Multicomponent Reactions of Furan-2,3-diones: Synthesis and Characterizations of Furo[3,2-*c*]pyran-4-ones

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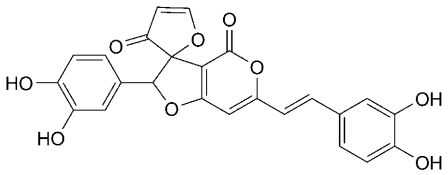
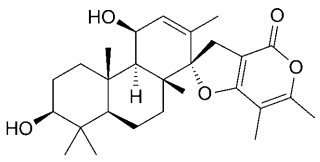
Furo[3,2-*c*]pyran-4-ones, which possess a natural-product skeleton, are synthesized *via* a simple, one-pot, three-component reaction of furan-2,3-diones with dialkyl acetylenedicarboxylates and Ph_3P.

Introduction. – Inoscavin A and phelligridin F, which possess a 2,3-dihydrofuro[3,2-*c*]pyran-4-one skeleton, are natural products that were isolated from a fungus. There are several reports about these compounds as free-radical scavengers with cytotoxic activities [1–4]. Niveulone, which also contains a 2,3-dihydrofuro[3,2-*c*]pyran-4-one moiety, which is linked to a more 'classical' terpenoid part in a heterocyclic spiro-compound, was isolated as one of several biologically active metabolites of the ascomycete *Dasyscyphus niveus*. It is weakly cytotoxic towards human cell lines and has an challenging structure with an interesting C-skeleton [5]. The phellifuropyranone, 2-(3,4-dihydroxyphenyl)-6-[(*E*)-2-(3,4-dihydroxyphenyl)ethenyl]furo[3,2-*c*]pyran-4-one, has antiproliferative activity against mouse melanoma cells and human lung cancer cells *in vitro* [6].



Inoscavin A



Niveulone

Some 4*H*-pyran derivatives are potential bioactive compounds, such as calcium antagonists [7] or potent apoptosis inducers [8][9]. Some 2-amino-4*H*-pyrans can be employed as photoactive materials [10]. 4*H*-Benzo[*b*]pyrans and their derivatives have attracted much interest due to their biological and pharmacological properties, such as anticoagulant, spasmolytic, diuretic, anticancer, and antianaphylactin characteristics [11][12]. Furthermore, the 4*H*-pyran group is a constituent of the structures of a series of natural products [13–15].

Furan-2,3-diones **1a**–**1d** are versatile starting materials for a variety of reactions, *e.g.*, generation of diacyl ketenes by thermolysis, cycloaddition of heterocumulenes,

photochemical reactions, as well as additon of nucleophiles, leading to a number of heterocyclic systems [16].

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis. Nowadays, the one-pot reactions involving multicomponent condensation are popular for the synthesis of heterocyclic compounds [17]. They are more convenient than multistep reactions, since they require shorter reaction time and give higher yields with easy workup. Multicomponent reactions constitute an especially attractive synthetic strategy, since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As multicomponent reactions are one-pot reactions, they are easier to carry out than multistep syntheses [18][19].

An experimental as well as theoretical article for multicomponent reactions of furan-2,3-diones has been published recently [20]. The aim of the present study was to accomplish multicomponent reactions of **1a**–**1d** with dialkyl acetylenedicarboxylates and Ph_3P. Here, we report the reaction mechanism, synthesis, and characterization of furo[3,2-*c*]pyran-4-one derivatives. Thus, compounds **3a**–**3h** have been first synthesized by these reactions (*Scheme 1*), and the experimental and spectroscopic results are discussed.

Results and Discussion. – The reaction of the acetylenedicarboxylates **2** with **1a**–**1d** in the presence of Ph_3P in benzene proceeded smoothly to afford the target compounds **3a**–**3h** in 33–51% yield. The structures of compounds **3a**–**3h** were determined by IR, ^{1}H- and ^{13}C-NMR spectra, and elemental analyses.

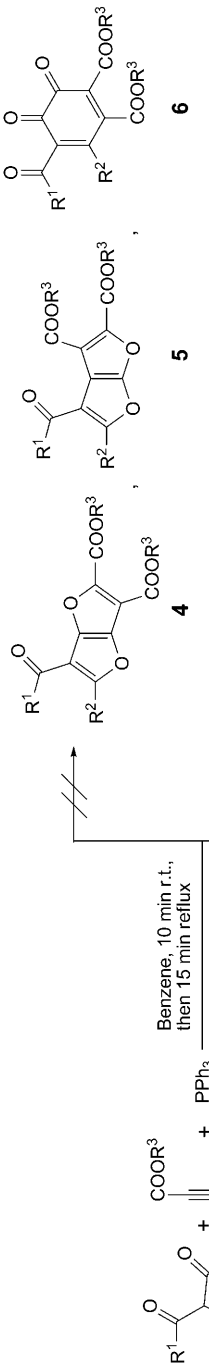
Due to the presence of three electrophilic sites with different reactivities (*i.e.*, C(2), C(3) and C(5)) in furandiones **1** that can react with nucleophiles [16][21][22], the reactions of **1** with the phosphonium intermediate formed from Ph_3P and **2** (acts as a carbanion) may produce four different isomeric novel compounds **3**–**6** (*Scheme 1*). However, TLC studies for each reaction indicated the presence of only one product, the structure of which was identified as alkyl 2-alkoxy-7-aroyl-6-aryl-4-oxo-4*H*-furo[3,2-*c*]pyran-3-carboxylate **3**.

The IR spectra of **3a** showed absorption bands at 1760, 1709, and 1649, and 1601–1472 cm^{-1} due to three C=O and aromatic bonds, respectively. The absorptions of C–O–C groups were observed at 1259 cm^{-1}. The ^{1}H-NMR spectrum of **3a** exhibited four sharp *singlet*s for the MeO groups at δ(H) 3.72, 3.80, 3.87, and 4.02. The signals of aromatic H-atoms were observed as *AA′BB′* system at δ(H) 6.72–7.80 ppm. The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 21 resonances, in good agreement with the proposed structure (see *Exper. Part*). The ^{1}H- and ^{13}C-NMR spectra of **3b**–**3h** were similar to those of **3a**, except for the signals of the substituent at C(6), C(7), and the ester moieties, which exhibited characteristic resonances with appropriate chemical shifts.

The structures of the products are based on an X-ray study of methyl 2-methoxy-7-(4-methoxybenzoyl)-6-(4-methoxyphenyl)-4-oxo-4*H*-furo[3,2-*c*]pyran-3-carboxylate (**3a**; *Fig.*) and methyl 2-methoxy-7-(4-methylbenzoyl)-6-(4-methylphenyl)-4-oxo-4*H*-furo[3,2-*c*]pyran-3-carboxylate (**3b**) [20], thus excluding the other possible isomers. An ORTEP representation of **3a** is shown in the *Figure*.

The compound crystallizes in the monoclinic space group *C*2/*c*, and there is one molecule in the asymmetric unit. The furo-pyran bicycle is not strictly planar; it is

Scheme 1. *Reaction of Furan-2,3-diones with Dialkyl Acetylenedicarboxylates and Ph_3P*



	R^1	R^2	R^3
3a	4-MeO–C_6H_4	4-MeO–C_6H_4	Me
3b	4-Me–C_6H_4	4-Me–C_6H_4	Me
3c	3,4-$(MeO)_2$–C_6H_3	3,4-$(MeO)_2$–C_6H_3	Me
3d	EtO	Ph	Me
3e	4-MeO–C_6H_4	4-MeO–C_6H_4	Et
3f	4-Me–C_6H_4	4-Me–C_6H_4	Et
3g	3,4-$(MeO)_2$–C_6H_3	3,4-$(MeO)_2$–C_6H_3	Et
3h	EtO	Ph	Et

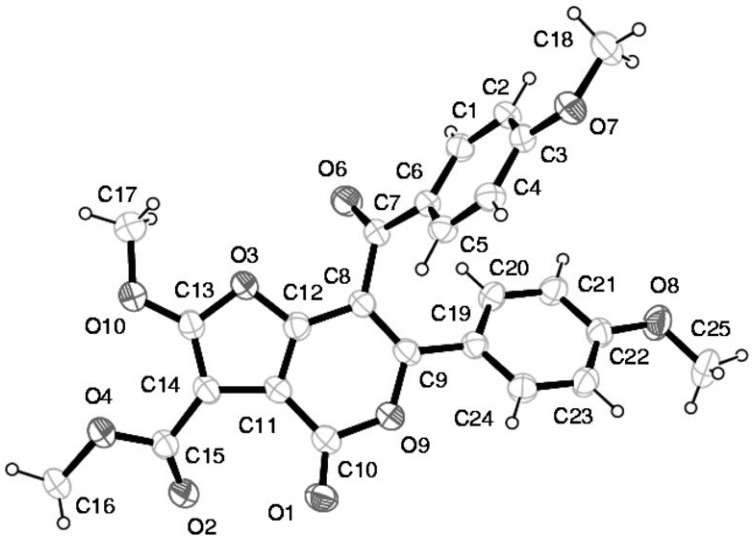
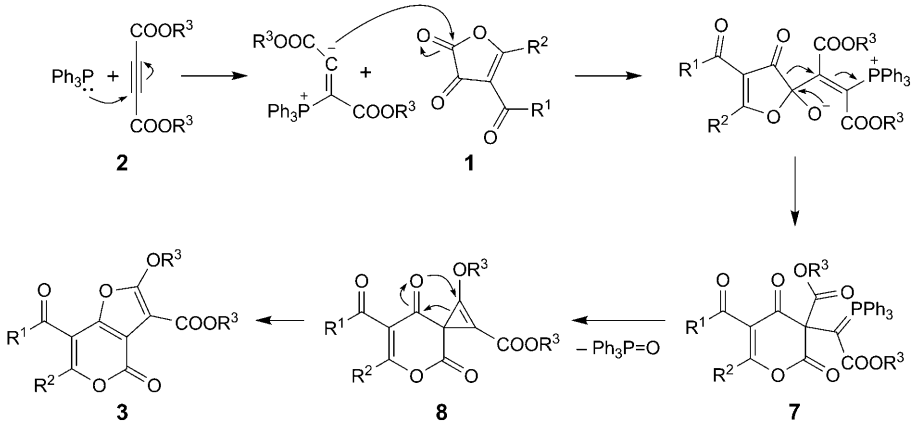


Figure. *ORTEP Plot of* **3a**, *with the atom-numbering scheme*. Displacement ellipsoids are drawn at the 50% probability level, and the H-atoms are shown as small spheres of arbitrary radii.

considerably strained due to the substituted units. Maximum deviation from the mean plane is 0.108 Å for C(10).

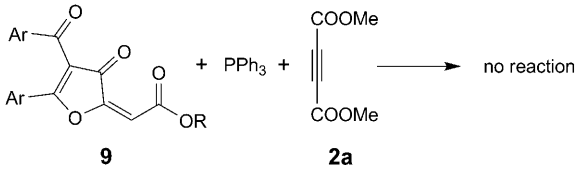
A reasonable reaction pathway from furan-2,3-diones **1** to furo[3,2-*c*]pyran-4-one derivatives **3** is outlined in *Scheme 2*. The first step may involve the addition of Ph_3P to the acetylenedicarboxylate **2** and formation of the zwitterionic 1:1 adduct. The subsequent step is the nucleophilic attack of the adduct to the lactone C=O group of **1**. Rearrangement of the intermediate (a betaine) thus formed may lead to pyrandione derivatives **7**. Next, an intramolecular *Wittig* reaction by elimination of Ph_3P=O yields the intermediate **8**, which would be transformed to the product **3** (see *Scheme 2*).

Scheme 2. *Formation of Furo[3,2-*c*]pyran-4-ones*



On the other hand, we investigated the reaction of the furan-3-one derivatives of type **9** [22] with **2a** in the presence of Ph_3P; but no reaction was observed (TLC control; *Scheme 3*). These studies confirm that the reactions with furan-2,3-diones **1** are initiated at the lactone group.

Scheme 3. *Attempted Reaction Furan-3-ones with Dimethyl Acetylenedicarboxylates and Ph_3P*



Conclusions. – Multicomponent reactions with furan-2,3-diones **1** have been reported here for the first time. We have developed a novel, one-pot, three-component synthesis of furo[3,2-*c*]pyran-4-ones **3a**–**3h**. These functionalized products are amenable to further transformations, and we anticipate that they may have important applications in medicinal and synthetic organic chemistry.

Experimental Part

General. Compounds **1** were prepared according to [21][23]. Compound **2** and other reagents or solvents were obtained from *Merck*, *Fluka*, and *Sigma*, and used without further purification. TLC: *Merck* precoated silica gel *60 F254*. M.p.: *Electrothermal 9200* apparatus; uncorrected. IR Spectra: *Jasco FT-IR-460 Plus* spectrometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AC300* instrument, in $CDCl_3$ at 300 and 75 MHz, resp.; δ in ppm, J in Hz. Elemental analyses (C, H): *LECO-932 CHNS-O* analyzer. X-Ray: *Rigaku R-AXIS RAPID-S* diffractometer.

General Procedure for the Preparation of Compounds **3a**–**3h**. To a stirred soln. of furan-2,3-diones **1** (1 mmol) and dialkyl acetylenedicarboxylates **2** (1 mmol) in benzene (20 ml) was added dropwise Ph_3P (1 mmol) in benzene (5 ml), and the mixture was stirred at r.t. for 10 min. Then, the mixture was heated at reflux for 15 min. The solvent was removed under reduced pressure, and the residue was treated with the proper alcohol to give the corresponding products **3**, which were filtered off, recrystallized from the proper alcohol or solvent and dried (P_2O_5).

*Methyl 2-Methoxy-6-(4-methoxyphenyl)-7-[(4-methoxyphenyl)carbonyl]-4-oxo-4*H*-furo[3,2-c]pyran-3-carboxylate* (**3a**). From treatment with i-PrOH; recrystallized from PrOH. Yield: 0.17 g (36%). Yellow crystals. M.p. 176°. IR (KBr): 1760, 1709, 1649 (C=O), 1601, 1550, 1511, 1472 (C=C), 1259 (C–O). ^1H-NMR (300.13 MHz, $CDCl_3$): 7.80–6.72 (2 *AA′BB′*, 8 arom. H); 4.02, 3.87, 3.80, 3.72 (4*s*, 4 MeO). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 188.36 (*t*, $^3J = 4.3$, Ar–*C*=O); 157.80 (*s*, C=O, ester); 155.56 (*s*, C=O, lactone); 167.89, 164.51, 163.18, 161.65, 151.56, 132.16, 130.14, 129.30, 123.57, 114.12, 114.07, 107.45, 106.87, 89.08 (C=C, arom., olef.); 59.34, 55.56, 55.32, 51.92 (4 MeO). Anal. calc. for $C_{25}H_{20}O_9$ (464.42): C 64.65, H 4.34; found: C 64.75, H 4.25.

*Methyl 2-Methoxy-6-(4-methylphenyl)-7-[(4-methylphenyl)carbonyl]-4-oxo-4*H*-furo[3,2-c]pyran-3-carboxylate* (**3b**). From treatment with MeOH; recrystallized from MeOH. Yield: 0.22 g (51%). Yellow crystals. M.p. 168–170°. IR (KBr): 1766, 1714, 1655 (C=O), 1604, 1570, 1510, 1475 (C=C), 1230 (C–O). ^1H-NMR (300.13 MHz, $CDCl_3$): 7.80–7.09 (2 *AA′BB′*, 8 arom. H); 4.09, 3.96 (2*s*, 2 MeO); 2.42, 2.33 (2*s*, 2 *Me*–Ar). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 191.46 (*t*, $^3J = 4.4$, Ar–*C*=O); 160.28 (*s*, C=O, ester); 157.49 (*s*, C=O, lactone); 165.22, 163.63, 153.27, 147.54, 143.50, 135.86, 131.82, 131.57, 131.33, 130.38, 130.28, 121.29, 109.85, 89.60 (C=C, arom., olef.); 61.30, 53.95 (2 MeO); 23.78, 23.41 (2 *Me*–Ar). Anal. calc. for $C_{25}H_{20}O_7$ (432.42): C 69.44, H 4.66; found: C 69.56, H 4.79.

*Methyl 6-(3,4-Dimethoxyphenyl)-7-[(3,4-dimethoxyphenyl)carbonyl]-2-methoxy-4-oxo-4*H-*furo[3,2-*c*]pyran-3-carboxylate* (**3c**). From treatment with MeOH; recrystallized from MeOH. Yield: 0.24 g (46%). Yellow crystals. M.p. 130°. IR (KBr): 1767, 1713, 1646 (C=O), 1611, 1581, 1514, 1468 (C=C), 1265 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.50–6.72 (*m*, 6 arom. H); 4.10, 3.92, 3.91, 3.90, 3.84, 3.78 (6*s*, 6 MeO). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 188.48 (*t*, ^3J = 4.2, Ar–*C*=O); 155.63 (*s*, C=O, ester); 154.49 (*s*, C=O, lactone); 163.22, 157.50, 155.63, 151.56, 151.28, 149.34, 148.80, 129.26, 125.61, 123.71, 122.15, 110.83, 110.74, 110.50, 110.17, 107.60, 106.87, 89.01 (C=C, arom., olef.); 59.42, 56.18, 56.03, 55.91, 53.67, 52.02 (6 MeO). Anal. calc. for $C_{27}H_{24}O_4$ (524.13): C 61.83, H 4.61; found: C 61.58, H, 4.76.

*7-Ethyl 3-Methyl 6-Ethoxy-2-methoxy-4-oxo-4*H-*furo[3,2-*c*]pyran-3,7-dicarboxylate* (**3d**). From treatment with MeOH; recrystallized from MeOH. Yield: 0.17 g (45%). Yellow crystals. M.p. 147°. IR (KBr): 1771, 1715 (C=O), 1614, 1577, 1553, 1473 (C=C), 1246 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.56–7.24 (*m*, 5 arom. H); 4.23 (*s*, MeO); 4.22 (*q*, ^3J = 7.1, CH_2O); 3.88 (*s*, MeO); 1.12 (*t*, ^3J = 7.1, Me). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 162.43 (*s*, C=O, ethyl ester); 161.63 (*s*, C=O, methyl ester); 161.59 (*s*, C=O, lactone); 163.34, 154.97, 150.34, 131.66, 130.07, 128.66, 128.34, 108.16, 102.86, 88.90 (C=C, arom., olef.); 62.02 (CH_2O); 59.40, 52.02 (2 MeO); 13.72 (Me). Anal. calc. for $C_{19}H_{16}O_8$ (372.33): C 61.29, H 4.66; found: C 61.01, H 4.48.

*Ethyl 2-Ethoxy-6-(4-methoxyphenyl)-7-[(4-methoxyphenyl)carbonyl]-4-oxo-4*H-*furo[3,2-*c*]pyran-3-carboxylate* (**3e**). From treatment with EtOH; recrystallized from MeOH. Yield: 0.25 g (51%). Yellow crystals. M.p. 120°. IR (KBr): 1765, 1709, 1645 (C=O), 1607, 1553, 1509, 1467 (C=C), 1259 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.77–6.71 (2 *AA′BB′*, 8 arom. H); 4.33 (*q*, ^3J = 7.1, CH_2O); 4.31 (*q*, ^3J = 7.1, CH_2O); 3.78, 3.70 (2*s*, 2 MeO); 1.34 (*t*, ^3J = 7.1, Me); 1.32 (*t*, ^3J = 7.1, Me). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 188.49 (*t*, ^3J = 4.3, Ar–*C*=O); 161.33 (*s*, C=O, ester); 157.67 (*s*, C=O, lactone); 164.50, 162.80, 161.57, 155.65, 151.64, 132.18, 130.07, 129.29, 123.57, 114.12, 114.04, 107.32, 106.93, 90.05 (C=C, arom., olef.); 69.75, 60.85 (2 CH_2O); 55.60, 55.33 (2 MeO); 14.74, 14.21 (Me). Anal. calc. for $C_{27}H_{24}O_9$ (492.14): C 65.85, H 4.91; found: C 65.50, H 4.78.

*Ethyl 2-Ethoxy-6-(4-methylphenyl)-7-[(4-methylphenyl)carbonyl]-4-oxo-4*H-*furo[3,2-*c*]pyran-3-carboxylate* (**3f**). From treatment with MeOH; recrystallized from DMF/H_2O (4:1). Yield: 0.15 g (33%). Yellow crystals. M.p. 136°. IR (KBr): 1762, 1717, 1665 (C=O), 1606, 1572, 1554, 1442 (C=C), 1234 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.73–7.03 (2 *AA′BB′*, 8 arom. H), 4.37 (*q*, ^3J = 7.1, CH_2O); 4.35 (*q*, ^3J = 7.1, CH_2O); 2.35, 2.26 (2*s*, 2 *Me*–Ar); 1.39 (*t*, ^3J = 7.1, Me); 1.35 (*t*, ^3J = 7.1, Me). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 189.58 (*t*, ^3J = 4.5, Ar–*C*=O); 158.14 (*s*, C=O, ester); 155.55 (*s*, C=O, lactone); 162.86, 161.30, 151.34, 145.49, 141.42, 133.95, 129.80, 129.55, 129.32, 128.33, 107.74, 107.62, 90.18 (C=C, arom., olef.); 69.76, 60.89 (2 CH_2O); 21.77, 21.40 (2 *Me*–Ar); 14.70, 14.19 (Me). Anal. calc. for $C_{27}H_{24}O_7$ (460.48): C 70.42, H 5.25; found: C 70.72, H 5.44.

*Ethyl 6-(3,4-Dimethoxyphenyl)-7-[(3,4-dimethoxyphenyl)carbonyl]-2-ethoxy-4-oxo-4*H-*furo[3,2-*c*]pyran-3-carboxylate* (**3g**). From treatment with MeOH; recrystallized from MeOH. Yield: 0.27 g (49%). Yellow crystals. M.p. 144°. IR (KBr): 1766, 1721, 1655 (C=O), 1610, 1579, 1513, 1462 (C=C), 1261 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.45–6.66 (*m*, 6 arom. H); 4.35 (*q*, ^3J = 7.1, CH_2O); 4.32 (*q*, ^3J = 7.1, CH_2O); 3.86, 3.84, 3.78, 3.72 (4*s*, 4 MeO); 1.35 (*t*, ^3J = 7.1, 2 Me). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 188.56 (*t*, ^3J = 4.4, Ar–*C*=O); 155.64 (*s*, C=O, ester); 154.46 (*s*, C=O, lactone); 162.85, 161.31, 157.35, 151.63, 151.22, 149.33, 148.79, 129.34, 125.58, 123.77, 122.05, 110.79, 110.50, 107.46, 106.94, 90.17 (C=C, arom., olef.); 69.84, 60.90 (CH_2O); 56.17, 56.02, 55.88 (MeO); 14.75, 14.20 (*s*, Me). Anal. calc. for $C_{29}H_{28}O_{10}$ (552.53): C 63.04, H 5.11; found: C 62.88, H 5.21.

*Diethyl 2,6-Diethoxy-4-oxo-4*H-*furo[3,2-*c*]pyran-3,7-dicarboxylate* (**3h**). From treatment with i-PrOH; recrystallized from EtOH. Yield: 0.20 g (50%). Yellow crystals. M.p. 126°. IR (KBr): 1759, 1727, 1707 (C=O), 1610, 1594, 1549, 1478 (C=C), 1241 (C–O). ^{1}H-NMR (300.13 MHz, $CDCl_3$): 7.53–7.34 (*m*, 5 arom. H); 4.53 (*q*, ^3J = 7.1, CH_2O); 4.30 (*q*, ^3J = 7.1, CH_2O); 4.18 (*q*, ^3J = 7.1, CH_2O); 1.46 (*t*, ^3J = 7.1, Me); 1.32 (*t*, ^3J = 7.1, Me); 1.07 (*t*, ^3J = 7.1, Me). ^{13}C-NMR (75.47 MHz, $CDCl_3$): 162.44 (*s*, C=O, ester at C(7)); 161.41 (*s*, C=O, ester at C(3)); 161.17 (*s*, C=O, lactone); 162.95, 154.95, 150.40, 131.69, 130.97, 128.58, 128.29, 108.02, 102.88, 89.93 (C=C, arom., olef.); 69.81, 61.97, 60.84 (3 CH_2O); 14.88, 14.18, 13.68 (Me). Anal. calc. for $C_{21}H_{20}O_8$ (400.38): C 63.00, H 5.03; found: C 62.80, H 5.09.

X-Ray Crystallography. For the crystal structure determination, the single-crystal of **3a** was used for data collection at r.t. on a four-circle *Rigaku R-AXIS RAPID-S* diffractometer (equipped with a two-

dimensional area IP detector). The graphite-monochromatized MoK_α radiation (λ 0.71073 Å) and oscillation-scan technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for *Lorentz* and polarization effects, and cell refinement was performed using CrystalClear (*Rigaku/MSC Inc.*, 2005) software [24]. The structures were solved by direct methods using SHELXS-97 [25] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [25]. The H-atoms were positioned geometrically and refined using a riding model. The final difference *Fourier* maps showed no peaks of chemical significance.

Crystal Data of **3a**. $C_{25}H_{20}O_9$, crystal system, space group: monoclinic, *C*2/*c*; unit-cell dimensions: $a = 25.3362(6)$, $b = 10.2945(2)$, $c = 17.5770(4)$ Å, $\beta = 105.231(1)°$; *V*: 4423.46(17) Å^3; $Z = 8$; calculated density: 1.39 mg/m^3; absorption coefficient: 0.107 mm^{-1}; *F*(000): 1936; θ range for data collection 2.2–26.4°; refinement method: full-matrix least-squares on F^2; data/parameters: 4519/311; goodness-of-fit on F^2: 1.051; final *R* indices [$I > 2\sigma(I)$]: $R_1 = 0.062$, $wR_2 = 0.128$; *R* indices (all data): $R_1 = 0.118$, $wR_2 = 0.152$; largest diff. peak and hole: 0.237 and -0.199 e Å^{-3}. Crystallographic data were deposited with CSD under CCDC registration number 732134. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre* (*CCDC*) *via* www.ccdc.cam.ac.uk/data_request/cif.

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