C−C Bond Formation at Ozonide Rings by Substitution of Chlorinated Ozonides

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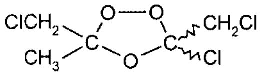
The $TiCl_4$-mediated substitution of 3-chloro-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolane (**1**) with 1-(trimethylsilyloxy)cyclopentene (**4**), 2-methyl-1-(trimethylsilyloxy)propene (**6**) and allyltrimethylsilane (**12**) gave the corresponding 2-oxocyclopentyl-, 1,1-dimethyl-2-oxo-ethyl- and allyl-substituted ozonides **5**, **7** and **13**, respectively. Substitution of 3,5-dichloro-3,5-bis(chloromethyl)-1,2,4-trioxolane (**2**) with allyltrimethylsilane (**12**) gave the diallyl-substituted ozonide **14**. Ozonolysis of the allyl-substituted ozonide **13** provided the corresponding diozonide **17**, and ozonolysis of the diallyl-substituted ozonide **14** provided the corresponding diozonide **18** and triozonide **19**.

Introduction

In previous work we have shown that in certain 3-chloro-substituted and 3,5-dichloro-substituted ozonides, such as **1** and **2**, chlorine can be replaced by F,[1] $O(CO)CH_3$,[1] OCH_3,[1] $OCH_2CH{=}CH_2$,[2] OCH_2CH_2OH,[2] and $OCH_2CH_2CH_2OH$.[2] Similarly, the Cl substituent in ozonide **3a** can be replaced by F to give ozonide **3b**,[3] whereas the $AlCl_3$-mediated reaction of **3a** with benzene gave non-peroxidic decomposition products instead of the expected ozonide **3c**.[3] Since treatment of independently prepared ozonide **3c** with $AlCl_3$ in benzene gave the same products in the same proportions[3] it is possible that **3c** may have been formed in the reaction of **3a** with benzene, but that it subsequently decomposed. This would be consistent with the experience that, with few exceptions,[4] reactions of Lewis acids with ozonides lead to ring opening, either with or without rupture of the peroxide bond.[5−9] More recently it has been found, however, that $TiCl_4$-mediated, low-temperature reactions of 3-alkoxy-1,2-dioxolanes with trimethylsilyl enol ethers or with allyltrimethylsilane result in the substitution of the alkoxy groups and concomitant formation of C−C bonds at the dioxolane rings.[10] In contrast, to the best of our knowledge, analogous C−C-bond formation by substitution reactions at ozonide rings are not known.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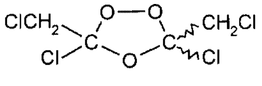
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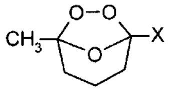
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a: X = Cl
b: X = F
c: X = C_6H_5

Results and Discussion

The reaction of ozonide **1**[11] with equimolar amounts of **4** and $TiCl_4$ in dichloromethane at −78 °C provided a product from which a mixture of two diastereomers of ozonide *cis*-**5** and peroxy ester **8** could be isolated in yields of 9% and 7%, respectively. The diastereomers of ozonide *cis*-**5**, denoted as *cis*-**5a** and *cis*-**5b**, were individually isolated in yields of 2% and 7%, respectively. From a similar reaction of **1** with **6** we obtained ozonide *cis*-**7** in 1.5% yield and peroxy ester **8** in 13% yield. It is obvious from these results that $TiCl_4$-mediated reaction of ozonide **1** to give the known acyclic isomerization product **8**[11] is preferred over C−C bond formation to give the substituted ozonides **5** and **7**.

Ozonides **5** and **7** are stable at room temperature. Their structures were established by ^1H and ^{13}C NMR spectroscopy and were verified by the results of reduction reactions with triphenylphosphane: ozonide **5** gave **9** and **10** (the latter was partly enolized) in a molar ratio of about 1:1, and ozonide **7** gave **9** and **11** in a molar ratio also of about 1:1. The structure of peroxy ester **8** was readily as-

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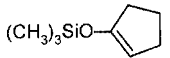
signed by comparison of its ^{1}H and ^{13}C NMR spectroscopic data with those reported previously.[11]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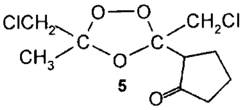
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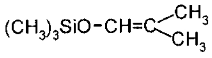
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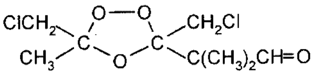
$(CH_3)_3SiO{-}CH{=}C(CH_3)_2$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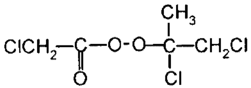
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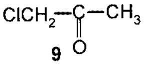
$ClCH_2{-}C(=O){-}O{-}O{-}C(CH_3)(Cl){-}CH_2Cl$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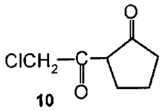
$ClCH_2{-}C(=O){-}CH_3$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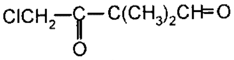
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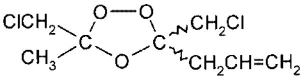
$ClCH_2{-}C(=O){-}C(CH_3)_2CH{=}O$

The difference between the yields of ozonides **5** and **7** suggests that C−C bond formation at an ozonide ring should be more favored if the nucleophilic carbon atom of the silicon-containing co-reactant were less highly substituted. Therefore, we continued our studies using allyltrimethylsilane (**12**). Indeed, reaction of ozonide **1** (*cis*/*trans* = 70:30) with approximately equimolar amounts of **12** and $TiCl_4$ in dichloromethane at −78 °C provided a 3:2 mixture of ozonides *cis*-**13** and *trans*-**13** in a combined yield of 45%. The stable liquid ozonides were isolated in yields of 21% (*cis*-**13**) and 15% (*trans*-**13**). In a similar manner, $TiCl_4$-mediated reaction of ozonide *trans*-**2**[11] with 2 mol-equiv. of **12** provided a 1:1 mixture of ozonides *cis*-**14** and *trans*-**14** in a combined yield of 68%, along with 10% of unchanged ozonide **2**. The stable liquid ozonides *cis*-**14** and *trans*-**14** were isolated in yields of 26% and 25%, respectively.

Despite the presence of unchanged substrate **2**, there was no evidence for the presence of a monosubstituted ozonide in the crude reaction mixture. This can be rationalized by analogy with the observation that monochloro-substituted ozonides are less stable and react faster than dichloro-substituted ozonides.[11] Moreover, the fact that $TiCl_4$-mediated substitution of ozonide *trans*-**2** provided both *cis*-**14** and *trans*-**14** is consistent with the intermediacy of the ozonide cation **15**.[12]

$(CH_3)_3Si{-}CH_2CH{=}CH_2$

12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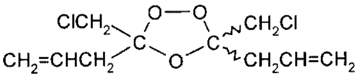
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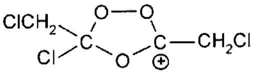
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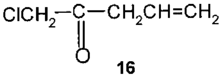
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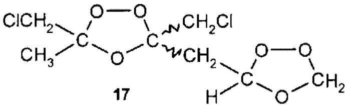
$ClCH_2{-}C(=O){-}CH_2CH{=}CH_2$

The structures of the isolated ozonides **13** and **14** were established by ^{1}H, ^{13}C and ^{17}O NMR spectroscopy. As expected, the reduction of ozonides **13** with triphenylphosphane gave equimolar quantities of **9** and **16**; reduction of the diastereomeric ozonides **14** gave **16** as the sole product.

The availability of the unsaturated ozonides **13** and **14** prompted us to examine whether their ozonolyses can provide stable diozonides and triozonides. To this end, they were ozonized in pentane at −78 °C. Ozonolysis of *cis*-**13** provided a mixture consisting of two diastereomers of diozonide *cis*-**17** in 84%. Similarly, ozonolysis of *trans*-**13** gave a mixture of two diastereomers of *trans*-**17** in 69%. Although the individual diastereomers were not isolated, their existence was obvious from their ^{1}H, ^{13}C and ^{17}O NMR spectra, in which the signals of some structural units appeared in duplicate. The liquid diozonides **17** appear to be stable at room temperature, whereas upon heating on a hot plate *trans*-**17** burns off and *cis*-**17** bursts.

Ozonolysis of *cis*-**14** and of *trans*-**14** provided, in each case, mixtures of the corresponding diozonides **18** and triozonides **19**, even though the passage of ozone was continued until the solutions had turned blue. The reason for this is probably the fact that some of the diozonides **18** co-precipitated with the triozonides **19** and hence became largely unreactive towards further ozonolysis.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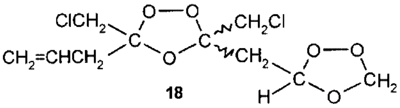
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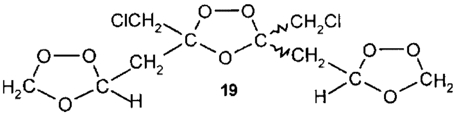
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The diozonides *cis*-**18** and *trans*-**18** were isolated in yields of 35% and 21%, respectively. They are colorless oils and consist of two diastereomers, the components of which were not isolated. They appear to be stable at room temperature, whereas upon heating on a hot plate *trans*-**18** burns off and *cis*-**18** bursts. The triozonides *cis*-**19** and *trans*-**19** were isolated in yields of 44% and 55%, respectively, as colorless oils which consisted of mixtures of all three diastereomers.[13] Although each of the three diastereomers of triozonide *cis*-**19** was isolated by HPLC separation, they were not stereochemically assigned. They are denoted as *cis*-**19a**, *cis*-**19b**, and *cis*-**19c** in the order of increasing retention times. Treatment of a dichloromethane solution containing all isolated diastereomers of triozonide *trans*-**19** with pentane, at room temperature, yielded crystalline material which was found to consist of a mixture of *trans*-**19a** and *trans*-**19b**. The triozonides **19** appear to be stable at room temperature, but upon heating on a hot plate *trans*-**19** bursts and *cis*-**19** explodes with a loud bang. The structural assignments of ozonides **17**−**19** are based on their ^{1}H, ^{13}C and ^{17}O NMR spectroscopic data.

Analysis of a crystal known to contain a mixture of the diastereomers **19a** and **19b** was attempted by X-ray crystallography. Although the crystal diffracted weakly and was prone to decomposition in the X-ray beam during data collection, the structure was solved and the central ozonide ring was found to be unambiguously of the *trans* configuration[14] (Figure 1). The structural features of one of the monosubstituted 1,2,4-trioxolane rings were also clearly defined. The remaining trioxolane ring consisted of unequal proportions of both configurations at the fourth chiral center (ca. 70:30), as expected, and there appeared to be a high degree of ring disorder. Nonetheless, on the basis of these results the configuration of the parent monoozonide *trans*-**14** and of the intermediate diozonide *trans*-**18**, as well as the configurations of *cis*-**14**, *cis*-**18** and *cis*-**19**, were also established.

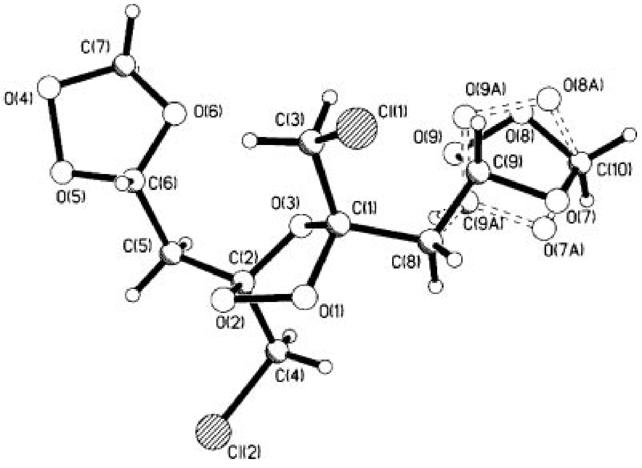

Figure 1. ORTEP diagram showing the X-ray structure of triozonide *trans*-**19a/b**

The configurations of ozonides **17a**,**b** were assigned with the help of ozonides **18a**,**b**, based on the following similarities in the ^{1}H NMR patterns of common structural units (Table 1): the CH_2 group between the two ozonide rings exhibits one ABX and one A_2X system for *cis*-**18a**,**b** but two ABX systems for *trans*-**18a**,**b**, and the CH_2 group in the ozonide ring exhibits one singlet for *cis*-**18a**,**b** but two singlets for *trans*-**18a**,**b**. Since the spectra of ozonides **17a**,**b** show the same differences in their patterns, their configurations were assigned accordingly, and these assignments were extended to their precursors *cis*-**13** and *trans*-**13**.

Table 1. ^{1}H NMR spectroscopic data of common structural units in diozonides **17a**,**b** and **18a**,**b**

	Chemical shifts (ppm) of structural units $-CH_2-(CH)$	$O-O-CH_2-O$
cis-**18a**,**b**	ABX: $\delta_A = 2.43$, $\delta_B = 2.36$	s: 5.14, 5.15
	A_2X: $\delta_A = 2.40$	s: 5.11
cis-**17a**,**b**	ABX: $\delta_A = 2.43$, $\delta_B = 2.36$	s: 5.14, 5.15
	A_2X: $\delta_A = 2.40$	s: 5.12
trans-**18a**,**b**	ABX: $\delta_A = 2.57$, $\delta_B = 2.31$	s: 5.15, 5.17
	ABX: $\delta_A = 2.49$, $\delta_B = 2.38$	s: 5.131, 5.134
trans-**17a**,**b**	ABX: $\delta_A = 2.56$, $\delta_B = 2.29$	s: 5.16, 5.17
	ABX: $\delta_A = 2.49$, $\delta_B = 2.36$	s: 5.13, 5.14

In the ^{13}C NMR spectra, the signals for the CH_3 groups at the ozonide rings of *cis*-**13** (δ = 20.70 ppm) and *cis*-**17a**,**b** (δ = 20.19, 20.22 ppm) appear downfield from those of *trans*-**13** (δ = 19.17 ppm) and *trans*-**17a**,**b** (δ = 19.40 ppm). Since the corresponding signals for **5a**,**b** (δ = 20.95 ppm) and **7** (δ = 20.26 ppm) also appear in the downfield range, we have assigned them as *cis* compounds. This assignment derives support from the observation that the signals for the CH_2Cl groups geminal to the CH_3 groups for *cis*-**13** (δ = 45.61 ppm) and *cis*-**17a**,**b** (δ = 45.59 ppm) appear upfield from those for *trans*-**13** (δ = 46.17 ppm) and *trans*-**17a**,**b** (δ = 46.01 ppm) and that the corresponding signals for **5a**,**b** (δ = 45.40, 45.44 ppm) and **7** (δ = 45.75 ppm) also appear in the upfield range.

Experimental Section

General: NMR spectra: Bruker AC 250. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with TMS as internal reference and ^{17}O NMR spectra in C_6D_6 by using H_2O as external reference. Chromatographic separations: Flash chromatography[15] on silica gel. HPLC separations: Knauer EUROPREP Si60 and Merck LICHROSORB Si60.

Caution: All reactions with ozone or ozonides and chromatographic separations were carried out behind protective safety-glass shields in a hood. Ozonides were invariably transported in thick-walled steel containers. Safety glasses and gloves must be worn at all times when working with ozone or ozonides.

Preparation of *cis*-3,5-Bis(chloromethyl)-3-methyl-5-(2-oxocyclopentyl)-1,2,4-trioxolane (*cis*-5a,b): A solution of 1,2,4-trichloro-3-methyl-2-butene (1.44 g, 8.3 mmol)[11] (65% *cis*, 35% *trans*) in 145 mL of pentane was treated with ozone at −78 °C until the solution turned blue. Residual ozone was flushed off with nitrogen, the reaction mixture was warmed up to 0 °C and stirred in the presence of solid K_2CO_3 for 30 min. The mixture was filtered and from the filtrate the solvent was distilled off at −10 °C under reduced pressure. Under nitrogen, and with stirring, the residue was dissolved in 5.5 mL of dichloromethane, cooled to −70 °C and admixed with 1-(trimethylsilyloxy)cyclopentene (**4**; 735 mg, 4.7 mmol). Then, 4.7 mL of a 1 M solution of $TiCl_4$ in dichloromethane was added within 5 min and the mixture was stirred for 2 h while the temperature rose to −50 °C. The mixture was poured into ice/water with stirring, the phases were separated, the aqueous phase was repeatedly extracted with dichloromethane and the extracts were added to the organic phase. The combined organic phases were extracted with an aqueous solution of $NaHCO_3$ and dried with $MgSO_4$. The solvent was distilled off at room temperature under reduced pressure to leave 1.4 g of a yellow viscous residue, which was purified by flash chromatography (petroleum ether/diethyl ether, 4:1) to give 210 mg (9%) of a mixture of ozonides *cis*-**5a**,**b** and 130 mg (7%) of peroxy ester **8**. HPLC separation of the ozonides (LICHROSORB Si60; petroleum ether/diethyl ether, 75:25) provided 32 mg (1%) of *cis*-**5a** and 90 mg (4%) of *cis*-**5b**.

***cis*-3,5-Bis(chloromethyl)-3-methyl-5-(2-oxocyclopentyl)-1,2,4-trioxolane (*cis*-5a):** Colorless viscous liquid. ^{1}H NMR: δ = 1.62 (s, 3 H), 1.67−2.45 (m, 6 H), 3.03 (ddd, J = 11.0, 8.0, 1.0 Hz, 1 H); AB system: δ_A = 3.71, δ_B = 3.64 (J = 12.2 Hz, 2 H); AB system: δ_A = 4.20, δ_B = 3.75 (J = 11.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 20.15, 20.95, 25.95, 39.45, 44.06, 45.50, 50.58, 109.43, 109.74, 213.78 ppm.

***cis*-3,5-Bis(chloromethyl)-3-methyl-5-(2-oxocyclopentyl)-1,2,4-trioxolane (*cis*-5b):** Colorless viscous liquid. ^{1}H NMR: δ = 1.62 (s, 3 H), 1.66−2.44 (m, 6 H); A-part of an AMNX system: δ_A = 3.06 (J_{AM} = 11.2, J_{AN} = 8.1, J_{AX} = 0.9 Hz, 1 H); AB system: δ_A = 3.68, δ_B = 3.62 (J_{AB} = 12.1 Hz, 2 H); AB system: δ_A = 4.21, δ_B = 3.87 (J_{AB} = 11.8 Hz, 2 H) ppm. ^{13}C NMR: δ = 20.10, 20.95, 24.72, 38.84, 43.18, 45.43, 49.19, 109.21, 109.79, 213.52 ppm. $C_{10}H_{14}Cl_2O_4$ (269.12): calcd. C 44.63, H 5.24; found C 44.69, H 5.10.

Chloroacetyl (1,2-Dichloro-1-methyl) Peroxide (8): Colorless liquid. ^{1}H NMR: ABX$_3$ system: δ_A = 4.21, δ_B = 3.93, δ_X = 2.00 (J_{AB} = 12.3, J_{AX} = 0.7 Hz); 4.17 (s) ppm. ^{13}C NMR: δ = 25.37, 37.81, 48.04, 104.41, 163.16 ppm.

Reduction of Ozonides *cis*-5a,b: A sample of a 1:2 mixture of *cis*-**5a** and *cis*-**5b** (12 mg, 45 μmol) in CDCl$_3$ was admixed with an excess of triphenylphosphane in an NMR tube and kept at room temperature for 5 d. ^{1}H NMR analysis showed the presence of **9** [δ = 2.31 (s), 4.09 (s) ppm] and **10** [δ = 1.80−2.88 (m), 1.97 (quint, J = 7.2 Hz), 2.46 (t, J = 7.9 Hz), 2.64 (t, J = 7.9 Hz), 3.62 (t, J = 8.5 Hz), 4.05 (s); AB system: δ_A = 4.53, δ_B = 4.32 (J = 16.0 Hz) ppm] in a ratio of about 1:1.

Synthesis of 2-(Chloroacetyl)cyclopentanone (10): The synthesis was performed according to a general procedure for the preparation of β-diketones:[16] Under nitrogen, 20 mL of a 1 M solution of TiCl$_4$ in dichloromethane was cooled to 0 °C. Then chloroacetyl chloride (**9**; 2.26 g, 20 mmol) and 1-(trimethylsilyloxy)cyclopentene (**4**; 3.13 g, 20 mmol) were successively added with stirring. After 1 h, the mixture was poured into ice/water with vigorous stirring. The aqueous phase was extracted with dichloromethane and the extract was combined with the organic phase. The mixture was dried with MgSO$_4$ and filtered. From the filtrate the solvent was distilled off at 40 °C and reduced pressure to leave 2.6 g of a yellow liquid residue, which was purified by flash chromatography (*n*-hexane/ethyl acetate/methanol, 60:32:8) and subsequent distillation at 80 °C and 10^{-3} Torr to give 33 mg of **10** as a yellow liquid. ^{1}H NMR: δ = 1.81−2.88 (m), 1.99 (quint, J = 7.5 Hz), 2.47 (t, J = 7.9 Hz), 2.65 (t, J = 7.2 Hz), 3.62 (t, J = 8.6 Hz), 4.05 (s); AB system: δ_A = 4.53, δ_B = 4.32 (J = 16.0 Hz) ppm. ^{13}C NMR: δ = 20.34, 20.76, 25.21, 25.34, 36.88, 38.67, 42.07, 48.39, 59.47, 110.59, 169.81, 196.06, 206.28, 211.89 ppm.

Preparation of *cis*-3,5-Bis(chloromethyl)-3-(1,1-dimethyl-2-oxoethyl)-5-methyl-1,2,4-trioxolane (7): A solution of 1,2,4-trichloro-3-methyl-2-butene[11] (6.06 g, 34.9 mmol; 65% *cis*, 35% *trans*) in 610 mL of pentane was treated with ozone at −78 °C until it turned blue. Residual ozone was flushed off with nitrogen, the reaction mixture was warmed up to room temperature, separated from an oily precipitate and stirred in the presence of solid K$_2$CO$_3$ for 1 h. The mixture was filtered and from the filtrate the solvent was distilled off at −10 °C and reduced pressure. Under nitrogen, and with stirring, the residue was dissolved in 50 mL of dichloromethane, cooled to −70 °C and admixed with 2-methyl-1-(trimethylsilyloxy)propene (**6**; 2.16 g, 15 mmol). Then 15 mL of a 1 M solution of TiCl$_4$ in dichloromethane was added within 5 min and the mixture was stirred at −70 °C for 45 min. The mixture was poured into ice/water with stirring, the phases were separated, the water phase was repeatedly extracted with dichloromethane and the extracts were added to the organic phase. The combined organic phases were dried with MgSO$_4$ and filtered. From the filtrate the solvent was distilled off at room temperature and reduced pressure to leave 4.59 g of a yellow liquid residue, which was separated by flash chromatography (petroleum ether/diethyl ether, 83:17) to give 290 mg of impure ozonide **7** and 1.02 g (13%) of peroxy ester **8**. HPLC separation of the impure ozonide (EUROPREP 60; *n*-hexane/diethyl ether, 82:18) provided 135 mg (1.5%) of *cis*-**7** as a colorless liquid. ^{1}H NMR: δ = 1.23 (s, 3 H), 1.25 (s, 3 H), 1.63 (s, 3 H); AB system: δ_A = 3.77, δ_B = 3.71 (J = 12.1 Hz); AB system: δ_A = 3.86, δ_B = 3.77 (J = 12.7 Hz); 9.68 (s, 1 H) ppm. ^{13}C NMR: δ = 18.33, 18.64, 20.26, 42.54, 45.75, 52.13, 109.90, 111.18, 200.07 ppm. $C_9H_{14}Cl_2O_4$ (257.11): calcd. C 42.04, H 5.49; found C 41.72, H 5.65.

Reduction of Ozonide *cis*-7: A sample of *cis*-**7** (7.3 mg, 29 μmol) in CDCl$_3$ was admixed with an excess of triphenylphosphane in an NMR tube and kept at room temperature for 3 h. ^{1}H NMR analysis showed the presence of **9** [δ = 2.31 (s), 4.09 (s) ppm] and **11** [δ = 1.40 (s, 6 H), 4.28 (s, 2 H), 9.58 (s, 1 H) ppm] in a ratio of about 1:1. The data for **11** were verified with the help of an independently prepared sample.[17]

Preparation of 3-Allyl-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolanes (*cis*-13 and *trans*-13): A solution of 1,2,4-trichloro-3-methyl-2-butene[11] (1.13 g, 6.5 mmol; 65% *cis*, 35% *trans*) in 110 mL of pentane was treated with ozone at −78 °C until it turned blue. Residual ozone was flushed off with nitrogen, the reaction mixture was warmed up to room temperature and the solvent was distilled off at reduced pressure. Under nitrogen, and with stirring, the residue was dissolved in 20 mL of dichloromethane, cooled to −75 °C and admixed with allyltrimethylsilane (**12**; 795 μL, 5.0 mmol). Then 4.5 mL of a 1 M solution of TiCl$_4$ in dichloromethane was added within 5 min and the mixture was stirred at −75 °C for 2 h. The mixture was poured into ice/water with stirring, the phases were separated, the water phase was repeatedly extracted with dichloromethane and the extracts were added to the organic phase. The combined organic phases were sequentially washed with a saturated aqueous solution of NaHCO$_3$ and water, dried with MgSO$_4$ and filtered. From the filtrate the solvent was distilled off at room temperature and reduced pressure to leave 2.0 g of a colorless liquid residue, which was purified by flash chromatography (petroleum ether/diethyl ether, 9:1) to give 670 mg (45%) of a mixture consisting of *cis*-**13** (60%) and *trans*-**13** (40%). HPLC separation of this mixture (EUROPREP Si60; *n*-hexane/diethyl ether, 96:4) provided 237 mg (21%) of *cis*-**13** and 174 mg (15%) of *trans*-**13**. They were further purified by distillation at 60 °C and 5×10^{-3} Torr.

***cis*-3-Allyl-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolane (*cis*-13):** Colorless liquid. ^{1}H NMR: δ = 1.63 (s, 3 H); AB part of an ABMNX system: δ_A = 2.74, δ_B = 2.67 (J_{AB} = 14.5, J_{AX} = 7.5, J_{BX} = 7.3, J_{AM} = J_{AN} = J_{BM} = J_{BN} = 1.1 Hz); AB system: δ_A = 3.70, δ_B = 3.61 (J = 12.2 Hz); AB system: δ_A = 3.72 δ_B = 3.61 (J = 12.0 Hz); 5.29−5.29 (m, 2 H), 5.71 −5.87 (m, 1 H) ppm. ^{13}C NMR: δ = 20.70, 38.59, 43.46, 45.61, 109.18, 109.58, 120.52, 130.42 ppm. ^{17}O NMR: δ = 122, 297 ppm. $C_8H_{12}Cl_2O_3$ (227.09): calcd. C 42.31, H 5.33; found C 42.17, H 5.39.

***trans*-3-Allyl-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolane (*trans*-13):** Colorless liquid. ^{1}H NMR: δ = 1.64 (s, 3 H); AB part of an ABMNX system: δ_A = 2.76, δ_B = 2.64 (J_{AB} = 14.6, J_{AX} = 7.4, J_{BX} = 7.3, J_{AM} = J_{AN} = 1.0, J_{BM} < 1, J_{BN} < 1 Hz); AB system: δ_A = 3.63, δ_B = 3.48 (J = 11.6 Hz); AB system: δ_A = 3.66, δ_B =

3.50 (J = 11.7 Hz); 5.17−5.31 (m, 2 H), 5.70 −5.87 (m, 1 H) ppm. ^{13}C NMR: δ = 19.17, 36.07, 44.34, 46.17, 109.09, 109.73, 121.10, 129.57 ppm. ^{17}O NMR: δ = 122, 298 ppm. $C_8H_{12}Cl_2O_3$ (227.09): calcd. C 42.31, H 5.33; found C 42.46, H 5.17.

Reduction of Ozonides *cis*- and *trans*-13: A sample of about 50−60 μmol of ozonide *cis*-**13** or *trans*-**13** in $CDCl_3$ was admixed with about 20 μmol of acetone (internal standard) and about 90 μmol of triphenylphosphane in a sealed NMR tube and the solution was heated to 50 °C for 90 min. ^{1}H NMR analysis showed the presence of **9** [δ = 2.31 (s, 3 H), δ = 4.08 (s, 2 H) ppm] and **16** [δ = 3.36−3.40 (m, 2 H), 4.13 (s, 2 H), 5.16−5.28 (m, 2 H), 5.84−6.00 (m, 1 H) ppm] in a molar ratio of about 1:1.

Preparation of 3,5-Diallyl-3,5-bis(chloromethyl)-1,2,4-trioxolanes (*cis*-14 and *trans*-14): 10 mL of a 1 M solution of $TiCl_4$ in dichloromethane was added within 10 min to a stirred solution of ozonide *trans*-**2**[12] (1.12 g, 4.6 mmol) in 20 mL of dichloromethane which was kept at −78 °C under nitrogen. Subsequently, allyltrimethylsilane (**12**; 1.60 mL, 10.0 mmol) was added and the mixture was stirred at −40 °C for 6 h. The mixture was poured into 50 mL of ice/water with stirring, the phases were separated, the water phase was repeatedly extracted with dichloromethane and the extracts were added to the organic phase. The combined organic phases were dried with $MgSO_4$ and filtered. From the filtrate the solvent was distilled off at room temperature and reduced pressure to leave 1.13 g of a yellow liquid residue, which was purified by flash chromatography (petroleum ether/diethyl ether, 97:3) to give 800 mg of a mixture consisting of 90% of ozonides *cis*-**14** and *trans*-**14** in a ratio of about 1:1 and 10% of unchanged **2**. HPLC separation of this mixture (EUROPREP Si60; petroleum ether/diethyl ether, 98:2) provided 305 mg (26%) of *cis*-**14** and 296 mg (25%) of *trans*-**14**.

***cis*-3,5-Diallyl-3,5-bis(chloromethyl)-1,2,4-trioxolane (*cis*-14):** Colorless liquid. ^{1}H NMR: AB part of an ABMNX system: δ_A = 2.68, δ_B = 2.67 (J_{AB} = 14.5, J_{AX} = 7.6, J_{BX} = 7.1, J_{AM} = J_{AN} = 1.0, J_{BM} < 1, J_{BN} < 1 Hz); AB system: δ_A = 3.73, δ_B = 3.63 (J = 12.2 Hz); 5.21−5.30 (m, 2 H), 5.71−5.88 (m, 1 H) ppm. ^{13}C NMR: δ = 38.20, 43.53, 109.75, 120.64, 130.29 ppm. ^{17}O NMR: δ = 126, 295 ppm. $C_{10}H_{14}Cl_2O_3$ (253.13): calcd. C 47.45, H 5.57; found C 47.52, H 5.65.

***trans*-3,5-Diallyl-3,5-bis(chloromethyl)-1,2,4-trioxolane (*trans*-14):** Colorless liquid. ^{1}H NMR: AB part of an ABMNX system: δ_A = 2.77, δ_B = 2.67 (J_{AB} = 14.6, J_{AX} = 7.3, J_{BX} = 7.4, J_{AM} = J_{AN} = 1.1, J_{BM} < 1, J_{BN} < 1 Hz); AB system: δ_A = 3.65, δ_B = 3.50 (J = 11.6 Hz); 5.24−5.32 (m, 2 H), 5.70−5.87 (m, 1 H) ppm. ^{13}C NMR: δ = 36.15, 44.51, 109.67, 121.15, 129.52 ppm. ^{17}O NMR: δ = 126, 297 ppm. $C_{10}H_{14}Cl_2O_3$ (253.13): calcd. C 47.45, H 5.57; found C 47.55, H 5.63.

Reduction of Ozonides *cis*- and *trans*-14: A sample of about 40 μmol of ozonide *cis*-**14** or *trans*-**14** in $CDCl_3$ was admixed with about 20 μmol of acetone (internal standard) and about 90 μmol of triphenylphosphane in a sealed NMR tube and the solution was heated to 50 °C for 90 min. ^{1}H NMR analysis showed the presence of **16** [δ = 3.36−3.40 (m, 2 H), 4.13 (s, 2 H), 5.16−5.28 (m, 2 H), 5.84−6.00 (m, 1 H) ppm] in a yield of 98%.

Ozonolysis of *cis*-3-Allyl-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolane (*cis*-13): A solution of *cis*-**13** (230 mg, 1.0 mmol) in 100 mL of pentane was treated with ozone at −78 °C until it turned blue. Residual ozone was flushed off with nitrogen, the reaction mixture was warmed up to room temperature and the pentane solution was decanted from a viscous precipitate. The precipitate was dissolved in dichloromethane and the solution was combined with the pentane solution. The solvents were distilled off at room temperature and reduced pressure to leave 260 mg of a colorless viscous oil. Purification by flash chromatography (petroleum ether/diethyl ether, 75:25) provided 232 mg (84%) of a mixture of the two diastereomers of *cis*-**17** as a colorless oil. ^{1}H NMR: δ = 1.66 (s), 1.67 (s); AB part of an ABX system: δ_A = 2.43, δ_B = 2.36 (J_{AB} = 14.8, J_{AX} = 5.6, J_{BX} = 4.9 Hz); A part of an A_2X system: δ_A = 2.40 (J_{AX} = 5.2 Hz); AB system: δ_A = 3.75, δ_B = 3.61 (J_{AB} = 11.9 Hz); AB system: δ_A = 3.81, δ_B = 3.72 (J_{AB} = 12.6 Hz); AB system: δ_A = 3.81, δ_B = 3.77 (J_{AB} = 12.7 Hz); 5.12 (s), 5.141 (s), 5.147 (s), 5.41 (t, J = 5.1 Hz), 5.43 (t, J = 5.2 Hz) ppm. ^{13}C NMR: δ = 20.19, 20.22, 36.77, 36.98, 43.69, 43.75, 45.59, 94.01, 94.10, 99.73, 99.75, 107.74, 107.80, 109.72 ppm. ^{17}O NMR: δ = 81, 121, 294 ppm. $C_8H_{12}Cl_2O_6$ (275.09): calcd. C 34.93, H 4.40; found C 34.91, H 4.43.

Ozonolysis of *trans*-3-Allyl-3,5-bis(chloromethyl)-5-methyl-1,2,4-trioxolane (*trans*-13): A solution of *trans*-**13** (230 mg, 1.0 mmol) in 100 mL of pentane was treated with ozone at −78 °C until it turned blue. Residual ozone was flushed off with nitrogen, and the solvent was distilled off at room temperature and reduced pressure to leave 265 mg of a colorless oil. Purification by flash chromatography (petroleum ether/diethyl ether, 4:1) provided 190 mg (69%) of a mixture of the two diastereomers of *trans*-**17** as a colorless oil. ^{1}H NMR: δ = 1.67 (s); AB part of an ABX system: δ_A = 2.49, δ_B = 2.36 (J_{AB} = 15.3, J_{AX} = 5.4, J_{BX} = 5.0 Hz); AB part of an ABX system: δ_A = 2.56, δ_B = 2.29 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.4 Hz); 3.76−3.53 (m), 5.49 (t, J = 5.3 Hz) ppm. ^{13}C NMR: δ = 19.40, 34.38, 34.49, 44.80, 44.84, 46.01, 94.04, 99.47, 108.06, 109.60, 109.62 ppm. ^{17}O NMR: δ = 88, 128, 296 ppm. $C_8H_{12}Cl_2O_6$ (275.09): calcd. C 34.93, H 4.40; found C 34.89, H 4.45.

Ozonolysis of *cis*-3,5-Diallyl-3,5-bis(chloromethyl)-1,2,4-trioxolane (*cis*-14): A solution of *cis*-**14** (290 mg, 1.15 mmol) in 115 mL of pentane was treated with ozone at −78 °C until it turned deep blue. During this procedure, a voluminous precipitate was formed. The suspension was flushed with nitrogen for 1 h and then warmed up to room temperature. The pentane solution was decanted, the residual precipitate was dissolved in dichloromethane and the solution was combined with the pentane solution. The solvents were distilled off at room temperature and reduced pressure to leave 432 mg of a colorless oil. HPLC separation (EUROPREP 60; petroleum ether/diethyl ether, 70:30) of this oil provided 120 mg (35%) of a mixture of two diastereomers of diozonide *cis*-**18** and 176 mg (44%) of a mixture of the three diastereomeric triozonides *cis*-**19a**,**b**,**c**. HPLC separation (LICHROSORB Si60; *n*-hexane/diethyl ether, 70:30) of this mixture by the two-column-cycle technique[18] provided 40 mg of *cis*-**19a**, 78 mg of *cis*-**19b** and 39 mg of *cis*-**19c**.

***cis*-3-Allyl-3,5-bis(chloromethyl)-5-(1,2,4-trioxolanylmethyl)-1,2,4-trioxolane (*cis*-18):** Colorless oil. Mixture of two diastereomers. ^{1}H NMR: A part of an A_2X system: δ_A = 2.40 (J_{AX} = 5.0 Hz); AB part of an ABX system: δ_A = 2.43, δ_B = 2.36 (J_{AB} = 14.8, J_{AX} = 5.8, J_{BX} = 4.6 Hz); AB part of an ABX system: δ_A = 2.78, δ_B = 2.69 (J_{AB} = 14.5, J_{AX} = 7.7, J_{BX} = 7.0 Hz); AB system: δ_A = 3.76, δ_B = 3.63 (J = 12.1 Hz, 4 H); AB system: δ_A = 3.83, δ_B = 3.73 (J = 12.6 Hz); AB system: δ_A = 3.84, δ_B = 3.79 (J = 12.4 Hz); 5.11 (s), 5.14 (s), 5.15 (s), 5.24−5.31 (m), 5.39−5.45 (m), 5.70−5.87 (m) ppm. ^{13}C NMR: δ = 36.53, 36.79, 37.61, 37.63, 43.68, 43.77, 43.80, 92.99, 94.10, 99.71, 107.88, 107.95, 110.36, 121.15, 129.87, 129.90 ppm. ^{17}O NMR: δ = 92, 138, 291 ppm. $C_{10}H_{14}Cl_2O_6$ (301.12): calcd. C 39.89, H 4.69; found C 39.57, H 4.77.

***cis*-3,5-Bis(chloromethyl-3,5-bis(1,2,4-trioxolanylmethyl)-1,2,4-trioxolane (*cis*-19a,b,c):** Colorless oil. Mixture of three diastereomers. ^{17}O NMR: δ = 89, 290 ppm. For safety reasons no elemental analysis of ozonide **19** was attempted.

***cis*-19a:** Colorless oil. HPLC: t_R = 13.05 min. ^{1}H NMR: AB system: δ_A = 3.86, δ_B = 3.78 (J = 12.5 Hz, 2 H); 5.15 (s, 1 H), 5.16 (s, 1 H); ABX system: δ_A = 2.49, δ_B = 2.36, δ_X = 5.44 (J_{AB} = 14.8, J_{AX} = 5.8, J_{BX} = 4.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 36.16, 43.88, 94.12, 99.49, 108.52 ppm.

***cis*-19b:** Colorless oil. HPLC: t_R = 13.35 min. ^{1}H NMR: δ = 2.32−2.55 (m, 4 H), 3.71−3.89 (m, 4 H, 5.12 (s, 1 H), 5.14 (s, 1 H), 5.16 (s, 1 H), 5.43−5.47 (m, 2 H) ppm. ^{13}C NMR: δ = 36.16, 43.88, 94.12, 99.49, 108.52 ppm.

***cis*-19c:** Colorless oil. HPLC: t_R = 13.80 min. ^{1}H NMR: AB system: δ_A = 3.85, δ_B = 3.73 (J = 12.5 Hz, 2 H), δ = 5.12 (s, 1 H), 5.17 (s, 1 H); ABX system: δ_A = 2.47, δ_B = 2.42, δ_X = 5.47 (J_{AB} = 15.1, J_{AX} = 5.8 Hz,, J_{BX} = 4.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 36.34, 44.00, 94.03, 99.52, 108.48 ppm.

Ozonolysis of *trans*-3,5-Diallyl-3,5-bis(chloromethyl)-1,2,4-trioxolane (*trans*-14): A solution of *trans*-**14** (296 mg, 1.17 mmol) in 130 mL of pentane was treated with ozone at −78 °C until it turned deep blue. During this procedure, a voluminous precipitate was formed. The suspension was flushed with nitrogen for 1 h and warmed up to room temperature. The pentane solution was decanted, the residual precipitate was dissolved in dichloromethane and the solution was combined with the pentane solution. The solvents were distilled off at room temperature and reduced pressure to leave 446 mg of a colorless oil. HPLC separation (EUROPREP 60; petroleum ether/diethyl ether, 70:30) of this oil provided 73 mg (21%) of a mixture of two diastereomers of diozonide *trans*-**18** and 226 mg (55%) of a mixture of the three diastereomeric triozonides *trans*-**19a**, **19b** and **19c** (*trans*-**19a**,**b**,**c**).

***trans*-3-Allyl-3,5-bis(chloromethyl)-5-(1,2,4-trioxolanylmethyl)-1,2,4-trioxolane (*trans*-18):** Colorless oil. Mixture of two diastereomers. ^{1}H NMR: AB part of an ABX system: δ_A = 2.49, δ_B = 2.38 (J_{AB} = 15.2, J_{AX} = 5.3, J_{BX} = 5.2 Hz); AB part of an ABX system: δ_A = 2.57, δ_B = 2.31 (J_{AB} = 15.1, J_{AX} = 5.0, J_{BX} = 5.6 Hz); AB part of an ABX system: δ_A = 2.80, δ_B = 2.69 (J_{AB} = 14.6, J_{AX} = 7.2, J_{BX} = 7.4 Hz); 3.54−3.75 (four overlapping AB systems, 15 of 16 signals resolved), 5.13 (s), 5.14 (s), 5.15 (s), 5.17 (s), 5.24−5.26 (m), 5.29−5.33 (m), 5.49 (t, J = 5.2 Hz), 5.70−5.87 (m) ppm. ^{13}C NMR: δ = 34.57, 34.67, 36.43, 44.33, 45.02, 45.06, 94.04, 94.06, 99.46, 108.06, 110.21, 110.23, 121.44, 129.35 ppm. ^{17}O NMR: δ = 88, 122, 295 ppm. $C_{10}H_{14}Cl_2O_6$ (301.12): calcd. C 39.89, H 4.69; found C 39.92, H 4.77.

***trans*-3,5-Bis(chloromethyl-3,5-bis(1,2,4-trioxolanylmethyl)-1,2,4-trioxolane (*trans*-19a,b,c):** Colorless oil. Mixture of three diastereomers. ^{1}H NMR: AB part of an ABX system: δ_A = 2.506, δ_B = 2.405 (J_{AB} = 15.1, J_{AX} = 5.2, J_{BX} = 5.3 Hz); AB part of an ABX system: δ_A = 2.505, δ_B = 2.410 (J_{AB} = 15.1, J_{AX} = 5.2, J_{BX} = 5.4 Hz); AB part of an ABX system: δ_A = 2.570, δ_B = 2.340 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.5 Hz); AB part of an ABX system: δ_A = 2.570, δ_B = 2.345 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.6 Hz); AB system: δ_A = 3.727, δ_B = 3.698 (J = 12.0 Hz,); AB system: δ_A = 3.743, δ_B = 3.651 (J = 11.9 Hz); AB system: δ_A = 3.744, δ_B = 3.719 (J = 12.1 Hz); AB system: δ_A = 3.757, δ_B = 3.671 (J = 12.1 Hz); 5.129 (s), 5.134 (s), 5.164 (s), 5.176 (s), 5.494 (t, J = 5.3 Hz) ppm. ^{13}C NMR: δ = 34.95, 35.07, 44.70, 44.74, 94.08, 99.33, 108.53 ppm. ^{17}O NMR: δ = 86, 292 ppm. For safety reasons no elemental analysis of ozonide **19** was attempted.

Isolation of a Crystalline Mixture of Triozonides *trans*-19a and *trans*-19b (*trans*-19a,b): In a test tube, a solution of *trans*-**19a**,**b**,**c** (200 mg) in 500 µL of dichloromethane was layered with 4 mL of *n*-pentane. The two-phase mixture was kept at room temperature for 24 h, whereby colorless crystals precipitated. The liquid was decanted, the crystals were washed with *n*-pentane, dissolved in 500 µL of dichloromethane and the crystallization procedure was repeated, using 3 mL of *n*-pentane, to yield 50 mg of crystalline *trans*-**19ab**.

***trans*-3,5-Bis(chloromethyl)-3,5-bis(1,2,4-trioxolanylmethyl)-1,2,4-trioxolane (*trans*-19a,b):** Colorless solid; m.p. 80−83 °C. Mixture of two diastereomers. ^{1}H NMR: AB part of an ABX system: δ_A = 2.505, δ_B = 2.412 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.4 Hz); AB part of an ABX system: δ_A = 2.570, δ_B = 2.342 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.7 Hz); AB part of an ABX system: δ_A = 2.570, δ_B = 2.346 (J_{AB} = 15.1, J_{AX} = 5.1, J_{BX} = 5.5 Hz). AB system: δ_A = 3.727, δ_B = 3.698 (J = 12.1 Hz,); AB system: δ_A = 3.743, δ_B = 3.652 (J = 11.9 Hz); AB system: δ_A = 3.743, δ_B = 3.719 (J = 12.1 Hz); 5.135 (s), 5.164 (s), 5.176 (s), 5.494 (t, J = 5.3 Hz) ppm.

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[13] Ozonide *cis*-**19** can exist as three diastereomers — two *meso* forms and one chiral form — consistent with the three distinct fractions isolated by chromatography and the NMR spectroscopic data obtained. Ozonide *trans*-**19** can potentially exist as four diastereomers — two with C_2 symmetry and two of lower symmetry.

[14] CCDC-233569 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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