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Synthesis and Structure of Biologically Active 1,2-Bis(2-oxocycloalkyl)ethane-1,2-diones and 3,4-Dioxo-4-(2-oxocycloalkyl)butanoic Acid Esters

P. P. Mukovoz[a]*, E. S. Dankovtseva[a], V. P. Mukovoz[a], V. V. Abramova[a], D. S. Korol'kova[b], A. N. Sizentsov[b], and E. A. Danilova[c]

[a] *All-Russian Research Institute of Phytopathology, ul. Institut 5, Bol'shie Vyazemy, Moscow oblast, 143050 Russia*
**e-mail: mpp27@mail.ru*

[b] *Orenburg State University, pr. Pobedy 13, Orenburg, 460018 Russia*

[c] *Ivanovo State University of Chemistry and Technology, Sheremetevskii pr. 7, Ivanovo, 153000 Russia*

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Abstract—A two-step procedure has been proposed for the synthesis of 1,2-bis(2-oxocycloalkyl)ethane-1,2-diones and 3,4-dioxo-4-(2-oxocycloalkyl)butanoic acid esters by condensation of cycloalkyl ketones with dimethyl oxalate or of alkyl acetates with dialkyl oxalates and cycloalkyl ketones, respectively. The structure of the synthesized compounds has been discussed on the basis of their IR, ^{1}H NMR, and mass spectra, and their antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhimurium* strains has been estimated.

Keywords: 1,3,4,6-tetracarbonyl compounds, cycloalkyl ketones, 1,2-bis(2-oxocycloalkyl)ethane-1,2-diones, 3,4-dioxo-4-(2-oxocycloalkyl)butanoic acid esters

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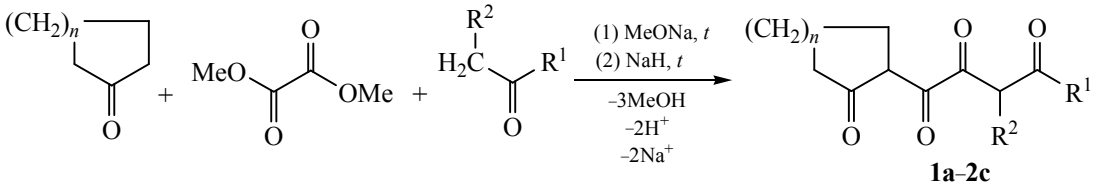
It is known that 1,3,4,6-tetracarbonyl compounds obtained by condensation of methylene carbonyl compounds (alkyl methyl ketones or alkyl acetates) with dialkyl oxalates (Claisen condensation) are successfully used in organic synthesis for the preparation of practically important products and biologically active substances [1, 2].

Published data on the synthesis of 1,3,4,6-tetracarbonyl compounds from cycloalkyl ketones as active methylene component are limited to a few studies where reactions of diethyl oxalate with ketones of the terpene series (camphor, norcamphor, nopinone) have been described [3–5]. These reactions afforded some 1,3,4,6-tetracarbonyl compounds containing cycloaliphatic fragments in the tetracarbonyl moiety, 1,2-bis-[(1*R*,4*R*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yl]-ethane-1,2-dione [3–5], 1,2-bis(3-oxobicyclo[2.2.1]-hept-2-yl)ethane-1,2-dione [5], and 1,2-bis[(1*R*,5*R*)-6,6-dimethyl-2-oxobicyclo[3.1.1]hept-3-yl]ethane-1,2-dione [5]. There are no published data on the synthesis of 1,3,4,6-tetracarbonyl compounds by condensation of other cycloalkyl ketones (e.g., cyclopentanone or cyclohexanone) with dialkyl oxalates.

We failed to obtain the corresponding 1,3,4,6-tetraketones by condensation of cyclopentanone or cyclohexanone with dimethyl, diethyl, dipropyl, or dibutyl oxalate under the reported conditions; obviously, the procedures described in [3–5] are not universal. The reactions were accompanied by tar formation, and we succeeded in isolating from the reaction mixtures only 2-oxo-2-(2-oxocycloalkyl)acetic acids [6] that are products of decomposition of the corresponding commercial esters. Presumably, the efficiency of the procedures proposed in [3, 5] is insufficient due to low reactivity of cycloalkyl ketones in comparison to alkyl methyl ketones and alkyl acetate (classical reagents in the Claisen condensation), as well as due to the fact that the synthesis is carried out in one step. Dis-advantages of one-step methods of synthesis of 1,3,4,6-tetracarbonyl compounds, in particular accumulation in the reaction system of alcohol resulting from elimination of alkoxy groups from the reactants, as well as long reaction time promoting formation of by-products in low-boiling solvents, were discussed by us previously [2].

To eliminate the above drawbacks, we have developed a simple and convenient two-step procedure

Scheme 1.



1a–**2c**

$R^1 + R^2 = (CH_2)_m$, $m = 3$, $n = 1$ (**1a**); $R^1 + R^2 = (CH_2)_m$, $m = 4$, $n = 2$ (**1b**); R^1 = OMe, R^2 = H, $n = 1$ (**2a**); R^1 = OMe, R^2 = H, $n = 2$ (**2b**); R^1 = OEt, R^2 = H, $n = 1$ (**2c**).

for the preparation of C^3–C^4-axisymmetric and unsymmetrical 1,3,4,6-tetracarbonyl compounds containing cycloaliphatic fragments in the tetracarbonyl moiety. A peculiar feature of the proposed procedure is the use of a minimum amount of a relatively high-boiling solvent (1,4-dioxane) and of different condensing agents in the first and second steps, namely sodium alkoxide in the first step and sodium hydride in the second step. These conditions simultaneously ensured maintenance of a high concentration of the reactants and reduced the accumulation of alcohol (departing group) which reacted with sodium hydride in the second step. A relatively high boiling temperature of the solvent (101°C) considerably improves the efficiency due to shortening of the reaction time (15–20 min), which minimizes formation of by-products [2, 7].

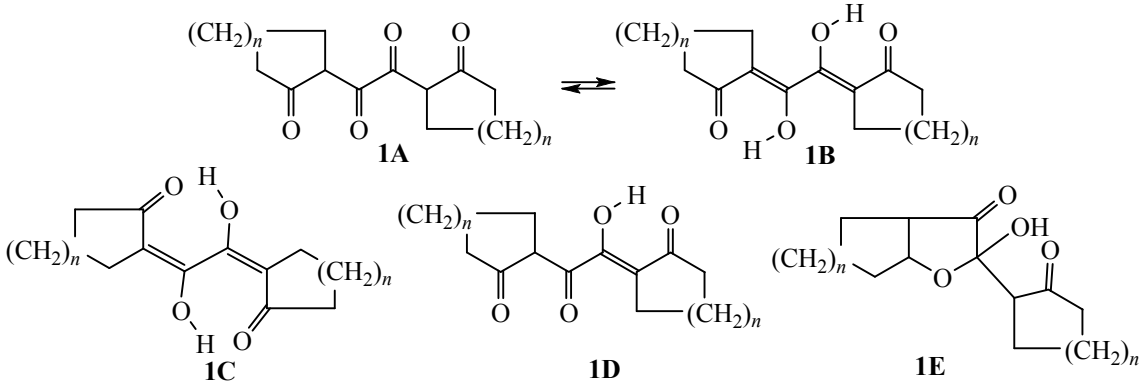
By the two-step reactions of cycloalkyl ketones with dimethyl oxalate we have synthesized for the first time 1,2-bis-(2-oxocycloalkyl)ethane-1,2-diones **1a** and **1b** in 34 and 27% yield, respectively (Scheme 1). The first step was the condensation of cyclopentanone or cyclohexanone and dimethyl oxalate (reactant ratio 1 : 1) in the presence of an equimolar amount of sodium methoxide. In the second step, equimolar amounts of the corresponding cycloalkyl ketone and sodium hydride were added to the reaction mixture.

The two-step reactions of alkyl acetates with dialkyl oxalates and cycloalkyl ketones afforded 29–41% of previously unknown 3,4-dioxo-4-(2-oxocycloalkyl)butanoic acid esters **2a**–**2c**. In the first step, alkyl acetate reacted with the corresponding dialkyl oxalate and sodium alkoxide, and subsequent addition of equimolar amounts of cyclopentanone or cyclohexanone and sodium hydride led to the formation of the target esters (Scheme 1).

Compounds **1a**, **1b**, and **2a**–**2c** are colorless crystalline solids that are insoluble in water and soluble in most organic solvents. Their structure was determined on the basis of IR, ^{1}H NMR, and high-resolution mass spectra.

Unlike all known tetracarbonyl compounds which exist in crystal as dioxodienol tautomers (bis-H-chelates), crystalline compounds **1a** and **1b** have tetraketone structure **1A** (Scheme 2). This follows from their IR spectra which show absorption bands at 2971–2854 cm^{-1} typical of stretching vibrations of methylene groups of the cycloaliphatic fragments and two relatively high-frequency carbonyl bands at 1728–1727 and 1689–1680 cm^{-1} due to unconjugated $C^{1(6)}$=O and $C^{3(4)}$=O carbonyl groups [2, 9, 8–12]. A strong band at 1460–1455 cm^{-1} corresponding to

Scheme 2.



scissoring vibrations of the methylene groups confirmed the presence of methylene chains closed to form aliphtaic rings [8]. The IR spectra of **1a** and **1b** contain no absorption bands in the regions 3400–2500 (νOH) and 1400–1200 cm^{-1} (δOH, in-plane), which rules out enol structure of their molecules in crystal. The tetraketone structure of **1a** and **1b** is also confirmed by the absence of bands in the region 1600–1450 cm^{-1} typical of the diene fragment of known tetracarbonyl compounds in the enol form [1, 2, 8–14].

Unlike crystalline state, compounds **1a** and **1b** in solution in both polar (DMSO-d_6) and nonpolar solvents ($CDCl_3$) exist in the dioxodienol bis-OH-chelate form **1B** which is typical of tetracarbonyl compounds (Scheme 2). The ^{1}H NMR spectra of **1a** and **1b** contain methylene proton signals of the cycloaliphatic fragments at δ 1.90–3.00 ppm and a singlet in the region δ 9.10–13.80 ppm due to two magnetically equivalent $C^{3(4)}$OH enol hydroxy groups of the C^3–C^4-axisymmetric *Z*,*Z*′-dienol tautomer **1B**. It should be noted in the ^{1}H NMR spectra of structurally related 1,6-dialkyl-1,3,4,6-tetraketones, signals of the $C^{3(4)}$OH protons of the *Z*,*Z*′ tautomer were located in a close region, at δ 14.60–14.92 ppm [2, 8–14].

There are no signals downfield from δ 15.50 ppm, which could be assigned to *E*,*E*′-dienol tautomer **1C** (Scheme 2). This structure is untypical of all known tetracarbonyl compounds but was identified for structurally related 1,2-bis[(1*R*,4*R*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yl]ethane-1,2-diones [3–5]. Furthermore, the ^{1}H NMR spectra of **1a** and **1b** lacks signals in the region δ 3.00–4.00 ppm characteristic of tetraketone structure **1A** and probable keto–enol tautomer **1D** found in solution of 3,4-dioxohexanedioic acid esters [2, 7, 12].

In the ^{1}H NMR spectra of **1a** and **1b** in DMSO-d_6 we observed no hemiacetal OH signal at δ 8.00–7.00 ppm; this signal is typical of ring oxofuran tautomer **1E** present in solutions of most known 1,3,4,6-tetraketones in DMSO [2, 12, 14, 15].

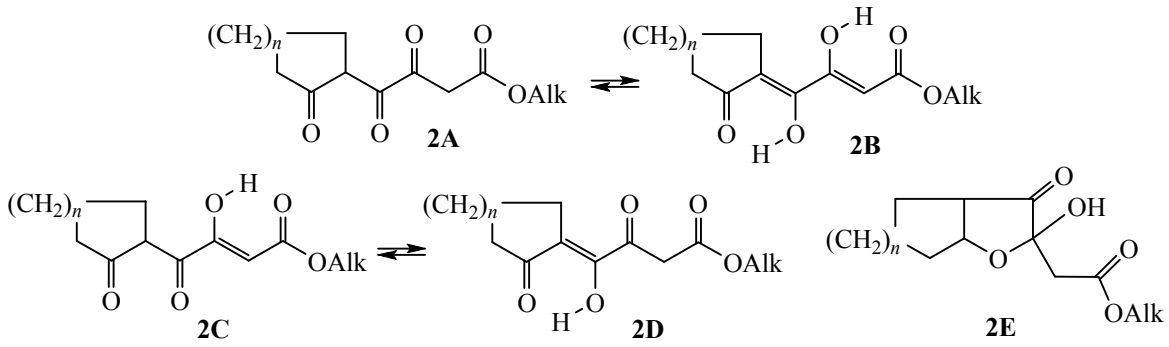
The structure of **1a** and **1b** is also confirmed by the high-resolution mass spectra (electrospray ionization from acetonitrile solution) which displayed protonated molecular ion peaks $[M + H]^+$.

Compounds **2a**–**2c** may be regarded as intermediate structures between their closest analogs, 3,4,6-trioxoalkanoic acid esters [1, 2], and tetraketones **1** [14, 15]. Like most known tetracarbonyl compounds, esters **2a**–**2c** in crystal have *Z*,*Z*′-dioxodienol structure **2A**. The IR spectra of crystalline samples of **2a**–**2c** showed a broadened low-frequency OH stretching band in the region 3400–2900 cm^{-1}, a strong absorption band at 1201–1176 cm^{-1} due to in-plane bending vibrations of the O–H groups, and bands typical of C–H stretching vibrations of alkoxy and endocyclic methylene groups (2956–2852 cm^{-1}). The low frequency and broadening of the νOH band suggests OH···O=C intramolecular hydrogen bonding in the dioxodienol fragment of **2a**–**2c** with the formation of two H-chelate rings. Structure **2A** is also supported by the presence of low-frequency ester carbonyl stretching band at 1639–1632 cm^{-1} (C^1=O) and broadened band at 1553–1548 cm^{-1} due to the C^6=O ketone carbonyl conjugated with the diene fragment. The band at 1129–1079 cm^{-1} was assigned to stretching vibrations of the ester C–O–C group. Similar spectral patterns were observed for structural analogs of compounds **2a**–**2c**, 3,4,6-trioxoalkanoic [3300–2400 (OH), 1653–1633 (AlkOC=O), 1616–1607 (AlkC=O), 1580–1566 cm^{-1} (C=C)] [1, 2] and 3,4-dioxohexanedioic acid esters [3480–2600 (OH), 1660–1638 (AlkOC=O), 1630–1589 (C=C), 1236–1166 cm^{-1} (AlkO–C)] [2, 7, 12] and 1,6-dialkyl-1,3,4,6-tetraketones [3300–2400 (OH), 1623–1607 (C=O), 1568–1557 cm^{-1} (C=C)] [2, 14, 15], which also have the structure of *Z*,*Z*′-dioxodienol tautomers in crystal.

According to the ^{1}H NMR data ($CDCl_3$), compounds **2a**–**2c** in nonpolar solvents are represented by oxo tautomer **2A** (17–11%) and dioxodienol structure **2B** (89–83%, Scheme 3); the latter is typical of nonpolar solutions of most known tetracarbonyl compounds [1, 2, 12, 13, 15]. Tautomer **2B** in $CDCl_3$ is characterized by methylene proton signals of the cycloaliphatic fragment at δ 0.91–3.00 ppm, signals of the alkoxy group, C^2H singlet at δ 5.54–5.97 ppm, and two signals of nonequivalent enolic C^3OH and C^4OH groups at δ 11.35–11.91 and 13.09–13.67 ppm. In the ^{1}H NMR spectra of analogs of **2a**–**2c**, 3,4-dioxohexanedioic acid esters, the $C^{2(5)}$H and $C^{3(4)}$OH signals are located at δ 5.79–5.88 and 11.64–11.80 ppm, respectively [2, 12]. Minor oxo tautomer **2A** in $CDCl_3$ gives rise to signals at δ 0.85–2.90 ppm due to methylene protons of the cycloaliphatic fragment and singlets at δ 3.84–3.93 (C^2H_2) and 3.27–3.51 ppm (C^5H).

As follows from the ^{1}H NMR spectra of compounds **2a**–**2c** in DMSO-d_6, the major tautomer in polar solvents is keto–enol **2C** (79–56%, Scheme 3), and structure **2D** differing by the position of the enol fragment is the minor one (21–44%). The major

Scheme 3.



tautomer is characterized by signals of the C^2H proton at δ 5.64–5.85 ppm and enol C^3OH proton at δ 11.90–11.98 ppm, as well as by a singlet at δ 3.58–3.62 ppm due to C^5H. Characteristic signals of minor tautomer **2D** are those of two equivalent methylene protons on C^2 (δ 3.75–3.77 ppm) and enol C^4OH group (δ 8.10–8.15 ppm). The absence of a signal at 8.00–7.00 ppm, which could be assigned to hemiacetal hydroxy group, excludes the presence of oxofuran tautomer **2E** typical of structurally related 3,4,6-trioxoalkanoic acid esters in polar solvents [2, 13].

The mass spectra of **2a**–**2c** showed the corresponding $[M + H]^+$ and $[M + Na]^+$ ion peaks.

Compounds **1a**, **1b**, and **2a**–**2c** were tested for antimicrobial activity against gram-positive (*Staphylococcus aureus* P–209) and gram-negative bacteria (*Escherichia coli* M_{17}, *Salmonella typhimurium* 14028S WT). It was found that the activity of **1a**, **2b**, and **2c** against *S. aureus* is comparable to the activity of ethacridine lactate (see the table). The activity of **2a** and **2c** against *E. coli* exceeded that of ethacridine lactate and were comparable to that of nitrofurazone. A similar level of activity was revealed for compounds **1a**, **1b**, and **2a** with respect to *Salmonella typhimurium*. Presumably, the antimicrobial activity of the examined compounds is determined by the presence of cycloaliphatic fragments in their molecules; such fragments are also present in the molecules of some known biologically active compounds (camphor, jasmone, tetracycline, etc.). Compounds **1a**, **2a**, and **2c** containing a cyclopentane fragment showed the highest antimicrobial activity.

In summary, we have developed a simple and convenient two-step procedure for the synthesis of 1,3,4,6-tetracarbonyl compounds containing cycloaliphatic fragments as a part of the tetracarbonyl moiety. The procedure implies carrying out the reaction in a minimum amount of 1,4-dioxane with the use of different condensing agents in the first and second steps. It makes it possible to obtain 1,3,4,6-tetracarbonyl compounds which were previously inaccessible by other methods. The synthesized compounds possess antimicrobial activity which is likely to originate from the presence of cycloaliphatic fragments in their molecules. Compounds containing a cyclopentanone fragment exhibit the highest antimicrobial activity.

Antimicrobial activity (minimum inhibitory concentration, μg/mL) of compounds **1a**, **1b**, and **2a**–**2c**[a]

Compound	*St. aureus* P–209	*E. coli* M_{17}	*S. typhimurium* 14028S WT
1a	500	2000	125
1b	1000	No activity	500
2a	500	500	500
2b	No activity	2000	No activity
2c	500	1000	1000
Ethacridine lactate	500	2000	1000
Nitrofurazone	125	500	125

[a] Statistically significant data with respect to control ($p = 0.001$).

EXPERIMENTAL

The IR spectra of crystalline samples were recorded on a Bruker Alpha spectrometer with Fourier transform, equipped with a ZnSe ATR accessory (incidence angle –45°). The ^{1}H NMR spectra were measured from solutions in $CDCl_3$ and DMSO-d_6 on a Bruker Avance II spectrometer at 400 MHz relative to tetramethylsilane as internal standard. The mass spectra were obtained on a Bruker Daltonik MaXis Impact HD quadrupole time-of-flight mass spectrometer (electrospray ionization from solutions in acetonitrile, flow rate 240 μL/h; default parameters for infusion analysis of small molecules; external mass calibration according to an improved quadratic method using an Agilent Technologies calibration solution, part no. G1969-85000.

The antimicrobial activity of compounds **1a**, **1b**, and **2a**–**2c** was evaluated by the serial dilution method in meat infusion broth at a bacterial load of 5×10^9 CFU/mL. Each experiment was performed in triplicate. The minimum inhibitory concentrations were determined. The inhibitory effect was confirmed by inoculation into solid nutrient media from each test tube. Nitrofurazone and ethacridine lactate were used as reference drugs. The results were statistically processed by calculating Student *t*-test using XL 2012 program. The effect was considered to be reliable at $p < 0.001$.

1,2-Bis(2-oxocycloalkyl)ethane-1,2-diones 1a and 1b and alkyl 3,4-dioxo-4-(2-oxocycloalkyl)butanoates 2a–2c *(general procedure).* A mixture of 20 mL of 1,4-dioxane, 2.0 g (50 mmol) of a 60% suspension of sodium hydride in mineral oil, and 2.0 mL of anhydrous methanol (in the synthesis of **1a**, **1b**, **2a**, and **2b**) or 2.9 mL of anhydrous ethanol (in the synthesis of **2c**) was refluxed for 10 min to obtain the corresponding sodium alkoxide. A mixture of 5.9 g (50 mmol) of dimethyl oxalate (**1a**, **1b**, **2a**, **2b**) and 4.4 mL (50 mmol) of cyclopentanone (**1a**) or 5.2 mL (50 mmol) of cyclohexanone (**1b**) or 4.0 mL (50 mmol) of methyl acetate (**2a**, **2b**) or 4.6 mL (50 mmol) of ethyl acetate (**2c**) was added, the mixture was refluxed for 10 min, 2.0 g (50 mmol) of a 60% suspension of sodium hydride in mineral oil was added, and a mixture of 10 mL of 1,4-dioxane and 4.4 mL (50 mmol) of cyclopentanone (**1a**, **2a**, **2c**) or 5.2 mL (50 mmol) of cyclohexanone (**1b**, **2b**) was then added. The resulting mixture was refluxed for 5 min; in the synthesis of **1b**, the mixture was stirred for 7–10 min without heating. The solvent was evaporated, 100 mL of cold 15% aqueous HCl was added to the residue, and the precipitate was filtered off on cooling and extracted with ethyl acetate on cooling. The extract was dried over anhydrous magnesium sulfate on cooling and evaporated, and the residue was crystallized from ethanol or ethyl acetate.

1,2-Bis(2-oxocyclopentyl)ethan-1,2-dione (1a). Yield 4.11 g (34%), mp 62–63°C. IR spectrum, ν, cm^{-1}: 2971 (CH_2, asym.), 2903 (CH_2, sym.), 1727 (C^1=O, C^6=O), 1680 (C^3=O, C^4=O), 1460 (δCH_2, scissor.), 1165, 1082, 1011, 839 (C–C, skeletal). ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$ (**1B**, 100%): 1.97 m (4H, 4′-H), 2.48 t (4H, 3′-H, J = 7.5 Hz), 3.00 t (4H, 5′-H, J = 7.5 Hz), 13.67 s (2H, OH); in DMSO-d_6 (**1B**, 100%): 1.96 m (4H, 4′-H), 2.47 t (4H, 3′-H, J = 7.4 Hz), 2.93 t (4H, 5′-H, J = 7.4 Hz), 9.10 s (2H, OH). Mass spectrum: m/z: 223.0967 $[M + H]^+$; calculated for $C_{12}H_{15}O_4$: 223.0965.

1,2-Bis(2-oxocyclohexyl)ethane-1,2-dione (1b). Yield 3.38 g (27%), mp 18–20°C. IR spectrum, ν, cm^{-1}: 2925 (CH_2, asym.), 2854 (CH_2, sym.), 1728 (C^1=O, C^6=O), 1689 (C^3=O, C^4=O), 1455 (δCH_2, scissor.), 1172, 1125, 1076, 1033, 975, 932, 886, 837 (C–C, skeletal)]. ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$ (**1B**, 100%): 1.90 m (8H, 4′-H, 5′-H), 2.41 t (4H, 6′-H, J = 7.6 Hz), 2.87 t (4H, 3′-H, J = 7.6 Hz), 13.80 s (2H, OH); in DMSO-d_6 (**1B**, 100%): 1.86 m (8H, 4'-H, 5′-H), 2.38 t (4H, 6′-H, J = 7.3 Hz), 2.78 t (4H, 3′-H, J = 7.3 Hz), 9.72 s (2H, OH). Mass spectrum: m/z: 251.1279 $[M + H]^+$; calculated for $C_{14}H_{19}O_4$: 251.1278.

Methyl 3,4-dioxo-4-(2-oxocyclopentyl)butanoate (2a). Yield 4.35 g (41%), mp 38–40°C. IR spectrum, ν, cm^{-1}: 3400–2900 br (OH), 3123 (=C–H), 2953 (CH_3, asym.), 2922 (CH_2, asym.), 2852 (CH_2-, sym.), 1639 (C^1=O), 1548 br (C^6=O), (C=C), 1443 (δCH_3, asym.), 1353 (δCH_3, sym.), 1181 (δC–OH, in-plane), 1079 (C–O–C, ester), 1022, 943, 921, 910, 872, 819 (C–C, skeletal). ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 1.77 m (2H, 4′-H, **2A**, 12%), 2.00 m (2H, 4′-H, **2B**, 88%), 2.36 m (2H, 3′-H, **2A**), 2.50 m (2H, 3′-H, **2B**), 2.90 m (2H, 5′-H, **2A**), 3.00 m (2H, 5′-H, **2B**), 3.51 s (1H, 5′-H, **2A**), 3.78 s (3H, OCH_3, **2A**), 3.82 s (3H, OCH_3, **2B**), 3.84 s (2H, 2-H, **2A**), 5.97 s (1H, 2-H, **2B**), 11.91 s (1H, 3-OH, **2B**), 13.38 s (1H, 4-OH, **2B**); in DMSO-d_6: 1.98 m (2H, 4′-H, **2B**, 56%), 2.00 m (2H, 4′-H, **2D**, 44%), 2.45 m (2H, 3′-H, **2B**), 2.49 m (2H, 3′-H, **2D**), 2.89 m (2H, 5′-H, **2C**), 2.98 m (2H, 5′-H, **2D**), 3.62 m (1H, 5-H, **2C**), 3.70 s (3H, OCH_3, **2C**), 3.77 s (2H,

2-H, **2D**), 3.80 s (3H, OCH_3, forma **2D**), 5.85 s (1H, 2-H, **2C**), 8.10 s (1H, 4-OH, **2D**), 11.90 s (1H, 3-OH, **2C**). Mass spectrum, *m*/*z*: 213.0756 $[M + H]^+$, 235.0578 $[M + Na]^+$; calculated for $C_{10}H_{13}O_5$: 213.0758.

Methyl 3,4-dioxo-4-(2-oxocyclohexyl)butanoate (2b). Yield 3.05 g (27%), mp 26–28°C. IR spectrum, ν, cm^{-1}: 3400–2900 br (OH), 3114 (=C–H), 2955 (CH_3, asym.), 2924 (CH_2-, asym.), 2854 (CH_2, sym.), 1632 (C^1=O), 1554 br (C^6=O, (C=C), 1450 (δCH_3, asym.), 1360 (δCH_3, sym.), 1201 (δC–OH, in-plane), 1129 (C–O–C, ester), 1021, 977, 960, 930, 775 (C–C, skeletal). ^{1}H NMR spectrum, δ, ppm: in $CDCl_3$: 0.85 m (4H, 4′-H, 5′-H, **2A**, 17%), 0.91 m (4H, 4′-H, 5′-H, **2B**, 83%), 2.03 m (2H, 3′-H, **2A**), 2.10 m (2H, 3′-H, **2B**), 2.50 m (2H, 6′-H, **2A**), 2.55 m (2H, 6′-H, **2B**), 3.27 s (1H, 5-H, **2A**), 3.71 s (3H, OCH_3, **2A**), 3.87 s (3H, OCH_3, **2B**), 3.93 s (2H, 2-H, **2A**), 5.11 s (1H, 2-H, **2B**), 11.35 s (1H, 3-OH, **2B**), 13.09 s (1H, 4-OH, **2B**); in DMSO-d_6: 0.99 m (4H, 4′-H, 5′-H, **2C**, 79%), 1.12 m (4H, 4′-H, 5′-H, **2D**, 21%), 2.24 m (2H, 3′-H, **2C**), 2.31 m (2H, 3′-H, **2D**, 2.82 m (2H, 6′-H, **2C**), 2.93 m (2H, 6′-H, **2D**), 3.58 m (1H, 5-H, **2C**), 3.72 s (3H, OCH_3, **2C**), 3.75 s (2H, 2-H, **2D**), 3.81 s (3H, OCH_3, **2D**), 5.82 s (1H, 2-H, **2C**), 8.15 s (1H, 4-OH, **2D**), 11.98 s (1H, 3-OH, **2C**). Mass spectrum, *m*/*z*: 227.0914 $[M + H]^+$, $[M + Na]^+$; calculated for $C_{11}H_{15}O_5$: 227.0914.

Ethyl 3,4-dioxo-4-(2-oxocyclopentyl)butanoate (2c). Yield 4.07 g (36%), mp 73–75°C. IR spectrum, ν, cm^{-1}: 3400–2900 br (OH), 3118 (=C–H), 2956 (CH_3, asym.), 2920 (CH_2, asym.), 2856 (CH_2, sym.), 1636 (C^1=O), 1553 br (C^6=O, (C=C), 1453 (δCH_3, asym.), 1359 (δCH_3, sym.), 1176 (δC–OH, in-plane), 1087 (C–O–C, ester), 1011, 965, 915, 887, 869 (C–C, skeletal). ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.4 Hz, **2A**, 11%), 1.22 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.5 Hz, **2B**, 89%), 1.77 m (2H, 4′-H, **2A**), 2.00 m (2H, 4′-H, **2B**, 12%), 2.36 m (2H, 3′-H, **2A**), 2.50 m (2H, 3′-H, **2B**), 2.90 m (2H, 5′-H, **2A**), 3.00 m (2H, 5′-H, **2B**), 3.43 s (1H, 5-H, **2A**), 3.87 s (2H, 2-H, **2A**), 4.20 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.4 Hz, **2A**), 4.22 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.5 Hz, **2B**), 5.54 s (1H, 2-H, **2B**), 11.75 s (1H, 3-OH, **2B**), 13.67 s (1H, 4-OH, **2B**); in DMSO-d_6: 1.08 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.3 Hz, **2C**, 61%), 1.10 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.3 Hz, **2D**, 39%), 1.71 m (2H, 4′-H, **2C**), 1.74 m (2H, 4′-H, **2D**), 2.38 m (2H, 3′-H, **2C**), 2.41 m (2H, 3′-H, **2D**), 2.85 m (2H, 5′-H, **2C**), 2.90 m (2H, 5′-H, **2D**), 3.60 m (1H, 5-H, **2C**), 3.76 s (2H, 2-H, **2D**), 4.01 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.3 Hz, **2C**), 4.05 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.3 Hz, **2D**), 5.64 s (1H, 2-H, **2C**), 8.13 s (1H, 4-OH, **2D**), 11.97 s (1H, 3-OH, **2C**). Mass spectrum, *m*/*z*: 227.0915 $[M + H]^+$, 249.0735 $[M + Na]^+$; calculated for $C_{11}H_{15}O_5$: 227.0914.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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