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Stereochemistry of hydroxylation of some chiral *spiro*-[2,5]octan-4-ones

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ABSTRACT

Stereoselective oxidative alpha hydroxylation of (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones has been found as a secondary process in the cyclopropanation of 2-arylidene isomenthanones with trimethylsulfoxonium iodide in DMSO/NaOH or DMF/NaOH system. Three stereoisomeric hydroxy ketones have been isolated from a reaction mixture of cyclopropanation reaction, but the reaction of oxidation carried out with isolated *spiro*-[2,5]octan-4-ones was stereoselective. The advantages of this method of stereoselective hydroxylation are room temperature of reaction and absence of expensive catalysts. The reduction of obtained hydroxy ketones was also stereoselective and gave the only *trans*-(4*R*,5*S*)-dioles. The structures have been confirmed with 1D and 2D ^{1}H and ^{13}C NMR, MS spectra and for stereoisomeric hydroxy ketones with X-ray analysis also.

1. Introduction

The reaction of cyclopropanation with sulfur ylides (Corey–Chaykovsky reaction) is attractive because of its potential for simple procedures in obtaining of three-membered rings [1–4] application-oriented in the synthesis of some biologically active compounds. Peculiarities of this reaction in modern synthesis remain the subject of studies [5–7]. Also, the substitution of double bond in arylidene derivatives of isomenthone with a cyclopropane cycle seems to be attractive for obtaining of photo stable chiral dopants to nematic liquid crystals [8].

Corey–Chaykovsky reaction behavior for (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones and its accompanying stereoselective oxidative alpha hydroxylation with dioxygen in NaOH/DMSO and NaOH/DMF is described in this paper.

α-Hydroxyketones, especially optically active, are interesting as important intermediate products for synthesis of different bioactive substances. Non-oxidative procedures for their obtaining are known (see [9] for review) but they are limited to the synthesis of acyclic derivatives. Recently, cesium formate using [10] and α-haloketones irradiation with ultra violet or micro-waves [11] were proposed for the transformation of α-haloketones to α-hydroxyketones.

The most common oxidative procedures for α-hydroxyketone obtaining are oxidation of O-sylil enolic ethers (epoxidation, Rubottom oxidation) or enolates of carbonyl compounds [12] with different oxidants. MoOPH or MoOPD [Ref. in 9] and dioxygen [13,9], and also dibenzyl peroxydicarbonate [14], molybdenum peroxide [15], osmium tetroxide/N-methylmorpholine-N-oxide [16], m-chloroperbenzoic acid [17], chiral oxaziridines (N-sulphonyloxaziridines) [9], nitroso and iodoso compounds [18], dioxiranes [19] were used predominately. Other ways include oxidation of enamines with molecular oxygen [20] or metal-catalyzed oxidation of olefins [21]. Last time strongly upcoming chemo-enzymatic reactions were applied to the synthesis of α-hydroxy ketones [22] also. To improve an enantiomeric excess (ee) in a synthesis of α-hydroxy substituted ketones and aldehydes it was proposed to pass oxygen through a reaction mixture at low temperatures (−25 °C) and use triethyl phosphite for hydroperoxides reduction [23–25], or to use amino acids as organocatalysts [9,26,27].

In this investigation, we have obtained α-hydroxyketones without reducing agents. We have separated intermediate hydroperoxide that confirms the mechanism of oxidative hydroxylation reaction in concerned case. Also we have studied stereoselectivity of this reaction and found configurations of new chiral centers. Molecular structures of compounds studied have been confirmed with 1D and 2D ^{1}H and ^{13}C NMR, MS, and for stereoisomeric hydroxy ketones with X-ray analysis also.

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2. Experimental

2.1. Preparation

The compounds described in this work and used synthetic procedures are shown in Fig. 1.

The syntheses of compounds **1** were described earlier [8]. Initial benzylidene cyclohexanones (**BC**) were obtained using published protocols [28].

2.1.1. (1R,5S,8R,3R)-1-Aryl-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-ones (**2a–e**)

To 8 mmol of compound **1** in 12 ml DMSO (or DMF) 960 mg (24 mmol) of powdered sodium hydroxide was added and stirred at room temperature in open vessel (using of protective tube some reduce the oxygen transport and therefore reduce the reaction). The reaction was completed usually during 24 h (control with thin layer chromatography (TLC), silica gel/dichloroethane). Then the reaction mixture was poured in water at 0 °C, neutralized with acetic acid, filtered. The precipitate was washed with water, dried in air and dissolved in DCM. Then solvent was evaporated with a rotary evaporator and a residue was crystallized from ethanol or hexane. All compounds (**2a–e**) were obtained as white solids. Finally, reaction mixtures had 80–90% of products **2a–e** (by HPLC).

(1R,5S,8R,3R)-1-(Biphenyl-4-yl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2a1**) (yield 78%). Mp 139–140 °C (ethanol). ^{1}H NMR (DMSO d_6), δ: 7.416, 7.463 (both d, 2H each, H arom., $3J$ = 8.2), 7.256 (t, 2H, *m*-H arom., $3J$ = 8.2 Hz); 7.186 (d, 2H, *o*-H arom., $3J$ = 8.2 Hz); 7.155 (t, 1H, *p*-H arom., $3J$ = 8.2 Hz); 5.088 (s, 1H, OH); 2.312 (dd, 1H, H(1), $3J$ = 8.7 Hz, $3J$ = 7.1 Hz); 2.295 (sept, 1H, H(10), $3J$ = 7.0 Hz); 1.907 (m, 1H, H(7 *trans*), $2J$ = −13.2 Hz, $2J$ = 13.6 Hz, $2J$ = 3.6 Hz, $2J$ = 2.9 Hz); 1.884 (m, 1H, H(6 *trans*), $2J$ = −13.5 Hz, $3J$ = 13.6 Hz, $3J$ = 2.6 Hz); 1.812 (dd, 1H, *cis*-H(2), $2J$ = −4.7 Hz, $3J$ = 8.7 Hz); 1.606 (m, 1H, H(6), $2J$ = −13.5 Hz, $3J$ = 2.9 Hz, $3J$ = 2.5 Hz); 1.295 (m, 1H, H(8), $3J$ = 7.1 Hz, $3J$ = 3.6 Hz, $3J$ = 2.0 Hz); 1.184 (dd, 1H, *trans*-H(2), $2J$ = −4.7 Hz, $3J$ = 7.1 Hz); 1.156 (m, 1H, H(7), $2J$ = −13.2 Hz, $3J$ = 2.9 Hz, $3J$ = 2.5 Hz, $3J$ = 2.0 Hz); 0.967 (d, 3H, C(9)Me, $3J$ = 7.1 Hz); 0.828, 0.934 (both d, 3H each, C(11)Me, C(12)Me, $3J$ = 7.0 Hz). ^{13}C NMR, $CDCl_3$: 213.105, 140.714, 139.701, 135.885, 129.845, 128.782, 127.272, 126.981, 126.900, 78.483, 38.229, 35.393, 32.556, 30.007, 27.162, 26.354, 19.094, 17.050, 16.641, 15.608. MS, *m*/*z* 348 (M+.). Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; found: C, 82.69; H, 8.15; $[\alpha]_D^{20}$ 236.36° (C = 1.15 g/100 cm^3, ethyl acetate).

(1R,5S,8R,3R)-1-(4-Bromophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2b**) (yield 76%). Mp 135–137 °C (ethanol). ^{1}H NMR, $CDCl_3$: 7.295 (m., 4H), 5.216 (s., 1H), 2.758, 2.252, 2.125, 1.831, 1.740, 1.531, 1.392, 1.232, 0.910, 0.853, 0.711. ^{13}C NMR, $CDCl_3$: 212.758, 135.918, 131.373, 131.110, 120.808, 78.519, 37.911, 34.383, 32.473, 30.163, 27.305, 26.367, 18.976, 16.956, 16.371, 15.587. MS, *m*/*z* 351 (M+.). Anal. Calcd. for $C_{18}H_{23}BrO_2$: C, 61.55; H, 6.60, Br 22.75; found: C, 61.52; H, 6.63, Br 22.73.

(1R,5S,8R,3R)-1-(4-Chlorophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2c**) (yield 76%). Mp 143–145 °C (ethanol, hexane). ^{1}H NMR, $CDCl_3$: 7.334 (m., 4H), 5.217 (s., 1H), 2.894 (s., 2H), 2.168 (dd., 1H), 1.987 (sept., 1H), 1.77 (m., 1H) 1.571 (m., 1H), 1.110, 1.095 (d.m., 3H), 0.96 (d., 3H), 0.952 (d., 3H), 0.818 (m., 3H). ^{13}C NMR, $CDCl_3$ (HMQC): 137.015, 131.795, 130.399, 127.982, 80.833, 75.257, 32.930, 31.874, 30.688, 28.252, 24.731, 24.529, 19.017, 15.813, 11.899. MS, *m*/*z* 306 (M+.). Anal. Calcd. for $C_{18}H_{23}ClO_2$: C, 70.46; H, 7.56, Cl 11.55; found: C, 70.38; H, 7.60, Cl 11.51.

(1R,5S,8R,3R)-1-(4-Fluorophenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2d**) (yield 77%). Mp 126–128 °C (ethanol, hexane). ^{1}H NMR, DMSO-d_6: 7.334 (Ar, 4H), 5.218 (s., 1H), 2.44 (s., 2H), 2.228 (dd., 2H), 1.754 (m., 1H), 1.515 (m., 1H), 1.077 (m., 3H), 0.848 (m., 6H), 0.716 (m., 3H); MS, *m*/*z* 290 (M+.). Anal. Calcd. for $C_{18}H_{23}FO_2$: C, 74.45; H, 7.98, F 6.54; found: C, 74.43; H, 8.03, F 6.51. MS, *m*/*z* 290 (M+.). Anal. Calcd. for $C_{18}H_{23}FO_2$: C, 74.45; H, 7.98, F 6.54; found: C, 74.43; H, 8.02, F 6.55.

(1R,5S,8R,3R)-1-(4-Methoxyphenyl)-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2e**) (yield 78%). Mp 96–97 °C (ethanol). ^{1}H NMR, DMSO-d_6: 7.030 (Ar, 4H), 5.161 (s., 1H), 3.712 (s., 3H), 2.216 (m., 2H), 1.830 (m., 2H), 1.704 (m., 1H) 1.501 (m., 1H), 1.021 (m., 4H), 0.842 (dd., 7H), 0.714 (d., 4H)). MS, *m*/*z* 302 (M+.). Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; found: C, 75.43; H, 8.69.

(1R,5S,8R,3R)-1-(4-bromophenyl)-5-isopropyl-5-hydroperoxy-8-methyl-3-spiro[2.5]octan-4-one (**2′b**) was obtained in similar procedure when reaction was carried in DMF. Yield 20%. Mp 158–160 °C (ethanol). ^{1}H NMR, DMSO-d_6: 11.183, 7.478, 7.305, 5.239, 2.601, 2.390, 1.905, 1.671, 1.101, 0.886, 0.843, 0.808, 0.757, 0.723. ^{13}C NMR, $CDCl_3$: 206.701, 135.989, 131.372, 131.166, 131.110, 131.026, 120.708, 88.011, 40.015, 35.337, 30.785, 26.452, 23.998, 22.147, 18.450, 18.024, 15.204, 13.943. MS, *m*/*z* 367 (M+.). Anal. Calcd. for $C_{19}H_{26}O_3$: C, 58.86; H, 6.31, Br 21.76; found: C, 58.78; H, 6.38, Br 21.73.

2.1.2. Isomeric 1-(4-phenyl)-phenyl-5-isopropyl-5-hydroxy-8(R)-methyl-3(R)-spiro[2.5]octan-4-ones (**2a1–2a3**)

(3*R*,6*R*)-3-methyl-6-isopropyl-2-(4-phenyl)benzylidenecyclohexanone (**PBC**) (1.9 g, 6 mmol) was dissolved in 20 ml DMSO and 0.6 g (15 mmol) of powdered NaOH was added to former. The resulting mixture was stirred for 2 days at a room temperature up to initial product disappearance on TLC. The mixture after reaction completion was poured into water, and a precipitate obtained was filtered and dried. Its crystallization from isopropanol yielded 1.4 g (78%) of **2a1** (data see in Section 2.1.1). According to TLC and HPLC, a mother stock contained additively two more polar reaction products. To obtain these products the solvent was removed, and residue was separated by column chromatography on silica gel

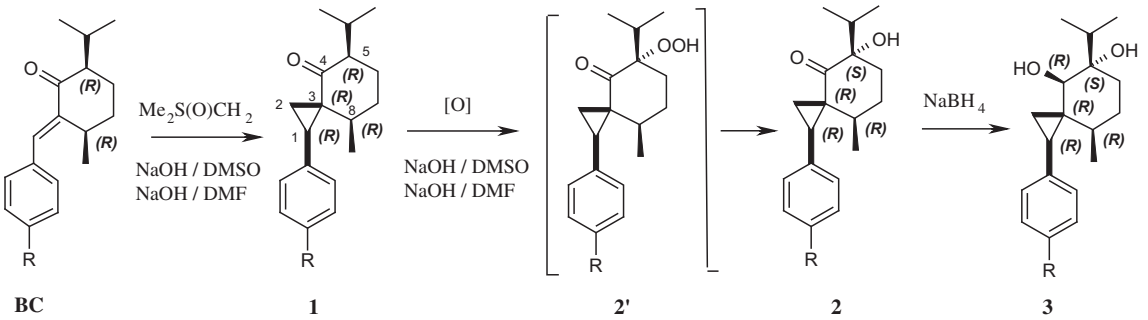

Fig. 1. Synthetical procedures used for obtaining spiro compounds, their hydroxylation and reduction.

Table 1
Chemical shifts of protons (δ, ppm) in ^{1}H NMR spectra for compounds **2a1**, **2a2**, **2a3.**

Compounds	H(8)	H(7a)	H(7e)	H(6a)	H(6e)	H(5)	H(10)	Me(9)	Me(11,12)	Benzene ring		Cyclopropane ring		
										Ho	Hm	H(1)	H(2c)	H(2t)
Isomeric 1-(4-phenyl)-phenyl-5-isopropyl-5-hydroxy-8(R)-methyl-3(R)-spiro[2.5]octan-4-ones														
$CDCl_3$														
2a1	1.608	1.876	1.395	2.132	1.756	2.589	2.279	0.755	0.871; 0.916	7.302	7.536	2.854	1.698	1.318
2a2	2.024	1.990	1.652	2.231	1.745	2.019	2.496	0.435	0.892; 1.001	7.335	7.532	2.801	1.505	1.660
2a3	2.286	1.826	1.629	2.262	1.691	3.317	1.710	0.996	−0.470; 0.784	7.240	7.463	2.878	1.113	2.305
C_6D_6														
2a1	1.408	1.781	1.044	1.884	1.592	1.312	2.226	0.612	0.816; 0.846	7.159	7.422	2.794	1.775	0.999
2a2	1.677	1.883	1.369	1.980	1.614	1.315	2.433	0.331	0.847; 0.924	7.113	7.374	3.024	1.517	1.247
DMSO-d_6														
2a1	1.244	1.884	1.100	1.858	1.569	5.197	2.295	0.758	0.868; 0.903	7.383	7.671	2.312	1.784	1.128
2a2	1.687	2.340	1.443	1.872	1.628	4.884	2.297	0.461	0.791; 0.869	7.303	7.517	3.105	1.156	1.590

Note. For **2a1** in $CDCl_3$: δHo′ 7.592, δHm′ 7.433, δHp′ 7.337, **2a1** in C_6D_6: δHo′ 7.458, δHm′ 7.212, δHp′ 7.126.
For **2a2** in $CDCl_3$: δHo′ 7.597, δHm′ 7.436, δHp′ 7.340, **2a2** in C_6D_6: δHo′ 7.464, δHm′ 7.222, δHp′ 7.135.
For **2a1** in $DMSO_2$-d_6: δHo′ 7.622, δHm′ 7.456, δHp′ 7.351.
For **2a2** in $DMSO_2$-d_6: δHo′ 7.595, δHm′ 7.412, δHp′ 7.301.

Table 2
Experimental values of vicinal coupling constants (*J*, Hz) in spectra ^{1}H NMR of compounds **2a1**, **2a2** and **2a3** in different solvents.

Protons	*J* (H,H), Hz						
	2a1			**2a2**			**2a3**
	$CDCl_3$	C_6D_6	DMSO-d_6	$CDCl_3$	C_6D_6	DMSO-d_6	$CDCl_3$
8,7a	4.3	4.5	3.6	3.4	3.5	3.4	3.1
8,7e	6.9	5.4	2.2	7.3	6.5	2.7	12.6
7a,6a	7.6	5.9	13.6	7.9	6.9	13.2	2.8
7a,6e	3.8	3.8	2.9	3.6	3.9	2.8	2.7
7e,6a	3.7	3.7	2.9	3.8	3.6	3.3	2.9
7e,6e	9.8	10.8	2.4	8.9	10.2	2.3	13.3
7a,7e	−13.7	−13.6	−13.2	−13.9	−13.8	−13.2	−13.5
6a,6e	−13.7	−14.4	−13.5	−14.4	−13.7	−13.2	−13.5
8,9(CH_3)	6.8	7.0	7.1	7.0	7.0	7.0	6.8
10,11,12(CH_3)	6.9	6.9	7.0	6.8	7.0	7.0	6.6
1,2cis	9.0	9.0	8.7	9.2	8.9	8.8	8.8
1,2′tr	7.1	7.4	7.2	7.4	7.2	7.0	6.8
2,2′	−4.7	−4.7	−4.7	−4.6	−4.4	−4.5	−5.4

60 (Merck), gradient elution benzene–ethyl acetate. Crystallization of fractions containing additional products from absolute isopropanol gave isomer **2a2** (0.167 g, 8%), Mp. 178–179 °C, MS, *m*/*z* 348 (M+). Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; found: C, 82.67; H, 8.17; $[\alpha]_D^{20}$ −187.75° (C = 0.81 g/100 cm^3, ethyl acetate) and isomer **2a3** (21 mg, 1%). Mp 205 °C, MS, *m*/*z* 348 (M+). Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10; found: C, 82.64; H, 8.15; $[\alpha]_D^{20}$ 124.77° (C = 0.29 g/100 cm^3, ethyl acetate). NMR spectral characteristics of **2a2** and **2a3** are given in Tables 1–3.

2.1.3. (1R,3R,4R,5S,8R)-1-Aryl-5-isopropyl-8-methyl-3-spiro[2.5]octan-4,5-dioles

(1R,3R,5S,8R)-1-aryl-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-one (**2**, 1 mmol) was dissolved in 2-propanol and $NaBH_4$ (1 mmol) was added slowly to the mixture at room temperature. The mixture was stirred for several hours up to initial substance **2** convert (control with TLC). Then the mixture was poured into water, extracted using EtOAc, dried (anhydrous $MgSO_4$), filtered, and concentrated using rotary evaporator. The mixture was purified with column chromatography (silica gel, hexane–EtOAc, 2:1) and furnished **3** after crystallization from methanol as white crystals. Yields 60–70%.

(1R,3R,4R,5S,8R)-1-(Biphenyl-4-yl)-5-isopropyl-8-methyl-3-spiro[2.5]octan-4,5-diole (**3a**)**.** Yield 70%. Mp 127–129 °C. ^{1}H NMR, $CDCl_3$: d., 2H 7.595, d. 2H, 7.513, m., 2H, 7.431, m., 3H, 7.339, c.1H, 2.943 dd.1H, 2.943, m.1H, 2.257, 2.001, m.1H, 1.793, m., 2H, 1.599, m., 4H, 1.136, m., 6H, 0.982, m, 2H 0.918, dd, 1H 0.863; ^{13}C NMR, $CDCl_3$: 140.896, 138.860, 137.406, 129.398, 128.694, 126.924, 126.551, 80.926, 75.210, 32.888, 31.963, 30.940, 28.115, 24.687, 24.609, 19.038, 15.854, 11.817. MS, *m*/*z* 308 (M+). Anal. Calcd. for $C_{24}H_{30}O_2$: C 82.24%, H 8.63%; found: C 82.20%, H 8.70%.

(1R,3R,4R,5S,8R)-1-(4-Bromophenyl)-5-isopropyl-8-methyl-3-spiro[2.5]octan-4,5-diole (**3b**). Yield 62%. Mp 110–111 °C. ^{1}H NMR, $CDCl_3$: 7.38 (d., 2H),7.66 (d., 2H Ar), 2.893 (c. 1H), 2.150 (dd., 1H), 1.987 (sept. 1H), 1.769 (m., 1H), 1.568 (m., 2H), 1.102, (d., 3H, m., 1H), 0.959 (d., 3H), 0.951 (d., 3H), 0.816 (m., 3H); ^{13}C NMR, $CDCl_3$: 137.563, 130.921, 130.819, 119.854, 80.809, 75.257, 32.919, 31.877, 30.755, 28.259, 24.726, 24.523, 19.025, 15.821,

Table 3
Chemical shifts in ^{13}C NMR spectra for compounds **2a1**, **2a2**, **2a3.**

Compounds	1	2	3	4	5	6,7	8	9	10	Me-11,12	Aryl
2a1	30.01	19.09	38.23	213.11	78.48	26.25; 27.16	35.39	15.61	32.56	16.64; 17.05	126.9–140.71
2a2	29.98	18.82	39.30	212.37	79.28	27.76; 29.23	34.45	15.79	32.67	16.92; 17.28	128.78–140.65
2a3	29.49	12.77	37.04	209.56	79.28	29.49; 29.23	34.36	17.02	30.88	14.31; 15.49	126.64–140.85

11.868. MS, *m*/*z* 353 (M+). Anal. Calcd. for $C_{18}H_{25}BrO_2$: C 61.19%, H 7.13%, Cl 22.62; found: C 61.16%, H 7.23%, Cl 22.59%.

(1R,3R,4R,5S,8R)-1-(4-Chlorophenyl)-5-isopropyl-8-methyl-3-spiro[2.5]octan-4,5-diole (**3c**). Yield 68%. Mp 127–129 °C. ^{1}H NMR, $CDCl_3$: 7.227 (Ar, 4H), 2.894 (s.1H), 2.168 (dd., 1H), 1.987 (sept., 1H), 1.77 (m., 1H) 1.571 (m., 3H), 1.110, 1.095 (d.,m., 4H), 0.96 (d., 3H)), 0.952 (d., 3H), 0.818 (m., 3H); ^{13}C NMR, $CDCl_3$ (HMQC): 137.015, 131.795, 130.399, 127.982, 80.833, 75.257, 32.930, 31.874, 30.688, 28.252, 24.731, 24.529, 19.017, 15.813, 11.899. MS, *m*/*z* 308 (M+). Anal. Calcd. for $C_{18}H_{25}ClO_2$: C 70.00%, H 8.16%, Cl 11.48; found: C 69.95%, H 8.36%, Cl 11.42%.

2.2. Physical measurements

The ^{1}H, ^{13}C and ^{1}H–^{13}C correlation (2D COSY, NOESY and HMQC) NMR spectra were obtained on a Varian Mercury 400 NMR spectrometer and Bruker AVANCE DRX 500 spectrometer. The ^{1}H chemical shifts were referred to $SiMe_4$ as an internal standard. For ^{13}C NMR spectra at 125 MHz $CDCl_3$ was used both as a solvent and the internal standard.

The high-pressure liquid chromatography (HPLC) analyses were carried out using a Bischoff system, reversed-phase Prontosil 120-3-C18–H column, UV detector, eluent acetonitrile–water 78:22 and direct phase Prontosil 120-3-Si column, eluent 1.5% BuOAc in heptane.

Elemental analyses were carried out using Element Analyzer EA-3000 (Eurovector, Italy).

FAB-mass-spectrometric analyses were performed in the liquid matrix of the m-nitrobenzyl alcohol using a magnetic sector mass spectrometer MI-1201E equipped with primary FAB ion source for generating a bombarding beam of argon atoms. The region of molecular ion is represented by ion-radical M^+ and protonated molecular ion $[MH]^+$.

The specific optical rotation $[\alpha]_D^{20}$ for stereoisomers was measured using the Perkin Elmer-343 polarimeter and ethyl acetate as a solvent.

Single crystals for X-ray diffraction study were grown from ethyl acetate (isomer (**2a1**) and isopropyl alcohol (**2a2** and **2a3**). Diffraction data were collected on an "Xcalibur 3" diffractometer (graphite monochromated Mo Kα, ω scans) at room temperature for **2a1** and **2a2**, and at 100 K for **2a3**. Structures were solved by direct method a refined against F^2 in anisotropic approximation for all non-hydrogen atoms using SHELX-97 software [29]. Hydrogen atoms were refined using "riding" model with Uiso = *n*Ueq of parent atom (*n* = 1.5 for CH_3 and OH, *n* = 1.2 for remaining H = atoms). As long as structures do not contain anomalously scattering atoms, Friedel equivalents were merged. *Crystal data for **2a1***: orthorhombic, space group $P2_12_12_1$, a = 16.7112(3) Å, b = 17.1736(3) Å, c = 20.9216(4) Å, V = 6004.33(19) Å^3, Z = 12, d_c = 1.16 g cm^{-1}, μ = 0.07 mm^{-1}, 26166 reflections were measured up to $2\theta_{max}$ = 55.5° of which 7011 were unique (R_{int} = 0.021), refinement converged at wR_2 = 0.101 (all data), R_1 = 0.038 (5232 reflections with $I > 2\sigma(I)$), GooF = 1.02. *Crystal data for **2a2***: orthorhombic, space group $P2_12_12_1$, a = 6.0342(6) Å, b = 9.6532(12) Å, c = 33.580(15) Å, V = 1956.0(9) Å^3, Z = 4, d_c = 1.18 g cm^{-1}, μ = 0.07 mm^{-1}, 11276 reflections were measured up to $2\theta_{max}$ = 50.0° of which 2031 were unique (R_{int} = 0.094), refinement converged at wR_2 = 0.109 (all data), R_1 = 0.060 (1226 reflections with $I > 2\sigma(I)$), GooF = 1.09. *Crystal data for **2a3***: orthorhombic, space group $P2_12_12_1$, a = 6.2393(3) Å, b = 9.8272(4) Å, c = 31.0724(13) Å, V = 1905.19(13) Å^3, Z = 4, d_c = 1.22 g cm^{-1}, μ = 0.08 mm^{-1}, 8928 reflections were measured up to $2\theta_{max}$ = 56.3° of which 2507 were unique (R_{int} = 0.036), refinement converged at wR_2 = 0.087 (all data), R_1 = 0.040 (2115 reflections with $I > 2\sigma(I)$), GooF = 1.04. Crystallographic data have been deposited to the Cambridge Crystallographic Data Center, deposition numbers are CCDC 854981–854983.

3. Results and discussion

3.1. Structures of the byproducts in cyclopropanation (Corey–Chaykovsky) reaction

When we carried Corey–Chaykovsky reaction with (3*R*,6*R*)-3-methyl-6-isopropylcyclohexanone (isomenthone) 2-arylidene derivatives in NaOH/DMSO and NaOH/DMF systems with oxygen admission, we detected more polar byproducts with chromatography (HPLC, TLC) (Fig. 2).

The isolation of these byproducts with column chromatography gave three stereoisomers, 1-aryl-5-hydroxy-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones with (1*R*,3*R*,5*S*,8*R*), (1*R*,3*S*,5*S*,8*R*) and (1*S*,3*S*,5*S*,8*R*) configurations. This hydroxylation was noticeably slower than cyclopropanation, and a hydroxylation rate essentially diminished when cyclopropanation was realized in inert atmosphere.

- When we put (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones **1** (the predominant products of cyclopropanation) to oxidation with atmospheric oxygen, we obtained exclusively (1*R*,5*S*,8*R*,3*R*)-1-aryl-5-hydroxy-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones **2**.

3.1.1. NMR study of the ***2a–2e*** compounds

The structures of obtained compounds **2** were proved with ^{1}H NMR and ^{13}C NMR (Tables 1–3) and signal attributions have been made on the base of their chemical shifts, scalar coupling constants and ^{1}H and ^{13}C homo and heteronuclear correlation spectra (HMQC, HMBC, COSY-45 and NOESY). Although the main products of the oxidative hydroxylation reaction were products **2a1–2e**, we also studied isomers of **2a1** (**2a2** and **2a3**) to exclude errors in the structure proving.

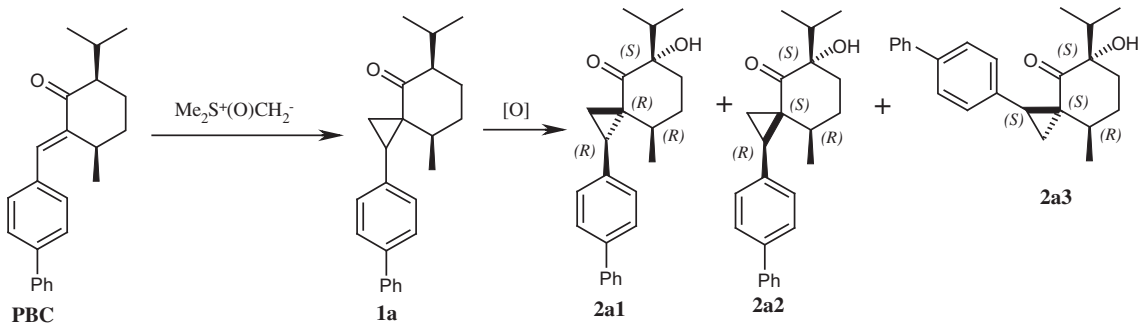

Fig. 2. Isomers obtained by means of Corey–Chaykovsky reaction.

Table 4
Correlations in 2D NMR for compound **2a1.**

δ, ppm	HMQC	HMBC	COSY	NOESY
7.59	127.2	139.9; 127.5	7.43	
7.53	127.1	140.9; 136.1; 130.1; 127.1	7.30	
7.43	129.0	140.9; 129.0	7.59; 7.34	
7.34	127.5	127.1	7.43	
7.30	130.1	139.9; 130.1; 127.1; 35.5	7.53	2.85; 1.87; 1.61; 1.31; 0.75
2.85	35.6	213.3; 130.1; 38.4; 16.9	1.70; 1.31	1.70; 1.31; 7.30
2.28	32.6	27.3; 17.3; 15.8; 78.7	0.91; 0.87	0.91; 0.87; 1.40
2.13	27.3	32.8; 30.2; 26.6; 78.7; 213.3	1.87; 1.76; 1.40	1.87; 1.76; 1.40; 0.91; 0.75
1.87	26.6	38.4; 30.2; 27.3; 19.3; 78.7	2.13; 1.61; 1.40	2.13; 1.61; 1.40
1.76	27.3	32.8; 30.2; 26.6; 213.3	2.13; 1.40	2.13; 0.87; 1.40
1.70	16.9	38.4; 35.6; 30.2; 136.1; 213.3	2.85; 1.31	2.87; 1.31
1.61	30.2	38.4; 35.6; 27.3; 19.5; 213.3	1.87; 0.75	1.87; 1.40; 0.75
1.40	26.6	38.4; 30.2; 78.7	2.13; 1.87; 1.76	2.28; 2.13; 1.87; 0.91; 0.75
1.31	16.9	38.4; 35.6; 30.2; 136.1; 213.3	2.85; 1.70	7.30; 1.75; 0.75
0.91	17.3	30.2; 15.8; 78.7	2.28	2.28; 2.13; 1.40
0.87	15.8	32.7; 17.3; 78.7	2.28	2.28; 1.76
0.75	19.3	38.4; 30.2; 26.6	1.61	2.13; 1.87; 1.61; 1.40; 1.31

Table 5
Correlations in 2D NMR for compound **2a2.**

δ, ppm	HMQC	HMBC	COSY	NOESY
7.59	127.1	139.7; 127.5	7.44	
7.53	127.0	140.8; 136.6; 129.7; 127.0	7.34	
7.44	129.0	140.8; 129.0	7.60; 7.34	
7.34	129.7; 127.5	139.7; 129.7; 127.1; 30.2	7.53; 7.44	1.51; 2.02; 2.80
2.80	30.2	39.5; 18.9; 129.7; 212.7	1.66; 1.51	1.66; 1.51
2.50	32.8	29.5; 17.1; 16.0; 79.4; 212.7	1.00; 0.89	1.00; 0.89
2.23	29.5	34.6; 79.4; 212.7	2.02; 1.75;	1.75; 2.02; 1.00; 0.43
2.02	28.0; 34.7	39.5; 29.5; 17.1	2.23; 1.75; 1.66; 0.43	2.23; 1.75; 1.66; 0.43
1.75	29.5	34.7; 32.8; 28.0; 79.4	2.23; 1.66; 0.43	2.23; 2.02
1.66	28.0; 18.9	39.5; 34.7; 29.5; 136.6; 212.7	2.80; 2.02; 1.51	2.80; 2.02; 1.51; 0.44
1.51	19.9	39.5; 34.7; 30.1; 136.6; 212.7	2.80; 1.66	
1.00	17.1	32.8; 17.1; 79.4	2.50	2.50; 2.23
0.89	16.0	32.8; 16.0; 79.4	2.50	2.50; 0.43
0.43	17.5	39.5; 34.6; 28.0	2.02	2.23; 2.02; 1.66; 1.51; 0.89

The isomeric structures of compounds **2a1–2a3** follow from the analysis of spectral parameters for protons above. ^{1}H NMR spectra of compounds **2a1–2a3** contain proton signals of all their structural fragments. Cyclic methylene protons C^{8}H, C^{7}H′a, C^{7}H′b, C^{6}H′a, C^{6}H′b form five-spin system and become apparent as multiplets in 1.629–2.286 ppm region. Protons of biphenyl fragment were found as multiplets at 7.26–7.62 ppm. It is visible and regular that signals of cyclopropane protons of isomers **2a1–2a3** are different in chemical shift values. Such differences are connected with the influence of carbonyl position against cyclopropane protons at their chemical shifts, owing to deshielding. In the same time the position of biphenyl substituent in a cyclopropane ring is important for chemical shift values of the methyl groups and, to a lesser degree, for shielding of other protons.

Signals of almost all the protons in the ^{1}H NMR spectra of compounds **2a1–2a3** in DMSO-d$_6$ are separated. Multiplets of all protons of cyclohexane ring are similar to the same of their arylidene precursors [30] that allows to suppose negligible changes in spatial structure of that part of molecule. Signals of three protons in cyclopropane ring form three spin system and are solved because of its typical multiplicity. Using of cross-peaks in 2D NMR spectroscopy (COSY-45 and HQMC) and simulation of spin systems (with NUTs program [31]) for protons of cyclohexanone and cyclopropane rings has allowed complete solving of all proton multiplets. Obtained ^{1}H NMR parameters (chemical shifts, δ, and coupling constants, *J*) for compounds **2a1–2a3** are given in Tables 1 and 2. Chemical shifts in ^{13}C NMR spectra for compounds **2a1**–**2a3** are given in Table 3.

Assignment for peaks was made also by the use of combined analysis of correlations in HMQC, HMBC, COSY and NOESY experiments (Tables 4 and 5, Figs. 3 and 4). So, proton signals of two methyl groups in molecules of **2a1** have correlations HMBC with carbon atom of neighboring CH group that absorb at 32.6 ppm. That atom has a HMQC correlation with proton signal at 2.28 ppm. So, proton at 2.28 ppm and ^{13}C at 32.6 ppm bound with chemical bond. This fact gives the assignment for signals of ^{1}H and ^{13}C in isopropyl group. All protons in isopropyl have HMBC correlations with quaternary carbon at 78.7 ppm. So that atom is carbon C5 in cyclohexanone ring bound with hydroxyl group.

The presence of correlation in COSY experiment for the methyl (chemical shift 0.75 ppm) with signal at 1.61 ppm allows assign this signal to H8. Signal at 1.87 ppm correlates in COSY with proton H8 that permits assign this signal to axial proton in neighboring methylene group. HMQC correlation between this signal and ^{13}C with chemical shift of 26.6 ppm proves this assignment also. Similar reasoning may be used for ^{1}H and ^{13}C assignments in aromatic ring and for other compounds.

For the identification of proton and methyl orientations at C-8 in cyclohexanone ring we used homonuclear decoupling experiments with suppression of the signal of methyl substituent at C-8 (to find necessary vicinal ^{1}H–^{1}H coupling constants). There were some problems with solvent selection as we needed solution where H–C8 signal would be separated. For **2a1** satisfying solvent was benzene-d$_6$ but for **2a2** it was DMSO-d$_6$. The results are given in Figs. 5 and 6.

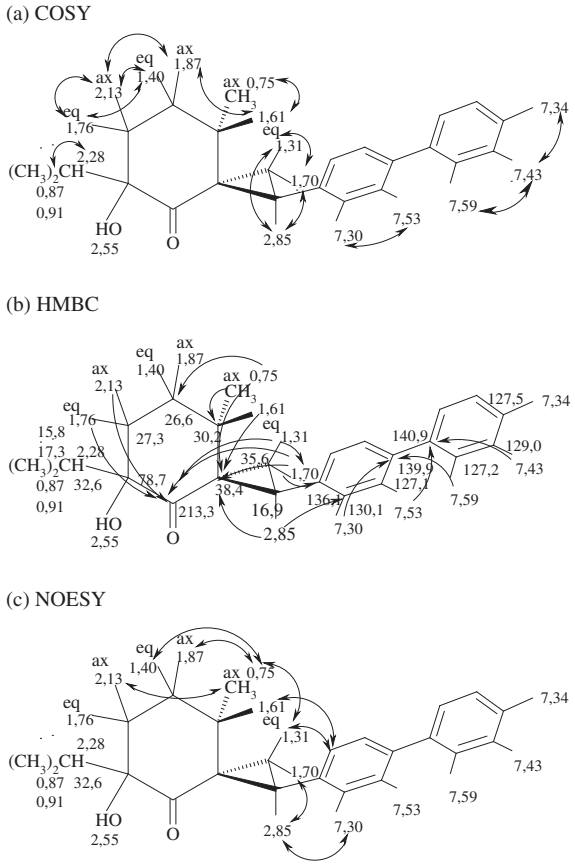

Fig. 3. The main correlations in NMR experiments for compound **2a1** used in assignments for signals.

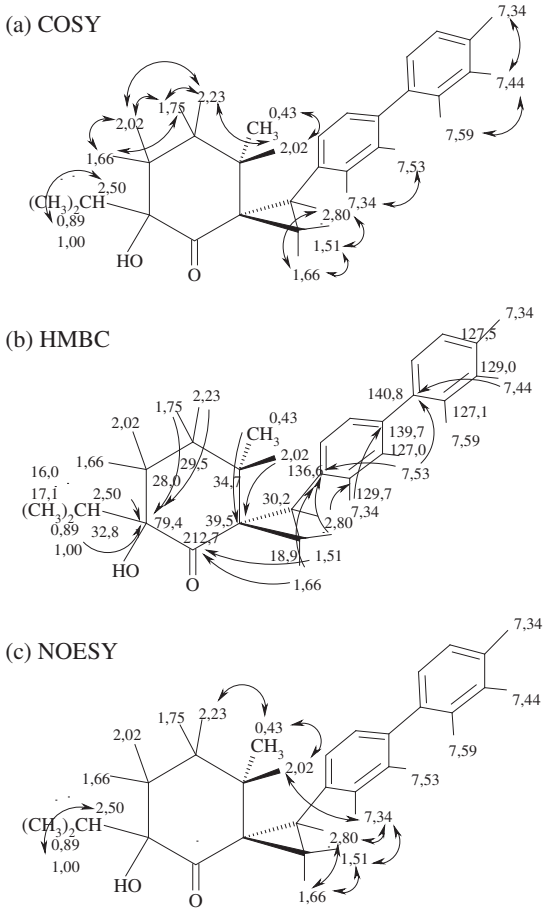

Fig. 4. The main correlations in NMR experiments for compound **2a2** used in assignments for signals.

As could be seen in Figs. 5 and 6 that in both cases proton H–C8 signal changes into triplet with vicinal coupling constants near 4 Hz. Equality of coupling constants of H–C8 with neighboring methylene protons evidences proximity of corresponding dihedral angles, and therefore equatorial orientation of H–C8 in both compounds **2a1** and **2a2** in solutions. Similar analysis gives the same orientation of methyl substituent in products **2b–e** also.

NOESY experiments were useful for determination of biphenyl substituent orientation. The most important correlations there were cross-peaks between signals of aromatic protons and H–C8 ones (in cyclohexanone ring). Such correlations are in NOESY for compounds **2a1** and **2a2**. It indicates similar orientation of biphenyl substituent relative to protons in cyclohexanone fragment (Figs. 3 and 4). Downfield shift of the methyl substitute at C8 in compound **2a2** in comparison with **2a1** takes place because of its nearer disposition to nearby benzene ring in biphenyle and corresponding shielding.

The signal of axial Me at C-8 in **2a2** compound is shifted at 0.32 ppm to high field as compared with **2a1**. Such a shift may be a result of a shielding from biphenyl group that is the only possible if the cyclopropane fragment has (1*R*,3*S*)-configuration. Therefore compound **2a2** is the result of hydroxylation not for a spiro product **1a** but for its isomer obtained from a cyclopropanation of (3*R*,6*R*)-3-methyl-6-isopropyl-2-(4-phenyl)benzylidenecyclohexanone (PBC) through dimethyloxosulfonium methylide attack on enone system from side opposite to axial 3*R*-methyl group.

The doublet at −0.47 ppm in ^{1}H NMR of compound **2a3** is attached to methyl group of isopropyl radical with correlation spectra ^{1}H COSY that is possible only for cis-orientation of carbonyl and biphenyl groups. The upfield shift of isopropyl protons and inversion of shifts of methylene protons in the cyclopropane ring adjust with these facts. Also, in NOESY maximal interaction was observed between 8-methyl group protons and cyclopropane proton H-1 (2.88 ppm) that demonstrates their approach. Molecular models analysis (MOPAC, PM6 [32]) proves that geometry corresponds to 1(*S*),3(*S*)-configuration of cyclopropane fragment. Therefore, compound **2a3** was formed as the result of rotation around C–C bond in intermediate betaine in the cyclopropanation reaction, with following hydroxylation.

3.1.2. X-ray diffraction study

The structures of compounds **2a1**, **2a2** and **2a3** as determined by X-ray crystallography are shown in Figs. 7 and 8. All three compounds crystallize in chiral $P2_12_12_1$ space group. The structures do not contain anomalously scattering atoms, which disallowed us to determine absolute configuration directly from diffraction data. Instead, absolute configuration was chosen as shown in Fig. 7.

The cyclohexane ring in molecules **2a1**, **2a2** and **2a3** adopts slightly deformed chair conformation with Zefirov-Palyulin [33] puckering amplitude S of 0.93–1.03 and puckering angle θ of 6.8–16.8°, whereas θ should be zero for ideal chair conformation.

- There are three symmetry unique molecules A–C in the crystal structure of **2a1** (Fig. 7).

Molecules A and B have similar conformation, which differs only by orientation of the hydrogen atom of the hydroxy group which is involved in intermolecular hydrogen bond. The molecule

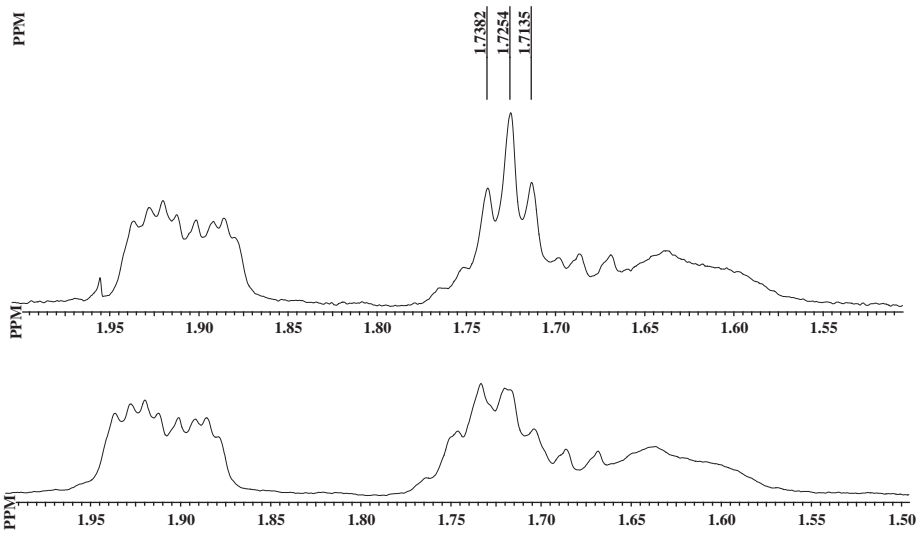

Fig. 5. Decoupling experiment with the suppression of methyl substituent at C-8 signal for compound **2a1** (solution in benzene-d_6).

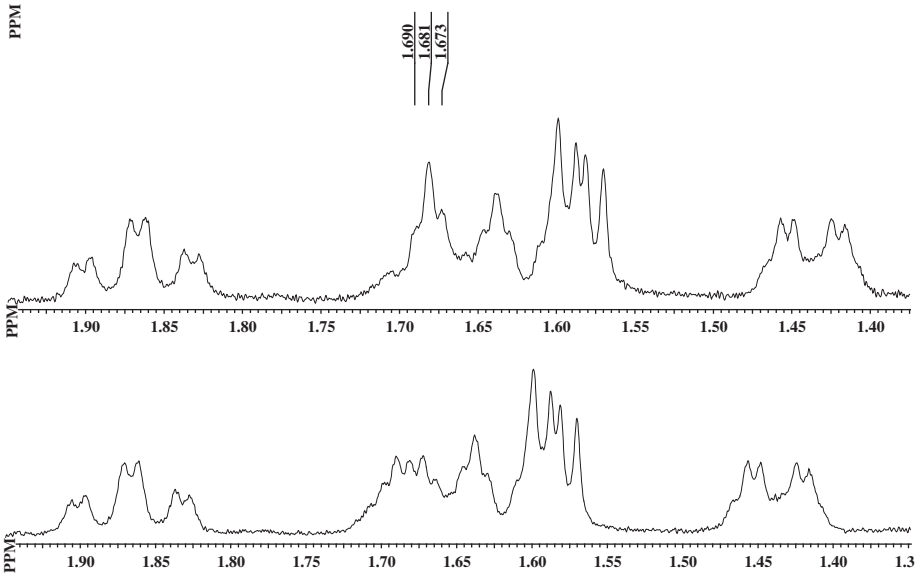

Fig. 6. Decoupling experiment with the suppression of methyl substituent at C-8 signal for compound **2a2** (solution in DMSO-d_6).

C shows inverted conformation of cyclohexane ring. The hydroxy and methyl substituents have axial orientation in molecules A and B, and equatorial in molecule C (corresponding torsion angles: C2–C1–C6–O2 86.7(2)° (A), 87.3(2)° (B), 170.16(19)° (C) and C1–C2–C3–C7 83.2(3)° (A), 78.0(3)° (B), 163.9(2)° (C)). The isopropyl substituent and methylene group of cyclopropane ring have equatorial orientation in molecules A and B, and axial in C (C2-C1-C6-C8–154.5(2)° (A), −158.2(2)° (B), −72.7(3)° (C); C6–C1–C2–C12 179.6(2)° (A), −175.86(19)° (B), 104.6(2)° (C)). The molecules A, B and C form hydrogen-bonded trimers (Fig. 7d, O2a–H···O2b: H···O 1.99 *E*, O–H···O 171°; O2b–H···O1c: H···O 2.07 *E*, O–H···O 147°; O2c–H···O1a: H···O 2.17 *E*, O–H···O 169°). Most probably, intermolecular hydrogen bonds are the driving force for conformational isomerism observed in the crystal of **2a1**.

The molecules **2a2** and **2a3** have the same absolute configuration of the cyclohexane ring atoms and differ only by configuration of the C11 atom (Fig. 8). However, these two molecules also show inverted conformation of the cyclohexane ring like molecule C in the crystal **2a1**. In the molecule **2a2** hydroxy, methyl substituents and methylene group of the cyclopropane ring have equatorial conformation, isopropyl substituent have axial conformation, and *vice versa* in **2a3** (corresponding torsion angles: C2–C1–C6–O2 162.3(3)° (**2a2**), 71.3(2)° (**2a3**); C1–C2–C3–C7 167.4(3)° (**2a2**), 76.5(2)° (**2a3**); C6–C1–C2–C12 176.1(3)° (**2a2**), −97.7(2)° (**2a3**); C2-C1-C6-C8–78.3(4)° (**2a2**), −170.27(18)° (**2a3**)). In crystal molecules **2a3** linked into zig-zag chains along (1 0 0) crystallographic direction by intermolecular hydrogen bonds O2–H···O1^{i} [i: $-S+x$, $S-y$, $-z$] (H···O 2.03 *E*, O–H···O 173°). In **2a2** hydroxy group is involved into weak intermolecular hydrogen O2–H···O1 (H···O 2.16 *E*, O–H···O 116°), thus no intermolecular hydrogen bonds are formed in this crystal.

The *trans*-orientation of the biphenyl group with respect to the carbonyl as could be seen both in Figs. 7a and 8a, but the biphenyl group is in the *cis*-disposition relatively to methyl substituent in

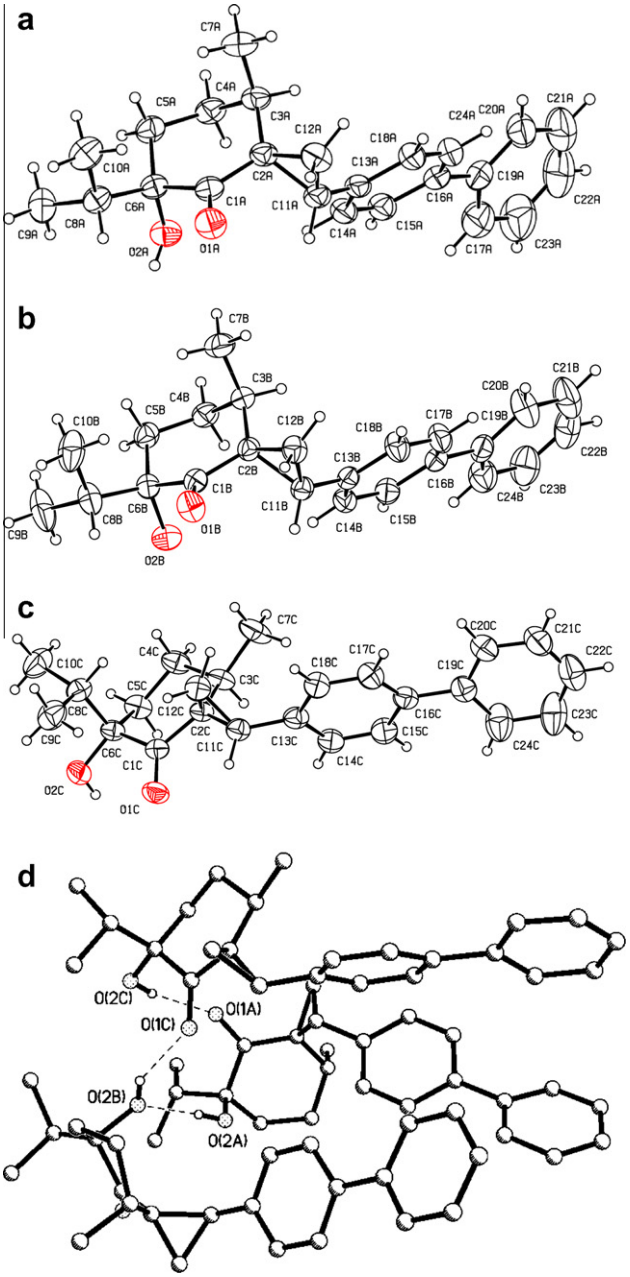

Fig. 7. Molecular structure of three symmetry unique molecules of **2a1** according to X-ray diffraction study (a–c), with thermal ellipsoids at 30% probability level, and asymmetric part of the unit cell showing hydrogen-bonded trimer (d).

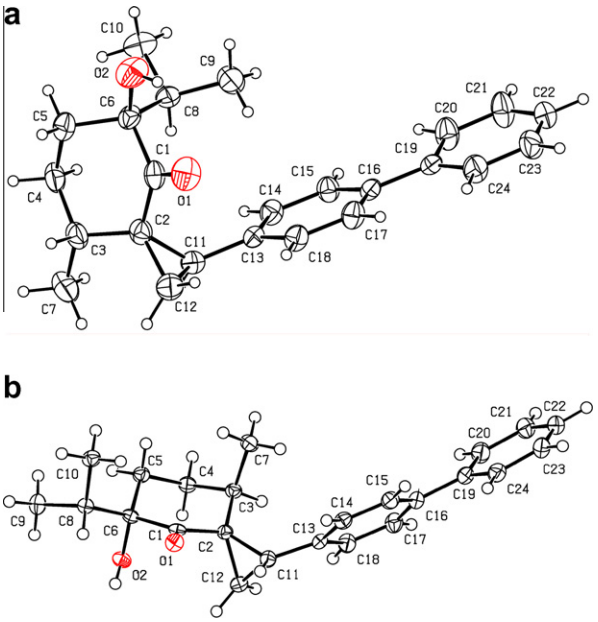

Fig. 8. Molecular structures for compounds **2a2** (a) and **2a3** (b) according to X-ray diffraction study. Thermal ellipsoids are shown at 30% for **2a2** and 50% for **2a3** probability levels.

the cyclohexanone ring. Thus, **2a2** is the *trans–cis* isomer with respect to carbonyl and methyl groups in the cyclohexanone ring correspondingly. The torsion angles determined show the molecular conformation in crystal of isomer **2a3** is *chair* with an equatorial methyl and hydroxyl groups and axial isopropyl one. Like to NMR analysis, this fact confirms that compound **2a3** is the *cis–cis* isomer and it was formed as the result of rotation in intermediate betaine in the previous cyclopropanation reaction, with following hydroxylation.

3.1.3. The peculiarities and mechanism of oxidative hydroxylation reaction

The hydroxylation of compounds **1a–e** obtained previously was carried in much the same way as the cyclopropanation reaction, by mixing an enolizable ketone in DMSO or DMF with powdered sodium hydroxide at room temperature till initial reagents disappear (control with TLC). However for the hydroxylation reaction access of oxygen is necessary whereas in the cyclopropanation reaction by Corey–Chaykovsky oxygen does not take part. Also the cyclopropanation of **1a–e** proceeds noticeably faster than hydroxylation (20 min – 1 h for the first and 6–48 h for the last).

The hydroxylation of **1a** and **1c–e** both in DMF and DMSO gave the only hydroxy ketones **2**, but when hydroxylation of **1b** was carried in DMF we separate from reaction mixture two products, hydroxy ketone **2b** and other product, **2′b**, different in melt points (correspondingly 135–137 °C and 158–160 °C).

Peaks corresponding to hydroxyl removal (*m*/*z* 333/335) and maximal peak was with *m*/*z* 307/309 (isopropyl removal for hydrated **2b**) were detected in mass spectrum of **2′b**. The signal at 5.21 ppm (hydroxyl) was observed in ^{1}H NMR spectrum of **2b** (in DMSO-d6) but it was absent in ^{1}H NMR spectrum of product **2′b**. However the signal at 11.18 ppm was observed for **2′b** that corresponds to published values of chemical shift for hydroperoxy group (near 10.3 ppm) [34,35]. It should be noted that we have found few solved NMR data of hydroperoxides in literature, especially about chemical shift of hydrogen in hydroperoxy group.

Electron-withdrawing carbonyl group in α-position to HOO group makes a significant low field shift in our case. This fact agrees with weak field shift of C-5 signal in ^{13}C NMR from 78.519 ppm for **2b** to 88.011 ppm for **2′b**. Maximal peak in MS for **2′b** corresponding to removal of hydroperoxide (*m*/*z* 333/335). The hydroperoxide formation unambiguously confirms that the hydroxylation of enolates of **1a–e** proceeds with dioxygen by the way of intermediate hydroperoxide formation and its subsequent decomposition to tertiary hydroxy ketones. In other cases peaks corresponding for hydroperoxides were detected by HPLC but we could not separate relevant substances over their instability at room temperature. The only enantiomerically pure tertiary hydroxy ketones **2a1** and **2c–e** were obtained. Probably, hydroperoxide **2′b** could be regarded as homochiral (enantiomerically pure) since it transforms to enantiomerically pure hydroxy ketone without additional chiral reagents. The only stereoisomer of this

compound was detected in ^{1}H NMR spectra and by HPLC. Corresponding peaks for other analogs **2′**were detected by HPLC in reaction mixtures, but we could not separate relevant substances because of their instability at room temperature. So, hydroxylation runs stereospecifically as the result of dioxygen axial attack on the corresponding enolate with following decomposition of intermediate hydroperoxide. This action does not affect the C-5 configuration. We can conclude that

- the ratio of stereoisomeric hydroxy ketones in the Corey–Chaykovsky reaction for 2-arylideneisomenthones with dimethyloxosulfonium methylide in DMSO (DMF)/NaOH system corresponds to the ratio of stereoisomeric spirooctanones.

We also quantify hydroperoxides in reaction mixtures of hydroxylation like to [36] and found approximately 10% of hydroperoxides when conversion of initial spiro compounds **1** was 75–85 % as the proof of proposed mechanism of hydroxylation.

- We have not found any traces of dimethylsulphide in reaction mixtures with GC–MS, so DMSO was not oxidizing agent in hydroxylation process.

Apparently, this oxidation of spiroketones **1** is similar to ketones and esters auto oxidation with dioxygen in a strong base media [37] that gives the formation of α-hydroperoxy, followed by α-hydroxy compounds formation. It should be noted that we obtain nonenolisable α-hydroxy ketones **2** with quite good yield although α-hydroxy ketones may be unstable due to various isomerization and disproportion processes, for example, formation of enols or hemiacetals followed by reactions of these products.

3.1.4. The reduction of hydroxy ketones with sodium borohydride

We also studied **2a–e** compounds reduction with sodium borohydride in isopropanol. The result of such reduction was exclusively formation of *trans*-(4*R*,5*S*)-dioles **3a–e** (Fig. 9).

Such conclusion has been made from NMR analysis. In ^{1}H NMR spectra of **3a–e** in DMSO-d6 signals of two hydroxyl groups were observed and an additional proton singlet was near 2.8 ppm (C-4). NOE measurements demonstrated strong coupling for protons at C-4 and C-1 (near 24%). Molecular modeling (MOPAC, PM6 [32]) showed that such effect is possible only for *trans*-4,5-dioles with equatorial proton orientation at C-4. *Cis*-4,5-diole conformer with inverted cyclohexane cycle, with axial isopropyl group and equatorial methyl at C-8, may be considered as alternative. However results of calculations favors the *trans* conformer by 4.5 kcal/mol. In *cis*-conformer in the most favorable conformation axial proton at C-9 would be the closest to H-4 (2.5 Å) but in experimental NOE spectra such interactions were absent.

Because of the reaction direction for reduction with borohydride is determined with orienting influence of axial hydroxyl at C-5 that provide an intramolecular delivery of the hydride ion to carbonyl group, the (4*R*,5*S*)-dioles **3a–e** formation in the reduction of **2a1–e** verifies their configuration at C-5.

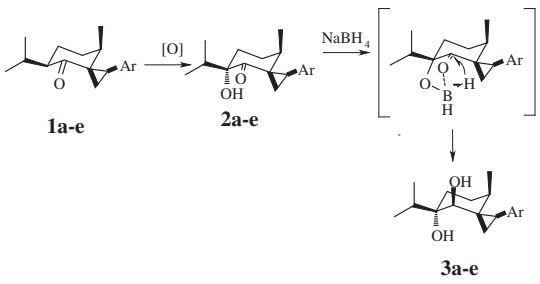

Fig. 9. Stereoselective formation of *trans*-4(*R*),5(*S*)-dioles **3a–e.**

The similar orienting axial hydroxyl effect was observed in the reduction of tertiary α-hydroxycyclohexanones [38,39] and β-hydroxycarbonyl compounds [40].

4. Conclusions

We have found

- stereoselective oxidative alpha hydroxylation of (1*R*,5*R*,8*R*,3*R*)-1-aryl-5-isopropyl-8-methyl-3-*spiro*-[2,5]octan-4-ones in DMSO/NaOH (or DMF/NaOH) system to (*1R,5S,8R,3R*)-1-aryl-5-isopropyl-5-hydroxy-8-methyl-3-spiro[2.5]octan-4-ones. We have isolated three stereoisomeric hydroxyketones from a reaction mixture of cyclopropanation reaction. But when reaction of oxidation was carried out with isolated *spiro*-[2,5]octan-4-ones, it was stereoselective. We have separated the intermediate hydroperoxide that is argument of reaction mechanism as oxygen addition in α-position.
- The reaction has been studied runs at room temperature and does not need in expensive catalysts. We confirmed that
- α-hydroxylated cyclohexanones with axial OH group in the reaction of reduction with $NaBH_4$ stereoselectively produce *trans*-(4*R*,5*S*)-dioles similarly to known processes [37,38]. Thereby spirocycle even with bulky spatial substitute do not affect stereochemistry of reduction with $NaBH_4$.

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