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SYNTHESIS OF AURONES BASED ON USNINIC ACID

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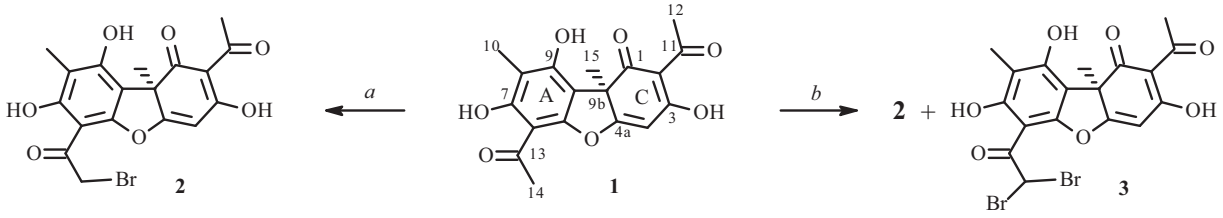
(+)-Usninic acid was brominated at the acetyl group located on the aromatic ring. Aurones were synthesized based on the intramolecular cyclization of monobrominated (+)-usninic acid.

Keywords: (+)-usninic acid, bromination, aurones.

Chemical modification of natural compounds is one of the leading areas of medicinal chemistry. A promising compound for carrying out synthetic transformations is the secondary metabolite of certain lichens, usninic acid (UA, **1**), which exhibits antiviral, antibiotic, analgesic, anti-tuberculosis, and insecticidal activity [1]. Examples of direct introduction into its structure of halide atoms have not been reported. However, the synthesis of a halo-substituted derivative of usninic acid is a direct pathway to its further functionalization.

The goal of the present work was direct halogenation (namely, bromination) of usninic acid and a study of possible further synthetic transformations for the preparation of new potentially biologically active compounds.

Compound (+)-**1** was brominated using a two-fold excess of Br_2 in dioxane in the presence of HBr. Of the two acetyls capable of reacting under these conditions, the group on aromatic ring A was brominated. Compound **2** was isolated in 67% yield after column chromatography as a result of the reaction at room temperature for seven days (Scheme 1). Increasing the content of Br_2 in the reaction mixture to a three-fold excess with respect to (+)-**1** facilitated the formation of dibromo-derivative **3** (ratio of **2** to **3**, 7:3 according to the PMR spectrum). Compound **3** was characterized by spectral methods from a mixture with the monobromo-derivative **2** because it could not be isolated pure by chromatographic methods.



a. $2Br_2$/HBr, dioxane, 2 d; *b*. $3Br_2$/HBr, dioxane, 2 d

Scheme 1

According to the literature, α-phenacylbromides react rather readily with *O*,*N*,*S*-nucleophiles [2–4]. In fact, **2** reacted with KOAc. However, the reaction did not stop with the formation of the nucleophilic substitution product of Br for AcO. Refluxing in acetone with KOAc produced **4** in 90% yield (Scheme 2). This was the product of intramolecular cyclization that was apparently formed in tandem as a result of two nucleophilic substitution reactions. The first of these was substitution of Br by AcO to form UA acetoxy derivative **5**; the second, intramolecular attack of the C-7 hydroxyl at the C atom containing the AcO group. According to the literature [5], the reaction of α-phenacylbromide with KOAc could stop at the formation of 2-acetoxy-2′-hydroxyacetophenone by varying the pH of the medium. In fact, carrying out the reaction in the presence of HOAc at room temperature led to the formation of **5** as the main product in a mixture with **4**. However, the yield of **5** was only 20% (Scheme 2).

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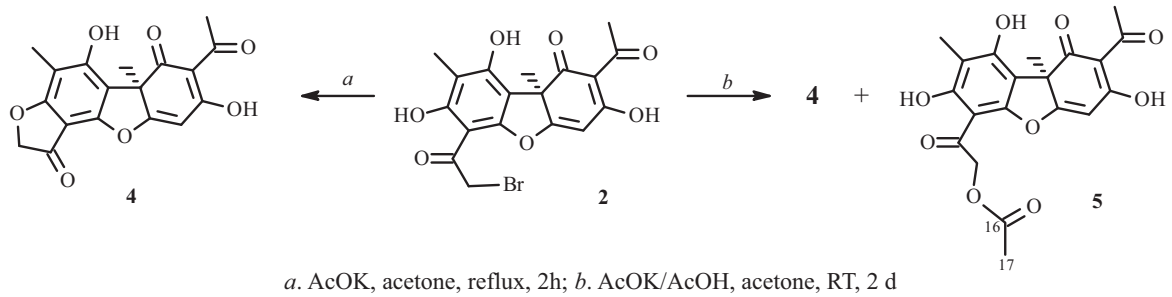
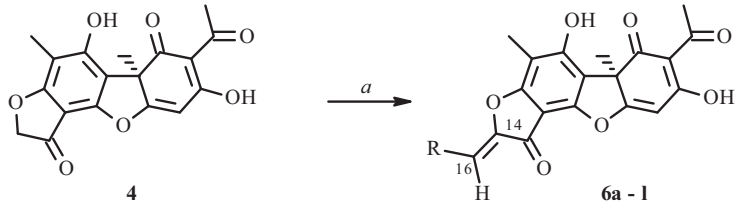


a. AcOK, acetone, reflux, 2h; *b*. AcOK/AcOH, acetone, RT, 2 d

Scheme 2

Compound **4**, which contained an active methylene, was condensed with aldehydes. Substituted benzofuranones are known to be used as starting compounds for synthesizing aurones (benzylidenebenzofuranones), natural compounds that are described in the literature as antifungal [6] and antibacterial agents [7]; insect antifeedants [8]; antioxidants [9]; inhibitors of tyrosinase [10] and acetylcholinesterase [11]; and antitumor [12] and anti-inflammatory agents [8].

The reaction of **4** with a slight excess (1:1.1) of aromatic benzaldehydes was carried out at 60°C for 1–1.5 h in aqueous MeOH in the presence of KOH. The yields of **6a–d** and **6f–i** were from 55 to 74% (Scheme 3). Benzaldehyde reacted with a strong acceptor, with a nitro group in the *m*-position, at room temperature. However, the aurone yield was the lowest in the studied series (35%, **6e**).



R = Ph (**6a**), 4-FC_6H_4 (**6b**), 4-ClC_6H_4 (**6c**), 4-BrC_6H_4 (**6d**), 3-NO_2-C_6H_4 (**6e**), 4-$MeOC_6H_4$ (**6f**), 2-$MeOC_6H_4$ (**6g**), 3,4-$MeOC_6H_3$ (**6h**), 3,4,5-$MeOC_6H_2$ (**6i**), furan-2-yl (**6j**), *n*-C_3H_7 (**6k**), *n*-C_9H_{19} (**6l**)

a. KOH, MeOH, 1–1.5 h

Scheme 3

Resonances corresponding to a single stereoisomer were observed in PMR spectra of all prepared compounds. The configuration of the C_{14}–C_{16} double bond was established for **6g** using quantum-chemical calculations and NMR spectra.

The SSCC between H-16 and C-13 in **6g** was 3.2 Hz in the single-resonance spectrum. However, we could not find literature data for the configuration determination of the double bond in aurones that were based on this constant. Therefore, conformational analysis and DFT quantum-chemical calculations were carried out in order to establish the configuration of the C_{14}–C_{16} double bond in **6g**. As a result, it was found that the *Z*-isomer had a principal conformer in which the aromatic substituent was situated in the same plane with the C_{14}–C_{16} double bond and the MeO group was located on the same side as the H-16 proton. Two conformers of energy greater than the ground state by 3.7 and 3.8 kcal/mol corresponded to placement of the MeO group over and below the molecular plane for the case where it was directed to the opposite side relative to the H-16 proton. Only one position of the aromatic substituent was possible for the *E*-isomer. The MeO group in this was directed toward the side of the H-16 proton. This structure was less stable than that of the principal *Z*-isomer by 2.6 kcal/mol. A comparison of the experimental chemical shifts (8.23 ppm) and those calculated for the *Z*-isomer (8.65) and *E*-isomer (10.75) of the C-22 *o*-proton showed better agreement with the *Z*-isomer. The same trend was observed for the shifts of C atoms of the C_{14}–C_{16} double bond (Table 1).

Data from NOESY spectra were also in good agreement with the *Z*-configuration of the C_{14}–C_{16} bond in **6g** and the calculated basic conformation for this case. Thus, cross peaks between H-22 and C-10 methyl protons (calculated distance ~2.9 Å) and between H-16 and the MeO protons were found in the NOE spectrum. Cross peaks between H-22 and H-16 and between methyl protons C-23 and C-10 were not observed.

TABLE 1. Experimental and Calculated Values of Several ^{1}H and ^{13}C Chemical Shifts of **6g**

Atom	δ, ppm, *Z*	δ, ppm, *E*	δ, ppm, exp.	Atom	δ, ppm, *Z*	δ, ppm, *E*	δ, ppm, exp.
H-16	7.58	7.80	7.39	C-16	102.25	114.66	106.26
H-19	6.84	6.80	6.91	C-17	124.08	124.19	121.15
H-20	7.36	7.46	7.35	C-18	161.92	160.05	158.65
H-21	7.13	7.17	7.05	C-19	107.92	106.17	110.63
H-22	8.65	10.75	8.23	C-20	130.54	133.13	131.29
H-23	3.95	3.93	3.89	C-21	120.19	120.70	120.75
C-13	174.61	173.76	179.60	C-22	132.74	134.35	131.56
C-14	151.50	154.08	147.49	C-23	52.24	52.15	55.46

We assigned the *Z*-configuration to **6a–6i** in analogy with the established structure of **6g** and in agreement with literature data [13] for the configuration of the double bond in aurones.

Thus, the condensation of **4** with substituted benzaldehydes enabled us to produce a series of compounds **6a–i** that were aurones with the *Z*-configuration of the double bond.

We found that heteroaromatic and aliphatic aldehydes also underwent condensation with **4**. Thus, the reaction with furfurol occurred at room temperature in MeOH:KOH (aqueous) to afford **6j** in 65% yield. The condensation with aliphatic aldehydes occurred at room temperature but not as smoothly. The desired condensation products with butyryl and decyl aldehydes were isolated in yields of 20 and 13%, respectively. The reaction with acrolein produced a complicated product mixture.

Thus, bromination of (+)-UA was carried out for the first time. The resulting mono-bromo derivative was converted readily by KOAc by intramolecular cyclization into the (+)-UA derivative containing an annelated dihydrofuran-3-one fragment. The furanone derivative was condensed with aldehydes. Aurones were synthesized by the reactions with aromatic aldehydes. Reactions with aliphatic aldehydes gave the lowest yields of the performed reactions.

EXPERIMENTAL

Analytical and spectral studies were carried out in the Chemical Collective Use Service Center of the SB RAS. PMR spectra and ^{13}C NMR spectra of **6g** were recorded on a DRX-500 spectrometer (operating frequencies 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C). Spectra of other compounds were recorded on an AV-400 spectrometer (operating frequencies 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) (Bruker). The internal standards were the $CD(H)Cl_3$ resonances (δ_H 7.24 ppm, δ_C 76.90 ppm). The structure was established using 1D and 2D spectra (with tuning on $^{1}J_{H,C}$ = 160 Hz for HSQC and $^{n}J_{H,C}$ = 7 Hz for HMBC).

The initial set of conformers for both possible isomers at the C_{14}–C_{16} double bond of **6g** was obtained using the ChemAxon Marvin (conformers plugin) program [14]. Then, the structures were optimized by the RM1 method [15] in the MOPAC2009 program [16]. Conformers for structures with the lowest energy were sought using the Confab systematic generator [17] and then optimized by the DFT method [PBE functional [18], L1 basis set (Λ01 [19], an analog of cc-pVDZ) of the PRIRODA program [20]). Chemical shifts were calculated by the GIAO/DFT/PBE method [L22 basis set Λ22, an analog of cc-pCVTZ) of the PRIRODA program]. Quantum-chemical calculations were carried out on the cluster of the Information-Calculation Center of Novosibirsk State University.

Mass spectra (ionizing-electron energy 70 eV) were recorded on a DFS high-resolution mass spectrometer (Thermo Scientific). Melting points were measured on a Kofler stage. Reactions were monitored using TLC. Specific rotation was expressed in $(deg \cdot mL) \cdot (g \cdot dm)^{-1}$; solution concentrations, $g \cdot (100\ mL)^{-1}$.

(+)-Usninic acid (**1**) was isolated from a mixture of lichens of the genus *Usnea* by the literature method [21], $[\alpha]_D$ +478° (*c* 0.1, $CHCl_3$). Column chromatography used silica gel (60-200 μm, Merck). TLC was performed on Sorbfil plates (UV 254). Atomic numbering in compounds was given for assigning resonances in NMR spectra and did not always agree with the systematic atomic numbering.

Reaction of (+)-Usninic Acid with a Two-fold Excess of Br_2. Usninic acid (1 mmol, 344 mg) was treated with the bromine–dioxane complex (2 mmol Br_2, 0.10 mL, dissolved in dioxane, 14 mL) and several drops of HBr and left for 7 d at

room temperature. The reaction mixture was concentrated in a rotary evaporator and chromatographed over silica gel (60–200 μm) with elution by CH_2Cl_2.

(*R*)-2-Acetyl-6-(2-bromoacetyl)-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (2). Yield 283 mg (67%), mp 97–100°C, $[\alpha]_D$ +349° (*c* 0.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 842, 1140, 1292, 1458, 1628, 3013, 3497.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.75 (3H, s, H-15), 2.08 (3H, s, H-10), 2.64 (3H, s, H-12), 4.52 (2H, dd, J = 12.4, 14.0, H-14), 6.00 (1H, s, H-4), 11.17 (1H, s, 9-OH), 12.68 (1H, s, 7-OH), 18.81 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.5 (C-10), 27.7 (C-12), 31.9 (C-15), 34.5 (C-14), 61.6 (C-9b), 98.7 (C-4), 99.0 (C-6), 104.3 (C-9a), 105.1 (C-2), 109.6 (C-8), 154.3 (C-5a), 158.4 (C-9), 164.1 (C-7), 178.5 (C-4a), 191.5 (C-3), 192.7 (C-13), 197.7 (C-1), 201.7 (C-11).

Found: *m*/*z* 421.9976 $[M]^+$, $C_{18}H_{15}O_7Br$; calcd: MW 421.9996.

Reaction of (+)-Usninic Acid with a Three-fold Excess of Br_2. Usninic acid (1 mmol, 344 mg) was treated with previously prepared bromine–dioxane complex (3 mmol Br_2, 0.15 mL, dioxane, 22 mL) and several drops of HBr and left for 7 d at room temperature. The reaction mixture was concentrated in a rotary evaporator to afford a mixture of **2** and **3** in a 7:3 ratio according to the PMR spectrum.

(*R*)-2-Acetyl-6-(2,2-dibromoacetyl)-3,7,9-trihydroxy-8,9b-dimethyldibenzo[*b*,*d*]furan-1(9b*H*)-one (3). IR spectrum (ν, cm^{-1}): 3499, 3012, 1628, 1458, 1292, 1189, 874.

PMR spectrum ($CDCl_3$, δ, ppm): 1.75 (3H, s, H-15), 2.10 (3H, s, H-10), 2.64 (3H, s, H-12), 6.09 (1H, s, H-4), 7.07 (1H, s, H-14), 11.33 (1H, s, 9-OH), 12.46 (1H, s, 7-OH), 18.81 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.6 (C-10), 27.7 (C-12), 31.8 (C-15), 41.5 (C-14), 58.8 (C-9b), 95.8 (C-6), 99.1 (C-4), 104.3 (C-9a), 104.9 (C-2), 110.2 (C-8), 153.5 (C-5a), 159.1 (C-9), 164.8 (C-7), 177.9 (C-4a), 187.4 (C-13), 191.4 (C-3), 197.6 (C-1), 201.8 (C-11).

Found: *m*/*z* 499.9096 $[M]^+$, $C_{18}H_{14}O_7Br_2$; calcd: MW 499.9101.

Reaction of 2 with KOAc. A solution of **2** (1 mmol, 423 mg) in acetone (25 mL) was treated with KOAc (150 mg, 1.5 mmol), refluxed for 2 h, diluted with H_2O (up to ~50–60 mL), acidified with HCl (1:4) to pH 3–4, and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried over calcined $MgSO_4$. The solvent was removed. The residue was chromatographed over a column of silica gel with elution by CH_2Cl_2.

(10*R*)-8,13-Dihydroxy-7,10-dimethyl-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (4). Yield 308 mg (90%), mp 202–203°C, $[\alpha]_D$ +397° (*c* 0.5, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.73 (3H, s, H-15), 2.13 (3H, s, H-10), 2.64 (3H, s, H-12), 4.66 (2H, s, H-14), 6.02 (1H, s, H-4), 11.27 (1H, s, 9-OH), 18.82 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 6.91 (C-10), 27.80 (C-12), 31.91 (C-15), 58.71 (C-9b), 75.70 (C-14), 99.01 (C-4), 100.61 (C-9a), 105.10 (C-6), 105.7 (C-2), 107.10 (C-8), 149.13 (C-5a), 159.80 (C-9), 173.81 (C-7), 179.61 (C-4a), 191.61 (C-3), 194.10 (C-13), 197.90 (C-1), 201.71 (C-11).

Found: *m*/*z* 342.0736 $[M]^+$, $C_{18}H_{14}O_7$; calcd: MW 342.0734.

Reaction of 2 with KOAc in the Presence of AcOH. A solution of **2** (1 mmol, 423 mg) in acetone (25 mL) was treated with AcOH (8 mL) and KOAc (150 mg, 1.5 mmol), stirred for 2 d, diluted with H_2O (up to ~50–60 mL), acidified with HCl (1:4) to pH 3–4, and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried over calcined $MgSO_4$. The solvent was removed. The residue was chromatographed over a column of silica gel with elution by CH_2Cl_2.

(9a*R*)-2-(8-Acetyl-1,3,7-trihydroxy-2,9a-dimethyl-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-yl)-2-oxoethyl Acetate (5). Yield 80 mg (20%), mp 107–110°C.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.76 (3H, s, H-15), 2.09 (3H, s, H-17), 2.24 (3H, s, H-10), 2.66 (3H, s, H-12), 5.26 (2H, dd, J = 17.3, 32.0, H-14), 5.99 (1H, s, H-4), 11.08 (1H, s, 9-OH), 12.61 (1H, s, H-7), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.39 (C-10), 20.37 (C-17), 27.69 (C-12), 31.89 (C-15), 58.79 (C-9b), 67.37 (C-14), 98.66 (C-9a), 98.75 (C-4), 104.00 (C-6), 105.13 (C-2), 109.58 (C-8), 154.55 (C-5a), 158.04 (C-9), 163.53 (C-7), 170.33 (C-16), 178.56 (C-4a), 191.52 (C-3), 194.09 (C-1), 197.73 (C-13), 201.67 (C-11).

Found: *m*/*z* 402.0943 $[M]^+$, $C_{20}H_{18}O_9$; calcd: MW 402.0945.

Reaction of 4 with Aldehydes (General Method). A solution of **4** (1 mmol, 342 mg) in MeOH (24 mL) was treated with the appropriate aldehyde (1.1 mmol) and aqueous KOH (1 mL, 50%), heated (for **6a–d** and **6f–i**) or stirred at room temperature for 1.5 h (for **6e** and **6j–l**), diluted with H_2O (up to ~50–60 mL), acidified with HCl (1:4) to pH 3–4, and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried over calcined $MgSO_4$. The solvent was removed. The residue was chromatographed over a column of silica gel with elution by CH_2Cl_2.

(10*R*,4*Z*)-4-(Benzylidene)-8,13-dihydroxy-7,10-dimethyl-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6a). Yield 262 mg (61%), mp 203°C, $[\alpha]_D$ +267° (*c* 0.45, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.78 (3H, s, H-15), 2.32 (3H, s, H-10), 2.67 (3H, s, H-12), 6.07 (1H, s, H-4), 6.81 (1H, s, H-16), 7.39 (1H, m, H-20), 7.46 (2H, m, H-19,21), 7.87 (2H, m, H-18,22), 11.42 (1H, s, 9-OH), 18.86 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.50 (C-10), 27.86 (C-12), 31.96 (C-15), 58.70 (C-9b), 99.13 (C-4), 100.85 (C-6), 105.12 (C-2), 105.77 (C-8), 108.23 (C-9a), 112.12 (C-16), 128.81 (C-18,22), 129.69 (C-20), 131.23 (C-19,21), 132.13 (C-17), 147.44 (C-14), 149.81 (C-5a), 159.36 (C-9), 165.72 (C-7), 179.57 (C-13,4a), 191.62 (C-3), 197.86 (C-1), 201.79 (C-11).

Found: *m*/*z* 430.1039 $[M]^+$, $C_{25}H_{18}O_7$; calcd: MW 430.1047.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(4-fluorobenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6b). Yield 273 mg (61%), mp 198°C, $[\alpha]_D$ +281° (*c* 0.4, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.75 (3H, s, H-15), 2.26 (3H, s, H-10), 2.66 (3H, s, H-12), 6.04 (1H, s, H-4), 6.69 (1H, s, H-16), 7.10 (2H, m, H-19,21), 7.81 (2H, m, H-18,22), 11.39 (1H, s, 9-OH), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 7.48 (C-10), 27.82 (C-12), 31.95 (C-15), 58.67 (C-9b), 99.10 (C-4), 100.76 (C-6), 105.10 (C-2), 105.69 (C-8), 108.27 (C-9a), 110.67 (C-16), 116.00 (d, J_{C-F} = 22, C-19,21), 128.43 (d, J_{C-F} = 3.18, C-17), 133.10 (d, J_{C-F} = 8.41, C-18,22), 147.01 (d, J_{C-F} = 2.64, C-14), 149.76 (C-5a), 159.29 (C-9), 163.00 (d, J_{C-F} = 252.39, C-20), 165.55 (C-7), 179.22 (C-4a), 179.48 (C-13), 191.60 (C-3), 197.82 (C-1), 201.77 (C-11).

Found: *m*/*z* 448.0957 $[M]^+$, $C_{25}H_{17}O_7F$; calcd: MW 448.0953.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(4-chlorobenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6c). Yield 255 mg (55%), mp 217°C, $[\alpha]_D$ +262° (*c* 0.3, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.75 (3H, s, H-15), 2.26 (3H, s, H-10), 2.66 (3H, s, H-12), 6.04 (1H, s, H-4), 6.67 (1H, s, H-16), 7.36 (2H, m, H-19,21), 7.74 (2H, m, H-18,22), 11.41 (1H, s, 9-OH), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.49 (C-10), 27.84 (C-12), 31.96 (C-15), 58.66 (C-9b), 99.14 (C-4), 100.68 (C-6), 105.12 (C-2), 105.75 (C-8), 108.35 (C-9a), 110.42 (C-16), 129.06 (C-19,21), 130.64 (C-17), 132.21 (C-18,22), 135.54 (C-14), 147.52 (C-20), 149.80 (C-5a), 159.41 (C-9), 165.53 (C-7), 179.15 (C-4a), 179.43 (C-13), 191.59 (C-3), 197.81 (C-1), 201.77 (C-11).

Found: *m*/*z* 464.0660 $[M]^+$, $C_{25}H_{17}O_7Cl$; calcd: MW 464.0657.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(4-bromobenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6d). Yield 270 mg (53%), mp 218–219°C, $[\alpha]_D$ +406° (*c* 0.3, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.76 (3H, s, H-15), 2.28 (3H, s, H-10), 2.65 (3H, s, H-12), 6.06 (1H, s, H-4), 6.72 (1H, s, H-16), 7.56 (2H, m, H-19,21), 7.70 (2H, m, H-18,22), 11.44 (1H, s, 9-OH), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.19 (C-10), 27.53 (C-12), 31.63 (C-15), 58.35 (C-9b), 98.88 (C-4), 100.41 (C-6), 104.81 (C-2), 105.49 (C-8), 108.05 (C-9a), 110.23 (C-16), 123.72 (C-20), 130.76 (C-17), 131.75 (C-19,21), 132.10 (C-18,22), 147.36 (C-14), 149.54 (C-5a), 159.18 (C-9), 165.28 (C-7), 178.97 (C-4a), 179.14 (C-13), 191.30 (C-3), 197.51 (C-1), 201.48 (C-11).

Found: *m*/*z* 508.0161 $[M]^+$, $C_{25}H_{17}O_7Br$; calc.: MW 508.0152.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(3-nitrobenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6e). Yield 167 mg (35%), mp 230°C (dec.), $[\alpha]_D$ +364° (*c* 0.2, CH_2Cl_2).

PMR spectrum (CD_2Cl_2, δ, ppm): 1.80 (3H, s, H-15), 2.34 (3H, s, H-10), 2.66 (3H, s, H-12), 6.09 (1H, s, H-4), 6.77 (1H, s, H-16), 7.64, 8.12, 8.21 (3H, 3m, H-20,21,22), 8.83 (4H, s, H-18), 11.53 (1H, s, 9-OH), 18.88 (1H, s, 3-OH).

^{13}C NMR spectrum (CD_2Cl_2, δ, ppm): 6.34 (C-10), 27.26 (C-12), 31.34 (C-15), 58.39 (C-9b), 98.81 (C-4), 100.05 (C-6), 104.89 (C-2), 105.63 (C-8), 107.73 (C-16), 108.49 (C-9a), 123.21, 124.81, 129.43, 136.06 (C-18,19,20,21), 133.60 (C-17), 148.17 (C-14), 148.46 (C-5a), 159.57 (C-9), 165.33 (C-7), 178.45 (C-4a), 179.09 (C-13), 191.38 (C-3), 197.70 (C-1), 201.62 (C-11).

Found: *m*/*z* 475.0895 $[M]^+$, $C_{25}H_{17}O_9N$; calcd: MW 475.0898.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(4-methoxybenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6f). Yield 300 mg (65%), mp 258–260°C, $[\alpha]_D$ +300° (*c* 0.45, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.75 (3H, s, H-15), 2.29 (3H, s, H-10), 2.65 (3H, s, H-12), 3.84 (3H, s, H-23), 6.04 (1H, s, H-4), 6.78 (1H, s, H-16), 6.95 (2H, m, H-19,21), 7.81 (2H, m, H-18,22), 11.34 (1H, s, 9-OH), 18.83 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.54 (C-10), 27.88 (C-12), 32.00 (C-15), 58.28 (C-23), 58.80 (C-9b), 99.06 (C-4), 102.93 (C-6), 105.14 (C-2), 105.65 (C-8), 108.06 (C-9a), 112.38 (C-16), 114.43 (C-19,21), 124.92 (C-17), 133.10

(C-18,22), 146.42 (C-14), 149.81 (C-5a), 158.99 (C-9), 160.85 (C-20), 165.56 (C-7), 179.42 (C-4a), 179.77 (C-13), 191.65 (C-3), 197.94 (C-1), 201.79 (C-11).

Found: *m*/*z* 460.1148 $[M]^+$, $C_{26}H_{20}O_8$; calcd: MW 460.1153.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(2-methoxybenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6g). Yield 340 mg (74%), mp 206–208°C, $[\alpha]_D$ +362° (*c* 0.4, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.76 (3H, s, H-15), 2.29 (3H, s, H-10), 2.65 (3H, s, H-14), 3.89 (3H, s, H-23), 6.06 (1H, s, H-4), 6.91 (1H, dd, $J_{19,20}$ = 8.3, $J_{19,21}$ = 0.7, H-19), 7.05 (1H, ddd, $J_{21,22}$ = 7.8, $J_{21.20}$ = 0.7, H-21), 7.35 (1H, ddd, $J_{20,19}$ = 8.3, $J_{20,21}$ = 7.4, $J_{20,22}$ = 1.7, H-20), 7.39 (1H, s, H-16), 8.23 (1H, dd, $J_{22,21}$ = 7.8, $J_{22.20}$ = 1.7, H-22), 11.37 (1H, s, 9-OH), 18.86 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.54 (C-10), 27.94 (C-12), 31.99 (C-15), 55.46 (C-23), 58.77 (C-9b), 99.08 (C-4), 101.14 (C-6), 105.11 (C-2), 105.69 (C-8), 106.26 (C-16), 108.02 (C-9a), 110.63 (C-19), 120.75 (C-21), 121.15 (C-17), 131.29 (C-20), 131.56 (C-22), 147.49 (C-14), 149.74 (C-5a), 158.65 (C-18), 159.06 (C-9), 165.62 (C-7), 179.60 (C-13), 179.76 (C-4a), 191.65 (C-3), 197.91 (C-1), 201.82 (C-11).

Found: *m*/*z* 460.1154 $[M]^+$, $C_{26}H_{20}O_8$; calcd: MW 460.1153.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(3,4-dimethoxybenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6h). Yield 295 mg (60%), mp 230°C (dec.), $[\alpha]_D$ +273° (*c* 0.2, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.74 (3H, s, H-15), 2.26 (3H, s, H-10), 2.65 (3H, s, H-12), 3.91, 3.95 (6H, 2s, H-23,24), 6.02 (1H, s, H-4), 6.72 (1H, s, H-6), 6.88 (1H, d, J = 8.5, H-21), 7.30 (1H, m, H-22), 7.54 (1H, d, J = 1.9, H-18), 11.38 (1H, s, 9-OH), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.34 (C-10), 27.84 (C-12), 32.02 (C-15), 55.50, 55.79 (C-23,24), 58.72 (C-9b), 99.00 (C-4), 101.08 (C-6), 105.08 (C-2), 105.31 (C-8), 108.09 (C-9a), 110.95 (C-18), 112.53 (C-16), 112.85 (C-21), 125.08 (C-17), 125.81 (C-22), 146.36 (C-14), 148.80 (C-20), 149.69 (C-5a), 150.49 (C-19), 158.09 (C-9), 165.34 (C-7), 179.10 (C-13), 179.56 (C-4a), 191.60 (C-3), 197.85 (C-1), 201.79 (C-11).

Found: *m*/*z* 490.1254 $[M]^+$, $C_{27}H_{22}O_9$; calcd: MW 490.1258.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(3,4,5-trimethoxybenzylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6i). Yield 385 mg (72%), mp 174–176°C, $[\alpha]_D$ +224° (*c* 0.4, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.72 (3H, s, H-15), 2.23 (3H, s, H-10), 2.63 (3H, s, H-12), 3.87 (3H, s, H-24), 3.89 (6H, s, H-23,25), 6.02 (1H, s, H-4), 6.65 (1H, s, H-16), 7.09 (2H, s, H-18,22), 11.39 (1H, s, 9-OH), 18.82 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.28 (C-10), 27.80 (C-12), 31.98 (C-15), 55.80 (C-24,25), 58.67 (C-9b), 60.83 (C-23), 99.11 (C-4), 100.87 (C-6), 105.09 (C-2), 105.32 (C-8), 108.24 (C-9a), 108.30 (C-18,22), 112.23 (C-16), 127.43 (C-17), 139.56 (C-20), 146.95 (C-14), 149.79 (C-5a), 153.04 (C-19,21), 159.15 (C-9), 165.41 (C-7), 179.11 (C-4a), 179.47 (C-13), 191.61 (C-3), 197.80 (C-1), 201.79 (C-11).

Found: *m*/*z* 520.1374 $[M]^+$, $C_{28}H_{24}O_{10}$; calcd: MW 520.1364.

(10*R*,4*Z*)-8,13-Dihydroxy-7,10-dimethyl-4-(furan-2-ylmethylene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}] hexadeca-1,6,8,12,14-pentaen-3,11-dione (6j). Yield 335 mg (65%), mp 188–192°C, $[\alpha]_D$ +365° (*c* 0.3, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 1.76 (3H, s, H-15), 2.29 (3H, s, H-10), 2.65 (3H, s, H-12), 6.05 (1H, s, H-4), 6.59 (1H, s, H-16), 6.83 (1H, m, H-19), 7.07 (1H, m, H-18), 7.58 (1H, m, H-20), 11.38 (1H, s, 9-OH), 18.83 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.41 (C-10), 27.89 (C-12), 31.96 (C-15), 58.72 (C-9b), 99.13 (C-4), 101.30 (C-6), 100.84 (C-19), 105.13 (C-2), 105.80 (C-8), 108.19 (C-9a), 113.01 (C-18), 116.69 (C-16), 145.03 (C-20), 145.70 (C-14), 148.65 (C-17), 149.67 (C-5a), 159.21 (C-9), 165.30 (C-7), 178.78 (C-4a), 179.63 (C-13), 191.64 (C-3), 197.89 (C-1), 201.81 (C-11).

Found: *m*/*z* 420.0839 $[M]^+$, $C_{23}H_{16}O_8$; calcd: MW 420.0840.

(10*R*)-4-(Butylidene)-8,13-dihydroxy-7,10-dimethyl-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6k). Yield 78 mg (20%), mp 65–70°C, $[\alpha]_D$ +242° (*c* 0.5, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.00 (3H, t, J = 7.4, H-19), 1.58 (2H, q, J = 7.4, H-18), 1.75 (3H, s, H-15), 2.21 (3H, s, H-10), 2.43 (2H, q, J = 7.4, H-17), 2.66 (3H, s, H-12), 6.04 (1H, s, H-4), 6.10 (1H, t, J = 7.9, H-16), 11.32 (1H, s, 9-OH), 18.84 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.39 (C-10), 13.75 (C-19), 21.76 (C-18), 27.80 (C-12), 29.55 (C-17), 31.98 (C-15), 58.74 (C-9b), 99.04 (C-4), 105.03 (C-6), 105.09 (C-2), 106.60 (C-8), 109.20 (C-9a), 116.60 (C-16), 149.50 (C-14), 149.63 (C-5a), 157.42 (C-9), 171.15 (C-7), 179.20 (C-4a), 179.30 (C-13), 191.63 (C-3), 197.92 (C-1), 201.78 (C-11).

Found: *m*/*z* 396.1207 $[M]^+$, $C_{22}H_{20}O_7$; calcd: MW 396.1204.

(10*R*)-8,13-Dihydroxy-7,10-dimethyl-4-(decylidene)-5,16-dioxatetracyclo[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1,6,8,12,14-pentaen-3,11-dione (6l). Yield 66 mg (13%), mp 65–70°C, $[\alpha]_D$ +304° (*c* 0.4, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84 (3H, t, J = 7.4, H-25), 1.24 (H, m, H-19–H-24), 1.53 (2H, m, H-18), 1.74 (3H, s, H-15), 2.19 (3H, s, H-10), 2.42 (2H, q, J = 7.4, H-17), 2.64 (3H, s, H-12), 6.03 (1H, s, H-4), 6.08 (1H, t, J = 7.9, H-16), 11.30 (1H, s, 9-OH), 18.82 (1H, s, 3-OH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 7.20 (C-10), 13.97 (C-25), 22.54 (C-24), 25.60, 28.41-29.48 (C-18–C-23), 27.87 (C-12), 31.95 (C-17), 58.75 (C-9b), 99.03 (C-4), 101.4 (C-6), 105.10 (C-2), 105.52 (C-8), 107.66 (C-9a), 116.66 (C-16), 149.52 (C-14), 149.77 (C-5a), 159.21 (C-9), 165.84 (C-7), 178.80 (C-4a), 179.77 (C-13), 191.64 (C-3), 197.93 (C-1), 201.77 (C-11).

Found: *m*/*z* 480.2144 $[M]^+$, $C_{28}H_{32}O_7$; calcd: MW 480.2143.

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