Notes

A Novel Outcome of the Hydroperoxide Rearrangement‡

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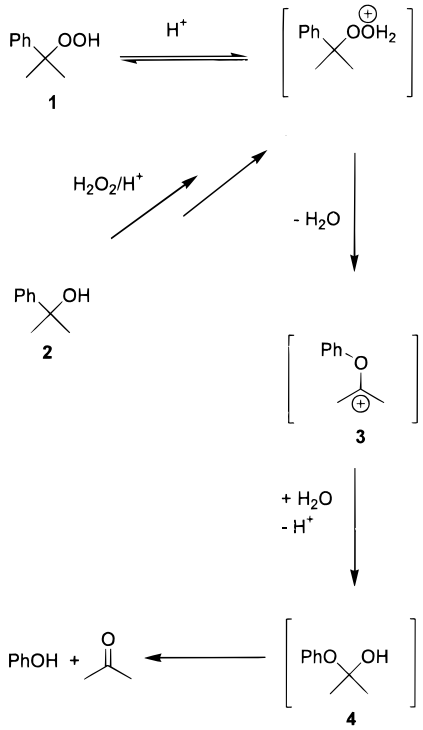
Received September 15, 1999

Hydroperoxides are important reagents in organic synthesis and play a considerable role as intermediates in industrial processes. Thus *tert*-butylhydroperoxide is extensively used in Sharpless epoxidations[1] of allylic alcohols and in the production of propylene oxide by the oxirane process.[2] Nowadays the industrial synthesis of phenol and acetone is mainly based on the Hock process, which uses cumene hydroperoxide **1**.[3] The rearrangement of cumene hydroperoxide **1** as a key step in the Hock process is a well-known reaction found in most basic textbooks of organic chemistry (Scheme 1). After protonation of the hydroxy group a concerted elimination of water and migration of the phenyl ring results in phenoxycarbenium ion **3**. Further addition of water affords an unstable hemiacetal **4**, which decomposes into phenol and acetone. The same reaction sequence could also be achieved if α,α-dimethylbenzyl alcohol **2** was treated with hydrogen peroxide in acid medium.[4]

Scheme 1



We report here a novel outcome of the hydroperoxide rearrangement giving rise to α-phenoxyhydroperoxide, geminal dihydroperoxide, and bis(hydroperoxy)-dialkylperoxide moieties. In connection with our investigation of optically active hydroperoxides[5] the synthesis of racemic tertiary indane, 1,2,3,4-tetrahydronaphthalene, and benzocycloheptane hydroperoxides **6** was approached. The 1,2,3,4-tetrahydronaphthalene hydroperoxide **6b** was synthesized by Hock et al. by a laborious multistep procedure including autoxidation of the corresponding hydrocarbon.[6] We tried to synthesize hydroperoxides **6** in a direct manner by adopting the known procedure for the transformation of tertiary alcohols into corresponding hydroperoxides by treatment with aqueous hydrogen peroxide in the presence of catalytic amounts of acids.[7] The starting bicyclic alcohols **5** can be considered as bridged analogues of α,α-dimethylbenzyl alcohol **2**. Surprisingly, after treatment of **5a**, **5b**, or **5c** with hydrogen peroxide and a catalytic amount of sulfuric acid for 3 days, neither the anticipated bicyclic hydroperoxides **6** nor *o*-hydroxyphenylalkyl ketones **10**, as expected products derived from a hydroperoxide rearrangement analogous to the cumene hydroperoxide rearrangement according to Scheme 1, could be obtained. Instead, novel cyclic 2-methylchroman-2-yl-hydroperoxide **11a**, (bishydroperoxyalkyl)-phenols **14**, and peroxide products presumably of structure **15** were obtained (Scheme 2). The structures of all products were confirmed by their spectroscopic data, and that of **14c** was confirmed by X-ray crystal analysis (see Figure 1). X-ray crystal analyses of geminal bishydroperoxides are very rare. In the case of **14c** no intramolecular but different types of intermolecular hydrogen bonding could be observed in the crystal. Interestingly, the compound forms chiral crystals (space group $P2_12_12_1$, orthorhombic), although it is achiral. Iodometric titration of compounds **14** and **15** revealed 2 equiv of active oxygen, which is in accordance with the bishydroperoxide structure.

The formation of products **11**, **14** and **15** can be explained (Scheme 2) by primary substitution of the hydroxy group by hydrogen peroxide, giving rise to

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‡ Dedicated to Professor Alfred Rieche.

(1) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; p 103. (b) Kasuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(2) (a) Sheldon, R. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, p 411. (b) Weissermel, K.; Arpe, H.-J. *Industrielle organische Chemie*, 5th ed.; VCH: Weinheim, 1998; p 293.

(3) Weissermel, K.; Arpe, H.-J. *Industrielle organische Chemie*, 5th ed.; VCH: Weinheim, 1998; p 383.

(4) Kharasch, M. S.; Fono, A.; Nudenberg, W.; Poshkus, A. C. *J. Am. Chem. Soc.* **1950**, *50*, 775.

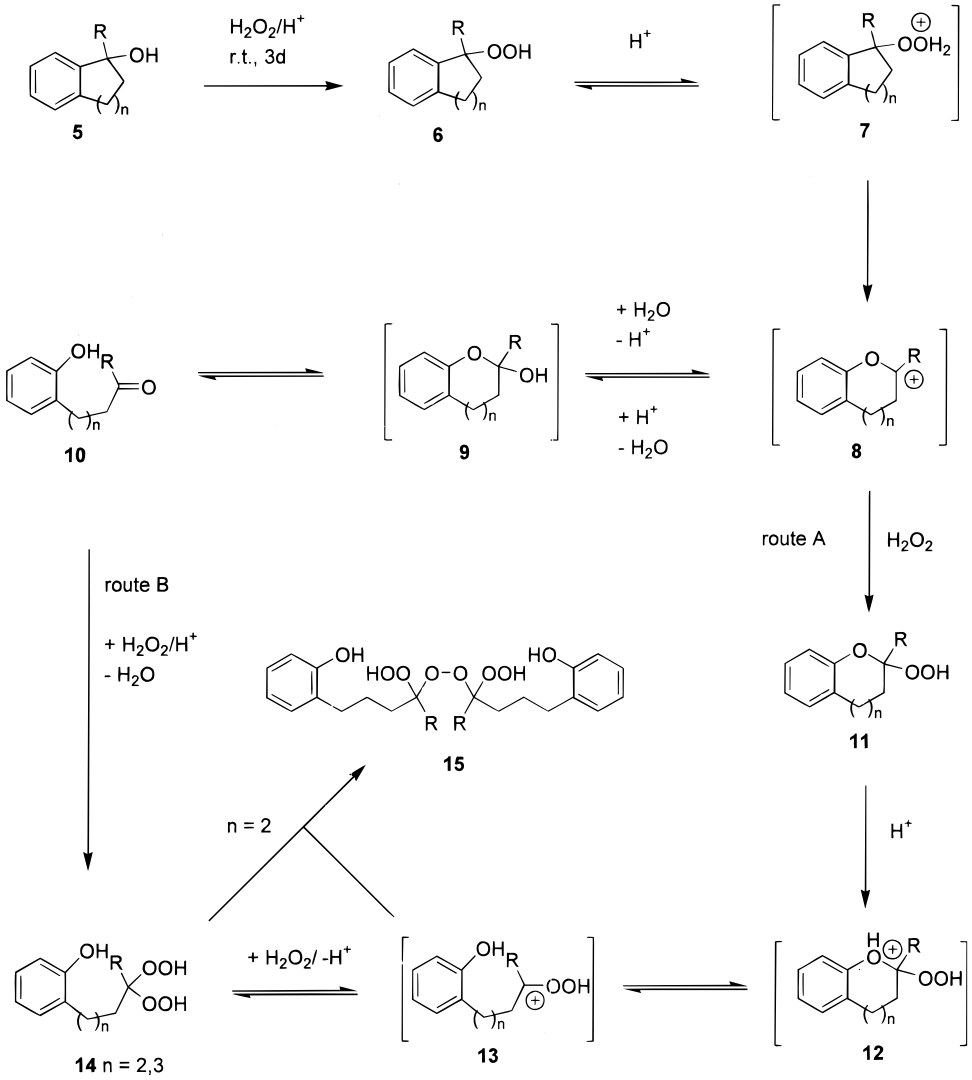
(5) (a) Höft, E.; Hamann, H.-J.; Kunath, A. *J. Prakt. Chem.* **1994**, *336*, 534. (b) Höft, E.; Hamann, H.-J.; Kunath, A., Adam, W.; Hoch, U.; Saha-Möller, C. R.; Schreier, P. *Tetrahedron: Asymmetry* **1995**, *6*, 603. (c) Hamann, H.-J.; Höft, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2217.

(6) (a) Hock, H.; Lang, S. *Chem. Ber.* **1942**, *75*, 302. (b) Hock, H.; Depke, F.; Knauel, G. *Chem. Ber.* **1950**, *83*, 238.

(7) Hägel, E.; Kropf, H.; Munke, S. *Methoden Der Organischen Chemie (Houben-Weyl)*, 4th ed.; Thieme: Stuttgart, 1988; Vol. E 13, p 146.

10.1021/jo991457y CCC: $19.00
Published on Web 03/02/2000

Scheme 2



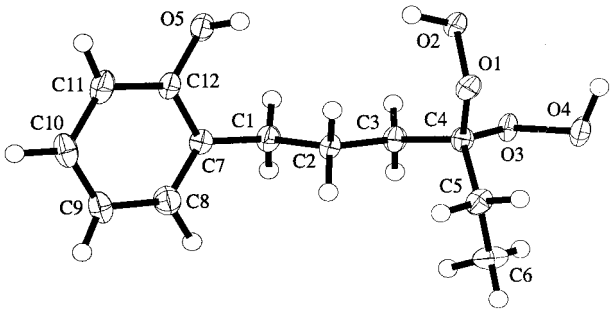


Figure 1. X-ray structural analysis of compound **14c**.

tertiary hydroperoxides **6**, which suffer an acid-catalyzed migration of the phenyl substituent, affording a cyclic phenoxycarbenium ion **8**. The latter add a second molecule of hydrogen peroxide to give the cyclic phenoxy-hydroperoxide **11**, which obviously is stable and was isolated as the main product in the case of the six-membered ring ($n = 1$) (route A). Seven-membered analogues **11** ($n = 2$) could not be isolated but opened the heterocyclic ring after protonation of the ring oxygen atom (**12**). The resulting *o*-hydroxyphenylalkyl-α-hydroperoxy carbenium ions **13** add a third molecule of hydrogen peroxide, generating geminal dihydroperoxides **14**. For $n = 2$ not only geminal dihydroperoxides **14** but also brown oils of limited stability were obtained, whose structure was assigned as 1:1 diastereomeric mixtures (meso-compound and racemate) of bridged bis(hydroperoxy)-dialkylperoxides **15** by ^{1}H and ^{13}C NMR spectroscopy**.** These products could be formed by reaction of the intermediate carbenium ion **13** with the geminal bishydroperoxide **14**. Using the same reaction conditions for the seven-membered ring **5** ($n = 3$) the expected tertiary hydroperoxide **6d** was obtained as main product together with some geminal dihydroperoxide **14d**. Obviously, the peroxide rearrangement by ring enlargement is hampered in this case by unfavorable eight-membered intermediates **8** ($n = 3$). Although semicyclic hemiacetals **9** and *o*-hydroxyphenyl-alkyl ketone **10**, as expected products of the common hydroperoxide rearrangement in analogy to Scheme 1, were not observed, their transient appearance is not unlikely. However, as a result of their bridged structures they are in an equilibrium with the intermediate **8** (Scheme 2). This equilibrium is continuously disturbed by irreversible transformation of **8** into the hydroperoxide **11** and further to bishydroperoxides **14** or **15** until all of **8** is consumed. The peroxides **15** could either be formed by reaction of the bisdihydroperoxide **14** with intermediate cations **13** or by condensation of two molecules of **14** under elimination of hydrogen

peroxide.[11] An alternative formation of geminal dihydroperoxides **14** by reaction of the ketone **10** with hydrogen peroxide under acid conditions according to route B also has to be taken into consideration. Indeed the ketone **10b**, obtained by a normal Hock-analogous hydroperoxide rearrangement of the hydroperoxide **6**,[6] could be transformed into the dihydroperoxide **14b** by route B. However, the reaction was sluggish and gave considerably low yields as compared with route A. Thus the alternative pathway via route B for the acid-catalyzed transformation of the alcohols **5** into hydroperoxides **14** and **15** is unlikely. Route B also could not account for the observed formation of **11**. Finally, it is to be mentioned that the originally anticipated peroxide **6b** was obtained in a straightforward way by treatment of the alcohol **5b** with hydrogen peroxide in the absence of acids. This is a preferable alternative to the hitherto known multistep procedure.[6]

So far α-alkoxyperoxide compounds were obtained from acetals and hydrogen peroxide, by autoxidation of ethers, or by ozonolysis of alkenes in the presence of aliphatic alcohols.[8] Such structural moieties are found in potent antimalarials.[9] Geminal dihydroperoxides are rare. They were synthesized according to the early works of Criegee from ketones and hydrogen peroxide.[10] In general the yields were poor with smaller molecules, and the isolation of pure geminal dihydroperoxides was difficult.[10] Recently Jefford et al. obtained geminal dihydroperoxides from ketals with hydrogen peroxides in the presence of H_2WO_4.[11]

The overall transformation of the tertiary alcohol **5** into the hydroperoxides **11**, **14**, and **15** represents a novel outcome of the well-known hydroperoxide rearrangement, as well as a novel route to such structural units. The extension of this method to other cyclic tertiary alcohols is currently underway.

Experimental Section

General. Melting points were determined with a hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, with TMS as internal standard. Silica gel (0.04−0.063, MERCK) was used for column chromatography. Starting materials **5** were prepared according known procedures.[12−15] All other reagents were reagent grade and were used without purification.

1-Methyl-1,2,3,4-tetrahydro-1-naphthalenyl Hydroperoxide (6b). Aqueous hydrogen peroxide (50%, 14 mL) was added to a solution of **5b** (3.24 g, 20 mmol) in benzene (10 mL) under stirring and ice cooling. After 15 min the mixture was allowed to warm to room temperature and was stirred for 1 day. After dilution of the mixture with water (15 mL), extraction with Et_2O (3 × 25 mL), and washing with water, the organic phase was dried with (Na_2SO_4). The solvent was removed under vacuum, and the products were separated by column chromatography: colorless oil;[6] yield 59%, R_f (hexane/EtOAc, 7:3) 0.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.93−7.35 (m, 5H), 2.58−2.66 (m, 2H), 2.22−2.28 (m, 1H), 1.80−1.84 (m, 1H), 1.62−1.70 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 138.9, 138.6, 129.5, 128.1, 126.8, 126.7, 83.4, 33.7, 30.3, 27.1, 20.9.

Table 1. Starting Materials 5 and Yields of Products 6, 11, 14, and 15

				yield (%)			
entry	R	*n*	**5** (**5**:H_2O_2)	**6**	**11**	**14**	**15**
1	Me	1	**a** (1:10)		**a** (65)		
2	Me	2	**b** (1:10)			**b** (30)	**b** (48)
3			**b** (1:5)			**b** (42)	b (24)
4			**b** (1:10)[a]	**b** (59)[a]			
5	Et	2	**c** (1:10)			**c** (26)	**c** (36)
6			**c** (1:5)			**c** (32)	**c** (28)
7	Me	3	**d** (1:10)	**d** (56)		**d** (12)	

[a] In the absence of acid.

General Procedure for Preparation of 6d, 11, 14, and 15 (Table 1). One drop of concentrated H_2SO_4 was added to a solution of **5** (20 mmol) in 50% aqueous hydrogen peroxide (14 mL) under stirring and ice cooling. After 15 min the mixture was allowed to warm to room temperature and was stirred for 3 days. After dilution of the mixture with water (15 mL), extraction with Et_2O (3 × 25 mL), and washing with saturated aqueous $NaHCO_3$ solution and water, the organic phase was dried with (Na_2SO_4). The solvent was removed under vacuum, and the products were separated by column chromatography.

5-Methyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl-hydroperoxide (6d): colorless oil; yield 56%, R_f (hexane/EtOAc, 6:4) 0.54; IR (film) 3402, 1448, 1172, 843, 562 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H,), 7.27−7.42 (m, 4H), 3.10−3.29 (m, 1H), 2.44−2.49 (m, 1H), 1.92.2.12 (m, 6H), 1.79 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.1, 141.4, 131.1, 127.7, 126.7, 126.3, 87.3, 37.4, 35.6, 27.4, 25.8, 24.6. Anal. Calcd for $C_{12}H_{16}O_2$: C 74.97; H 8.39. Found: C 74.85; H 8.41

2-Methylchroman-2-yl-hydroperoxide (11a): colorless oil; yield 65%, R_f (hexane/EtOAc, 7:3) 0.44; IR (film) 3424, 1456, 1142, 837, 587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H,), 6,90−6.95 (m, 2H), 6.71−6.78 (m, 2H), 2.47−2.49 (m, 1H), 2.02−2.05 (m, 1H), 1.97−2.00 (m, 1H), 1.68−1.79 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.0, 129.3, 127.4, 121.9, 121.3, 117.1, 103.4, 29.3, 23.0, 21.3. Anal. Calcd for $C_{10}H_{12}O_3$: C 66.65; H 6.71. Found: C 66.60; H 6.89. HRMS (LSIMS) calcd for (M^+ + Na) 203.06841, found 203.06903

2-(4,4-Bishydroperoxy-pentyl)-phenol (14b): mp 67−68 °C; yield 30%, R_f (hexane/EtOAc, 1:1) 0.38; IR (KBr) 3410, 1455, 1121, 847, 577, cm^{-1}; ^{1}H NMR (300 MHz), $CDCl_3$) δ 9.72 (s, 2H,), 7.03−7.12 (m, 2H), 6.79−6.87 (m, 2H), 6.55 (s, 1H), 2.63−2.68 (t, 2H), 1.72−1.87 (m, 4H), 1.41 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.7, 128.3, 126.3, 125.3, 118.8, 113.6, 110.4, 30.8, 28.0, 22.3, 15.9; Anal. Calcd for $C_{11}H_{16}O_5$: C 57.89; H 7.07. Found: C 57.82; H 6.99

2-(4,4-Bishydroperoxy-hexyl)-phenol (14c): mp 89−90 °C; yield 26%, R_f (hexane/EtOAc, 7:3) 0.1; IR (KBr) 3335, 1455, 1113, 850, 595, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 2H), 6.95−7.17 (m, 2H), 6.68−6.80 (m, 2H), 5.96 (s, 1H,), 2.52−2.57 (m, 2H), 1.57−1.71 (m, 6H), 0.79−0.84 (t, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.3, 130.3, 128.1, 127.4, 121.0, 115.6, 114.8, 30.0, 28.3, 23.9, 22.9, 7.9. Anal. Calcd for $C_{12}H_{18}O_5$: C 59.48; H 7.49. Found: C 59.45; H 7.58. HRMS (LSIMS) calcd for (M^+ + Na) 265.10519, found 265.10404

2-(5,5-Bishydroperoxy-hexyl)-phenol (14d): mp 71−72 °C; yield 12%, R_f (hexane/EtOAc, 6:4) 0.25; IR (KBr) 3329, 1457, 1186, 837, 577, cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.15 (s, 2H), 6.68−7.03 (m, 4H), 5.22 (s, 1H), 2.51−2.56 (t, 2H), 1.69−1.74 (m, 2H), 1.51−1.58 (m, 2H), 1.37−1.46 (m, 2H), 1.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.2, 130.9, 128.4, 127.2, 121.0, 115.5, 112.5, 32.3, 29.8, 29.6, 23.6, 17.8. Anal. Calcd for $C_{12}H_{18}O_5$: C 59.48; H 7.49. Found: C 59.26; H 7.12. HRMS (LSIMS) calcd for (M^+ + Na) 265.10519, found 265.10480

Bis[1-hydroperoxy-1-methyl-4-(2-hydroxyphenyl)-butyl]-peroxide (15b): brown oil; yield 48%, R_f (hexane/EtOAc, 1:1) 0.44; IR (film) 3415, 1455, 1121, 847, 587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 9.77 (s, 1H), 7.07−7.17 (m, 4H), 6.82−6.9 (m, 4H), 6.75 (s, 1H), 6.70 (s, 1H9, 2.62−2.74 (m, 4H), 1.85−1.94 (m, 8H), 1.48 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75.5 MHz,

(8) (a) Rieche, A. *Angew. Chem.* **1958**, *70*, 251. (b) *Ullmanns Encyklopädie der technischen Chemie*, 4th ed.; VCH: Weinheim, 1972−1984; Vol. 17, p 680.
(9) Cumming, J. N.; Wang, D.; Park, S. B.; Shapiro, T. A.; Posner, G. H. *J. Med. Chem.* **1998**, *41*, 952.
(10) (a) Criegee, R.; Dietrich, H. *Liebigs Ann. Chem.* **1948**, *560*, 135. (b) Kropf, H.; Nürnberg, W. *Methoden Der Organischen Chemie (Houben-Weyl)*, 4th ed.; Thieme: Stuttgart, 1988; Vol. E 13, p 548.
(11) Jefford, C. W.; Li, Y.; Jaber, A.; Boukouvalas, J. *Synth. Commun.* **1990**, *20*, 2589.
(12) Auers, K. *Liebigs Ann. Chem.* **1918**, *415*, 162.
(13) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117.
(14) Stoermer, R.; Laage, E. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 981.
(15) Treibs, W.; Klinkhammer, H. J. *Chem. Ber.* **1950**, *83*, 367.

$CDCl_3$) δ 154.7, 154.4, 130.6, 128.6, 128.0, 127.9, 127.7, 120.8, 120.7, 116.1, 115.7, 113.0, 33.6, 33.4, 30.4, 30.3, 24.6, 24.5, 18.6, 18.5; HRMS (LSIMS) calcd for (M^+ + Na) 445.18384, found 445.18311

Bis[1-hydroperoxy-1-ethyl-4-(2-hydroxyphenyl)-butyl]-peroxide (15c): brown oil; yield 36%, R_f (hexane/EtOAc, 7:3) 0.19; IR (film) 3400, 2946, 1456, 1179, 856, 588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (s,1H), 9.51 (s, 1H), 6.96−7.05 (m, 4H), 6.65−6.79 (m, 4H), 5.46 (s, 1H), 5.37 (s, 1H), 2.57−2.58 (m, 4H), 1.57−1.76 (m, 12H), 0.80−0.85 (t, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.6, 130.2, 130.0, 128.0, 127.9, 127.3, 127.2, 120.68, 120.66, 115.3, 115.1, 115.0, 29.8, 29.5, 28.9, 28.6, 23.6, 23.5, 22.9, 22.7, 8.0, 7.8; HRMS (LSIMS) calcd for (M^+ + Na) 473.2151, found 473.2167

Crystal Structure Determination for Compound 14c.[16] Crystals were obtained by crystallization from EtOH. A colorless crystal of **14c** with the dimensions 1.20 × 0.56 × 0.40 mm^3 was measured on a ST′OE IPDS diffractometer using Mo Kα radiation (λ = 0.71073 Å). Crystal data: $C_{12}H_{18}O_5$, MW = 242.26, orthorhombic space group $P2_12_12_1$; a = 11.749(2) Å, b = 11.931(3) Å, c = 26.770(6) Å, α = 90°, V = 3752.8(13) $Å^3$; Z = 12, D_c = 1.286 mg/m^3, F(000) = 1560, μ(Mo Kα) = 0.100 mm^{-1}. At 180(2) K in the range of 2.43° < θ < 25.25° 23321 reflections were measured ($R_{(sig)}$ = 0.0458) of which 6770 were unique ($R_{(int)}$ = 0.1277). The structure was solved by direct methods and refined by least-squares procedure within the SHELX program system. The final residuals were $wR_{2(all)}$ = 0.0976, $R_{1(all)}$ = 0.0551 and $R_{1(obs)}$ = 0.0458. The maximum and minimum peaks in the final difmap were 0.277 and −0.255 e $Å^3$, respectively.

(16) Full details of the structure determination have been deposited (registration no. CCDC 138787) at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.

Acknowledgment. This project was financed by Deutsche Forschungsgemeinschaft, Schwerpunktprogramm “Peroxidchemie: Mechanistische und präparative Aspekte des Sauerstoff-Transfer” (SPP 462).

JO991457Y