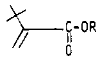


$\overset{\oplus}{C}H_2{-}O{-}\overset{\ominus}{O}$

7



8



9

a: R=t-Bu
b: R=H

Ozonide **8** is thermally unstable. At ambient temperatures it was converted into a mixture of **9a,b**, formaldehyde, and isobutene. This conversion is catalyzed by silica gel, and hence the isolation of **8** by column chromatography is affected. Reduction of **8** by triphenylphosphine afforded the expected ketone **6**.

The foregoing results show that the ozonolysis of olefins on polyethylene opens a new route to types of ozonides which are otherwise not accessible. It is noteworthy in this respect, that, as it had been reported for **1**,[5] the ozonolysis of **5** adsorbed on silica gel did not afford ozonide **8** either.[7] It appears, thus, that polyethylene has properties that are very conducive to ozonide formation. This view is confirmed by recent results of our continuing investigations, which are aimed at the preparation of hitherto not accessible classes of ozonides.

---

(4) For a summary of references, see: Den Besten, I. E.; Kinstle, T. H. *J. Am. Chem. Soc.* **1980**, *102*, 5969.

(5) Aronovitch, C.; Tal, D.; Mazur, Y. *Tetrahedron Lett.* **1982**, 3623.

(6) Elemental analysis gave satisfactory results.

(7) Volpp, W., unpublished results.

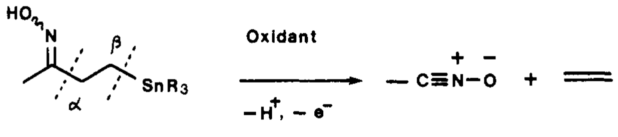
Oxidative Fragmentation of β-Stannyl Oximes: Stereospecific Formation of Unsaturated Nitrile Oxides

Hisao Nishiyama,* Hiroyuki Arai, Takashi Ohki, and Kenji Itoh

School of Materials Science
Toyohashi University of Technology
Tempaku-cho, Toyohashi 440, Japan

Received March 4, 1985

New versions of fragmentation reactions have been recently devised and envisioned as versatile synthetic methodology with high stereochemical controllability,[1] utilizing organosilyl[2] or organostannyl[3] functions. In connection with our recent work on silicon-directed Beckmann fragmentations,[2ab] we became interested in oxidative reactions of β-silyl oximes. However, only known reactions at the oxime group were observed, such as formation of ketones and vicinal acetoxynitroso compounds.[4] Since the oxidation of oximes is known to form stable iminoxyl radicals,[5] we have chosen a β-stannyl group as a directing group to cause easily radical fission or transmetalation rather than a silyl group. We report here a new homolytic fragmentation of β-stannyl oximes by oxidation with lead tetraacetate (LTA). Selective formation of nitrile oxides and subsequent intramolecular cycloaddition are described. In addition, a direct cyclization between N–*O* and *C*–Sn from *Z* oximes has also been discovered.



---

(1) For review of fragmentation reactions, see: (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Ibid.* **1969**, *8*, 535. (c) Marshall, J. A. *Synthesis* **1971**, 221. For recent paper, see: (d) Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1979**, *101*, 3567 and references cited therein.

(2) (a) Nishiyama, H.; Sakuta, K.; Osaka, N.; Itoh, K. *Tetrahedron Lett.* **1983**, *24*, 4021. (b) Nishiyama, H.; Sakuta, K.; Itoh, K. *Ibid.* **1984**, *25*, 223. (c) Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chen, E. *J. Am. Chem. Soc.* **1980**, *102*, 6896. (d) Hudrlik, P. F.; Waugh, M. A.; Hudrlik, A. M. *J. Organomet. Chem.* **1984**, *271*, 69. (e) Wilson, S. R.; Zucker, P. A.; Kim, C.; Villa, C. A. *Tetrahedron Lett.* **1985**, *26*, 1969.

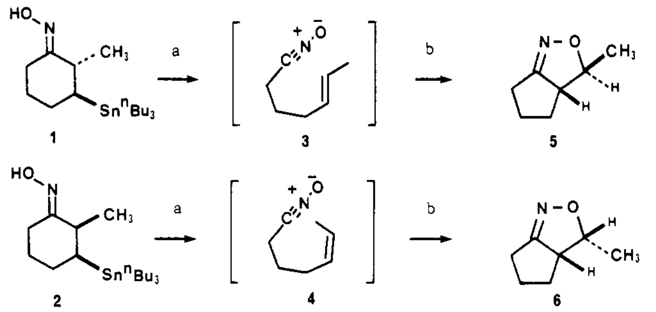
(3) (a) Nakatani, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 5335; **1985**, *26*, 2209. (b) Ochiai, M.; Ukita, T.; Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1984**, 1007.

(4) (a) Kropf, h. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 983. (b) Kropf, H. *Justus Liebigs Ann. Chem.* **1966**, *700*, 1. (c) Yukawa, Y.; Sakai, M.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2266.

(5) For ESR spectroscopy, see: (a) Gilbert, B. C.; Norman, R. O. C. *J. Chem. Soc. B* **1966**, 87. (b) Gilbert, B. C.; Norman, R. O. C. *Ibid.* **1966**, 123. (c) Caragheorgheopol, A.; Caldararu, H.; Badilescu, I. I.; Sahini, V. E. *Rev. Roum. Chim.* **1980**, *25*, 307. (d) Grossi, L.; Lunazzi, L.; Placucci, G. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1831 and references cited therein. For the reaction of iminoxyl radicals, see: (e) Frojimovic, M. M.; Just, G. *Can. J. Chem.* **1968**, *46*, 3719. (f) Just, G.; Dahl, K. *Ibid.* **1970**, *48*, 966. (g) Schenk, C.; de Boer, Th. J. *Tetrahedron* **1979**, *35*, 2119, (h) Atmaram, S.; Forrester, A. R.; Gill, M.; Napier, G. J.; Thomson, R. H. *Acta Chem. Scand. B* **1982**, *36*, 641. (i) Lub, J.; Beekes, M. L.; de Boer, Th. J. *J. Chem. Soc. Perkin Trans. 2* **1983**, 721. Also see ref 4.

0002-7863/85/1507-5310$01.50/0 © 1985 American Chemical Society

Scheme I[a]

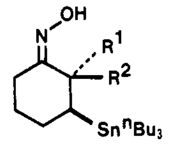


[a] (a) LTA, CH_2Cl_2, −60 °C (10 min), −20 °C (10 min); (b) addition of aqueous $NaHCO_3$ and Et_2O, room temperature.

Starting β-stannyl oximes were prepared by oximation[6] of the corresponding β-stannyl ketones with $HONH_2·HCl$ and NaOAc in methanol at room temperature or by direct stannylmethylation[7] of dilithio derivatives of oximes with ICH_2Sn-*n*-Bu_3.

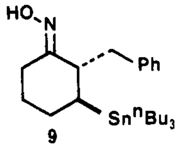
Addition of LTA (1.3 equiv) to a dichloromethane solution of the cyclic (*E*)-β-tributylstannyl oximes **1** or **2** at or below −60 °C gave a clear yellow solution. When the reaction mixture was allowed to warm to −20 °C, a white precipitate of $Pb(OAc)_2$ was observed. Interestingly, formation of the unsaturated nitrile oxides **3** and **4** could be confirmed by sg TLC as an intense UV absorbing spot (R_f 0.72 vs. 0.50, **1** and **3**; R_f 0.67 vs. 0.46, **2** and **4**; ether–hexane = 2:3), respectively.[8] After addition of aqueous $NaHCO_3$ and dilution with ether (ca. 0.1 M), the reaction mixture was then kept at ambient temperature (ca. 20 °C, 6 h for **3** → **5**, 2 h for **4** → **6**) to give the Δ^2-isoxazolines **5** (69%) and **6** (71%),[9,10] respectively (Scheme I). Dramatic ring-contractive conversion of the stannyl oximes to the isoxazolines with stereochemical control was realized in one pot brought about by strong directivity of the stannyl group followed by the 1,3-dipolar cycloaddition.[11]

For the *Z* oxime isomers **7** and **8**, the same fragmentation–cyclization was also observed, respectively. Other examples include **9** and **10** which generated bicyclic isoxazolines **11** and **12** in good yields.

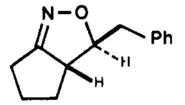


7 R^1 = Me, R^2 = H (**5**, 81%)

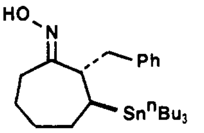
8 R^1 = H, R^2 = Me (**6**, 85%)



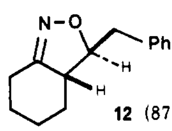
9



11 (81%)

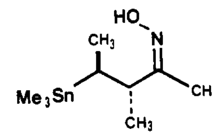


10

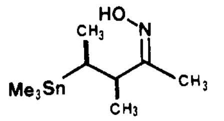


12 (87%)

Linear 2,3-dimethyl substituted *Z* oximes **13** and **14**[12] gave



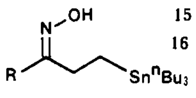
13



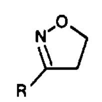
14

stereospecifically *trans*-2-butene (77%) and *cis*-2-butene (83%), respectively.[13]

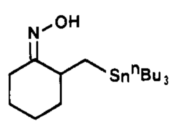
It is noteworthy that the (*Z*)-β-stannyl oximes **15**, **16**, and **17** gave directly the cyclization products **18**, **19**, and **20**, respectively,



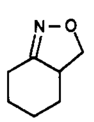
15 R = Ph
16 R = ${}^tBu$



18 R = Ph (78%)
19 R = ${}^tBu$ (83%)



17

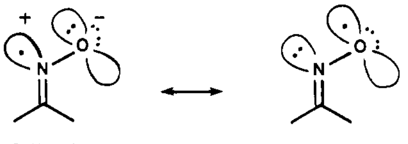


20 (84%)

at −20 °C for 10 min. The expected nitrile oxides could not be detected by carefull TLC examination, and the isoxazolines were instantaneously formed.

These results show the remarkable variation of the reaction course with respect to the stereochemistry of the oxime group and the position of the stannyl group.[14]

That iminoxyl radicals arise from oxidation of oximes has been well investigated spectroscopically, and they show the characteristic σ-radical structure having a three-electron system.[5] Accordingly,



we propose a following mechanism for the reaction. The oximes (**1**, **2**, **7–10**) having a stannyl group too far from the iminoxyl skeleton to interact directly cause the fragmentation pathway to be followed (path A); while the *Z* oximes (**15–17**) bearing a primary stannyl group on a flexible side chain and sufficiently near to be able to interact to the iminoxyl moiety proceed by a

---

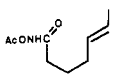
(6) Separation of *E* and *Z* isomers of the oximes can easily be performed by silica gel column chromatography with ether–hexane as an eluent; for all cases in this text, the *E* oximes are forerun. For identification, see supplementary material. For preparation of the starting stannyl ketones, see: (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186; **1977**, *99*, 4836. (b) Piers, E.; Morton, H. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1033. (c) Fleming, I.; Urch, C. J. *Tetrahedron Lett.* **1983**, *24*, 4591. For utilizing lithio enamines and ICH_2Sn-*n*-Bu_3, see ref 3a.

(7) Fraser, R. R. In "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; pp 82–86. For **15** and **16**, 30–50% yields.

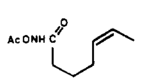
(8) Quick separation of **3** and **4** and the identification are possible: IR (film) 2280 cm^{-1}; ^1H NMR, olefinic protons; $T_{1/2}$ = ca. 0.5–1 h.

(9) Isolated yields; KF workup is recommended for efficient removal of tri-*n*-butylstannyl residue. See: Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.

(10) If aqueous $NaHCO_3$ was not added to the reaction mixture, the unsaturated acetyl hydroxamates **21** and **22** respectively were isolated from



21



22

1 (67% of **21** and 14% of **5**) and **2** (27% of **22** and 40% of **6**). Cleavage of oximes with LTA has been reported, but the reaction was limited only to hindered ketoximes and formation of nitrile oxides was also indicated; see: ref 5f. Just, G.; Dahl, K. *Tetrahedron Lett.* **1966**, 2441.

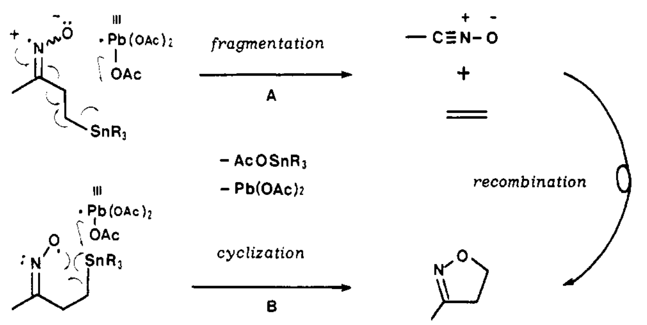
(11) For recent examples of intramolecular cycloadditions of nitrile oxides (INOC); (a) Confalone, P. F.; Lollar, E. D.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 6291. (b) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (c) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (d) Curran, D. P. *Ibid.* **1982**, *104*, 4024. (e) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762. (f) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *Ibid.* **1984**, *49*, 3474. For review, see: (g) Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123. (h) Oppolzer, W. *Ibid.* **1977**, *16*, 10. (i) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(12) For preparation of the starting ketones, see ref 6c and supplementary data.

(13) At 0 °C, for 30 min; yields based on GLPC and ^1H NMR examination. On standing for 2 h at ca. 20 °C, the recombination products between 2-butenes and acetonitrile oxides were given in 5–30% yields.

(14) In contrast to above examples, the corresponding *E* oximes (the isomers of **13**, **14**, and **17**) did not give the olefins and the nitrile oxides but gave complicated products.

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

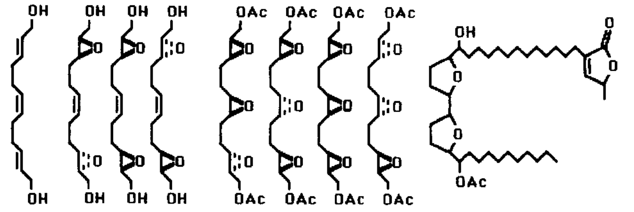
Thomas R. Hoye* and Joseph C. Suhadolnik

*Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455*

Received April 19, 1985

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.

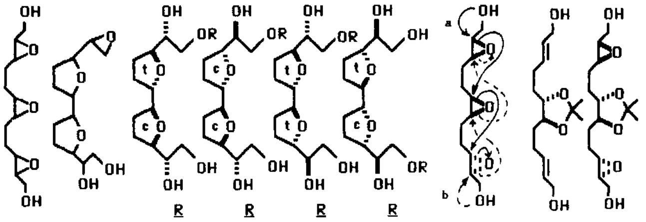
One strategy for controlled generation of a relative stereorelationship is to establish two independent stereogenic centers, each in an absolute sense. In the present case triene **1**[5a] of C_{2v} symmetry (prepared from (*Z*)-oct-4-enedial by a double Horner–Emmons reaction and DIBALH reduction) was 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 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



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

---

(1) Schultz, W. J.; Etter, M. C.; Pocius, A. V.; Smith, S. *J. Am. Chem. Soc.* **1980**, *102*, 7981.

(2) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

(3) Cane, D. E.; Liang, T.-C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274.

(4) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691.

(5) This compound has been characterized by ^{1}H NMR, IR, and (a) elemental combustion analysis (b) high-resolution mass spectrometry.

(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(7) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2783.

(8) Jolad, S. D.; Hoffman, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, O. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151.

0002-7863/85/1507-5312$01.50/0