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SYNTHESIS OF SULFIDES BASED ON (+)-USNINIC ACID

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Sulfides containing the pharmacophore (+)-usninic acid and its methyl ether were synthesized from monobrominated precursors.

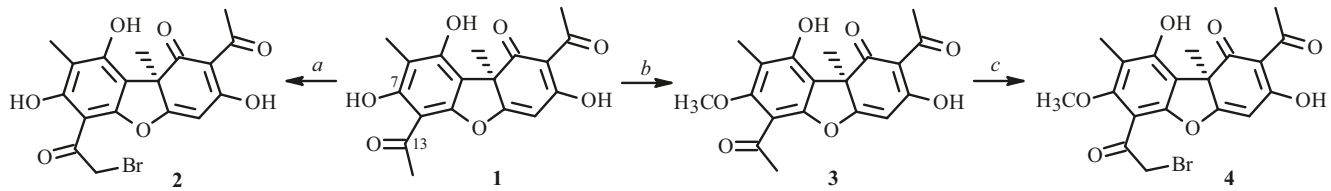
Keywords: (+)-usninic acid, β-phenacylbromides, thiols, sulfides.

Synthetic transformations of plant metabolites represent an important area of medicinal chemistry and allow new effective drugs to be discovered. Research on plant metabolites for which reliable information on the biological activity and available raw-material base exists is considered to be very promising. Usninic acid is actually one of these compounds and the major secondary metabolite of several lichens. Both enantiomers of usninic acid have to different extents native antiviral, antibiotic, analgesic, antituberculosis, and insecticidal activity [1].

Herein were present data on the functionalization of (+)-usninic acid (**1**, UA) and its methyl ether by various pharmacophores by the reaction of the corresponding mono-bromo derivatives with S-containing thiol nucleophiles.

We reported earlier [2] on a method for selective preparation of the mono-bromo-substituted derivative at the acetyl on ring A of UA (Scheme 1). Bromination products of the acetyl on ring C were not observed. It is known that all UA carbonyls are involved in intramolecular H-bonds [3], the strongest of which is that of the exocyclic carbonyl of ring C. The H-bond of the carbonyl of ring A is weaker. Apparently, the strengths of these H-bonds differentiated the reactivity of these groups for electrophilic bromination. The reactions occurred slowly. Sufficient conversion was achieved after 7 d. The yield of **2** was 67%. Increasing the reaction temperature decreased the yield of the mono-bromo derivative and led to the accumulation in the reaction mixture of polybromination products.

According to theoretical concepts that the mechanism of bromination occurs through the formation of the enol form of the acetyl, formation of the enol is facilitated considerably by the destruction of the O–H-7…O=C-13 H-bond, e.g., by adding a protecting group on the C-7 phenyl hydroxyl. The preparation of usninic acid ethers selectively at the C-7 phenol hydroxyl was described. However, using the literature method [4] to prepare usninic methyl ether by refluxing with MeI in Me_2CO in the presence of K_2CO_3, we, like the researchers, were able to isolate only small quantities of it. We proposed a modified methylation method. The reaction was carried out in DMF at room temperature. First, usninic acid phenolate ion was generated by stirring in DMF for 2 h in the presence of K_2CO_3. A sign of its formation was the gradual color change from yellow to green, after which a many-fold excess of MeI was added. The mixture was stirred for 2 d to afford **3** in 82% yield (Scheme 1).



a. Br_2/HBr, dioxane, 7 days; *b*. MeI, K_2CO_3, DMF; *c*. Br_2/HBr, dioxane 20 min

Scheme 1

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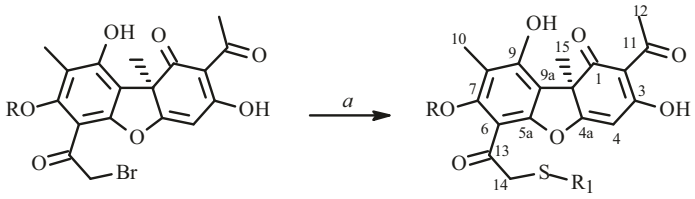
The resulting methyl ether was used in the electrophilic bromination under the aforementioned conditions. Compound **3** showed considerably higher activity in the bromination than starting usninic acid. The reaction occurred in 20 min at room temperature with a 1:1 mole ratio of reagents. The resulting product (**4**) was isolated in 73% yield by column chromatography (Scheme 1).

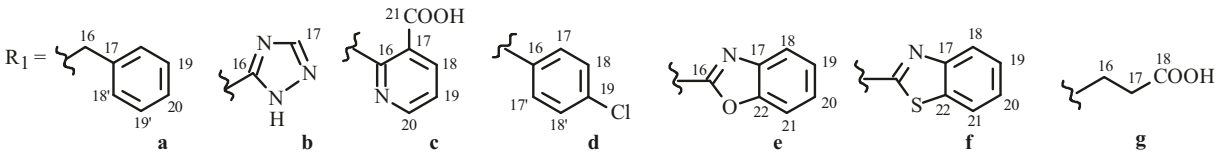
α-Phenacylbromides are known to react rather readily with *O*-, *N*-, and *S*-nucleophiles. This type of reaction can produce hybrid molecules [5] of a substrate with various pharmacophores, leaving the structural backbone of the natural compound unchanged.

Then, both bromo-derivatives were reacted with several *S*-nucleophiles such as aromatic, aliphatic, and heterocyclic thiols (Scheme 2). Thio-compounds containing various pharmacophores were selected for the reaction. Addition of them favored the discovery of new potentially biologically active compounds. Furthermore, sulfide compounds are important intermediates in organic synthesis that can be used as universal building blocks for various chemical purposes, e.g., preparation of sulfones and sulfoxides [6, 7].



2, 4 **5a-g, 6a-g**

2, 5a-g: R = H; **4, 6a-g:** R = Me



a **b** **c** **d** **e** **f** **g**

a. R_1SH/KOH, MeOH, 1–3 h

Scheme 2

The reaction with thiols of UA methyl ether and UA itself occurred smoothly at room temperature. According to HPLC, the conversion was complete. The main products were the corresponding α-phenacylsulfides **5a**–**g** and **6a**–**g** (Scheme 2).

Thio-derivatives of the methyl ether (**6a**–**g**) were isolated by column chromatography in good (53–90%) yields. α-Phenacylsulfides based on UA itself (**5a**–**g**) were isolated in lower (16–82%) yields. Apparently, the significant losses during chromatographic isolation were related to intra- and intermolecular rearrangements that involved the free phenolic 7-OH and the chromatography support.

Thus, preparation of UA methyl ether enhanced considerably electrophilic bromination of the acetyl on UA ring C. α-Phenacylsulfides were synthesized from the bromo-derivatives of (+)-UA and its methyl ether. The presence of the methyl protecting group on the phenolic 7-OH simplified considerably the isolation of the products from the reaction mixture.

EXPERIMENTAL

Analytical and spectral studies were carried out at the Chemical Service, Center for Collective Use, Siberian Branch, Russian Academy of Sciences. PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using solvent resonances (δ_H 7.24 ppm, δ_C 76.90 ppm) as standards on a Bruker AV-400 spectrometer (operating frequencies 400.13 MHz for ^1H and 100.61, for ^{13}C). Mass spectra (ionizing-electron energy 70 eV) were measured in a DFS Thermo Scientific high-resolution mass spectrometer. Melting points were measured on a Kofler block. The reaction was monitored by TLC. Specific rotation was expressed in $(deg \cdot mL) \cdot (g \cdot dm)^{-1}$; solution concentration, in $g \cdot (100\ mL)^{-1}$.

(+)-UA {**1**, $[\alpha]_D$ +478° (*c* 0.1, $CHCl_3$)} was isolated from a mixture of *Usnea* lichen species using the literature method [8]. Column chromatography used Merck silica gel (60–200 μm). TLC was performed on Sorbfil plates (UV 254).

The course of reactions and analysis of fractions were monitored during purification of the compounds by column chromatography using HPLC on a Milikhrom A-02 microcolumn chromatograph (ZAO EkoNova, Novosibirsk) with a standard

chromatography column (2 × 75 mm) packed with reversed-phase sorbent (ProntoSIL 120-5-C18, 5 μm, Bischoff, Germany). Gradient elution used trifluoroacetic acid (0.1%) in MeOH (from 0 to 100% MeOH in 25 min) with simultaneous multi-wavelength detection at eight wavelengths (210, 230, 250, 260, 280, 300, 340, and 360 nm). The temperature was 35°C; pressure, 30–36 atm; flow rate, 150 μL/min. The resulting chromatograms were processed using the MultiKhrom 1.5x-E program (ZAO Ampersand, Moscow).

We used commercially available thiols (95–99% pure, Acros Organics) in the reactions.

The atomic numbering in the compounds was given in order to assign the NMR spectra and did not always agree with the nomenclature atomic numbering.

Reaction of UA with MeI. UA (1 mmol, 344 mg) in DMF (20 mL) (distilled over BaO and passed immediately before the reaction over a column of calcined Al_2O_3) was stirred with calcined K_2CO_3 (828 mg) for 2 h at room temperature until the solution became dark-green. Then, MeI (0.5 mL) was added. The mixture was stirred for 2 d at room temperature and diluted with H_2O. The resulting resinous precipitate was filtered off on filter paper, washed with H_2O, dried, rinsed off with $CHCl_3$, and concentrated in a rotary evaporator. The resulting precipitate was chromatographed over silica gel using CH_2Cl_2 eluent.

(*R*)-1,1′-(3,9-Dihydroxy-7-methoxy-8,9b-dimethyl-1-oxo-1,9b-dihydrodibenzo[*b*,*d*]furan-2,6-diyl)diethanone (3). $C_{19}H_{18}O_7$. Viscous yellow amorphous substance, yield 293 mg (82%), $[\alpha]_D^{27}$ +460° (*c* 0.48; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.71 (3H, s, H-15), 2.12 (3H, s, H-10), 2.55 (3H, s, H-12), 2.59 (3H, s, H-14), 3.71 (3H, s, H-16), 5.88 (1H, s, H-4), 10.76 (1H, s, OH-9), 18.76 (1H, s, OH-3). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.60 (C-10), 27.84 (C-12), 31.79 (C-15), 31.81 (C-14), 50.04 (C-9b), 62.20 (C-16), 97.87 (C-4), 108.32 (C-9a), 112.30 (C-6), 104.99 (C-2), 116.30 (C-8), 152.68 (C-5a), 154.81 (C-9), 159.35 (C-7), 179.97 (C-4a), 191.58 (C-13), 196.61 (C-3), 197.78 (C-1), 201.58 (C-11). Found: *m/z* 358.1046 $[M]^+$. Calcd: M 358.1046.

Reaction of 3 with Br_2. Compound **3** (358 mg, 1 mmol) in dioxane (20 mL) was added to the previously prepared Br_2:dioxane complex [Br_2 (0.05 mL, 1 mmol) dissolved in dioxane (10 mL)] and several drops of HBr, stirred for 20 min at room temperature, and concentrated in a rotary evaporator. The solid was chromatographed over silica gel using CH_2Cl_2 eluent.

(*R*)-2-Acetyl-6-(2-bromoacetyl)-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (4). $C_{19}H_{17}O_7{}^{79}Br$. Viscous yellow amorphous substance, yield 319 mg (73%), $[\alpha]_D^{29}$ +202° (*c* 0.2; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.73 (3H, s, H-15), 2.13 (3H, s, H-10), 2.60 (3H, s, H-12), 3.75 (3H, s, H-16), 4.43 (2H, dd, J = 13.1, 14, H-14), 5.91 (1H, s, H-4), 10.91 (1H, s, OH-9), 18.78 (1H, s, OH-3). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.64 (C-10), 27.75 (C-12), 31.74 (C-15), 36.07 (C-14), 58.9 (C-9b), 62.3 (C-16), 98.16 (C-4), 108.45 (C-9a), 108.53 (C-6), 104.99 (C-2), 116.49 (C-8), 153.07 (C-5a), 155.75 (C-9), 159.60 (C-7), 179.32 (C-4a), 189.25 (C-13), 191.48 (C-3), 197.56 (C-1), 201.57 (C-11). Found: *m/z* 436.0159 $[M]^+$. Calcd: M 436.0152.

Reaction of 2 and 4 with Thiols (general method). A weighed portion of KOH (1.1 mmol), MeOH (6 mL), and the appropriate thiol (1.1 mmol) were placed into a flask, stirred at room temperature for 10–15 min, treated with a solution of **2** (or **4**) (1 mmol) in CH_2Cl_2 (2 mL), stirred at room temperature for 2–3 h until the reaction was finished (TLC monitoring), washed with distilled H_2O (two times the volume), dried over $MgSO_4$, and concentrated. The solid was chromatographed over silica gel using CH_2Cl_2 eluent.

(*R*)-2-Acetyl-6-[2-(benzylthio)acetyl]-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (5a). $C_{25}H_{22}O_7S$. Yellow amorphous powder, yield 238 mg (51%), mp. 124–125°C, $[\alpha]_D^{27}$ +353° (*c* 0.45; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.72 (3H, s, H-15), 2.10 (3H, s, H-10), 2.63 (3H, s, H-12), 3.66 (2H, dd, J = 14.0, 18.0, H-16), 3.73 (2H, s, H-14), 5.88 (1H, s, H-4), 7.23 (1H, m, H-20), 7.31 (4H, m, H-arom.), 11.06 (1H, s, OH-9), 13.01 (1H, s, OH-7), 18.79 (1H, s, OH-3). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.45 (C-10), 27.72 (C-12), 31.88 (C-15), 35.68 (C-16), 39.60 (C-14), 58.82 (C-9b), 98.27 (C-4), 99.66 (C-9a), 104.05 (C-6), 105.10 (C-2), 109.47 (C-8), 127.12 (C-20), 128.39 (C-19, 19′), 129.11 (C-18, 18′), 137.18 (C-17), 154.39 (C-5a), 157.64 (C-9), 164.37 (C-7), 178.81 (C-4a), 191.48 (C-13), 196.64 (C-3), 197.83 (C-1), 201.62 (C-11). Found: *m/z* 466.1077 $[M]^+$. Calcd: M 466.1081.

(*R*)-6-[2-(1*H*-1,2,4-Triazol-3-ylthio)acetyl]-2-acetyl-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (5b). $C_{20}H_{17}N_3O_7S$. Yellow amorphous powder, yield 142 mg (32%), mp 176–178°C, $[\alpha]_D^{27}$ +324° (*c* 0.21; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.72 (3H, s, H-15), 2.06 (3H, s, H-10), 2.63 (3H, s, H-12), 4.62 (2H, dd, J = 16.9, 18.4, H-14), 6.00 (1H, s, H-4), 7.56 (1H, br.s, N-H), 8.37 (1H, s, H-17), 11.15 (1H, s, 9-OH), 12.54 (1H, s, 7-OH), 18.80 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.41 (C-10), 27.71 (C-12), 31.86 (C-15), 42.56 (C-14), 58.68 (C-9b), 98.83 (C-4), 99.81 (C-9a), 104.37 (C-6), 105.05 (C-2), 109.45 (C-8), 128.16 (C-17), 154.59 (C-9), 155.60 (C-5a), 158.25 (C-16),

163.65 (C-7), 178.32 (C-4a), 191.47 (C-13), 194.82 (C-3), 197.67 (C-1), 201.69 (C-11). Found: *m/z* 443.0775 $[M]^+$. Calcd: M 443.0782.

(*R*)-2-[2-(8-Acetyl-1,3,7-trihydroxy-2,9a-dimethyl-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-yl)-2-oxoethylthio]nicotinic Acid (5c). $C_{24}H_{19}NO_9S$. Yellow amorphous powder, yield 303 mg (61%), mp 195–197°C, $[\alpha]_D^{25}$ +307° (*c* 0.23; acetone). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.83 (3H, s, H-15), 2.04 (3H, s, H-10), 2.63 (3H, s, H-12), 3.23 (1H, br.s, COOH), 4.74 (2H, dd, J = 17.1, 45.7, H-14), 6.17 (1H, s, H-4), 7.18 (1H, dd, J = 7.7, 4.7, H-19), 8.30 (1H, dd, J = 1.8, 7.7, H-18), 8.43 (2H, dd, J = 1.8, 4.7, H-17), 11.23 (1H, s, OH-9), 13.05 (1H, s, 7-OH), 18.94 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 6.62 (C-10), 26.84 (C-12), 31.12 (C-15), 40.27 (C-14), 58.90 (C-9b), 97.90 (C-4), 100.82 (C-9a), 104.49 (C-6), 105.09 (C-2), 108.00 (C-8), 118.58 (C-18), 122.67 (C-20), 138.87 (C-19), 151.49 (C-17), 155.04 (C-5a), 157.10 (C-9), 160.46 (C-7), 163.17 (C-16), 165.42 (C-21), 179.34 (C-4a), 191.83 (C-13), 197.12 (C-3), 198.35 (C-1), 201.74 (C-11). Found: *m/z* 497.0770 $[M]^+$. Calcd: M 497.0775.

(*R*)-2-Acetyl-6-[2-(4-chlorophenylthio)acetyl]-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (5d). $C_{24}H_{19}O_7SCl$. Yellow amorphous powder, yield 398 mg (82%), mp 147–148°C, $[\alpha]_D^{27}$ +365° (*c* 0.34; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.72 (3H, s, H-15), 2.06 (3H, s, H-10), 2.63 (3H, s, H-12), 4.17 (2H, dd, J = 14.5, 25.6, H-14), 5.92 (1H, s, H-4), 7.20 (2H, d, J = 8.4, H-17, 17′), 7.28 (2H, d, J = 8.4, H-18, 18′), 11.07 (1H, s, 9-OH), 12.74 (1H, s, 7-OH), 18.79 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.46 (C-10), 27.72 (C-12), 31.88 (C-15), 44.46 (C-14), 58.79 (C-9b), 98.47 (C-4), 99.75 (C-9a), 104.15 (C-6), 105.14 (C-2), 109.60 (C-8), 129.08 (C-18, 18′), 132.19 (C-17, 17′), 132.81 (C-19), 133.47 (C-16), 154.36 (C-5a), 157.97 (C-9), 164.19 (C-7), 178.63 (C-4a), 191.48 (C-13), 195.87 (C-3), 197.77 (C-1), 201.68 (C-11). Found: *m/z* 486.0529 $[M]^+$. Calcd: M 486.0535.

(*R*)-2-Acetyl-6-[2-(benzo[*d*]oxazole-2-ylthio)acetyl]-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (5e). $C_{25}H_{19}O_8NS$. Yellow amorphous powder, yield 79 mg (16%), mp 155–156°C, $[\alpha]_D^{27}$ +217° (*c* 0.32; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.80 (3H, s, H-15), 2.12 (3H, s, H-10), 2.68 (3H, s, H-12), 4.90 (2H, dd, J = 17.3, 16.7, H-14), 6.06 (1H, s, H-4), 7.27 (2H, m, H-arom.), 7.44 (1H, m, H-arom.), 7.57 (1H, m, H-arom.), 11.17 (1H, s, 9-OH), 12.63 (1H, s, 7-OH), 18.84 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.44 (C-10), 27.67 (C-12), 31.90 (C-15), 43.07 (C-14), 58.80 (C-9b), 98.84 (C-4), 100.09 (C-9a), 104.30 (C-6), 105.14 (C-2), 109.60 (C-8), 109.86, 118.42, 124.01, 124.27 (C-18, 19, 20, 21), 141.55, 151.89 (C-17, 22), 154.67 (C-5a), 158.23 (C-9), 163.41 (C-7), 163.68 (C-16), 178.50 (C-4a), 191.50 (C-13), 193.43 (C-3), 197.76 (C-1), 201.66 (C-11). Found: *m/z* 493.0830 $[M]^+$. Calcd: M 493.0826.

(*R*)-2-Acetyl-6-[2-(benzo[*d*]thiazol-2-ylthio)acetyl]-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (5f). $C_{25}H_{19}O_7NS_2$. Yellow amorphous powder, yield 81 mg (16%), mp 159–160°C, $[\alpha]_D^{27}$ +207° (*c* 0.32; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.76 (3H, s, H-15), 2.08 (3H, s, H-10), 2.65 (3H, s, H-12), 4.91 (2H, dd, J = 16.8, 19.0, H-14), 5.98 (1H, s, H-4), 7.27 (1H, m, H-arom), 7.37 (1H, m, H-arom), 7.72 (1H, m, H-arom), 7.80 (1H, m, H-arom), 11.12 (1H, s, 9-OH), 12.64 (1H, s, 7-OH), 18.79 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.46 (C-10), 27.74 (C-12), 31.90 (C-15), 43.76 (C-14), 58.75 (C-9b), 98.66 (C-4), 100.07 (C-9a), 104.20 (C-6), 105.05 (C-2), 109.46 (C-8), 120.90, 121.38, 124.40, 126.00 (C-18, C-19, C-20, C-21), 135.17 (C-22), 152.48 (C-17), 154.57 (C-5a), 158.02 (C-9), 163.63 (C-7), 164.91 (C-16), 178.52 (C-4a), 191.46 (C-13), 193.87 (C-3), 197.69 (C-1), 201.64 (C-11). Found: *m/z* 509.0593 $[M]^+$. Calcd: M 509.0598.

(*R*)-3-[2-(8-Acetyl-1,3,7-trihydroxy-2,9a-dimethyl-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-yl)-2-oxoethylthio]propanoic Acid (5g). $C_{21}H_{20}O_9S$. Yellow amorphous powder, yield 278 mg (62%), mp 165–166°C, $[\alpha]_D^{27}$ +413° (*c* 0.34; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.726 (3H, s, H-15), 2.06 (3H, s, H-10), 2.62 (3H, s, H-12), 2.67 (2H, t, J = 7, H-17), 2.81 (2H, t, J = 7, H-16), 3.80 (2H, dd, J = 14.1, 17.0, H-14), 5.95 (1H, s, H-4), 9.28 (1H, br.s, COOH), 11.09 (1H, s, 9-OH), 12.92 (1H, s, 7-OH), 18.80 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.44 (C-10), 26.19 (C-16), 27.77 (C-12), 31.89 (C-15), 33.81 (C-17), 40.66 (C-14), 58.76 (C-9b), 98.36 (C-4), 99.37 (C-9a), 104.11 (C-6), 105.04 (C-2), 109.44 (C-8), 154.34 (C-5a), 157.71 (C-9), 164.28 (C-7), 177.50, 178.70 (C-4a, 18), 191.46 (C-13), 196.50 (C-3), 197.76 (C-1), 201.67 (C-11). Found: *m/z* 448.0822 $[M]^+$. Calcd: M 448.0823.

(*R*)-2-Acetyl-6-[2-(benzylthio)acetyl]-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (6a). $C_{26}H_{24}O_7S$. Viscous amorphous yellow substance, yield 432 mg (90%), $[\alpha]_D^{29}$ +292° (*c* 0.29; $CHCl_3$). ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.75 (3H, s, H-15), 2.17 (3H, s, H-10), 2.64 (3H, s, H-12), 3.65 (2H, dd, J = 14.3, 16.5, H-17), 3.73 (3H, s, H-14), 3.76 (3H, s, OMe), 5.91 (1H, s, H-4), 7.21 (1H, m, H-21), 7.26–7.32 (4H, m, H-19, 19′, 20, 20′), 10.86 (1H, s, 9-OH), 18.83 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.39 (C-10), 27.52 (C-12), 31.51 (C-15), 35.49 (C-16), 40.40 (C-14), 58.74 (C-9b), 62.04 (OMe), 97.66 (C-4), 104.73 (C-9a), 108.06 (C-6), 109.92 (C-2), 116.08 (C-8), 126.70 (C-20), 128.02 (C-18, 18′), 128.77 (C-19, 19′), 136.91 (C-17), 152.79 (C-5a), 154.77 (C-9), 159.02 (C-7), 179.39 (C-4a), 191.22 (C-13), 192.99 (C-3), 197.37 (C-1), 201.27 (C-11). Found: *m/z* 480.1242 $[M]^+$. Calcd: M 480.1237.

(*R*)-6-[2-(1*H*-1,2,4-Triazol-5-ylthio)acetyl]-2-acetyl-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (6b). $C_{21}H_{19}N_3O_7S$. Yellow amorphous powder, yield 306 mg (67%), mp 151–153°C, $[\alpha]_D^{29}$ +176° (*c* 0.23; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.66 (3H, s, H-15), 2.15 (3H, s, H-10), 2.62 (3H, s, H-12), 3.75 (3H, s, OMe), 4.52 (2H, dd, J = 16.8, 29.4, H-14), 5.97 (1H, s, H-4), 8.12 (1H, s, H-17), 9.74 (1H, br.s, NH), 10.84 (1H, s, 9-OH), 18.65 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.72 (C-10), 27.69 (C-12), 31.81 (C-15), 43.18 (C-14), 58.68 (C-9b), 62.16 (OMe), 98.21 (C-4), 104.73 (C-9a), 108.44 (C-6), 109.73 (C-2), 116.48 (C-8), 145.49 (C-5a), 153.25 (C-5a), 155.71 (C-9), 156.22 (C-16), 159.75 (C-7), 178.97 (C-4a), 191.31 (C-13), 192.87 (C-1), 197.39 (C-3), 201.58 (C-11). Found: *m/z* 457.0944 $[M]^+$. Calcd: M 457.0938.

(*R*)-2-[2-(8-Acetyl-1,7-dihydroxy-3-methoxy-2,9a-dimethyl-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-yl)-2-oxoethylthio]nicotinic Acid (6c). $C_{25}H_{21}NO_9S$. Yellow amorphous powder, yield 460 mg (90%), mp 79–81°C, $[\alpha]_D$ +222° (*c* 0.26; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.71 (3H, s, H-15), 2.15 (3H, s, H-10), 2.60 (3H, s, H-12), 3.75 (3H, s, OMe), 4.41 (2H, s, H-14), 5.85 (1H, s, H-4), 7.03 (1H, dd, J = 4.7, 7.8, H-19), 8.23 (1H, dd, J = 1.7, 7.8, H-18), 8.34 (1H, dd, J = 1.7, 4.7, H-20), 10.76 (1H, s, 9-OH), 10.91 (1H, br.s, COOH), 18.74 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.61 (C-10), 27.72 (C-12), 31.73 (C-15), 41.89 (C-14), 59.02 (C-9b), 62.20 (OMe), 97.62 (C-4), 104.90 (C-9a), 108.24 (C-6), 111.26 (C-2), 116.09 (C-8), 118.51 (C-19), 121.74 (C-17), 139.64 (C-18), 151.83 (C-20), 152.50 (C-5a), 154.63 (C-9), 159.12 (C-7), 161.15 (C-16), 169.71 (C-21), 179.85 (C-4a), 191.45 (C-3), 197.61 (C-1), 201.45 (C-11). Found: *m/z* 511.0929 $[M]^+$. Calcd: M 511.0932.

(*R*)-2-Acetyl-6-[2-(4-chlorophenylthio)acetyl]-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (6d). $C_{25}H_{21}ClO_7S$. Viscous yellow amorphous substance, yield 330 mg (66%), $[\alpha]_D^{27}$ +272° (*c* 0.5; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm): 1.68 (3H, s, H-15), 2.12 (3H, s, H-10), 2.60 (3H, s, H-12), 3.68 (3H, s, OMe), 4.13 (2H, s, H-14), 5.82 (1H, s, H-4), 7.14 (4H, m, H-17, 17′, 18, 18′), 10.80 (1H, s, 9-OH), 18.76 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.56 (C-10), 27.69 (C-12), 31.63 (C-15), 45.20 (C-14), 58.85 (C-9b), 62.20 (OMe), 97.86 (C-4), 104.94 (C-9a), 108.22 (C-6), 109.90 (C-2), 116.31 (C-8), 128.71 (C-18, 18′), 131.55 (C-17, 17′), 132.76 (C-19), 133.20 (C-16), 152.80 (C-5a), 155.20 (C-9), 159.29 (C-7), 179.39 (C-4a), 191.41 (C-13), 192.64 (C-3), 197.52 (C-1), 201.49 (C-11). Found: *m/z* 500.0682 $[M]^+$. Calcd: M 500.0691.

(*R*)-2-Acetyl-6-[2-(benzo[*d*]oxazol-2-ylthio)acetyl]-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (6e). $C_{26}H_{21}NO_8S$. Yellow amorphous powder, yield 319 mg (63%), mp 64–66°C, $[\alpha]_D^{27}$ +190° (*c* 0.36; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.71 (3H, s, H-15), 2.18 (3H, s, H-10), 2.63 (3H, s, H-12), 3.80 (3H, s, OMe), 4.74 (2H, dd, J = 17.0, 17.8, H-14), 5.88 (1H, s, H-4), 7.22 (2H, m, H-arom.), 7.39 (1H, m, H-arom.), 7.49 (1H, m, H-arom.), 10.95 (1H, s, 9-OH), 18.81 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.69 (C-10), 27.84 (C-12), 31.71 (C-15), 43.83 (C-14), 58.89 (C-9b), 62.35 (OMe), 98.14 (C-4), 104.96 (C-9a), 108.60 (C-6), 109.65 (C-2), 109.77 (C-21), 116.47 (C-8), 118.27 (C-18), 123.85 (C-20), 124.17 (C-19), 141.59 (C-17), 151.81 (C-22), 153.19 (C-5a), 155.77 (C-9), 159.66 (C-7), 163.60 (C-16), 179.50 (C-4a), 190.83 (C-13), 191.51 (C-3), 197.61 (C-1), 201.62 (C-11). Found: *m/z* 507.0979 $[M]^+$. Calcd: M 507.0982.

(*R*)-2-Acetyl-6-[2-(benzo[*d*]thiazol-2-ylthio)acetyl]-3,9-dihydroxy-7-methoxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (6f). $C_{26}H_{21}NO_7S_2$. Yield 277 mg (53%), mp 63–65°C, $[\alpha]_D^{27}$ +279° (*c* 0.39; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm): 1.68 (3H, s, H-15), 2.17 (3H, s, H-10), 2.62 (3H, s, H-12), 3.78 (3H, s, OMe), 4.73 (2H, s, H-14), 5.80 (1H, s, H-4), 7.23 (1H, m, H-arom.), 7.32 (1H, m, H-arom.), 7.69 (2H, m, H-arom.), 10.87 (1H, s, 9-OH), 18.76 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.68 (C-10), 27.80 (C-12), 31.69 (C-15), 44.48 (C-14), 58.94 (C-9b), 62.34 (OMe), 98.02 (C-4), 104.98 (C-9a), 108.49 (C-6), 110.03 (C-2), 116.37 (C-8), 120.87, 121.33 (C-21, 22), 124.25 (C-20), 125.85 (C-19), 135.40 (C-22), 152.67 (C-17), 153.06 (C-5a), 155.53 (C-9), 159.60 (C-7), 165.04 (C-16), 179.590 (C-4a), 191.38 (C-13), 191.50 (C-3), 197.64 (C-1), 201.56 (C-11). Found: *m/z* 523.0752 $[M]^+$. Calcd: M 523.0754.

(*R*)-3-[2-(8-Acetyl-1,7-dihydroxy-3-methoxy-2,9a-dimethyl-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-yl)-2-oxoethylthio]propanoic Acid (6g). $C_{22}H_{22}O_9S$. Viscous yellow amorphous substance, yield 272 mg (58%), $[\alpha]_D^{27}$ +296° (*c* 0.32; $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.75 (3H, s, H-15), 2.15 (3H, s, H-10), 2.62 (3H, s, H-12), 2.65 (2H, t, J = 6.9, H-16), 2.79 (2H, t, J = 6.9, H-17), 3.75 (3H, s, OMe), 3.79 (2H, dd, J = 14.0, 23.0, H-14), 5.92 (1H, s, H-4), 7.95 (1H, br.s, COOH), 7.32 (1H, m, H-arom.), 10.84 (1H, s, 9-OH), 18.76 (1H, s, 3-OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 8.68 (C-10), 26.56 (C-16), 27.80 (C-12), 31.78 (C-15), 33.87 (C-17), 41.94 (C-14), 59.04 (C-9b), 62.36 (OMe), 98.05 (C-4), 105.06 (C-9a), 108.46 (C-6), 109.92 (C-2), 116.45 (C-8), 153.19 (C-5a), 155.23 (C-9), 159.37 (C-7), 177.06 (C-18), 179.67 (C-4a), 191.56 (C-13), 193.33 (C-3), 197.72 (C-1), 201.60 (C-11). Found: *m/z* 462.0978 $[M]^+$. Calcd: M 462.0979.

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REFERENCES

1. K. Ingolfsdottir, *Phytochemistry*, **61**, 729 (2002).
2. O. A. Luzina, D. N. Sokolov, A. V. Shernyukov, and N. F. Salakhutdinov, *Chem. Nat. Compd.*, **48**, 385 (2012).
3. G. M. Konig and A. D. Wright, *Phytochem. Anal.*, **10**, 279 (1999).
4. L. Bertilsson and C. Wachtmeister, *Acta Chem. Scand.*, **22**, 1791 (1968).
5. V. E. Romanov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Dokl. Akad. Nauk*, No. 3, 337 (2010).
6. N. K. Konduru, S. Dey, M. Sajid, M. Owais, and N. Ahmed, *Eur. J. Med. Chem.*, **59**, 23 (2013).
7. K. Kaczorowska, Z. Kolarska, K. Mitka, and P. Kowalski, *Tetrahedron*, **61**, 8315 (2005).
8. N. F. Salakhutdinov, M. P. Polovinka, and M. Yu. Panchenko, RU Pat. No. 2,317,076 C1, Feb. 20, 2008; *Byull. Izobret.*, No. 5 (2008).