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

Isabelle Kondolff,[a] Marie Feuerstein,[a] Céline Reynaud,[a] Michel Giorgi,[b]
Henri Doucet[c],* and Maurice Santelli[a],*

[a]*Laboratoire de Synthèse Organique, UMR 6180 CNRS, France*
[b]*Spectropôle, Faculté des Sciences de St-Jérôme, Aix-Marseille Université, Avenue Escadrille Normandie-Niemen,
13397 Marseille Cedex 20, France*
[c]*Institut Sciences Chimique de Rennes, 'Catalyse et Organométalliques',
Université de Rennes, Campus de Beaulieu, 35042 Rennes, France*

Abstract—This paper describes mechanistic studies on the ozonolysis of bicyclo[2.2.1]heptene derivatives **6** and **7** obtained from (*R*)-(+)-pulegone through the cyclopentadiene **5** and its Diels–Alder reaction with maleic anhydride. The ozonolysis of the tricyclic diol **7** led to the ketone **8** with the same skeleton while the anhydride **6** gave rise to the epoxide **10** and the bis-lactone **11**. The structure of **8**, **10** and **11** are confirmed by X-ray analysis. These unexpected results are discussed in terms of a π complex between ozone and the double bond.
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1. Introduction

In the course of the synthesis of a new ligand, Tedicyp, useful for the palladium-catalysed reactions,[1] we had previously reported the easy conversion of norbornene derivative **1** into an acetonide of *cis,cis,cis*-tetrakis(hydroxymethyl)cyclopentane **2** by ozonolysis followed by a reductive treatment in the same flask with NaBH$_4$ (Scheme 1).[2]
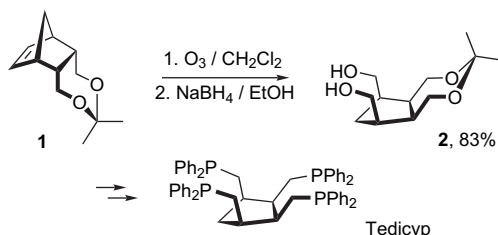
Scheme 1.

2. Results and discussion

In order to prepare a new chiral tetrapodal phosphine ligand, we considered its preparation from (*R*)-(+)-pulegone. The known stereoselective addition of allyl Grignard reagent[3]
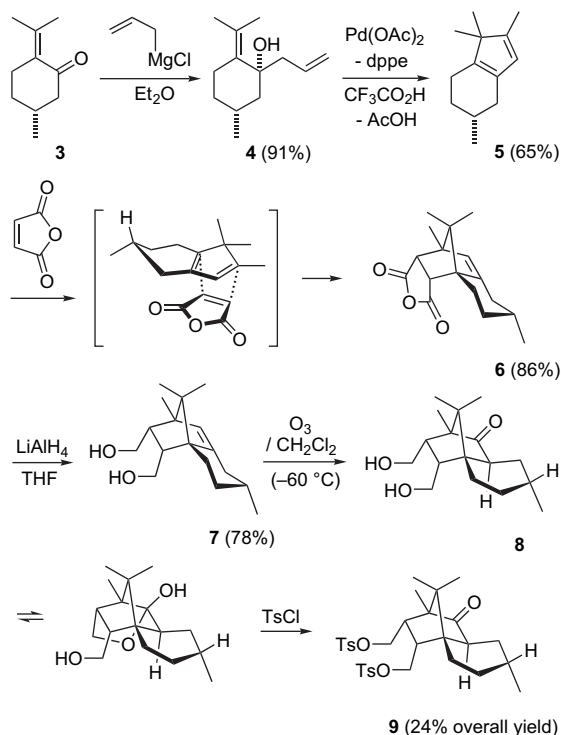
to pulegone **3** gave the dienic alcohol **4**, which was cyclised into cyclopentadiene **5** using a palladium-catalysed reaction.[4] A stereoselective Diels–Alder addition with maleic anhydride[5] followed by LiAlH$_4$ reduction led to a very interesting compound **7**, quite similar to **1**, and able to give an optically active tetrapodal ligand if the conversion in the tetraol by ozonolysis is a success. To our great surprise, the action of ozone[6] on **7** followed by a reductive treatment in the same flask with NaBH$_4$, afforded a ketone **8** (Scheme 2) which appeared as hemiketal instead of the expected tetraol.[7] In order to confirm the structure of **8**, the ditosylate **9** was prepared by a classical tosylation reaction in 24% overall yield from **7** (9.5% overall yield from (*R*)-(+)-pulegone). Its crystals were suitable for X-ray analysis (Fig. 1). Interestingly, we noted that the α-hydrogen atom to the ketone is in *endo* position (*S*-configuration).

The presence of two polar hydroxymethyl groups near the double bond could induce this abnormal ozonolysis. In order to verify this, we examined the reactivity towards ozonolysis of the olefin **6**. With this substrate, a very slow reaction occurred (reaction time 6 h) giving rise to a mixture of the epoxide **10** together with the bis-lactone-alcohol **11**. Gratifying, the epoxide **10** appears as the result of an *exo* attack of ozone (Scheme 3). The structures of **10** and **11** were confirmed by X-ray analysis (Figs. 2 and 3).
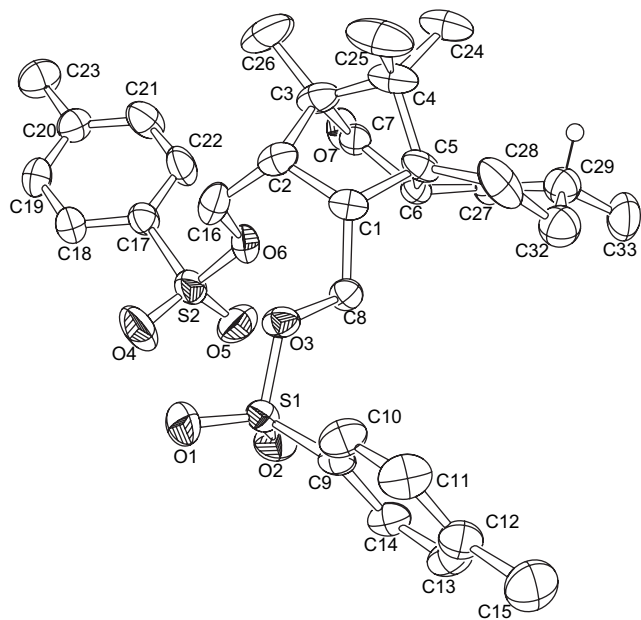
The mechanism of ozonolysis reaction[9] has been thoroughly studied, and the Criegee mechanism with the formation of the 1,2,3-trioxolane (primary ozonide)[10,11] has been

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Scheme 2.

Scheme 3.

the course of the ozonolysis reaction or during the purification steps.[23] According to Bailey, the formation of an epoxide (with retaining the stereochemistry of the olefin)[17a] results from an addition of ozone to the double bond giving rise to the open π complex[24] **a** precursor of the epoxide **d** via intermediates **b** or **c** with release of oxygen (Scheme 4).[25] According to this process, an alkyl or hydrogen migration can lead to the formation of carbonyl compound **e**. Such compound has been observed by Schank in the course of the ozonolysis of 9,9′-bifluoronylidene (Scheme 5).[26]

The most recent calculations on the mechanisms of ozonolysis of propene revealed that the partial ozonolysis mechanism as the source of epoxide and singlet molecular oxygen can be a favoured channel. In the transition state of this process, ozone attacks the terminal alkenic carbon

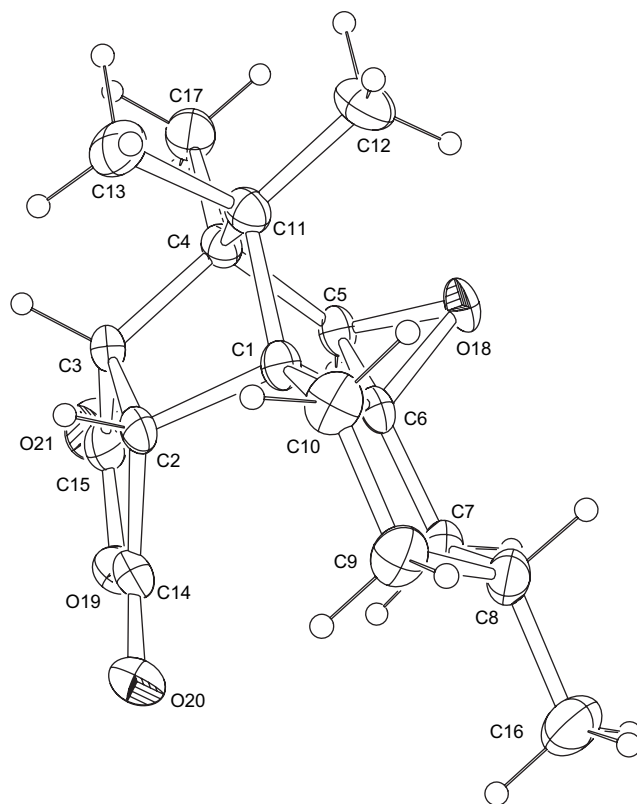Figure 1. ORTEP drawing of **9**.[8]

accepted.[12] 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'.[13–15] It is well known that the ozone can react with hindered olefins to give an epoxide[16–19] with release of singlet molecular oxygen.[20] But, to the best of our knowledge, no ketones with the same skeleton than the reacting alkenes were the primary products of the ozonolysis.[21,22] Some ketones have been obtained but these compounds resulted from the rearrangement of epoxides in

Figure 2. ORTEP drawing for **10**. Non-hydrogen atoms are drawn with 25% probability thermal ellipsoids, while the hydrogen atoms are portrayed with an artificial small radius.

Figure 3. ORTEP drawing for **11**. Non-hydrogen atoms are drawn with 25% probability thermal ellipsoids, while the hydrogen atoms are portrayed with an artificial small radius.
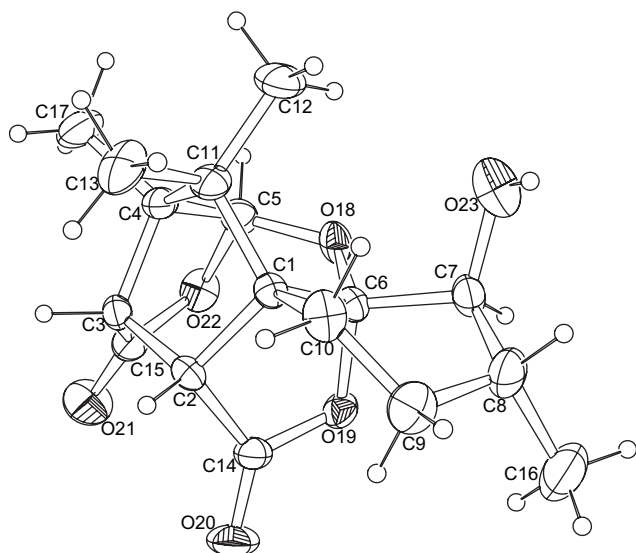
atom followed by a dissociation of the O–O bond to form molecular oxygen and propenyl oxyl diradical, which collapses into methyloxirane.[27]

As noted by Hochstetler, in the course of the epoxide formation from a highly substituted olefin, the attack of ozone occurred from the apparent more hindered face of the olefins and led to the isomer of the epoxide coming from the peracid reaction (Scheme 6).[28]

In the course of the ozonolysis of the 1-(*ortho*-carboxyphenyl)-1-phenylethene, Bailey has obtained 35% of phthalide resulting from a cyclisation of the corresponding intermediate **b** (Scheme 7).[17b]

Applied to the case of the ozonolysis of **6** or **7**, we can consider that ozone attacks the *exo* face of the double bond[29] on the less substituted side to give the corresponding intermediate **b**. Then, after release of molecular oxygen, a zwitterionic intermediate **f** is obtained. With the anhydride **6**, **f** quickly collapses into epoxide **10**, while for the diol **7**, a more polar environment makes a 1,2-migration of the *endo* hydrogen atom easier, which gave the ketone **8** (Scheme 8). This
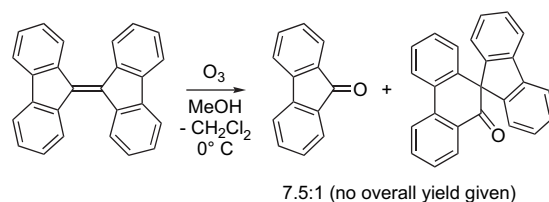
Scheme 5.
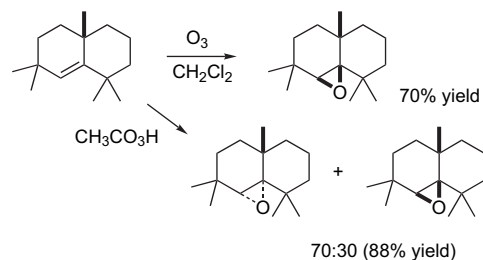
Scheme 6.
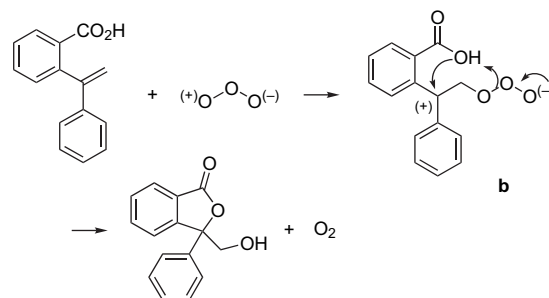
Scheme 7.

unified mechanism explains the formation of **8** and **10** from the same intermediate **f**.

Further works are running to explain the formation of polyoxygenated compound **11**.

3. Conclusion

We have observed that the double bond of norbornene derivatives presents a very particular reactivity towards ozone.

Scheme 4.

Scheme 8.

Although numerous 1,3-dipolar additions to norbornene derivatives have been described,[30] it seems that the primary interaction of the ozon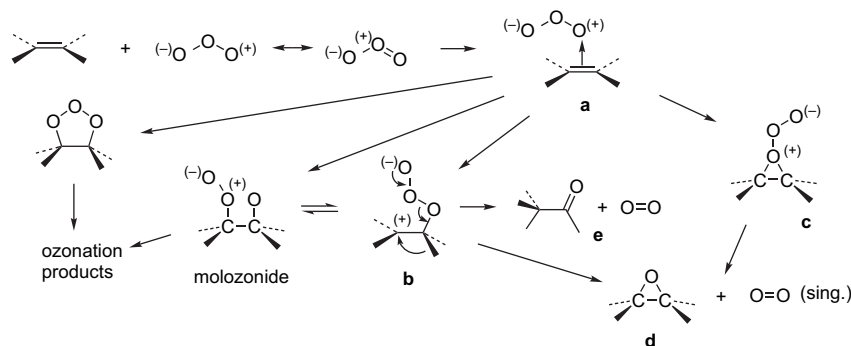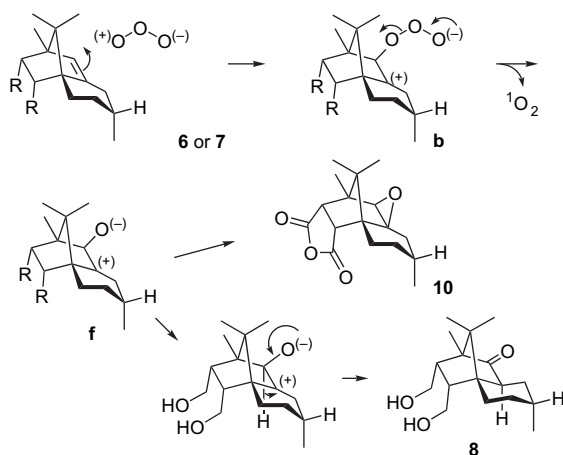e with the double bond did not follow a 1,3-dipolar addition but more likely an electrophilic addition with the formation of a π complex in the early stage of the reaction.

3.1. X-ray crystallography

CCDC-623382 (for **9**), CCDC-644677 (for **10**) and CCDC-647538 (for **11**), 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; or e-mail: deposit@ccdc.cam.ac.uk]. A summary of the crystal data, data collection, and refinements are given in Table 1.

4. Experimental section

4.1. General

TLC was performed on silica gel 60 F_{254}. Flash chromatography was performed on silica gel (230–400 mesh) obtained from Macherey–Nagel and Co. CH_2Cl_2 was distilled before use from calcium hydride and THF was distilled from sodium-benzophenone. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 300, and 75 MHz, respectively. Chemical shifts are reported in parts per million relative to $CDCl_3$ (signals for residual $CHCl_3$ in the $CDCl_3$: 7.24 for ^1H NMR and 77.16 (central) for ^{13}C NMR). Carbon–proton couplings were determined by DEPT sequence experiments.

4.1.1. (3R)-3,7,7,8-Tetramethylbicyclo[4.3.0]nona-1(6),8-diene (5).
In a Schlenk tube under argon atmosphere, palladium acetate (0.5 g, 2.2 mmol, 2.5%) and 1,2-bis(diphenylphosphino)ethane (0.87 g, 2.2 mmol, 2.5%) were added to degassed CH_2Cl_2 (10 mL). After 10 min of stirring, CH_2Cl_2 was removed under vacuum. With a syringe, acetic acid (100 mL), **4** (17.3 g, 89 mmol) and trifluoroacetic acid (0.6 mL) were added and the reaction was then refluxed for 20 h. The reaction mixture was poured into water and the aqueous phase was extracted several times with diethyl ether. The combined organic layers were washed with saturated sodium hydrogenocarbonate, dried (MgSO₄) and evaporated in vacuo to give an oil, which is distilled (53 °C/0.2 Torr) to give **5** (10.2 g, 65%).[4]

4.1.2. (1R,5R,8S,9S,13R)-1,5,14,14-Tetramethyl-11-oxa-tetracyclo[6.5.1.0³,⁸.0⁹,¹³]tetradec-2-en-10,12-dione (6).
To a solution of the diene **5** (19 g, 0.11 mol) in toluene (300 mL) was added maleic anhydride (13.19 g, 0.13 mol). The stirred solution was refluxed for 2 h. After concentration under reduced pressure, the crude product (25.91 g, 86%) was used in the following step.[4]

Table 1. Crystal data and structure refinement for **9**, **10**, and **11**

	9	**10**	**11**
Formula	$C_{31}H_{40}O_7S_2$	$C_{17}H_{22}O_4$	$C_{17}H_{22}O_6$
M_w	588.78	290.35	322.35
Crystal colour	colourless	colourless	colourless
Crystal size/mm³	0.6×0.4×0.3	0.4×0.2×0.05	0.4×0.2×0.2
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1/c$	$P2_12_12_1$	$P2_12_12_1$
a/Å	17.2494(6)	6.7184(1)	10.0718(2)
b/Å	11.4532(4)	13.0938(3)	10.8913(2)
c/Å	15.7494(3)	17.0682(5)	14.2773(4)
β/°	104.994(2)		
V/Å³	3005.5(2)	1501.48(6)	1566.15(6)
Z	4	4	4
D_c/g cm⁻³	1.299	1.284	1.367
μ(Mo Kα)/cm⁻¹	2.23	0.9	1.03
No. of unique data	5747	2107	1655
No. parameters refined	359	190	213
No. refl. in refinement	(5740; $F^2>4\sigma F^2$: 5323)	(2107; $F^2>4\sigma F^2$: 1734)	(1655; $F^2>4\sigma F^2$: 1655)
R	0.0832 [$F^2>4\sigma F^2$]	0.0644 [$F^2>4\sigma F^2$]	0.057 [$F^2>4\sigma F^2$]
wR	0.1782[a]	0.1678 [$F^2>4\sigma F^2$][b]	0.1642 [$F^2>4\sigma F^2$][c]
Goodness of fit	1.175	1.219	1.068
Residual Fourier/eÅ⁻³	−0.583; 0.886	−0.337; 0.541	−0.388; 0.23

[a] $w = 1/[\sigma^2(F_0^2) + 8.0959P]$ where $P = (F_0^2 + 2F_c^2)/3$.
[b] $w = 1/[\sigma^2(F_0^2) + (0.0738P)^2 + 0.266P]$ where $P = (F_0^2 + 2F_c^2)/3$.
[c] $w = 1/[\sigma^2(F_0^2)(0.1165P)^2 + 0.5311P]$ where $P = (F_0^2 + 2F_c^2)/3$.

4.1.3. (+)-(1R,5R,8S,9S,10R)-1,5,11,11-Tetramethyl-9,10-di(hydroxymethyl)tricyclo[6.2.1.0^{3,8}]undec-2-ene (7).

To a stirred solution of LiAlH$_4$ (10 g, 3 equiv, 263 mmol)) in anhydrous THF (200 mL) at 0 °C under argon was added the anhydride **6** (24 g, 87 mmol) in anhydrous THF (300 mL). The stirred reaction mixture was heated at 60 °C for 2 h. The suspension was cooled and slowly added to ice saturated with aqueous ammonium chloride and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with brine, dried (MgSO$_4$) and evaporated in vacuo to give an oil, which is purified by flash chromatography on silica gel (CH$_2$Cl$_2$/AcOEt (50:50)) to give diol **7** (17.9 g, 68 mmol, 78% for the two steps). White crystals, mp 92 °C, [α]$_D^{20}$ 57.8 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.10 (1H, br s), 4.6 (2H, br s), 3.76 (1H, dd, *J*=10.8, 3.2 Hz), 3.61 (1H, dd, *J*=11.2, 2.8 Hz), 3.39 (2H, td, *J*=11.2, 2.5 Hz), 2.40 (1H, ddd, *J*=11.6, 8.6, 3.3 Hz), 2.26 (2H, br dd, *J*=11.5, 2.2 Hz), 1.76–1.15 (6H, m), 0.92 (3H, s), 0.84 (3H, d, *J*=6.4 Hz), 0.65 (3H, s), 0.58 (3H, s); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 145.1 (s), 128.7 (d), 62.7 (t), 61.9 (t), 60.8 (s), 56.0 (s), 55.3 (s), 52.9 (d), 50.5 (d), 37.8 (t), 33.9 (t), 30.2 (d), 24.8 (t), 22.4 (q), 17.5 (q), 17.1 (q), 14.1 (q). Anal. Calcd for C$_{17}$H$_{28}$O$_2$: C, 77.22; H, 10.67. Found: C, 77.17; H, 10.81.

4.1.4. (1R,3R,5R,8S,9S,10R)-1,5,11,11-Tetramethyl-9,10-di(tosyloxymethyl)tricyclo[6.2.1.0^{3,8}]undecan-2-one (9).

Ozone in oxygen was bubbled through a stirred solution of **7** (6 g, 22.7 mmol) in CH$_2$Cl$_2$ (200 mL) containing 2 drops of an ethanolic solution of 'Sudan III'(Eastman Kodak) (ozonizable red dye as internal standard)[31] at −60 °C until the red colour disappeared. The mixture was flushed with argon and cooled to −80 °C. A suspension of NaBH$_4$ (2.5 g, 3 equiv, 68.1 mmol) in EtOH was slowly added. After stirring at room temperature overnight, the crude mixture was filtered on Celite®. To a stirred solution of tosyl chloride (18 g, 4 equiv, 95 mmol) in anhydrous pyridine (200 mL) cooled to −20 °C was added crude **8**. After 5 h stirring at 0 °C, the solution was poured onto crushed ice and CH$_2$Cl$_2$ (200 mL) was added, the mixture was stirred and layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ and the combined organic phases were washed with 1 N HCl, water, brine and then dried over MgSO$_4$. After filtration and concentration in vacuo, the colourless residue was purified by flash-chromatography on silica gel eluting with petroleum ether/diethyl ether 3:1 to give white crystals of **9** (3.2 g, 5.4 mmol, 24% from **7**), mp 117 °C, [α]$_D^{26}$ 7.8 (*c* 1.0, CH$_2$Cl$_2$). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.79 (2H, d, *J*=8.1 Hz), 7.72 (2H, d, *J*=8.1 Hz), 7.36 (2H, d, *J*=8.1 Hz), 7.32 (2H, d, *J*=8.1 Hz), 4.26–4.09 (2H, m), 3.95–3.88 (1H, m), 3.80–3.73 (1H, m), 2.44 (6H, s), 2.21 (1H, m), 2.0–1.41 (9H, m), 1.23 (3H, s), 0.80 (3H, s), 0.76 (3H, s), 0.72 (3H, s); the ^{13}C NMR spectra revealed a conformationally mobile system at room temperature: (CDCl$_3$, 75 MHz) δ 219.2 (s), 218.0 (s), 145.3 (s), 145.2 (s), 132.8 (s), 132.7 (s), 132.4 (s), 132.3 (s), 130.2 (d) (2C), 130.0 (d) (2C), 128.3 (d), 128.26 (d), 128.2 (d), 128.1 (d), 68.2 (t), 68.0 (t), 67.1 (t), 61.8 (s), 61.7 (s), 51.0 (s), 50.7 (s), 48.1 (s), 47.8 (s), 45.3 (d), 42.5 (d), 41.1 (d), 31.6 (t), 28.4 (t), 26.2 (t), 21.8 (q) (2C), 19.1 (q), 18.2 (q), 17.3 (q), 17.25 (q), 8.8 (q), 8.7 (q). Anal. Calcd for C$_{31}$H$_{40}$O$_7$S$_2$: C, 63.24; H, 6.85. Found: C, 63.18; H, 6.98.

4.1.5. (1R,2S,4R,6S,9S,10S,14R)-1,6,15,15-Tetramethyl-3,12-dioxapentacyclo[7.5.1.0^{2,4}.0^{4,9}.0^{10,14}]tetradecan-11,13-dione (10) and (1S,2S,4S,5S,6R,9R,10R,11S)-10,11-dicarboxy-2,4-dihydroxy-3-oxa-1,6,12,12-tetramethyl-tricyclo[7.2.1.0^{4,9}]dodecan-5-ol dilactone (11).

Ozone in oxygen was bubbled through a stirred solution of **6** (800 mg, 2.92 mmol) in CH$_2$Cl$_2$ (130 mL) and methanol (70 mL) at −60 °C until a blue colour appeared (∼6 h). The mixture was flushed with argon and dimethylsulfide (5 mL) is added. After stirring at room temperature overnight, the crude mixture was washed with water, dried and evaporated in vacuo to give an oil, which is purified by flash-chromatography on silica gel eluting with petroleum ether/diethyl ether 3:2 to give white crystals of **10** (170 mg, 0.58 mmol, 20% from **6**) and white crystals of **11** (284 mg, 0.88 mmol, 30% from **6**). Compound **10**: mp 125 °C, [α]$_D^{24}$ −16 (*c* 1.7, CH$_2$Cl$_2$); 1H (CDCl$_3$, 300 MHz) δ 3.14 (2H, d, *J*=4.2 Hz), 3.10 (1H, s), 2.24–2.16 (1H, m), 1.95 (1H, td, *J*=13.4, 4.9 Hz), 1.87–1.55 (3H, m), 1.34 (6H, s), 1.06 (3H, d, *J*=5.85 Hz), 1.01 (1H, s), 0.94 (1H, br d, *J*=4.7 Hz), 0.74 (3H, s); the ^{13}C NMR spectra revealed a conformationally mobile system at room temperature: (CDCl$_3$, 75 MHz) δ 173.4 (s), 171.3 (s), 60.0 (s), 59.4 (d), 58.0 (s), 57.2 (d), 57.1 (s), 54.3 (d), 54.0 (d), 53.7 (d), 52.2 (s), 52.1 (s), 49.9 (s), 49.8 (s), 34.5 (t), 31.6 (t), 30.1 (d), 29.1 (t), 27.1 (d), 26.1 (t), 25.1 (t), 22.0 (q), 21.75 (q), 20.5 (q), 20.4 (q), 20.0 (t), 18.0 (q), 11.7 (q), 11.6 (q). Anal. Calcd for C$_{17}$H$_{22}$O$_4$: C, 70.32; H, 7.64. Found: C, 70.43; H, 7.72.

Compound **11**: mp 220 °C, [α]$_D^{24}$ −19 (*c* 2.2, CH$_2$Cl$_2$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.58 (1H, s), 3.81 (1H, s), 3.05 (2H, m), 2.05–1.75 (4H, m), 1.70–1.51 (2H, m), 1.24 (3H, s), 1.11 (3H, s), 1.05 (3H, d *J*=6.8 Hz), 0.88 (3H, s); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 173.7 (s), 172.6 (s), 109.9 (s), 105.8 (d), 73.4 (d), 56.0 (s), 54.8 (s), 52.7 (d), 50.4 (d), 43.8 (s), 35.6 (d), 25.4 (t), 24.6 (t), 21.8 (q), 21.2 (q), 17.8 (q), 15.3 (q). Anal. Calcd for C$_{17}$H$_{22}$O$_6$: C, 63.34; H, 6.88. Found: C, 63.40; H, 6.92.

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