Intramolecular Homolytic Displacements. 25. Efficient Access to Epoxides via Induced Decomposition of Unsaturated Peroxyketals Prepared by Addition of a Hydroperoxide to 2-Methoxypropene

Fabienne Ramon, Marie Degueil-Castaing, and Bernard Maillard*

Laboratoire de Chimie Organique et Organométallique, Associé au CNRS, URA 35, Université Bordeaux 1, 351 Cours de la Libération, F-33405 Talence Cedex, France

Received October 2, 1995[⊗]

The synthetic potential of homolytically induced decompositions of peroxyketals possessing a 1-methoxy-1-methylethoxy fragment, as a means of access to epoxides, was demonstrated. The propagation step of this free radical reaction proceeds via (i) the addition of a carbon-centered radical to the double bond followed by an S_Hi reaction on the peroxidic bond with the generation of a 1-methoxy-1-methylethoxy radical, (ii) formation of a methyl radical from the latter by β-elimination, and (iii) regeneration of the carbon-centered radical via iodine atom abstraction by the methyl radical from an alkyl iodide. These reactions afforded various functionalized epoxides in good yields.

Introduction

Over the last decade, we have focused our attention on homolytically induced decompositions of unsaturated peroxy derivatives in order to prepare oxygenated heterocycles.[1−6] The formation of the heterocycle results from the addition of a radical Z• to the double bond of the peroxidic derivative, followed by an S_Hi reaction on the O−O bond, which generates an oxyl radical WO• (Figure 1).

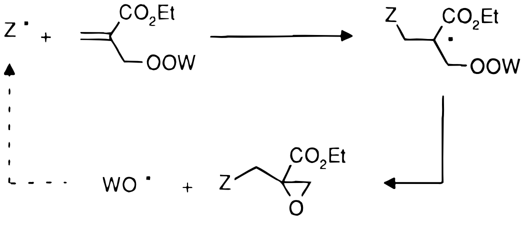


Figure 1.

For the propagation step of this reaction, the WO• species must be able to produce an alkyl radical Z• which is responsible for the induced decomposition of unsaturated peroxides. Several ways to generate carbon-centered radicals from oxyl radicals are available (Figure 2).

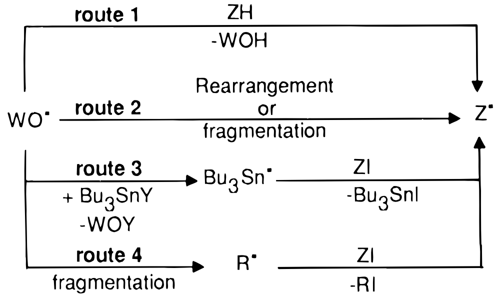


Figure 2.

The first method (Figure 2, route 1) consists of hydrogen atom abstraction by oxyl species, especially alkoxyl radicals, from a solvent ZH. Studies[1−3] of the induced decomposition of 3-[(1,1-dimethylethyl)peroxy]propene and ethyl [(1,1-dimethylethyl)peroxy]methyl propenoate showed the synthetic potential of such a method. However, this reaction is efficient only for solvents bearing a single type of hydrogen atom, or those containing hydrogen atoms of very different homolytic reactivity.[1−3] This drawback prompted us to consider other methods (Figure 2, routes 2 and 3) to selectively produce the required alkyl radical Z•.

Rearrangements or fragmentations of oxygen-centered radicals into carbon-centered species are an efficient and easy way to generate alkyl radicals (route 2). Thus, the induced decomposition of peroxyketals liberating alkoxyl radicals or 1-alkoxyalkyloxyl radicals, in solvents inert toward free radical attack, led to various glycidic esters in high yields.[4,5] The limitation of this method is, however, the necessary synthesis of several kinds of unsaturated peroxyketals. Indeed, only a single epoxide could be produced from each peroxyketal.

Carbon-centered radicals could also be generated by abstraction of an iodine atom from an alkyl iodide (ZI) by the use of a mediator, such as a tributylstannyl radical[6] (route 3). The synthetic potential of this method is, however, limited by the difficulty of separation of the epoxide from the tin residues.

The fast abstraction of an iodine atom by a carbon-centered radical, such as methyl or phenyl, could be another alternative for the production of carbon-centered radicals. This method requires that the oxyl radical, liberated during the induced decomposition of the peroxidic derivative, fragments rapidly to generate the R• radical (Figure 2, route 4). The efficient β-elimination reaction observed for 1-methoxy-1-methylethoxyl radicals

---

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1996.

[1] (a) Montaudon, E.; Rakotomanana, F.; Maillard, B. *Bull. Soc. Chim. Fr.* **1987**, 375. (b) Montaudon, E.; Agorrody, M.; Rakotomanana, F.; Maillard, B. *Bull. Soc. Chim. Belg.* **1987**, *96*, 769. (c) Bourgeois, M. J.; Maillard, B.; Montaudon, E. *Tetrahedron* **1986**, *42*, 5309. (d) Montaudon, E.; Rakoromanana, F.; Maillard, B. *Tetrahedron* **1985**, *41*, 2727. (e) Montaudon, E.; Rakotomana, F.; Maillard, B.; Bourgeois, M. J. *Tetrahedron* **1985**, *41*, 5039.

[2] Navarro, C.; Degueil-Castaing, M.; Colombani, D.; Maillard, B. *Synlett* **1992**, 587.

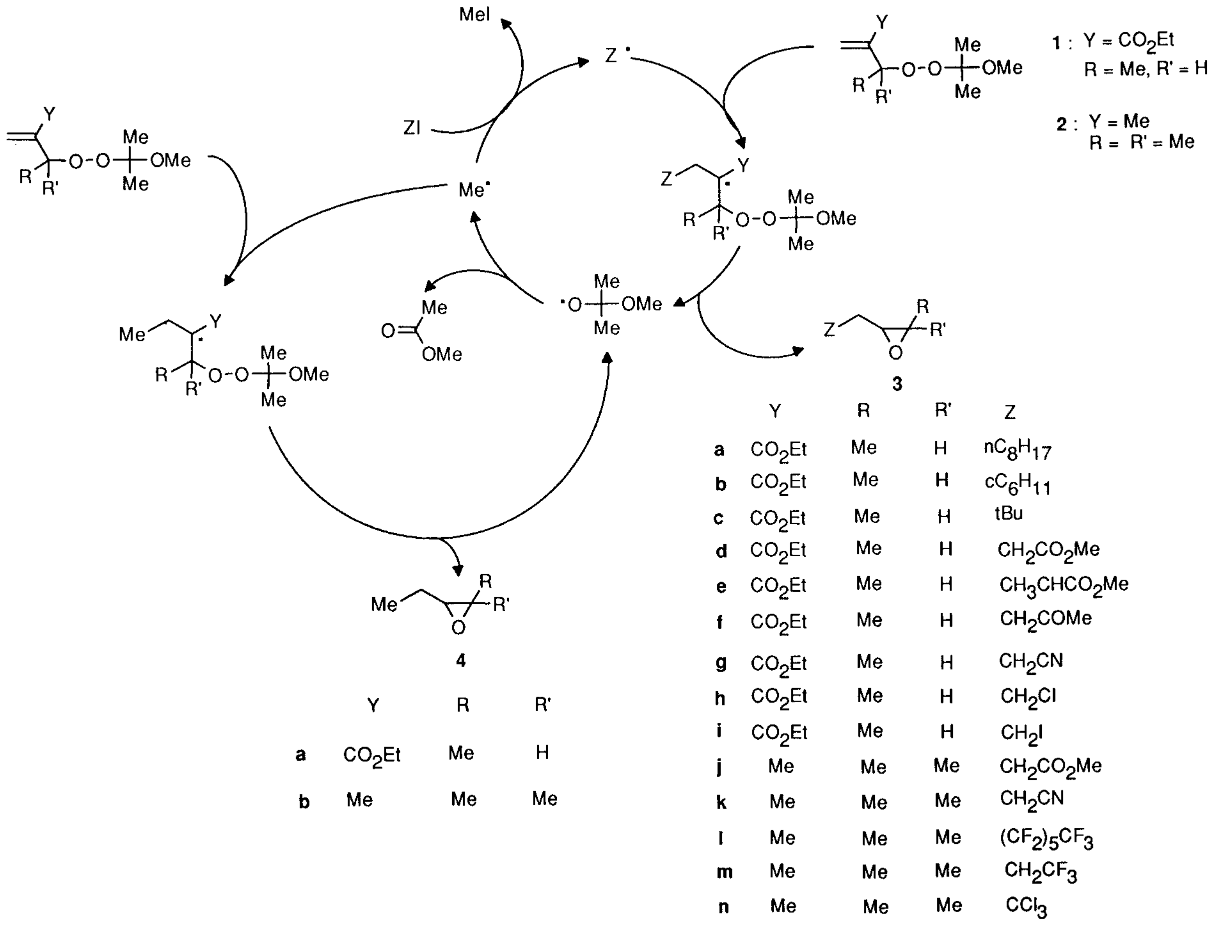
[3] Colombani, D.; Maillard, B. *J. Chem. Soc., Perkin Trans. 2* **1994**, 745.

[4] Colombani, D.; Maillard, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1259.

[5] Colombani, D.; Maillard, B. *J. Org. Chem.* **1994**, *59*, 4765.

[6] Degueil-Castaing, M.; Navarro, C.; Ramon, F.; Maillard, B. *Aust. J. Chem.* **1995**, *48*, 233.

0022-3263/96/1961-2071$12.00/0



	Y	R	R'	Z
a	CO_2Et	Me	H	nC_8H_{17}
b	CO_2Et	Me	H	cC_6H_{11}
c	CO_2Et	Me	H	tBu
d	CO_2Et	Me	H	CH_2CO_2Me
e	CO_2Et	Me	H	CH_3CHCO_2Me
f	CO_2Et	Me	H	CH_2COMe
g	CO_2Et	Me	H	CH_2CN
h	CO_2Et	Me	H	CH_2Cl
i	CO_2Et	Me	H	CH_2I
j	Me	Me	Me	CH_2CO_2Me
k	Me	Me	Me	CH_2CN
l	Me	Me	Me	$(CF_2)_5CF_3$
m	Me	Me	Me	CH_2CF_3
n	Me	Me	Me	CCl_3

	Y	R	R'
a	CO_2Et	Me	H
b	Me	Me	Me

Figure 3.

derived from "acrylic" peroxyketals[3] led us to study the induced decomposition of peroxyketals containing that moiety, in the presence of an alkyl iodide.

Results and Discussion

Peroxyketals **1** and **2** were synthesized by the reaction of a hydroperoxide (respectively, ethyl 2-(1-hydroperoxyethyl)propenoate and 3-hydroperoxy-2,3-dimethyl-1-butene) with 2-methoxypropene. The induced decompositions of the peroxy compounds were carried out in benzene for **1** at 80 °C (AIBN initiation) and for **1** and **2** at 20 °C (Et_3B/O_2 system as the initiator), using equimolar amounts of iodide and substrate **1** or **2**.

Methyl radical, produced by the fragmentation of the 1-methoxy-1-methylethoxyl radical liberated during the induced decomposition of the peroxyketals generates the expected radical $Z^\bullet$ by reaction with an alkyl iodide (ZI). Radical $Z^\bullet$, by addition to the unsaturation of the peroxy compound, yields epoxides **3**. However, another epoxide **4** can be produced, due to the reaction of methyl radicals with the unsaturated peroxides, particularly **1** (Figure 3). From a synthetic point of view, this side-reaction is not a serious drawback since **4** is generally easily separated from epoxide **3**, because of its low boiling point.

When simple alkyl iodides were used as precursors with the peroxyketal **1**, an increase in the yields of epoxides **3** was observed at the expense of **4a** in the series iodooctane, iodocyclohexane, *tert*-butyl iodide (Table 1), whatever the reaction temperature. Since allylic attack on **1** is inefficient,[3] this result was attributed to the increase in the rate constant of iodine abstraction, by a methyl radical, from the primary to the tertiary alkyl iodide.[7] Moreover the faster addition of *tert*-butyl radical to the double bond of the peroxyketal, compared with that of cyclohexyl or *n*-octyl radicals, contributed to this result by shifting the equilibrium $CH_3^\bullet + ZI \rightleftharpoons CH_3I + Z^\bullet$, in favor of the formation of the radical $Z^\bullet$. Thus, we conclude that when the carbon-centered radical is not stabilized, the reaction shows synthetic promise only for secondary and tertiary radicals. However, when the radical, $Z^\bullet$, bears an electron-withdrawing group, an increase in the yields of epoxides **3** is observed (Table 2, entries 1−6) in comparison with the *n*-octyl radical (Table 1, **3a**). This observation must reflect an increase in the rate constant of the iodine atom abstraction when yielding a more stabilized radical. The equilibrium, previously mentioned, is then shifted to the right, which disfavors the addition of the methyl radical to the double bond of **1**.

Table 1. Yields (%) of Epoxides 3 from Induced Decomposition of 1 in Benzene at 80 or 20 °C with an Alkyl Iodide Derivative

	20 °C		80 °C	
	yield of **3**[a]	yield of **4a**[a]	yield of **3**[a]	yield of **4a**[a]
a	20 (27[b])	55[b]	25 (27[b])	58[b]
b	50	35	50	40
c	75	traces[b]	*c*	*c*

[a] Yield of isolated epoxide relative to **1**. [b] Yield of **4a** determined on the reaction mixture by GC analysis. [c] **3c** was not produced at 80 °C due to the instability of *tert*-butyl iodide at this temperature.

---

(7) Ingold, K. U. *Free Radicals*; Kochi, J. K., Ed.; Wiley Interscience: New York, 1973; Vol. I, Chap. 2, pp 83−85.

Table 2. Yields (%) of Epoxides 3 from Induced Decomposition of 1 in Benzene at 20 °C with Functionalized Iodide Derivatives

entry	**3**	yield of **3**,[a]
1	d	72
2	e	77
3	f	53
4	g	69
5	h	66
6	i	51

[a] Yield of isolated epoxide relative to **1**.

Table 3. Yields (%) of Epoxides 3 from Induced Decomposition of 2 in Benzene at 20 °C with Functionalized Iodide Derivatives

entry	**3**	yield of **3**,[a]
1	j	92
2	k	82
3	l	68
4	m	30

[a] Yield of isolated epoxide relative to **2**.

The result obtained for chloroiodomethane (Table 2, entry 5) shows a strong preference for iodine abstraction by methyl radicals, because no epoxide **3i** was identified by GC during the course of the reaction. Moreover, in the case of diiodomethane (Table 2, entry 6), the formation of a diepoxide, corresponding to the abstraction of an iodine atom from the epoxy compound, was not observed.

In the case of "simple" alkyl-substituted epoxides, no selective method of preparation is so far available from peroxy compounds. Therefore, we decided to extend our study to the peroxyketal **2**, with a methyl group on the nonterminal carbon of the double bond. Unlike **1**, the double bond of **2** is electron rich. In contrast to the reaction of **1**, **2** did not react with *tert*-butyl iodide at 20 °C to lead to the expected epoxide; the formation of the epoxide **4b** was also not observed. In fact, **2** was recovered quantitatively, which indicated either a short or negligible chain reaction. One explanation of this result could be the small rate constant for addition of alkyl radicals to nonactivated double bonds,[8] such as the one of **2**. An increase in the temperature enhances the rate constant of radical addition to double bonds. Since *tert*-butyl iodide is unstable at 80 °C, the induced decomposition of **2** was checked at 80 °C (lauroyl peroxide as initiator) and at 110 °C (1,1-dimethylethyl peracetate as initiator) with iodocyclohexane. Whatever the temperature, little of the expected epoxide 1-cyclohexyl-2,3-epoxy-2,3-dimethylbutane (yield < 10%) and no epoxide **4b** could be identified.

When the carbon-centered radical contained an electron-withdrawing substituent, **2** reacted to give the corresponding epoxides in fair yields (Table 3). Particularly, the oxygenated heterocycles derived from iodoacetonitrile (**3k**) and methyl iodoethanoate (**3j**) were obtained in higher yield from **2** than from **1** (**3d** and **3g**). This result expresses the preference of methyl radicals to abstract an iodine atom rather than to add to the electron rich double bond of **2**.

Since methyl radicals do not add to the double bond of **2**, it seemed interesting to check the efficiency of bromine atom abstraction by these species. While methyl iodoethanoate led to **3j** in good yield, **2** did not lead to the expected epoxide under the same conditions when methyl bromoethanoate was used. However, the induced decomposition of **2** with bromotrichloromethane resulted in the formation of epoxide **3n** in 60% yield. Bromine atom abstraction by methyl radicals seems to be of limited efficiency.

Conclusion

The strategy of carbon-centered radical generation by iodine abstraction by methyl radicals (generated from β-elimination of 1-methoxy-1-methylethoxy radical), in order to promote induced decomposition of unsaturated peroxyketals with production of epoxides, is easy and efficient and thus synthetically useful, provided the unsaturated hydroperoxide is readily available. Such a free radical reaction occured with electron rich and electron poor double bonds. This method is particularly efficient when the intermediate alkyl radicals are slightly stabilized, which allows for high conversion of the chain carrying methyl radicals and preferential formation of functionalized epoxides.

Experimental Section

General Procedure and Materials. ^{1}H NMR spectra were recorded at 250 MHz and the ^{13}C NMR data were obtained at 62.9 MHz. The solvent was $CDCl_3$ and chemical shifts are reported relative to tetramethylsilane; *J* values are quoted in Hz. The chemical shifts of major diastereoisomers are underlined when possible. Gas chromatography was performed with a silica capillary column DB5 (25 m by 0.1 mm). Elemental analysis were performed by CNRS, Vernaison, France. Flash column chromatographic purifications of peroxyketals were carried out on SDS silica gel (200−400 mesh) and monitored by TLC using Schleider and Schuell precoated silica gel F1500/LS254 (0.25 mm thickness) plastic-backed plates. The plates were visualized under UV or iodine vapor. Mixtures of light petroleum ether (bp 45−55 °C) and diethyl ether were used as eluant. The purification of epoxides was performed by a bulb-to-bulb distillation under reduced pressure using a Büchi Kugelrohr oven. Benzene was dried over sodium. The other products were obtained commercially and used without any further purification. α,α'-Azobis(isobutyronitrile) was obtained from Fluka. 1 M solution of triethylborane in hexane, iodooctane, iodocyclohexane, *tert*-butyl iodide, iodoacetonitrile, iodochloromethane, and diiodomethane were purchased from Aldrich. Noncommercial alkyl iodides were synthesized according to the classical method[9] from the commercially available chloride or bromide derivatives.

Preparation of Peroxyketals. They were prepared from 2-methoxypropene and the corresponding hydroperoxide (obtained by the procedure developed by Adam and Griesbeck[10]) using the method described by Colombani and Maillard[5] for peroxyketal **1**.

2,3-Dimethyl-3-[(1-methoxy-1-methylethyl)peroxy]but-1-ene (2): 85%; $R_f = 0.6$ (petroleum ether/Et_2O = 98/2); ^{1}H NMR δ 4.84 (s, 1H), 4.78 (s, 1H), 3.22 (s, 3H), 1.75 (s, 3H), 1.30 and 1.28 (s, 12H); ^{13}C NMR δ 149.3, 110.6, 103.5, 82.3, 48.9, 24.5, 22.9, 18.5. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64. Found: C, 64.02; H, 10.55.

Preparation of Epoxides. **AIBN Initiator**. A mixture of peroxyketal (10 mmol), iodide precursor (10 mmol), and AIBN (1 mmol) in benzene (15 mL) was heated 12 h at 80 °C in a glass autoclave. The solvent was evaporated under vacuum, and the epoxide was isolated by bulb-to-bulb distillation under reduced pressure.

---

[8] Howard, J. C.; Scaiano, J. C. *Reactions rates in liquids*, Springer-Verlag: Berlin, Landolt-Börnstein, New series, 1984; Vol. II/13, pp 12−26.

[9] Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A.R. *Vogel's text book of practical chemistry*, 4th ed.; Longman: New York, 1978; p 1087.

[10] Adam, W.; Griesbeck, A. *Synthesis* **1986**, 1050.

Et_3B/O_2 Initiating System. A 1 M solution of triethylborane in hexane (1 mL) was added dropwise, directly in a solution of peroxyketal (10 mmol) and iodide or bromide (in the case of **3n**) precursor (10 mmol) in benzene (15 mL). The reaction was monitored by GC by following the disappearance of the peroxyketal. If peroxyketal remained after the addition of 1 mL of triethylborane/hexane solution, the same portion of initiator was added to the medium until the complete disappearance of the peroxy derivative. The solvent was evaporated under vacuum and the epoxide was isolated by bulb-to-bulb distillation under reduced pressure.

Products **3b**, **3c**, **3d**, **3g**, **3h**, and **4a** were previously prepared by our group.[4, 5]

Ethyl 2,3-epoxy-2-nonylbutanoate (3a): $bp_{0.1}$ = 100 °C; ^1H NMR δ 4.22−4.00 (m, 2H), *3.16* (q, J = 5.4 Hz) and 2.97 (q, J = 5.4 Hz, 1H), 2.18−0.80 (m, 25H); ^{13}C NMR δ 171.0, *61.2*, 61.1, 61.0, 58.3, *58.0*, 35.9, 33.1, 31.8, 29.6, 29.4, 29.3, 29.2, 27.4, 25.1, 24.7, 22.6, *14.2*, *14.0*, 13.9, 13.8, *13.7*, 13.5. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.10; H, 11.14.

Methyl 4,5-epoxy-4-(ethoxycarbonyl)-2-methylhexanoate (3e): $bp_{0.1}$ = 90 °C; ^1H NMR δ 4.10−3.91 (m, 2H), 3.46 (s, 3H), 3.05 (q, J = 5.4 Hz) and 2.99 (q, J = 5.4 Hz, 1H), 2.62−1.34 (m, 3H), 1.15 (d, J = 5.4 Hz) and 1.14 (d, J = 5.4 Hz, 6H), 1.08 (t, J = 6.8 Hz) and 1.00 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ 176.0, 175.8, 170.7, 170.5, 61.4, 61.3, 59.3, 58.3, 57.7, 51.6, 51.5, 36.1, 36.0, 30.7, 30.4, 17.3, 16.9, 14.1, 13.9, 13.4, 13.3. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 57.30; H, 7.71.

Ethyl 2,3-epoxy-2-(3-oxobutyl)butanoate (3f): $bp_{0.1}$ = 85 °C; ^1H NMR δ 4.07−3.89 (m, 2H), *3.08* (q, J = 5.5 Hz) and 2.89 (q, J = 5.5Hz, 1H), 2.49−2.37 (m, 2H), 2.20−2.00 and 1.86−1.55 (m, 2H), 1.95 (s, 3H), 1.15 (d, J = 5.5 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 206.9, 170.5, 62.0, *59.9*, *61.4*, 61.3, 58.9, *58.6*, *38.9*, 38.2, 29.6, 26.7, *21.2*, 14.1, *13.9*, 13.5, *13.4*. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.07. Found: C, 59.87; H, 7.97.

Ethyl 2,3-epoxy-2-(2-iodoethyl)butanoate (3i): $bp_{0.01}$ = 100 °C; ^1H NMR δ 4.15−3.96 (m, 2H), 3.26−2.98 (m, 3H), 2.61−2.46 and 2.09−1.95 (m, 2H), 1.24 (d, J = 5.4 Hz, 3H), 1.14 (t, J = 6.9 Hz, 3H). ^{13}C NMR δ *170.0*, 168.5, 62.8, *60.8*, *61.7*, 61.6, 58.7, *58.3*, 37.7, *32.5*, 14.3, *14.1*, 13.8, *13.5*, *−2.3*, −2.5. Anal. Calcd for $C_8H_{13}IO_3$: C, 33.81; H, 4.58; I, 44.72. Found: C, 34.04; H, 4.85; I, 45.05.

Methyl 4,5-epoxy-4,5-dimethylhexanoate (3j): $bp_{0.01}$ = 45 °C; ^1H NMR δ 3.60 (s, 3H), 2.37 (t, J = 8.5 Hz, 2H), 2.10−1.69 (m, 2H), 1.25, 1.24 and 1.23 (s, 9H). ^{13}C NMR δ 173.4, 63.4, 62.4, 51.5, 30.1, 29.8, 21.2, 20.7, 18.3. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.37; H, 9.31.

4,5-epoxy-4,5-dimethylhexanenitrile (3k): $bp_{0.2}$ = 70 °C; ^1H NMR δ 2.30 (t, J = 8 Hz, 2H), 1.96−1.62 (m, 2H), 1.16, 1.15 and 1.14 (s, 9H). ^{13}C NMR δ 119.4, 62.6, 62.5, 30.2, 21.0, 20.9, 18.0, 13.3. Anal. Calcd for $C_8H_{13}NO_3$: C, 69.03; H, 9.41; N, 10.07. Found: C, 69.31; H, 9.49; N, 10.33.

2,3-Epoxy-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-2,3-dimethyldecane (3l): $bp_{0.3}$ = 70 °C; ^1H NMR δ 2.33−1.81 (m, 2H), 1.15−0.9 (m, 9H). ^{13}C NMR δ 133.1−110.8, 62.3, 59.7, 36.0 (t, J = 20.8 Hz), 20.8, 20.5, 19.8. Anal. Calcd for $C_{12}H_{11}F_{13}O$: C, 34.47; H, 2.65; F, 59.06. Found: C, 34.67; H, 2.67; F, 59.73.

2,3-Epoxy-6,6,6-trifluoro-2,3-dimethylhexane (3m): bp_1 = 50 °C; ^1H NMR δ 2.05−1.73 (m, 2H), 1.59−1.32 (m, 2H), 1.02−0.85 (m, 9H). ^{13}C NMR δ 126.5 (q, J = 275.8 Hz), 62.3, 62.1, 29.5 (q, J = 29.1 Hz), 26.7, 20.5, 20.1, 17.7. Anal. Calcd for $C_8H_{13}F_3O$: C, 52.74; H, 7.19; F, 31.28. Found: C, 52.47; H, 7.27; F, 30.50.

5,5,5-Trichloro-2,3-epoxy-2,3-dimethylpentane (3n): bp_1 = 60 °C; ^1H NMR 2.81−2.62 (m, 2H), 1.28 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR 96.0, 62.5, 61.8, 58.4, 21.6, 21.4, 19.4. Anal. Calcd for $C_8H_{13}Cl_3O$: C, 41.50; H, 5.66; Cl, 45.93. Found: C, 41.22; H, 5.39; Cl, 46.25.

Acknowledgment. The authors acknowledge Akzo Nobel for a fellowship to one of us (F.R.), Dr. A. J. De Jongh, Dr. P. Hope, Dr. J. Meijer (Akzo Nobel Deventer), and Dr. L. Vertommen (Akzo Nobel Ahrnem) for very fruitful discussions during the course of this study, and Dr. D. Colombani for preliminary experiments.

JO951783N