Synthesis of new (+)-usnic acid derivatives with the flavone structure

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Reactions of a chalcone derivative (synthesized earlier from usnic acid) with various oxidants (hydrogen peroxide, *tert*-butyl hydroperoxide, and dichlorodicyanobenzoquinone) gave new flavonols, dihydroflavonols, and flavones. Treatment of the starting chalcone with a nucleophilic reagent ($NH_2NH_2 \cdot H_2O$) afforded a dihydropyrazole-containing derivative.

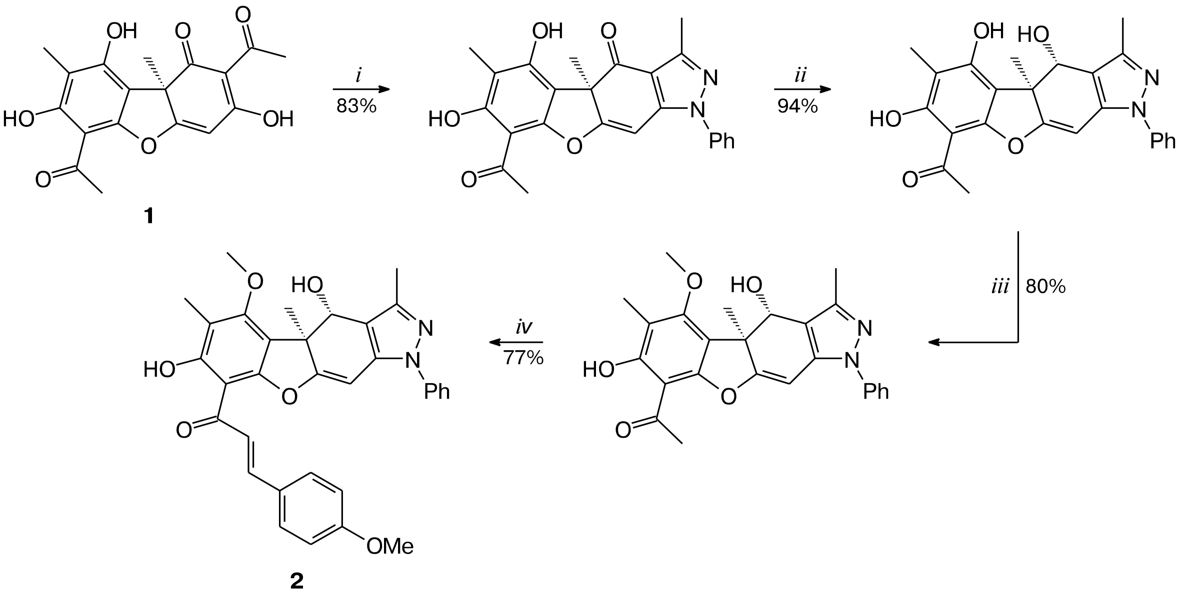
Key words: (+)-usnic acid, chalcones, flavonoids.

A constantly growing interest in natural and synthetic flavonoids (chalcones, flavones, and aurones) is largely due to their antioxidant activity and the associated tendency of metabolites of this class to prevent or inhibit tumor formation, strengthen blood vessels, and protect liver and the gastrointestinal tract.[1] Particular attention in relevant investigations is given to a structure—activity relationship. In connection with this, it seems to be promising to make a flavonoid structure biologically active *via* introduction of a fragment possessing native activity. Usnic acid (**1**), a unique and accessible plant metabolite, can serve as an appropriate synthon because of its high optical purity and various biological properties.[2] However, the polyvariant (and hence highly unpredictable) reactivity of usnic acid deters researchers from its extensive use in synthetic practice.

Earlier,[3] we have proposed a four-step procedure for the synthesis of chalcones from usnic acid (**1**) (Scheme 1).

This work was intended to study further transformations of the chalcones obtained earlier and develop meth-

Scheme 1



Reagents and conditions: *i*. $PhNHNH_2$, EtOH, reflux; *ii*. $NaBH_4$, THF, –20 °C; *iii*. CH_2N_2, $CHCl_3$, Et_2O; *iv*. 4-$MeOC_6H_4CHO$, KOH, MeOH, H_2O, 70 °C.

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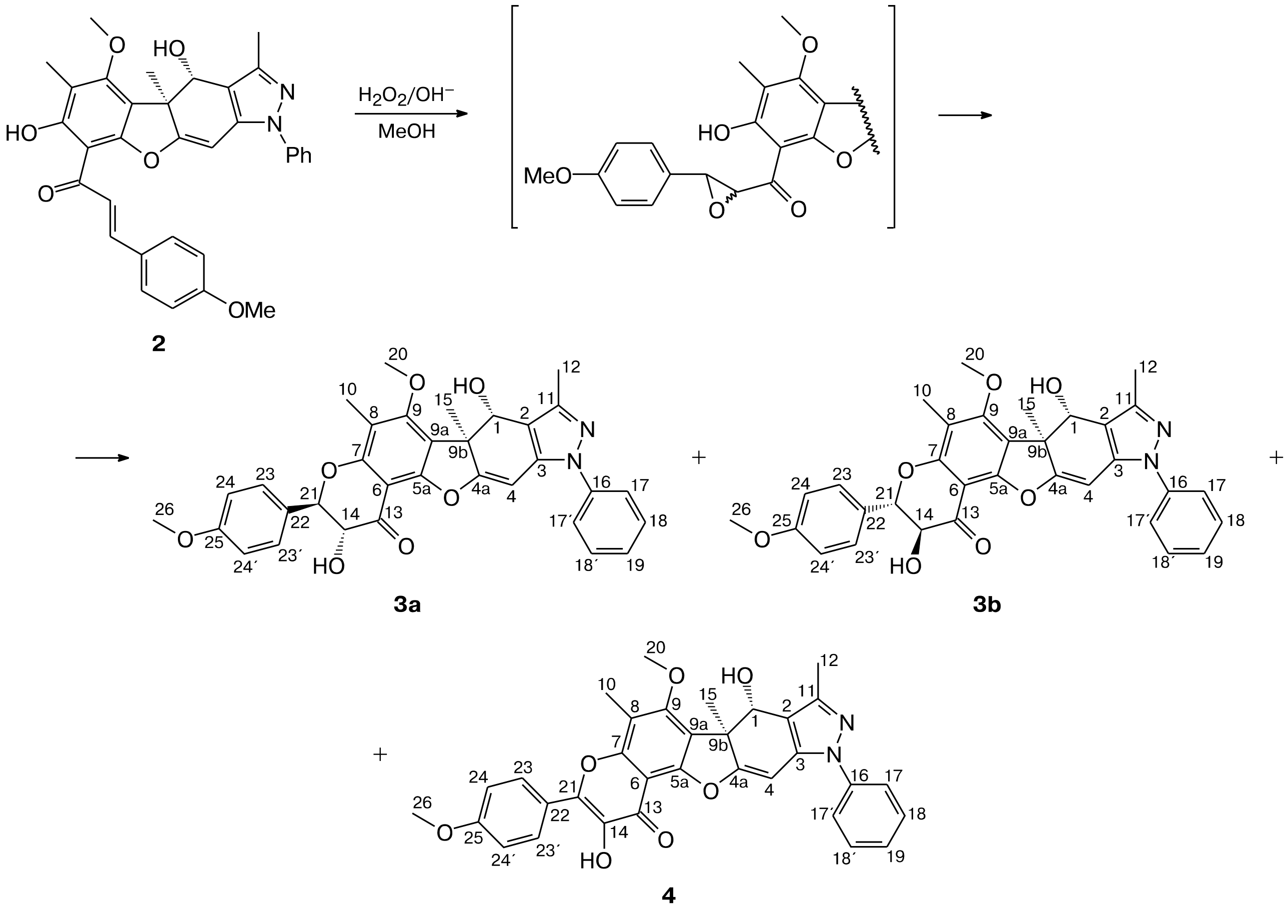
Scheme 2



ods for the synthesis of new flavonoids with the usnic acid core as the main structural element.

Treatment of chalcones with H_2O_2 in the presence of alkali results in epoxidation at the exocyclic double bond. Such epoxides derived from 2-hydroxychalcones are unstable and readily undergo intramolecular cyclization into dihydroflavonols. For instance, a reaction of compound **2** with H_2O_2 in methanol in the presence of aqueous alkali gave a mixture of compounds **3a**,**b** and **4** in a total yield of ~80%; the ratio of the products varies with the reaction conditions. Structurally, compounds **3a**,**b** and **4** are classified among dihydroflavonols and flavonols, respectively. Compound **3** was obtained as a 1 : 1 mixture of *trans*-diastereomers. The arrangement of the substituents was confirmed by ^{1}H NMR data. Flavonol **4** seems to be a product of further oxidation of compound **3** (Scheme 2).

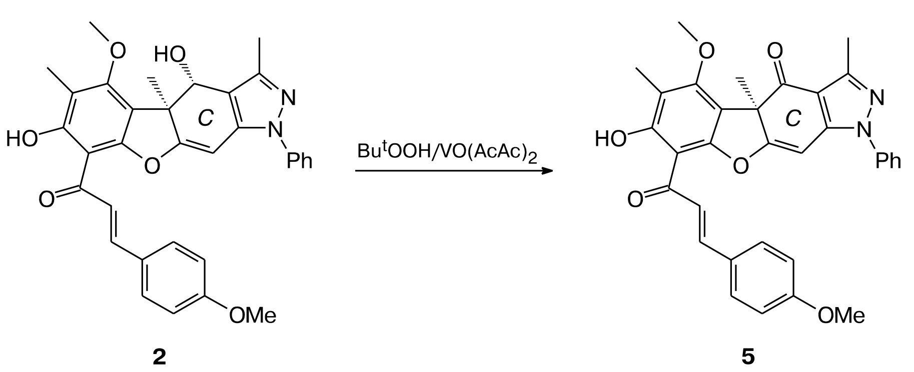
When treated with another epoxidating oxidant (Bu^tOOH), compound **2** yields no cyclization products. Instead, the hydroxy group in the ring ***C*** is oxidized only (Scheme 3). Product **5** was isolated by column chromatography in 67% yield.

Dichlorodicyanobenzoquinone (DDQ) employed for cyclodehydration of 2´-hydroxychalcones[4] also oxidizes the hydroxy group in the ring ***C*** of compound **2**. However, this is accompanied by intramolecular heterocyclization leading to flavone **6** (Scheme 4). We found that a reaction of chalcone **2** with DDQ under reflux for 10 h gives a 1 : 3 mixture of compounds **5** and **6** (^{1}H NMR data). More prolonged reflux (15 h) affords compound **6** in 75% yield.

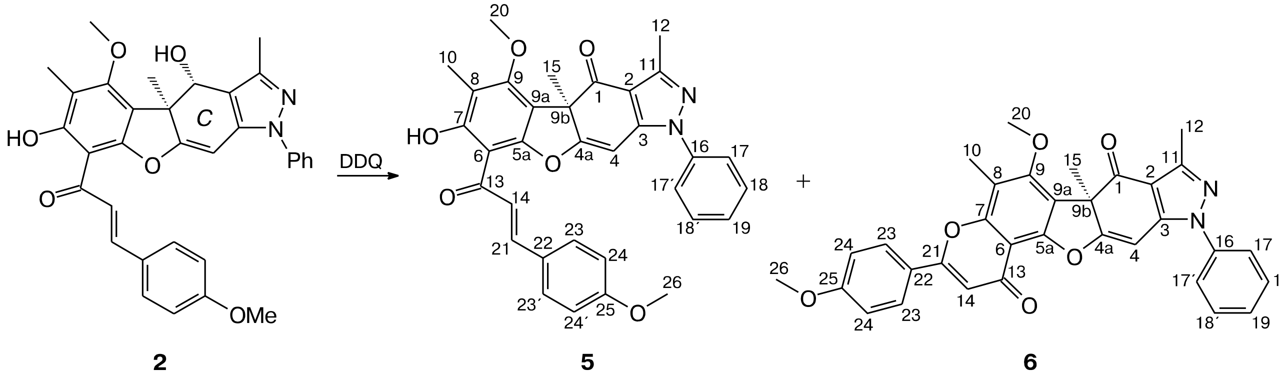
2-Hydroxychalcones are known to undergo intramolecular cyclization into flavanones in the presence of an acid[5] or ethylenediamine.[6] However, no flavanone products are formed from compound **2** under the reaction conditions studied.

A reaction of chalcone **2** with a nucleophilic reagent ($NH_2NH_2 \cdot H_2O$) affords a 1 : 1 mixture of isomeric dihydropyrazoles **7a**,**b** in a total yield of 82% (Scheme 5). The reaction occurs in boiling ethanol, and an equimolar amount of $NH_2NH_2 \cdot H_2O$ should be used. A decrease in the hydrazine amount results in a lower content of compounds **7a**,**b** in the reaction mixture. The structures of compounds **7a**,**b** were determined by NMR spectroscopy as well as by comparing the experimental chemical shifts

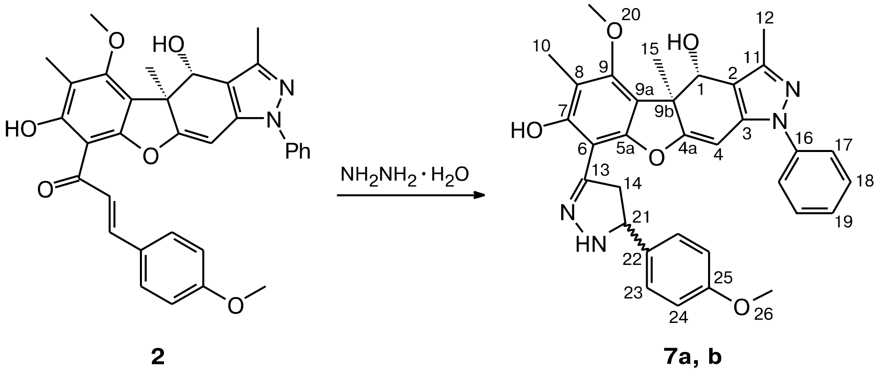
Scheme 3



Scheme 4



Scheme 5



of the signals for the dihydropyrazole ring with the literature data.[7,8] Note that phenylhydrazine is inert under these conditions.

To sum up, using methoxychalcone **2** derived from usnic acid as a starting material, we obtained flavonols, dihydroflavonols, and flavones. A reaction of compound **2** with hydrazine hydrate gives dihydropyrazole-containing products.

Experimental

Analytical and spectroscopic investigations were performed at the Chemistry Service Joint Center of the Siberian Branch of the Russian Academy of Sciences. NMR spectra were recorded on Bruker AV-400 (400.13 (^{1}H) and 100.61 MHz (^{13}C)), Bruker DRX-500 (500.13 (^{1}H) and 125.76 MHz (^{13}C)), and Bruker AV-600 spectrometers (600.3 (^{1}H) and 150.95 MHz (^{13}C)) in

$CDCl_3$ with the signals for chloroform (δ_H 7.24, δ_C 76.90) as the internal standards. The products obtained were identified and structurally characterized by NMR spectroscopy using 2D techniques (^1H—^1H COSY, ^{13}C—^1H COSY, COLOC, HMBC, and HSQC). The atomic numbering in the structural formulas of the compounds refers to signal assignments in the NMR spectra and may differ from the numbering implied by their IUPAC names. The signal multiplicity in the ^{13}C NMR spectra was determined using the JMOD mode. Mass spectra were recorded on a DFS Thermo Scientific high-resolution mass spectrometer (ionizing energy 70 eV). Melting points were measured on a Kofler hot stage.

(+)-Usnic acid (**1**) ($[\alpha]_D$ +478 (*c* 0.1, $CHCl_3$)) was isolated from a blend of lichens of the *Usnea* genus as described earlier.[9] For column chromatography, silica gel (60—200 μm, Merck) was used.

Compound **2** was prepared as described earlier.[3] The ^{13}C NMR spectra of compounds **3**—**7** are given in Table 1.

Reaction of compound 2 with hydrogen peroxide. A 33% solution of H_2O_2 (0.15 mL) and 6 *M* NaOH (0.025 mL) were added to a solution of compound **2** (220 mg, 0.4 mmol) in methanol (5 mL). The reaction mixture was stirred at 10—14 °C for 4 h until the substrate was consumed completely (monitoring by TLC). Then the mixture was warmed to ~20 °C, diluted with water, and neutralized with dilute HCl. The precipitate that formed was filtered off, dried in air, and chromatographed on silica gel. Gradient elution with CH_2Cl_2—ethanol (0→20%) gave a 1 : 1 : 1 mixture of compounds **3a,b** and **4** in a total yield of 60—65%. Compound **4** was isolated in the individual state (17% yield).

Compounds **3a,b** are *trans*-diastereomers about the C(14) and C(21) atoms. The signals in the NMR spectra were assigned using a diastereomerically enriched sample.

(2*S*,3*R*,15*R*,16*R*)-3,15-Dihydroxy-20-methoxy-16-(4-methoxyphenyl)-2,5,19-trimethyl-7-phenyl-11,17-dioxa-6,7-diazapentacyclo[10.8.0.$0^{2,10}$.$0^{4,8}$.$0^{13,18}$]icosa-1(12),4(8),5,9,13(18),19-hexaen-14-one (3a or 3b). ^1H NMR (500 MHz, $CDCl_3$), δ: 1.51 (s, 3 H, H(15)); 2.13 (s, 3 H, H(10)); 2.45 (d, 3 H, H(12), $J_{H(12),H(1)}$ = 0.3 Hz); 3.76 (ws, 1 H, OH(14)); 3.82 (d, 1 H, OH(1), $J_{OH,H(1)}$ = 1.6 Hz); 3.83 (s, 3 H, H(26)); 3.95 (s, 3 H, H(20)); 4.49 (d, 1 H, H(14), $J_{H(14),H(21)}$ = 12.2 Hz); 5.06 (d, 1 H, H(21), $J_{H(21),H(14)}$ = 12.2 Hz); 5.42 (dd, 1 H, H(1), $J_{H(1),OH}$ = = 1.6 Hz, $J_{H(1),H(12)}$ = 0.3 Hz); 6.99 (d, 2 H, H(24), $J_{H(24),H(23)}$ = = 8.8 Hz); 7.48 (d, 2 H, H(23), $J_{H(23),H(24)}$ = 8.8 Hz); 7.46—7.51 (m, 2 H, H(17)); 7.41—7.46 (m, 2 H, H(18)); 7.28—7.32 (m, 1 H, H(19)).

(2*S*,3*R*,15*S*,16*S*)-3,15-Dihydroxy-20-methoxy-16-(4-methoxyphenyl)-2,5,19-trimethyl-7-phenyl-11,17-dioxa-6,7-diaza-

Table 1. ^{13}C NMR spectra ($CDCl_3$) of compounds **3**—**7**[a]

Atom	δ						
	3a[a]	**3b**[a]	**4**[a]	**5**[a]	**6**[a]	**7a**[b]	**7b**[b]
1	74.43 (d)	74.38 (d)	74.38 (d)	192.73 (s)	192.32 (s)	74.65 (d)	74.66 (d)
2	112.08 (s)	112.12 (s)	111.81 (s)	111.28 (s)	110.97 (s)	112.22 (s)	112.27 (s)
3	136.37 (s)	136.41 (s)	136.50 (s)	145.48 (s)	145.94 (s)	136.75 (s)	136.76 (s)
4	91.15 (d)	91.95 (d)	91.24 (d)	88.69 (d)	89.57 (d)	89.21 (d)	89.23 (d)
4a	167.39 (s)	167.39 (s)	167.46 (s)	172.12 (s)	172.72 (s)	167.75 (s)	167.75 (s)
5a	156.61 (s)	156.61 (s)	156.39 (s)	156.02 (s)	153.81 (s)	154.57 (s)	154.59 (s)
6	102.85 (s)	102.55 (s)	105.75 (s)	104.22 (s)	108.10 (s)	99.37 (s)	99.37 (s)
7	154.61 (s)	154.66 (s)	154.71 (s)	164.64 (s)	155.95 (s)	157.88 (s)	157.88 (s)
8	113.09 (s)	113.10 (s)	113.22 (s)	115.21 (s)	115.79 (s)	111.85 (s)	111.85 (s)
9	160.14 (s)	160.47 (s)	157.50 (s)	162.14 (s)	159.83 (s)	154.97 (s)	154.97 (s)
9a	118.84 (s)	118.84 (s)	120.90 (s)	110.96 (s)	117.88 (s)	114.81 (s)	114.84 (s)
9b	52.16 (s)	52.08 (s)	52.65 (s)	61.05 (s)	61.08 (c)	52.69 (s)	52.70 (s)
10	9.53 (q)	9.72 (q)	9.79 (q)	9.45 (q)	9.94 (q)	9.48 (q)	9.48 (q)
11	147.47 (s)	147.75 (s)	147.17 (s)	150.69 (s)	150.68 (s)	147.71 (s)	147.74 (s)
12	12.81 (q)	12.80 (q)	12.82 (q)	12.94 (q)	13.01 (q)	12.78 (q)	12.78 (q)
13	191.28 (s)	191.25 (s)	171.10 (s)	190.99 (s)	176.60 (s)	151.26 (s)	151.34 (s)
14	73.11 (d)	73.23 (d)	137.39 (d)	122.45 (d)	106.39 (d)	41.12 (t)	41.12 (t)
15	18.07 (q)	17.97 (q)	18.18 (q)	27.73 (q)	29.96 (q)	18.20 (q)	18.25 (q)
16	139.12 (s)	139.13 (s)	139.14 (s)	138.31 (s)	138.21 (c)	139.22 (s)	139.23 (s)
17	122.80 (d)	122.81 (d)	122.76 (d)	123.68 (d)	123.49 (d)	122.86 (d)	122.92 (d)
18	129.11 (d)	129.11 (d)	129.11 (d)	129.45 (d)	129.38 (d)	129.02 (d)	129.02 (d)
19	126.84 (d)	126.84 (d)	126.82 (d)	128.00 (d)	128.05 (d)	126.65 (d)	126.69 (d)
20	61.96 (q)	61.85 (q)	62.46 (q)	62.38 (q)	63.06 (q)	61.69 (q)	61.69 (q)
21	83.14 (d)	83.12 (d)	144.42 (s)	145.06 (s)	162.39 (s)	62.08 (d)	62.20 (d)
22	128.20 (s)	128.16 (s)	123.33 (s)	127.50 (s)	123.75 (s)	133.96 (s)	134.08 (s)
23	128.65 (d)	128.68 (d)	129.11 (d)	130.52 (d)	127.75 (d)	127.35 (d)	127.38 (d)
24	114.01 (d)	114.02 (d)	114.13 (d)	114.37 (d)	114.51 (d)	114.11 (d)	114.11 (d)
25	160.22 (s)	160.22 (s)	161.02 (s)	161.79 (c)	162.41 (s)	159.23 (s)	159.23 (s)
26	55.22 (q)	55.22 (q)	55.30 (q)	55.30 (q)	55.42 (q)	55.17(q)	55.20 (q)

[a] The operating frequency is 125 MHz.

[b] The operating frequency is 150 MHz.

pentacyclo[10.8.0.0^{2,10}.0^{4,8}.0^{13,18}]icosa-1(12),4(8),5,9,13(18),19-hexaen-14-one (3a or 3b). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.49 (s, 3 H, H(15)); 2.13 (s, 3 H, H(10)); 2.45 (d, 3 H, H(12), $J_{H(12),H(1)}$ = 0.3 Hz); 3.76 (ws, 1 H, OH(14)); 3.82 (d, 1 H, OH(1), $J_{OH,H(1)}$ = 1.6 Hz); 3.83 (s, 3 H, H(26)); 3.96 (s, 3 H, H(20)); 4.50 (d, 1 H, H(14), $J_{H(14),H(21)}$ = 12.2 Hz); 5.03 (d, 1 H, H(21), $J_{H(21),H(14)}$ = 12.2 Hz); 5.43 (dd, 1 H, H(1), $J_{H(1),OH}$ = = 1.6 Hz, $J_{H(1),H(12)}$ = 0.3 Hz); 6.99 (d, 2 H, H(24), $J_{H(24),H(23)}$ = = 8.8 Hz); 7.48 (d, 2 H, H(23), $J_{H(23),H(24)}$ = 8.8 Hz); 7.46—7.51 (m, 2 H, H(17)); 7.41—7.46 (m, 2 H, H(18)); 7.28—7.32 (m, 1 H, H(19)).

(2*S*,3*R*)-3,15-Dihydroxy-20-methoxy-16-(4-methoxyphenyl)-2,5,19-trimethyl-7-phenyl-11,17-dioxa-6,7-diazapentacyclo[10.8.0.0^{2,10}.0^{4,8}.0^{13,18}]icosa-1(12),4(8),5,9,13(18),15,19-heptaen-14-one (4), m.p. 156—159 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.55 (s, 3 H, H(15)); 2.50 (s, 3 H, H(10)); 2.46 (d, 3 H, H(12), $J_{H(12),H(1)}$ = 0.3 Hz); 3.89 (d, 1 H, OH(1), $J_{OH,H(1)}$ = = 1.6 Hz); 3.87 (s, 3 H, H(26)); 4.02 (s, 3 H, H(20)); 5.50 (dd, 1 H, H(1), $J_{H(1),OH}$ = 1.6 Hz, $J_{H(1),H(12)}$ = 0.3 Hz); 7.03 (d, 2 H, H(24), $J_{H(24),H(23)}$ = 9.1 Hz); 7.04 (ws, 1 H, OH(14)); 8.19 (d, 2 H, H(23), $J_{H(23),H(24)}$ = 9.1 Hz); 7.46—7.51 (m, 2 H, H(17)); 7.41—7.46 (m, 2 H, H(18)); 7.28—7.32 (m, 1 H, H(19)). Found: *m/z* 564.1887 $[M]^+$. $C_{33}H_{28}O_7N_2$. Calculated: M = 564.1891.

Reaction of compound 2 with *tert*-butyl hydroperoxide. A 5.5 *M* solution of Bu^tOOH (0.3 mL) in hexane and seven crystalline grains of $VO(acac)_2$ were added to a solution of compound **2** (163 mg, 0.3 mmol) in dry toluene (10 mL). The reaction mixture was stirred at 55 °C for 2 h, cooled to 20 °C, and diluted with water. The product was extracted with chloroform and the organic extract was concentrated. The residue was chromatographed on silica gel (gradient elution with $CHCl_3$—ethanol (0→20%)).

(*R*,*E*)-7-Hydroxy-5-methoxy-8-[3-(4-methoxyphenyl)acryloyl]-3,4a,6-trimethyl-1-phenyl-1*H*-benzofuro[3,2-*f*]indazol-4(4a*H*)-one (5). Yield 67%, m.p. 155—157 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.89 (s, 3 H, H(15)); 2.20 (s, 3 H, H(10)); 2.55 (s, 3 H, H(12)); 3.83 (s, 3 H, H(26)); 4.10 (s, 3 H, H(20)); 6.17 (s, 1 H, H(4)); 6.90 (d, 2 H, H(24), H(24´), *J* = 8.5 Hz); 7.35—7.60 (m, 7 H, H_{arom}); 7.74 (d, 1 H, H(14), *J* = 15.5 Hz); 7.89 (d, 1 H, H(21), *J* = 15.5 Hz); 13.96 (s, 1 H, H(7)). Found: *m/z* 548.1937 $[M]^+$ $C_{33}H_{28}O_6N_2$. Calculated: M = 548.1942.

Reaction of compound 2 with DDQ. Dichlorodicyanobenzoquinone (184 mg, 0.72 mmol) was added to a solution of compound **2** (200 mg, 0.36 mmol) in dioxane (10 mL). The reaction mixture was refluxed for 15 h, cooled to 20 °C, and diluted with water. Then a saturated solution of $NaHCO_3$ was added and the product was extracted with chloroform. The organic extract was concentrated. The residue was chromatographed on silica gel (gradient elution with CH_2Cl_2—methanol (0→20%)).

(2*R*)-20-Methoxy-16-(4-methoxyphenyl)-2,5,19-trimethyl-7-phenyl-11,17-dioxa-6,7-diazapentacyclo[10.8.0.0^{2,10}.0^{4,8}.0^{13,18}]icosa-1(12),4(8),5,9,13(18),15,19-heptaene-3,14-dione (6). Yield 75%, m.p. 140—142 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.89 (s, 3 H, H(15)); 2.51 (s, 3 H, H(10)); 2.56 (s, 3 H, H(12)); 3.88 (s, 3 H, H(26)); 4.17 (s, 3 H, H(20)); 6.40 (s, 1 H, H(4)); 6.65 (s, 1 H, H(14)); 7.02 (d, 2 H, H(24), $J_{H(24),H(23)}$ = 9.0 Hz); 7.38—7.42 (m, 1 H, H(19)); 7.47—7.52 (m, 2 H, H(18)); 7.53—7.57 (m, 2 H, H(17)); 7.84 (d, 2 H, H(23), $J_{H(23),H(24)}$ = = 9.0 Hz). Found: *m/z* 546.1788 $[M]^+$ $C_{33}H_{26}O_6N_2$. Calculated: M = 546.1785.

Reaction of compound 2 with $NH_2NH_2 \cdot H_2O$. Hydrazine hydrate (0.5 mmol) and acetic acid (0.5 mmol) were added to a solution of compound **2** (260 mg, 0.5 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 2 h, cooled to 20 °C, and diluted with water. The precipitate that formed was filtered off, dried in air, and chromatographed on silica gel (gradient elution with $CHCl_3$—ethanol (0→20%)). Yield 82%, m.p. 117—119 °C. Found: *m/z* 564.2360 $[M]^+$. $C_{33}H_{32}O_5N_4$. Calculated: M = 564.2373. NMR spectra were recorded for a sample containing a 1 : 1 mixture of diastereomers.

(4*R*,4a*S*)-5-Methoxy-8-[(5*R*)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-3,4a,6-trimethyl-1-phenylbenzofuro[3,2-*f*]indazole-4,7-diol (7a) and (4*R*,4a*S*)-5-methoxy-8-[(5*S*)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-3,4a,6-trimethyl-1-phenylbenzofuro[3,2-*f*]indazole-4,7-diol (7b). ^{1}H NMR (600 MHz, $CDCl_3$), δ: 1.47 (s, 3 H, H(15)); 1.49 (s, 3 H, H(15)); 2.19 (s, 3 H, H(10)); 2.19 (s, 3 H, H(10)); 2.44 (s, 3 H, H(12)); 2.45 (s, 3 H, H(12)); 3.27 (dd, 1 H, H(14), ^2J = 17.4 Hz, $J_{H(14),H(21)}$ = 9.2 Hz); 3.28 (dd, 1 H, H(14), ^2J = 17.4 Hz, $J_{H(14),H(21)}$ = 9.2 Hz); 3.71 (dd, 1 H, H(14), ^2J = 17.4 Hz, $J_{H(14),H(21)}$ = 10.2 Hz); 3.71 (dd, 1 H, H(14), ^2J = 17.4 Hz, $J_{H(14),H(21)}$ = 10.2 Hz); 3.76 (s, 3 H, H(26)); 3.78 (s, 3 H, H(26)); 3.90 (s, 3 H, H(20)); 3.91 (s, 3 H, H(20)); 4.11 (d, 1 H, OH(1), $J_{OH,H(1)}$ = 1.4 Hz); 4.12 (d, 1 H, OH(1), $J_{OH,H(1)}$ = 1.4 Hz); 4.78 (dd, 1 H, H(21), $J_{H(21),H(14)}$ = 10.2 Hz, $J_{H(21),H(14)}$ = 9.2 Hz); 4.79 (dd, 1 H, H(21), $J_{H(21),H(14)}$ = 10.2 Hz, $J_{H(21),H(14)}$ = = 9.2 Hz); 5.39 (d, 1 H, H(1), $J_{H(1),OH}$ = 1.4 Hz); 5.39 (d, 1 H, H(1), $J_{H(1),OH}$ = 1.4 Hz); 6.84 (d, 2 H, H(24), $J_{H(24),H(23)}$ = = 8.7 Hz); 6.86 (d, 2 H, H(24), $J_{H(24),H(23)}$ = 8.7 Hz); 7.25 (d, 2 H, H(23), $J_{H(23),H(24)}$ = 8.7 Hz); 7.26 (d, 2 H, H(23), $J_{H(23),H(24)}$ = = 8.7 Hz); 7.44—7.56 (m, 2 H, H(17)); 7.44—7.56 (m, 2 H, H(17)); 7.38—7.41 (m, 2 H, H(18)); 7.38—7.41 (m, 2 H, H(18)); 7.24—7.28 (m, 1 H, H(19)); 7.24—7.28 (m, 1 H, H(19)).

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