the halo diols were obtained which were contaminated with unreacted epoxy alcohol (ca. 50%) and unidentified products. However when an equivalent amount of Ti(O-i-Pr)$_4$ was added, the good regioselectivity and yield reported in Table I (entry 1) were obtained, without contaminated products.[8]

The method is not applicable when groups highly sensitive to acid are present. Thus, while epoxy alcohol **2** was treated with I_2 under the reported conditions and the iodo diols were obtained with good yields (85%) and a C-3/C-2 regioselectivity of 7:1 (entry 2), the treatment at the same conditions of epoxy alcohols **3** yielded a nonisolable mixture (entry 3), probably by acidic deprotection of the THP group and competitive intramolecular openings of the epoxides.[2a,9]

The opening procedure (I_2) is also applicable to lineal homoallylic epoxy alcohols from *E*-olefins with even greater regioselectivity than with allylic epoxyalcohols (entry 4). However when homoallylic epoxy alcohols from *Z*-olefins (entry 5) are opened, a 1:1 mixture of iododiols was obtained.

Lineal *erythro*- and *threo*-1,2-epoxy alcohols yield cleanly the primary halide without any contamination of other regioisomers (entries 6 and 7). The reaction is also applicable to other epoxy alcohols when such a unit is located in a ring. However, in such cases, stereochemistry and the relative position of the epoxide and the hydroxy group should receive special consideration. Thus, while *cis*-2,3-epoxycyclohexan-1-ol (**4**) was submitted to the described conditions with I_2 and Br_2, giving rise to the expected 3-halo 1,2-diol (entry 8) as the only detectable product, the trans isomer **5** yielded the isopropyl ether **6**. In the homoallylic epoxycyclohexanol, however, both isomers (entries 9 and 10) yielded the opening in C-4 as in the acyclic cases.

The increase in rate and regioselectivity of the opening reaction of trans-allylic and homoallylic epoxy alcohols with halogen in presence of Ti(O-i-Pr)$_4$ suggests that the complexation of the epoxy alcohol to the metal center proposed by Sharpless et al. in other Ti-assisted openings[5] also occurs in our system, with further delivery of the halogen. The clear effect of the free hydroxy group on access to the metal is shown by the fact that epoxy alcohol acetates scarcely react under the described conditions (I_2, 0.5 h) (entry 12). In order to clarify such halogen delivery we have performed the Ti(O-i-Pr)$_4$–X_2 (1:1 molar) mixture, in $CDCl_3$ and observed it by ^{1}H NMR spectroscopy. When Br_2 was used, after 10 min (the deep red color of the bromine changed to yellow) the presence of acetone was detected in a ratio of ≈1:6 of the integrals corresponding to the methyl in the acetone and the isopropyl groups. These data led to the conclusion that some halo–Ti–alkoxide species[10] are formed by a redox reaction of the type

$$\text{Ti(O-i-Pr)}_4 + x\text{Br}_2 \rightarrow \text{Br}_x\text{Ti(O-i-Pr)}_{4-x} + x\text{HBr} + x\underset{\mathbf{7}}{(\text{CH}_3)\text{C=O}}$$

where **7** would be responsible for the regioselectivity observed, in accordance with other halo–Ti-assisted openings.[6a] Thus when to the performed mixture Ti(O-i-Pr)$_4$–Br_2 (1 h aged, in CH_2Cl_2) was added the olefinic epoxy alcohol **8**, the bromo diol **9** was the observed product with the expected regioselectivity (>20:1), with no trace of bromine added to the double bond. When similar experiments were performed with the Ti(O-i-Pr)$_4$–I_2 mixture (even after 24 h of standing) only traces of acetone were observed by NMR and the cyclic compound **10** was the only product[12] showing the presence of free I_2. Studies of the described procedure directed to proposing a more complete mechanistic scheme together with synthetic applications to the enantioselective synthesis of natural compounds are in due course and will be published elsewhere.

Acknowledgment. We are grateful to the DGICYT of Spain (Grant PB86-0322). Special thanks are given to Professor K. Barry Sharpless for helpful discussions. E.A. and M.T.N. thank the MEC of Spain for a Reincorporation and FPI fellowship, respectively.

Supplementary Material Available: Characterization data, including ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data, for the obtained compounds (7 pages). Ordering information is given on any current masthead page.

(8) To the best of our knowledge the opening of epoxides with bromine or iodine not precedented.

(9) (a) Doherty, A. M.; Ley, S. V. *Tetrahedron Lett.* **1986**, *27*, 105. (b) Evans, D. A.; Bender, S. L.; Morr, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(10) The low value of the integral for the methyl in the acetone is interpreted by its conversion to aldolic condensed products in the HBr medium formed. Although the equilibrium

$$\text{HX} + \text{X}_n\text{Ti(O-i-Pr)}_{4-n} \rightleftarrows \text{X}_{n+1}\text{Ti(O-i-Pr)}_{3-n} + \text{i-PrOH}$$

is well known,[11] we have not observed 2-propanol in our NMR experiments.

(11) McAuliffe, C. A.; Barrat, D. S. *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1987; Vol. 3, p 333.

(12) The exact stereochemistry of this compound has not yet been completely established. Añorbe, B.; Nuñez, M. T.; Martín, V. S., unpublished results.

An Intramolecular Diels–Alder Approach to the Synthesis of Chlorothricolide. Synthesis of (±)-24-*O*-Methylchlorothricolide

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Received April 3, 1990

Summary: Cycloaddition of α-(acyloxy)-γ-methylene-β-tetronate **16**, obtained by condensation of three segments ((±)-**11**, **12**, and **15**), affords four diastereomeric macrolides **17a–d** (1:2.8:1.9:0.9 ratio). The exo mode adduct **17a** has been converted to (±)-24-*O*-methylchlorothricolide (**19**).

Chlorothricolide (**1**) is the aglycon of antibiotic chlorothricin isolated from the culture of *Streptomyces antibioticus* in 1969.[1] This structurally novel macrolide as well as the closely related aglycons, tetronolide (**2**)[2] and kijanolide (**3**),[3] have long been highly attractive targets for total synthesis. In spite of extensive efforts[4] directed toward the synthesis of **1**, including pioneering works by Ire-

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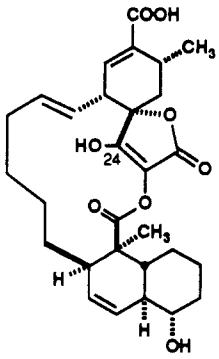
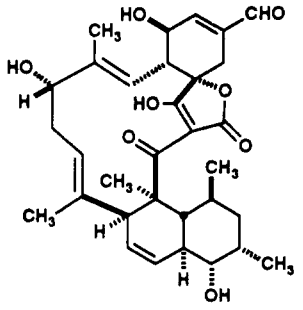
0022-3263/90/1955-3431$02.50/0

land[4e,m-p] and Roush,[4b,j,l] its total synthesis has not been reported to date. Herein we describe the first synthesis of (±)-chlorothricolide as its 24-*O*-methyl derivative **19**.



1



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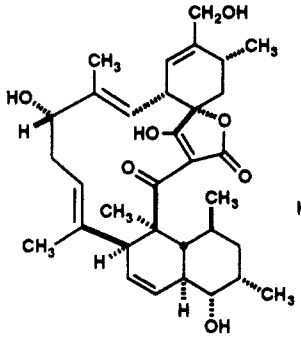

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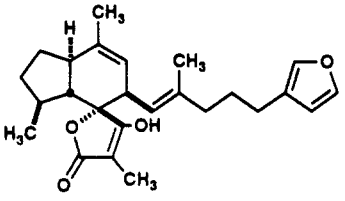
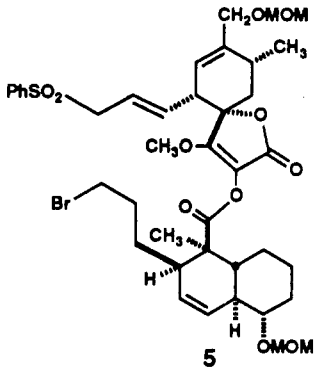


4

For the synthesis of the macrolide structure, we first investigated[5] an internal alkylation of a bifunctional intermediate **5**[6] prepared via connection of an α-hydroxy-spirotetronate (top half) and an appropriate octalin carboxylic acid (bottom half). Unfortunately, however, treatment of **5** with various bases resulted in extensive degradation of the spirotetronate nucleus, although the top half sulfone **6**[6] was uneventfully alkylated with ethyl bromide. We therefore turned our attention to an intramolecular Diels–Alder (IMDA) reaction of γ-methylene-β-tetronate derivative **16**, by which simultaneous construction of the macrolide and spirotetronate structures would be achieved.[7] We had utilized the same IMDA technique for the total synthesis of ircinianin (**4**),[8] a marine sponge sesterterpene, and an intermolecular version in the synthesis[4a,9] of functionalized top halves of **1** and **3**.



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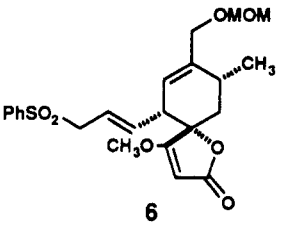

6

The IMDA substrate **16** (racemic) was prepared as follows. Cycloaddition of hexatrienal **7**[4d] in refluxing toluene in the presence of $Yb(fod)_3$ (0.01 equiv) afforded in 87% yield a mixture of four stereoisomeric octalins (**8a**/**8b**/**9a**,**b** = 2.2:1:1.4). These diastereomers could be separated by MPLC, but much better separation for the desired trans-fused epimer (eq-OMOM) was obtained after conversion to the corresponding carboxylic acids by $NaClO_2$ oxidation[10] and then esterification with CH_2N_2 to give **10a** in 29% yield from **7** (16% for **10b**). Compound **10a** was then converted to aldehyde **11** in 79% yield by debenzylation (H_2, Pd–C, EtOH–HCl) followed by oxidation with pyridinium chlorochromate. A *n*-BuLi-mediated Horner–Emmons reaction of **11** with dienyl phosphonate **12**[11] provided triene **13** in 60% yield as a 1.1:1 mixture of 9′*Z*/9′*E* isomers. The mixture, which was difficult to separate, was used for the next step, since it has been found that *Z*/*E* isomerization of the terminal olefin occurs during the key IMDA reaction of **16**. The carboxylic acid **14** obtained by saponification of **13** (20% KOH in MeOH–H_2O, reflux) (95% yield based on the recovered ester) was treated with α-hydroxy-γ-methylenetetronate **15**[4a] in the presence of DCC and DMAP,[12] affording **16** in 54% yield.

The IMDA reaction of **16** was carried out by heating in

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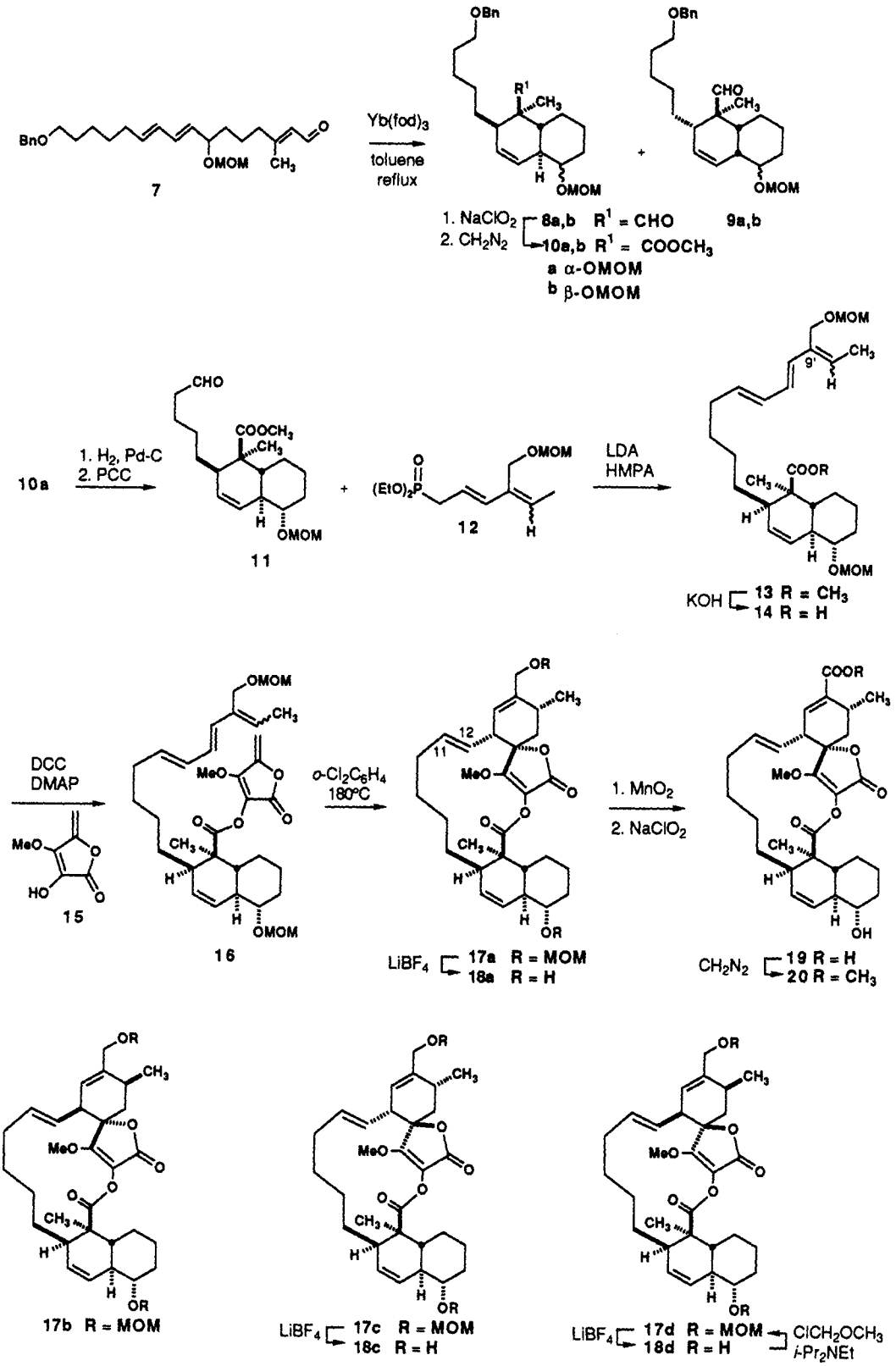
(11) This compound was prepared by phosphorylation of 4-[(methoxymethoxy)methyl]-2,4-hexadienol derived from methyl 4,5-dihydroxy-2-pentenoate:[7c] (a) Reaction of its *p*-toluenesulfonate with $(EtO)_2PONa$ (69%, 4*E*/4*Z* = 1:6.0). (b) Bromination with NBS and Me_2S in CH_2Cl_2 followed by Arbuzov reaction with $(EtO)_3P$ at 120 °C (ca. 60%, 4*E*/4*Z* = 1:1.7–3.8). Stereochemical outcome in the ensuing Horner–Emmons reaction was essentially independent of the *E*/*Z* ratios of **12**.

Scheme I[6]



o-dichlorobenzene at 180 °C for 7.5 h to afford a mixture of four cycloadducts, from which the desired exo mode adduct **17a** was isolated by MPLC in 9% yield. The stereostructure of **17a** was assigned on the basis of ^{1}H NMR analysis, the chemical shifts and coupling constants of the macroring olefin protons being quite similar to those reported for 24-*O*-methylchlorothricolide methyl ester (**20**).[13] Rechromatography of the remaining diastereomeric mixture (**17b**/**17c**/**17d** = 3:2:1) (51% combined yield) provided endo adduct **17b**, and a mixture of **17c** (endo adduct) and **17d** (exo adduct) which could be separated after removal

(12) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475–4476.

(13) **17a**: δ 5.39 (H-11, ddd, *J* = 15.2, 8.3, 4.0 Hz), 5.13 (H-12, dd, *J* = 15.2, 8.3 Hz). **20**:[1b] δ 5.41 (H-11, ddd, *J* = 15, 8, 3.5 Hz), 5.15 (H-12, dd, *J* = 15, 8 Hz).

of the MOM protecting group by Lipshutz procedure.[4e,14] The stereochemistries of these three diastereomers were determined by X-ray crystallographic analysis. The observed endo preference (**17a,d/17b,c** = 1:2.4), which is essentially independent of E/Z ratio of the precursor **16** and the reaction conditions, can be explained by secondary orbital interactions as observed in intermolecular version and/or less predictable conformational factors.

Finally, reaction of **17a** with $LiBF_4$ in aqueous MeCN at reflux for 10 h afforded diol **18a** in 73% yield. The diol was transformed into (±)-24-*O*-methylchlorothricolide (**19**) by sequential oxidation with active MnO_2 and $NaClO_2$. The stereostructure was confirmed by X-ray crystallographic analysis of the methyl ester **20** (CH_2N_2).

In conclusion, the first synthesis of (±)-24-*O*-methylchlorothricolide has been achieved. Although the key internal cycloaddition (**16** to **17a**) is not efficient in terms of diastereofacial selectivity, we believe that simplicity of the overall scheme compensates for the drawback.

Supplementary Material Available: Complete experimental procedure including copies of ^1H NMR spectra, X-ray crystallographic data, and ORTEP drawings for compounds **17b**, **17d**, **18c**, and **20** (37 pages). Ordering information is given on any current masthead page.

(14) Lipshutz, B. H.; Harrey, D. F. *Synth. Commun.* **1982**, *12*, 267-277.

Nucleophilic Cleavages of One-Electron σ Bonds Are Predicted To Proceed with Stereoinversion

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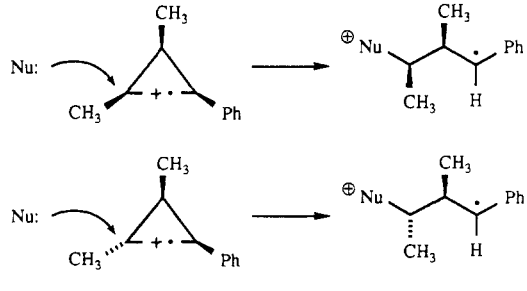
Received January 26, 1990

Summary: The valence-bond curve crossing model is used to analyze the stereochemistry of nucleophilic displacements on one-electron σ bonds. The model predicts that the stereochemistry of cleavage of one-electron σ bond by nucleophiles will be governed by the σ* orbital of the one-electron bonds. As a result such nucleophilic cleavages are predicted to proceed with inversion of stereochemistry at the center of attack. This prediction is in accord with recent experimental findings.

The cation radicals of several arylcyclopropanes have recently been generated by photooxidation and found to undergo cyclopropane ring cleavage in the presence of a variety of nucleophiles.[1] As previously suggested, these reactions can be rationalized as nucleophilic displacements on one-electron σ bonds. A stereochemical analysis of these reactions has shown that they occur with essentially complete inversion of configuration at the carbon atom undergoing nucleophilic substitution.



These stereochemical results are surprising because according to *perturbational* MO reasoning, both the SOMO σ orbital and the LUMO σ* orbital of the one-electron bond are capable of undergoing orbital interactions with the nucleophile, and with no obvious a priori preference for either one of these orbitals. At the simplest qualitative level, the number of electrons in the interaction (two vs three) will prefer the HOMO(Nu)–LUMO(σ*) interaction while the orbital energy gap factor will prefer the HOMO(Nu)–SOMO(σ) interaction. Therefore, no clear cut general prediction can be made about the stereospecificity of these nucleophilic reactions. Understanding the origins of this stereospecificity is thus required along with an analysis of the expected stereochemistry in the broader area of nucleophilic displacements on one-electron σ bonds.[2]

A theoretical model for nucleophilic attacks on cation radicals has recently been proposed by Pross based upon valence-bond curve crossing diagrams.[3] This model has subsequently been criticized,[4] and, despite a rebuttal of the main critical points,[5] there still exist doubts about the usefulness of the model.[6] The secondary purpose of this paper is to reclaim the usefulness of the curve crossing model by projecting the insight it provides onto the problem of stereospecificity in nucleophilic cleavages of one-electron σ bonds. As will be shown, the model predicts that the course of a nucleophilic cleavage of a one-electron σ bond is governed by the σ* orbital of the one-electron bond. As a result such nucleophilic cleavages *are predicted*

† Ben-Gurion University.
‡ University of Rochester.
§ Fellow of the Alfred P. Sloan Foundation, 1988-1990.

(1) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462.
(2) Nucleophilic cleavages of one-electron σ bonds in several silane cation radicals have recently been observed: Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P.; Mattes, S. *J. Am. Chem. Soc.* **1989**, *111*, 8973. The stereochemistries of these cleavages are not yet known.
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