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SYNTHESIS OF 4-YLIDENEBUTENOLIDES AND 4-OXO-2-ENOIC ACID METHYL ESTERS FROM 5-METHOXY-2-FURYL CARBINOLS

M. D'AURIA, G. PIANCATELLI* and A. SCETTRI
Centro di Studio del CNR per la Chimica delle Sostanze Organiche Naturali, c/o Istituto di Chimica Organica dell'Università di Roma, Italia

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Abstract—5-methoxy-2-furyl carbinols (**8**) were converted by $ZnCl_2$ catalysis into a 3:1 mixture of 4-ylidenebutenolides (**9**) and 4-oxo-2-enoic acid methyl esters (**10**). The carbonium ion **12** is the key intermediate, the stability of which made the conversion very fast providing high yields.

Recently we reported that both 2-furylcarbinols (**1a**) and their 5-Me derivatives (**1b**) could be turned into the corresponding cyclopentanones (**2a-b**) through a molecular rearrangement catalysed by acids[1] (**1a**) or zinc chloride[2] (**1b**) respectively. The key-step in the conversion, explained in terms of a thermal electrocyclic reaction of a 4π electron system, was the formation of the carbonium ion (**3**) which first led to the pentadienyl cation (**4**) and then to the final products (**2**).

The stability of **3** (and therefore the reaction rate and yield) was found to depend upon the nature of R and R' substituents.

In order to determine exactly the role of the key-intermediate (**3**), we investigated the behaviour of 5-methoxy-2-furyl carbinols (**8**) under the same reaction conditions as **1**; in this case the strong electron donor effect of MeO-group favoured the formation of a carbonium ion of type **3** ($R = -OCH_3$), increasing both the reaction rate and yield.

Since compounds **8** belong to an unknown class of furan derivatives, we carried out a simple effective method of synthesis (Scheme 1).

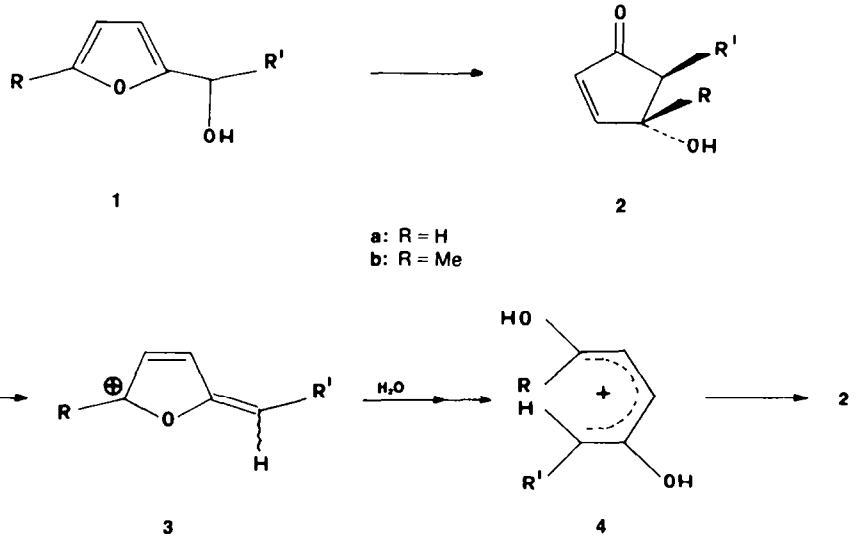
The starting materials, 5-bromo-2-furyl carbinols (**5**), were easily obtained by a Grignard reaction between 5-bromo-2-formyl furan and the corresponding alkylmagnesium bromides.[3]

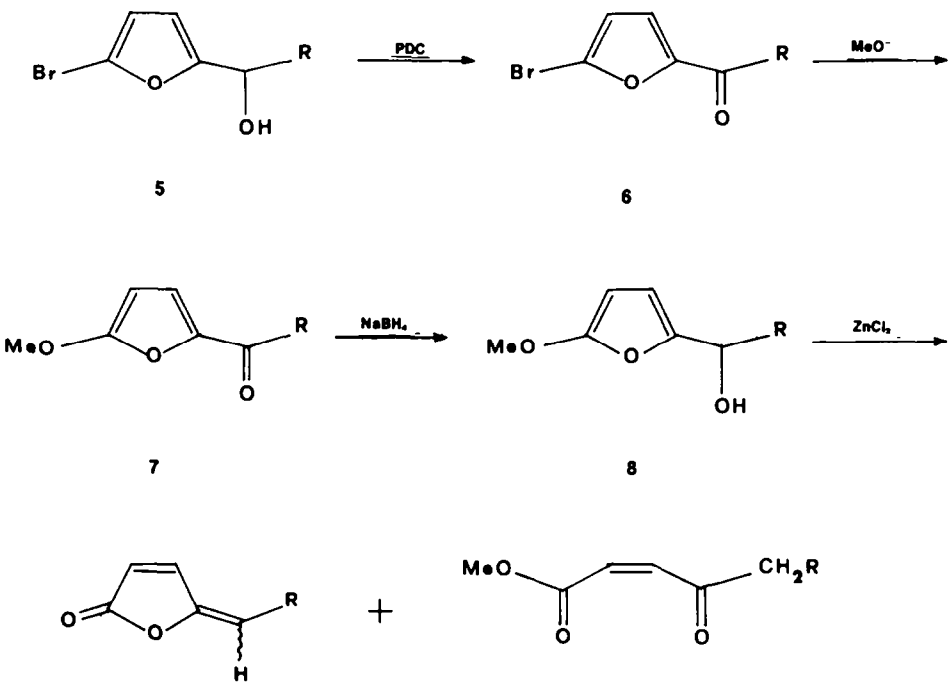
The oxidation of **5** with pyridinium dichromate (PDC)[4] furnished the ketones **6** in high yields (80%). Compounds **6**, by the action of boiling 0.75 N MexONa soln, were converted into 5-methoxy derivatives **7** (70%). Finally, the reduction of the ketonic function with $NaBH_4$ gave quantitatively 5-methoxy-2-furyl carbinols (**8**), which showed spectroscopic data in agreement with the proposed structures and a high instability both at room temperature and in slightly acidic medium.

In contrast, treatment immediately after preparation, with zinc chloride in acetone–water mixture,† converted **8**, in very high yields (Table 1), into two products, the 4-ylidenebutenolides (**9**) and the 4-oxo-2-enoic acid methyl esters (**10**), in *ca* 3:1 ratio. All new compounds showed spectral data in full agreement with the proposed structures. Compound **9a**‡ (*Z* isomer): IR (1% CCl_4, ν_{max}

†Under these conditions $ZnCl_2$ solutions shows pH = 6–7.[2]

‡Products **9** were obtained as a mixture 1:2.5 of E,Z stereoisomer.





5 6 7 8 9 10

a: R = *n*-decyl
b: R = *n*-octyl
c: R = *n*-dodecyl

Scheme 1.

Table 1. Reaction times and yields of the rearrangements*

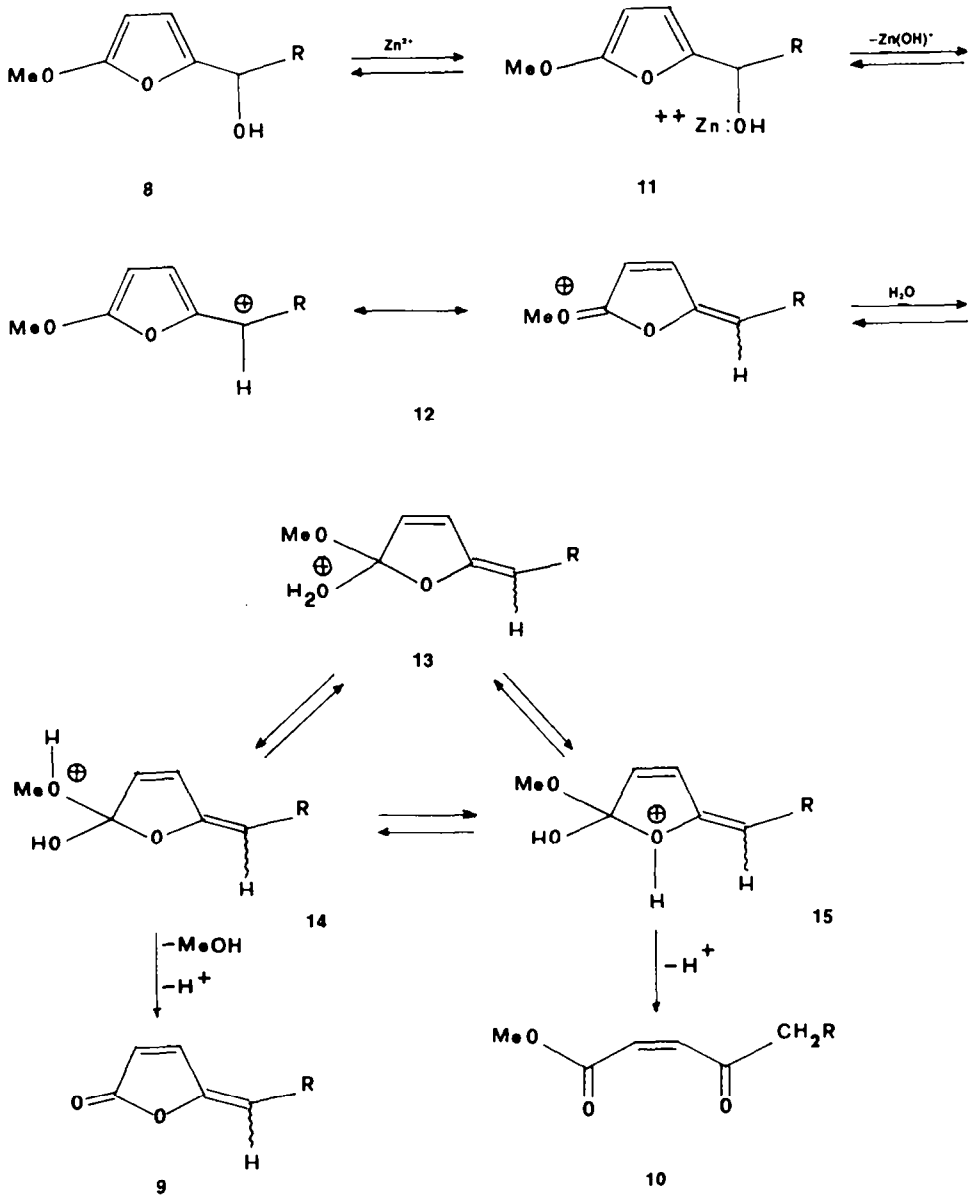
R	R'	T°C	Reaction times, h	yields (%)
CH_3	allyl	70	72	35[2]
CH_3	n-butyl	70	72	18[2]
CH_3	phenyl	70	24	70[2]
CH_3	2-thienyl	70	4	85[2]
CH_3	p-tolyl	70	4	65[2]
CH_3O	n-decyl	20	0.25	90
CH_3O	n-octyl	20	0.25	89
CH_3O	n-dodecyl	20	0.25	85

* - 5-bromo-2-furyl carbinols and 5-nitro-2-furyl carbinols[3] were tested too. As expected, they did not react under the same conditions as 1b and 8.

cm^{-1}): 1782, 1667. ^1H NMR (CCl_4, δ): 7.18 (d, 1 H, J = 6 Hz), 6.05 (d, 1 H, J = 6 Hz), 5.12 (t, 1 H, J = 7 Hz), 1.62 (m, 2 H), 1.27 (s, 16 H), 0.92 (t, 3 H). Compound **10a**: IR (1% CCl_4, ν_{max} cm^{-1}): 1730, 1707, 1625, 1393, 1210. ^1H NMR (CCl_4, δ): 6.40 (d, 1 H, J = 12 Hz), 5.93 (d, 1 H, J = 12 Hz), 3.72 (s, 3H), 2.53 (t, 2 H, J = 7 Hz), 1.70 (m, 2 H), 1.32 (s, 16 H), 0.93 (t, 3 H).

Even though cyclopentene-1,3-dione derivatives were expected, the formation of **9** and **10** was in agreement with the presence of a common key-intermediate, the reactivity of which was governed by the MeO-group on the furan ring (Scheme 2).

In fact, the key-step was the formation of the carbonium ion **12** (of the same type as **3**) promoted by the



Scheme 2.

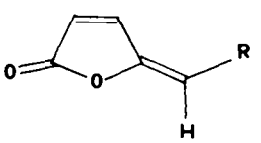
initial attack of a Zn ion upon the alcoholic function, which first led to **11** and then **12**. Finally, the nucleophilic addition of water and the resulting prototropic equilibria between **13**, **14** and **15** explained the origin of the products **9** and **10**.

5-Methoxy-2-furyl carbinols (**8**) reacted much faster than the corresponding 5-Me derivatives **1b** (Table 1): thus the MeO-group on the furan ring increased the stability of **12** by dispersion of the positive charge. The reaction rate and yield enhancement could be attributed to the powerful electron donor capacity of the MeO-substituent, which lowered the energy barrier in the formation of **12**.

Scheme 1 represents a new synthetic route to a class of very interesting compounds, the 4-ylidene-butenolides,† including many natural substances of widespread biological importance.[5]

In particular, protoanemonin **16** (R = H), the simplest possible compound of this structure and a constituent of the essential oil of buttercup and other ranunculaceae, shows marked antibiotic activity.[6]

In conclusion, we have developed a simple and convenient method for the preparation of protoanemonin analogs **16** (R ≠ H), for which a few synthetic approaches have been achieved during the last twenty years.[5,7]



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†Also 4-oxo-2-enoic acid methyl esters, as well known, give **9** by intramolecular cyclisation.[5]

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were taken with a Perkin–Elmer R32 spectrometer, using CCl_4 soln with TMS as an internal standard. IR spectra were taken with a Perkin–Elmer 257 spectrometer. Mass spectra were obtained with AEI MS-12 spectrometer at 70 eV, by using direct insertion at source temp of 150°. Commercial Merck silica gel were used for column chromatography. Carlo Erba precoated silica gel plates with fluorescent indicator were used in tlc. The chromatograms were detected by using Mineral Lamp (short wave UV-254 nm) and by spraying with 5N H_2SO_4 and heating at 110° for 10 min.

Compounds **6**—*general procedure*

PDC (22.5 mmoles) was added to 15 mmoles of **5**,[3] diluted in 150 ml of anhyd CH_2Cl_2. The mixture was refluxed at 55° for 2 hr. Then, the mixture was diluted with Et_2O and filtered. The removal of the solvent gave a crude product which was chromatographed on SiO_2: elution with n-hexane–Et_2O 9:1 yielded pure **6**.

1-(5-*Bromo*-2-*furyl*)-*n*-*undecyl*-1-*one* **6a**, (80%), plates from MeOH, m.p. 77°. ^{1}H NMR (CCl_4, δ): 7.02 (d, 1 H, J = 4 Hz), 6.43 (d, 1 H, J = 4 Hz), 2.74 (t, 2 H, J = 6 Hz), 1.62 (m, 2 H), 1.30 (s, 14 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1680, 1580, 1460, 1008, 922. MS (*m/e*): 314 (M^+), 316 ($M^+ + 2$). Found: C, 77.20; H, 7.80. Calc. for $C_{15}H_{23}BrO_2$: C, 77.15; H, 7.87%.

1-(5-*Bromo*-2-*furyl*)-*n*-*nonyl*-1-*one* **6b**, (82%), plates from MeOH, m.p. 78–79°. ^{1}H NMR (CCl_4, δ): 7.00 (d, 1 H, J = 4 Hz), 6.42 (d, 1H, J = 4 Hz), 2.73 (t, 2 H, J = 7 Hz), 1.70 (m, 2 H), 1.30 (s, 12 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1680, 1580, 1460, 1008, 992. MS (*m/e*): 286 (M^+), 228 ($M^+ + 2$). Found: C, 54.41; H, 6.74. Calc. for $C_{13}H_{19}BrO_2$: C, 54.37; H, 6.67%).

1-(5-*Bromo*-2-*furyl*)-*n*-*tridecyl*-1-*one* **6c**, (79%), plates from MeOH, m.p. 76–78°. ^{1}H NMR (CCl_4, δ): 6.98 (d, 1 H, J = 4 Hz), 6.39 (d, 1H, J = 4 Hz), 2.74 (t, 2 H, J = 7 Hz), 1.68 (m, 2 H), 1.28 (s, 18 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1687, 1580, 1460, 1010, 922. MS (*m/e*): 342 (M^+), 344 ($M^+ + 2$). Found: C, 59.60; H, 7.98. Calc. for $C_{17}H_{27}BrO_2$: C, 59.47; H, 7.92%.

Compounds **7**—*general procedure*

2N MeONa (10 ml) in MeOH were added to 10 mmoles of **6**, dissolved in 20 ml of anhyd MeOH, at 70°. After 2 hr, the mixture was poured into 0.01 N HCl and extracted 3 times with Et_2O. The neutral extracts were dried over Na_2SO_4. The removal of the solvent yielded the crude product that was chromatographed on SiO_2. The elution with n-hexane–Et_2O 4:1 gave pure **7**.

1-(5-*Methoxy*-2-*furyl*)-*n*-*undecyl*-1-*one* **7a**, (71%), prisms from MeOH, m.p. 55–57°. ^{1}H NMR (CCl_4, δ): 6.99 (d, 1 H, J = 4Hz), 5.30 (d, 1 H, J = 4 Hz), 3.96 (s, 3H), 2.60 (t, 2H, J = 8 Hz), 1.65 (m, 2 H), 1.28 (s, 14 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1665, 1597, 1528, 1430, 1378, 1057, 1016, 955. MS (*m/e*): 266 (M^+). Found: C, 72.26; H, 9.95. Calc. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.

1-(5-*Methoxy*-2-*furyl*)-*n*-*nonyl*-1-*one* **7b**, (69%), prisms from MeOH, m.p. 56–57°. ^{1}H NMR (CCl_4, δ): 6.98 (d, 1 H, J = 4 Hz), 5.28 (d, 1 H, J = 4 Hz), 3.93 (s, 3 H), 2.60 (t, 2H, J = 8 Hz), 1.65 (m, 2 H), 1.32 (s, 10 H), 0.90 (t, 3H). IR (1% CCl_4, ν_{max} cm^{-1}): 1668, 1597, 1530, 1430, 1380, 1058, 1018, 958. MS (*m/e*): 238 (M^+). Found: C, 70.64; H, 9.38. Calc. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%.

1-(5-*Methoxy*-2-*furyl*)-*n*-*tridecyl*-1-*one* **7c**, (67%), needles from MeOH, m.p. 56–57°. ^{1}H NMR (CCl_4, δ): 6.98 (d, 1 H, J = 4 Hz), 5.28 (d, 1 H, J = 4 Hz), 3.94 (s, 3 H), 2.60 (t, 2 H, J = 8 Hz), 1.65 (m, 2 H), 1.28 (s, 18 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1670, 1597, 1524, 1430, 1382, 1060, 1018, 960. MS (*m/e*): 294 (M^+). Found: C, 73.57; H, 10.22. Calc. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27%.

Compounds **8**—*general procedure*

$NaBH_4$ (1.2 g) were added to a soln of 5 mmoles of **7**, 24 ml MeOH, 24 ml diethylendioxide, 2.1 ml H_2O, at 20°. The mixture was poured in H_2O, satd with NaCl, and extracted with Et_2O. The neutral extracts were dried over Na_2SO_4. The removal of the solvent yielded pure **8**.

1-(5-*Methoxy*-2-*furyl*)-*n*-*undecyl*-1-*ol* **8a**, (100%), oil. ^{1}H NMR (CCl_4, δ): 5.94 (d, 1 H, J = 3 Hz), 4.95 (d, 1 H, J = 3 Hz), 4.37 (t, 1 H, J = 7 Hz), 3.76 (s, 3 H), 2.40 (s, 1 H), 1.63 (m, 2 H), 1.26 (s, 14 H), 0.90 (t, 3 H).

1-(5-*Methoxy*-2-*furyl*)-*n*-*nonyl*-1-*ol* **8b**, (100%), oil. ^{1}H NMR (CCl_4, δ): 5.96 (d, 1 H, J = 3 Hz), 4.96 (d, 1 H, J = 3 Hz), 4.40 (t, 1 H, J = 7 Hz), 3.78 (s, 3 H), 2.20 (s, 1 H), 1.65 (m, 2 H), 1.28 (s, 10 H), 0.90 (t, 3 H).

1-(5-*Methoxy*-2-*furyl*)-*n*-*tridecyl*-1-*ol* **8c**, (100%), oil. ^{1}H NMR (CCl_4, δ): 5.96 (d, 1 H, J = 3 Hz), 4.95 (d, 1 H, J = 3 Hz), 4.38 (t, 1 H, J = 7 Hz), 3.78 (s, 3 H), 2.20 (s, 1 H), 1.65 (m, 2 H), 1.28 (s, 18 H), 0.90 (t, 3 H).

Compounds **9** *and* **10**—*general procedure*

$ZnCl_2$ (2 g) were added to a soln of **8** (5 mmoles) in 135 ml of Me_2CO and 5.4 ml H_2O, at 20°. After 15 min the mixture was diluted with Et_2O and washed with H_2O, satd with NaCl. The neutral organic layer was dried over Na_2SO_4. The removal of the solvent yielded the crude product that was chromatographed on SiO_2: elution with C_6H_6 gave pure **9** (E + Z stereoisomers) and then **10**.

(E + Z)-2(5H)-*Furanone*-5-(*n*-*decylmethylene*) **9a**, (65%), oil. ^{1}H NMR (CCl_4, δ): *Z* isomer: 7.18 (d, 1 H, J = 6 Hz), 6.05 (d, 1 H, J = 6 Hz), 5.12 (t, 1 H, J = 7 Hz), 1.62 (m, 2 H), 1.27 (s, 16 H), 0.92 (t, 3 H); *E* isomer: 7.65 (d, 1 H, J = 6 Hz), 6.05 (d, 1 H, J = 6 Hz), 5.65 (t, 1 H, J = 7 Hz), 1.62 (m, 2 H), 1.28 (s, 16 H), 0.90 (s, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1782, 1667. MS (*m/e*): 236 (M^+). Found: C, 76.35; H, 10.32. Calc. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.21%.

cis-2-*Pentadecenoic acid*-4-*oxo*-*methyl ester* **10a**, (25%), oil. ^{1}H NMR (CCl_4, δ): 6.40 (d, 1 H, J = 12 Hz), 5.93 (d, 1 H, J = 12 Hz), 3.72 (s, 3 H), 2.53 (t, 2 H, J = 7 Hz), 1.70 (m, 2 H), 1.32 (s, 16 H), 0.93 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1730, 1707, 1625, 1393, 1210. MS (*m/e*): 268 (M^+). Found: C, 71.68; H, 10.63. Calc. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%.

(E + Z)-2(5H)-*Furanone*-5-(*n*-*octylmethylene*) **9b**, (66%), oil. ^{1}H NMR (CCl_4, δ): *Z* isomer: 7.24 (d, 1 H, J = 6 Hz), 6.04 (d, 1 H, J = 6 Hz), 5.16 (t, 1 H, J = 7 Hz), 1.64 (m, 2 H), 1.30 (s, 12 H), 0.90 (t, 3 H); *E* isomer: 7.58 (d, 1 H, J = 6 Hz), 6.04 (d, 1 H, J = 6 Hz), 5.66 (t, 1 H, J = 7 Hz), 1.63 (m, 2 H), 1.30 (s, 12 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1785, 1668. MS (*m/e*): 208 (M^+). Found: C, 75.05; H, 9.74. Calc. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%.

cis-2-*Tridecenoic acid*-4-*oxo*-*methyl ester* **10b**, (23%), oil. ^{1}H NMR (CCl_4, δ): 6.33 (d, 1 H, J = 12 Hz), 5.90 (d, 1 H, J = 12 Hz), 3.70 (s, 3 H), 1.62 (m, 2 H), 1.30 (s, 12 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1730, 1710, 1630, 1212. MS (*m/e*): 240 (M^+). Found: C, 70.08; H, 10.15. Calc. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

(E + Z)-2(5H)-*Furanone*-5-(*n*-*dodecylmethylene*) **9c**, (55%), oil. ^{1}H NMR (CCl_4, δ): *Z* isomer: 7.20 (d, 1 H, J = 6 Hz), 6.02 (d, 1 H, J = 6 Hz), 5.13 (t, 1 H, J = 7 Hz), 1.64 (m, 2 H), 1.27 (s, 20 H), 0.90 (t, 3 H); *E* isomer: 7.58 (d, 1 H, J = 6 Hz), 6.03 (d, 1 H, J = 6 Hz), 5.66 (t, 1 H, J = 7 Hz), 1.64 (m, 2 H), 1.28 (s, 20 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1786, 1670, 1470, 1287, 1120, 877. MS (*m/e*): 264 (M^+). Found: C, 77.42; H, 10.57. Calc. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67%.

cis-2-*Heptadecenoic acid*-4-*oxo*-*methyl ester* **10c**, (30%), oil. ^{1}H NMR (CCl_4, δ): 6.35 (d, 1 H, J = 12 Hz), 5.88 (d, 1 H, J = 12 Hz), 3.68 (s, 3 H), 2.51 (t, 2 H, J = 7 Hz), 1.64 (m, 2 H), 1.28 (s, 20 H), 0.90 (t, 3 H). IR (1% CCl_4, ν_{max} cm^{-1}): 1742, 1710, 1630, 1388, 1216. MS (*m/e*): 296 (M^+). Found: C, 73.00; H, 10.96. Calc. for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%.

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