centration of materials and temperature). Specialized apparatus and techniques (e.g., potentiostats and use of reference electrodes) are not required.

Experimental Section

Flash column chromatography[12] was performed on silica gel (Merck Art 9385). Laudanosine (now available from Aldrich) and norlaudanosine were prepared by standard methods.[2,4]

Constant-Current Electrolysis of (±)-Laudanosine (2) to *O*-Methylflavinantine (4). To a 250-cm^3 beaker containing acetonitrile (149 cm^3), purified as described below, and 50% aqueous HBF_4 (5.7 M, 0.75 cm^3) was added (±)-laudanosine (1.07 g, 3.0 mmol). Two square platinum foil electrodes (7.3 cm^2/face) were then placed 3.0 cm apart, and a direct current of 50 mA (V = 3.5 V) was passed through the magnetically stirred solution, initially at room temperature and without enforced cooling, for 3.5 h (2.2 faradays/mol). The acetonitrile was removed under reduced pressure, a 5% aqueous solution of sodium bicarbonate was then added (to pH 8–9), and the solution was extracted with methylene chloride (3 × 30 cm^3). After isolation, the remaining brown gum was purified by flash column chromatography with elution by 7% v/v methanol/dichloromethane, and the product 4 was crystallized from acetone: yield 0.77 g (75%); mp 159–160 °C (lit.[13] mp 158–160 °C); starting material (ca. 10%) recovered by further elution.

This synthesis was repeated in 65% yield (HPLC) using 10 cm^3 of solution in a test tube with 1 cm^2 electrodes 1 cm apart. A current of 7 mA was passed for 1.8 h, so that the current/unit area of electrode was the same as for the larger scale experiments. A good commercial grade of acetonitrile was used without further purification—see below.

Larger Scale Oxidation. Isolation of 10α-Methoxy-*O*-methylflavinantine (6). The reaction was performed in 1-L beaker containing acetonitrile (800 cm^3), laudanosine (5.71 g, 0.016 mol), and 50% aqueous HBF_4 (4 mL). The electrodes were concentric pieces of platinized titanium (Marstons Excelsior Ltd., Wolverhampton), 15 cm × 5 cm. The anode was made into a cylinder of fine mesh, held in its circular shape by fine platinum wire, and almost completely surrounded by the sheet cathode at a distance of about 0.5 cm. Constant-current (150 mA) or controlled-potential (1.03 V, reference 0.1 M Ag^+/Ag, initial current 400 mA) electrolyses of the stirred solution gave high yields of crystalline dienone [4: 4.2–4.4 g (77–82%], a small amount of recovered laudanosine [0.1–0.4 g (2–7%)], and a faster eluting dienone containing four OCH_3 signals in the ^1H NMR; yield 0.10 g (2%). Smaller scale electrolyses of 0.02 M **2** in acetonitrile containing added methanol gave higher yields of the new dienone **6**. Yields: 14% (with 1% $MeOH/CH_3CN$), 16% (with 5% $MeOH/CH_3CN$), and 11% (with 10% $MeOH/CH_3CN$). The product was isolated by flash column chromatography (elution by 2% methanol/dichloromethane) and was recrystallized twice from benzene and then from acetone: mp 178.5–180.0 °C; IR, $\nu_{\max}$ 1625, 1647, 1675 cm^{-1}; NMR, δ 3.90 (2), 3.80, 3.46 (4 × 3 H, s, CH_3O), 4.59 and 3.75 (1 H, sharpened by decoupling, J = 1 Hz); other decoupling experiments consistent with previous assignments for amurine;[14] mass spectrum, m/e 371 (M^+, base beak), 356, 340, 313. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 68.0; H, 6.6; N, 3.7.

Purification of Solvents for Electrosynthesis. Acetonitrile (Aldrich) was purified in 5-kg batches by heating under reflux with phosphorus pentoxide (30 g) for 1 h. It was then fractionally distilled through a triple-pass fractionating column (Widmer, 3 × 24 cm), collecting only the middle 70% fraction for immediate use and recycling the remainder. After the acetonitrile had been recycled up to three or four times, the background current during electrosyntheses became too high (water hydrolyzes some of the nitrile, but most of this water could have been removed in a preliminary step with calcium hydride or silica gel[15]). The specific conductivity at 25.0 °C of the middle 70% of distillate was 3.4 × 10^{-7} Ω^{-1} cm^{-1} (good commercial grades, e.g., Fisons HPLC, are within this specification *before* purification), and corresponding values of other fractions were as follows: original supply (9.6), first 15% of distillate (23.6), four times recycled (13.4); lit.[15] 0.7–1.5 × 10^{-7} Ω^{-1} cm^{-1} (extensive purification). Acetone (A.R., 5 L) was passed through a column of anhydrous potassium carbonate and was then fractionally distilled as described above (specific conductivity of middle 70%, 0.72 × 10^{-7} Ω^{-1} cm^{-1}; original supply, 1.89).

Equipment. Electrosyntheses in a beaker do not necessarily require glass/metal seals,[1c] but White[16] described how a simple platinum/glass seal could be made. We used similar platinum/glass seals but avoided the use of mercury for electrical contact between the electrode and the connections to the voltage source,[16] by spot-welding copper/nickel braid directly to the platinum wire that supported the platinum sheet electrode. The electrodes were cleaned regularly by immersing them in concentrated nitric acid.

Acknowledgment. This work was supported by an SERC/CASE studentship in collaboration with Reckitt and Colman, Pharmaceutical Division. We are grateful to A. C. W. Curran, K. Godfrey, T. Joslin, R. Kobylecki, S. Turner, and J. H. P. Utley for helpful contributions and suggestions.

Registry No. (±)-**2**, 1699-51-0; (±)-**4**, 22169-18-2; (±)-**6**, 104910-83-0.

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Factors Influencing the Competitive Rates of Free Radical Addition of Ethyl 2-Bromo Carboxylates to Selected Alkene Pairs[1]

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Ever since Kharasch and his co-workers first observed the anti-Markovnikov addition of hydrogen bromide to alkenes,[2] explanations as to why free radicals prefer to add to the less substituted end of a carbon–carbon double bond have been of two general types. The first, which will be referred to as the "electronic effect", is formulated in terms of a favored generation of more highly substituted carbon radicals. The vast majority of textbooks of elementary organic chemistry still promote this rationale.[3] The second general explanation will be termed a "steric effect". Tedder and Walton have most strongly drawn attention to the fact that all radicals, irrespective of their electrophilic or nucleophilic character, will prefer to attack the more accessible or less hindered end of the double bond.[4] Giese has generated much support for this view,[5] and a recent paper

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[1] Taken from the M.S. thesis of V.G. Preliminary presentation at 41st Northwest Regional Meeting of the American Chemical Society, Portland, OR, June 17, 1986.

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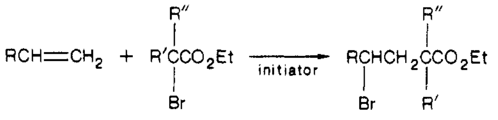
by Münger and Fischer has even demonstrated how electronic and steric effects may be separated in the case of *tert*-butyl radical addition to alkenes.[6] All three of these groups point out that both of the general effects may be operative for radical additions. The phrase "complex interplay of polar, steric and bond strength terms", first employed by Tedder and Walton,[4] has been quoted in almost all subsequent papers. Without modifying the aforementioned success of Münger and Fischer, it must be pointed out that frequently electronic and steric effects may so strongly parallel each other so as to make any separation of effects impossible. The addition of electrophilic radicals to simple alkenes may be one such instance.

Although the importance of steric factors on the rates of radical addition are not universally accepted (Boldt and co-workers, for example, prefer an electronic explanation involving the superdelocalizability of the alkene[7]), it was felt that a study of the effect of a systematic variation of the steric requirements of a series of nearly electronically equivalent radicals undergoing addition would be useful. Forty years ago Kharash reported the addition of ethyl 2-bromo carboxylates to alkenes (eq 1).[8] The anti-Markovnikov free-radical nature of the process has long been known.[9] The ethyl esters of secondary 2-bromo carboxylates (R′ = H; R″ = alkyl) are precursors of the nearly electronically equivalent but sterically variable radicals proposed above. The traditional series of alkyl groups, methyl, ethyl, isopropyl, and *tert*-butyl have been utilized. As a complement to this series of secondary carbethoxyalkyl radicals, the corresponding primary system (R′ = R″ = H) and two tertiary systems (R′ = R″ = methyl or ethyl) have also been investigated.



$$\mathrm{RCH{=}CH_2} + \mathrm{R'\overset{R''}{\underset{Br}{C}}CO_2Et} \xrightarrow[\text{initiator}]{} \mathrm{\underset{Br}{RCH}CH_2\overset{R''}{\underset{R'}{C}}CO_2Et} \tag{1}$$

I

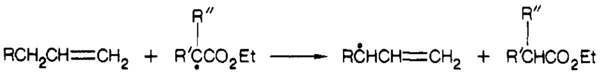
The approach adopted in this investigation is to allow individual ethyl 2-bromo carboxylates to react with pairs of alkenes at 70 °C. The ability of any of the carbethoxyalkyl radicals to distinguish between the two substrates is a measure of the selectivity of the particular radical involved. Two alkene pairs were chosen for investigation. The first consisted of 1-octene and 3-propoxypropene. Both these terminal alkene systems should show minimal steric hindrance toward radical addition. Differences in electron density of the double bonds, however, could clearly influence selectivity patterns. This would be particularly true if a relatively early transition state were involved in the addition step. The second alkene pair consisted of 1-octene and 1-methylcyclohexene. The double bond of this last molecule is much less sterically accessible than those in the other alkenes used. It should be mentioned that while 1-octene is common to both alkene pairs, in the first pair it contains the double bond of higher electron density, whereas in the second pair its relative position has been reversed.

Results and Discussion

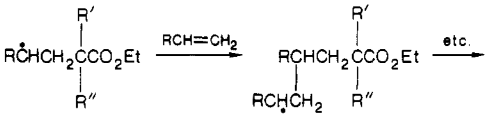
All selectivities were obtained from direct competitive data. All runs were carried out in replicate on a minimum of five samples. The selectivity for any of the carbethoxyalkyl radicals investigated is taken as the relative reactivity of the two alkenes for the radical in question (eq 2).

$$\text{selectivity} = \frac{k_{\text{3-propoxypropene(or 1-methylcyclohexene)}}}{k_{\text{1-octene}}} \tag{2}$$

It is necessary to show that the alkene substrates do not disappear through side reactions before the observed relative reactivities can be equated solely with the addition process. Two particularly relevant possibilities are allylic hydrogen atom abstraction from the alkenes by carbethoxyalkyl radicals (eq 3) and polymerization (or telomerization) of the initial adduct (eq 4). Terminal alkenes normally undergo addition much more readily than allylic hydrogen atom abstraction. Huyser, for example, showed that in the reaction of 1-octene with trichloromethyl radical the relative rates of addition to abstraction was 44 to 1.[10] It should be noted, however, that the adjacent oxygen atom in 3-propoxypropene should somewhat increase the ease of allylic hydrogen atom abstraction.[11] An alkene such as 1-methylcyclohexene should also have a greatly reduced addition to abstraction ratio since the number of available allylic hydrogens of the system increases while the accessibility of the double bond is diminished.[10] Despite these considerations, it is felt that allylic hydrogen atom abstraction does not occur in the systems under present study since no nonbrominated ethyl carboxylates can be detected in our reaction mixtures. Polymerization will be disfavored by maintaining a significant excess of ethyl 2-bromo carboxylate relative to the combined alkenes. This was done in all runs. It was observed that the ratio of total alkene consumed to 2-bromo carboxylate consumed was nearly unity (1.04 ± 0.06), thus suggesting that the formation of 1:1 adducts is probably the exclusive reaction occurring. Product studies on 3-propoxypropene and 1-methylcyclohexene showed the formation of 1:1 adducts or, in some cases, dehydrobromination products in reasonable yields (60–80%). No product studies on 1-octene were evaluated as an extensive literature on this subject exists.[8,9]



$$\mathrm{RCH_2CH{=}CH_2} + \mathrm{R'\overset{R''}{\dot{C}}CO_2Et} \longrightarrow \mathrm{R\dot{C}HCH{=}CH_2} + \mathrm{R'\overset{R''}{C}HCO_2Et} \tag{3}$$



$$\mathrm{R\dot{C}HCH_2\overset{R'}{\underset{R''}{C}}CO_2Et} \xrightarrow{\mathrm{RCH{=}CH_2}} \mathrm{\underset{R\dot{C}HCH_2}{RCH}CH_2\overset{R'}{\underset{R''}{C}}CO_2Et} \xrightarrow{\text{etc.}} \tag{4}$$

It should also be mentioned that the addition of carbethoxyalkyl radical to alkenes is apparently an irreversible process. Studies on *cis*-2-heptene showed that no isomerization of starting material could be detected after nearly 20% of adduct formation. Giese has reported similar findings for simple alkyl radicals.[5]

The selectivities of radical addition to the 3-propoxypropene/1-octene alkene pair should be largely governed by the decreased electron density found in the double bond of the former compound. Electrophilic radicals prefer to add to terminal alkenes rather than allyl ethers. Martin and Gleicher observed a selectivity of approximately 0.6 between 3-methoxypropene and 1-octene in reaction, with trichloromethyl radical at 70 °C.[12] The dicarbethoxymethyl radical, generated from diethyl bromomalonate in an identical manner to other carbethoxyalkyl radicals,

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Table I. Selectivities for the Addition of Ethyl 2-Bromo Carboxylates [RC(R′)(Br)CO$_2$Et] to Alkene Pairs

	3-propoxypropene/1-octene		1-methylcyclohexene/1-octene	
ester	selectivity	no. of runs	selectivity	no. of runs
R = R′ = H	0.98 ± 0.03	6	1.18 ± 0.04	6
R = H; R′ = CH$_3$	1.06 ± 0.03	5	1.25 ± 0.02	6
R = H; R′ = CH$_3$CH$_2$	1.08 ± 0.02	6	1.31 ± 0.02	5
R = H; R′ = (CH$_3$)$_2$CH	1.14 ± 0.02	6	1.48 ± 0.04	6
R = H; R′ = (CH$_3$)$_3$C	1.24 ± 0.03	6	2.19 ± 0.04	6
R = R′ = CH$_3$	1.31 ± 0.03	5	1.18 ± 0.04	6
R = R′ = CH$_3$CH$_2$	1.36 ± 0.04	6	1.24 ± 0.02	6

showed a selectivity of 0.5 ± 0.01.

Table I contains the selectivities for seven carbethoxyalkyl radicals with the 3-propoxypropene/1-octene alkene pair. Only one radical, the primary carbethoxymethyl species, shows a slight preference to react with 1-octene. Analogies with closely related species such as carboxymethyl[13] and acetylmethyl,[14] which show electrophilic character in addition and aromatic substitution reactions, suggest that carbethoxymethyl should be an electrophilic radical. Replacement of one or both of the hydrogen atoms at the radical center of carbethoxymethyl by alkyl groups should lead to new secondary or tertiary species of increased stability. These new species will certainly be less electrophilic than the parent species. The data in Table I indicates this to be the case. All these latter systems undergo preferred reaction with 3-propoxypropene.

Linear free-energy relationships involving the logarithms of the selectivities can be formulated with either the steric or electronic substituent parameters of the groups attached to the radical center of the carbethoxyalkyl radicals. The best of the correlations are respectively with E_s[15] parameters (slope = −0.05; c.c. = −0.93) and σ^*[15] parameters (slope = −0.13; c.c. = −0.96). The signs of the slopes are in keeping with an increased selectivity due to either the increasing size of the attacking carbethoxyalkyl radical or a probable internal increase in stability of the radicals themselves as hydrogen atoms are replaced by alkyl groups. Unfortunately, it is difficult to decide whether steric or electronic factor play the predominant role in determining selectivity since E_s and σ^* parameters for alkyl groups are directly proportional to each other.

Table I also contains the selectivity data for the 1-methylcyclohexene/1-octene alkene pair. Electrophilic radicals should prefer to attack the former molecule in the absence of steric effects. The selectivities for the series carbethoxymethyl (1.18 ± 0.04), dicarbethoxymethyl (1.10 ± 0.02), and tricarbethoxymethyl (2.13 ± 0.03) do not, however, show a monotonic trend, thus suggesting variable steric effects. More puzzling is the fact that the secondary and tertiary carbethoxyalkyl radicals now exhibit a selectivity opposite to that expected. These radicals, which are more nucleophilic than carbethoxymethyl, also prefer to react with 1-methylcyclohexene rather than 1-octene. Neither of the simple steric or electronic parameters discussed previously can correlate the data for all of the seven ethyl 2-bromo carboxylates investigated. The major question, however, is why should the most bulky of the secondary radicals be the one with the greatest tendency to attack the relatively hindered double bond of 1-methylcyclohexene?

The concept of radical persistence, as developed by Griller and Ingold may provide a possible explanation.[16] The introduction of large groups at the radical center can effectively shield the radical from reaction with probable substrates. Tertiary systems should be more persistent than secondary systems for groups of comparable size. A single, large alkyl group, however, might be more effective at causing persistence than two smaller alkyl groups. When the reaction of a more persistent radical is considered, it will be less exothermic or more endothermic than that for some related, nonpersistent species. In terms of Hammond's postulate, the reaction of a persistent species should involve a transition state which shows a greater resemblance to the product radical.[17] In the present system this would favor addition to 1-methylcyclohexene, since the radical derived from that alkene is tertiary.

As in related addition reactions, it is proposed that both ground-state and transition-state factors are operative in all reactions but in a variable ratio.[18] The following summary is applicable to the results under discussion.

A. Primary Carbethoxyalkyl Radical. This is the least persistent of the radicals investigated. Ground-state factors based on the electrophilicity of this species favor attack at the more electron-rich double bond. Product-state effects coincidently favor the same system. A relatively early transition state, however, is probably present.

B. Secondary Carbethoxyalkyl Radicals. These are more persistent than the primary radical both on electronic and steric grounds. The steric requirements of the four systems studied differ greatly among themselves in monotonic fashion with more product-state control found for the largest alkyl substituent. The extent of nucleophilic character associated with these species may be rather small, thus accounting for the lack of a ground-state alkene electron density effect. This would mean that the effects of the single alkyl group and the carbethoxy group at the radical center approximately neutralize each other.

C. Tertiary Carbethoxyalkyl Radicals. These must be nucleophilic in nature and moderately persistent. Based upon the E_s values, however, the two tertiary systems studied have smaller steric demands than the secondary system containing the *tert*-butyl group. Based solely on persistance, a transition state comparable to that for a secondary system possessing an isopropyl group may be envisioned. The much greater nucleophilic character of the tertiary radicals, however, will result in more control by ground-state electronic factors and in a partial decrease in the selectivity for these systems.

It should also be noted that the presence of both alkyl groups and the carbethoxy function at the radical center may add to the persistence of the system by a hyperconjugative captodative effect.[19] The relative importance of this effect to those previously discussed is difficult to assess.

It is agreed that the "complex interplay of terms" previously mentioned also is operative in the present system. It is also felt that there exists a variable ratio of ground-state–transition-state factors attributable to the nature of the attacking radical that also plays a role.

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Experimental Section

Materials. The majority of reagents and solvents used in this investigation were obtained from commercial sources. Compounds synthesized in our laboratory were ethyl 2-bromo-3-methylbutanoate, ethyl 2-bromo-3,3-dimethylbutanoate, and ethyl 2-bromo-2-ethylbutanoate prepared from the corresponding nonbrominated acids,[20] bromotricarbethoxymethane prepared from the corresponding nonbrominated triester,[21] and 3-propoxypropene prepared by a standard Williamson synthesis.[22] All materials were purified before use. Properties agreed with the literature values.

Determination of Selectivities. A standard competitive kinetic approach was used.[23] Stock solutions of either 3-propoxypropene or 1-methylcyclohexene, 1-octene, ethyl 2-bromo carboxylate, chlorobenzene (internal GLC standard), benzoyl peroxide (radical chain initiator), and benzene (solvent) were prepared in approximate relative molar ratios of 1:1:4:1:0.1:13. The solution was divided among several reaction tubes. Air was removed from the samples by repeated freeze–thaw cycles. Tubes were sealed while samples were under a nitrogen atmosphere at reduced pressure. One tube was reserved as a starting mixture sample, and the remainder were put in a 70.0 ± 0.1 °C constant-temperature bath for 24 h. Relative rates of disappearance of the two competing alkenes were determined by GLC evaluation of relative concentrations. All GLC analyses were carried out on a Varian 200 chromatograph. A 15 ft × $^1/_4$ in. packed column of 5% SE-30 on Chromasorb-W was used throughout this study. The 24-h reaction time employed corresponded to 15-35% disappearance of each alkene in any given run.

Acknowledgment. M.K. expresses his graditude to the Orgeon State University Undergraduate Honors Program for providing financial support.

Registry No. $BrCH_2CO_2Et$, 105-36-2; $BrCH(Me)CO_2Et$, 535-11-5; $BrCN(Et)CO_2Et$, 533-68-6; $BrCN(i\text{-}Pr)CO_2Et$, 609-12-1; $BrCH(t\text{-}Bu)CO_2Et$, 20201-39-2; $BrC(Me)_2CO_2Et$, 600-00-0; $BrC(Et)_2CO_2Et$, 6937-28-6; $\cdot CH_2CO_2Et$, 21946-41-8; $\cdot CH(Me)CO_2Et$, 37999-08-9; $\cdot CH(Et)CO_2Et$, 105019-17-8; $\cdot CH(i\text{-}Pr)CO_2Et$, 105019-18-9; $\cdot CH(t\text{-}Bu)CO_2Et$, 105019-19-0; $\cdot C(Me)_2CO_2Et$, 37999-09-0; $\cdot C(Et)_2CO_2Et$, 105019-20-3; 3-propoxypropene, 1471-03-0; 1-octene, 111-66-0; 1-methylcyclohexene, 591-49-1.

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Epoxide Opening with *tert*-Butyldimethylsilyl Cyanide–Zinc Iodide. Evidence for a Stepwise Process in the Opening of a Sterically Hindered Epoxide

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Recently, we have described the opening of oxiranes (epoxides)[2] and oxetanes[3] with trimethylsilyl cyanide–zinc iodide to produce high yields of 1 and 2, respectively. Because of the ease with which 1 could be converted into β-amino alcohols 3, and 2 could serve as a source of γ-amino alcohols 4, these reactions appeared to have considerable potential as a new synthetic route to these bifunctional molecules. In order to establish whether we could introduce the more stable *tert*-butyldimethylsilyl protecting group via this method, we investigated the opening of epoxides with *tert*-butyldimethylsilyl cyanide[4]–zinc iodide. This paper presents the details of this investigation.

Scheme I

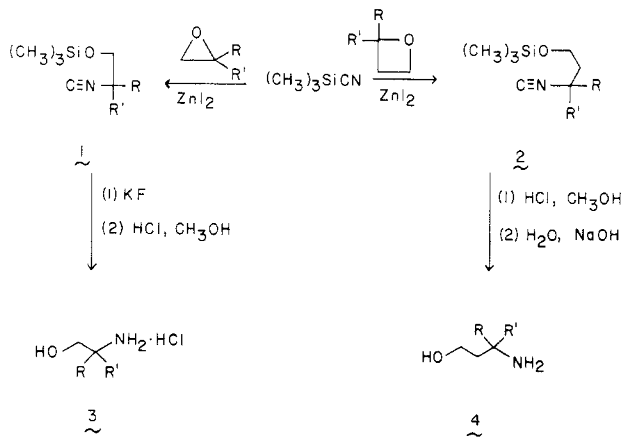
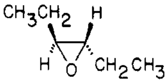
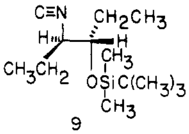
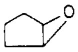
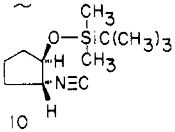
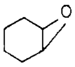
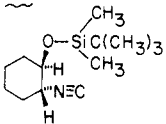
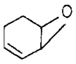
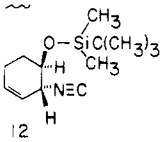


Table I. Opening of Epoxides with *tert*-Butyldimethylsilyl Cyanide–Zinc Iodide in Refluxing Methylene Chloride

epoxide	product	reactn time, h	% yield
 5	 9	48	74
 6	 10	48	81
 7	 11	48	87
 8	 12	48	87

As shown in Table I, when a series of epoxides 5–8 was allowed to react with *tert*-butyldimethylsilyl cyanide and zinc iodide in methylene chloride, the corresponding *tert*-butyldimethylsilyl ether of the β-hydroxy isonitriles 9–12, respectively, were obtained in 74–87% yield. In most respects these reactions paralleled the related opening of these same epoxides with trimethylsilyl cyanide–zinc iodide.[2] However, certain differences did exist. The first major difference involved the rate of the epoxide ring opening. In general, those reactions involving *tert*-bu-

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[1] 3M Fellow, 1984–1985.

[2] Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 5849. Gassman, P. G.; Gremban, R. S. *Tetrahedron Lett.* **1984**, *25*, 3259. See also: Spessard, G. O.; Ritter, A. R.; Johnson, D. M.; Montgomery, A. M. *Ibid.* **1983**, *24*, 655.

[3] Gassman, P. G.; Haberman, L. M. *Tetrahedron Lett.* **1985**, *26*, 4971. See also: Carr, S. A.; Weber, W. P. *Synth. Commun.* **1985**, *15*, 775.

[4] *tert*-Butyldimethylsilyl cyanide could be prepared either by the method of Treichel and Shaw[5] or through an adaptation of the procedure of Zubrick, Dunbar, and Durst.[6]

[5] Treichel, P. M.; Shaw, D. B. *J. Organomet. Chem.* **1977**, *139*, 21. Although our melting point approached that of these authors, NMR analysis indicated the presence of 35–40% contamination of the *tert*-butyldimethylsilyl cyanide by *tert*-butyldimethylsilyl chloride.

[6] Zubrick, J. W.; Dunbar, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, 71.

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