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Malonylation/Decarbalkoxylation of Furan Derivatives as Key Steps for the Preparation of Nonactic Acid Derivatives. Part II [1]

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Summary. A malonylation/decarbalkoxylation sequence from 2-substituted furans was investigated in view of developing a scalable synthesis of hydrophobic nonactic acid analogues.

Keywords. Heterocycles; Decarbalkoxylation; Nonactic acid; Natural-like.

Introduction

The ionophore nonactin is used in ion selective sensors because of its selectivity for ammonium and potassium cations [2]. The life time of these electrodes is limited due to the loss of nonactin through bleeding. In the course of our studies for the preparation of hydrophobic nonactin derivatives [3], we described a rapid synthesis of derivatives of nonactic acid from furan applying different radical couplings for the introduction of the first aliphatic side chain [4]. In Ref. [1], we described the introduction of the second aliphatic chain starting from malonyl derivatives as reagents. This transformation could be achieved in good yields and under total conversion of our starting materials. In this paper we present our results on the second decarbalkoxylation step (Scheme 1).

Results and Discussion

We first investigated the decarbalkoxylation of our dimethyl malonates **1**–**3**. We studied the enzymatic mono-hydrolysis with pig liver esterase (*PLE*), followed by decarboxylation [5]. Applying *PLE* to this reaction is justified by the soft reaction conditions which are compatible with the heat-sensitivity of the furan derivatives. The selective enzymatic monomethylester hydrolysis for the two first products **1** and **2** occurred smoothly to give **4** and **5** in 63–64% yields (Scheme 2). To achieve complete hydrolysis of **2** proved to be more difficult; 24 h were required instead of the 4 h which were sufficient for the transformation of **1**. The additional steric hindrance conferred to **2** by the introduction of the additional methyl group is probably responsible for the longer reaction times needed [6]. For **4** we measured the optical rotation, indicating that the enzyme is capable of distinguishing between the two enantiotopic ester groups. The enzyme was not able to hydrolyse the hydrophobic derivative **3**. After heating **4** from 100 to 200°C at 0.019 Torr in the *Kugelrohr* in order to achieve the decarboxylation, only 43% of **6** were obtained. As the heat-sensitivity of furans is well documented this result did not come as a surprise (Scheme 2).

Since the enzymatic hydrolysis was not adequate for the transformation of the hydrophobic **3**, we searched for alternative methods. *Krapcho* [7] and *Van der Gen* [8] use NaCl in wet *DMSO*. This reaction was successfully applied to **3** and gave **7** in 56% yield (Scheme 3). Total conversion of **3** was observed. The R_f values on TLC of both **3** and **7** were almost the same. Separation

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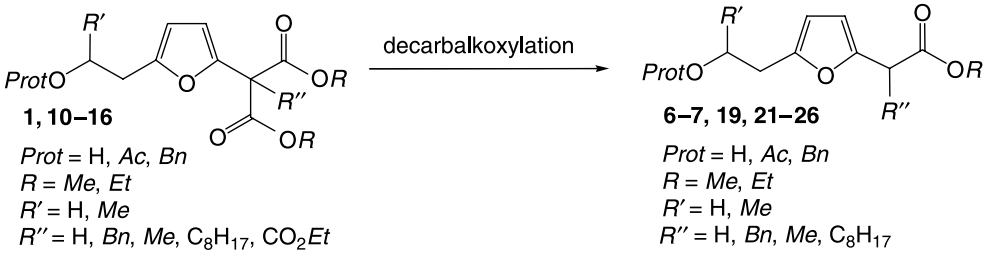
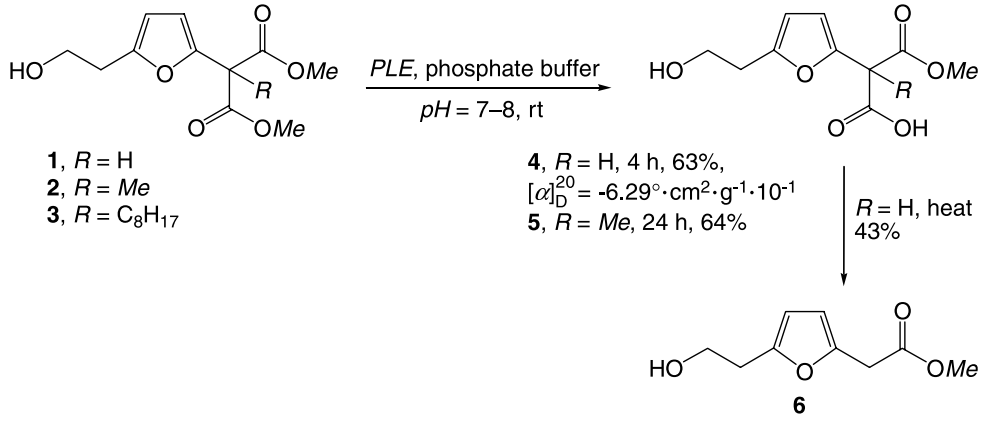
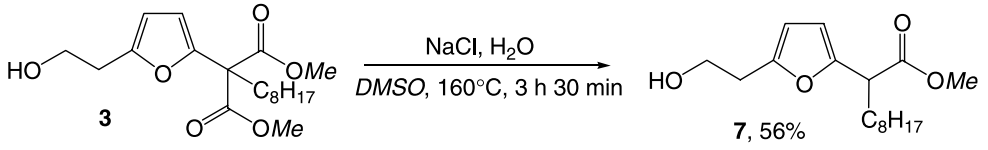


Scheme 1



Scheme 2



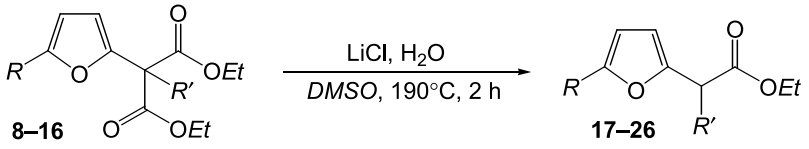
Scheme 3

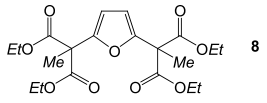
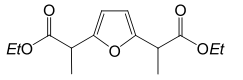
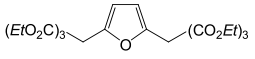
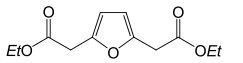
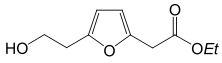
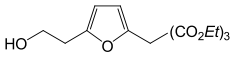
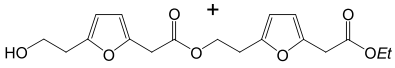
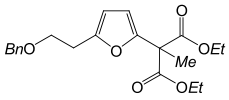
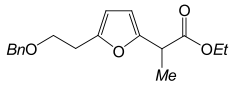
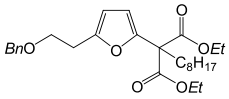
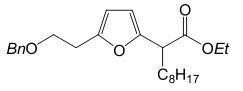
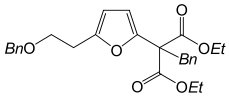
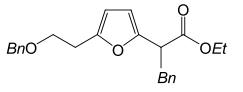
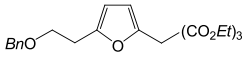
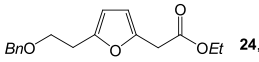
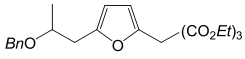
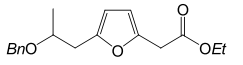
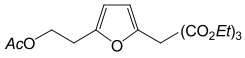
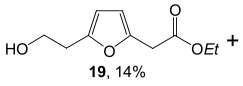
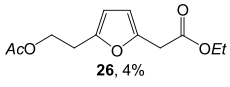
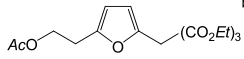
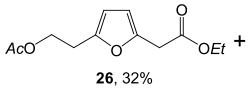
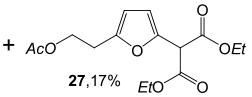
by column chromatography under the conditions studied would not have been possible. The heat sensitivity of furan derivatives can tentatively explain the loss of product once more.

To improve the yields we checked the consequence of reducing the reaction time. Under the conditions reported by *Rapoport* NaCl is replaced by LiCl [9]. Good yields could be obtained under these conditions heating for only 2 h at 190°C (Table 1). The first attempts using our model compounds **8** and **9** gave low yields of 25 and 23% of **17** and **18**. To obtain these products two or four decarbethoxylations have to occur in sequence. The overall yield of such a transformation composed of several steps are by necessity relatively low even if the yield of the individual reaction is good to acceptable. We did not optimise these two transformations and focused our efforts on our target molecules **21**–**26**. Transforming the free alcohol **10** under these conditions the yield of **19** was only 19%. We could isolate traces of the dimer **20** as side product. The formation of **20** can be explained as a transesterification of the ethylester part of one molecule of **20** with the alcohol part of a second molecule of **19**. We assumed that other heavier oligomers and/or polymers were formed by poly-transesterification of **19**, which could explain the low yield of isolated **19**.

To avoid side reactions, we used the O-protected molecules **11**–**16**. Under the same reaction conditions the O-benzylated molecules **11**–**15** gave **21**–**25** with satisfactory 63–91% yields. The O-acetyl protecting group of **16** was not resistant enough towards the reaction conditions. In this case, the yield in **26** was only 4%, and 14% of the deprotected product **19**

Table 1. Decarbethoxylation in *Rapoport* conditions, with LiCl



Reagent	Product and yield
 **8**	 **17**, 25%
 **9**	 **18**, 23%
	 **19**, 19%
 **10**	+  **20**, 1%
 **11**	 **21**, 91%
 **12**	 **22**, 73%
 **13**	 **23**, 65%
 **14**	 **24**, 67–80%[a]
 **15**	 **25**, 63%
 **16**	 **19**, 14% +  **26**, 4%
 [b] **16**	 **26**, 32% +  **27**,17%

[a] Reaction performed several times in this reproducible range of yields; [b] reaction performed at 160°C instead of 190°C

were obtained. We then tried to reduce the reaction temperature to 160°C with an aim to prevent the O-acetyl cleavage, but the reaction was not complete. At 160°C, the yield in **26** was only 32%, and we isolated 17% of **27**, where only one of the two ethoxycarbonyl groups of **16** was removed.

Conclusions

A set of nonactic acid derivatives precursors were successfully prepared. For the two target products **21** and **24**, the best overall yields of the malonylation/decarbalkoxylation sequence were 74 and 71%. The hydrophobic precursor **12** afforded 45% of **22** over the two-step sequence. The reported yields were determined using chromatography for the purification of the products obtained after each step. The purification by chromatography is not obligatory. However, the overall yields for the two step sequence malonylation/decarbalkoxylation were slightly better if the intermediate was purified by chromatography.

This efficient and scalable strategy will be applied for the preparation of macrocyclic analogues of the natural product nonactin.

Experimental

All moisture-sensitive reactions were carried out under Ar and N_2 using oven-dried glassware. All reagents were of commercial quality if not specifically mentioned. Solvents were freshly distilled prior to use. Flash chromatography (FC): Brunschwig silica gel 60, 0.032–0.063 mm, under positive pressure. TLC: Merck precoated silica gel thin-layer sheets 60 F 254, detection by UV and treatment with basic $KMnO_4$ sol. Mp: Gallenkamp MFB-595. IR spectra: Perkin Elmer Spectrum One FT-IR, in cm^{-1}. NMR spectra: Bruker Avance-400 (400 MHz (^{1}H) and 100 MHz (^{13}C)), at rt, chemical shifts δ in ppm rel. to $CDCl_3$ (^{1}H: 7.264 ppm, ^{13}C: 77.0 ppm) as internal reference, coupling constants J in Hz. ESI-MS: Finnigan LCQ. Elemental analyses or HR-ESI-MS of novel compounds agreed favourably with calculated values.

2-(5-(2-Hydroxyethyl)furan-2-yl)-3-methoxy-3-oxopropanoic acid (**4**, $C_{10}H_{12}O_6$)

A mixture of diester **1** (440 mg, 1.72 mmol) and *PLE* (3 mg, 130 units/mg, 390 units) in 1 cm^3 *Me*OH and 10 cm^3 *pH* = 8.0 phosphate buffer was stirred at room temperature for 4 h. During the hydrolysis, 0.1 *M* NaOH solution was periodically added to maintain the *pH* of the solution at 7–8 (total 17.2 cm^3 0.1 *M* NaOH). The aqueous layer was basified to *pH* = 9.0 by the addition of more NaOH solution and washed 5 times with diethyl ether. After the enzyme was filtered off, the aqueous layer was acidified to *pH* < 3 with 1 *M* HCl solution, and the products were extracted 5 times with diethyl ether, dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. Separation by chromatography afforded unreacted starting material **1** (44 mg, 0.18 mmol, 15%) and **4** (245 mg, 1.07 mmol, 63%) as a colorless oil. R_f = 0.22 (CH_2Cl_2/*Et*$_2$O/*Et*OH = 8/2/1); IR (film): $\bar{\nu}$ = 3475, 2958, 2602, 1741, 1560, 1439, 1391, 1278, 1231, 1161, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (d, J = 3.2 Hz, H-4), 6.10 (d, J = 3.2 Hz, H-5), 4.77 (s, H-2), 4.75 (*br*, OH), 3.87 (t, J = 6.2 Hz, H-8), 3.78 (s, H-1^1), 2.88 (t, J = 6.2 Hz, H-7), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (*C*=O), 167.0 (*C*=O), 153.6 (C-3), 144.0 (C-6), 110.5 (C-4), 107.8 (C-5), 60.9 (C-8), 53.3 (C-1^1), 51.4 (C-2), 31.4 (C-7) ppm; EI-MS: m/z = 227 (traces, $[M-H]^+$), 184 (37, $[M-CO_2]^+$), 154 (35), 153 (35), 111 (76), 106 (47), 95 (52), 94 (100), 65 (38).

2-(5-(2-Hydroxyethyl)furan-2-yl)-3-methoxy-2-methyl-3-oxopropanoic acid (**5**, $C_{11}H_{14}O_6$)

A mixture of diester **2** (270 mg, 1.07 mmol) and *PLE* (2.23 mg, 220 units/mg, 490 units) in 0.5 cm^3 *Me*OH and 7 cm^3 *pH* = 8.0 phosphate buffer was stirred at room temperature for 24 h. During the hydrolysis, 0.1 *M* NaOH solution was periodically added to maintain the *pH* of the solution at 7–8 (total 10.7 cm^3 0.1 *M* NaOH). The aqueous layer was basified to *pH* = 9.0 by the addition of more NaOH solution and washed with brine, the aqueous layer was then acidified to *pH* = 1 with 1 *M* HCl solution, and extracted 5 times with diethyl ether, dried (Na_2SO_4), and the solvent was evaporated *in vacuo* to afford **5** (165 mg, 0.68 mmol, 64%). Oil; R_f = 0.46 (*Et*$_2$O/*Me*OH = 50/50); IR (film): $\bar{\nu}$ = 3474, 2999, 2955, 2612, 1960, 1730, 1610, 1555, 1456, 1437, 1380, 1250, 1125, 1110, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (d, J = 3.2 Hz, H-4), 6.10 (d, J = 3.2 Hz, H-5), 5.97 (*br*, OH), 3.87 (t, J = 6.2 Hz, H-8), 3.81 (s, H-1^1), 2.89 (t, J = 6.2 Hz, H-7), 1.85 (s, H-2^1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (*C*=O), 170.2 (*C*=O), 153.1 (C-3), 148.9 (C-6), 108.9 (C-4), 107.3 (C-5), 60.9 (C-8), 54.7 (C-2), 53.2 (C-1^1), 31.2 (C-7), 20.1 ((C-2^1) ppm; EI-MS: m/z = 198 (34, $[M-CO_2]^+$), 181 (13), 180 (21, $[M-CO_2-H_2O]^+$), 168 (44), 167 (31), 166 (11), 140 (12), 139 (100), 135 (16), 121 (76), 111 (38), 109 (20), 108 (30), 107 (14), 81 (44), 80 (21), 79 (24), 77 (17), 65 (12), 45 (20); ESI-HR-MS: m/z $[M+Na]^+$ = calcd 265.0683, found 265.0682.

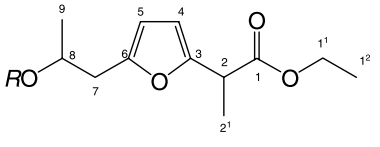


Fig. 1. Labeling used for NMR assignment

Methyl 2-(5-(2-hydroxyethyl)furan-2-yl)acetate (**6**, $C_9H_{12}O_4$)

Distillation of **4** (129 mg, 0.565 mmol) in a *Kugelrohr* apparatus from 100 to 200°C at 0.019 Torr afforded **6** (45 mg, 0.244 mmol, 43%). Oil; R_f = 0.26 (CH_2Cl_2/*Et*$_2$O = 75/25); IR (film): $\bar{\nu}$ = 3136, 2956, 1742, 1615, 1566, 1439, 1406, 1337, 1275, 1228, 1198, 1158, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (d, J = 3.1 Hz, H-4), 6.02 (d, J = 3.1 Hz, H-5), 3.81 (t, J = 6.3 Hz, H-8), 3.69 (s, H-1^1), 3.62 (s, H-2), 2.82 (t, J = 6.3 Hz, H-7), 2.18 (br, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (*C*=O), 152.5, 146.3 (C-3, C-6), 108.8 (C-4), 107.4 (C-5), 60.9 (C-8), 53.0 (C-1^1), 33.8 (C-2), 31.6 (C-7) ppm; EI-MS: m/z = 184 (26, $[M]^+$), 154 (26), 153 (22, $[M-CH_3O]^+$), 125 (32, $[M-CH_3OCO]^+$), 111 (73), 107 (33), 95 (55), 94 (100), 81 (41), 65 (47).

General Procedure for Decarbalkoxylation

A solution of the triester or the malonate (1 eq), NaCl or LiCl (1–10 eq), and H_2O (1–3 eq) in *DMSO* was heated at 160–190°C for several h. After cooling at rt, the product was extracted with diethyl ether or *Ac*O*Et*. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* afforded the product, which was purified by chromatography on a silica gel column if necessary.

Methyl 2-(5-(2-hydroxyethyl)furan-2-yl)decanoate (**3**, $C_{17}H_{28}O_4$)

General procedure with **7** (1.29 g, 3.6 mmol), NaCl (0.21 g, 3.6 mmol), and H_2O (0.13 g, 7.2 mmol) in 45 cm^3 *DMSO* heated at 160°C for 3.5 h. Chromatography afforded **7** (0.60 g, 2.03 mmol, 56%). Oil; R_f = 0.29 (CH_2Cl_2/*Et*$_2$O = 75/25); IR (film): $\bar{\nu}$ = 3108, 2954, 2928, 2857, 1742, 1610, 1561, 1461, 1436, 1379, 1212, 1161, 1121, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (d, J = 3.1 Hz, H-4), 6.03 (d, J = 3.1 Hz, H-5), 3.84 (t, J = 6.2 Hz, H-8), 3.69 (*s*, H-1^1), 2.86 (t, J = 6.2 Hz, H-7), 1.98–1.85 (m, H-2^1), 1.77 (br, OH), 1.29–1.15 (m, H-2^2 to H-2^7), 0.87 (t, J = 6.7 Hz, H-2^8) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.7$ (*C*=O), 152.0 (C-3), 151.3 (C-6), 107.2 (C-4), 105.8 (C-5), 61.0 (C-8), 52.1 (C-1^1), 45.6 (C-2), 31.6 (C-7), 30.9 C(2^1), 31.8, 29.3, 29.2, 29.1, 27.3, 22.6 (C-2^2 to C-2^7), 14.0 (C-2^8) ppm; EI-MS: $m/z = 296$ (15, $[M]^+$), 267 (11), 266 (46), 265 (14, $[M - CH_3O]^+$), 238 (13), 237 (75, $[M - CH_3OCO]^+$), 219 (21), 208 (21), 207 (100), 205 (11), 191 (10), 183 (13), 165 (15), 153 (42), 152 (11), 149 (11), 125 (52), 121 (40), 111 (25), 107 (47), 95 (30), 94 (14), 91 (11), 86 (15), 84 (24), 83 (20), 82 (16), 81 (69), 80 (30), 79 (23), 77 (20), 73 (39), 71 (17), 69 (19), 67 (13), 65 (11), 55 (18), 44 (12); ESI-HR-MS: m/z $[M + Na]^+$ = calcd 319.1880, found 319.1885.

Ethyl 2-(5-(1-ethoxycarbonyl-ethyl)-furan-2-yl)propionate (**17**, $C_{14}H_{20}O_5$)

General procedure with **8** (700 mg, 1.70 mmol), LiCl (0.44 g, 10.4 mmol), and H_2O (60 mg, 3.3 mmol) in 3 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **17** (113 mg, 4.2 mmol, 25%). Oil; $R_f = 0.35$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 2985$, 2942, 2908, 2883, 1738, 1643, 1607, 1457, 1377, 1320, 1252, 1204, 1162, 1095, 1072, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.060$ and 6.057 (2s, H-4 *rac* and H-4 *meso*), 4.12 (q, $J = 7.1$ Hz, H-1^1), 3.72 (q, $J = 7.3$ Hz, H-2), 1.45 (d, $J = 7.3$ Hz, H-2^1), 1.20 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.42$ and 172.46 (*C*=O *rac* and *C*=O *meso*), 152.46 and 152.41 (C-3 *rac* and C-3 *meso*), 106.4 (C-4 *rac*, C-4 *meso*), 60.8 (C-1^1 *rac*, C-1^1 *meso*), 39.4 (C-2 *rac*, C-2 *meso*), 15.57 and 15.61 (C-2^1 *rac* and C-2^1 *meso*), 14.0 (C-1^2 *rac*, C-1^2 *meso*) ppm; EI-MS: $m/z = 269$ (3, $[M + H]^+$), 268 (14, $[M]^+$), 196 (11, $[M + H - CO_2C_2H_5]^+$), 195 (100, $[M - CO_2C_2H_5]^+$), 139 (11), 122 (22), 121 (18), 111 (22), 107 (27); ESI-HR-MS: m/z $[M + Na]^+$ = calcd 291.1203, found 291.1202.

Ethyl (5-ethoxycarbonyl-methyl-furan-2-yl)acetate (**18**, $C_{12}H_{16}O_5$)

General procedure with **9** (4.27 g, 8.08 mmol), LiCl (2.05 g, 48.5 mmol), and H_2O (315 mg, 17.5 mmol) in 20 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **18** (442 mg, 1.84 mmol, 23%). Oil; $R_f = 0.24$ (*n*-hexane/ *AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 2984$, 2939; 2908, 1742, 1649, 1617, 1566, 1466, 1447, 1396, 1370, 1338, 1302, 1266, 1224, 1181, 1097, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.18$ (s, H-4), 4.19 (q, $J = 7.1$ Hz, H-1^1), 3.66 (s, H-2), 1.29 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.8$ (*C*=O), 147.7 (C-3), 109.3 (C-4), 61.5 (C-1^1), 34.6 (C-2), 14.6 (C-1^2) ppm; EI-MS: $m/z = 263$ (17, $[M + Na]^+$), 260 (20), 258 (100, $[M + H_2O]^+$), 243 (15), 241 (16), 241 (10).

Ethyl 2-(5-(2-hydroxyethyl)furan-2-yl)acetate (**19**, $C_{10}H_{14}O_4$) and *2-(5-Ethoxycarbonylmethyl furan-2-yl)ethyl (5-(2-hydroxyethyl)furan-2-yl)-3-acatate* (**20**, $C_{18}H_{22}O_7$)

General procedure with **10** (1.44 g, 4.22 mmol), LiCl (0.55 g, 13.0 mmol), and H_2O (80 mg, 4.4 mmol) in 11 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **19** (160 mg, 0.808 mmol, 19%) and **20** (18.4 mg, 0.053 mmol, 1%).

19: Data were the same than under *Baciocchi* conditions. See data reported in the previous paper [4].

20: Oil; $R_f = 0.06$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.13$ (d, $J = 3.1$ Hz, H-4, H-8^4), 6.06 and 6.01 (2d, $J = 3.1$ Hz, H-5 and H-8^5), 4.36 (t, $J = 6.8$ Hz, H-8), 4.20 (q, $J = 7.1$ Hz, H-1^1), 3.86 (t, $J = 6.2$ Hz, H-8^8), 3.66 and 3.64 (2s, H-2 and H-8^2), 2.97 (t, $J = 6.8$ Hz, H-7), 2.87 (t, $J = 6.2$ Hz, H-8^7), 1.77 (br, OH), 1.29 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$ (*C*=O), 169.8 (*C*=O), 152.8, 151.5, 147.1, 146.8 (C-3, C-8^3, C-6, C-8^6), 109.2, 109.1 (C-4, C-8^4), 107.9, 107.8 (C-5, C-8^5), 63.4, 61.6 (C-8, C-8^8), 61.5 (C-1^1), 34.6, 34.5 (C-2, C-8^2), 32.0, 28.1 (C-7, C-8^7), 14.6 (C-1^2) ppm; EI-MS: $m/z = 553$ (23), 525 (3), 473 (10), 445 (32), 389 (35), 373 (100, $[M + Na]^+$).

Ethyl 2-(5-(2-(benzyloxy)ethyl)furan-2-yl)propanoate (**21**, $C_{18}H_{22}O_4$)

General procedure with **11** (300 mg, 0.8 mmol), LiCl (410 mg, 0.97 mmol), and H_2O (44 mg, 0.48 mmol) in 1.5 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **21** (220 mg, 0.73 mmol, 91%). Oil; $R_f = 0.23$ (*n*-hexane/ *AcOEt* = 75/25); IR (film): $\bar{\nu} = 3088$, 3063, 3030, 2982, 2937, 2863, 1958, 173, 1640, 1561, 1496, 1454, 1366, 1202, 1178, 1100, 1027, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.28 (m, *Ph*), 6.09 (dd, $J = 3.1$, 0.5 Hz, H-4), 6.02 (d, $J = 3.1$ Hz, H-5), 4.55 (s, CH_2–*Ph*), 4.17 (q, $J = 7.1$ Hz, H-1^1), 3.77 (q, $J = 7.3$ Hz, H-2), 3.73 (t, $J = 6.9$ Hz, H-8), 2.94 (t, $J = 6.9$ Hz, H-7), 1.50 (d, $J = 7.3$ Hz, H-2^1), 1.26 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.2$ (*C*=O), 152.6 (C-3), 152.3 (C-6), 138.7 (1C, *Ph*), 128.8, 127.8, 128.0 (5C, *Ph*), 107.1 (C-4), 106.9 (C-5), 73.4 (*C*H_2-*Ph*), 68.7 (C-8), 63.4 (C-1^1), 39.9 (C-2), 29.3 (C-7), 16.2 C(2^1), 14.6 (C-1^2) ppm; EI-MS: $m/z = 302$ (10, $[M]^+$), 257 (20), 229 (30), 199 (15), 181 (100), 125.23 (46), 122.30 (33), 97.47 (50), 91.49 (80), 77.39 (22).

Ethyl 2-(5-(2-(benzyloxy)ethyl)furan-2-yl)decanoate (**22**, $C_{25}H_{36}O_4$)

General procedure with **12** (2.82 g, 6.0 mmol), LiCl (267 mg, 6.3 mmol), and H_2O (337 mg, 18.7 mmol) in 9 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **22** (1.76 g, 4.4 mmol, 73%). Oil; $R_f = 0.42$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 3030$, 2954, 2927, 2857, 1950, 1874, 1738, 1610, 1561, 1455, 1367, 1334, 1299, 1234, 1202, 1176, 1154, 1113, 1029, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.26 (m, *Ph*), 6.07 (d, $J = 3.2$ Hz, H-4), 6.00 (d, $J = 3.2$ Hz, H-5), 4.53 (s, CH_2–*Ph*), 4.18–4.12 (m, $J = 7.1$ Hz, H-1^1, ABX_3 system not fully resolved), 3.71 (t, $J = 6.9$ Hz, H-8), 2.92 (td, $J = 6.9$, 0.5 Hz, H-7), 1.99–1.93 (m, H-2^{1a}), 1.86–1.81 (m, H-2^{1b}), 1.29–1.22 (m, H-2^2 to H-2^7, H-1^2), 0.88 (t, $J = 6.9$ Hz, H-2^8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.3$ (*C*=O), 152.1 (C-3), 151.0 (C-6), 138.2 (1C, *Ph*), 128.3, 127.6, 127.5 (5C, *Ph*), 107.0 (C-4), 106.6 (C-5), 72.9 (*C*H_2-*Ph*), 68.3 (C-8), 60.8 (C-1^1), 45.4 (C-2), 31.0 C(2^1), 31.8, 29.3, 29.2 (2C), 28.9, 27.3, 22.6 (C-2^2 to C-2^7, C-7), 14.1 (C-1^2), 14.0 (C-2^8) ppm; ESI-MS: $m/z = 424$ (14, $[M + H + Na]^+$), 419 (27, $[M + H + H_2O]^+$), 418 (98, $[M + H_2O]^+$), 405 (26), 401 (100,

$[M+H]^+$), 327 (31); ESI-HR-MS: m/z $[M+H]^+$ = calcd 401.2686, found 401.2681.

Ethyl 2-(5-(2-(benzyloxy)ethyl)furan-2-yl)-3-phenylpropanoate (**23**, $C_{24}H_{26}O_4$)

General procedure with **13** (2.40 g, 5.3 mmol), LiCl (730 mg, 17.2 mmol), and H_2O (347 mg, 19.3 mmol) in 10 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **23** (1.30 g, 3.4 mmol, 65%). Oil; $R_f = 0.40$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 3030$, 2980, 2958, 2929, 2861, 1951, 1880, 1809, 1736, 1605, 1496, 1455, 1367, 1333, 1275, 1211, 1150, 1101, 1080, 1029, 1016, 699, 404 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.16 (m, *Ph*), 6.10 (d, $J = 3.0$ Hz, H-4), 6.02 (d, $J = 3.0$ Hz, H-5), 4.56 (s, CH_2–*Ph*), 4.11 (q, $J = 7.1$ Hz, H-1^1), 3.99–3.93 (m, H-2), 3.73 (t, $J = 6.9$ Hz, H-8), 3.31 (dd, $J = 13.7$, 8.6 Hz, H-2^{1a}), 3.19 (dd, $J = 13.7$, 7.2 Hz, H-2^{1b}), 2.96 (t, $J = 6.9$ Hz, H-7), 1.17 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$ (*C*=O), 152.3 (C-3), 149.9 (C-6), 138.5, 138.2, 128.8, 128.3, 128.2, 127.6, 127.5, 126.4 (12C, *Ph*), 107.6, 106.8 (2C, C-4, C-5), 72.9 (*C*H_2–*Ph*), 68.2 (C-8), 60.9 (C-1^1), 37.1 (C-2^1), 28.8 (C-7), 14.0 (C-1^2) ppm; ESI-MS: $m/z = 449$ (15), 449 (11), 433 (32), 418 (16), 417 (61), 402 (26), 401 (100, $[M+Na]^+$); ESI-HR-MS: m/z $[M+Na]^+$ = calcd 401.1729, found 401.1722.

Ethyl 2-(5-(2-(benzyloxy)ethyl)furan-2-yl)acetate (**24**, $C_{17}H_{20}O_4$)

General procedure with **14** (2.42 g, 5.6 mmol), LiCl (730 mg, 17.2 mmol), and H_2O (100 mg, 5.6 mmol) in 10 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **24** (1.08 g, 3.74 mmol, 67%). Oil; $R_f = 0.33$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 3031$, 2988, 2960, 2906, 2862, 1955, 1879, 1741, 1613, 1566, 1496, 1478, 1455, 1368, 1336, 1310, 1265, 1229, 1181, 1141, 1104, 1030, 1015, 788, 738, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.28 (m, *Ph*), 6.15 (d, $J = 3.1$ Hz, H-4), 6.04 (d, $J = 3.1$ Hz, H-5), 4.56 (s, CH_2–*Ph*), 4.20 (q, $J = 7.1$ Hz, H-1^1), 3.74 (t, $J = 6.9$ Hz, H-8), 3.65 (s, H-2), 2.96 (t, $J = 6.9$ Hz, H-7), 1.29 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$ (*C*=O), 153.0 (C-3), 146.6 (C-6), 138.7 (1C, *Ph*), 128.8, 128.1, 128.0 (5C, *Ph*), 109.0 (C-4), 107.4 (C-5), 73.4 (*C*H_2–*Ph*), 68.7 (C-8), 61.5 (C-1^1), 34.7 (C-2), 29.3 (C-7), 14.6 (C-1^2) ppm; ESI-MS: $m/z = 312$ (10), 311 (59, $[M+Na]^+$), 306 (51, $[M+H_2O]^+$), 290 (21), 289 (100, $[M+H]^+$), 215 (12).

Ethyl 2-(5-(2-(benzyloxy)propyl)furan-2-yl)acetate (**25**, $C_{18}H_{22}O_4$)

General procedure with **15** (2.419 g, 5.42 mmol), LiCl (706 mg, 16.65 mmol), and H_2O (181 mg, 10 mmol) in 10 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **25** (1.035 g, 3.42 mmol, 63%). Oil; $R_f = 0.36$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); IR (film): $\bar{\nu} = 3031$, 2977, 2930, 2871, 1741, 1454, 1374, 1338, 1216, 1180, 1133, 1097, 1029, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.27 (m, *Ph*), 6.16 (d, $J = 3.0$ Hz, H-4), 6.05 (d, $J = 3.0$ Hz, H-5), 4.57 (d, $J = 11.8$ Hz, CH*H*–*Ph*), 4.51 (d, $J = 11.8$ Hz, C*H*H–*Ph*), 4.20 (q, $J = 7.1$ Hz, H-1^1), 3.85 (sext, $J \approx 6.4$ Hz, H-8), 3.66 (s, H-2), 2.96 (dd, $J = 14.9$, 6.3 Hz, H-7a), 2.75 (dd, $J = 14.9$, 6.5 Hz, H-7b), 1.28 (t, $J = 7.1$ Hz, H-1^2), 1.26 (d, $J = 6.3$ Hz, H-9) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 170.0 (*C*=O), 153.0 (C-3), 146.6 (C-6), 139.2, 128.7, 128.0, 127.8 (6C, *Ph*), 109.1 (C-4), 108.3 (C-5), 74.3 (C-8), 71.1 (*C*H_2–*Ph*), 61.5 (C-1^1), 35.8 (C-7), 34.7 (C-2), 20.2 (C-9), 14.6 (C-1^2) ppm; ESI-MS: $m/z = 341$ (13), 326 (23), 325 (100, $[M+Na]^+$), 324 (25), 315 (15).

Ethyl 2-(5-(2-acetoxy-ethyl)-furan-2-yl)acetate (**26**, $C_{12}H_{16}O_5$) and *Diethyl 2-(5-(2-acetoxyethyl)furan-2-yl)malonate* (**27**, $C_{15}H_{20}O_7$)

General procedure with **16** (128 mg, 0.33 mmol), LiCl (43.6 mg, 1.03 mmol), and H_2O (23.5 mg, 1.31 mmol) in 1.35 cm^3 *DMSO* heated at 160°C for 2 h. According to NMR, **26** (0.107 mmol, 32%) and **27** (0.056 mmol, 17%) were afforded. They were partially separated by chromatography for characterization.

26: Oil; $R_f = 0.27$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.14$ (d, $J = 3.1$ Hz, H-4), 6.04 (d, $J = 3.1$ Hz, H-5), 4.31 (t, $J = 6.9$ Hz, H-8), 4.20 (q, $J = 7.1$ Hz, H-1^1), 3.65 (*s*, C-2), 2.96 (t, $J = 6.9$ Hz, H-7), 2.07 (s (CH_3–C=O), 1.29 (t, $J = 7.1$ Hz, H-1^2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$ (CH_3–*C*=O), 169.9 (C=O), 151.7 (C-3), 147.1 (C-6), 109.1 (C-4), 107.7 (C-5), 62.7 (C-8), 61.5 (C-1^1), 34.6 (C-2), 28.1 (C-7), 21.3 (*C*H_3–C=O), 14.6 (C-1^2) ppm; ESI-MS: $m/z = 264$ (11, $[M+H+Na]^+$), 263 (100, $[M+Na]^+$).

27: Oil; $R_f = 0.35$ (*n*-hexane/*AcOEt* = 75/25 + 1% *Me*OH); ESI-MS: $m/z = 351$ (52), 336 (16), 335 (100, $[M+Na]^+$).

Ethyl 2-(5-(2-acetoxyethyl)furan-2-yl)acetate (**26**, $C_{12}H_{16}O_5$) and *Ethyl 2-(5-(2-hydroxyethyl)furan-2-yl)acetate* (**19**, $C_{10}H_{14}O_4$)

General procedure with **16** (2.85 g, 7.42 mmol), LiCl (960 mg, 22.6 mmol), and H_2O (130 mg, 7.22 mmol) in 19 cm^3 *DMSO* heated at 190°C for 2 h. Chromatography afforded **26** (70.8 mg, 0.295 mmol, 4%) and **19** (204.3 mg, 1.032 mmol, 14%). Data for **26** were the same as above, data for **19** were the same as previously described by our group [4].

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