ondary orbital overlaps involving the nitrogen atom of the 1,3-dipole give rise to a higher destabilization of the endo form of $\simeq$0.5 kcal mol^{-1} with respect to the exo orientation whereas electrostatic effects appear to favor endo orientation and, on the whole, the two oriented complexes have quite similar total energies.[14] Destabilization of the endo form as a result of secondary overlap can be attributed, in PMO terms, to a prevalence of closed-shell repulsions over filled-unfilled attractive interactions.

The present data and previous findings[3-5,15] allow us to conclude that: (i) high endo diastereoselectivity cannot be achieved even in the reaction of sterically low demanding nitrones with electron-poor *Z* dipolarophiles, (ii) factors which favor endo orientation in 1,3-dipolar cycloadditions are still to be clearly identified.[16] In this connection it should be stressed that the very same statement seems to hold for the Diels-Alder reaction. In fact, the role of secondary orbital interaction as major endo orienting factors has recently been questioned.[17]

Additional experiments are in progress as well as more sophisticated computational studies in an attempt to shed some light on the elusive endo-orienting factors.

Acknowledgment. We thank the Ministero della Pubblica Istruzione and CNR for financial support.

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(13) Mc Douall, J. J. W.; Robb, M. A.; Niazi, U.; Bernardi, F.; Schlegel, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 4642.

(14) The parent nitrone was used in order to have a system in which the only secondary orbital interaction is that involving the nitrogen atom of the nitrone. The electrostatic effect has been estimated by the difference between the total energy of the oriented complex (where the intermolecular delocalization had been suppressed by removing all the intermolecular overlap integrals) and the energy of the separated molecules. Likewise, the effect of secondary interactions between the π-orbital of the nitrogen atom of the dipole and the π-system of the dipolarophile has been estimated by removing the corresponding overlap integrals. For C-INDO procedure, see: Momicchioli, F.; Baraldi, I.; Bruni, M. *Chem. Phys.* **1982**, *70*, 161.

(15) Burdisso, M.; Gamba, A.; Gandolfi, R.; Pevarello, P.; Oberti, R. *Tetrahedron* **1988**, *44*, 3735 and references cited therein. See also: Asrof Ali, S.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 597.

(16) Aside from electrostatic and van der Waals forces, steric repulsions, and secondary overlap interactions, primary overlaps (Baldwin, J. E.; Prakash Reddy, V. *J. Org. Chem.* **1989**, *54*, 5264 and references cited therein) can also play a role in determining endo/exo selectivity in gas phase. In solution also solvent "polarity" effects (due to internal pressure, solvation ability, etc.) come into play.

(17) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129 and references cited therein. Sodupe, M.; Oliva, A.; Bertran, J.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 2488. Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mugnoli, A.; Abbondanti, E. *J. Org. Chem.* **1985**, *50*, 1853. Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172.

Mild and Stereocontrolled Synthesis of Iodo- and Bromohydrins by X_2–Ti(O-i-Pr)$_4$ Opening of Epoxy Alcohols

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Summary: A mild procedure to obtain halo diols by opening epoxy alcohols with halogen is described. The method is based on the use of Ti(O-i-Pr)$_4$ and the suitable halogen over allylic and homoallylic epoxy alcohols, affording high regioselectivities and yields. Reaction with enantiomerically enriched epoxides leads selectively to chiral halohydrins.

In the course of our synthetic studies directed toward the enantioselective total synthesis of marine natural compounds[1] containing polyfunctionalized cyclic ethers,[2] we have been very interested in the possibility of using chiral vicinal iodo- or bromohydrins as fragments to further produce cyclization in an electrophilic manner.[3] An attractive way to achieve this goal could be the regioselective opening of epoxides, having in mind the availability of 2,3-epoxy alcohols by asymmetric epoxidation of the suitable allylic alcohol,[4] in which case chiral compounds would be obtained. Few reagents are known to convert epoxy alcohols to halohydrins.[5,6] We now report that the treatment of allylic and homoallylic epoxy alcohols with an equivalent amount of halogen (Br_2, I_2) in presence of a stoichiometric amount of Ti(O-i-Pr)$_4$ provides a mild procedure to synthesize halohydrins with a high degree of generality, mildness, and regioselectivity (Table I).[7]

The regioselectivity and purities of the resulting halo diols obtained with the addition of Ti(O-i-Pr)$_4$ are markedly greater than those obtained in the absence of the metal mediation. When epoxy alcohol 1 was treated with iodine or bromine, at room temperature, a 1:1 mixture of

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(1) Erickson, R. E. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1986; Vol. V, p 131.

(2) (a) Nuñez, M. T.; Rodríguez, M. L.; Martín, V. S. *Tetrahedron Lett.* **1988**, *29*, 1979. (b) Tonn, C. E.; Palazón, J. M.; Ruiz-Pérez, C.; Rodriguez, M. L.; Martín, V. S. *Tetrahedron Lett.* **1988**, *29*, 3149. (c) Alvarez, E.; Manta, E.; Martín, J. D. *Tetrahedron Lett.* **1988**, *29*, 2093.

(3) Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411.

(4) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martín, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

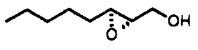
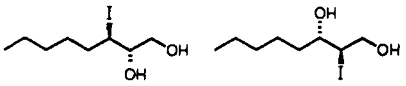
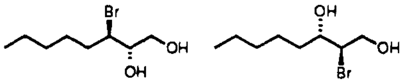
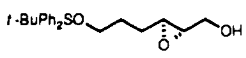
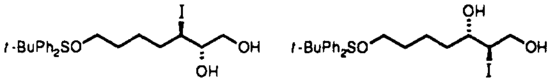
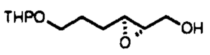
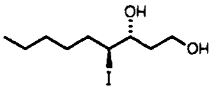
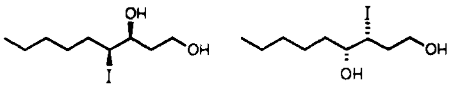
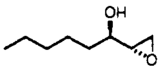
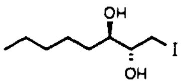
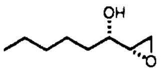
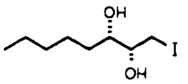
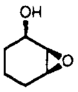
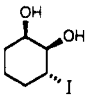
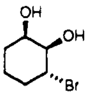
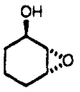
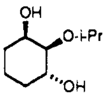
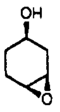
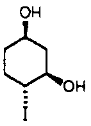
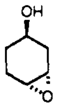
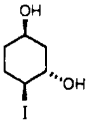
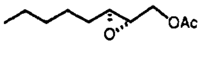
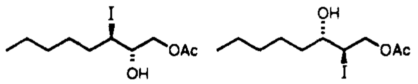
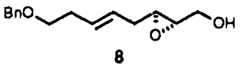
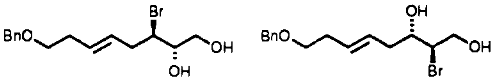
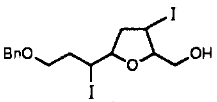
(5) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

(6) (a) Lu, L. D.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 731. (b) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173. (c) While this work was being written up, a recently published communication reported that dialkylamine hydrohalides, Ti(O-i-Pr)$_4$-mediated ring openings of 2,3-epoxy alcohols at the 3-position have been performed efficiently: Gao, L.; Murai, A. *Chem. Lett.* **1989**, 357.

(7) In a typical experiment, to a stirred solution of iodine (or bromine) (1.1 mmol) in 10 mL of dry dichloromethane (methanol-fre) were sequentially added Ti(O-i-Pr)$_4$ (1.2 mmol) [smaller values on the regioselectivities have been obtained when less than 1 equiv of Ti(O-i-Pr)$_4$ was used] and the epoxy alcohol (1.0 mmol) dissolved in 2 mL of CH_2Cl_2, under inert atmosphere at 0 °C.[8] The reaction was stirred at the temperature and for the time indicated in Table I. After the reaction was completed (TLC) 15% aqueous tartaric acid solution (20 mL) [in most cases dilute H_2SO_4 (5%) equally suitable] and solid $NaHSO_3$ (500 mg) were added with vigorous stirring until clear phases were reached. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) (with some CH_2Cl_2 insoluble halo diols, EtOAc may be more convenient as extracting solvent), and the combined organic phases washed with saturated $NaHCO_3$ solution (20 mL) and saturated brine (20 mL), dried ($MgSO_4$), and concentrated to afford a crude reaction mixture containing the desired halo diols, which were purified by column chromatography.

0022-3263/90/1955-3429$02.50/0

Table I. Ring-Opening Reaction of Epoxy Alcohols with X_2–Ti(O-i-Pr)$_4$

entry	starting epoxy alcohol	X_2	reactn time, h	temp, °C	products[a] (ratio)	combined yields,[b] %
1	 1					
		I_2	0.5	0	(7:1)	89[c]
		I_2	0.5	25	(1:1)	–[c–e]
						
		Br_2	2	0	(15:1)	78[c]
		Br_2	2.5	25	(1:1)	–[c–e]
2	 2					
		I_2	0.5	0	(7:1)	85[c]
3	 3	I_2	0.5	0	nonisolable product	–[c]
		Br_2	0:5	0	nonisolable product	–[c]
4		I_2	5	0		80[f]
5						
		I_2	3	0	(1:1)	80
6		I_2	0.5	0		63[c,f]
7		I_2	0:5	0		73[c,f]
8	 4	I_2	4	20–25		80[f]
		Br_2	4	20–25		73[f]
9	 5	I_2	4	20–25	 6	73[f]
		Br_2	4	20–25		52[g]
		–	4	20–25		82[f,h]
10		I_2	4	20–25		82[f]
11		I_2	4	20–25		78[f]
12						
		I_2	0.5	0	(1:1)	–[c,e]
13	 8					
		Br_2	2	0	9 (>20:1)	83[c,i]
		I_2	4	0	 10	75[c,f,i]

[a] The ratio has been determined by ^1H NMR analysis of the peracetylated products. [b] Isolated yields which have not been optimized. [c] Used in enantiomeric form. [d] No Ti(O-i-Pr)$_4$ was used in the reaction. [e] Contaminated with unreacted epoxyalcohol and/or unidentified substances. [f] Only one isomer was detected. [g] The isopropyl ether was the major product observed, although two more unidentified product containing bromine were observed. [h] No halogen was used in the reaction. [i] Ti(O-i-Pr)$_4$–X_2 mixture was aged before the epoxy alcohol was added.

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

$$\mathrm{Ti(O\text{-}i\text{-}Pr)_4} + x\mathrm{Br_2} \rightarrow \mathrm{Br}_x\mathrm{Ti(O\text{-}i\text{-}Pr)}_{4-x} + x\mathrm{HBr} + x\underset{\mathbf{7}}{\mathrm{(CH_3)C{=}O}}$$

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$_2$Cl$_2$) 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.

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[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

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

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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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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[†] Showa University.