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EFFECT OF SUBSTITUENTS IN THE CUMULENE AND ARYL FRAGMENTS OF AROYLKETENES ON THE STEREOSELECTIVITY OF DIELS-ALDER HETEROREACTION WITH MONO-, BI-, AND POLYCYCLIC TERPENOIDS CONTAINING A CARBONYL GROUP

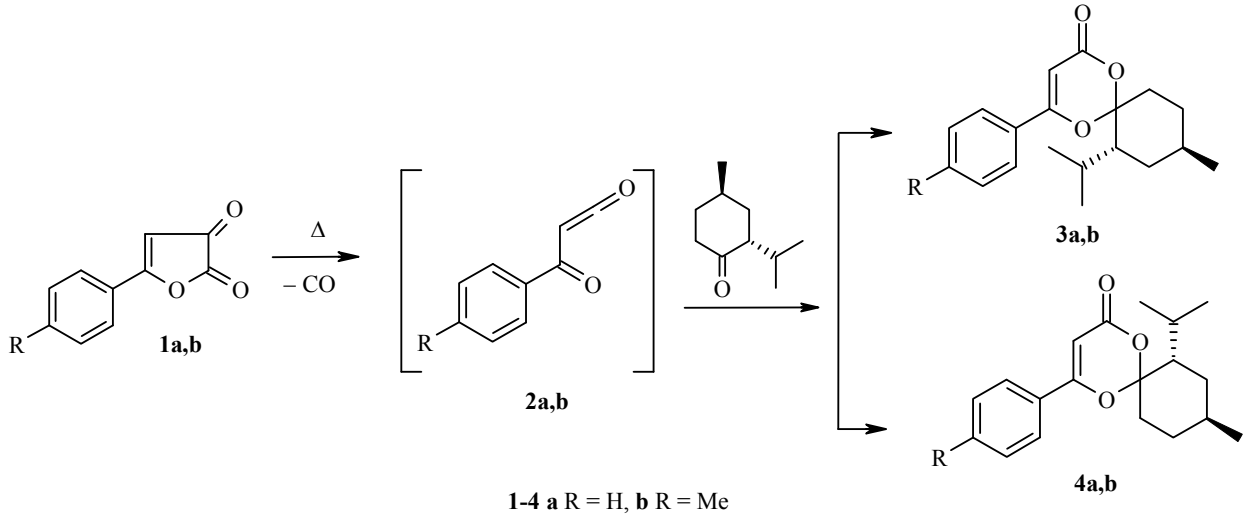
D. D. Nekrasov[1]*, A. S. Obukhova[1], N. Yu. Lisovenko[1], and A. E. Roubtsov[1]

Stereoisomeric adducts, substituted (R)-, (S)-spiro[6-aryldioxin-4-ones] have been obtained by thermolysis of 5-arylfuran-2,3-diones in the presence of menthone and allobetulone.

Keywords: aroylketenes, (*R*)-, (*S*)-spiro-1,3-dioxin-4-ones, terpenoids, (4+2) cycloaddition.

Substituted furan-2,3-diones react with aldehydes and ketones with the formation of substituted 6-aryl-1,3-dioxin-4-ones [1,2], displaying biological activity [3]. Continuing these studies we have investigated the effect of substituents in furandiones on the course of the reaction with optically active *l*-menthone, camphor, and allobetulone.

As a result of the interaction of 5-arylfuran-2,3-diones **1a,b** with menthone we obtained a mixture of approximately equal quantities of the stereoisomeric adducts spiro[(6-aryl-3,4-dihydro-2H-1,3-dioxin)-2,2'-(1-isopropyl-4-methylcyclohexan)]-4-ones **3a,b** and **4a,b**. According to data of ^{1}H NMR spectroscopy, compounds **3** and **4** exist as a mixture of diastereoisomers with (*R*)- and (*S*)-configurations of the spiro carbon atom.



1-4 a R = H, **b** R = Me

* To whom correspondence should be addressed, e-mail: kpibas@psu.ru.
[1]Perm State University, Perm 614990, Russia.

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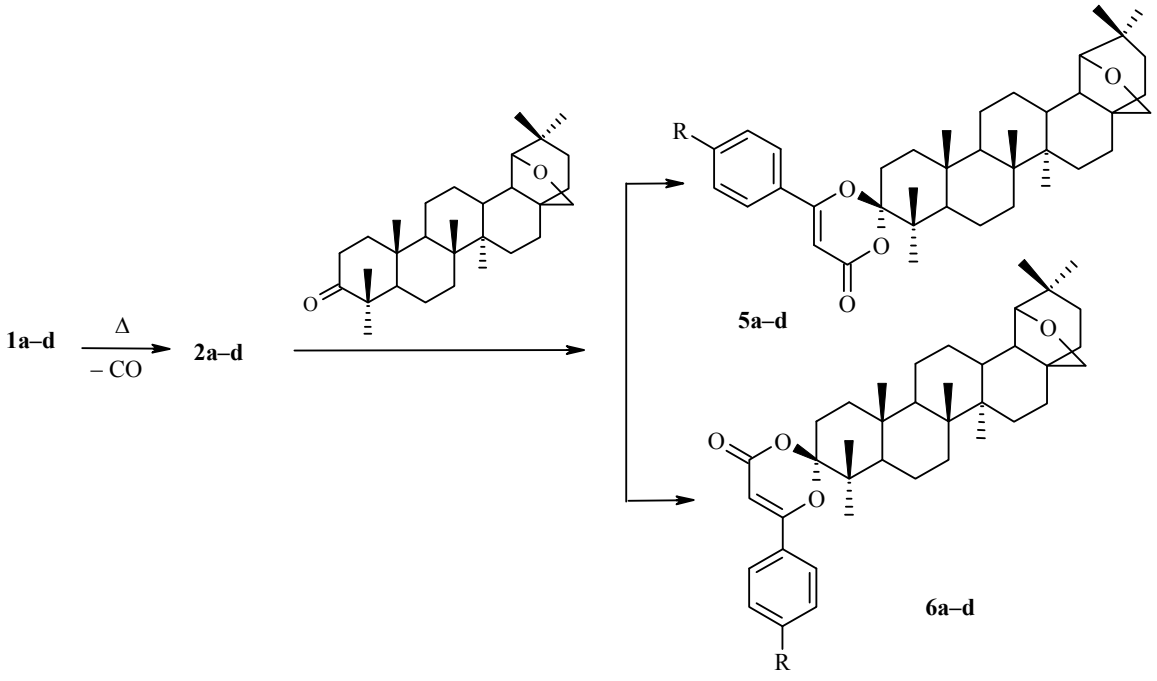
Analogous dioxinones were obtained previously in the example of formylketene and menthone, however the presence of stereoisomers was not reported [4].

The formation of compounds **3a,b** and **4a,b** occurs as a result of the thermal generation of aroylketenes **2a,b** from arylfurandiones **1a,b** and their subsequent [4+2] cycloaddition at the C=O bond of *l*-menthone. Since the planar fragment including the menthone carbonyl group may be attacked by the aroylketene from both sides, the formation of cycloadducts **3a,b** and **4a,b** with (*R*)- and (*S*)-configurations of the spiro carbon atom is possible.

In order to explain the possibility of forming cycloadducts **3a,b** and **4a,b** with (*R*)- and (*S*)-configurations at the spiro carbon atom modeling was carried out of the interaction of benzoylketene with menthone by the SSP MO LCAO semiempirical method in the MNDO-PM3 approximation [5]. Calculations were in good agreement with the obtained experimental data.

On thermolysis of 4-unsubstituted 5-arylfuran-2,3-diones **1a-d** in the presence of allobetulone the reaction proceeded to a different ratio of stereoisomers **5** and **6**.

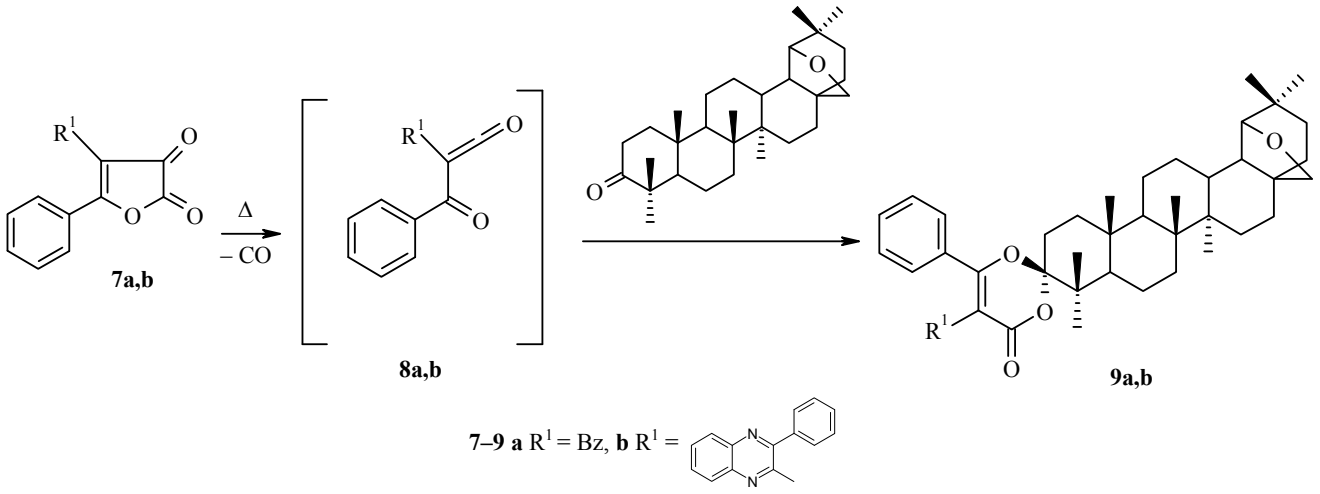


1, **2**, **5**, **6 a** R=H, **b** R = Me, **c** R = Cl, **d** R = Br

The ratio of compounds **5** and **6** in the reaction mixture were **5a**:**6a** = 50:50; **5b**:**6b** = 22:78; **5c**:**6c** = 14:86; **5d**:**6d** = 18:82%. The ratios of isomers in the reaction mixture were determined from the integral intensities of the H-4 proton singlet of the dioxinone ring in the ^{1}H NMR spectra.

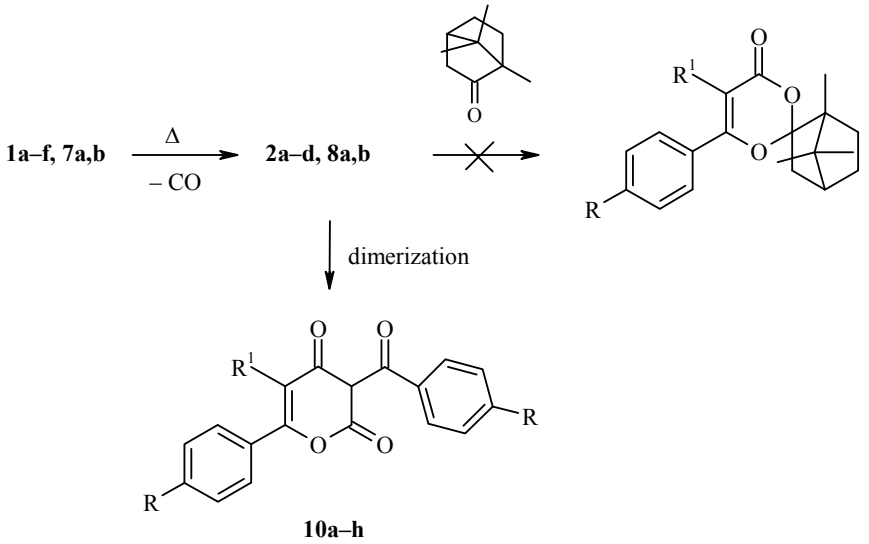
Probably the substituents in the *para* position of the benzene ring of furandiones **1** have an effect on the ratio of isomers. This is confirmed by the fact that in the case of the interaction of 5-(*p*-alkoxyphenyl)furan-2,3-diones **1e,f** with allobetulone only the products of dimerization of the aroylketenes, substituted pyrandiones **10e,f** and unreacted allobetulone, were isolated from the reaction mixture. The electron-donating effect of the alkoxy groups in these aroylketenes aids their stabilization with predominance of the dimerization reaction and the formation of pyranone derivatives **10e,f** characterized previously in [1].

The presence of the bulky benzoyl or 3-phenylquinoxalin-2-yl substituents in position 4 of 5-arylfuran-2,3-diones **7a,b** displaces the direction of the reaction to the side of forming only the (*S*)-isomer of **9a,b**. Assignment of the spiro atom to the (*S*)-configuration was made by comparing the physicochemical properties and spectral data of compounds **9a,b** with compounds **5a,b** and **6a,b**, the configuration of which was established previously by X-ray structural analysis [6].



The formation of dioxinones **9a,b** occurs as a result of thermolysis of furandiones **7a,b** and the generation of aroylketenes **8a,b**, which under the reaction conditions undergo a [4+2] cyclocondensation at the C=O bond of allobetulone.

Unlike menthone and allobetulone camphor does not react under these conditions, probably linked with steric difficulties created by the three methyl groups in the reactant. In the course of the reaction only dimers **10a-h** were isolated, the physicochemical characteristics of which also coincided with those of samples obtained previously [1].



1, **2**, **10 a** R = H, **b** R = Me, **c** R = Cl, **d** R = Br, **e** R = MeO, **f** R = EtO, R^1 = H; **10g**,**h** R = H;

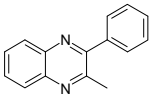
7a, **8a**, **10g**, R^1 = Bz; **7b**, **8b**, **10 h**, R^1 = 

TABLE 1. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)
	C=O	C=C	
3a, **4a**	1720	1610	7.36-7.68 (5H, m, C_6H_5); 5.83 (1H, s, =CH); 5.77 (1H, s, =CH); 0.79-2.70 (18H, set of signals of aliphatic protons)
3b, **4b**	1710	1605	7.35-7.91 (4H, 2d, *J* = 8.4, Ar); 5.78 (1H, s, =CH); 5.72 (1H, s, =CH); 2.35 (3H, s, CH_3); 0.79-2.69 (18H, set of signals of aliphatic protons)
5a	1725	1615	7.45-7.81 (5H, m, C_6H_5); 5.81 (1H, s, =CH-); 3.72 (1H, d, *J* = 7.8, H-28); 3.46 (1H, s, H-19); 3.39 (1H, d, *J* = 8.1, H-28); 2.48 (1H, m, H-2); 2.43 (1H, m, H-2); 1.90 (2H, td, *J* = 14.4, *J* = 4.4, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
5b	1724	1616	7.18, 7.50 (4H, 2d, *J* = 7.5, Ar); 5.82 (1H, s, =CH-); 3.72 (1H, d, *J* = 7.5, H-28); 3.46 (1H, s, H-19); 3.39 (1H, d, *J* = 7.5, H-28); 2.48 (1H, m, H-2); 2.43 (1H, m, H-2); 2.20 (3H, s, CH_3); 1.90 (2H, td, *J* = 14.8, *J* = 3.0, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
5c	1726	1616	7.41, 7.60 (4H, 2d, *J* = 8.7, Ar); 5.77 (1H, s, =CH-); 3.90 (1H, d, *J* = 7.2, H-28); 3.46 (1H, s, H-19); 3.38 (1H, d, *J* = 7.2, H-28); 2.48 (1H, m, H-2); 2.43 (1H, m, H-2); 2.20 (3H, s, CH_3); 1.89 (2H, td, *J* = 14.4, *J* = 3.8, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons).
5d	1725	1615	7.35, 7.60 (4H, 2d, *J* = 8.4, Ar); 5.86 (1H, s, =CH-); 3.72 (1H, d, *J* = 7.3, H-28); 3.42 (1H, s, H-19); 3.36 (1H, d, *J* = 7.4, H-28); 2.48 (1H, m, H-2); 2.42 (1H, m, H-2); 1.90 (2H, td, *J* = 11.5, *J* = 3.1, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
6a	1715	1615	7.45-7.64 (5H, m, C_6H_5); 5.78 (1H, s, =CH-); 3.71 (1H, d, *J* = 7.8, H-28); 3.71 (1H, s, H-19); 3.38 (1H, d, *J* = 7.8, H-28); 2.48 (1H, m, H-2); 2.44 (1H, m, H-2); 1.84 (2H, td, *J* = 14.1, *J* = 3.6, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
6b	1716	1618	7.18, 7.50 (4H, 2d, *J* = 7.8, Ar); 5.76 (1H, s, =CH-); 3.71 (1H, d, *J* = 8.1, H-28); 3.71 (1H, s, H-19); 3.38 (1H, d, *J* = 5.7, H-28); 2.48 (1H, m, H-2); 2.44 (1H, m, H-2); 2.20 (3H, s, CH_3); 1.84 (2H, td, *J* = 10.5, *J* = 3.0, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
6c	1714	1619	7.41, 7.60 (4H, 2d, *J* = 8.7, Ar); 5.79 (1H, s, =CH-); 3.71 (1H, d, *J* = 7.5, H-28); 3.70 (1H, s, H-19); 3.38 (1H, d, *J* = 7.5, H-28); 2.48 (1H, m, H-2); 2.44 (1H, m, H-2); 2.20 (3H, s, CH_3); 1.84 (2H, td, *J* = 14.4, *J* = 3.9, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
6d	1715	1615	7.35, 7.60 (4H, 2d, *J* = 8.5, Ar); 5.78 (1H, s, =CH-); 3.72 (1H, d, *J* = 7.4, H-28); 3.71 (1H, s, H-19); 3.38 (1H, d, *J* = 7.4, H-28); 2.49 (1H, m, H-2); 2.40 (1H, m, H-2); 1.84 (2H, td, *J* = 11.5, *J* = 3.1, H-1); 0.74-1.80 (41H, set of signals of aliphatic protons)
9a	1710	1620	7.45-7.66 (10H, m, C_6H_5); 3.74 (1H, d, *J* = 8.1, H-28); 3.47 (1H, s, H-19); 3.40 (1H, d, *J* = 8.2, H-28); 2.60 (1H, m, H-2); 2.40 (1H, m, H-2); 1.90 (2H, td, *J* = 14.8, *J* = 4.0, H-1); 0.75-1.80 (41H, set of signals of aliphatic protons)
9b	1720	1620	7.30-8.80 (14H, m, Ar); 3.70 (1H, d, *J* = 7.2, H-28); 3.40 (1H, s, H-19); 3.60 (1H, d, *J* = 8.5, H-28); 2.50 (1H, t, *J* = 8.5, H-2); 2.40 (1H, m, H-2); 1.75 (2H, td, *J* = 14.6, *J* = 3.8, H-1); 0.75-1.73 (41H, set of signals of aliphatic protons)

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in nujol. The ^{1}H NMR spectra were recorded on a Mercury Plus 300 instrument (300 MHz) in $CDCl_3$, internal standard was HMDS (δ 0.05 ppm). Angles of rotation were determined on a Perkin-Elmer 341 polarimeter (*concn.* = 1, $CHCl_3$).

TABLE 2. Physicochemical Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Angle of rotation*[2], $[\alpha]_D^{22}$	Yield, %
		C	H	Hal (N)			
3a,4a	$C_{19}H_{24}O_3$	75.99 / 75.97	8.04 / 8.05		Oil		55
3b, 4b	$C_{20}H_{26}O_3$	76.35 / 76.40	8.30 / 8.33		Oil		60
5a	$C_{39}H_{54}O_4$	79.85 / 79.82	9.26 / 9.27		152-153	52.2	45
5b	$C_{40}H_{56}O_4$	79.97 / 79.96	9.38 / 9.39		163-165	79.8	16
5c	$C_{39}H_{53}ClO_4$	75.40 / 75.39	8.61 / 8.60	5.70 / 5.71	152-154	16.7	10
5d	$C_{39}H_{53}BrO_4$	70.35 / 70.36	8.03 / 8.02	12.00 / 12.00	162-163	17.5	12
6a	$C_{39}H_{54}O_4$	79.81 / 79.82	9.28 / 9.27		201-202	17.5	45
6b	$C_{40}H_{56}O_4$	79.97 / 79.96	9.39 / 9.39		210-212	17.8	66
6c	$C_{39}H_{53}ClO_4$	75.40 / 75.39	8.61 / 8.60	5.70 / 5.71	212-214	56.1	70
6d	$C_{39}H_{53}BrO_4$	70.35 / 70.36	8.01 / 8.02	12.01 / 12.00	209-210	52.2	69
9a	$C_{46}H_{58}O_5$	79.97 / 79.96	8.47 / 8.46		215-217	85.13	53
9b	$C_{53}H_{62}N_2O_4$	80.45 / 80.47	7.91 / 7.90	(3.55) / (3.54)	166-168	82.7	51

* Solvents: hexane (compounds **5a-d, 6a-d**, and **9a**) and ethyl acetate (compound **9b**).

*[2] For compounds **5d** and **6d** the angle of rotation was measured at 18°C; for compound **9b** at 24°C.

Spiro[(6-phenyl-3,4-dihydro-2H-1,3-dioxin)-2,2'-(1-isopropyl-4-methylcyclohexan)]-4-ones (3a, 4a). A solution of compound **1a** (0.01mol) and menthone (0.01 mol) in anhydrous toluene (20 ml) was boiled for 1 h. The solvent was removed and an oily mixture of diastereoisomers was obtained.

Spiro[(6-*p*-tolyl-3,4-dihydro-2H-1,3-dioxin)-2,2'-(1-isopropyl-4-methylcyclohexan)]-4-ones (3b, 4b) were synthesized analogously from compound **1b** and menthone.

Spiro[(6-phenyl-3,4-dihydro-2H-1,3-dioxin)-(2*S*)-3'-(19',28'-oxidooleanan)]-4-one (5a) and Spiro-[(6-phenyl-3,4-dihydro-2H-1,3-dioxin)-(2*R*)-3'-(19',28'-oxidooleanan)]-4-one (6a). A solution of compound **1a** (0.01 mol) and allobetulone (0.01 mol) in anhydrous benzene was boiled for 5 h. The solvent was removed, and the oily residue was chromatographed on a column of silica gel (L 100/250) in ethyl acetate–hexane, 1:5. The obtained compounds **5a** and **6a** were recrystallized from hexane.

Spiro[(6-*p*-tolyl-3,4-dihydro-2H-1,3-dioxin)-(2*S*)-3'-(19',28'-oxidooleanan)]-4-one (5b) and Spiro-[(6-*p*-tolyl-3,4-dihydro-2H-1,3-dioxin)-(2*R*)-3'-(19',28'-oxido-oleanan)]-4-one (6b) were synthesized analogously from compound **1b** and allobetulone.

Spiro[(6-(4-chlorophenyl)-3,4-dihydro-2H-1,3-dioxin)-(2*S*)-3'-(19',28'-oxidooleanan)]-4-one (5c) and Spiro[(6-(4-chlorophenyl)-3,4-dihydro-2H-1,3-dioxin)-(2*R*)-3'-(19',28'-oxidooleanan)]-4-one (6c) were synthesized analogously from compound **1c** and allobetulone.

Spiro[(6-(4-bromophenyl)-3,4-dihydro-2H-1,3-dioxin)-(2*S*)-3'-(19',28'-oxidooleanan)]-4-one (5d) and Spiro[(6-(4-bromophenyl)-3,4-dihydro-2H-1,3-dioxin)-(2*R*)-3'-(19',28'-oxidooleanan)]-4-one (6d) were synthesized analogously from compound **1d** and allobetulone.

Spiro[5-benzoyl-6-phenyl-3,4-dihydro-2H-1,3-dioxin]-(2*S*)-3'-(19',28'-oxidooleanan)]-4-one (9a). A solution of compound **7a** (0.01 mol) and allobetulone (0.01 mol) in anhydrous *p*-xylene (20 ml) was boiled for 1 h. The solvent was removed and the residue recrystallized from hexane.

Spiro[6-phenyl-5-(3-phenylquinoxalin-2-yl)-3,4-dihydro-2H-1,3-dioxin]-(2*S*)-3'-(19',28'-oxidooleanan)]- 4-one (9b) was synthesized analogously from compound **7b** and allobetulone. The residue was recrystallized from ethyl acetate.

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