ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 3, pp. 613–621. © Pleiades Publishing, Ltd., 2016.
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To the 100th Anniversary of A.N. Pudovik

Reactions of Terpene Alcohols and Diols with Chlorine Dioxide in Dimethylformamide

L. L. Frolova[a], A. V. Popov[a], L. V. Bezuglaya[a], I. N. Alekseev[a], P. A. Slepukhin[b,c], and A. V. Kutchin[a]

[a] *Institute of Chemistry, Komi Research Center, Ural Branch, Russian Academy of Sciences, ul. Pervomaiskaya 48, Syktyvkar, 167982 Russia*
e-mail: frolova-ll@chemi.komisc.ru

[b] *Postovskii Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences, ul. S. Kovalevskoi/Akademicheskaya 22/20, Yekaterinburg, 620990 Russia*

[c] *Yeltsin Ural Federal University, ul. Mira 19, Yekaterinburg, 620002 Russia*

Received January 14, 2016

Abstract—The system chlorine dioxide–dimethylformamide in combination with or without a catalytic amount of $MoCl_5$, $CeCl_3$, $ZrOCl_2$, or $VO(acac)_2$ induces oxidative chlorination of a number of bicyclic terpene alcohols and vicinal diols. 2α-Chloropinan-3-one, 3α-chloro-10β-pinan-4-one, 5α-chloro-3α-hydroxycaran-4-one, 5β-chloro-3β-hydroxycaran-4-one, and 4α-chloro-2α-hydroxypinan-3-one were thus synthesized in good preparative yields.

Keywords: terpene alcohols, diols, α-chloroketones, α-chlorohydroxyketones, chlorine dioxide, selectivity
DOI: 10.1134/S107036321603018X

α-Chloroketones are widely used as intermediate products in the synthesis of heterocyclic compounds, epoxides (Darsens condensation), α-alkyl(aryl) thiocarbonyl compounds, β-ketoesters, etc. Numerous methods for the preparation of α-chloroketones are known, most of which are based on the α-chlorination of ketones with gaseous chlorine [1], *N*-chlorosuccinimide [2], sulfuryl chloride [3], selenonyl chloride [4], copper(II) chloride [5], trichloroisocyanuric acid [6], $NaClO_2$–$Mn(acac)_3$–Al_2O_3 [7], and a polymeric analog of *N*,*N*-dichloro-4-methylbenzenesulfonamide in the presence of acid catalysts [8]. However, only a few examples of direct transformation of secondary alcohols into α-chloroketones have been reported. For instance, 2-chloroacetophenone was obtained in 16% yield by treatment of 1-phenylethanol with Cl_2 in methylene chloride at –50°C [9]. Oxidative chlorination of steroidal alcohols with *tert*-butyl hypochlorite in acetic acid at 70°C afforded about 50% of 2-chloro-3-keto steroids [10]. The yield of α-chloro-3-ketosteroids increased to 57–84% when *N*-chlorosuccinimide or *t*-BuOCl in *tert*-butyl alcohol containing a small amount of water was used [11].

Kim et al. [12] proposed a one-pot procedure for the synthesis of α-chloroketones from secondary benzylic alcohols using the system *m*-chloroperoxybenzoic acid (*m*-CPBA)–HCl–DMF. The selectivity for the target products was 80–98%, and the yield reached 80–84%. Oxidative chlorination of the same substrates was also accomplished with *N*,*N*-dichloro-4-methylbenzenesulfonamide in acetonitrile, the yield being 92–94% [13]. The direct transformation of 1,2,3,4-tetrahydronaphthalen-1-ol into 2-chloro-1,2,3,4-tetrahydronaphthalen-1-one by the action of *N*-chlorosuccinimide in methylene chloride in the presence of a composite catalyst was reported in [14]. α-Chloroketones were also synthesized in 38–79% yield by direct oxidation of di- and trisubstituted ethenes with chromyl chloride (CrO_2Cl_2) in acetone at –70°C [15]. Swern oxidation of secondary alcohols with excess (necessary condition) oxalyl chloride–DMSO afforded ~50% of α-chloroketones [16].

α-Chloroisopulegone (a 3:2 mixture of stereoisomers) was synthesized in 75% yield by treatment of pulegone with 1 equiv of HOCl in CH_2Cl_2 at –60°C

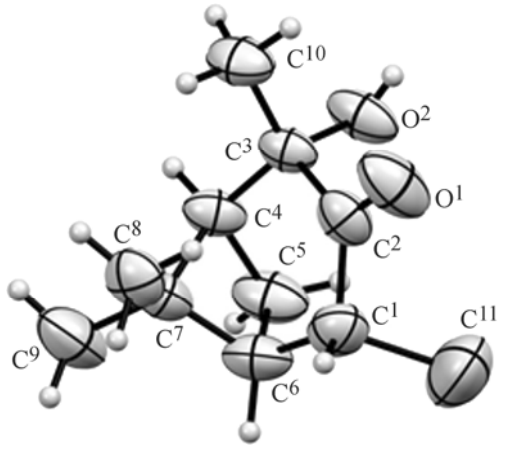


Fig. 1. Structure of the molecule of 4α-chloro-2α-hydroxypinan-3-one according to the X-ray diffraction data with atom numbering.

[17]. Pinocarveol reacted with HCl in anhydrous diethyl ether, and subsequent oxidation of of the corresponding hydrochloride afforded 2-chloropinan-3-one [18].

We previously showed that the oxidation of 3α,4α-caranediol with chlorine dioxide in DMF gave 40% of 5α-chloro-3α-hydroxycaran-4-one [19]. By treatment of racemic 2α-hydroxypinan-3-one with ClO_2 in DMF for 4 days we obtained 45% (preparative yield) of racemic 4α-chloro,2α-hydroxypinan-4-one whose structure was later confirmed by X-ray analysis (Fig. 1). According to the X-ray diffraction data, the bond lengths in the molecule of 4α-chloro-2α-hydroxypinan-4-one approach the corresponding reference values, while bond angles at some sp^3-carbon atoms considerably deviate from the ideal tetrahedral values due to presence of a strained four-membered ring. The methylene group of the four-membered ring, hydroxy group, and chlorine atom are located at one side of the $O^1C^1C^2C^3$ mean-square plane. 4α-Chloro-2α-hydroxypinan-4-one molecules in crystal are linked to centrosymmetric dimers through intermolecular hydrogen bonds O^1–H···O^1 [$-x$, $1-y$, $1-z$] between the hydroxy group and carbonyl oxygen atom. The other noticeable intermolecular contact is related to acidity of the proton on C^1 due to joint electron-withdrawing effects of the carbonyl group and chlorine atom on C^1. As a result, hydrogen bond C^1–H···O^2 [$-x$, $0.5+y$, $0.5-z$] is formed with an H···O distance of 2.3 Å, which is shorter by 0.4 Å than the sum of the corresponding van der Waals radii.

Table 1. Oxidation of compound **1** with chlorine dioxide[a]

Catalyst	Reaction time, h	Conversion, %	Selectivity for **14**, %
–	6	55	69
–	12	96	77
$ZrOCl_2$	3	100	76
$VO(acac)_2$	3	100	70
$MoCl_5$	3	92	76
–	2	95[b]	–

[a] Reaction conditions: DMF, 20°C, 1.5 mol % of catalyst.
[b] In pyridine.

In continuation of this study, in the present work we examined reactions of ClO_2 with other terpene alcohols and 1,2-diols in DMF in the absence and in the presence of transition metal catalysts [$MoCl_5$, $ZrOCl_2$, $VO(acac)_2$, and $CeCl_3$). The substrates were isopinocampheol (**1**), neoisoverbanol (**2**), borneol (**3**), isoborneol (**4**), isocaran-4-ol (**5**), *cis*-verbenol (**6**), *trans*-verbenol (**7**), carane-3α,4α-diol (**8**), carane-3β,4β-diol (**9**), carane-3β,4α-diol (**10**), pinane-2α,3α-diol (**11**), and pinane-2α,3β-diol (**12**).

The oxidative chlorination of isopinocampheol (**1**) in DMF in the absence of a catalyst was fairly slow. The complete conversion of the substrate was attained only in 12 h, but addition of a catalyst strongly accelerated the reaction. The selectivity for α-chloroketone **14** was 70–76% (Table 1). When the reaction was carried out in pyridine for 2 h, the substrate conversion was 95%, and isopinocamphone (**13**) was formed in 95% yield, whereas no chlorine-containing products were detected. Unlike initial alcohol **1**, the ^{1}H NMR spectrum of **14** contained a singlet (rather than doublet) from the $C^{10}H_3$ group, which was displaced downfield, indicating the presence of a heteroatom (chlorine or oxygen) on C^2. In addition, no signal assignable to C**H**OH proton was observed. Compound **14** showed in the ^{13}C NMR spectrum signals from three carbon atoms with no protons attached thereto, including the carbonyl carbon signal at δ_C 206 ppm. The formation of chloroketone rather than hydroxyketone follows from comparison with the NMR spectra of known 2α-hydroxypinan-3-one (**29**). The reaction may be accompanied by epimerization at C^2 after eliminations of the 2-H proton. However, the observed NOE between 8-H and 10-H indicated that the configuration of C^2 was retained (Scheme 1).

Unlike compound **1**, oxidative chlorination of neoisoverbanol (**2**) was very fast in the absence of a catalyst. By contrast, addition of catalysts reduced the concentration of α-chloroketone **16** in the reaction mixture (Table 2). In the NMR spectra of **16** we observed signals of only one methylene group instead of two methylene groups in **2**, and a carbonyl carbon signal appeared instead of CHOH. The configuration of **16** was confirmed by the NOEs 3-H/8-H, 3-H/10-H, 8-H/10-H, and 2-H/7-*endo*-H. The fraction of dichloroketone **17** among the products was 1–3%. This compound was isolated and characterized by IR and NMR spectra. The ^{13}C NMR spectrum of **17** lacked one methylene carbon signal, but a signal typical of $C_{sp^3}Cl_2$ group appeared at δ_C 89.3 ppm. The *cis* orientation of the CMe_2 group with respect to C^{10} was confirmed by the NOEs 8-H/10-H and 2-H/7-*endo*-H. The major product of the oxidation of **2** in pyridine was *cis*-verbanone **15** (Scheme 2).

Under analogous conditions, borneol (**3**), isoborneol (**4**), and *cis*- and *trans*-verbenols **6** and **7** were converted, respectively, into camphor (**18**) and verbenone (**20**) with high selectivity [20] (Scheme 3). Unexpectedly, isocaran-4-ol (**5**) in DMF was neither oxidized nor chlorinated, whereas in pyridine ketone **19** was formed with a selectivity of 81–91% (Table 3).

Compound **22** was synthesized previously by prolonged oxidation of diol **8** at room temperature (~15 h) [19]. In order to accelerate oxidative chlorination of **8**, the reaction temperature was raised to 40°C, catalysts ($ZrOCl_2$, $MoCl_5$, $CeCl_3$) were added, and the concentration of $CeCl_3$ was increased from 1.5 to 9.0 mol % (Table 4). The optimal conditions for the formation of **22** were room temperature, reaction time 7 h, and $CeCl_3$ concentration 5–9 mol %. The isolated yield of **22** was 51% (after column chromatography on silica gel). We also succeeded in isolating pure isomer **23** whose fraction in the product mixture was as low as 3–5% (Scheme 4).

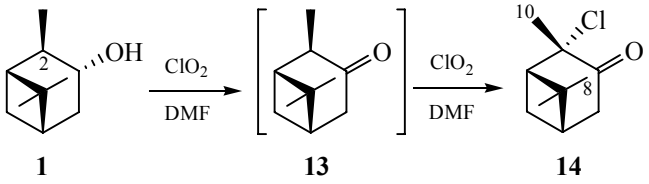
The oxidation of carane-3β,4β-diol (**9**) with ClO_2 in DMF (5–6 h) afforded 5α-chloro-3β-hydroxycaran-4-one (**25**, t_R = 16.56 min) with a selectivity of 91%. It was identified by NMR spectroscopy without isolation

Table 2. Oxidation of compound **2** with chlorine dioxide[a]

Catalyst	Conversion, %	Selectivity for **16**, %
–	100	75
$VO(acac)_2$	100	61
$ZrOCl_2$	100	48
$MoCl_5$	59	28
–	100[b]	5

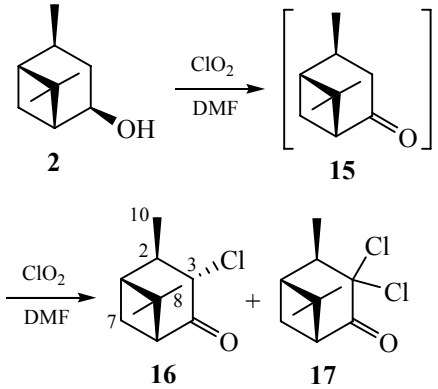
[a] Reaction conditions: DMF, 20°C, 2 h, 1.5 mol % of catalyst.
[b] In pyridine.

Scheme 1.



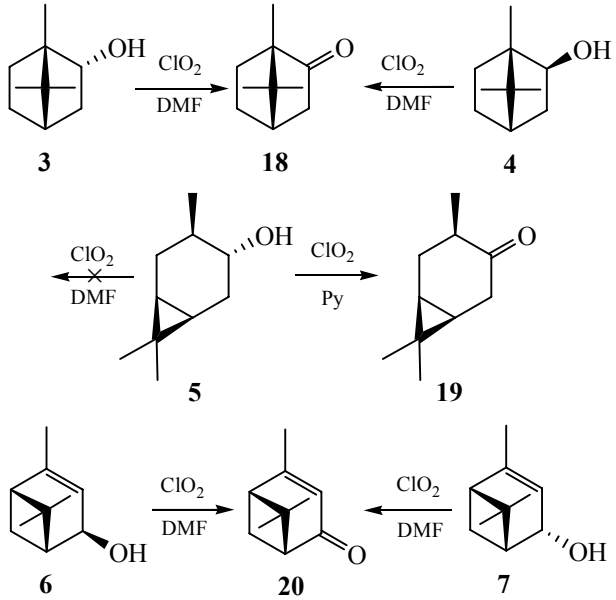
1 **13** **14**

Scheme 2.



2 **15** **16** **17**

Scheme 3.



3 **18** **4** **5** **19** **6** **20** **7**

Table 3. Oxidation of compounds **3**–**7** with chlorine dioxide[a]

Comp. no.	Solvent	Catalyst	Reaction time, h	Conversion, %	Selectivity for **18**–**20**, %
3	DMF	$VO(acac)_2$	3	98	100
	DMF	$ZrOCl_2$	3	99	100
4	DMF	$VO(acac)_2$	3	100	98
	DMF	$ZrOCl_2$	3	100	99
5	DMF	$VO(acac)_2$, $ZrOCl_2$, $MoCl_5$	3	No reaction	
	Pyridine	–	3	78	91
	Pyridine	$VO(acac)_2$	3	94	81
	Pyridine	$MoCl_5$	3	100	83
6	Pyridine	–	2	100	79
	DMF	–	3	100	88
7	Pyridine	–	4	89	76
	DMF	–	3	100	84

[a] Reaction conditions: 20°C, 1.5 mol % of catalyst.

Table 4. Oxidation of compounds **8** and **9** with chlorine dioxide in DMF

Comp. no.	Catalyst, mol %	Reaction time, h	Temperature, °C	Conversion, %	Selectivity for **22** or **25**, %
8	–	5	40	60	53
	–	10	40	81	75
	$ZrOCl_2$ (1,5)	15	20	83	65
	$MoCl_5$ (1,5)	15	40	47	72
	$CeCl_3$ (1,5)	15	20	63	76
	$CeCl_3$ (2,5)	7	20	77	57
	$CeCl_3$ (5,0)	7	20	93	72
	$CeCl_3$ (9,0)	7	20	98	80
9	–	2	20	90	67
	–	6	20	100	91

(Table 4). An attempt to isolate chloroketone **25** by silica gel column chromatography (hexane–Et_2O) led to its complete isomerization to 5β-chloro-3β-hydroxycaran-4-one (**26**, t_R = 17.61 min) whose structure was determined by X-ray analysis (Fig. 2, Scheme 5). According to the X-ray diffraction data, compound **26** crystallized in a chiral space group belonging to the monoclinic crystal system. Its unit cell included two crystallographically independent molecules with *S* configuration of the CCl carbon atom. The configuration was determined on the basis of anomalous scattering data. The Flack parameter was characterized by a significant error. Nevertheless, the absolute configuration determined in this way was consistent with that expected from the corresponding chemical transformations. Figure 2 shows the structure of molecule **26** with atom numbering, where atoms of the second molecule are marked with additional

superscript "*A*." The geometric parameters of both molecules are close to the corresponding standard values with insignificant differences from each other. The cyclohexane fragment has a pseudo-*sofa* conformation in which five ring atoms lie in one plane within 0.070 and 0.085 Å, and the carbon atom bearing hydroxy group deviates from that plane by 0.719 and 0.651 Å, respectively. The OH oxygen atom is located in the equatorial plane, and the chlorine atom occupies pseudoequatorial position. The molecular conformation is determined by intra- and intermolecular hydrogen bonds which link molecules **26** to dimers, and the latter underlie the crystal packing motif. In addition, strongly shortened ClC–H···O contact with the OH oxygen atom should be noted due to acidity of the ClCH proton in the α-position with respect to the carbonyl group.

The NMR spectra of **25** and **26**, as well as of the other two isomers **22** and **23**, differed not only by the signal position and multiplicity of the 5-H signal but also by the character of NOE correlations.

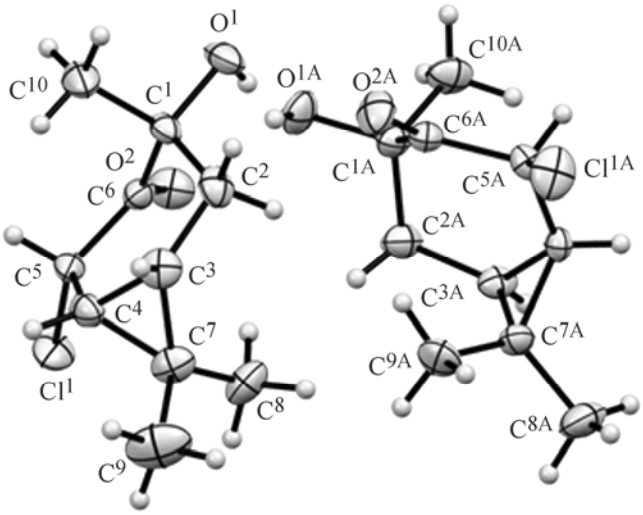
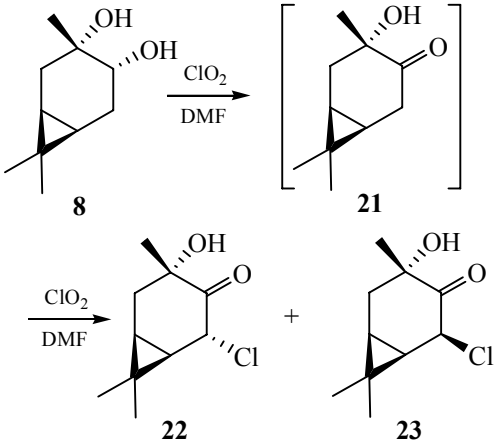


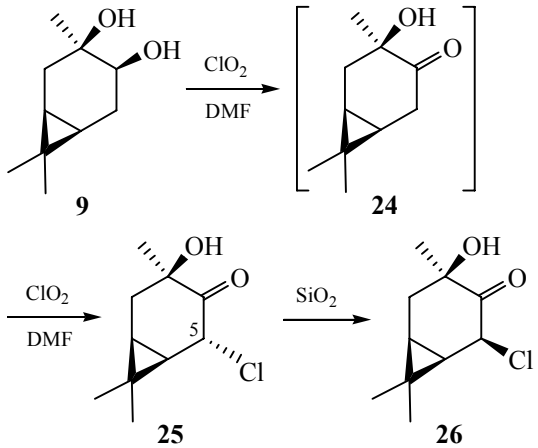
Fig. 2. Structure of the molecule of 5β-chloro-3β-hydroxycaran-3-one (**26**) according to the X-ray diffraction data with atom numbering.

Scheme 4.



The oxidation of carane-3β,4α-diol (**10**) with chlorine dioxide in DMF was not selective. Among the products, we succeeded in isolating only two minor ones, *meta*-menthane derivatives **27** and **28** (Scheme 6). Opening of the three-membered ring in carane derivatives usually gives *para*-menthane structures, whereas the formation of *meta*-menthane or cycloheptane skeleton is observed much more rarely. In our case, it was impossible to assign the entire set of functional groups to *para*-menthane or cycloheptane structure on the basis of spectral data. Compound **27** contained a *cis*-configured disubstituted double bond

Scheme 5.



Scheme 6.

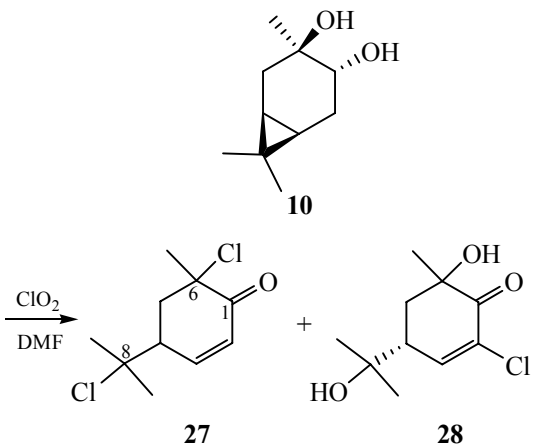


Table 5. Oxidation of compounds **11** and **12** with chlorine dioxide[a]

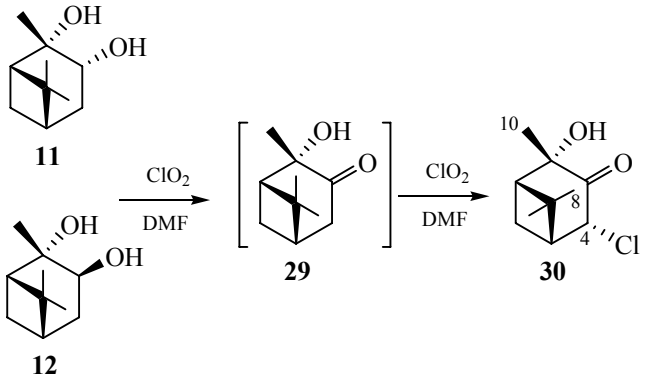
Comp. no.	Catalyst	Reaction time, h	Conversion, %	Selectivity for **30**, %
11	–	7	100	17
	$MoCl_5$	7	100	21
	$VO(acac)_2$	7	100	23
	$CeCl_3$	7	100	20
	$CeCl_3$	15	100	35
	$CeCl_3$	24	100	62
	$CeCl_3$	48	100	90
12	–	2	64	11
	–	6	79	11

[a] Reaction conditions: DMF, 20°C, 5 mol % of catalyst.

conjugated with a carbonyl group, as followed from the presence of an absorption band at 1690 cm^{-1} in the IR spectrum and of a signal at δ_C 197 ppm in the ^{13}C NMR spectrum. Two quaternary carbon signals were observed in the region δ_C 84–85 ppm, which is typical of chloro derivatives. Analogous reasoning lead to structure **28** which also possesses a carbonyl group conjugated with a double bond, but the latter is trisubstituted. The double-bonded carbon atom attached to heteroatom resonated at δ_C 130 ppm, and two signals at δ_C 73–74 ppm were typical of C–OH carbon atoms.

Neither oxidation nor chlorination occurred when diols **9** and **10** dissolved in DMF were treated with an aqueous solution of chlorine dioxide. After 24 h, the pure initial compounds were recovered from the reaction mixtures.

Scheme 7.



Diol **11** was fairly rapidly oxidized with ClO_2–DMF even in the absence of a catalyst (7 h, 100% conversion); however, the chlorination of 2α-hydroxypinan-3-one thus obtained was much slower. Only after 48 h in the presence of 5 mol % of $CeCl_3$ the concentration of chloro hydroxy ketone **30** attained 90%. The product was isolated by crystallization. The oxidative chlorination of isomeric pinane-2α,3β-diol (**12**) was characterized by lower rate and selectivity. After 6 h, the conversion of diol **12** was 79%, and the product mixture contained (according to the GLV data), 45% of hydroxy ketone **29** and 9% of chloro hydroxy ketone **30**, while the other products were not identified (Table 5, Scheme 7).

Thus, the system ClO_2–DMF acts as not only oxidant but also chlorinating agent. The product structure (α-chloroketone or α-chlorohydroxyketone) is determined by both substrate nature and stereochemical orientation of the hydroxy groups in initial isomeric terpene diols. *cis*-Diols are converted into the corresponding chlorohydroxyketones with fairly high selectivity, whereas the oxidatibe chlorination of *trans*-diols is much less selective. In some cases, the system ClO_2–DMF may be recommended for one-pot preparation of α-chloroketones or α-chlorohydroxyketones.

EXPERIMENTAL

GLC analysis was performed on a Shimadzu GC-2010AF chromatograph (HP1 column, flame ionization detector, carrier gas helium). The IR spectra were recorded from thin films or KBr pellets on a Shimadzu IR Prestige 21 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II-300 spectrometer at 300 and 75 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as solvent. The melting points were determined on a TP melting point apparatus. The optical rotations were measured on a Kruss P3002RS automated polarimeter. Silica gel 60 (70–230 mesh, Alfa Aesar) was used for column chromatography. Analytical TLC was performed on Sorbfil plates using hexane and petroleum ether–diethyl ether as eluents; spots were visualized by treatment with a 10% solution of phosphomolybdic acid in ethanol or a 3% solution of vanillin in ethanol.

An aqueous solution of chlorine dioxide with a concentration of 8–9 g/L was provided by *Mondi*

Syktyvkarskii LPK public corporation. All reactions were carried out in freshly distilled solvents.

X-Ray analysis of compound 30. Intensities of 9524 reflections, including 2651 independent reflections (R_{int} = 0.0272) and 1147 reflections with $I > 2\sigma(I)$, were measured on an Xcalibur S automated diffractometer according to standard procedure (MoK_α radiation, graphite monochromator; 295 K; ω-scanning with a step of 1°; 3.18° < θ < 28.31°). No correction for absorption was applied (μ = 0.323 mm^{-1}). Monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 7.7339(9), b = 11.5784(14), c = 12.0715(12) Å; β = 96.824(9)°; V = 1073.3(2) Å^3; Z = 4. The structure was solved by the direct method and refined against F^2 by the full-matrix least-squares procedure in anisotropic approximation for all non-hydrogen atoms using SHELXTL package [21]. Hydrogen atoms were placed in geometrically calculated positions, and their positions were refined according to the riding model with dependent isotropic thermal parameters. The OH proton was refined independently in isotropic approximation. Final divergence factors: R_1 = 0.0499, wR_2 = 0.1371 [for reflections with $I > 2\sigma(I)$]; R_1 = 0.1069, wR_2 = 0.1464 (all reflections); goodness of fit 1.008; residual electron density $\Delta\rho_{\bar{e}}$ = 0.371/–0.398 $\bar{e}$/Å^3.

X-Ray analysis of compound 26. Intensities of 5054 reflections, including 3740 independent reflections (R_{int} = 0.0265) and 3430 reflections with $I > 2\sigma(I)$ were measured on an Xcalibur S automated diffractometer according to standard procedure [MoK_α radiation, graphite monochromator; 150.01(10) K; ω-scanning with a step of 1°; 1.90° < θ < 30.67°]. A correction for absorption was applied empirically μ(MoK_α) = 0.329 mm^{-1}. Monoclinic crystal system, space group $P2_1$; unit cell parameters: a = 8.8353(4), b = 11.1445(5), c = 10.7336(4) Å; β = 92.638(4)°; V = 1055.77(8) Å^3; Z = 4; Flack parameter –0.07(6). The structure was solved by the direct method and refined against F^2 by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms using Olex2 [22] and SHELXTL packages [21]. Hydrogen atoms of the OH groups and those attached to tertiary carbon atoms were refined independently in isotropic approximation. The other hydrogen atoms were placed in geometrically calculated positions, and their positions were refined according to the riding model with dependent thermal parameters. Final divergence factors: R_1 = 0.0368, wR_2 = 0.0908 [for reflections with $I > 2\sigma(I)$]; R_1 = 0.0419, wR_2 = 0.0990 (for all reflections); goodness of fit 1.002; residual electron density $\Delta\rho_{\bar{e}}$ = 0.234/–0.211 $\bar{e}$/Å^3.

General procedure for the oxidation of terpene alcohols and diols. Gaseous chlorine dioxide was passed through a solution of 0.2–0.5 g of compound **1**–**12** in dimethylformamide containing $MoCl_5$, $ZrOCl_2$, $VO(acac)_2$, or $CeCl_3$ as catalyst (or not). The progress of the reaction was monitored by TLC and GLC. When the reaction was complete, the solvent was distilled off, and the residue was diluted with water and extracted with diethyl ether. The extract was washed with brine and dried over anhydrous. The solvent was removed, and the residue was analyzed by GLC. The products were isolated by column chromatography on silica gel or by crystallization. Isopinocamphone (**13**), *cis*-verbanone (**15**), camphor (**18**), verbenone (**20**), 3α-hydroxycaran-4-one (**21**), 3β-hydroxycaran-4-one (**24**), and 2α-hydroxypinan-3-one (**29**) were identified by GLC.

2α-Chloropinan-3-one (14). Yield 0.355 g (71.0%), mp 51–52°C, R_f 0.72 (hexane–Et_2O, 2:1), $[\alpha]_D^{25}$ = 96.4 (c = 1.1, EtOH). IR spectrum, ν, cm^{-1}: 2978, 2935, 2875, 1728 (C=O), 1471, 1448, 1409, 1373, 1321, 1267, 1240, 1209, 1145, 1099, 1047, 945, 914, 866, 831, 729 (C–Cl), 628, 551. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, (J, Hz): 0.93 s (3H, C^{8}H$_3$), 1.41 s (3H, C^{9}H$_3$), 1.79 s (3H, C^{10}H$_3$), 1.91 d (1H, 7-H, J = 11), 2.17 m (1H, 5-H, J = 2.4, 6.1), 2.41 d.d (1H, 1-H, J = 6.1, 6.2), 2.59 m (1H, 7-H, J = 11.0), 2.70 d.d.d (1H, 4-H, J = 3.0, 6.2, 19.0), 2.77 d.d (1H, 4-H, J = 2.4, 19.0). ^{13}C NMR spectrum, ($CDCl_3$), δ_C, ppm: 206.02 (C^3), 73.98 (C^2), 52.84 (C^1), 43.06 (C^4), 40.26 (C^6), 38.27 (C^5), 31.55 (C^7), 27.47 (C^9), 27.50 (C^{10}), 22.79 (C^8).

3α-Chloro-10β-pinan-4-one (16). Yield 0.164 g (63.0%), mp 65–66°C, R_f 0.58 (hexane–Et_2O, 1:1), $[\alpha]_D^{25}$ = 1.8 (c = 0.4, EtOH). IR spectrum, ν, cm^{-1}: 2958, 2939, 2879, 1728 (C=O), 1467, 1382, 1294, 1249, 1188, 983, 881, 773 (C–Cl), 650, 626, 586, 503. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 0.98 s (3H, C^{8}H$_3$), 1.24 d (3H, C^{10}H$_3$, J = 7.4), 1.32 s (3H, C^{9}H$_3$), 1.39 d (1H, 7-H, J = 11.0), 2.16 d.d.d (1H, 1-H, J = 2.3, 5.7, 5.8), 2.42 d.d.q (1H, 2-H, J = 2.3, 5.7, 7.4), 2.68 d.d (1H, 5-H, J = 5.5, 5.8), 2.77 d.d.d (1H, 7-H, J = 4.8, 6.0, 11.0), 4.59 d (1H, 3-H, J = 5.7). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 206.08 (C^4), 62.25 (C^3), 58.49 (C^5), 47.80 (C^1), 45.38 (C^2), 39.62 (C^6), 29.37 (C^7), 26.96 (C^9), 24.93 (C^8), 19.11 (C^{10}).

3,3-Dichloro-10β-pinan-4-one (17). IR spectrum, ν, cm^{-1}: 2932, 2878, 1736 (C=O), 1474, 1385, 1244,

1186, 1096, 980, 808, 772 (C–Cl), 681, 569. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.93 s (3H, C^8H_3), 1.35 d (3H, $C^{10}H_3$, *J* = 7.5), 1.37 s (3H, C^9H_3), 2.02 d (1H, 7-H, *J* = 11.0), 2.29 d.d.d (1H, 1-H, *J* = 2.8, 5.6, 7.0), 2.70 d.d.d (1H, 7-H, *J* = 5.5, 7.0, 11), 2.86 d.d (1H, 5-H, *J* = 5.5, 5.6), 3.36 d.q (1H, 2-H, *J* = 2.8, 7.5). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 199.59 (C^4), 89.35 (C^3), 56.86 (C^5), 51.28 (C^2), 47.74 (C^1), 43.52 (C^6), 26.84 (C^9), 26.64 (C^7), 25.05 (C^8), 19.76 (C^{10}).

Isocaran-4-one (19). Yield 65%, $[\alpha]_D^{25}$ = –134° (*c* = 1.5, EtOH). IR spectrum: ν 1710 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.80 s (3H, C^8H_3), 0.91 d (3H, $C^{10}H_3$, *J* = 6.5), 0.99 s (3H, C^9H_3), 0.90–1.10 m (2H, 1-H, 6-H), 1.21 m and 2.23 m (1H each, 2-H), 2.30 m (1H, 5-H), 2.32 m (1H, 3-H), 2.48 d.d (1H, 5-H, *J* = 8.3, 18). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 216.48 (C^4), 41.88 (C^3), 36.74 (C^5), 29.71 (C^2), 27.83 (C^9), 20.28 and 22.78 (C^1, C^6), 19.37 (C^7), 14.78 (C^8), 14.02 (C^{10}).

5α-Chloro-3α-hydroxycaran-4-one (22). Yield 0.26 g (51%), mp 97–98°C, R_f 0.62 (Et_2O–hexane, 2 : 1), $[\alpha]_D^{25}$ = –340.8 (*c* = 0.3, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3516 (OH), 1730 (C=O), 1139 (C–O), 769 (C–Cl). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.9–1.2 m (2H, 1-H, 6-H); 1.10 s, 1.15 s, and 1.19 s (3H each, C^8H_3, C^9H_3, $C^{10}H_3$), 1.57 d.d (1H, 2-H, *J* = 9.4, 15.3), 1.97 d.d (1H, 2-H, *J* = 7.4, 15.3), 4.75 d (1H, 5-H, *J* = 8.0), 5.53 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 206.17 (C^4), 74.39 (C^3), 61.02 (C^5), 32.81 (C^2), 29.30 (C^6), 27.76 (C^9), 25.39 (C^{10}), 21.55 (C^7), 21.44 (C^1), 14.31 (C^8).

5β-Chloro-3α-hydroxycaran-4-one (23). Yield 0.06 g (2%), mp 128–129°C (decomp.), $[\alpha]_D^{25}$ = 195.1° (*c* = 0.3, EtOH). IR spectrum, ν, cm^{-1}: 3512 (OH), 3021, 2984, 2949, 2926, 1730 (C=O), 1450, 1373, 1134, 926, 858, 752 (C–Cl), 503. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.82 s (3H, C^8H_3), 1.05 s (3H, C^9H_3), 1.10 d.d.d (1H, 1-H, *J* = 3.3, 8.7, 9.5), 1.15 s (3H, $C^{10}H_3$), 1.62 d.d (1H, 2-H, *J* = 3.3, 15.5), 1.83 d.d (1H, 6-H, *J* = 8.5, 8.7), 2.35 d.d (1H, 2-H, *J* = 9.5, 15.5), 5.70 s (1H, OH), 5.74 d (1H, 5-H, *J* = 8.5). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 207.6 (C^4), 75.4 (C^3), 65.0 (C^5), 37.0 (C^2), 34.4 (C^6), 28.6 (C^9), 23.9 (C^{10}), 22.2 (C^7), 22.1 (C^1), 15.5 (C^8).

5α-Chloro-3β-hydroxycaran-4-one (25). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.95–1.05 m (2H, 1-H, 6-H), 1.09 s and 1.11 s (3H each, C^8H_3, C^9H_3), 1.35 s (3H, $C^{10}H_3$), 1.59 d.d (1H, 2-H, *J* = 8.8, 14.3), 2.00 d.d (1H, 2-H, *J* = 7.7, 14.3), 4.57 d (1H, 5-H, *J* = 6.6). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 206.6 (C^4), 74.0 (C^3), 59.3 (C^5), 33.0 (C^2), 28.0 (C^6), 27.3 (C^8), 25.7 (C^{10}), 21.1 (C^7), 20.6 (C^1), 14.4 (C^9).

5β-Chloro-3β-hydroxycaran-4-one (26). Yield 0.161 g (77%), mp 85–87°C, R_f 0.38 (Et_2O–hexane, 1 : 1), $[\alpha]_D^{25}$ = 179.1 (*c* = 0.3, EtOH). IR spectrum, ν, cm^{-1}: 3495 (OH), 3012, 2983, 2954, 2933, 2912, 1724 (C=O), 1450, 1382, 1361, 1282, 1226, 1186, 1145, 1089, 1033, 970, 939, 812, 790, 759 (C–Cl), 734. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, (*J*, Hz): 0.84 s (3H, C^8H_3), 1.04 s (3H, C^9H_3), 1.16 d.d.d (H, 1-H, *J* = 3.9, 8.5, 9.8), 1.39 s (3H, $C^{10}H_3$), 1.72 d.d (1H, 2-H, *J* = 3.8, 14.6), 1.76 d.d (1H, 6-H, *J* = 8.5, 8.5), 2.23 d.d (1H, 2-H, *J* = 9.8, 14.6), 5.73 d (1H, 5-H, *J* = 8.4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 207.8 (C^4), 76.7 (C^3), 64.8 (C^5), 37.4 (C^2), 33.0 (C^6), 28.2 (C^9), 25.7 (C^{10}), 22.3 (C^7), 22.2 (C^1), 16.0 (C^8).

6-Chloro-4-(2-chloropropan-2-yl)-6-methylcyclohex-2-en-1-one (27). Concentration 97% (GLC). IR spectrum, ν, cm^{-1}: 3041 (=C–H), 2978, 2933, 1691 (C=O), 1462, 1373, 1275, 1255, 1196, 1173, 1126, 1085, 968, 893, 827 (C–Cl), 678, 521. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.10 s (3H, $C^{10}H_3$), 1.27 s (3H, C^7H_3), 1.38 s (3H, C^9H_3), 1.95 d (1H, 5-H, *J* = 12.0), 2.35 d.d.d (1H, 5-H, *J* = 1.5, 4.0, 12), 2.92 d.d (1H, 4-H, *J* = 4.0, 7.0), 6.00 d (1H, 2-H, *J* = 9.5), 7.40 d.d.d (1H, 3-H, *J* = 1.5, 7.0, 9.5). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 197.27 (C^1), 155.56 (C^3), 128.05 (C^2), 85.32 and 84.11 (C^6, C^8), 47.91 (C^4), 45.74 (C^5), 29.96 (C^9), 25.64 (C^{10}), 19.28 (C^7).

2-Chloro-6-hydroxy-4-(2-hydroxypropan-2-yl)-6-methylcyclohex-2-en-1-one (28). Concentration 80% (GLC). IR spectrum, ν, cm^{-1}: 3520 (OH), 3491 (OH), 2978, 2933, 1703 (C=O), 1606, 1450, 1371, 1342, 1257, 1213, 1142, 1089, 977, 918, 889, 862 (C–Cl), 808, 472. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.27 (3H, C^7H_3), 1.59 (3H, $C^{10}H_3$), 1.73 (3H, C^9H_3), 1.97 d.d (1H, 5-H, *J* = 11, 12), 2.14 d.d.d (1H, 5-H, *J* = 1.8, 4.7, 12), 3.06 d.d.d (1H, 4-H, *J* = 1.8, 4.7, 11), 5.59 br.s (1H, OH), 7.36 d.d (1H, 3-H, *J* = 1.8, 2.1). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 195.29 (C^1), 146.68 (C^3), 130.26 (C^2), 74.04 and 73.57 (C^6, C^8), 47.65 (C^4), 38.91 (C^5), 30.96 and 30.16 (C^9, C^{10}), 24.54 (C^7).

4α-Chloro-2α-hydroxypinan-3-one (30). Yield 0.36 g (72%), mp 69–70°C, R_f 0.52 (Et_2O–hexane, 1 : 1), $[\alpha]_D^{25}$ = –9.3 (*c* = 0.6, $CHCl_3$), $[\alpha]_D^{25}$ = 6.6 (*c* =

0.8, EtOH). IR spectrum, ν, cm^{-1}: 3477 (OH), 1724 (C=O), 719 (C–Cl). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.83 s (3H, C^8H_3), 1.29 s (3H, $C^{10}H_3$), 1.36 s (3H, C^9H_3), 2.02 d (1H, 7-H, *J* = 10), 2.03 d.d (1H, 1-H, *J* = 5.8, 6.3), 2.30 m (1H, 5-H), 2.32 m (1H, 7-H, *J* = 10), 4.69 d.d (1H, 4-H, *J* = 2.8, 3.1). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 207.7 (C^3), 76.4 (C^2), 61.7 (C^4), 50.4 (C^1), 46.3 (C^5), 39.2 (C^6), 27.8 (C^9), 25.4 (C^{10}), 24.6 (C^7), 22.3 (C^8).

ACKNOWLEDGMENTS

This study was performed under partial financial support by the Ural Branch of the Russian Academy of Sciences (project no. 15-21-3-16) using the equipment of the *Khimiya* Joint Center (Komi Research Center, Ural Branch, Russian Academy of Sciences).

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