Efficient Access to Novel Furanofurone Compounds from Quinic Acid: Studies of Inter-and Intramolecular Wittig Reactions on Lactones

Lúcia Helena Brito Baptistella,* André de Carvalho Jorge

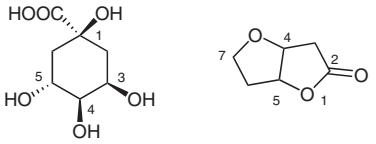
Instituto de Química, UNICAMP, CP 6154, 13084-971 Campinas, SP, Brazil
Fax +55(19)35213023; E-mail: lhbb@iqm.unicamp.br

Received 23 May 2007

Abstract: (–)-Quinic acid has been converted into derivatives of a furo[3,2-*b*]furan-2-one system using Wittig olefination reactions of lactones. Studies for this transformation included the use of microwave-assisted reactions.

Key words: quinic acid, furanofurone systems, Wittig olefination reactions on lactones, microwave-assisted reactions, heterocycles

(–)-Quinic acid (**1**, Figure 1) is a very attractive starting material for the synthesis of naturally occurring substances and related compounds,[1] but, even considering its versatile structure, only a few reports describe its use for the preparation of oxygenated heterocycles.[2–4] In the scope of our ongoing work related to this utilization of quinic acid,[3] we turned our attention to some fused oxyheterocycles, especially to the furo[3,2-*b*]furan-2-one system **2** (Figure 1), present in a great number of interesting natural products. These skeletons, also referred to as furanofurones (or furano-furones), may be found, for example, among styryl lactones,[5] nortriterpenoids,[6] iridoids[7] and alkaloids,[8] among others,[9,10] and a great number of these compounds present impressive pharmacological activity.

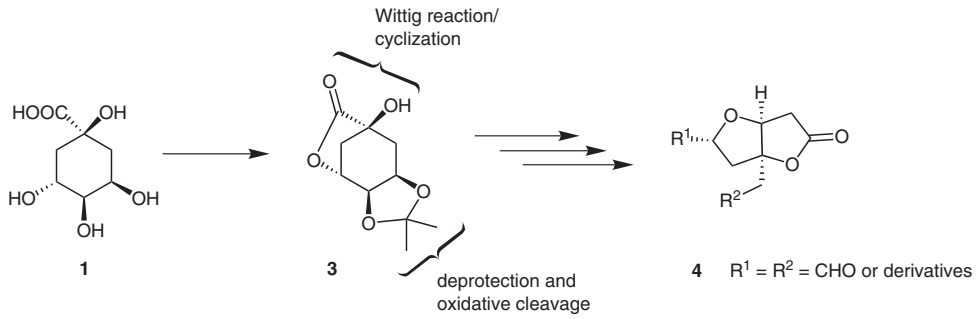


1 **2**

Figure 1

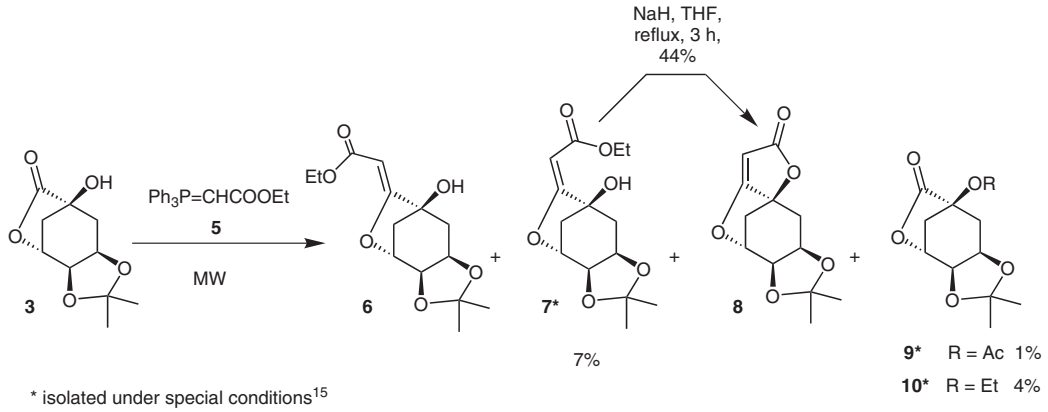
So, with these premises in mind and envisaging the preparation of new compounds with this core structure, we proceeded to synthesize some derivatives like **4** from the acetal quinide **3**, a readily available derivative of quinic acid (Scheme 1). For the preparation of the furone ring of **4**, a Wittig olefination on the lactone system of **3**, which could occur, in principle, via an inter- or intramolecular reaction, was explored.

The low reactivity of carboxylic acid derivatives towards phosphoranylidenes is well known, but it is also known that under forcing conditions, such as higher temperatures[11] or the use of microwave-assisted reactions,[12] some of these substrates may lead to heterosubstituted olefinic linkages in good yields. Treating the γ-lactone **3**[3] with ethoxycarbonylmethylene(triphenyl) phosphorane **5**, either using reflux in toluene[11a] or using long periods of heating in sealed vessels,[11b] the reactions failed completely. The lactone was recovered and the phosphorane did not withstand the applied conditions. In a microwave-assisted reaction[13] without solvents, as described by Sabitha for other esters and amides,[12] the starting material **3** was also recovered intact. On the other hand, using microwave irradiation in reactions in toluene or more polar solvents such as chlorobenzene or diethylene glycol dimethyl ether, better results were obtained (Scheme 2). With chlorobenzene as solvent and temperatures varying in the range from 150–180 °C (reached in about 15 min), it was possible to isolate two major products after one hour, the *Z*-olefin **6** (39%) and the unsaturated furanofurone system **8** (46%), besides some unchanged lactone **3** (10%).[14]



Scheme 1

SYNLETT 2007, No. 19, pp 3045–3049
Advanced online publication: 08.11.2007
DOI: 10.1055/s-2007-992356; Art ID: S03707ST

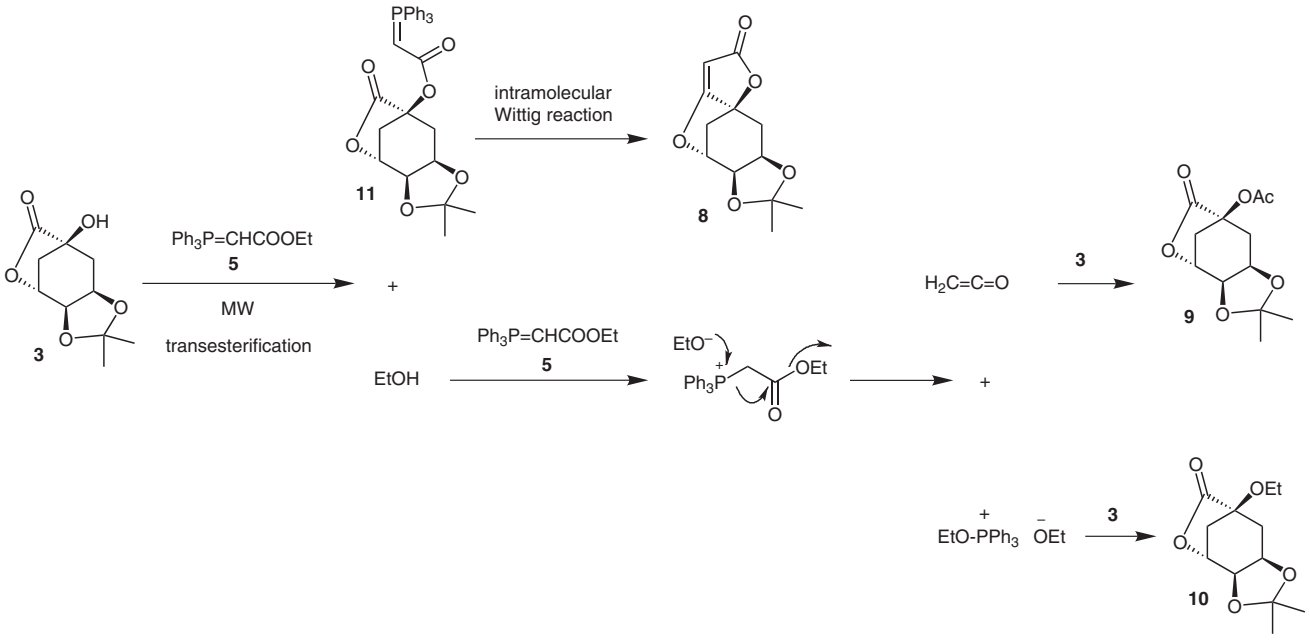


Scheme 2

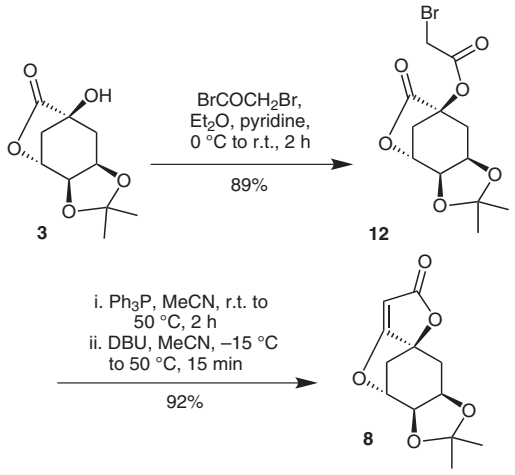
From these results, our first consideration was a nonselective Wittig olefination of **3**, with the furanofurone derivative **8** arising from a spontaneous cyclization of an *E*-olefin. However, when some minor products, isolated under special conditions,[15] were identified as the *E*-olefin **7**, the ester **9**, and the ether **10**, and,[16] additionally, the *E*-olefin **7** was revealed to be very resistant to intramolecular transesterification (see Scheme 2 – reflux of **7** with Et_3N or DBU in THF or toluene, or even microwave-assisted treatment of **7** with the Wittig reagent **5**, failed), we reasoned that two mechanistic routes might be occurring at the same time: on the one hand, a microwave-assisted Wittig olefination of the carbonyl group, leading to a mixture of *Z*- and *E*-olefins **6** and **7**, and on the other hand, an initial transesterification of the phosphoranylidene reagent by **3**, followed by an intramolecular Wittig reaction, leading to **8** (Scheme 3). In this case, the ethanol released in the first step would be involved in a sequence of protonation and dissociation reactions, producing a ketene and a phosphonium salt, reagents for the formation of **9** and **10**, respectively, from **3** (Scheme 3). Previously reported alkylation and acylation of amines by this Wittig reagent in hydroxylic solvents[17] supports this proposition.

It is not possible, with these results, to assert that **8** arose only by an intramolecular Wittig reaction from **3**; however, to test the ease of this transformation, the lactone **3** was sequentially treated[18] with bromoacetyl bromide, triphenylphosphine, and DBU (Scheme 4). All steps were performed without purification of the intermediates.[19] Even considering the steric hindrance of the tertiary hydroxyl group of **3**, this sequence provided **8** in very good yield (Scheme 4 – 82% overall yield from **3**), better than those obtained under microwave-assisted olefination conditions. The ease of the conversion [**12** → **8**] also supports the transient formation of the ylide **11** under microwave-assisted olefination of **3**, as proposed in Scheme 3.

Concerning the stereoselectivity of the intermolecular microwave-assisted Wittig reaction of **3**, it is also not possible to assert, with the results shown in Scheme 2, that the



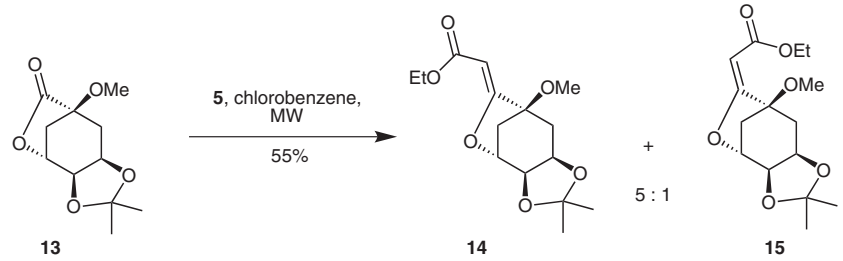
Scheme 3 Proposition for the synthesis of **8**, **9**, and **10** from **3**



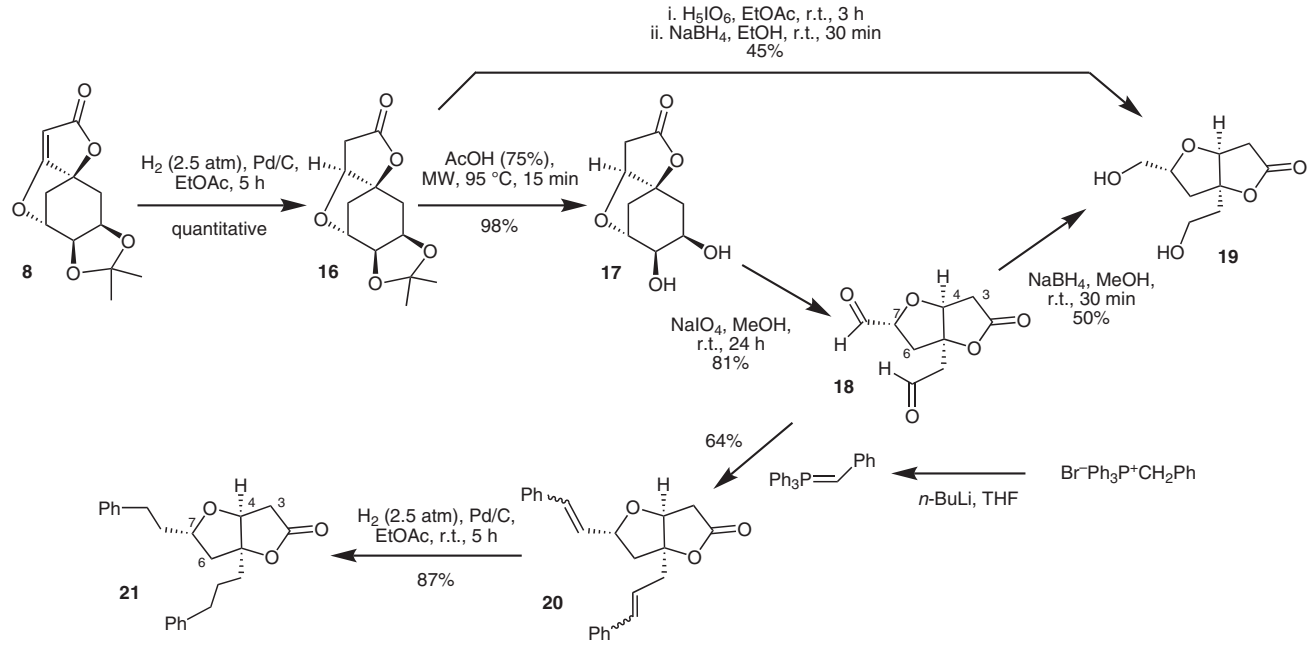
Scheme 4

ratio *Z*/*E* is 5.6:1 (as observed for **6**:**7**), but applying the same treatment on compound **13** (Scheme 5) with the tertiary hydroxyl group protected, the ratio of *Z*/*E* tetrahydrofurylidene acetates **14**:**15** was 5:1 – almost the same. Thus, this ratio may be considered as a good indication of stereoselectivity of these lactones under microwave-assisted Wittig olefination conditions.

In a continuation of our synthesis, compound **8** was subjected to a catalytic hydrogenation to give, after a slow reaction (5 h), the saturated furanofurone **16** in quantitative yield (Scheme 6). The deprotection of the diol system was accomplished by a microwave-activated reaction with aqueous acetic acid, giving **17** in 98% yield. Finally, with the desired functionality on the cyclohexane system, an oxidative cleavage was applied. After a slow reaction (24 h) with sodium periodate, the unstable dialdehyde **18** was isolated in 81% yield. Reduction with sodium borohydride gave the furanofurone diol **19** in 50% yield, which was revealed to be a very polar compound. Better results were achieved when **16** was treated with periodic acid, followed by reduction of the crude aldehyde with sodium borohydride. The desired diol **19** was isolated in 45% yield.[20] Additionally, a less polar furanofurone derivative was also prepared from **18** (Scheme 6), using a Wittig reaction with the ylide obtained from benzyltriphenylphosphonium bromide. By catalytic hydrogenation of the resulting olefins **20**, the branched furanofurone **21** was isolated in 56% overall yield.[21] A 1D NOESY experiment on **21** did not show correlations between H4 and H7, and presented sufficient characteristic NOE (between H7–H6$_{endo}$ and H7–H3$_{endo}$) to allow for the confirmation that the C7 substituent was kept as *exo*.



Scheme 5



Scheme 6

In summary, investigation of microwave-assisted reactions in the quinide system **3** permitted us to establish viable routes to disubstituted derivatives of furanofurone compounds from quinic acid. A direct microwave-assisted treatment of **3** and stabilized phosphoranylidenes allow us a better understanding of the possible pathways concerning the Wittig olefinations of these α-hydroxy lactone skeletons, but the best results concerning the desired preparations were obtained when intramolecular Wittig reactions were performed. The furanofurone dialdehyde **18** and some of its derivatives, such as the diol **19**, the styryl lactones **20**, and the dialkylated compound **21** have been prepared in good overall yields, and their cytotoxic activities, as well as those of their intermediates, are under investigation. Further synthetic applications of tetrahydrofurylidene **6** are also in progress in our laboratory.

Acknowledgment

We are grateful to Prof. Paulo M. Imamura for his helpful discussions and Prof. Carol H. Collins for revising this manuscript. A.C.J. thanks CNPq for a fellowship and we gratefully acknowledge FAPESP for financial support.

References and Notes

(1) (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3515. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970. (c) Hanessian, S.; Wang, J.; Montgomery, D.; Stoll, V.; Stewart, K. D.; Kati, W.; Maring, C.; Kempf, D.; Hutchins, C.; Laver, W. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3425.

(2) (a) Matsuo, K.; Matsumoto, T.; Nishiwaki, K. *Heterocycles* **1998**, *48*, 1213. (b) Matsuo, K.; Sugimura, W.; Shimizu, Y.; Nishiwaki, K.; Kuwajima, H. *Heterocycles* **2000**, *53*, 1505.

(3) Baptistella, L. H. B.; Cerchiaro, G. *Carbohydr. Res.* **2004**, *339*, 665.

(4) Barnwell, M. G.; Hungerford, N. L.; Jolliffe, K. A. *Org. Lett.* **2004**, *6*, 2737.

(5) Cytotoxic compounds isolated from plants of *Goniothala mus* species. See: (a) Ruiz, P.; Murga, J.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 713. (b) Lopez-Lazaro, M.; Martin-Cordero, C.; Bermejo, A.; Cortés, D.; Ayuso, M. J. *Anticancer Res.* **2001**, *21*, 3493.

(6) Found in plants of Schisandraceae family, used in Chinese traditional medicine. See: Li, R.-T.; Li, S.-H.; Zhao, Q.-S.; Lin, Z.-W.; Sun, H.-D.; Lu, Y.; Wang, C.; Zheng, Q.-T. *Tetrahedron Lett.* **2003**, *44*, 3531.

(7) Isolated from plants of *Scrophularia* species and used in Asian herbal medicine. See: Han, J. S.; Lowary, T. L. *J. Org. Chem.* **2003**, *68*, 4116.

(8) Isolated from *Stemona* species, which present insecticidal activities. See: Kaltenegger, E.; Brem, B.; Mereiter, K.; Kalchhauser, H.; Kählig, H.; Hofer, O.; Vajrodaya, S.; Greger, H. *Phytochemistry* **2003**, *63*, 803.

(9) A potent enzyme activator used for cardiac irregularities, isolated from Caribbean sponges of the genus *Plakortis*. See: Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, *124*, 9718.

(10) Compounds found in braconid wasps. See: Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 743.

(11) (a) Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1; and references cited therein. (b) Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 750. (c) Lakhrissi, Y.; Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 417.

(12) Sabitha, G.; Reddy, M. M.; Srinivas, D.; Yadov, J. S. *Tetrahedron Lett.* **1999**, *40*, 165.

(13) Microwave labstation MicroSYNTH (Millestone) operating at 2.45 GHz, dual magnetron system with delivered microwave power of 1000 W (pulsed irradiation), equipped with a thermocouple temperature control system. All experiments were conduced in sealed vessels (20 mL – the volume of the reactions were no more than 10% of this) with magnetic stirring.

(14) The lactone **3** was recovered intact when treated, with or without the assistance of microwaves, with diethylphosphonoacetate and bases (Horner–Wadsworth–Emmons olefinations).

(15) Batches of several reaction mixtures were combined for chromatographic purification.

(16) **Reaction of Lactone 3 with $Ph_3PCHCOOEt$ under Microwave Irradiation**

A 20 mL microwave vessel (for reactions up to 4 bar) containing a mixture of **3** (200 mg, 0.93 mmol), freshly distilled chlorobenzene (2 mL), and ethoxycarbonylmethylene(triphenyl) phosphorane (**5**, 500 mg, 1.43 mmol) was connected to a temperature sensor, and the apparatus was irradiated for 1 h in a microwave equipment programmed for temperature control: 15 min to reach 180 °C and then 1 h at this temperature. After cooling, the mixture was evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc 15%) to give **6** (39%) and **8** (46%), besides unchanged lactone **3** (10%). When batches of several reaction mixtures were combined for chromatographic purification, compounds **7** (7%), **9** (1%), and **10** (4%) were also isolated.

Compound **6**: $[\alpha]_D^{20}$ 47.6 (*c* 0.58, $CHCl_3$). IR (film): ν_{max} = 3392, 1687, 1650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, *J* = 7.0 Hz), 1.28 and 1.48 (2 × s, 2 × 3 H), 2.08 (dd, 1 H, *J* = 4.3, 13.7 Hz), 2.11 (dddd, 1 H, *J* = 1.0, 2.6, 6.1, 11.5 Hz), 2.27 (ddd, 1 H, *J* = 2.6, 8.2, 13.7 Hz), 2.38 (d, 1 H, *J* = 11.5 Hz), 3.35 (br s, 1 H), 4.11 (q, 2 H, *J* = 7.0 Hz), 4.28 (ddd, 1 H, *J* = 1.0, 2.9, 6.2 Hz), 4.38 (ddd, 1 H, *J* = 4.3, 6.2, 8.2 Hz), 4.82 (dd, 1 H, *J* = 2.9, 6.1 Hz), 5.05 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 24.7, 27.3, 36.0, 42.0, 59.8, 71.7, 72.6, 76.2, 79.8, 86.7, 110.0, 166.4, 174.6. HRMS (EI): *m/z* calcd for $C_{14}H_{20}O_6$: 284.12598; found: 284.12726.

Compound **8**: mp 77.5–78.1 °C. $[\alpha]_D^{20}$ –135.5 (*c* 0.34, $CHCl_3$). IR (KBr): ν_{max} = 1767, 1664 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 and 1.51 (2 × s, 2 × 3 H), 2.10 (ddd, 1 H, *J* = 2.1, 7.1, 15.1 Hz), 2.18 (dddd, 1 H, *J* = 1.9, 2.1, 6.3, 11.4 Hz), 2.59 (dd, 1 H, *J* = 1.6, 15.1 Hz), 2.74 (d, 1 H, *J* = 11.4 Hz), 4.36 (dt, 1 H, *J* = 1.9, 7.1 Hz), 4.61 (tdd, 1 H, *J* = 1.0, 1.6, 7.1 Hz), 4.87 (s, 1 H) 5.03 (ddd, 1 H, *J* = 1.0, 1.9, 6.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 26.8, 32.7, 35.9, 71.8, 73.1, 82.4, 84.0, 89.2, 109.7, 173.4, 187.7. HRMS (EI): *m/z* calcd for $C_{12}H_{14}O_5$: 238.08412; found: 238.08394.

Compound **7**: $[\alpha]_D^{20}$ –47.7 (*c* 0.28, $CHCl_3$). IR (film): ν_{max} = 3268, 1685, 1676 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, 3 H, *J* = 7.1 Hz), 1.32 and 1.51 (2 × s, 2 × 3 H), 2.09 (dd, 1 H, *J* = 4.9, 13.4 Hz), 2.27 (dddd, 1 H, *J* = 1.2, 2.5, 6.0, 11.7 Hz), 2.46 (d, 1 H, *J* = 11.7 Hz), 2.60 (ddd, 1 H, *J* = 2.5, 8.2, 13.4 Hz), 4.18 (m, 2 H), 4.21 (m, 1 H), 4.35 (ddd, 1 H, *J* = 4.9, 6.3, 8.2 Hz), 4.78 (dd, 1 H, *J* = 3.0, 6.0 Hz), 5.30 (s, 1 H), 7.03 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1,

24.9, 27.3, 37.1, 41.6, 60.6, 71.9, 73.0, 76.3, 79.6, 90.5, 110.0, 170.2, 180.2. HRMS (EI): *m/z* calcd for $C_{14}H_{20}O_6$: 284.12598; found: 284.12315.
Compound **9**: IR (film): ν_{max} = 1802, 1748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 and 1.52 (2 × s, 2 × 3 H), 2.12 (s, 3 H) 2.31 (dd, 1 H, *J* = 3.0, 14.5 Hz), 2.45 (ddd, 1 H, *J* = 2.1, 7.3, 14.5 Hz), 2.54 (d, 1 H, *J* = 11.3 Hz), 3.05 (dddd, 1 H, *J* = 1.2, 2.1, 6.2, 11.3 Hz), 4.32 (ddd, 1 H, *J* = 1.2, 2.4, 7.3 Hz), 4.53 (td, 1 H, *J* = 3.0, 7.3 Hz), 4.78 (dd, 1 H, *J* = 2.4, 6.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.3, 26.9, 30.3, 35.5, 71.0, 72.4, 75.3, 76.0, 109.9, 169.2, 173.5. HRMS (EI): *m/z* calcd for $C_{12}H_{16}O_6$: 256.09468; found: 256.09362.
Compound **10**: IR (film): ν_{max} = 1791 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (t, 1 H, *J* = 7 Hz) 1.32 and 1.51 (2 × s, 2 × 3 H), 2.17 (m, 1 H), 2.39 (dd, 1 H, *J* = 1.8, 13.0 Hz), 2.42 (m, 2 H), 3.57 and 3.63 (2 × m, 2 × 1 H), 4.28 (dd, 1 H, *J* = 1.8, 6.8 Hz), 4.51 (td, 1 H, *J* = 2.5, 6.8 Hz), 4.67 (dd, 1 H, *J* = 2.5, 5.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.5, 24.3, 27.0, 30.3, 36.0, 60.2, 71.4, 72.3, 74.9, 76.5, 109.6, 175.9. HRMS (EI): *m/z* calcd for $C_{12}H_{18}O_5$: 242.11543; found: 242.11399.

(17) Desmaële, D. *Tetrahedron Lett.* **1996**, *37*, 1233.

(18) Bittner, C.; Burgo, A.; Murphy, P. J.; Sung, C. H.; Thornhill, A. J. *Tetrahedron Lett.* **1999**, *40*, 3455.

(19) **Preparation of 8 via the Bromoacetyl Derivative 12**
1) A solution of **3** (200 mg, 0.93 mmol) in anhyd Et_2O (15 mL), under argon atmosphere, was stirred at 0 °C, and anhyd pyridine (100 μL, 1.2 mmol) was added, followed by bromoacetyl bromide (100 μL, 1.15 mmol). The solution was slowly warmed to r.t., in the absence of light, and the stirring was maintained for 2 h. Then, H_2O (15 mL) was added and the aqueous layer was separated and extracted two more times with Et_2O (15 mL). The combined organic layers were washed sequentially with H_2O (25 mL), sat. $CuSO_4$ solution (25 mL), H_2O (25 mL) and brine (25 mL), separated, and dried ($MgSO_4$). After filtration, the solvent was concentrated to give crude **12** in 89% yield (278 mg), used without purification in the next step. For characterization, a small sample was purified by flash chromatography (hexane–EtOAc 20%), to give **12** as white crystals; mp 85.0–87.5 °C. $[\alpha]_D^{20}$ 1.69 (*c* 1.4, $CHCl_3$). IR (KBr): ν_{max} = 2809, 1759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 and 1.53 (2 × s, 2 × 3 H), 2.37 (dd, 1 H, *J* = 3.3, 14.6 Hz), 2.50 (ddd, 1 H, *J* = 2.4, 7.2, 14.6 Hz), 2.63 (d, 1 H, *J* = 11.4 Hz), 3.02 (dddd, 1 H, *J* = 1.3, 2.4, 6.2, 11.4 Hz), 3.88 (s, 2 H) 4.33 (ddd, 1 H, *J* = 1.3, 2.5, 7.2 Hz), 4.55 (td, 1 H, *J* = 3.3, 7.2 Hz), 4.80 (dd, 1 H, *J* = 2.5, 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 25.2, 26.9, 30.3, 35.3, 71.0, 72.3, 75.4, 77.6, 110.1, 165.4, 172.6. HRMS (EI): *m/z* calcd for $C_{12}H_{15}BrO_6$: 335.00862; found: 320.9851 [M – CH_3]. 2) Triphenylphosphine (188 mg, 0.72 mmol) was added to a solution of **12** (200 mg, 0.6 mmol) in anhyd MeCN (2 mL) at r.t.; and the resulting mixture was warmed to 50 °C and maintained for 2 h. After cooling (–15 °C), DBU (73 mg, 0.48 mmol) was slowly added. The mixture was stirred at this temperature for 10 min and then warmed to 50 °C for 15 min. The reaction was then cooled (0 °C), diluted with Et_2O (30 mL), and filtered through a short silica column, which was washed with further Et_2O. Evaporation of the solvent and flash chromatography (hexane–EtOAc 15%) of the crude residue gave **8** as a white crystalline solid in 92% yield (131 mg).

(20) Small signals, always presented on the spectral data of crude **19**, were attributed to the C7-epimer of **19** (less than 8% yield). This compound probably arises from a minor C7-epimer of the dialdehyde **18**. A seven-membered lactone, possible by intramolecular transesterification reaction of **19**, was not observed..

(21) **Data for Compound 21 – [(4*S*,5*S*,7*S*)-7-(2-Phenylethyl)-5-(3-phenylpropyl)tetrahydrofuro[3,2-*b*]furan-2 (3*H*)-one]**
$[\alpha]_D^{20}$ –14.5 (*c* 0.27, $CHCl_3$). IR (film): ν_{max} = 1779 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59 (dd, 1 H, *J* = 10.3, 13.4 Hz), 1.70–1.97 (m, 6 H), 2.37 (dd, 1 H, *J* = 4.6, 13.4 Hz), 2.61–2.79 (m, 4 H), 2.65 (d, 1 H, *J* = 18.8 Hz), 2.79 (dd, 1 H, *J* = 6.2, 18.8 Hz), 4.46 (d, 1 H, *J* = 6.2 Hz), 4.73 (m, 1 H), 7.16–7.34 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0, 32.2, 35.6, 36.2, 36.3, 37.0, 42.8, 77.7, 80.7, 96.5, 125.9, 126.0, 128.2, 128.3, 128.4, 141.2, 141.3, 175.5. HRMS (EI): *m/z* calcd for $C_{23}H_{26}O_3$: 350.45094; found: 350.45186.