Regio- and Stereocontrolled Synthesis of (2*R**,3*R**,4*R**)-3,4-Dichloro-1,2,3,4,5,8-hexahydronaphthalen-2-yl Acetate *via* Tandem S_N2' Reactions

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The hydroperoxy endoperoxide **3**, obtained by photooxygenation of isotetralin (=1,4,5,8-tetrahydronaphthalene; **1**), was reduced with thiourea, and the resulting intermediate **4** was converted, after acetylation with acetyl chloride, to the interesting, double-chlorinated acetate **5** in an unprecedented tandem reaction (*Scheme 1*). The structures and relative configurations of **3** and **5** were determined by NMR spectroscopy and by single-crystal X-ray-diffraction analyses (*Figs. 1* and *2*, resp.). A mechanistic rationalization for the conversion of **4** to **5** is proposed (*Scheme 2*).

Introduction. – Polyhydroxy cyclohexanes are of interest to those concerned with carbohydrates [1]. Carbohydrates are densely functionalized molecules, and as a result, their synthetic application often requires many reaction steps, usually for the manipulation of different protecting groups. Endoperoxides (of carbohydrates and other compounds) serve as key substances in a variety of chemical [1] and biological [1][2] transformations. The O–O bond undergoes either homolytic or heterolytic cleavage, depending on the reaction conditions. Also, selective reductions of peroxide linkages have been performed with either thiourea or $LiAlH_4$ under very mild conditions to give *cis*-1,4-dihydroxy compounds.

Balci and co-workers [3] achieved the synthesis of some quercitols *via* an ene reaction of singlet oxygen ($^1O_2$) combined with the $^1O_2$ [4+2] cycloaddition to cyclohexadiene [3]. We have successively used isotetralin (=1,4,5,8-tetrahydronaphthalene; **1**) for the short and stereocontrolled synthesis of a new class of double endoperoxides [4]. Recently, *Baran et al.* [5] have reported stereoselective ring-opening reactions of allylic epoxides and the formation of haloconduritols by an S_N2'-type substitution. Here, we report for the first time the introduction of *two* Cl-atoms into an alcohol by tandem reaction, as exemplified for photooxygenized isotetralin (**1**) as starting material.

Results and Discussion. – 1. *Synthesis.* When **1** was exposed to $^1O_2$ in CH_2Cl_2 in the presence of tetraphenylporphyrin (TPP), the unstable peroxide **2** was formed *in situ*, which reacted with another molecule of $^1O_2$ to the hydroperoxy endoperoxide **3** in 80% yield, as described in the literature (*Scheme 1*) [4]. The structure of **3** was con-

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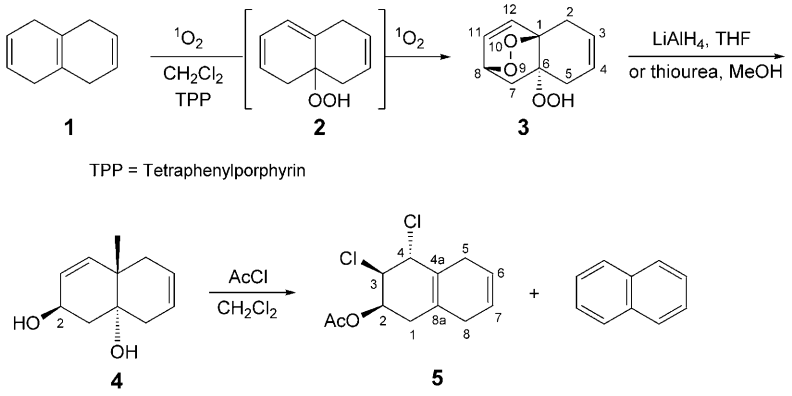
Scheme 1



firmed spectroscopically and by X-ray analysis (see *Fig. 1* below). Peroxide linkages are known to be highly susceptible to reductive cleavage by a variety of reductants [1a]. Thus, selective reduction of both peroxide linkages in **3** could be performed with either thiourea or $LiAlH_4$ under very mild conditions to afford (2*R**,4a*R**,8a*R**)-1,2,5,8-tetrahydronaphthalene-2,4a,8a-triol (**4**). Since only O–O bonds are broken in this reaction, the configurations at all stereogenic centers of **3** are preserved.

Next, we attempted the acetylation of compound **4**. It is well known that both Ac_2O and AcCl are very useful acetylation reagents in general. We, thus, tried both methods. Unfortunately, upon exposure to Ac_2O/pyridine, only a tar-like material was obtained. However, when the triol **4** was reacted with AcCl *without* a base, the very interesting, doubly chlorinated rearrangement product **5** was isolated in 80% yield. In the ^{1}H-NMR spectrum of **5**, the resonances of two olefinic H-atoms, one oxygenated methine (H–C(2)), and two chlorinated methines (H–C(3,4)) were observed. The corresponding ^{13}C-NMR spectrum indicated four olefinic C-atoms, two of which were quaternary (C(4a) and C(8a)). Although the NMR data fully support the proposed structure, we decided to corroborate the configuration of **5** by single-crystal X-ray diffraction (see *Fig. 2* below).

2. *X-Ray Diffraction Studies*[2]). Compounds **3** and **5** were analyzed by single-crystal X-ray crystallography. Their molecular structures, along with the atom-numbering scheme, are shown in *Figs. 1* and *2*, respectively, and selected bond lengths and angles are collected in *Table 1*. Further crystallographic data are summarized in *Table 2* in the *Exper. Part*.

2.1. *Structure of* **3**. The two carbocyclic rings in **3** had the following conformations: a 'boat-type' ring [C(1)–C(2)–C(4)–C(5)–C(6)–C(3)] and a 'twisted-chair' ring [C(1)–C(3)–C(10)–C(9)–C(8)–C(7)]. The two heterocycles, *i.e.*, [C(3)–O(1)–O(2)–C(4)–C(5)–C(6)] and [C(3)–C(1)–C(2)–C(4)–O(2)–O(1)], were in boat conformations (*Fig. 1*, *a*). The peroxy bridge between C(3) and C(4), and the bridging positions, were in accord with the proposed structure based on the spectroscopic data. Since

[2]) Arbitrary atom numbering (see *Figs. 1* and *2*).

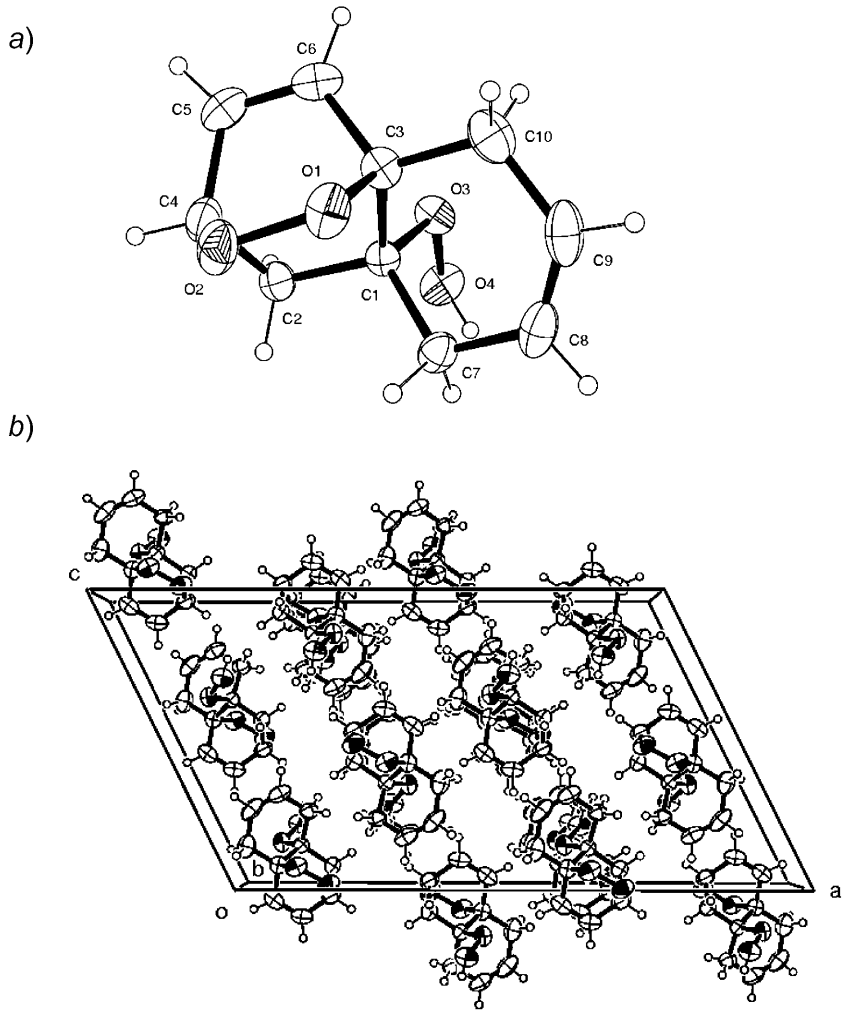


Fig. 1. *Crystal structure of compound* **3**. *a*) Molecular structure (50% probability ellipsoids); *b*) crystal packing, viewed down the *b*-axis.

hybridization of C(3) and C(4) changes with the addition of $^1O_2$, the endoperoxide has a bent structure, like triptycene. The bond angles of the bridgehead C-atoms range from 105.0° [C(1)–C(3)–O(1)] to 111.3° (C(6)–C(3)–C(1)] (*Table 1*). The O–O bond length for **3** was unusually long (1.478 Å), probably to reduce the electronic repulsion between the electron lone pairs on the O-atoms, which are in an eclipsed conformation (C–O–O–C dihedral angle: −3.9°). Further, O(1) and O(3) were found *trans* to each other (O(1)–C(3)–C(1)–O(3) torsion angle: −175.8°). Such a *trans* arrangement is lower in energy than the corresponding *cis* conformation because it prevents close steric interactions between the H-atoms on the adjacent C-atoms, and also between the O-atoms.

Table 1. *Selected Bond Lengths and Angles for* **3** *and* **5**[2])

3		**5**	
Bond length [Å]:			
O(1)–O(2)	1.478(3)	Cl(1)–C(9)	1.800(2)
O(1)–C(3)	1.462(3)	C(11)–C(12)	1.491(4)
O(2)–C(4)	1.463(3)	Cl(2)–C(8)	1.829(2)
O(3)–O(4)	1.454(2)	O(1)–C(10)	1.446(3)
O(3)–C(1)	1.442(3)	O(1)–C(11)	1.348(3)
C(1)–C(2)	1.537(3)	O(2)–C(11)	1.186(3)
C(1)–C(7)	1.520(3)	C(1)–C(2)	1.489(3)
C(1)–C(3)	1.548(3)	C(1)–C(6)	1.502(3)
C(3)–C(6)	1.501(3)	C(2)–C(3)	1.320(4)
C(4)–C(5)	1.485(4)	C(5)–C(6)	1.335(3)
C(5)–C(6)	1.312(4)	C(7)–C(10)	1.505(3)
C(8)–C(9)	1.305(5)	C(9)–C(10)	1.511(3)
Bond angle [°]:			
O(2)–O(1)–C(3)	111.20(15)	C(10)–O(1)–C(11	116.94(16)
O(1)–O(2)–C(4)	109.24(18)	C(2)–C(1)–C(6)	114.15(19)
O(4)–O(3)–C(1)	108.83(16)	C(1)–C(2) –C(3)	123.3(2)
O(3)–C(1)–C(3)	102.07(17)	C(2)–C(3)–C(4)	123.6(2)
O(3)–C(1)–C(7)	110.96(16)	C(3)–C(4)–C(5)	113.30(19)
C(2)–C(1)–C(3)	108.04(16)	Cl(1)–C(9)–C(8)	107.94(15)
C(2)–C(1)–C(7)	112.20(19)	O(1)–C(11)–O(2)	123.4(2)
C(8)–C(9)–C(10)	123.7(3)	O(1)–C(11)–C(12)	111.17(19)

Regarding the crystal lattice of **3** (*Fig. 1*,*b*), there were no significant intermolecular interactions. The C(6) atom, however, was involved in a weak H-bond with O(3) of a vicinal host molecule ($C(6) \cdots O(3)^i = 3.405(3)$ Å; $i = -x, 1-y, -z$). As seen from the packing diagram, the molecules extend parallel to the *c*-axis, and are stacked along the *b*-axis.

2.2. *Structure of* **5**. The molecular structure of **5** ($C_{12}H_{14}O_2Cl_2$) is shown in *Fig. 2*,*a*. The compound crystallized in the triclinic form, with two molecules per unit cell (*Fig. 2*,*b*). The bicyclic system contains two annulated six-membered carbocyclic rings sharing a common C=C bond. The fused-ring structure is virtually planar, but C(9) and C(10)[2]) are significantly twisted with respect to the other members of the bicyclic system. Atoms C(9) and C(10) are located 0.253(2) and −0.470(2) Å, respectively, from the mean molecular plane defined by C(1)/C(2)/C(3)/C(4)/C(5)/C(6)/C(7)/C(8). The cyclohexene ring is in a 'half-chair' conformation, and the puckering parameters of this ring are $Q = 0.472(2)$ Å, $\theta = 50.3(2)^\circ$, and $\phi = 204.4(4)^\circ$, as calculated according to *Cremer* and *Pople* [6]. The two Cl-atoms are *trans*-related to each other. The C(9)−Cl(1) and C(8)−Cl(2) bond lengths are 1.800(2) and 1.829(2) Å, respectively. The three stereogenic centers are all (*R*)-configured (relative configuration). There is no significant interaction between adjacent molecules (*Fig. 2*,*b*).

3. *Mechanistic Aspects.* From a mechanistic point of view, the conversion of **4** to **5** might involve two S_N2' reactions, as shown in *Scheme 2*. After threefold acetylation of **4**, followed by (stepwise) protonation, the resulting intermediate **A** is attacked by Cl^- at C(3) under loss of AcOH. The resulting intermediate **B** then adds another Cl^-

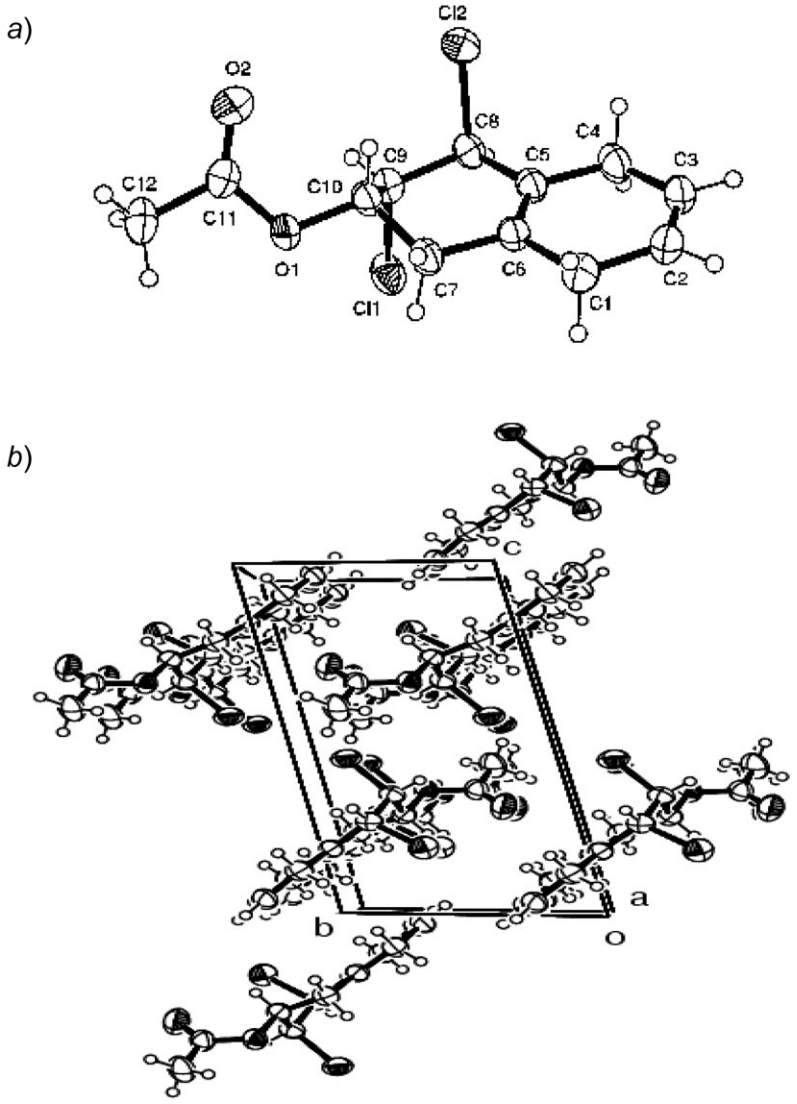
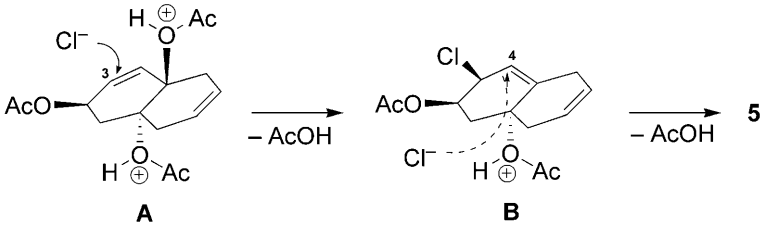


Fig. 2. *Crystal structure of compound* **5**. *a*) Molecular structure (50% probability ellipsoids); *b*) crystal packing, viewed down the *a*-axis.

to afford **5**, again under elimination of AcOH. All OH groups of **4** must be acetylated to give **A** and HCl. The first addition of Cl^- at C(3) then takes place on the *syn* face with respect to the AcO group in allylic position at C(4a). In **B**, the AcO group at C(8a) is now also in allylic (and tertiary) position, so that a second S_N2' reaction can occur. Therefore, the second attack should be at C(4) to give the final dichloroacetate **5**.

To our knowledge, this tandem reaction represents the first example of the chlorination of an alcohol with AcCl. As chlorination of C=C bonds with Cl_2 mostly proceeds

Scheme 2



under multiple rearrangement, the present method might be used as an alternative, stereospecific protocol for the introduction of Cl-atoms into similar systems.

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Experimental Part

General. Column chromatography (CC): silica gel *60* (70–230 mesh) and *Alox* (neutral Al_2O_3, type-III). Solvents were purified and dried by standard procedures before use. M.p.: *Büchi-539* cap. melting-point apparatus; uncorrected. IR Spectra: *Mattson-1000 FT-IR* spectrophotometer, with KBr discs; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian* spectrometer, at 400 or 100 MHz; δ in ppm, J in Hz. Elemental analyses: *Leco CHNS-932* instrument.

*(1*R**,6*R**,8*R**)-9,10-Dioxatricyclo[6.2.2.0^{1,6}]dodeca-3,11-dien-6-yl Hydroperoxide* (**3**). To a stirred soln. of **1** (2.0 g, 15.15 mmol) in CH_2Cl_2 (150 ml) was added tetraphenylporphyrin (TPP; 20 mg). The resulting mixture was irradiated with a tungsten-halogen projection lamp (500 W) while O_2 was passed through the soln. The mixture was stirred at r.t. for 2 h. The solvent was evaporated at 30° (20 Torr), and the residue was purified by CC on a jacket column (20 g Al_2O_3; AcOEt/hexanes 20:80) to afford TLC-pure **3** in 80% yield. The compound was recrystallized from CH_2Cl_2/hexane (2.0 g, 68%). M.p. 103–104°. IR (KBr): 3400, 3033, 2936, 2902, 1662, 1417, 1374, 1237, 1092, 851. ^1H-NMR (400 MHz, $CDCl_3$): 7.64 (*s*, OOH); 6.72 (*A*-part of *AB*-type *dd*, J=8.4, 6.2, H–C(12)); 6.25 (*B*-part of *AB*-type *dd*, J=8.4, 1.5, H–C(11)); 5.68–5.61 (*m*, H–C(3), H–C(4)); 4.77–4.74 (*m*, H–C(8)); 2.88 (*A*-part of *AB*-type *dd*, H_a–C(5), J=18.8, 5.1); 2.51–2.44 (*m*, *B*-part of *AB* system, H_b–C(5)); 2.67–2.57, 2.39–2.33 (*m*, H_a–C(2), H_b–C(2)); 2.14 (*A*-part of *AB*-type *dd*, J=13.5, 4.0, H_a–C(7)); 2.02 (*B*-part of *AB*-type *dd*, H_b–C(7), J=13.9, 1.6). ^{13}C-NMR (100 MHz, $CDCl_3$): 134.16; 132.83; 124.47; 122.75; 79.24; 75.09; 71.99; 37.17; 32.62; 30.05. Anal. calc. for $C_{12}H_{18}O_6$ (258.1): C 55.81, H 7.02; found: C 55.71, H 7.08.

*(2*R**,4a*R**,8a*R**)-1,2,5,8-Tetrahydronaphthalene-2,4a,8a-triol* (**4**). *Method A*. To a magnetically stirred slurry of $LiAlH_4$ (213 mg, 5.6 mmol) in anh. THF (50 ml) was added a soln. of **3** (500 mg, 2.55 mmol) in THF (25 ml) over 3 h at 0° under N_2 atmosphere. The mixture was stirred at r.t. for 3 h. Then, MeOH (50 ml) was added, and the mixture was filtered. The solvents were evaporated under reduced pressure, and the residue was purified by CC (20 g Al_2O_3; MeOH/$CHCl_3$ 2:98) to afford pure **4** (310 mg, 67%) as a pale-yellow liquid. For anal. data, see below.

Method B. To a magnetically stirred slurry of thiourea (410 mg, 5.4 mmol) in MeOH (25 ml) was added a soln. of **3** (500 mg, 2.55 mmol) in MeOH (25 ml) at r.t. over ca. 10 min. Then, the mixture was stirred for 2 h, the solids were removed by filtration, and the solvent was evaporated under reduced pressure. The resulting residue was purified by CC (20 g Al_2O_3; MeOH/$CHCl_3$ 2:98) to afford pure **4** (322 mg, 70%).

Data of **4**. IR (KBr): 3412, 3038, 2937, 1631, 1420, 1374, 1234, 1109, 1012, 853, 836, 756, 648, 535. ^{1}H-NMR (400 MHz, D_2O): 5.69 (*A*-part of *AB*-type *dt*, *J* = 10.3, 1.5, H–C(3)); 5.51 (*B*-part of *AB*-type *d*, *J* = 1.5, H–C(4)); 5.49 (*m*, H–C(6), H–C(7)); 4.27 (*ddt*, H–C(2), *J* = 2.2, 6.2, 12.1); 2.24–2.12 (*m*, *A*-part of *AB* system, H_a–C(5), H_a–C(8)); 1.95–1.82 (*m*, *AB* system, H_b–C(5,8), H_a–C(1)); 1.67 (*B*-part of *AB*-type *dd*, *J* = 9.9, 13.2, H_b–C(1)). ^{13}C-NMR (100 MHz, D_2O): 132.6; 130.7; 124.7; 124.5; 72.6; 68.1; 65.1; 37.6; 35.7; 33.8.

*(2*R**,3*R**,4*R**)-3,4-Dichloro-1,2,3,4,5,8-hexahydronaphthalene-2-yl Acetate* (**5**). To a magnetically stirred soln. of **4** (250 mg, 1.37 mmol) in CH_2Cl_2 (25 ml) was added AcCl (540 mg, 6.87 mmol), and the mixture was stirred at r.t. for 6 h. Then, H_2O (50 ml) was added, the org. phase was washed with aq. $NaHCO_3$ soln. (50 ml) and H_2O (50 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by CC (35 g SiO_2; $CHCl_3$/hexane 20:80) to afford pure **5** (246 mg, 80%). Colorless solid. M.p. 86–87° (CH_2Cl_2/hexane). IR (KBr): 3462, 3032, 2945, 2876, 2813, 1742, 1242, 1123, 1045, 881. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.77–5.73 (*A*-part of *AB*-type *dm*, *J* = 10.2, H–C(6)); 5.68–5.63 (*B*-part of *AB*-type *dm*, *J* = 10.2, H–C(7)); 5.53 (*ddd*, *J* = 2.5, 6.2, 9.5, H–C(1)); 4.56 (*t*, *J* = 2.5, H–C(3)); 4.42 (*m*, H–C(4)); 3.06–2.28 (*m*, CH_2(1), CH_2(5), CH_2(8)); 2.11 (*s*, Ac). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.4; 130.0; 124.0; 122.9; 122.5; 66.9; 61.9; 61.0; 31.6; 31.0; 28.8; 21.3.

Table 2. *Crystal Data and Structure Refinement for* **3** *and* **5**

	3	**5**
Chemical formula	$C_{10}H_{12}O_4$	$C_{12}H_{14}O_2Cl_2$
Formula weight	392.4	261.13
Temperature [K]	293(2)	293(2)
Wavelength [Å]	0.71073	0.71073
Crystal system, space group	Monoclinic, *C*2/*c*	Triclinic, *P*-1
Unit-cell dimensions [Å][°]	*a* = 22.9510(14)	*a* = 6.91380(10)
	b = 6.7600(4)	*b* = 7.1755(2)
	c = 13.2435(7)	*c* = 13.1330(2)
	β = 116.59(4)	*α* = 76.497(4)
		β = 89.004(5)
		γ = 77.141(4)
Volume [Å^3]	1837	617
Z	4	2
Calc. density [Mg/m^3]	1.42	1.405
Absorption coefficient [mm^{-1}]	0.110	0.508
F(000)	832	272
Crystal size [mm]	0.20 × 0.17 × 0.15	0.23 × 0.20 × 0.17
θ [°]	3.1–30.6	3.0–33.18
Miller indices:	$-32 \le h \le 32$	$-10 \le h \le 10$
	$-8 \le k \le 9$	$-11 \le k \le 11$
	$-18 \le l \le 18$	$-20 \le l \le 20$
Reflections collected	19991	40701
Independent reflections	2823 (R_{int} = 0.0421)	4699 (R_{int} = 0.0532)
Reflections observed	2563 ($I > 2\sigma(I)$)	3951 ($I > 2\sigma(I)$)
Data, restraints, parameters	2563, 0, 127	3951, 0, 149
Goodness-of-fit on F^2	1.24	1.23
Final *R* [$I > 2\sigma(I)$][a])	R_1 = 0.080, wR_2 = 0.213	R_1 = 0.068, wR_2 = 0.150
R (all data)	R_1 = 0.087, wR_2 = 0.219	R_1 = 0.084, wR_2 = 0.157
Largest diff. peak and hole [Å^{-3}]	0.432, 0.521	0.31, 0.26

[a]) $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, $wR_2 = \left\{ \sum \left[w\left(F_o^2 - F_c^2\right)^2 \right] / \sum \left[w\left(F_o^2\right)^2 \right] \right\}^{1/2}$.

X-Ray Analysis. For the crystal-structure determinations, single-crystals of **3** ($C_{10}H_{12}O_4$) and **5** ($C_{12}H_{14}O_2Cl_2$) were used for data collection on a four-circle *Rigaku R-AXIS RAPID-S* diffractometer equipped with a two-dimensional area IP detector. Graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å) was used, with oscillation-scan technique ($\Delta\omega = 5°$) for each image. For each compound, 216 images for six different runs, covering *ca.* 99.8% of the *Ewald* sphere, were obtained. The lattice parameters were determined by least-squares methods on the basis of all reflections, with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for *Lorentz* and polarization effects, and cell refinement were performed with CrystalClear software (*Rigaku/MSC, Inc.*, 2005) [7]. The structures were solved by direct methods, and refined by the full-matrix least-squares method using the SHELXL-97 program [8], with anisotropic thermal parameters for all non-H-atoms. For H-atoms, U_{iso} was $1.2U_{iso}$, *i.e.*, 20% higher than for the C-atom directly bonded to the H-atom. The final difference *Fourier* maps showed no peaks of chemical significance.

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