molecular weight (126) has, however, encountered difficulties. Various molecular weight determinations have yielded differing results. Early work using the Rast method revealed a value of 165.[1] By osmometry, a freshly prepared sample yielded a value of 131.[1] Mass spectrometry methods repeatedly suggested m/z 98 as the molecular ion corresponding to $C_5H_6O_2$.[3,13] Domburgs et al.[13] reported a peak at m/z 126 when the mass spectrometry analyses were conducted with fresh samples obtained by preparative gas chromatography. Aged samples revealed m/z 98 as the ion of highest mass.

We have concluded that the reactive nature of this compound has complicated its analysis. Since mass spectrometry analyses have not been definitive, we experimented with combined gas chromatography–mass spectrometry (GC–MS) using both electron impact and chemical ionization techniques. It is the purpose of this note to publish the methodology, the electron and chemical ionization data, and the elemental compositions determined by accurate mass measurements.

Results and Discussion

Mass spectra were consistent with the structure of levoglucosenone (**1**). Measurements made by using high resolution techniques revealed an accurate mass of 126.0327 for the molecular ion corresponding to an empirical formula of $C_6H_6O_3$. The base peak ($C_5H_6O_2$) yielded an accurate mass of 98.0381. The errors in measurement were 12 ppm and 9 ppm, respectively. The neutral loss of 27.9946 corresponds to the elimination of carbon monoxide. The molecular weight of 126 was established by the molecular ion m/z 126 in the 70-eV spectrum and by the protonated molecular ion m/z 127 in the chemical ionization spectra. The quasimolecular ion m/z 127 resulted from a proton donation by the isobutane reagent ion $C_4H_9^+$.

In conclusion, we have shown that the molecular weight of levoglucosenone is indeed 126 and can be determined accurately by GC–MS techniques. The mass spectra recorded in this work support the accepted structure for levoglucosenone and add an important proof to its identity.

Experimental Section

Preparation of Levoglucosenone. For the reported study, levoglucosenone was prepared by the pyrolysis of kraft paper. The paper was moistened with a solution of 5% phosphoric acid and placed in a glass tube continually purged with helium. The tube was heated to 300 °C. The tar fraction of interest was protected from light, taken up in chloroform, and immediately analyzed.

Mass Spectrometry Analyses. The data reported herein were obtained on a VG Analytical Model 7350 (70/70) mass spectrometer and a Hewlett-Packard Model 5840 gas chromatograph. Using splitless injection, the samples were analyzed on SE-54 capillary columns. The columns were 25-m fused silica having an internal diameter of 0.3 mm. These columns were siloxane deactivated and coated with SE-54 at a phase ratio of 150. The temperature program involved an initial temperature of 50 °C with a 5-min hold followed by a 10 °/min program to 250 °C. The retention time observed for the levoglucosenone under these conditions was 9.8 min. This retention time corresponded to 288 scans. Mass spectra were recorded by using electron ionization (70 eV) and also by chemical ionization with isobutane as the reagent gas.

Acknowledgment. Helpful comments by Dr. Edward Leon are gratefully acknowledged.

Registry No. 1, 37112-31-5.

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Communications

$Ti(O\text{-}i\text{-}Pr)_4$-Mediated Nucleophilic Openings of 2,3-Epoxy Alcohols. A Mild Procedure for Regioselective Ring-Opening

Summary: The presence of $Ti(O\text{-}i\text{-}Pr)_4$ during the openings of 2,3-epoxy alcohol 1 with a variety of nucleophiles markedly increases the rates and regioselectivities of these processes. The magnitude of these effects was found to be nucleophile dependent.

Sir: The facility and selectivity of enzymic reactions is often attributed to the efficient preassembly of the reactants in a highly ordered manner. Juxtaposition of reactants through their coordination to the same metal center has provided an effective nonenzymic approach for achieving similar rate and selectivity benefits. This strategy is well exemplified by rhodium-catalyzed asymmetric hydrogenation[2] and by titanium-catalyzed asymmetric epoxidation.[3] The latter process depends crucially on the facile exchange of titanium alkoxides with alcohols in solution. In 1981 we reported that early transition-metal alkoxides, especially $Ti(OR)_4$, can also effect highly selective intramolecular rearrangements of certain epoxy alcohols.[4,5] These results were rationalized by invoking

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(1) Holder of a NSERC postdoctoral fellowship (1982–1984).

(2) Halpern, J. *Science (Washington, D.C.)* **1982**, *217*, 401 and references cited therein.

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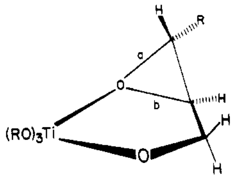
Table I. Nucleophilic Openings of 3-Propyloxiranemethanol (1)[a]

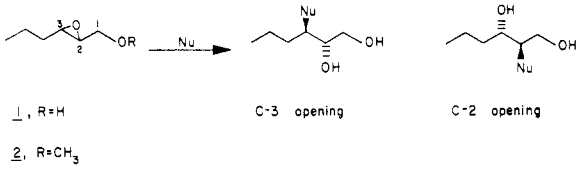
entry	nucleophile	$Ti(O\text{-}i\text{-}Pr)_4$ equiv	reaction conditions	regioselectivity (C-3/C-2)[b,c]	yield, %
1	Et_2NH	0	Et_2NH (excess), reflux, 18 h	3.7/1	4[d,g]
2	Et_2NH	1.5	Et_2NH (excess), rt,[n] 5 h	20/1	90[g]
3	$(allyl)_2NH$	1.5	$(allyl)_2NH$ (excess), rt, 3 h	100/1[e]	96[g]
4	$n\text{-}BuNH_2$	1.5	$n\text{-}BuNH_2$ (excess), rt, 16 h, then reflux 2 h		0[o]
5	*i*-PrOH	0	*i*-PrOH (excess), reflux, 18 h		0[f]
6	*i*-PrOH	1.5	*i*-PrOH (excess), reflux, 18 h	100/1[e]	88[h]
7	allyl alcohol	1.5	allyl alcohol (excess), reflux, 30 min	100/1[e]	90[h]
8	PhSH	0	PhSH (5.0 equiv), benzene, rt, 22 h		0[f]
9	PhSH	1.5	PhSH (1.6 equiv), benzene, rt, 5 min	6.4/1	95[h]
10	PhSeH	1.5	PhSeH (1.6 equiv), benzene, rt, 5 min	6.4/1	95[h]
11	PhSNa	0	PhSNa (2.4 equiv), PhSH (2.4 equiv), benzene, rt, 2 h 30 min	7.0/1	85[h]
12	PhSNa	1.5	PhSNa (2.0 equiv), PhSH (2.0 equiv), benzene, rt, 5 min	9.0/1	68[h,j]
13	Me_3SiN_3	0	Me_3SiN_3 (3.0 equiv), benzene, reflux, 3 h		0[k]
14	NaN_3	0	NaN_3 (5.0 equiv), NH_4Cl (2.2 equiv), $MeOH/H_2O$ (8/1), reflux, 7 h	5.8/1	95[h]
15	Me_3SiN_3	1.5	Me_3SiN_3 (3.0 equiv), benzene, reflux, 3 h	14/1	74[h]
16	Me_3SiCN	0	Me_3SiCN (3.0 equiv), DME, reflux, 5 h		0[k]
17	Me_3SiCN	1.5	Me_3SiCN (3.0 equiv), DME, reflux, 24 h	4.9/1	32[h]
18	KCN	0	KCN (2.0 equiv), Bu_4NI (1.6 equiv), Me_2SO, rt, 72 h		0[f]
19	KCN	2.2	KCN (2.0 equiv), Bu_4NI (1.6 equiv), Me_2SO, rt, 72 h	1.3/1	91[h]
20	KCN	1.7	KCN (2.0 equiv), 18-crown-6 (2.0 equiv), benzene, rt, 72 h	2.4/1	76[h]
21	NH_4Cl	1.5	NH_4Cl (2.0 equiv), Me_2SO, rt, 15 min	2.8/1	84[h]
22	NH_4Cl	1.5	NH_4Cl (2.0 equiv), THF, rt, 40 h	3.0/1	71[i]
23	NH_4Cl	0	NH_4Cl (2.0 equiv), Me_2SO, rt, 18 h		0[j]
24	NH_4Br	1.5	NH_4Br (1.5 equiv), THF, rt, 40 h	3.0/1	73[i]
25	NH_4SCN	1.5	NH_4SCN (1.5 equiv), THF, rt, 15 min	5.6/1	71[i]
26	NH_4OBz	1.5	NH_4OBz (1.5 equiv), THF, rt, 15 min	100/1[e]	74[i]
27	NH_4OAc	1.5	NH_4OAc (1.5 equiv), THF, rt, 15 min	65/1[l]	73[i]
28	PhCOOH	1.2	PhCOOH (1.1 equiv), CH_2Cl_2, rt, 15 min	100/1[e]	74[h]
29	*t*-BuCOOH	1.5	*t*-BuCOOH (1.3 equiv), benzene, rt, 15 min	100/1[e]	59[h]
30	LPTS	1.2	LPTS (1.05 equiv), CH_2Cl_2, rt, 15 min	100/1[e]	64[h,m]

[a] All reactions (except entry 14) were carried out under exclusion of moisture and oxygen (nitrogen or argon). In a typical experiment $Ti(O\text{-}i\text{-}Pr)_4$ is added to a 0.10–0.15 M solution of the epoxy alcohol containing the desired nucleophile (except for entries 11 and 12 where the epoxy alcohol is added to the reaction mixture). Reaction was monitored by TLC, and, when complete, worked up according to the type of nucleophiles used: (i) Entries 1–4, reaction mixture is diluted with Et_2O and 10% NaOH in brine is added. The resulting milky solution is stirred vigorously for 5–15 h and then filtered through a pad of Celite (CH_2Cl_2 rinse), dried, and concentrated. (ii) Entries 5–27 (except entry 14), reaction mixture is diluted with Et_2O and 5% H_2SO_4 is added. The two-phase mixture is stirred vigorously until two clear layers form (1–5 h) and then extractive workup is performed. Benzene is generally removed prior to dilution with ether. In the presence of tetraalkylammonium salts two clear layers do not form. (iii) Entry 14, reaction mixture is concentrated and passed through a short silica gel column to remove the inorganic salts. [b] The assignment of the ratio was based on the ^1H NMR (250 MHz) analysis of the unpurified reaction mixture after peracetylation. [c] ^1H NMR analysis (250 MHz) on the purified reaction mixture after peracetylation was required for entries 17, 19, and 20. [d] The rest is starting material. [e] Only one isomer detected by ^1H NMR (250 MHz). [f] No reaction, starting material was recovered. [g] Yield based on purified peracetylated products. [h] Yield based on purified opened products. [i] Yield based on unpurified opened products. [j] Experiment performed by K. S. Kirshenbaum. [k] No reaction, silylated starting material was recovered. [l] Based on the optical rotation of the corresponding triol. [m] This reaction is accompanied by formation of the 3-isopropyl ether 1,2-diol (10% yield). [n] rt = room temperature. [o] A complex mixture was obtained.

Scheme I



Scheme II



coordination of the epoxy alcohol to the metal center in the rigid, bidentate manner depicted in Scheme I. Enforced propinquity assured by the hydroxyl renders this coordination likely, even though epoxides are weak Lewis bases and titanium alkoxides are weak Lewis acids. We now report that coordination of epoxy alcohols to metal alkoxides also greatly facilitates their opening reactions with intermolecular[6] nucleophiles. Moreover, in the presence of the metal alkoxide, most of these external nucleophiles show a very strong preference for attack at C-3 of the epoxy alcohol (Scheme II).[7–9] For this study

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(5) For a recent interesting example of a metal alkoxide catalyzed rearrangement of an epoxy alcohol, see: (a) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731. (b) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455. See also: Fujiwara, S.; Aoki, M.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1984**, *25*, 3003.

(6) We do not yet know whether any of these opening processes are truly intermolecular (i.e., bimolecular). Some of them (e.g., the amine openings) probably are bimolecular but others may well involve metal alkoxide clusters wherein a nucleophile coordinated to one metal is delivered to an epoxy alcohol coordinated to an adjacent metal center.

(7) The ability of different transition-metal alkoxide species to change the regioselectivity of an epoxy alcohol opening was first noted in our laboratory by Dr. Roy A. Johnson, see ref 16 in Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.

(8) For other cases where nearby hydroxyls have been shown to affect the regioselectivity of epoxide opening processes; see: (a) Glotter, E.; Greenfield, S.; Lavie, D. *Tetrahedron Lett.* **1967**, *8*, 5261. (b) Hartman, B. C.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 4246. (c) Danishefsky, S.; Tsai, M.-Y.; Katahara, T. *J. Org. Chem.* **1977**, 42, 396 and references cited therein. (d) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597 and references cited therein. (e) Matthews, R. S.; Mihelich, E. D.; McGowan, L. S.; Daniels, K. *J. Org. Chem.* **1983**, *48*, 409. (f) Gassman, P. G.; Gremban, R. S. *Tetrahedron Lett.* **1984**, *25*, 3259. (g) For the opening of an epoxy alcohol with Et_2AlCN, see ref 19.

3-propyloxiranemethanol (1)[10] was chosen as the substrate and Ti(O-*i*-Pr)$_4$ as the metal alkoxide. Ring-opening of epoxy alcohol 1 occurs under mild conditions with a wide variety of nucleophiles in the presence of Ti(O-*i*-Pr)$_4$. The results are presented in Table I. We have also found that, under otherwise identical reaction conditions, no ring-openings occur when Ti(O-*i*-Pr)$_4$ is omitted except in the case of the powerful nucleophile PhSNa (entry 11).

Our study first focused on the utilization of an amine as nucleophile. When epoxy alcohol 1 is refluxed for 18 h in neat Et$_2$NH, only 4% of the starting material is consumed (entry 1). The opened products show a ratio of 3.7/1 of C-3 to C-2 isomer.[11] However, in the presence of 1.5 equiv[12] of Ti(O-*i*-Pr)$_4$, the reaction goes to completion in 5 h at room temperature. An overall yield of 90% is obtained after acetylation of the amino diols and an enhanced regioselectivity of C-3 to C-2 products (20/1) is observed by ^{1}H NMR analysis (entry 2). Opening of 1 by diallylamine (entry 3) in the presence of Ti(O-*i*-Pr)$_4$ gave a 96% yield of the corresponding amino diol, and the C-3 opened product was now the only isomer detected by ^{1}H NMR analysis. The essential involvement of the hydroxyl group of epoxy alcohol 1 in the reaction was revealed by the following control experiment. Methyl ether 2 was subjected to standard opening conditions (Et$_2$NH, 1.5 equiv of Ti(O-*i*-Pr)$_4$, 5 h, room temperature) and found to undergo no reaction. An attempt with a primary amine (*n*-BuNH$_2$, entry 4) required more vigorous conditions (16 h, room temperature, then 2-h reflux) and the ^{1}H NMR analysis of the acetylated opened products revealed a complex mixture, presumably resulting from the polyalkylation of the amine.

We have also examined the opening of 1 by alcohols and thiophenol. Entries 6 and 7 of Table I show that when an alcohol is used as the nucleophile a highly regioselective ring-opening takes place. Refluxing the epoxy alcohol in isopropyl alcohol (18 h) or allyl alcohol (30 min) in the presence of 1.5 equiv of Ti(O-*i*-Pr)$_4$ gave only the C-3 opened products in 88% and 90% yield, respectively. Without Ti(O-*i*-Pr)$_4$ no reaction occured when 1 was refluxed in isopropyl alcohol for 18 h (entry 5). Much greater reactivity for Ti(O-*i*-Pr)$_4$-mediated ring-opening is exhibited by thiophenol (entry 9). Epoxy alcohol 1 reacted with 1.6 equiv of PhSH and 1.5 equiv of Ti(O-*i*-Pr)$_4$[13] in benzene at room temperature within 5 min, affording a 95% yield of the sulfide diols. Unfortunately, and in contrast to the amine or alcohol openings, the regioselectivity of the thiophenol reaction was only 6.4/1 in favor of the C-3 isomer.[15] The uncatalyzed reaction revealed no ring-opening after 22 h at room temperature using 5 equiv of PhSH (entry 8). Entry 10 shows that selenophenol can be substituted for thiophenol to give identical regioselectivity in the presence of Ti(O-*i*-Pr)$_4$. We have also observed that in the absence of Ti(O-*i*-Pr)$_4$, ring-opening with sodium benzenethiolate proceeds at room temperature in benzene in 2.5 h (entry 11). The regioselectivity of the reaction is similar to the PhSH/Ti(O-*i*-Pr)$_4$ opening, giving a ratio of C-3 to C-2 isomers of 7.0/1. When the benzenethiolate ring-opening was repeated in the presence of Ti(O-*i*-Pr)$_4$, reaction time was shorter (5 min) and the regioselectivity only slightly better (C-3 to C-2 = 9.0/1, entry 12).

Azide and cyanide are also effective nucleophiles under Ti(O-*i*-Pr)$_4$-mediated conditions. Refluxing 1 in benzene with 3.0 equiv of Me$_3$SiN$_3$ and 1.5 equiv of Ti(O-*i*-Pr)$_4$ for 3 h gave a 74% yield of the azido diols in a C-3 to C-2 ratio of 14/1 (entry 15). Again, a control experiment indicated that without Ti(O-*i*-Pr)$_4$ there is no ring-opening, and silylated starting material is recovered (entry 13). For comparison we have opened 1 with azide without metal alkoxide assistance (NH$_4$N$_3$, MeOH/H$_2$O, 7-h reflux)[16] (entry 14) and observed that the C-3 to C-2 ratio decreased to 5.8/1. Again, the presence of the metal alkoxide increases both the rate and the regioselectivity of the reaction.[17] Entry 17 shows that the titanium-catalyzed cyanide opening of 1 proceeds differently from the Me$_3$SiN$_3$ opening. When the epoxy alcohol was refluxed for 24 h in DME with 3.0 equiv of Me$_3$SiCN and 1.5 equiv of Ti(O-*i*-Pr)$_4$, many products were formed. After chromatography a mixture of the cyano diols was obtained in 32% yield (C-3 to C-2 ratio = 4.9/1). The use of 2.0 equiv of potassium cyanide, 1.6 equiv of tetrabutylammonium iodide, and 2.2 equiv of titanium isopropoxide in dimethyl sulfoxide affords an excellent yield of cyano diols[18] (91%), but almost no selectivity is observed in this ring-opening (C-3/C-2 = 1.3/1, entry 19). Under different reaction conditions (2.0 equiv of KCN, 2.0 equiv of 18-crown-6, 1.7 equiv of Ti(O-*i*-Pr)$_4$, room temperature, 72 h), a slightly better regioselectivity (C-3/C-2 = 2.4/1, entry 20) was obtained. Entry 18 reveals that starting material was recovered when uncatalyzed cyanide opening was attempted.[19] Thus, the titanium-catalyzed cyanide opening

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[9] This C-3 selectivity nicely complements the intramolecular strategy wherein nucleophiles are delivered selectively to C-2 through attachment to the C-1 hydroxyl (see ref 11a). Dr. Stuart W. McCombie of Schering Corp. has recently developed an efficient method for the intramolecular delivery of a carbon nucleophile to C-2 (private communication from Dr. McCombie).

[10] The homochiral epoxy alcohol (2*S*,3*S*)-3-propyloxiranemethanol can be easily made by asymmetric epoxidation on a 1/4 molar scale. Hill, J. G.; Sharpless, K. B.; Exon, C. M.; Regenye, R. "Organic Syntheses"; Wiley: New York, 1984; Collect. Vol 63, p 66.

[11] Recent work in this laboratory had shown that there is a modest tendency toward regioselective opening at C-3 using external nucleophiles in simple 3-monoalkylsubstituted-2,3-epoxy alcohols (Scheme II). The electron-withdrawing inductive effect of the C-1 hydroxyl group is believed to be responsible for the C-2 deactivation. (a) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* 1983, *16*, 67 and references cited therein. (b) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.*, submitted for publication.

[12] We have verified that the titanium-mediated nucleophilic opening of 2,3-epoxy alcohols requires at least 1.0 equiv of Ti(O-*i*-Pr)$_4$. Under standard conditions starting material was recovered when less than 1.0 equiv was used. Under more vigorous conditions (reflux), starting material was consumed but new side products were formed.

[13] The following metal alkoxides were also effective in the thiophenol-opening of 1: Ta(OEt)$_5$, Al(O-*i*-Pr)$_3$, Lu(O-*i*-Pr)$_3$,[14] Zr(O-*i*-Pr)$_4$·-*i*-PrOH. They showed respectively the following regioselectivity at the C-3 position (CH$_2$Cl$_2$): 1.3/1, 2.4/1, 4.6/1, 8.9/1. In the amine-opening of epoxy alcohols, Zr(O-*i*-Pr)$_4$·-*i*-PrOH was also slightly superior to Ti(O-*i*-Pr)$_4$ (rate/regioselectivity).

[14] Kirshenbaum, K. S., unpublished results. For the preparation of Lu(O-*i*-Pr)$_3$, see: Kirshenbaum, K. S. *Nouv. J. Chim.* 1983, *7*, 699 and references cited therein.

[15] The regioselectivity of this particular reaction was sensitive to the solvent as shown by the following observed C-3/C-2 ratios: pyridine, 0.7/1; isopropyl alcohol and acetonitrile, 1.0/1; methylene chloride, 1.6/1; pentane, 4.2/1.

[16] Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* 1963, 5288.

[17] We have recently found that Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ is a superior reagent for the azide opening of 2,3-epoxy alcohols. For example, addition of 1 to refluxing benzene containing 1.2 equiv of Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ gave an 88% yield of the corresponding azido diols. A C$_3$/C$_2$ ratio of 36/1 was observed. The utilization of this new reagent will be the subject of a future publication. For the preparation and use of Ti(O-*i*-Pr)$_2$(N$_3$)$_2$ for the opening of isolated epoxides, see: (a) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* 1980, 1800. (b) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* 1983, *24*, 4189.

[18] Tetrabutylammonium bromide and tetrabutylammonium cyanide exhibited the same behavior (presumably playing a solid/liquid phase-transfer role) as tetrabutylammonium iodide during the cyanide opening of 1.

proved to be the least selective among all the ring-openings tried.[20]

We have observed in the course of these experiments that the nucleophilic anion of a variety of ammonium salts opened epoxy alcohol 1 when catalyzed by $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$. This is illustrated in entries 21, 22, and 24–27. For example, treatment of 1 with ammonium chloride in dimethyl sulfoxide and 1.5 equiv of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ (15 min, room temperature) gave an 84% yield of the chloro diols. The regioselectivity of the reaction was C-3/C-2 = 2.8/1 (entry 21). A longer reaction time (40 h) was required when the reaction was run in THF (entry 22). The ring-opening using ammonium bromide gave identical results (entry 24). A control experiment shows that no reaction takes place in the absence of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ (entry 23). Ring-opening of 1 by the ambident nucleophile ammonium thiocyanate (THF, room temperature, 15 min) gave the corresponding thiocyanate diols in 71% yield. A C-3 to C-2 isomer ratio of 5.6/1 was observed (entry 25). Ammonium carboxylates (benzoate or acetate) also proved to be competent nucleophiles. Reactions took place in 15 min in THF at room temperature (entries 26 and 27). The acetylated crude material from the benzoate opening showed only the C-3 isomer by ^{1}H NMR analysis. The acetate opening gave a C-3 to C-2 isomer ratio estimated to be 65/1 on the basis of the optical rotation of the corresponding triol (see Supplementary Material section).

Carboxylic acids can be used directly and also exhibit regioselective ring-opening at C-3. The epoxy alcohol reacts within 15 min in CH_2Cl_2 with 1.1 equiv of benzoic acid and 1.2 equiv of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$, affording a 74% yield of the benzoate diol (entry 28). In a similar manner ring-opening of 1 with 1.3 equiv of pivalic acid and 1.5 equiv of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ in benzene gives a 59% yield of the pivalate diol (entry 29). We have also extended our list of nucleophiles to include the tosylate anion: highly regioselective ring-opening at C-3 occurs upon treatment of the epoxy alcohol with 1.2 equiv of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ and 1.05 equiv of 2,6-lutidinium *p*-toluenesulfonate (LPTS) in CH_2Cl_2 for 15 min. A 64% yield of the *p*-toluenesulfonate diol was obtained (entry 30).

Interestingly, the benzoic acid opening (entry 28) and the tosylate opening (entry 30) demonstrate that large excesses of metal alkoxide and/or nucleophile are not required for these openings. In fact, for most of the reactions described here, a stoichiometric amount of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ and nucleophile should suffice to bring the reaction to completion. The amine and alcohol openings, where excess nucleophile is required to achieve reasonable rates, are exceptions.

This study has shown that in the presence of titanium alkoxides, nucleophilic opening reactions of *trans*-2,3-epoxy alcohols occur under extremely mild conditions. Our rationale for these dramatic rate enhancements invokes complexation (via metal alkoxide/hydroxyl group exchange) of the epoxy alcohol to the metal center as shown in Scheme I. While the regioselectivity is generally very good,[21] we cannot yet explain why its magnitude is nucleophile dependent.[22,25] Homochiral 2,3-epoxy alcohols have already proven to be useful in organic synthesis.[23] This new titanium-mediated nucleophilic opening procedure should extend their utility for the synthesis of polyfunctional homochiral organic molecules.

We are presently studying the metal alkoxide assisted openings of the erythro and threo epoxy alcohols which derive from chiral secondary allylic alcohols, and our initial results on $\mathrm{Ti(OR)_4}$-mediated openings of glycidic acids and amides appear in the following communication.[24]

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Supplementary Material Available: Additional experimental details for the $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$-mediated nucleophilic openings of 3-propyloxiranemethanol (1); sequence carried out to assign the ratio of isomers in the ammonium acetate opening; and ^{1}H NMR data of all peracetylated-opened products prepared in this work (28 pages). Ordering information is given on any current masthead page.

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(19) For an example of an unsuccessful attempted cyanide opening of an epoxy alcohol using uncatalyzed conditions (KCN, 18-crown-6, benzene), see: Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 139.

(20) Although disappointing, this result does not mean that a 2,3-epoxy alcohol cannot be opened by cyanide with a reasonable degree of selectivity. For example, when 1 was treated with Nagata's reagent, (Et_2AlCN, 2.3 equiv, toluene, −20 °C, 1 h and then room temperature, 3 h), the corresponding cyano diols were obtained in a C_3/C_2 ratio of 15/1 in a combined yield of 87%. See ref 19 for the utilization of this reagent with another epoxy alcohol. In contrast to Nagata's reagent for opening with cyanide, we found $\mathrm{Al}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_3$ to be inferior to $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ (regarding both rate and regioselectivity).

(21) At present we can only speculate on the origins of the enhanced C-3 selectivity in openings of the coordinated epoxy alcohols. Examination of the putative intermediate complex in Scheme I suggests one attractive possibility. The bond between C-3 and oxygen (bond a) appears much better oriented to overlap with an empty d orbital on titanium than does the bond between C-2 and oxygen (bond b) which lies nearly in the plane of the five-membered ring.

(22) Whatever the significance, one notices that it is generally the "softer" nucleophiles which are the least regioselective.

(23) (a) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589; ref 11a, this paper. (b) Finn, M. G.; Sharpless, K. B. in "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8. (c) Rossiter, B. E. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7.

(24) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.*, the following communication in this issue.

(25) **Note Added in Proof**: The regioselective (C-3:C-2 > 50:1) openings of 1 with NH_4NO_3 (2 equiv, THF, room temperature) and with CH_3COSH (5 equiv, CH_2Cl_2, room temperature) in the presence of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$ proceed in excellent yield. For the ambident nucleophile thioacetic acid, it is the C-3 thioacetate which is formed. Gao, Y.; Sharpless, K. B., unpublished results.

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Nucleophilic Openings of 2,3-Epoxy Acids and Amides Mediated by $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$. Reliable C-3 Selectivity

Summary: 2,3-Epoxy acids and amides are opened regioselectively at C-3 by nucleophiles in the presence of $\mathrm{Ti}(\mathrm{O}\text{-}i\text{-}\mathrm{Pr})_4$.

Sir: As part of continuing efforts to expand the synthetic utility of 2,3-epoxy alcohols, substances readily available in high enantiomeric excess via asymmetric epoxidation,[1] we have examined the openings of these compounds and some of their derivatives.[2] Previous results from these

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