Ozonolyses of Indene and of 1-Alkyl- and 1,1-Dialkyl-Substituted Indenes in Protic Solvents. Remarkable Effects of the Substituent Steric Bulk and the Solvent Nucleophilicity on the Direction of Cleavage of the Primary Ozonides and on the Mode of Capture of the Carbonyl Oxide Intermediates by the Solvents

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Received March 27, 1995[⊗]

Ozonolyses of indene (**1a**) and of 1-alkyl- and 1,1-dialkyl-substituted indenes **1b–h** in protic solvents including methanol, 2-propanol, and trifluoroethanol revealed that (i) two types of the solvent-derived products, a hemiperacetal and/or an isochroman derivative, are produced depending on the nucleophilicity of the solvent and the steric bulk of the alkyl substituent(s), and (ii) the regiochemistry of the fragmentation of a primary ozonide is a marked function of the nature of the 1-alkyl-substituent. In the case of indene (**1a**) and 1-substituted indenes **1b–e**, both possible modes of primary ozonide cleavage operate competitively yielding two carbonyl oxide intermediates in roughly equal amounts, whereas in the case of 1,1-dialkyl-substituted indenes **1f–h** the contribution of the less-hindered carbonyl oxide predominates.

Introduction

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.[2] Apart from the long-established utility of ozonolysis in synthesis and structure determination, much of the current interest in this process centers on the factors affecting the direction of cleavage of the primary ozonide (PO; 1,2,3-trioxolane) and the nature of the transient carbonyl oxide intermediate formed along with a stable carbonyl compound by fragmentation of the PO.[3] In this respect, ozonolysis in a protic solvent is informative because the structures of the solvent-derived products provide direct information on the mode of interaction of a carbonyl oxide with the solvent, and the product composition reflects the regioselectivity in the PO cleavage.[4] During our continuing interest in the mechanism of ozonolysis of indene derivatives,[5] we have conducted ozonolyses of indene and of 1-alkyl- and 1,1-dialkyl-substituted indenes in protic solvents including MeOH, 2-propanol, and 2,2,2-trifluoroethanol (TFE) and have found that (i) the steric bulk of the allylic dialkyl-substituents affects remarkably the direction of cleavage of the PO such that the substituents tend to be incorporated into the carbonyl fragment, and (ii) the structures of the solvent-derived products are particularly sensitive to the nucleophilicity of the solvent.

Results and Discussion

Ozonolysis of Indene. Ozonolysis of indene (**1a**) in MeOH–CH_2Cl_2 (1:2, v/v) at −70 °C gave a 1:1 mixture of two regioisomeric hemiperacetals, **15a** and **17a**, in 85% yield (Scheme 1 and Table 1). This is in harmony with the previous observation by Fliszar and co-workers[6] that the reaction in EtOH also gave a 1:1 mixture of the corresponding hemiperacetals. Treatment of either **15a** or **17a** with a catalytic amount of concd HCl in MeOH led to the formation of the same dimethoxy-substituted dioxepane **19a** (Scheme 2) (for the assignment of the structures of **15a** and **17a**, see the Experimental Section). Reaction of **1a** with ozone in *i*-PrOH–CH_2Cl_2 (1:2, v/v) also gave two hemiperacetals, **16a** (29%) and **18a** (37%), together with a small amount of indene ozonide (**10a**) (13%).

These results imply that the reaction between indene **1a** and ozone produces approximately equal quantities of both possible carbonyl oxide–carbonyl pairs, **3a** and **4a** (paths a and b in Scheme 1), which are immediately captured by MeOH yielding the α-methoxyalkyl hydroperoxides, **8a** and **11a**. Subsequent intramolecular additions of the hydroperoxy group to the adjacent formyl group produce the corresponding hemiperacetals, **15a** and **17a**, respectively (Scheme 1).

Remarkably different trends were observed for the ozonolysis in the less-nucleophilic solvent system, TFE–CH_2Cl_2 (1:2, v/v) (Table 1). The product consisted of an isochroman derivative **13a** (a 3:1 mixture of two stereoisomers; 26%) and indene ozonide (**10a**) (20%). Also, significant amounts of unidentified polyozonide was obtained. In connection with the latter, ozonolyses in aprotic solvents such as CH_2Cl_2 and ether gave mainly the oligomeric peroxide, together with **10a** (ca. 15%).

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1995.

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(2) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *11*, 745.

(3) (a) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978, Vol. 1; 1982, Vol. 2. (b) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335. (c) McCullough, K. J.; Nojima, M. In *Organic Peroxides*; Ando, W., Ed., Wiley: New York, 1992.

(4) (a) Griesbaum, K.; Kiesel, G. *Chem. Ber.* **1989**, *122*, 145. (b) Paryzek, Z.: Martynow, J.; Swoboda, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1222. (c) Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729.

(5) (a) McCullough, K. J.; Nakamura, N.; T. Fujisaka, T; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1991**, *113*, 1786. (b) Nakamura, N.; Fujisaka, T.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Am. Chem. Soc.* **1989**, *111*, 1799. (c) McCullough, K. J.; Nojima, M.; Miura, M.; Fujisaka, T.; Kusabayashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 35.

(6) Fliszar, S.; Belzecki, C.; Chylinska, J. B. *Can. J. Chem.* **1967**, *45*, 221.

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Scheme 1

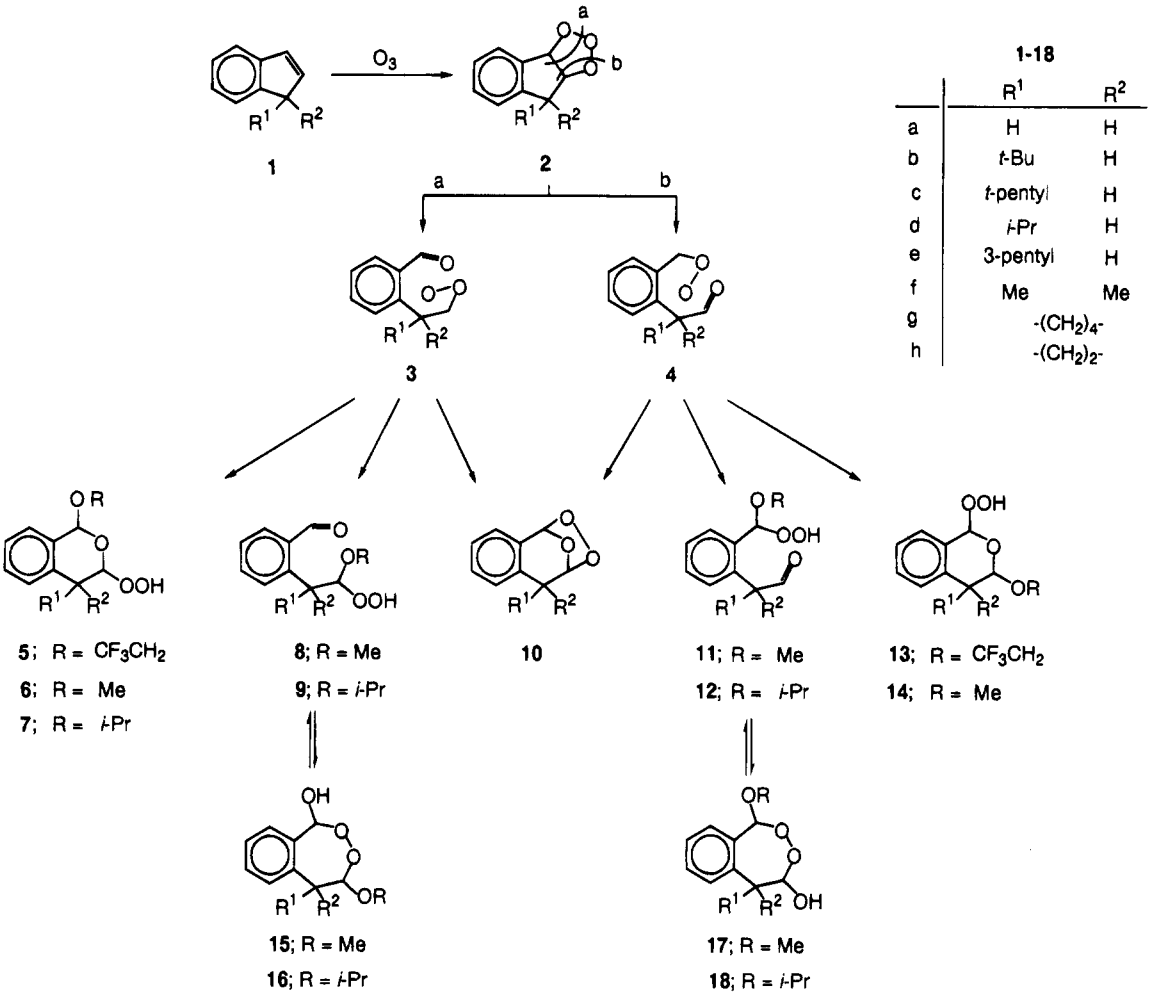


Table 1. Ozonolysis of Indenes 1a–h[a]

sbstr	solvent	products (% yield)
1a	CH_2Cl_2	**10a** (16)[b]
1a	MeOH–CH_2Cl_2	**15a** (43), **17a** (43)
1a	*i*-PrOH–CH_2Cl_2	**10a** (13), **16a** (29), **18a** (37)
1a	TFE–CH_2Cl_2	**10a** (20), **13a** (26)[b,c]
1b	MeOH–CH_2Cl_2	**6b** (11), **8b** + **15b** (43), **14b** (44),
1b	TFE–CH_2Cl_2	**5b** (55), **13b** (31),
1c	TFE–CH_2Cl_2	**5c** (50), **13c** (22)
1d	TFE–CH_2Cl_2	**5d** (22), **10d** (22), **13d** (15)
1e	TFE–CH_2Cl_2	**5e** (23), **10e** (30), **13e** (15)
1f	CH_2Cl_2	**10f** (7)[b]
1f	MeOH–CH_2Cl_2	**14f** (41),[c] **17f** (49)
1f	TFE–CH_2Cl_2	**10f** (12), **13f** (34)[c]
1g	CH_2Cl_2	**10g** (3)[b]
1g	MeOH–CH_2Cl_2	**14g** (50), **17g** (35)
1g	TFE–CH_2Cl_2	**10g** (5), **13g** (51)[b]
1h	CH_2Cl_2	**10h** (10)[b]
1h	MeOH–CH_2Cl_2	**15h** (19), **17h** (61)
1h	*i*-PrOH–CH_2Cl_2	**7h** (9), **10h** (4), **12h** + **18h** (60)
1h	TFE–CH_2Cl_2	**10h** (19), **13h** (39)[b]

[a] Reaction of indene with 1.5 equiv of ozone. [b] Considerable amounts of oligoozonide was also obtained. [c] Isochromans **13a**, **14f**, and **13f** were obtained as mixtures of two streoisomers.

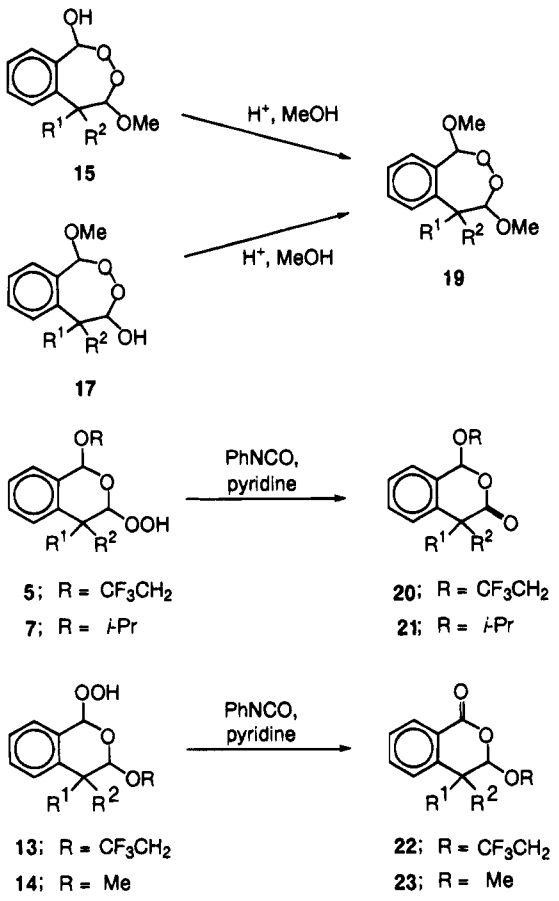
Consistent with the isochroman structure of **13a**, treatment with 2 equiv of phenyl isocyanate in the presence of a catalytic amount of pyridine led to the formation of lactone **22a** (Scheme 2).

Thus, the corresponding mixtures of two possible hemiperacetals, **15a,17a** or **16a,18a**, are produced from the ozonolyses in MeOH–CH_2Cl_2 and in *i*-PrOH–CH_2Cl_2, while the isochroman derivative **13a** is the sole solvent-derived product in the reaction in TFE–CH_2Cl_2. This is, to our knowledge, the first example that *the difference in nucleophilicity of protic solvents alters the course of capture of carbonyl oxide by the solvents.* Carbonyl oxides are well known to be captured by MeOH and *i*-PrOH producing the corresponding α-alkoxyalkyl hydroperoxides in high yields.[3] In the case of the less nucleophilic solvent, TFE, however, this process does not seem to occur.[7] Thus, as an alternative mode of decay of the carbonyl oxide/carbonyl pair **4a**, the carbonyl group oxygen may attack the electron-deficient carbon of the protonated carbonyl oxide yielding the pivotal intermediate **25a** (Scheme 3; R = CH_2CF_3). Subsequent attack by the solvent on the incipient carbocation center of **25a** produces the isochroman derivative **13a.** It is interesting to note that no TFE-participated product derived from the alternative intermediate **3a** is obtained. Thus, in TFE, **3a** is most likely to undergo the intramolecular cyclization or the intermolecular coupling yielding ozonide **10a** and unidentified polyozonides, respectively. The reason for the difference in behavior between **3a** and **4a** is, however, obscure.

Ozonolysis of 1-Alkyl-Substituted Indenes. To investigate the steric effect of the alkyl-substituent at C-1, we conducted ozonolyses of a series of 1-alkyl-substituted indenes **1b–e** in TFE–CH_2Cl_2. The data

(7) Some support for this notion comes from the experimental observation that in TFE–CH_2Cl_2 ozonolysis of β-methoxystyrene via benzaldehyde *O*-oxide does not give the solvent-captured product but instead a complex mixture of products including benzaldehyde.

Scheme 2



summarized in Table 1 indicate that the bulky alkyl-substituent exerts a remarkable influence on the efficiency of capture of both carbonyl oxide intermediates, **3** and **4**, by TFE (Scheme 1).

Reaction of 1-*tert*-butylindene (**1b**) with ozone in TFE–CH_2Cl_2 gave two regioisomeric isochroman derivatives, **5b** and **13b**, in high yields of 55% and 31%, respectively. This is in marked contrast to the fact that **13a** via the carbonyl oxide intermediate **4a** is the sole isochroman derivative obtained from indene (**1a**). As expected from the structure of **5b**, treatment with PhNCO led to the formation of lactone **20b**. Under similar conditions, lactone **22b** was obtained from **13b** (Scheme 2).

Although isochromans **5b** and **13b** could be obtained as several possible stereoisomers, in reality only one isomer was actually isolated in each case. X-ray crystallographic analysis of a suitable single crystal of **13b** shows unambiguously that it is indeed an isochroman derivative in which there is a *trans* relationship between the vicinal *tert*-butyl and trifluoroethoxy groups and the 1,3-trifluoroethoxy and hydroperoxy groups are *cis* (Figure 1). In difference nuclear Overhauser effect (NOE) experiments on isochroman **13b** using the methyl groups of *tert*-butyl group as the irradiation target, significant NOEs of 9% and 19% was observed for each of the signals corresponding to hydrogen atoms at C1 and C9 respectively (Figure 2). These observations suggest that the structure of **13b** in solution phase is similar to that in the solid state. Moreover, since similar large NOEs between the *tert*-butyl group and the hydrogen atoms at C-1 and C-9 were also observed for **5b**, it must have the same relative configuration as **13b**.

On the basis of the structures of the solvent-derived products and their compositions, a probable mechanism of ozonolysis of 1-*tert*-butylindene is summarized in Scheme 3. As a consequence of the sterically congested nature of indene **1b**, the approach of ozone should be restricted to the least hindered face of the olefinic double bond, consistent with the results of semiempirical calculations (PM3)[8,9] for the heat of formation of the PO **2b** (Figure 3). Thus, a concerted cycloaddition of ozone with retention of configuration would give the corresponding PO **2b**, which can undergo cleavage by either of the two possible modes (paths a and b), providing the carbonyl oxide intermediates **3b** and **4b**, respectively. In the intermediate **3b**, the resulting carbonyl and carbonyl oxide groups are formed on the same side of the molecular plane. Thus, protonation of the carbonyl oxide moiety is followed by the immediate partial capture by the adjacent aldehyde group oxygen to yield the cyclic intermediate **24b** (R = CH_2CF_3). Subsequent attack of TFE on the incipient carbocation center of **24b** from the less-hindered face *anti* to the *tert*-butyl group results in the stereoselective formation of **5b**. By the similar sequence of events, isochroman **13b** is selectively produced from carbonyl oxide **4b** (Scheme 3).

The identity of the alkyl-substituent of indene at C-1 was found to exert a small but significant influence on the course of the reaction. From the ozonolysis of 1-*t*-pentylindene (**1c**) in TFE–CH_2Cl_2, isochromans **5c** and **13c** were obtained in yields of 50% and 22%, respectively; no evidence was obtained for the formation of the corresponding ozonide **10c**. In contrast, the reaction of the less-crowded 1-isopropylindene (**1d**) with ozone gave a significant amount of ozonide **10d** (22%), together with the solvent-derived products **5d** (22%) and **13d** (15%). Ozonolysis of 1-(3-pentyl)indene (**1e**) also gave a mixture of ozonide **10e** and two isochroman derivatives **5e** and **13e** in similar relative proportions (Table 1). These results imply that in the cyclized intermediates **24b,c** and/or **25b,c** derived from the ozonolysis of *tert*-alkyl-substituted indenes **1b,c**, capture by TFE predominates, whereas, in the case of the sterically less-congested intermediates **24d,e** and/or **25d,e** from *sec*-alkyl-substituted indenes **1d,e**, intramolecular attack by the pendant hydroperoxy group can compete for capture by TFE. Arguably, the large steric requirements of the *tert*-alkyl-substituents make intramolecular cyclization to the ozonides **10b,c** less favorable. As judged from the magnitude of the observed NOE between *tert*-butyl group and the hydrogen at C-1 (Figure 2), the steric congestion in the bicyclic ozonide **10b**[10] seems to be significantly larger than that in the monocyclic hydroperoxides, **5b** and **13b**. In the case of *exo*-1-isopropylindene ozonide (*exo*-**10d**), no meaningful NOE is observed between the isopropyl group and the hydrogen at the 1-position.

Ozonolysis of 1-*tert*-butylindene (**1b**) in MeOH–CH_2Cl_2 also produced significantly different results from those obtained for indene (**1a**) in the same solvent system. Treatment of 1-*tert*-butylindene (**1b**) with ozone in MeOH–CH_2Cl_2 at −70 °C afforded two regioisomeric isochroman derivatives, **6b** (11%) and **14b** (44%), together with an equilibrium mixture of hemiperacetal **8b** and α-methoxyalkyl hydroperoxide **15b** (43%). It should be noticed that in the case of indene (**1a**) the product was a mixture of two hemiperacetals, **15a** and **17a**. The mixture of **8b**

(8) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209, 221.
(9) Toyoda, J. *JCPE News Lett.* **1990**, *2*, 37.
(10) Ozonide **10b** is prepared in 11% yield by the acidolysis of isochroman **5b**. Kawamura, S.; Teshima, K.; Nojima, M. Unpublished result.

Scheme 3

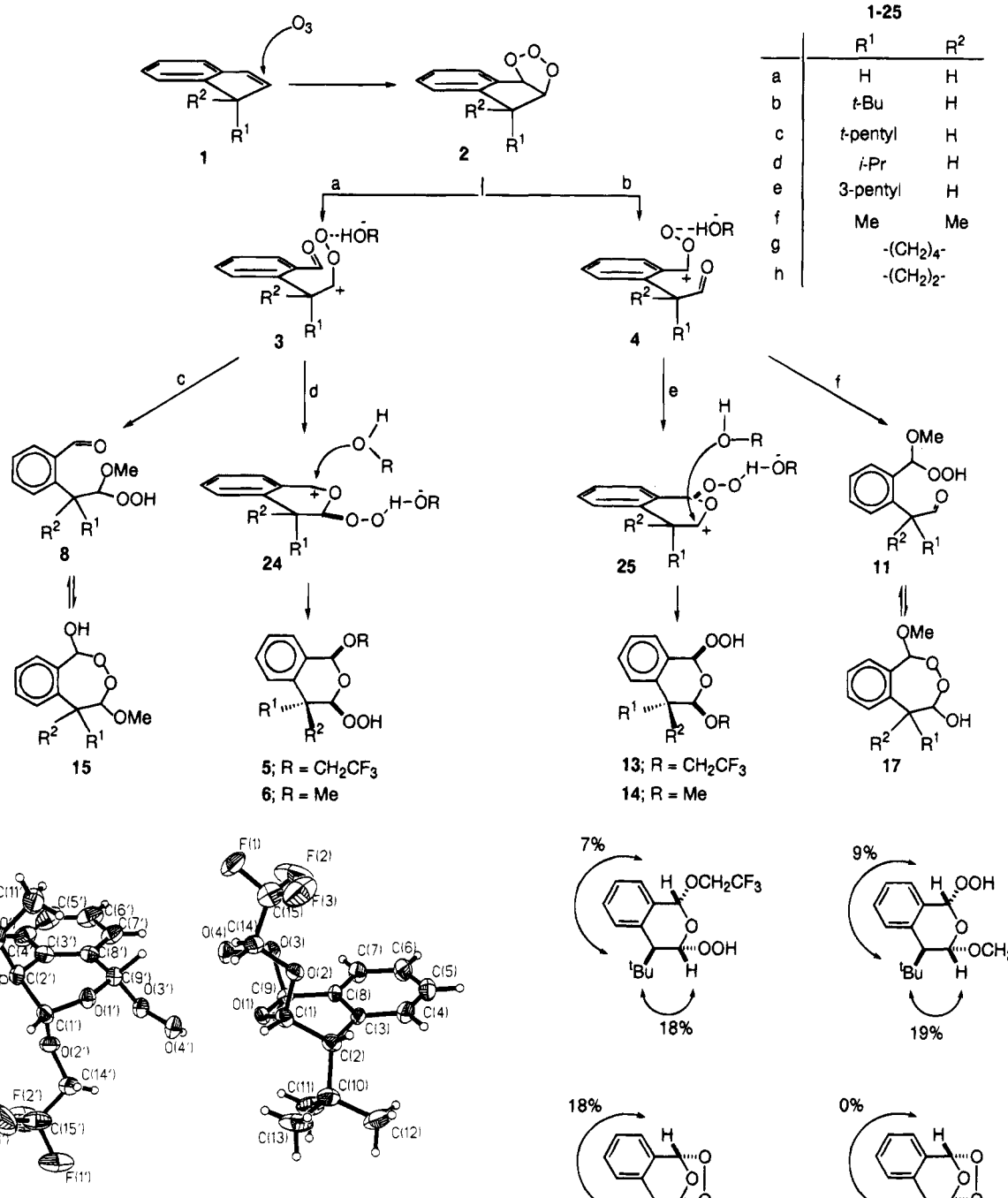


Figure 1. X-ray crystal structure of **13b** (two molecules per asymmetric unit, ORTEP[17] 30% probability ellipsoids).

Figure 2. NOE of isochroman derivatives and ozonides.

and **15b** was transformed into ester **27b** by the reaction sequence illustrated in Scheme 4. On the other hand, the isochroman derivative **14b** was converted into the corresponding lactone **23b** by dehydration with PhNCO/pyridine (Scheme 2).

Thus, capture of the carbonyl oxide intermediate **4b** by a highly nucleophilic solvent, MeOH, does not yield the α-methoxyalkyl hydroperoxide **11b** or the sequential product **17b** but instead gives exclusively the isochroman derivative **14b**. This suggests that in the tight conformer **4b**, the aldehyde oxygen atom is located in close proximity to the hydroperoxy carbon to minimize the steric repulsion with the bulky *tert*-butyl group and, as a consequence, partial capture of the incipient carbenium ion center by the adjacent formyl group (path e in Scheme 3) occurs much faster than the attack by the solvent (path f). In the case of the carbonyl oxide intermediate **3b**, however, two pathways c and d participate competitively. Moreover, the contribution of the former pathway involving direct attack of the carbonyl oxide moiety by the solvent is significantly larger than that of the latter involving partial capture by the adjacent carbonyl group.

Ozonolysis of 1,1-Dialkyl-Substituted Indenes. The most striking feature observed in the ozonolysis of 1,1-dialkyl-substituted indenes **1f–h** was the remarkably high regioselectivity in fragmentation of the corresponding PO **2f–h**. Ozonolysis of 1,1-dimethylindene (**1f**) in MeOH–CH_2Cl_2 gave a mixture of hemiperacetal **17f** (49%) and isochroman **14f** (41%), both of which are

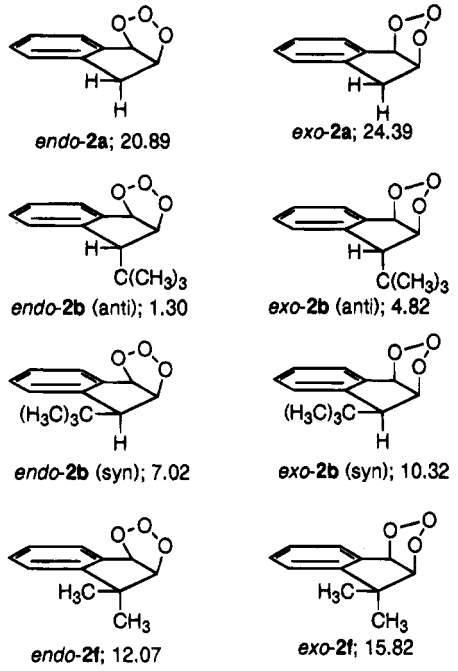
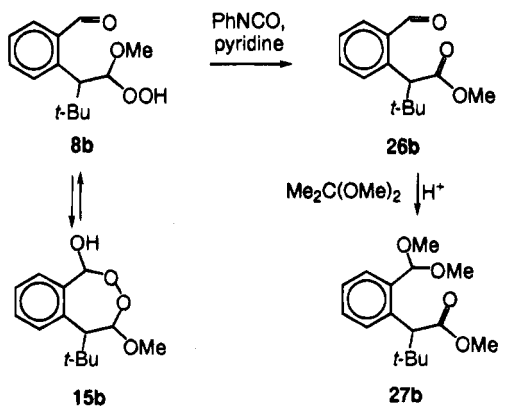


Figure 3. Heat of formation of primary ozonides (kcal/mol).

Scheme 4

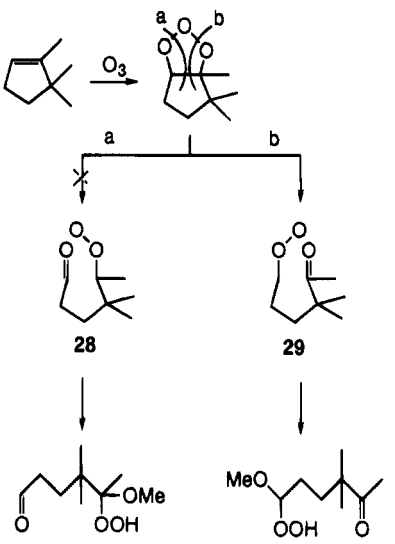


derived from capture of the same carbonyl oxide intermediate **4f** by methanol (Table 1 and Scheme 1). Because of the high yield of the methanol-derived products, it may be concluded that of the two possible intermediates **3f** and **4f**, only the latter contributes in the reaction. From the ozonolysis in TFE–CH_2Cl_2, isochroman **13f** (a 1:1 mixture of two isomers) was isolated in 34% yield, together with a small amount of ozonide **10f** (12%) and unidentified polymeric peroxides (ca. 30%). Similar trends were observed for the ozonolyses of indene **1g**, too.

Ozonolysis of the sterically less-congested indene **1h** in MeOH–CH_2Cl_2 gave, however, a mixture of two hemiperacetals **15h** and **17h** in a ratio of 1:3 (80% yield), suggesting that in the case of PO **2h** both possible scission pathways (paths a and b in Scheme 1) participate, although the contribution of the latter producing the carbonyl oxide intermediate **4h** is significantly larger than that leading to the formation of **3h**. Ozonolysis of **1h** in TFE/CH_2Cl_2 gave the isochroman derivative **13h** (39%) and ozonide **10h** (19%).

To understand the notable directive effect of the allylic dialkyl-substituents on the fission of PO **2**, semiempirical calculations on the structures of PO **2b** and **2f** were undertaken (Figure 3). In both cases the lowest energy conformation has the 1,2,3-trioxolane ring in an *endo*-folded envelope (Figure 3).[11,12] A least-motion fragmentation from the structure **2f** would lead to the formation of either **3f** or **4f** depending on the fission pathway. In the *syn*-carbonyl oxide **3f** (Scheme 1)[12] the steric interaction between the terminal oxygen of the carbonyl oxide moiety and one of the adjacent methyl groups would be significant, thereby making the formation of this intermediate significantly disfavored. In the case of 1-*tert*-butylindene the *tert*-butyl group and the trioxolane ring are *anti* to each other and therefore, no significant disadvantage is expected for the cycloreversion leading to the relevant intermediate **3b**.

Scheme 5



In this connection, there are some precedents which imply that the steric effects play an important role in determining the direction of cleavage of PO.[13] The most clear-cut example is the ozonolysis of 1,5,5-trimethylcyclopentene (Scheme 5).[13c] It would be reasonable to expect that, on the basis of electronic considerations, the formation of the corresponding ketone oxide **28** should be favored,[4a,c] whereas a preponderance of the aldehyde oxide **29** would arise from the influence of steric effects. Since only the less-hindered aldehyde oxide **29** is actually produced, the steric effect of the allylic methyl groups is decisive.

Conclusion. We have found that the solvent nucleophilicity can alter the mode of capture of the carbonyl oxide intermediates by the protic solvent. Since both types of the solvent-derived products, hemiperacetals and isochromans, are potentially useful precursors of cyclic peroxides,[3c] the above finding may be important from the point of view of the selective preparation of the desired solvent-derived products. The notable directing effect of the allylic substituents on the regiochemistry of the fragmentation of a PO is also interesting. Thus, from an appropriately substituted cycloalkene, the sterically less-congested carbonyl oxide may be generated exclusively.

(11) The primary ozonide from 1-alkylcyclopentene also has the lowest-energy conformation of the 1,2,3-trioxolane ring in an *endo*-folded envelope.[11]

(12) Bunnelle, W. H.; Lee, S.-G. *J. Am. Chem. Soc.* **1992**, *114*, 7577.
(13) (a) Criegee, R. *Chem. Ber.* **1975**, *108*, 743. (b) Griesbaum, K.; Volpp, W. *Chem. Ber.* **1988**, *121*, 1795. (c) Mayr, H.; Baran, J.; Will, E.; Yamakoshi, H.; Teshima, K.; Nojima, M. *J. Org. Chem.* **1994**, *59*, 5055.

Experimental Section

General. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise noted) with $SiMe_4$ as standard. Indenes **1b**–**e**[14] and **1f**–**h**[15] were prepared by the reported methods; indene **1c**: bp 105–107 °C (15 mmHg); ^1H NMR (CCl_4) δ 0.8–1.8 (m, 11 H), 3.38 (br s, 1 H), 6.40 (d, J = 9 Hz, 1 H), 6.73 (d, J = 9 Hz, 1 H), 7.0–7.5 (m, 4 H); indene **1e**: bp 103–105 °C (15 mmHg); ^1H NMR (CCl_4) δ 0.4–2.2 (m, 11 H), 3.55 (br s, 1 H), 6.42 (d, J = 6 Hz, 1 H), 6.77 (d, J = 6 Hz, 1 H), 7.0–7.5 (m, 4 H). The method of ozonolysis was previously described.[5a]

Caution: Since organic ozonides and peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions. No particular difficulties were experienced in handling any of the new organic ozonides or peroxides synthesized in this work using the reaction scales and procedures described below together with the safeguard mentioned above.

Ozonolysis of Indene (1a) in CH_2Cl_2. To a solution of indene (**1a**) (232 mg, 2 mol) in CH_2Cl_2 (20 mL) was passed a slow stream of ozone (1.5 equiv) at −70 °C. After evaporation of the solvent, the crude products were separated by column chromatography on silica gel. Elution with ether–hexane (1:9, v/v) gave ozonide **10a**. Subsequent elution with ether–hexane (1:1, v/v) gave oligoozonide: mp 100–103 °C (from hexane); ^1H NMR (CCl_4) δ 2.7–3.5 (br s), 5.5–6.6 (br s), 6.9–7.9 (br s), the ratio of the peak areas being 1:1:2; IR 3600–3200, 1720, 1690, 1600, 1480, 1320, 1200, 1090, 750, 670 cm^{-1}; molecular weight (vapor-pressure osmometry; $CHCl_3$) 1068. Anal. Calcd for $(C_9H_8O_3)_n$: C, 65.84; H, 4.92. Found: C, 64.72; H, 5.73.

4,5-Dihydro-1,4-epoxy-1*H*-2,3-benzodioxepin (indene ozonide; 10a): mp 55–56 °C (lit.[6] 62–63 °C) (from hexane); ^1H NMR (CCl_4) δ 2.83 (d, J = 17 Hz, 1 H), 3.23 (dd, J = 17 and 2 Hz, 1 H), 5.98 (d, J = 2 Hz, 1 H), 6.18 (s, 1 H), 7.0–7.6 (m, 4 H). Anal. Calcd for $C_9H_8O_3$: C, 65.84; H, 4.92. Found: C, 65.69; H, 4.92.

Ozonolysis of Indene (1a) in MeOH–CH_2Cl_2. To a solution of indene (**1a**) (232 mg, 2 mol) in MeOH–CH_2Cl_2 (20 mL, 1:2, v/v) was passed a slow stream of ozone (1.5 equiv) at −70 °C. Then, the reaction mixture was poured into ice-cold aqueous $NaHCO_3$ and was extracted with ether. After the products were dried and concentrated, they were separated by column chromatography on silica gel (column, 2 × 50 cm; 20 g of silica gel; elution with ether–hexane, 1:10 to 1:5). The hemiperacetal **15a** (188 mg, 48%) was eluted first followed by the isomeric hemiperacetal **17a** (184 mg, 47%).

1-Hydroxy-4-methoxy-4,5-dihydro-1*H*-2,3-benzodioxepin (15a): mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 2.80 (dd, J = 14 and 4 Hz, 1 H), 3.47 (s, 3 H), 3.66 (dd, J = 14 and 9 Hz, 1 H), 4.05 (br s, 1 H; H-D exchange in D_2O), 4.95 (ddd, J = 9, 4, and 2 Hz, 1 H), 6.35 (br s, 1 H; s in D_2O), 7.1–7.8 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 37.42, 55.42, 101.44, 108.74, 127.92, 128.36, 128.60, 130.37, 132.64, 137.05; IR 3600–3000, 1450, 1300, 1100, 960, 730 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 9.18. Found: C, 61.50; H, 9.05.

1-Methoxy-4-hydroxy-4,5-dihydro-1*H*-2,3-benzodioxepin (17a): mp 111–113 °C; ^1H NMR δ 2.86 (dd, J = 14 and 4 Hz, 1 H), 3.65 (s, 3 H), 3.66 (dd, J = 14 and 9 Hz, 1 H), 5.44 (ddd, J = 9, 4, and 2 Hz, 1 H), 5.94 (s, 1 H), 7.1–7.5 (m, 4 H) (the OH proton could not be detected; no change in spectra in D_2O); ^{13}C NMR δ 38.76, 55.54, 102.17, 107.71, 127.83, 128.33, 128.56, 130.27, 132.60, 135.23; IR 3600–3100, 1450, 1340, 1195, 1080, 980, 740 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 9.18. Found: C, 61.01; H, 9.15.

Assignment of the Regiochemistry of Two Isomeric Hemiperacetals, 15 and 17. In ^1H NMR spectra of 1,4-disubstituted 4,5-dihydro-*1H*-2,3-benzodioxepin **15** and **17**, the characteristic differences in chemical shift of the protons at C-1 and of the protons at C-4 between **15** and **17** made the assignment of the structures possible. In two pairs the phenyl-substituted methine at C-1 was consistently downfield of the methine proton at C-4 (0.5-1.4 ppm). When the protons at the same position (C-1 or C-4) were compared, the hydroxy-substituted methine resonanced at a lower field compared to the methoxy-substituted one (ca. 0.2 ppm). Thus, of the two possible regioisomers, the one which showed the peak with the higher field δ value for the proton at C-1 and the lower field δ value for the proton at C-4 was assigned as **17**. The same relations holded for the chemical shifts of the C-1 and C-4 carbons in ^{13}C NMR spectra.

Ozonolysis of Indene (1a) in *i*-PrOH–CH_2Cl_2. A solution of indene (**1a**) (232 mg, 2 mmol) in *i*-PrOH–CH_2Cl_2 (20 mL, 1:2, v/v) was treated with 1.5 equiv of ozone at −70 °C. After workup as above, the crude products were separated by column chromatography on silica gel. The first fraction (elution with benzene–hexane, 1:1) contained indene ozonide (**10a**) (43 mg, 13%). From the second fraction (elution with ether–benzene, 98:2), was obtained hemiperacetal **16a** (130 mg, 29%). The third fraction (ether–benzene; 96:4) contained hemiperacetal **18a** (166 mg, 37%).

Hemiperacetal 16a: mp 88–89 °C (from ether–hexane); ^1H NMR δ 1.0–1.5 (m, 6 H), 2.72 (dd, J = 14 and 4 Hz, 1 H), 3.70 (dd, J = 14 and 9 Hz, 1 H), 3.7–4.3 (m, 1 H), 5.17 (ddd, J = 9, 4, and 2 Hz, 1 H), 6.37 (br s, 1 H), 7.0–7.7 (m, 4 H); IR 3600–3100, 1445, 1320, 1180, 1040, 975, 725 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.25; H, 7.21. Found: C, 64.20; H, 7.24.

Hemiperacetal 18a: mp 130–131 °C (from ether–hexane); ^{1}NMR δ 1.0–1.5 (m, 6 H), 2.75 (dd, J = 14 and 4 Hz, 1 H), 3.67 (dd, J = 14 and 9 Hz, 1 H), 3.8–4.3 (m, 1 H), 5.42 (ddd, J = 9, 4, and 2 Hz, 1 H), 6.13 (br s, 1 H), 6.9–7.6 (m, 4 H); IR 3600–3100, 1450, 1110, 1070, 970, 740 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.25; H, 7.21. Found: C, 64.04; H, 7.28.

Ozonolysis of Indene (1a) in CF_3CH_2OH–CH_2Cl_2. A solution of indene (**1a**) (232 mg, 2 mmol) in CF_3CH_2OH–CH_2Cl_2 (20 mL, 1:2, v/v) was treated with 1.5 equiv of ozone at 0 °C. After workup as above, the crude products were separated by column chromatography on silica gel. The first fraction (elution with ether–hexane 1:15) contained ozonide **10a** (66 mg, 20%). From the second fraction (elution with ether–hexane 1:5) was obtained the isochroman **13a** (137 mg, 26%; a 3:1 mixture of two stereoisomers; only the major isomer could be isolated in a pure state by the repeated column chromatography on silica gel). Subsequent elution with ether–hexane (1:3) gave the unidentified oligomers (140 mg). The ^1H NMR spectra showed three broad signals at δ around 3.0, 6.0, and 7.2; the strong absorption band assignable to OH group(s) in IR spectra; the elemental analysis data were very similar to those calculated for $(C_9H_8O_3)_n$.

3,4-Dihydro-3-(trifluoroethoxy)-1*H*-2-benzopyran-1-yl hydroperoxide (13a) (major isomer): oil; ^1H NMR (CCl_4) δ 3.03 (d, J = 4 Hz, 2 H), 4.08 (q, J = 9 Hz, 2 H), 5.25 (t, J = 4 Hz, 1 H), 6.04 (s, 1 H), 6.8–7.3 (m, 4 H), 8.90 (s, 1 H); ^{13}C NMR δ 32.71, 64.77 (q, J = 34 Hz), 96.85, 100.68, 124.01 (q, J = 278 Hz), 126.86, 127.17, 128.59, 129.35, 129.73, 131.31; IR 3550–3200, 1280, 1150, 1070, 740 cm^{-1}. Anal. Calcd for $C_{11}H_{11}F_3O_4$: C, 50.00; H, 4.21. Found: C, 50.27; H, 4.43.

Isochroman 13a (minor isomer; in admixture with 60% of the major one): oil; ^1H NMR (CCl_4) δ 2.86 (d, J = 6 Hz, 2 H), 4.08 (q, J = 9 Hz, 2 H), 5.59 (t, J = 6 Hz, 1 H), 5.79 (s, 1 H), 6.9–7.4 (m, 4 H); ^{13}C NMR δ 30.12, 61.13, (q, J = 35 Hz), 98.53, 98.61 (only some characteristic signals could be differentiated).

Ozonolysis of 1-Alkyl-Substituted Indene 1b–e in MeOH–CH_2Cl_2. Ozonolysis of 1-*tert*-butylindene (**1b**) is representative. After treating a MeOH–CH_2Cl_2 solution (20 mL, 1:2, v/v) of indene **1b** (364 mg, 2 mmol) with ozone (1.5 equiv) at −70 °C, the crude products were separated by column chromatography on silica gel. The first fraction (elution with benzene) contained isochroman **6b** (55 mg, 11%). From the second fraction (elution with ether–benzene, 1:99) was isolated isochroman **14b** (222 mg, 44%). The third fraction (elution with ether–benzene; 3:97) contained a 1:1 mixture of methoxyalkyl hydroperoxide **8b** and hemiperacetal **15b** (217 mg, 43%).

Isochroman 6b: mp 69–70 °C (from hexane); ^1H NMR (CCl_4) δ 0.98 (s, 9 H), 2.50 (s, 1 H), 3.72 (s, 1 H), 5.43 (s, 1 H), 5.60 (s, 1 H), 7.0-7.5 (m, 4 H), 8.60 (s, 1 H); IR 3600–3200,

(14) Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454.
(15) Cedheim, L.; Eberson, L. *Synthesis* **1973**, 159.

1450, 1350, 1210, 1060, 745 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 8.01. Found: C, 66.60; H, 7.97.

Isochroman 14b: oil; ^1H NMR (CCl_4) δ 0.95 (s, 9 H), 2.52 (s, 1 H), 3.34 (s, 3 H), 5.12 (s, 1 H), 5.97 (s, 1 H), 7.0-7.6 (m, 4 H), 9.54 (br s, 1 H); IR 3600–3200, 1450, 1360, 1120, 1060, 745 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 8.01. Found: C, 66.66; H, 8.12.

A 1:1 mixture of 8b and 15b: oil; ^1H NMR (CCl_4) δ 0.96 (s, 9 H), 2.86 (d, J = 1 Hz, 0.5 H, **8b**), 3.37 (s, 1.5 H), 3.41 (s, 1.5 H), 4.32 (d, J = 10 Hz, 0.5 H, **15b**), 5.09 (d, J = 10 Hz, 0.5 H, **15b**), 5.24 (d, J = 1 Hz, 0.5 H, **8b**), 6.12 (br s, 1 H, **15b**), 7.0–7.8 (m, 4 H), 9.43 (br s, 0.5 H, **8b**), 10.20 (s, 0.5 H, **8b**).

Transformation of a Mixture of 8b and 15b into Ester 27b. By treating with phenyl isocyanate (2 equiv) in the presence of pyridine, the mixture of **8b** and **15b** (252 mg, 1 mmol) was transformed into aldehyde ester **26b** (150 mg, 64% yield): oil; ^1H NMR (CCl_4) δ 1.00 (s, 9 H), 3.60 (s, 3 H), 5.02 (s, 1 H), 7.2–8.0 (m, 4 H), 10.25 (s, 1 H); IR 1730, 1700, 1600, 1150, 755 cm^{-1}. Subsequent treatment of **26b** (150 mg) with 2,2-dimethoxypropane (2 mL) in the presence of a crop of *p*-toluenesulfonic acid at room temperature for 2 h gave ester **27b** (91 mg, 61%).

Ester 27b: oil; ^1H NMR (CCl_4) δ 1.03 (s, 9 H), 3.10 (s, 3 H), 3.37 (s, 3 H), 3.58 (s, 3 H), 4.08 (s, 1 H), 5.59 (s, 1 H), 7.1–7.8 (m, 4 H); ^{13}C NMR δ 28.19, 35.22, 51.37, 51.48, 53.56, 53.98, 101.00, 126.63, 126.90, 127.77, 129.70, 134.86, 136.56, 173.82; IR 1730, 1440, 1350, 1140, 1050, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.53; H, 8.64. Found: C, 68.48; H, 8.46.

Ozonolysis of 1-Alkyl-Substituted Indene 1b–e in CF_3CH_2OH–CH_2Cl_2. Ozonolysis of 1-*tert*-butylindene (**1b**) is representative. A solution of **1b** (364 mg, 2 mmol) in CF_3CH_2OH–CH_2Cl_2 (20 mL, 1:2, v/v) was treated with 1.5 equiv of ozone at 0 °C. After workup as above, the crude products were separated by column chromatography on silica gel. From the first fraction (elution with benzene) was obtained isochroman **5b** (352 mg, 55%). Subsequent elution with ether–benzene (2:98, v/v) gave isochroman **13b** (198 mg, 31%).

Isochroman 5b: oil; ^1H NMR δ 0.97 (s, 9 H), 2.62 (s, 1 H), 4.29 (q, J = 9 Hz, 2 H), 5.75 (s, 2 H), 7.0–7.5 (m, 4 H), 8.55 (s, 1 H); ^{13}C NMR δ 28.11, 34.41, 48.65, 65.64 (q, J = 34 Hz), 95.88, 99.74, 123.95 (q, J = 279 Hz), 126.45, 127.14, 128.21, 130.50, 131.80, 131.86; IR 3600–3200, 1280, 1160, 1090, 750 cm^{-1}. Anal. Calcd for $C_{15}H_{19}F_3O_4$: C, 56.24; H, 5.99. Found: C, 55.62; H, 6.10.

Isochroman 13b: mp 133–134 °C (from benzene); ^1H NMR δ 0.96 (s, 9 H), 2.71 (s, 1 H), 4.03 (q, J = 9 Hz, 1 H), 4.07 (q, J = 9 Hz, 1 H), 5.49 (s, 2 H), 6.10 (s, 1 H), 7.1–7.5 (m, 4 H), 8.66 (s, 1 H); ^{13}C NMR δ 28.12, 33.98, 51.33, 64.07 (q, J = 34 Hz), 97.30, 99.13, 124.21 (q, J = 279 Hz), 126.57, 127.00, 128.50, 128.93, 131.29, 133.00; IR 3600–3200, 1280, 1160, 1090, 755 cm^{-1}. Anal. Calcd for $C_{15}H_{19}F_3O_4$: C, 56.24; H, 5.99. Found: C, 55.96; H, 5.94.

Isochroman 5c: oil; ^1H NMR (CCl_4) δ 0.88 (s, 6 H), 0.92 (t, J = 7 Hz, 3 H), 1.38 (q, J = 7 Hz, 1 H), 1.45 (q, J = 7 Hz, 1 H), 2.74 (s, 1 H), 4.26 (q, J = 9 Hz, 1 H), 4.33 (q, J = 9 Hz, 1 H), 5.71 (s, 1 H), 5.57 (s, 1 H), 7.1–7.4 (m, 4 H), 8.50 (s, 1 H).

Isochroman 13c: mp 121–122 °C (ether–hexane); ^1H NMR (CCl_4) δ 0.85 (s, 3 H), 0.88 (s, 3 H), 0.92 (t, J = 7 Hz, 1 H), 1.36 (q, J = 7 Hz, 1 H), 1.47 (q, J = 7 Hz, 1 H), 2.83 (s, 1 H), 4.00 (q, J = 9 Hz, 1 H), 4.10 (q, J = 9 Hz, 1 H), 5.44 (s, 1 H), 6.11 (s, 1 H), 7.1–7.4 (m, 4 H). Anal. Calcd for $C_{16}H_{21}F_3O_4$: C, 57.48; H, 6.33. Found: C, 57.20; H, 6.43.

Ozonide 10d: oil; ^1H NMR (CCl_4) δ 0.89 (d, J = 15 Hz, 3 H), 1.15 (d, J = 15 Hz, 3 H), 1.7–2.5 (m, 1 H), 2.68 (d, J = 4 Hz, 1 H), 5.90 (s, 1 H), 6.11 (s, 1 H), 7.0–7.5 (m, 4 H); ^{13}C NMR δ 18.70, 21.00, 31.33, 48.80, 99.78, 101.86, 124.83, 126.14, 126.51, 129.74, 133.32, 133.85.

Isochroman 5d: oil; ^1H NMR (CCl_4) δ 0.92 (d, J = 6 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.5–2.1 (m, 1 H), 2.57 (d, J = 6 Hz, 1 H), 4.24 (q, J = 9 Hz, 2 H), 5.53 (s, 1 H), 5.57 (s, 1 H), 7.0–7.5 (m, 4 H), 8.60 (s, 1 H); ^{13}C NMR δ 19.74, 20.40, 32.23, 45.55, 65.75 (q, J = 34 Hz), 95.93, 100.76, 123.95 (q, J = 279 Hz), 126.58, 127.00, 128.70, 129.18, 130.83, 133.46.

Isochroman 13d: mp 81–83 °C (ether–hexane); ^1H NMR (CCl_4) δ 0.90 (d, J = 6 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.6–2.2 (m, 1 H), 2.73 (d, J = 6 Hz,1 H), 4.03 (q, J = 9 Hz, 2 H), 5.28 (s, 1 H), 6.03 (s, 1 H), 7.0–7.5 (m, 4 H), 9.07 (s, 1 H); ^{13}C NMR δ 19.69, 20.23, 31.99, 47.79, 64.14 (q, J =34 Hz), 98.06, 99.24, 124.20 (q, J = 279 Hz), 126.70, 126.88, 128.28, 129.02, 129.77, 134.43. Anal. Calcd for $C_{14}H_{17}F_3O_4$: C, 54.89; H, 5.61. Found: C, 54.89; H 5.65.

Ozonide 10e: oil; ^1H NMR (CCl_4) δ 0.5–2.0 (m, 11 H), 2.96 (s, 1 H), 5.86 (s, 1 H), 6.16 (s, 1 H), 7.1–7.5 (m, 4 H). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.76; H, 7.76. Found: C, 71.95; H, 7.75.

Isochroman 5e: oil; ^1H NMR (CCl_4) δ 0.7–1.9 (m, 11 H), 2.86 (d, J = 6 Hz, 1 H), 4.21 (q, J = 9 Hz, 2 H), 5.47 (s, 1 H), 5.75 (s, 1 H), 7.0–7.5 (m, 4 H), 8.75 (s, 1 H); ^{13}C NMR δ 11.37, 11.71, 22.34, 22.73, 40.55, 45.76, 65.91 (q, J = 35 Hz), 96.17, 100.61, 123.93 (q, J = 278 Hz), 126.59, 126.73, 128.31, 128.73, 128.94, 134.13.

Isochroman 13e: mp 67–68 °C (hexane); ^1H NMR (CCl_4) δ 0.7–1.8 (m, 11 H), 2.99 (d, J = 3 Hz, 1 H), 4.02 (q, J = 9 Hz, 2 H), 5.23 (s, 1 H), 6.05 (s, 1 H), 7.0–7.5 (m, 4 H), 9.32 (s, 1 H); ^{13}C NMR δ 11.55, 11.71, 22.43, 22.95, 42.89, 45.70, 62.21 (q, J = 34 Hz), 97.82, 99.45, 124.23 (q, J = 279 Hz), 126.54, 126.94, 128.31, 129.20, 129.29, 135.17. Anal. Calcd for $C_{16}H_{21}F_3O_4$: C, 57.48; H, 6.33. Found: C, 57.53; H, 6.43.

Ozonolysis of Dialkyl-Substituted Indene 1f–h in MeOH–CH_2Cl_2. Ozonolysis of **1g** is representative. A MeOH–CH_2Cl_2 solution of **1g** (340 mg, 2 mmol) was treated with 1.5 equiv of ozone at −70 °C. After workup as above, the products were separated by column chromatography on silica gel (elution with ether–hexane, 1:4 and then 3:7). Isochroman **14g** (250 mg, 50%) was isolated first and then the hemiperacetal **17g** (175 mg, 35%).

Isochroman 14g: oil; ^1H NMR (CCl_4) δ 1.4–2.1 (m, 8 H), 3.50 (s, 3 H) 4.77 (s, 1 H), 6.05 (s, 1 H), 7.0–7.3 (m, 4 H), 9.45 (s, 1 H); ^{13}C NMR δ 26.97, 27.06, 35.60, 37.53, 49.08, 56.79, 101.66, 103.44, 125.76, 125.91, 127.15, 127.42, 129.84, 145.11; IR 3600–3150, 2950, 1445, 1200, 1070, 750 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26. Found: C, 66.99; H, 7.68.

Hemiperacetal 17g: oil; ^1H NMR (CCl_4) δ 1.4–2.0 (m, 8 H), 3.47 (s, 3 H), 4.18 (d, J = 5 Hz, 1 H; H–D exchange in D_2O), 4.97 (dd, J = 5 and 2 Hz, 1 H) (d, J = 2 Hz in D_2O), 5.76 (d, J = 2 Hz, 1 H), 7.0–7.5 (m, 4 H); ^{13}C NMR δ 22.93, 25.10, 34.31, 34.45, 54.94, 55.41, 104.83, 107.44, 125.95, 127.16, 128.15, 129.24, 135.10, 140.70; IR 3600–3150, 2950, 1440, 1320, 1180, 1075, 740 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26. Found: C, 66.82; H, 7.43.

Isochroman 14f: oil (a 1:1 mixture of two stereoisomers); ^1H NMR δ 1.15 (s, 1.5 H), 1.20 (s, 1.5 H), 1.27 (s, 1.5 H), 1.29 (s, 1.5 H), 3.45 (s, 1.5 H), 3.55 (s, 1.5 H), 4.50 (s, 0.5 H), 4.73 (s, 0.5 H), 6.07 (s, 1 H), 7.1–7.5 (m, 4 H), 9.22 (s, 0.5 H), 9.38 (s, 0.5 H); ^{13}C NMR δ 22.77, 22.93, 23.86, 29.08, 37.63, 37.92, 56.60, 57.05, 100.03, 102.04, 102.58, 105.04, 124.80, 125.42, 126.21, 126.24, 127.13, 127.53, 127.56, 128.28, 129.57, 129.86, 141.88, 144.32; IR 3650–3150, 1450, 1310, 1200, 1030, 750, 550 cm^{-1}.

Hemiperacetal 17f: oil; ^1H NMR (CCl_4) δ 1.47 (s, 6 H), 3.20 (d, J = 6 Hz, 1 H) (H–D exchange in D_2O), 3.53 (s, 3 H), 4.93 (dd, J = 6 and 2 Hz, 1 H) (d, J = 2 Hz in D_2O), 5.78 (d, J = 2 Hz, 1 H), 7.1–7.5 (m, 4 H); ^{13}C NMR δ 25.26, 27.44, 43.90, 55.48, 106.13, 107.75, 125.97, 127.28, 128.66, 129.14, 135.26, 142.08; IR 3600–3200, 1470, 1330, 1190, 1070, 775 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.25; H, 7.21. Found: C, 63.95; H, 7.24.

Hemiperacetal 15h: (in admixture with 50% of **17h**); oil; ^1H NMR δ 0.4–1.6 (m, 4 H), 3.40 (s, 3 H), 4.98 (d, J = 2 Hz, 1 H), 6.38 (br s, 1 H), 7.1–7.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 6.31, 10.75, 25.38, 55.84, 101.39, 109.34, 127.83, 127.84, 128.14, 128.61, 137.88, 138.99. Treatment with a catalytic amount of concd HCl in MeOH gave dimethoxydioxepane **19h** in 85% yield (for the detail, see the latter).

Hemiperacetal 17h: mp 104–105 °C (from ether–hexane); ^1H NMR δ 0.4–1.6 (m, 4H), 3.13 (br s, 1 H; H–D exchange in D_2O), 3.67 (s, 3 H), 5.50 (br s, 1 H), 6.00 (br s, 1 H), 7.1–7.5 (m, 4 H); ^{13}C NMR δ 6.33, 9.86, 26.06, 55.48, 102.52, 107.61, 127.75, 127.77, 128.17, 128.53, 137.21, 137.66; IR 3600–3200, 1340, 1190, 1080, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.84; H, 6.36. Found: C, 64.62; H, 6.30.

Ozonolysis of Indene 1h in *i*-PrOH−CH_2Cl_2. A solution of indene **1h** (284 mg, 2 mmol) in *i*-PrOH−CH_2Cl_2 (20 mL, 1:2, v/v) was treated with 1.5 equiv of ozone at −70 °C. After workup as above, the crude products were separated by column chromatography on silica gel. The first fraction (elution with benzene−hexane, 1:1) contained ozonide **10h** (14 mg, 4%). From the second fraction (elution with ether−benzene, 99:1) was obtained isochroman **7h** (45 mg, 9%). The third fraction (elution with ether−benzene; 97:3) contained a 1:2 mixture of hydroperoxide **12h** and hemiperacetal **18h** (298 mg, 60%).

Ozonide 10h: mp 105−106 °C (from benzene−hexane); ^{1}H NMR (CCl_4) δ 0.7−1.4 (m, 4 H), 5.00 (s, 1 H), 6.23 (s, 1 H), 7.0−7.5 (m, 4 H). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.45; H, 5.31. Found: C, 69.16; H, 5.23.

Isochroman 7h: oil; ^{1}H NMR δ 0.5−1.7 (m, 10 H), 3.9−4.5 (m, 1 H), 4.80 (s, 1 H), 5.93 (s, 1 H), 7.1−7.7 (m, 4 H), 9.53 (s, 1 H); IR 3550−3200, 1380, 1320, 1070, 755 cm^{-1}.

A 1:2 mixture of hydroperoxide 12h and hemiperacetal 18h: mp 118−120 °C (from CCl_4); ^{1}H NMR (**12h**) δ 0.4−1.7 (m, 10 H), 3.9−4.5 (m, 1 H), 6.30 (s, 1 H), 7.1−7.7 (m, 4 H), 8.65 (br s, 1 H; H−D exchange in D_2O), 9.08 (s, 1 H); (**18h**) δ 0.4−1.7 (m, 10 H), 3.16 (br s, 1 H; H−D exchange in D_2O), 3.9−4.5 (m, 1 H), 5.51 (br s, 1 H), 6.21 (br s, 1 H), 7.1−7.7 (m, 4 H); IR 3600−3200, 1720, 1380, 1300, 1040, 750 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26. Found: C, 67.07; H, 7.22.

Ozonolysis of Dialkyl-Substituted Indene 1f−h in CF_3CH_2OH−CH_2Cl_2. Ozonolysis of indene **1f** is representative. A solution of indene **1f** (288 mg, 2 mmol) in CF_3CH_2OH−CH_2Cl_2 (20 mL, 1:2, v/v) was treated with 1.5 equiv of ozone at 0 °C. After workup as above, the crude products were separated by column chromatography on silica gel. The first fraction (ether−hexane, 1:9, v/v) contained oligoozonide (58 mg, ca. 15%): oil; ^{1}H NMR δ 1.23 (br s), 1.39 (br s), 4.15 (br q, J = 9 Hz), 4.78 (br s) + 5.03 (br s) + 5.10 (br s), 6.32 (br s) + 6.45 (br s), 7.2-7.5 (m), the ratio of peak areas being 3:3:2:1:1:4; IR 1450, 1280; 1150, 960, 750 cm^{-1}. Anal. Calcd for $(C_{11}H_{12}O_3)_n$: C, 68.73; H, 6.30. Found: C, 69.22; H, 6.15. From the second fraction (elution with ether−hexane, 1:9, v/v) was obtained the ozonide **10f** (46 mg, 12%). Subsequent elution with ether−hexane (1:4, v/v) gave isochroman **13f** (200 mg, 34%).

Ozonide 10f: mp 58−59 °C (from hexane); ^{1}H NMR (CCl_4) δ 1.28 (s, 3 H), 1.32 (s, 3 H), 5.33 (s, 1 H), 6.10 (s, 1 H), 7.0−7.4 (m, 4 H). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.81; H, 6.20.

Isochroman 13f: oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR (CCl_4) δ 1.1−1.6 (m, 6 H), 3.8−4.4 (m, 2 H), 5.00 (br s) + 5.13 (br s) (1 H), 6.08 (br s, 1 H), 7.1−7.5 (m, 4 H), 9.23 (br s, 1 H); IR 3550−3200, 1450, 1280, 1150, 750 cm^{-1}.

Ozonide 10g: oil; ^{1}H NMR δ 1.4−2.2 (m, 8 H), 5.39 (s, 1 H), 6.10 (s, 1 H), 7.0−7.5 (m, 4 H); ^{13}C NMR δ 26.17, 26.50, 35.63, 39.90, 51.70, 100.23, 105.52, 124.59, 126.04, 126.51, 130.47, 131.77, 141.87. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.53; H, 6.48. Found: C, 71.35; H, 6.35.

Isochroman 13g: oil; ^{1}H NMR δ 1.4−2.3 (m, 8 H), 4.10 (q, J = 9 Hz, 2 H), 4.89 (s, 1 H), 6.13 (s, 1 H), 7.1−7.5 (m, 4 H), 9.09 (s, 1 H); ^{13}C NMR δ 25.46, 26.68, 34.19, 40.51, 49.34, 64.87 (q, J = 34 Hz), 100.13, 103.12, 124.58 (q, J = 279 Hz), 125.69, 126.48, 127.32, 127.47, 130.14, 141.71; IR 3550−3200, 1275, 1150, 750 cm^{-1}.

Isochroman 13h: oil; ^{1}H NMR (CCl_4) δ 0.7−1.6 (m, 4 H), 4.03 (q, J = 9 Hz, 2 H), 4.43 (s, 1 H), 6.11 (s, 1 H), 7.1−7.6 (m, 4 H), 9.29 (s, 1 H); ^{13}C NMR δ 10.52, 18.86, 21.79, 64.33 (q, J = 34 Hz), 100.77, 102.58, 121.52, 124.22 (q, J = 278 Hz), 125.82, 127.46, 128.36, 129.94, 136.24; IR 3550−3200, 1610, 1280, 1150, 750 cm^{-1}. Anal. Calcd for $C_{13}H_{12}F_3O_4$: C, 53.79; H, 4.52. Found: C, 53.43; H, 4.68.

Reaction of Hemiperacetal with Methanol in the Presence of Concd HCl. Reaction of hemiperacetal **15a** is representative. To a 50 mL round-bottomed flask containing hemiperacetal **15a** (196 mg, 1 mmol), CH_2Cl_2 (5 mL), MeOH (10 mL), was added one drop of concd HCl, and the mixture was stirred at room temperature for 15 h. Then, the reaction mixture was poured into ice-cold aqueous $NaHCO_3$ and was extracted with ether. After the products were dried and concentrated, they were were separated by column chromatography on silica gel. Elution with ether−hexane (1:4) gave **19a** (173 mg, 80%).

1,4-Dimethoxy-4,5-dihydro-1*H*-2,3-benzodioxepin (19a): mp 81−82 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (dd, J = 14 and 4 Hz, 1 H), 3.39 (s, 3 H), 3.55 (s, 3 H), 3.73 (dd, J = 14 and 9 Hz, 1 H), 4.81 (ddd, J = 9, 4, and 2 Hz, 1 H), 5.76 (d, J = 2 Hz, 1 H), 6.8−7.5 (m, 4 H); ^{13}C NMR δ 37.64, 55.63, 55.71, 107.88, 108.96, 127.82, 128.45, 128.58, 130.38, 132.72, 135.51; IR 1450, 1330, 1100, 970, 735 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.83; H, 6.73. Found: C, 62.77; H, 6.73.

Dimethoxydioxepane 19f: oil; ^{1}H NMR (CCl_4) δ 1.12 (s, 3 H), 1.27 (s, 3 H), 3.52 (s, 3 H), 3.54 (s, 3 H), 4.65 (s, 1 H), 5.49 (s, 1 H), 7.0−7.4 (m, 4 H); ^{13}C NMR δ 23.26, 23.86, 38.31, 55.78, 57.37, 99.47, 101.99, 125.68, 126.44, 127.10, 129.23, 132.13, 143.65; IR 1460, 1370, 1220, 1110, 1030, 770 cm^{-1}.

Dimethoxydioxepane 19g: oil; ^{1}H NMR (CCl_4) δ 1.3−2.1 (m, 8 H), 3.49 (s, 6 H), 4.71 (s, 1 H), 5.48 (s, 1 H), 7.0−7.3 (m, 3 H); ^{13}C NMR δ 27.35, 27.39, 35.97, 37.18, 49.08, 55.09, 56.79, 98.71, 102.19, 125.76, 125.81, 126.26, 128.97, 130.38, 144.71; IR 2940, 1440, 1190, 1080, 1010, 745 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.64. Found: C, 67.93; H, 7.80.

Dimethoxydioxepane 19h: mp 70−71 °C (from hexane); ^{1}H NMR δ 0.4−1.7 (m, 4 H), 3.40 (s, 3 H), 3.63 (s, 3 H), 4.95 (d, J = 2 Hz, 1 H), 5.95 (d, J = 2 Hz, 1 H), 7.2−7.7 (m, 4 H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.07; H, 6.84. Found: C, 65.79; H, 6.77.

Reaction of Isochroman with Phenyl Isocyanate in the Presence of Catalytic Amounts of Pyridine. The reaction of isochroman **13a** is representative. To a benzene solution (20 mL) of **13a** (264 mg, 1 mmol) and phenyl isocyanate (240 mg, 2 equiv) was added one drop of pyridine, and the mixture was stirred at room temperature for 15 h. Then, the reaction mixture was poured into water and was extracted with ether. After the products were dried and concentrated, they were separated by column chromatography on silica gel. Elution with ether−hexane (1:4) gave lactone **22a** (225 mg, 65%).

Lactone 22a: oil; ^{1}H NMR (CCl_4) δ 3.03 (dd, J = 17 and 6 Hz, 1 H), 3.31 (dd, J = 17 and 6 Hz, 1 H), 4.07 (q, J = 9 Hz, 2 H), 5.60 (t, J = 6 Hz, 1 H), 7.0−7.6 (m, 3 H), 7.9−8.1 (m, 1 H); ^{13}C NMR δ 32.60, 65.35 (q, J = 34 Hz), 100.24, 123.32 (q, J = 278 Hz), 124.27, 127.80, 128.12, 130.01, 134.31, 135.54, 162.77; IR 1730, 1280, 1160, 730 cm^{-1}. Anal. Calcd for $C_{11}H_9F_3O_3$: C, 53.66; H, 3.69. Found: C, 54.18; H, 3.57.

Lactone 20b: oil (30% from **5b**); ^{1}H NMR (CCl_4) δ 1.02 (s, 9 H), 3.36 (s, 1 H), 4.18 (q, J = 9 Hz, 2 H), 6.45 (s, 1 H), 7.1−7.6 (m, 4 H); ^{13}C NMR δ 28.23, 37.67, 55.97, 65.14 (q, J = 35 Hz), 101.06, 123.52 (q, J = 279 Hz), 125.14, 128.00, 129.49, 129.81, 130.48, 131.59, 168.06; IR 1740, 1280, 1160, 1000, 750 cm^{-1}. Anal. Calcd for $C_{15}H_{17}F_3O_3$: C, 59.59; H 5.68. Found: C, 60.98; H, 5.89.

Lactone 22b: mp 84−85 °C (hexane) (73% from **13b**); ^{1}H NMR δ 1.02 (s, 9 H), 2.83 (s, 1 H), 4.01 (q, J = 9 Hz, 1 H), 4.04 (q, J = 9 Hz, 1 H), 5.68 (s, 1 H), 7.2−7.8 (m, 3 H), 8.1−8.3 (m, 1 H); ^{13}C NMR δ 27.94, 33.88, 51.68, 65.14 (q, J = 35 Hz), 101.69, 123.47 (q, J = 278 Hz), 124.92, 127.73, 129.46, 130.60, 133.14, 137.59, 162.77; IR 1720, 1280, 1170, 1075, 1000, 940, 720 cm^{-1}. Anal. Calcd for $C_{15}H_{17}F_3O_3$: C, 59.59; H, 5.68. Found: C, 59.49; H, 5.58.

Lactone 23b: mp 105−106 °C (from ether−hexane) (85% from **14b**); ^{1}H NMR (CCl_4) δ 0.97 (s, 9 H), 2.70 (s, 1 H), 3.38 (s, 3 H), 5.43 (s, 1 H), 7.0−7.6 (m, 3 H), 8.0−8.2 (m, 1 H); IR 1720, 1600, 1440, 1220, 1110, 1060, 930, 740 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.76; H, 7.76. Found: C, 71.68; H, 7.54.

Lactone 20c: oil (36% from **5c**); ^{1}H NMR (CCl_4) δ 0.6−1.3 (m, 9 H), 1.3−1.7 (m, 2 H), 3.61 (s, 1 H), 4.27 (q, J = 9 Hz, 2 H), 6.50 (s, 1 H), 7.0−7.5 (m, 4 H); ^{13}C NMR δ 8.40, 24.68, 24.81, 32.75, 40.60, 54.04, 65.17 (q, J = 35 Hz) 101.10, 123.57 (q, J = 278 Hz), 125.20, 127.97, 129.50, 129.77, 130.83, 131.62, 168.11; IR 1740, 1460, 1370, 1285, 1160, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{19}F_3O_3$: C, 60.75; H, 6.05. Found: C, 61.05; H, 6.19.

Lactone 22c: mp 93−94 °C (hexane) (53% from **13c**); ^{1}H NMR δ 0.7−1.3 (m, 9 H), 1.3−1.7 (m, 2 H), 3.01 (s, 1 H), 4.08 (q, J = 9 Hz, 2 H), 5.71 (s, 1 H), 7.2−7.7 (m, 4 H); ^{13}C NMR δ 8.13, 24.37, 24.95, 32.76, 36.53, 49.27, 65.15 (q, J = 35 Hz)

101.59, 123.54 (q, J = 278 Hz), 125.29, 127.70, 129.51, 130.50, 133.18, 137.68, 162.92; IR 1730, 1460, 1385, 1290, 1160, 940 cm^{-1}. Anal. Calcd for $C_{16}H_{19}F_3O_3$: C, 60.75; H, 6.05. Found: C, 60.46; H, 6.09.

Lactone 22d: oil (70% from **13d**); ^1H NMR (CCl_4) δ 0.93 (d, J = 6 Hz, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.7–2.3 (m, 1 H), 4.08 (q, J = 9 Hz, 2 H), 5.60 (s, 1 H), 7.1–7.6 (m, 4 H); IR 2960, 1730, 1600, 1390, 1280, 1160, 750 cm^{-1}.

Lactone 20e: an oil (32% from **5e**); ^1H NMR (CCl_4) δ 0.7–1.7 (m, 11 H), 3.71 (d, J = 4 Hz, 1 H), 4.20 (q, J = 9 Hz, 2 H), 6.41 (s, 1 H), 7.2–7.7 (m, 4 H); IR 2950, 1750, 1610, 1290, 1170, 760 cm^{-1}.

Lactone 22e: mp 48–49 °C (hexane) (72% from **13e**); ^1H NMR δ 0.7–1.7 (m, 11 H), 3.12 (d, J = 4 Hz, 1 H), 4.07 (d, J = 9 Hz, 2 H), 5.69 (s, 1 H), 7.2–7.7 (m, 4 H); IR 2980, 1730, 1610, 1290, 1170, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{19}F_3O_3$: C, 60.75; H, 6.05. Found: C, 60.76; H, 6.13.

Lactone 22f: oil (69% from **13f**); ^1H NMR (CCl_4) δ 1.37 (s, 3 H), 1.40 (s, 3 H), 4.11 (q, J = 8 Hz, 2 H), 5.16 (s, 1 H), 7.2–7.7 (m, 3 H), 7.9–8.2 (m, 1 H); ^{13}C NMR δ 21.73, 27.00, 38.03, 65.71 (q, J = 35 Hz), 106.98, 123.08, 123.45 (q, J = 278 Hz), 124.44, 127.28, 130.21, 134.64, 145.74, 162.96; IR 1730, 1600, 1270, 1150, 1020, 750, 700, 550 cm^{-1}. Anal. Calcd for $C_{13}H_{13}F_3O_3$: C, 56.93; H, 4.79. Found: C, 57.08; H, 4.75.

Lactone 23f: oil (79% from **14f**); ^1H NMR (CCl_4) δ 1.32 (s, 6 H), 3.47 (s, 3 H), 4.90 (s, 1 H), 7.0–7.6 (m, 3 H), 7.9–8.1 (m, 1 H); IR 1730, 1610, 1370, 1250, 1090, 750, 700 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.86. Found C, 69.94; H, 7.04.

Lactone 22g: oil (75% from **13g**); ^1H NMR (CCl_4) δ 1.4–2.4 (m, 8 H), 4.05 (q, J = 9 Hz, 1 H), 5.20 (s, 1 H), 7.1–7.7 (m, 3 H), 7.9–8.2 (m, 1 H); ^{13}C NMR δ 25.15, 25.85, 33.02, 38.60, 49.31, 65.52 (q, J = 35 Hz), 106.63, 123.48 (q, J = 279 Hz), 123.17, 124.74, 127.04, 130.14, 134.47, 145.68, 163.15; IR 2950, 1730, 1600, 1275, 1155, 745 cm^{-1}. Anal. Calcd for $C_{15}H_{15}F_3O_3$: C, 59.99; H, 5.05. Found: C, 59.87; H, 5.07.

Lactone 23g: oil (74% from **14g**); ^1H NMR (CCl_4) δ 1.3–2.1 (m, 8 H), 3.47 (s, 3 H), 4.90 (s, 1 H), 6.9–7.7 (m, 3 H), 7.9–8.1 (m, 1 H); ^{13}C NMR δ 25.13, 25.90, 33.09, 38.57, 49.54, 57.16, 108.48, 123.65, 124.58, 126.74, 129.92, 134.02, 146.13, 163.96; IR 2950, 1720, 1600, 1375, 745 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.96. Found: C, 71.87; H, 6.86.

Lactone 22h: oil (73% from **13h**); ^1H NMR (CCl_4) δ 0.7–1.5 (m, 4 H), 4.05 (q, J = 9 Hz, 2 H), 4.86 (s, 1 H), 6.83 (dd, J = 6 and 1 Hz, 1 H), 7.1–7.6 (m, 2 H), 8.08 (dd, J = 6 and 2 Hz, 1 H); ^{13}C NMR δ 9.91, 17.02, 21.88, 65.21 (q, J = 35 Hz), 105.24, 121.71, 123.46 (q, J = 279 Hz), 124.68, 126.83, 130.32, 134.65, 140.64, 163.13; IR 1730, 1280, 1160, 1000, 750 cm^{-1}. Anal. Calcd for $C_{13}H_{11}F_3O_3$: C, 57.35; H, 4.08. Found: C, 57.22; H, 4.08.

Lactone 21h: oil (46% from **7h**); ^1H NMR (CCl_4) δ 0.5–1.7 (m, 10 H), 3.8–4.5 (m, 1 H), 6.17 (s, 1 H), 7.1–7.7 (m, 4 H); IR 1730, 1600, 1380, 1250, 1070, 750 cm^{-1}.

Theoretical Calculations. The theoretical studies were performed by PM3 molecular orbital method.[8] The MOPAC program (QCPE No. 455), which was revised as OS/2 Version 5.01 to adapt for the use of a NECPC computer, was obtained through the Japan Chemistry Program Exchange (JCPE).[9] Final geometries and energetics were obtained by optimizing the total molecular energy with respect to all structural variables.

X-ray Crystallographic Analysis of Isochroman 13b. A single crystal of **13b** (from ethyl acetate/hexane, approximate size 0.6 × 0.35 × 0.25 mm), mounted in a Lindemann tube, was used for X-ray data collection.

Crystal Data: $C_{15}H_{19}F_3O_4$, M = 302.26, colorless needles, monoclinic, space group $P2_1/a$ (nonstandard setting of no. 14), a 10.165 (3), b 14.5094 (10), c 21.8601 (14) Å, β 94.290 (11)°, U 3215.2 (8) $Å^3$, Z = 8, D_c 1.323 g cm^{-3}, F(000) 1344, μ(Mo-K_α) 1.11 cm^{-1}.

Data Collection, Structure Solution, and Refinement. The intensity data were collected over a hemisphere (2θ range: 0–60°) on an Enraf-Nonius CAD4 diffractometer equipped with a FAST area detector using Mo-K_α X-radiation (λ 0.710693 Å). Details of the diffractometer settings have been published elsewhere.[16] Of the 7694 unique data measured, 1646 had $I > 2\sigma(I)$ and were used in subsequent structural solution and refinement. The data were corrected for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods (SHELXS86[17]) and refined by full-matrix least squares methods (SHELX76[17]) using anisotropic temperature factors for all the non-hydrogen atoms. All the hydrogen atoms were located on difference Fourier maps and included in the refinement process at idealized positions (d_{C-H} 0.95 Å) with a fixed isotropic temperature factor (U_{iso} 0.10 $Å^2$). At convergence, the discrepancy factors R and R_w were 0.056 and 0.073, respectively. The weighting scheme, $w^{-1} = [\sigma^2(F) + 0.001\ (F)^2]$, was found to give satisfactory analyses of variance. The final difference Fourier map was essentially featureless (general noise level less that ±0.25 e $Å^{-3}$). Incidental crystallographic calculations and compilation of tables were carried out using the computer program CALC.[17,18]

Acknowledgment. We thank British Council (Tokyo) for the award of travel grants to M.N. and K.J.Mc.

JO950590X

(16) Hursthouse, M. B.; Karaulov, A. I.; Ciechanowicz-Rutkowska, M.; Kolasa, A.; Zankowska-Jasinka, W. *Acta Crystallogr.* **1992**, *C48*, 1257.

(17) Sheldrick, G. M. SHELXS86. *Acta Crystallogr. A* **1990**, *A46*, 467. Sheldrick, G. M. SHELX76, University of Cambridge, England, 1976. Gould, R. O.; Taylor, P. CALC, University of Edinburgh, Scotland, 1983. Johnson, C. K. ORTEP Report ORNL-5183, Oak Ridge National Laboratory, Tennesse, 1976.

(18) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.