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Unusual reactivity of bicyclo[2.2.1]heptene derivatives during the ozonolysis. Part 2

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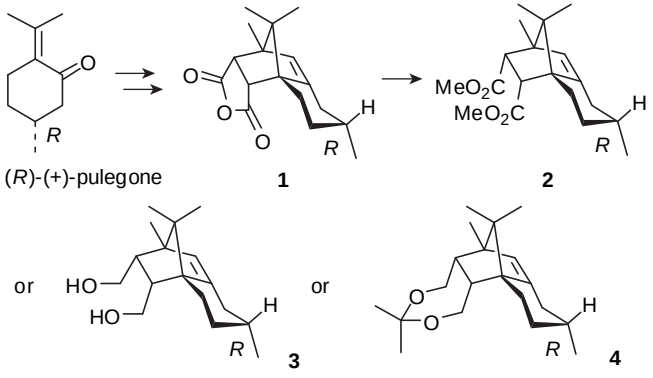
ABSTRACT

The ozonation of four bornene derivatives, prepared from (*R*)-(+)-pulegone, which possess a particularly hindered double bond, led to the formation of unexpected products depending on the nature of the solvent. The formation of the corresponding epoxides, ketones with the same skeleton, various lactones and even an allyl alcohol and an allyl chloride (allylic functionalisation) was observed. In two cases, products presenting a pulegone modified skeleton resulting from a Wagner–Meerwein rearrangement were obtained. The structure of three products was confirmed by crystallographic X-ray analysis. Mechanisms taking into account the rigid and congested structure of the reactants explain these results. The most striking steps were backed up by theoretical calculations.

1. Introduction

Ozone is one of the most reactive chemicals and it has long been recognized that the reaction of ozone with alkenes play an important role in organic chemistry.[1] Although ozone–olefin reaction has been the subject of intensive studies for over 100 years, in some cases, in the presence of unusual substrates, some abnormal results are observed. The general mechanism of ozonolysis reaction[2,3] has been thoroughly studied, and the Criegee mechanism with the formation of the 1,2,3-trioxolane (primary ozonide) has been accepted.[4] However, as Murray has underlined 'it is difficult to come to any definite conclusions regarding a complete mechanism of ozonolysis other than that it is more complicated than originally thought'.[5] Particularly, it is well known that the ozone can react with hindered olefins to give various products as epoxides with release of singlet molecular oxygen. The interest concerning the reactivity of ozone has increased in recent years due to studies suggesting that the antibody-catalysed water-oxidation pathway produces an additional molecular species with a chemical signature similar to that of ozone.[6] Particularly, a fascinating area is the biological ozonolysis of cholesterol to give 5,6-secosterols, atheronal-A and -B.[7] These compounds present proatherogenic effects[8] and induce aggregation of methylated amyloid-β peptides.[9] Finally, ozonides of three triterpenes have been isolated from leaves of plants.[10]

Recently, in the course of the synthesis of new polydentate ligands, useful for palladium-catalysed cross-coupling reactions or allylic substitution,[11] we explored, in the first part,[12] the ozonolysis of bicyclo[2.2.1]heptene derivatives arising from (*R*)-(+)-pulegone (Scheme 1).



Scheme 1. Bornene derivatives from (*R*)-(+)-pulegone.

We have shown that from anhydride **1**, some unexpected products such as **5** or **6** can been obtained by ozonolysis in CH_2Cl_2/MeOH (~2:1) at −60 °C, followed by treatment with dimethylsulfur. The structures of **5** and **6** were confirmed by X-ray analysis[12] (Scheme 2).

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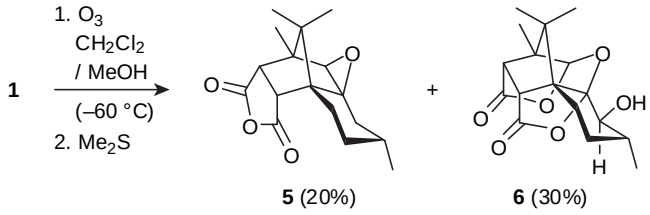


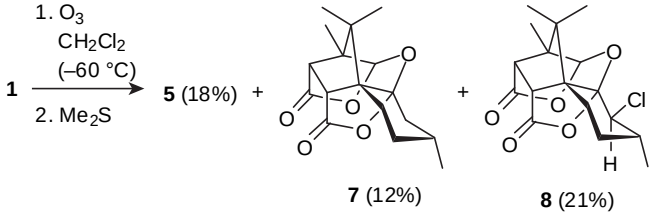
Scheme 2. Ozonation of anhydride **1** in CH_2Cl_2/MeOH.

2. Results

2.1. Ozonation of anhydride 1

During our continuing interest in the understanding of the mechanism of ozonolysis of hindered bornene derivatives, we have conducted ozonolysis reactions of **1**–**4** in various solvents and with various reductive work-up. We began by a systematic reinvestigation of the ozonolysis of anhydride **1**.

First, the ozonolysis of **1** in CH_2Cl_2 at −60 °C, until the persistence of the blue colour of ozone (7 h), gave rise mainly to three products: the epoxide **5**, the bis-lactone **7** and, surprisingly, the chloro-bislactone **8** (Scheme 3) analogous to the hydroxy-bislactone **6** (Scheme 2). Fortunately, crystals of **7** and **8** were suitable for X-ray analysis.[13]



Scheme 3. Ozonation of anhydride **1** in CH_2Cl_2 followed by the addition of Me_2S.

The ozonolysis of **1** in CH_2Cl_2 at −60 °C followed by the treatment of the crude ozonolysis mixture by an excess of $NaBH_4$, led mainly to the dihydroxylactone **9**, arising from the reduction of **5** followed by base-catalysed opening of the epoxide by a carboxylate anion.

The structure of **9** has been confirmed by X-ray analysis (Fig. 1). It reveals that the reduction of the anhydride moiety of **5** occurs on the most accessible carboxyl group of the anhydride. The formation of the lactone **10** result from the partial reduction of the corresponding chloro-bis-lactone **8** (Scheme 4).

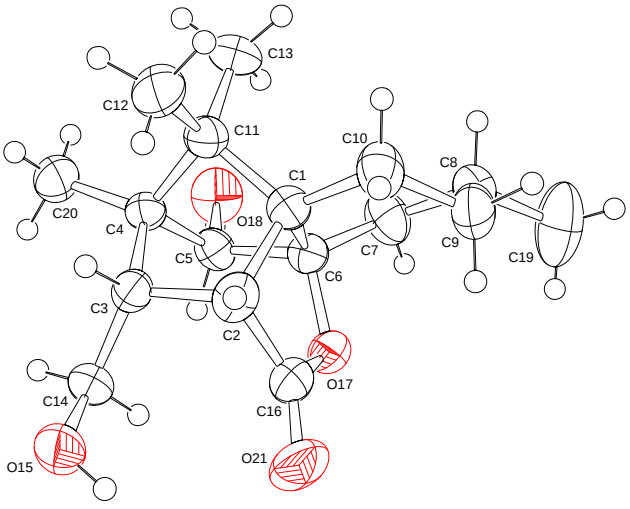
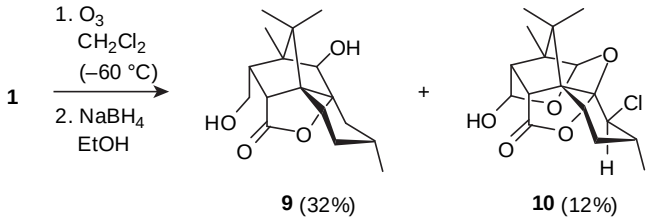
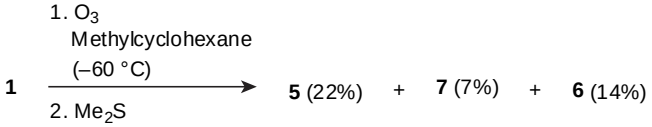


Figure 1. ORTEP diagram of compound **9**.

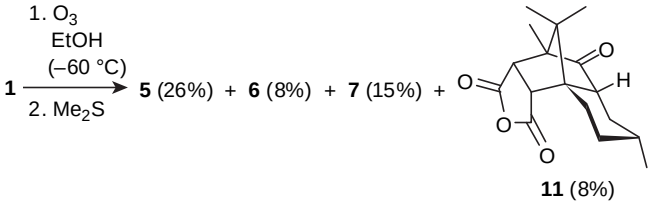


Scheme 4. Ozonation of anhydride **1** in CH_2Cl_2 followed by the addition of $NaBH_4$.

A very low reaction rate was observed when methylcyclohexane was employed as the ozonolysis solvent (Scheme 5). In contrast, the use of ethanol gave rise to five poly-oxygenated compounds, including the epoxide **5** as the major one, and the new ketone **11** resulting from the rearrangement of **5** (Scheme 6).

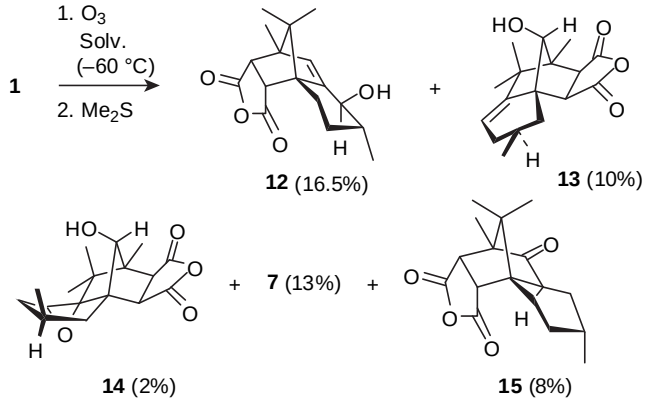


Scheme 5. Ozonation of anhydride **1** in methylcyclohexane followed by the addition of Me_2S.



Scheme 6. Ozonation of anhydride **1** in ethanol followed by the addition of Me_2S.

The formation of the chloro derivative **8**, when CH_2Cl_2 was the solvent of the ozonolysis, prompted us to employ a fluorinated solvent. Indeed, the use of a mixture of perfluorocompound FC-77® and trifluoroethanol (3:1) induces only the formation of the oxygenated compounds, including the epoxide **14**, in very low yield (Scheme 7). Crystals of **14** were suitable for X-ray analysis (Fig. 2). In contrast, the ozonolysis in trifluoroethanol proceed slowly and led only to the formation of allylic alcohol **12**.



Scheme 7. Ozonation of anhydride **1** in fluorinated solvent followed by the addition of Me_2S.

2.2. Ozonation of diester 2

The ozonolysis of the diester **2** in methylcyclohexane led mainly to the formation of products **16** and **18** coming from an epoxide, which was not isolated (Scheme 8), (Fig. 3).

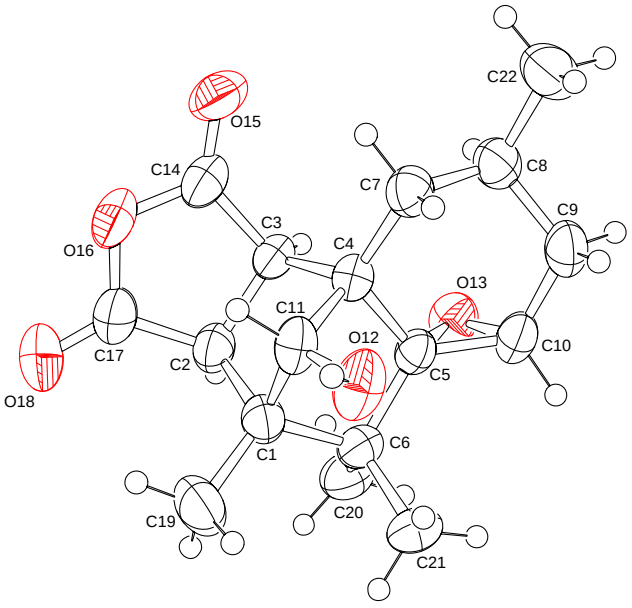
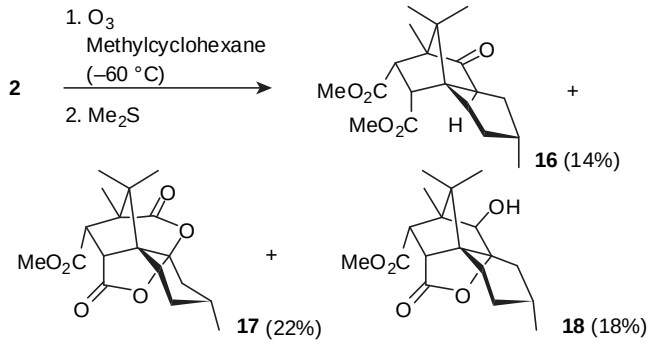


Figure 2. ORTEP diagram of compound **14**.



Scheme 8. Ozonation of anhydride **2** in methylcyclohexane followed by the addition of Me_2S.

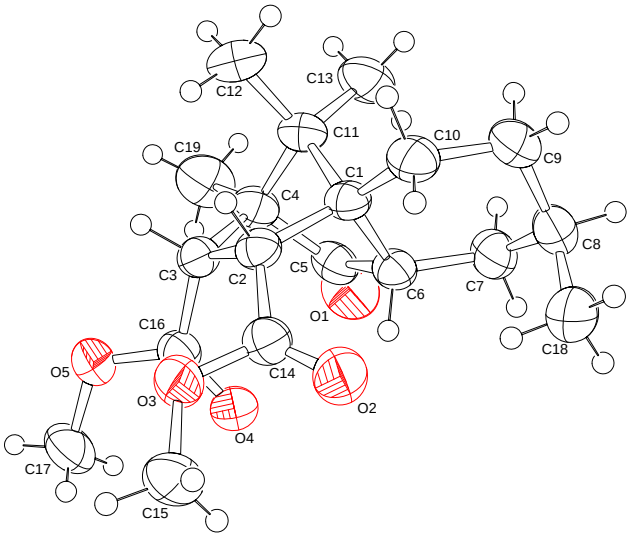
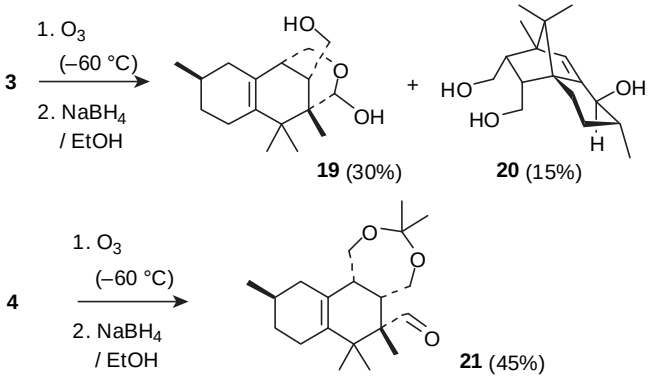


Figure 3. ORTEP diagram of compound **16**.

2.3. Ozonation of diol 3

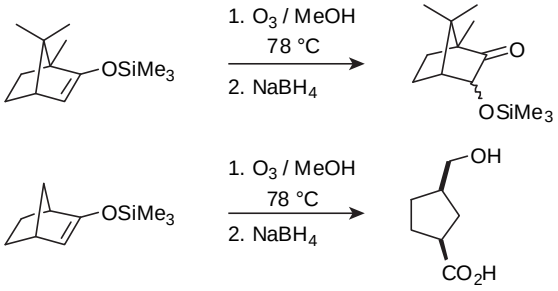
Surprisingly, the ozonolysis of the diol **3** in methylcyclohexane/chloroform, in the presence of a small amount of pyridine, gave rise mainly to the lactol **19** (structure confirmed by X-ray analysis)[14] and to the allylic alcohol **20**. A similar result was observed in the course of the ozonolysis of the acetonide **4** with the formation of **21** in 45% yield (Scheme 9).



Scheme 9. Ozonation of diol **3** and acetonide **4** followed by the addition of $NaBH_4$.

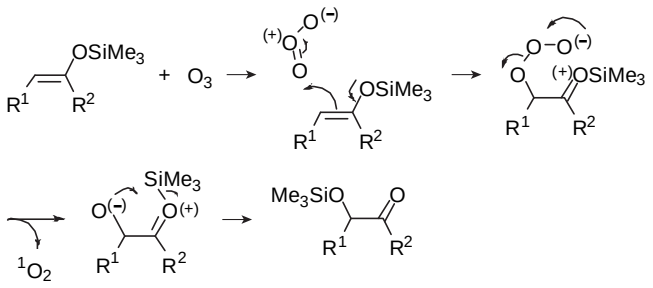
3. Discussion

The double bonds of the bicyclo[2.2.1]heptene derivatives **1**–**4** are highly hindered. Previous reports concerning the ozonolysis of relatively similar compounds, described, in some cases, the formation of unexpected oxidation products. For example, the ozonolysis of a silylenol ether of camphor led quantitatively to α-*tert*-butyldimethylsilyloxycamphor (Scheme 10, top). On the other hand, a silylenol ether of norbornanone was found to react normally (Scheme 10, bottom).[15]



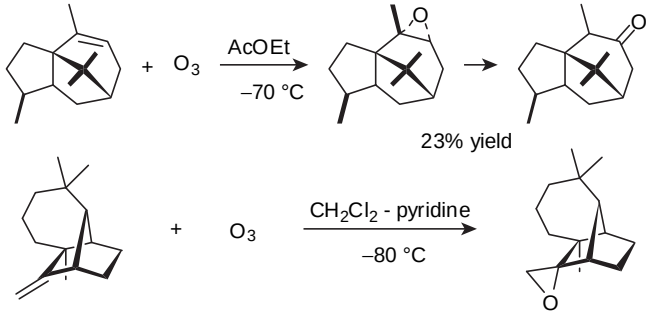
Scheme 10. Ozonolyse of bicyclo[2.2.1]heptene derivatives.

The following mechanism, involving the electrophilic character of ozone, might explain these anomalous oxidations (Scheme 11).[16]



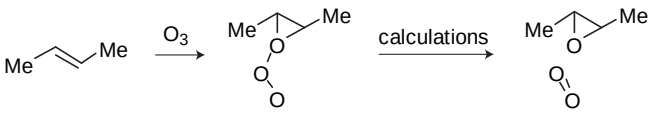
Scheme 11. Ozonolyse of silylenol ethers.

Some years ago, in the course of the ozonolysis of α-patchoulene, Büchi obtained an epoxide, which was isomerised in patchoulione by chromatography on alumina.[17] In a similar manner, the ozonation of longifolene in CH_2Cl_2, in the presence of a small amount of pyridine, gave rise only to an *endo* epoxide (Scheme 12).[18]



Scheme 12. Ozonation of α-patchoulene and longifolene.

The formation of such epoxides occurs in the presence of severe steric hindrance of the double bond[19] and can result from the addition of one extremity of ozone to the alkene to give a peroxyepoxide. Calculations of the structure of the peroxyepoxide resulting from the addition of ozone to *trans*-2-butene at the (U)B3LYP/6-311++G(3df, 3pd) or (U)MP2/6-311++G(3df, 3pd) level of the theory[20] led to the corresponding epoxide with loss of singlet molecular oxygen, confirming that the peroxyepoxide is an unstable species (Scheme 13).[21]



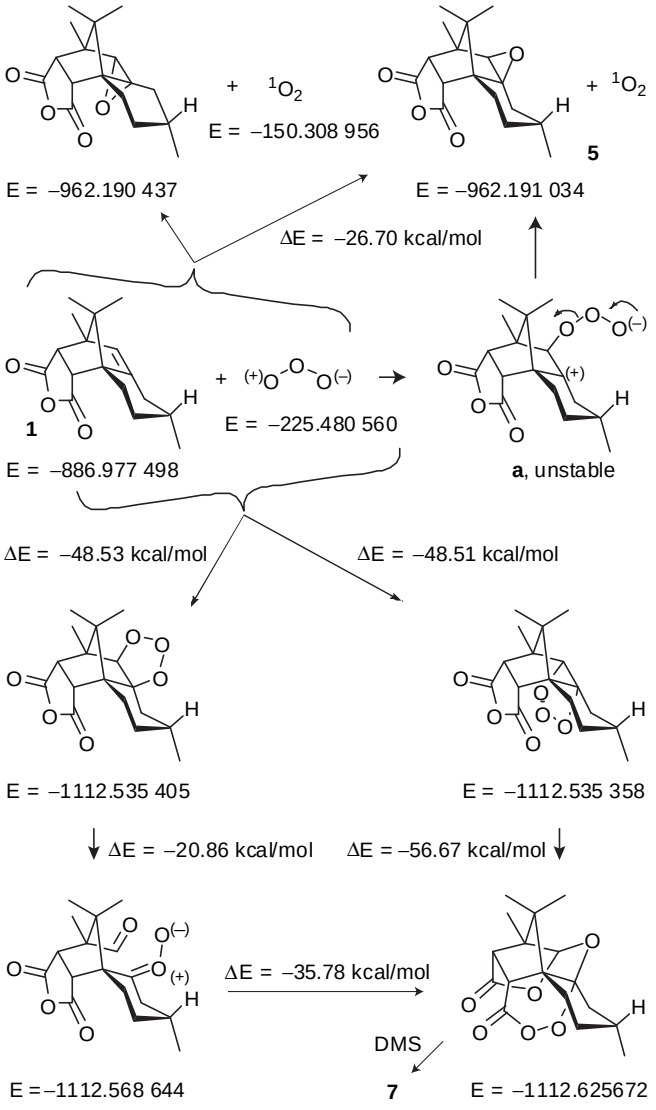
Scheme 13. Peroxyepoxide from *trans*-2-butene.

At the (*R*)B3LYP/6-311++G(d,p) level of the theory and without zero point energy correction, the *exo* and *endo* primary ozonide or the *exo* and *endo* epoxyde are of similar energies (Scheme 14). The two carbon atoms of the double bond of **1** present a similar steric hindrance. Interestingly, for the *exo* epoxide **5**, the calculated bond lengths and angles are very closed to those of the X-ray analysis[12] at ±0.6%.

The DFT studies at the (*R*)B3LYP/6-311++G(d,p) level of the zwitterions **a**, showed that it is not a minimum on the potential energy surface, and that it spontaneously rearranges into the epoxyde **5** and in singlet oxygen.

All the reactions from the anhydride **1** and ozone are highly exothermic (Scheme 14). The addition of ozone to **1** to give **5** and singlet oxygen is a less exothermic reaction that the formation of the *exo* primary ozonide (Δ*E*=22.2 kcal/mol).

The most striking feature observed in the course of the ozonolysis of **1**–**4** was the formation of the bislactones **6**, **7** and **8**. A reasonable mechanistic hypothesis, which explains these anomalous oxidations, involves the formation of the *endo* primary ozonide (1,2,3-trioxolane) **a** (Scheme 15); its fragmentation into aldehyde and ketone oxide **b**,[22] followed by a nucleophilic attack of the oxygen of ketone oxide to the adjacent carboxylic group to give carboxylate anion **c**. Then, a nucleophilic addition of this carboxylate anion to the aldehyde and finally, the addition of the oxy anion of the resulting tetrahedral intermediate to the *O*-acyloxy ketone gave rise to **d**. Treatment by dimethylsulfur induces the reduction of the peroxy bond with the release of DMSO and the formation of **7**.[23] The formation of the bislactone **7** has been interpreted in term of near attack conformation (NAC)[24,25] in our preliminary publication.[13]

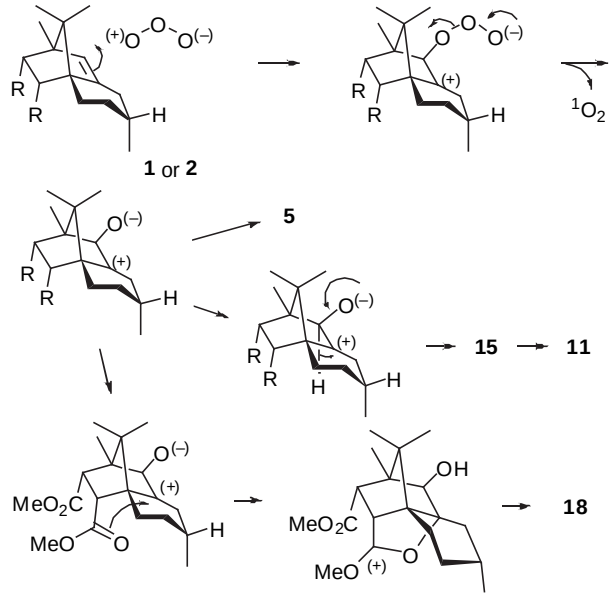


Scheme 14. Calculations at the (*R*)B3LYP/6-311++G(d,p) level of the theory (without zero point energy correction) of the structure of various intermediates involved in the course of the ozonolysis of **1** (energies in hartrees).

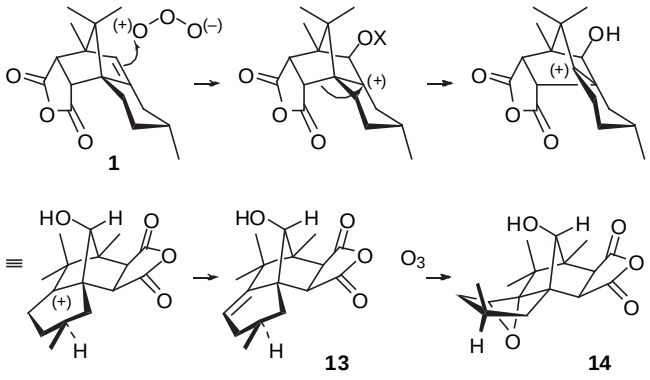
Some products such as **9**, **11**, **15**, or **18** can be considered as epoxide derivatives. These products arose from the electrophilic attack of ozone to the double bond, to give a zwitterion and singlet oxygen.[12] Epoxide **5** result from a cyclisation, and an 1,2 hydride shift gave rise to the ketones **11** and **15**. An intramolecular nucleophilic attack of the methoxycarbonyl group could explain the formation of the lactone **18** (Scheme 16).

The structure of compound **14** can be explained by a unique process involving a Wagner–Meerwein rearrangement. Ozone electrophilic attack of the double bond gave rise to a tertiary carbocation, which induces a Wagner–Meerwein rearrangement[26] leading to a new tertiary carbocation, which is a precursor of the double bond of **13**. The epoxidation of the less hindered face of the double bond of **13** led to the formation of **14** (Scheme 17).

The functionalisation of an allylic position, leading to **6**, **8**, or **12**, result from the formation of hydrotrioxides, which are generally stable below −40 °C. The reaction of ozone with C–H bonds has been shown to occur with retention of the configuration and to have a pronounced kinetic isotope effect.[27] The observation that equatorial tertiary hydrogens react seven times faster than the axial tertiary hydrogens, suggests that this reaction has considerable steric requirements.

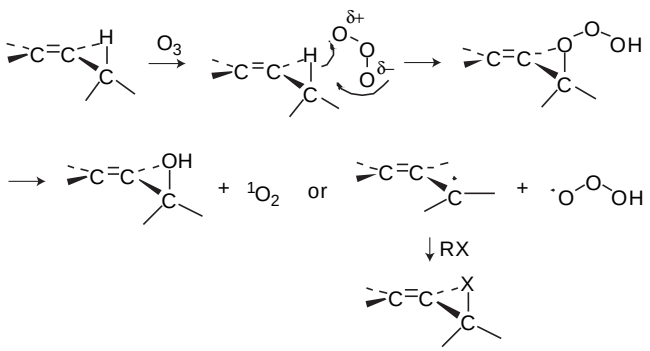


Scheme 16. Electrophilic attack of ozone to **1** or **2**.



Scheme 17. Mechanism of formation of **13** and **14**.

The Hammett ρ for the oxidation of substituted toluenes was found to be −2.07.[28] Plesničar reported evidence of the presence of HOOO radicals in the formation of alkyl hydrotrioxides, in the course of the ozonation of hydrocarbons.[29] Interestingly, the ozonation of various bicyclic alcanes as norbornane in CCl_4, led to chloro derivatives (*exo*- and *endo*-2-chlorononorbornane). These chlorinated products represent up to 40% of the products.[30] In the course of the ozonolysis of trisubstituted alkenes, Pryor has detected free radicals by using an electron spin resonance spin-trapping method; but the yields of the radicals were lower than 1% on the basis of consumed ozone.[31] To the best of our knowledge, such allylic functionalisations, to give an allylic alcohol or allylic chloride, have never been reported so far. The Scheme 18 describes a plausible mechanism for the allylic functionalisation of the anhydride **1**.



Scheme 18. Mechanism of allylic functionalization.

The poly-oxygenated compounds **6**, **8** and **10** seem to result from an allylic functionalisation followed by the ozonolysis of the double bond.

4. Conclusion

The ozonation of our bornene derivatives occurs without any chemoselectivity and led to various products according to the reaction conditions (nine different compounds from the ozonation of **1**!). Moreover, the yields of the reactions were weakly reproducible and the reported yields are the average of several experiments. Some previously reported results concerning the ozonolysis of tetrasubstituted double bonds also led to discrepancy results.[32]

5. Experimental section

5.1. General

TLC was performed on silica gel 60 F_{254}. Flash chromatography was performed on silica gel (230–400 mesh) obtained from Macherey–Nagel & Co. CH_2Cl_2 was distilled before use from calcium hydride. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300 and 75 MHz, respectively. Chemical shift are reported in parts per million relative to $CDCl_3$ (signals for residual $CHCl_3$ in the $CDCl_3$: 7.25 for ^1H NMR and 77.00 (central) for ^{13}C NMR). Carbon-proton couplings were determined by DEPT sequence experiments. Perfluorocompound FC-77® (Acrôs Organics), CAS registry number: 86,508-42-1.

*5.1.1. (1S,5R,8S,9R,13S)-1,5,14,14-Tetramethyl-11-oxatetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-ene-10,12-dione (**1**).* To a solution of the following diene, (3*R*)-3,7,7,8-tetramethylbicyclo[4.3.0]nona-1(6),8-diene prepared according to the reported method[12] (17.6 g, 0.1 mol) in toluene (250 mL) was added maleic anhydride (11.8 g, 0.12 mol). The stirred solution under argon atmosphere was refluxed for 3 h. After filtration and concentration under reduced pressure, the crude product was purified by flash-chromatography on silica gel eluting with petroleum ether/diethyl ether 9:1 to give **1** (23.6 g, 86 mmol, 86%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.48 (br s, 1H), 3.30 (m, 2H), 2.31 (m, 1H) 1.86 (m, 2H), 1.58 (m, 4H), 1.30 (s, 3H), 0.95 (d, *J*=6.2 Hz, 3H), 0.74 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6 (s), 172.1 (s), 146.5 (s), 128.7 (d), 65.5 (s), 60.4 (s), 58.4 (s), 54.0 (d), 53.7 (d), 35.2 (t), 30.4 (t), 30.3 (d), 25.6 (t), 22.1 (q), 17.3 (q)(2C), 12.6 (q).

*5.1.2. (1S,5R,8S,9R,10S)-9,10-Dicarboxy-1,5,11,11-tetramethyltricyclo[6.2.1.0^{3,8}]undec-2-ene dimethylester (**2**).* Anhydride **1** (2.05 g, 7.5 mmol) in anhydrous methanol (60 mL) containing some crystals of camphorsulfonic acid was stored for 2 weeks at room temperature. After concentration under reduced pressure, the crude mixture was poured into ice-cold aqueous $HNaCO_3$ and was extracted with ether, dried on $MgSO_4$ and evaporated in vacuo to give an oil, which was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:3 to give an yellow oil of **2** (1.08 g, 3.4 mmol, 45%). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.68 (d, *J*=2.5 Hz, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.21 (d, *J*=9.6 Hz, 1H), 3.00 (d, *J*=9.6 Hz, 1H), 2.29 (m, 1H), 1.64 (m, 4H), 1.22 (t, *J*=7.2 Hz, 2H), 1.09 (s, 3H), 0.85 (d, *J*=6.8 Hz, 3H), 0.70 (s, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (s), 172.5 (s), 142.2 (s), 130.7 (d), 61.1 (s), 59.5 (s), 55.4 (s), 54.2 (d), 53.9 (d), 51.3 (q), 50.9 (q), 36.1 (t), 31.8 (t),

30.0 (d), 24.7 (t), 22.3 (q), 17.4 (q), 17.0 (q), 12.5 (q). $C_{19}H_{28}O_4$ (320.20): C, 71.22, H, 8.81. Found: C, 71.31; H, 8.78.

*5.1.3. (1S,5R,8S,9R,10S)-1,5,11,11-Tetramethyl-9,10-di(hydroxymethyl)tricyclo[6.2.1.0^{3,8}]undec-2-ene acetonide (**4**).* To diol **3** (1 g, 3.79 mmol) prepared by the reported method[13] in anhydrous CH_2Cl_2 (25 mL) was added 2-methoxypropene (0.72 mL, 7.58 mmol) and *p*-toluenesulfonic acid (82 mg). After an overnight of stirring, some mg of anhydrous K_2CO_3 were added. After filtration and concentration under reduced pressure, the crude product was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 9:1 to give an yellow oil of **4** (740 mg, 2.43 mmol, 64%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.27 (m, 1H), 3.74 (m, 4H), 2.43 (m, 1H), 2.27 (m, 2H), 2.10 (m, 4H), 1.68 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 0.89 (d, *J*=6.5 Hz, 3H), 0.79 (s, 3H), 0.77 (s, 3H), 0.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.6 (s), 125.7 (d), 101.0 (s), 64.9 (t), 60.8 (t), 53.1 (s), 52.9 (d), 51.0 (d), 47.7 (s), 47.6 (s), 35.1 (t), 30.7 (d), 29.8 (t), 24.7 (t), 21.9 (q), 17.6 (q), 17.0 (q), 15.7 (q)(2C), 14.6 (q). $C_{20}H_{32}O_2$ (304.24): C, 78.90, H, 10.59. Found: C, 79.25; H, 10.68.

5.2. Ozonolysis of anhydride 1 in CH_2Cl_2

Ozone in oxygen was bubbled through a stirred solution of **1** (1 g, 3.65 mmol) in CH_2Cl_2 (130 mL) at −60 °C until a blue colour appeared (~7 h). The mixture was flushed with argon and dimethylsulfide (5 mL) was added. After stirring at room temperature overnight, the crude mixture was washed with water, dried on $MgSO_4$ and evaporated in vacuo to give an oil, which was purified by flash-chromatography on silica gel eluting with petroleum ether/diethyl ether 3:2 to give white crystals of **5** (191 mg, 0.66 mmol, 18% from **1**),[13] white crystals of **7** (134 mg, 0.44 mmol, 12%) and **8** (0.77 mmol, 260 mg, 21%).

*5.2.1. (+)-(1S,2S,4R,6R,9R,10R,11S)-10,11-Dicarboxy-2,4-dihydroxy-3-oxa-1,6,12,12-tetramethyltricyclo[7.2.1.0^{4,9}]dode-cane di-γ-lactone (**7**).* White crystals, mp 196 °C, $[\alpha]_D^{24}$ +3.02 (*c* 6.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.37 (s, 1H), 3.00 (s, 1H), 2.99 (s, 1H), 1.99–1.88 (m, 4H), 1.80–1.69 (m, 2H), 1.14 (s, 3H), 1.02 (s, 3H), 0.96 (d, *J*=6.7 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.2 (s), 172.9 (s), 111.5 (s), 105.5 (d), 55.9 (s), 54.7 (s), 52.7 (d), 50.7 (d), 44.0 (s), 36.4 (t), 26.5 (t), 25.8 (t), 25.5 (d), 22.6 (q), 21.4 (q), 16.1 (q), 15.4 (q). $C_{17}H_{22}O_5$ (306.15) C, 66.65; H, 7.24. Found: C, 66.52; H, 7.32.

*5.2.2. (−)-(1S,2S,4S,5S,6R,9R,10R,11S)-5-Chloro-10,11-dicarboxy-2,4-dihydroxy-3-oxa-1,6,12,12-tetramethyltricyclo[7.2.1.0^{4,9}]dode-cane di-γ-lactone (**8**).* White crystals, mp 226 °C, $[\alpha]_D^{24}$ −11.8 (*c* 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.54 (s, 1H), 4.06 (d, *J*=1.77 Hz, 1H), 3.04 (m, 2H), 2.04–1.95 (m, 3H), 1.75 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.12 (d, *J*=7.2 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3 (s), 171.5 (s), 109.9 (s), 105.6 (d), 60.2 (d), 56.4 (s), 54.8 (s), 52.9 (d), 50.4 (d), 43.7 (s), 39.1 (d), 25.8 (t), 24.4 (t), 22.6 (q), 22.3 (q), 18.9 (q), 15.4 (q).

5.3. Ozonolysis of anhydride 1 in CH_2Cl_2

After ozonolysis as above, $NaBH_4$ (280 mg, 7.3 mmol) in EtOH (5 mL) was added. After stirring at room temperature overnight, the crude mixture was poured into ice-cold aqueous NH_4Cl and was extracted with CH_2Cl_2. After the products were dried on $MgSO_4$ and concentrated in vacuo to give an oil, which was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 then 7:3 to give an yellow oil of **10** (144 mg, 0.44 mmol, 12%) and white crystals of **9** (350 mg, 1.18 mmol, 32%).

*5.3.1. (−)-(1S,2R,3R,5R,8R,9R,10S)-9-Carboxy-10-hydroxymethyl-1,5,11,11-tetramethyltricyclo[6.2.1.0^{3,8}]undecan-2,3-diol γ-lactone (**9**).* White crystals, mp 187 °C, $[\alpha]_D^{24}$ −1.8 (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (br s, 1H), 3.71 (m, 2H), 2.58 (br s, 1H), 2.55 (br s, 1H), 1.90 (m, 1H), 1.50 (m, 2H), 1.23 (d, *J*=4.4 Hz, 2H), 1.19 (t, *J*=6.5 Hz, 2H), 1.06 (s, 3H), 0.97 (s, 3H), 0.85 (d, *J*=6.7 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.6 (s), 95.4 (s), 79.5 (d), 60.4 (t), 58.6 (s), 53.7 (s), 53.2 (d), 51.3 (s), 48.0 (d), 31.0 (t), 27.4 (t), 25.5 (d), 22.0 (q), 21.0 (q), 20.1 (q), 19.6 (q), 10.5 (q). $C_{17}H_{26}O_4$ (394.18): C, 69.36; H, 8.90. Found: C, 69.27; H, 8.72.

*5.3.2. (−)-(1S,2R,4S,5S,6R,9R,10R,11S)-11-Carbaldehyde-5-chloro-10-carboxy-2,4-dihydroxy-3-oxa-1,6,12,12-tetramethyltricyclo[7.2.1.0^{4,9}]dode-cane γ-lactol γ-lactone (**10**).* $[\alpha]_D^{24}$ −5.9 (*c* 3.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (br s, 1H), 5.37 (br s, 1H), 4.01 (d, *J*=1.8 Hz, 1H), 2.87 (d, *J*=11.6 Hz, 1H), 2.61 (d, *J*=11.4 Hz, 1H), 2.02 (br s, 1H), 1.37 (s, 3H), 1.24 (t, *J*=7.2 Hz, 2H), 1.04 (m, 2H), 1.17 (s, 3H), 1.12 (d, *J*=4.8 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2 (s), 110.4 (s), 108.8 (d), 100.8 (d), 60.7 (d), 56.3 (s), 56.0 (s), 53.0 (d), 52.7 (d), 46.8 (s), 39.3 (d), 26.0 (t), 24.9 (t), 22.3 (q)(2C), 19.6 (q), 16.6 (q). $C_{17}H_{23}ClO_5$ (342.12): C, 59.56; H, 6.76; Cl, 10.34. Found: C, 59.47; H, 6.72; Cl, 10.50.

5.4. Ozonolysis of anhydride 1 in methylcyclohexane

To a solution of anhydride **1** (860 mg, 3.14 mmol) in methylcyclohexane (60 mL) was passed a stream of ozone in oxygen at −60 °C for 7.5 h. The mixture was flushed with argon and dimethylsulfide (5 mL) was added. After usual work-up the crude product was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 6.5:3.5 to give white crystals of **5** (190 mg, 0.65 mmol, 22%), white crystals of **7** (60 mg, 0.19 mmol, 7%) and white crystals of **6** (139 mg, 0.43 mmol, 14%).

5.5. Ozonolysis of anhydride 1 in ethanol

To a solution of anhydride **1** (1.17 g, 4.29 mmol) in ethanol (60 mL) was passed a stream of ozone in oxygen at −60 °C for 7.5 h. The mixture was flushed with argon and dimethylsulfide (5 mL) was added. After stirring at room temperature overnight. After concentration under reduced pressure, the crude mixture was poured into ice-cold water and was extracted with ether, dried on $MgSO_4$ and concentrated in vacuo to give an oil, which was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 7:3 to give white crystals of **5** (271 mg, 0.935 mmol, 26%), a yellow oil of **11** (85 mg, 0.293, 8%), white crystals of **7** (167 mg, 0.546 mmol, 15%) and white crystals of **6** (92 mg, 0.286 mmol, 8%).

*5.5.1. (+)-(1S,3R,5R,8R,9R,13S)-1,5,14,14-Tetramethyl-11-oxatetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradecane-2-10,12-trione (**11**).* $[\alpha]_D^{24}$ +1.1 (*c* 3.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, *J*=10.7 Hz, 1H), 3.22 (d, *J*=9.9 Hz, 1H), 2.01 (m, 1H), 1.66 (m, 6H), 1.48 (br s, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.12 (d, *J*=3.8 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.0 (s), 172.4 (s), 169.0 (s), 76.4 (d), 63.3 (s), 61.4 (s), 54.7 (s), 52.4 (d), 50.6 (d), 36.3 (t), 27.7 (t), 26.1 (d), 23.3 (q), 22.2 (t), 20.2 (q), 19.0 (q), 9.2 (q). $C_{17}H_{22}O_4$ (290.15): C, 70.32; H, 7.64. Found: C, 70.41; H, 7.72.

5.6. Ozonolysis of anhydride 1 in perfluorocompound FC-77® and trifluoroethanol

*5.6.1. (+)-(1R,5R,8S,9S,13R)-1,5,14,14-Tetramethyl-11-oxa-4-hydroxytetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradec-2-ene-10,12-dione (**12**).* $[\alpha]_D^{24}$ 6.8 (*c* 6.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (br. s, 1H), 3.97 (br. d, *J*=1.7 Hz, 1H), 3.23 (br. s, 2H), 3.20 (br. s, 1H), 1.80 (m, 4H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5 (s), 171.8 (s), 140.9 (s), 133.2 (d), 73.6 (d), 55.6 (s), 55.0 (s),

54.3 (s), 53.4 (d), 52.3 (d), 30.6 (d), 26.4 (t), 24.4 (t), 20.7 (q), 18.9 (q), 17.1 (q), 10.3 (q). SM (ESI+) *m/z* 290.15 (M^+).

*5.6.2. (−)-(1S,6R,8R,9R,13S,14R)-1,2,2,6-Tetramethyl-11-oxa-14-hydroxytetracyclo[6.5.1.0^{3,8}.0^{9,13}]tetradec-3-ene-10,12-dione (**13**).* Mp 180 °C; $[\alpha]_D^{24}$ −23.2 (*c* 3.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.73 (dd, *J*=3.2, 5.3 Hz, 1H), 3.40 (d, *J*=4.9 Hz, 1H), 3.12 (dd, *J*=3.7, 8.6 Hz, 2H), 2.84 (d, *J*=8.6 Hz, 1H), 2.13 (m, 2H), 1.80 (m, 2H), 1.03 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1 (s), 170.4 (s), 148.5 (s), 120.7 (d), 82.5 (d), 53.3 (s), 51.9 (s), 48.2 (d), 46.5 (d), 42.0 (s), 32.1 (t), 30.3 (t), 27.6 (d), 27.5 (q), 26.1 (q), 21.3 (q), 9.2 (q). $C_{17}H_{22}O_4$ (290.15): C, 70.32; H, 7.64. Found: C, 70.28; H, 7.55.

*5.6.3. (+)-(1S,3S,5R,8R,9R,13S)-1,5,14,14-Tetramethyl-11-oxa-tetracyclo[6.5.1. 0^{3,8}.0^{9,13}]tetradecane-2-10,12-trione (**15**).* $[\alpha]_D^{24}$ +11.0 (*c* 3.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.36 (m, 2H), 3.30 (s, 1H), 2.16 (m, 3H), 1.80 (m, 2H), 1.60 (m, 2H), 1.15 (s, 6H), 0.95 (s, 3H), 0.90 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.7 (s), 171.8 (s), 169.9 (s), 63.9 (s), 55.3 (s), 54.2 (d), 51.0 (s), 49.5 (d), 43.9 (d), 32.0 (t), 27.6 (t), 25.7 (d), 22.1 (q), 18.9 (t), 17.8 (q), 16.3 (q), 9.3 (q). $C_{17}H_{22}O_4$ (290.15): C, 70.32; H, 7.64. Found: C, 70.38; H, 7.57.

5.7. Ozonolysis of diester 2 in methylcyclohexane

To a solution of diester **2** (456 mg, 1.42 mmol) in methylcyclohexane (60 mL) was passed a stream of ozone in oxygen at −55 °C for 7.5 h. The mixture was flushed with argon and dimethylsulfide (5 mL) was added. After usual work-up the crude product was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 8:2 to give white crystals of **16** (64 mg, 0.192 mmol, 14%), white crystals of **18** (80 mg, 0.248 mmol, 18%) and an yellow oil of **17** (108 mg, 0.321 mmol, 22%).

*5.7.1. (−)-(1S,3S,5R,8R,9R,10S)-9,10-Dicarboxy-1,5,11,11-tetramethyltricyclo[6.2.1.0^{3,8}]undecan-2-one dimethylester (**16**).* Mp 112 °C; $[\alpha]_D^{24}$ −13.6 (*c* 2.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.57 (s, 3H), 3.56 (s, 3H), 3.07 (m, 3H), 1.90 (m, 2H), 1.60 (m, 4H), 2.21 (m, 1H), 1.06 (d, *J*=6.96 Hz, 3H), 0.88 (s, 6H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 218.8 (s), 172.3 (s), 171.9 (s), 62.3 (s), 52.0 (s), 51.9 (s), 51.3 (q), 50.9 (d), 50.4 (q), 48.2 (s), 41.1 (d), 31.7 (t), 28.3 (t), 26.3 (d), 21.9 (q), 19.4 (t), 17.8 (q), 17.4 (q), 9.0 (q). $C_{19}H_{28}O_5$ (336.19): C, 67.83; H, 8.39. Found: C, 67.88; H, 8.45.

*5.7.2. (−)-(1S,4S,6R,9R,10R,11S)-10-Carboxy-4-hydroxy-11-methoxycarbonyl-3-oxa-1,6,12,12-tetramethyltri-cyclo[7.2.1.0^{4,9}]dodecan-2-one γ-lactone (**17**).* Mp 205 °C; $[\alpha]_D^{24}$ −3.6 (*c* 4.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, 3H), 3.26 (d, *J*=11.7 Hz, 1H), 2.94 (d, *J*=11.9 Hz, 1H), 2.00 (br s, 1H), 1.79 (m, 2H), 1.19 (m, 4H), 1.24 (s, 3H), 1.08 (s, 6H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.2 (s), 170.9 (s), 169.5 (s), 110.4 (s), 58.2 (s), 55.9 (s), 52.7 (d or q), 52.4 (d or q), 52.0 (d or q), 47.0 (s), 36.3 (t), 26.4 (t), 25.8 (t), 25.8 (d), 21.7 (q), 19.8 (q), 18.2 (q), 14.75 (q). $C_{18}H_{24}O_6$ (336.16): C, 64.27; H, 7.19. Found: C, 64.32; H, 7.15.

*5.7.3. (+)-(1S,2R,3R,5R,8R,9R,10S)-9-Carboxy-10-methoxycarbonyl-1,5,11,11-tetramethyltri-cyclo[6.2.1.0^{3,8}]undecan-2,3-diol γ-lactone (**18**).* $[\alpha]_D^{24}$ +7.5 (*c* 5.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.41 (s, 1H), 3.64 (s, 3H), 3.04 (d, *J*=10.7 Hz, 1H), 2.48 (d, *J*=10.7 Hz, 1H), 1.63 (m, 2H), 1.22 (m, 1H), 1.08 (s, 3H), 1.03 (d, *J*=7.4 Hz, 3H), 1.00 (s, 3H), 0.93 (m, 4H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.0 (s), 171.6 (s), 94.3 (s), 78.1 (d), 59.9 (s), 54.9 (s), 52.2 (d), 51.8 (d), 51.1 (s), 50.3 (d), 30.8 (t), 27.2 (t), 25.4 (d), 20.9 (q), 20.0 (q), 19.9 (q), 19.1 (q), 10.4 (q). $C_{18}H_{26}O_5$ (322.18): C, 67.06; H, 8.13. Found: C, 67.13; H, 8.15.

5.8. Ozonolysis of diol 3 in methylcyclohexane

Ozone in oxygen was bubbled through a stirred solution of **1** (528 mg, 2 mmol) in methylcyclohexane (30 mL) and chloroform (5 mL) containing 0.3 mL of pyridine and two drops of an ethanolic solution of 'Sudan III'(Eastman Kodak) (ozonizable red dye as internal standard)[33] at −60 °C until the red colour disappeared. The mixture was flushed with argon and cooled to −80 °C. A suspension of $NaBH_4$ (0.14 g, 3.7 mmol) in EtOH was slowly added. After stirring at room temperature overnight, the crude mixture was filtered on Celite®. After concentration in vacuo, the colourless residue was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 1:1 to give white crystals of **19** (168 mg, 0.6 mmol, 30% from **1**) and an yellow oil of **20** (84 mg, 0.3 mmol, 15%).

*5.8.1. (−)-(3S,4S,5R,8R)-3-Carbaldehyde-4,5-di(hydroxy-methyl)-2,2,3,8-tetramethylbicyclo[4.4.0]dec-1(6)-ene δ-lactol (**19**).* Mp 145 °C; $[\alpha]_D^{22}$ −12.0 (*c* 1.59, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.89 (br s, 1H), 4.13 (d, *J*=11.0 Hz, 1H), 4.03 (m, 2H), 3.76 (d, *J*=11.3 Hz, 1H), 3.15 (d, *J*=11.0 Hz, 1H), 2.01 (m, 2H), 1.56 (m, 2H), 1.22 (td, *J*=7.1, 1.4 Hz, 1H), 1.05 (m, 2H), 0.96 (s, 3H), 0.90 (s, 6H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.1 (s), 128.5 (s), 94.7 (d), 62.5 (t), 57.6 (t), 42.3 (s), 42.1 (s), 39.1 (d), 39.0 (d), 37.4 (t), 32.1 (t), 29.3 (d), 25.7 (t), 23.8 (q), 22.2 (q), 20.7 (q), 16.5 (q).

*5.8.2. (−)-(1S,4S,5R,8R,9R,10S)-1,5,11,11-Tetramethyl-9,10-di(hydroxymethyl)tricyclo[6.2.1.0^{3,8}]undec-2-en-4-ol (**20**).* $[\alpha]_D^{22}$ −7.8 (*c* 4.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.55 (m, 1H), 5.70 (br s, 1H), 5.54 (dd, *J*=2.9, 5.5 Hz, 2H), 5.35 (m, 2H), 3.66 (m, 3H), 1.54 (m, 4H), 1.10 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5 (s), 116.8 (d), 83.8 (d), 61.4 (t), 60.6 (t), 52.0 (s), 51.2 (s), 50.6 (s), 45.8 (d), 42.1 (d), 32.6 (t), 31.9 (t), 28.6 (d), 28.2 (q), 26.3 (q), 21.6 (q), 10.4 (q). $C_{17}H_{28}O_3$ (280.20): C, 72.82; H, 10.06. Found: C, 72.88; H, 10.12.

5.9. Ozonolysis of acetonide 4 in methylcyclohexane

Compound **4** (228 mg, 0.75 mmol) in methylcyclohexane (20 mL) containing 2 mL of pyridine was ozonolyzed in the same conditions for **3**. The residue was purified by flash-chromatography on silica gel eluting with petroleum ether/ethyl acetate 4:1 to give yellow oil of **21** (108 mg, 0.34 mmol, 45% yield).

*5.9.1. (3S,4S,5R,8R)-3-Carbaldehyde-4,5-di(hydroxy-methyl)-2,2,3,8-tetramethylbicyclo[4.4.0]dec-1(6)-ene acetonide (**21**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.91 (s, 1H), 4.05 (d, *J*=7.1 Hz, 1H), 3.91 (dd, *J*=5.7, 9.5 Hz, 2H), 3.76 (dd, *J*=1.9, 5.7 Hz, 2H), 3.50 (m, 1H), 2.29 (m, 4H), 2.04 (m, 1H), 1.54 (m, 2H), 1.29 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.91 (s, 3H), 0.83 (d, *J*=4.5 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (CDCl3, 75 MHz) δ 206.2 (d), 135.6 (s), 125.1 (s), 101.5 (s), 61.8 (t), 60.2 (t), 53.5 (s), 51.8 (s), 43.3 (d), 41.1 (d), 37.2 (t), 31.6 (t), 28.5 (d), 28.6 (t), 24.5 (q), 24.1 (q), 23.7 (q), 21.8 (q), 21.5 (q), 17.5 (q). $C_{20}H_{32}O_3$ (320.23): C, 74.96; H, 10.06. Found: C, 75.06; H, 10.11.

5.10. X-ray crystallography

CCDC-763701 (for **9**), CCDC-763703 (for **14**), CCDC-763702 (for **16**), contain 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: (internet.) +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk]

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