

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

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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 acids¹ (**1a**) or zinc chloride² (**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.

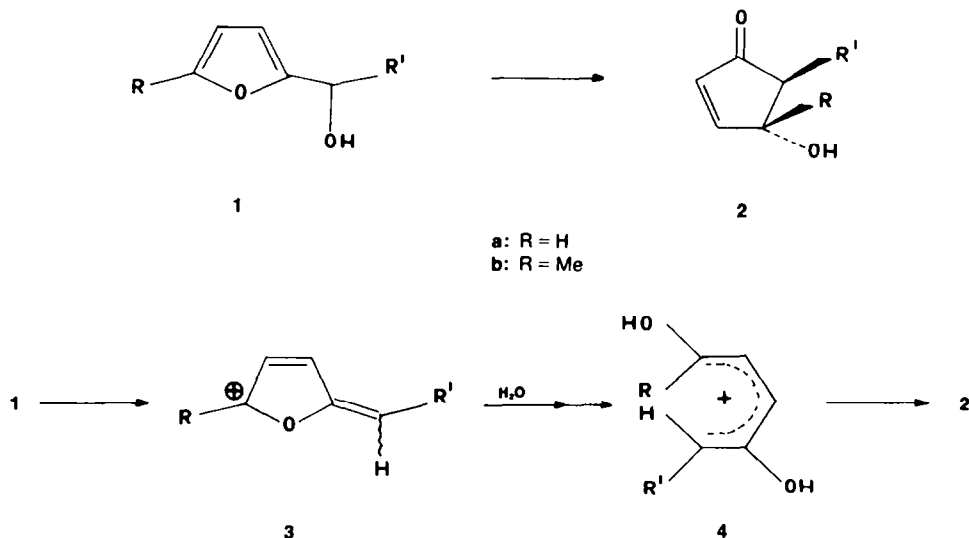
In order to determine exactly the role of the key-intermediate (**3**), we investigated the behaviour of 5-methoxy-2-furyl carbinols (**8**) under the same reaction conditions as **1**; in this case the strong electron donor effect of MeO-group favoured the formation of a carbonium ion of type **3** ($\text{R} = -\text{OCH}_3$), increasing both the reaction rate and yield.

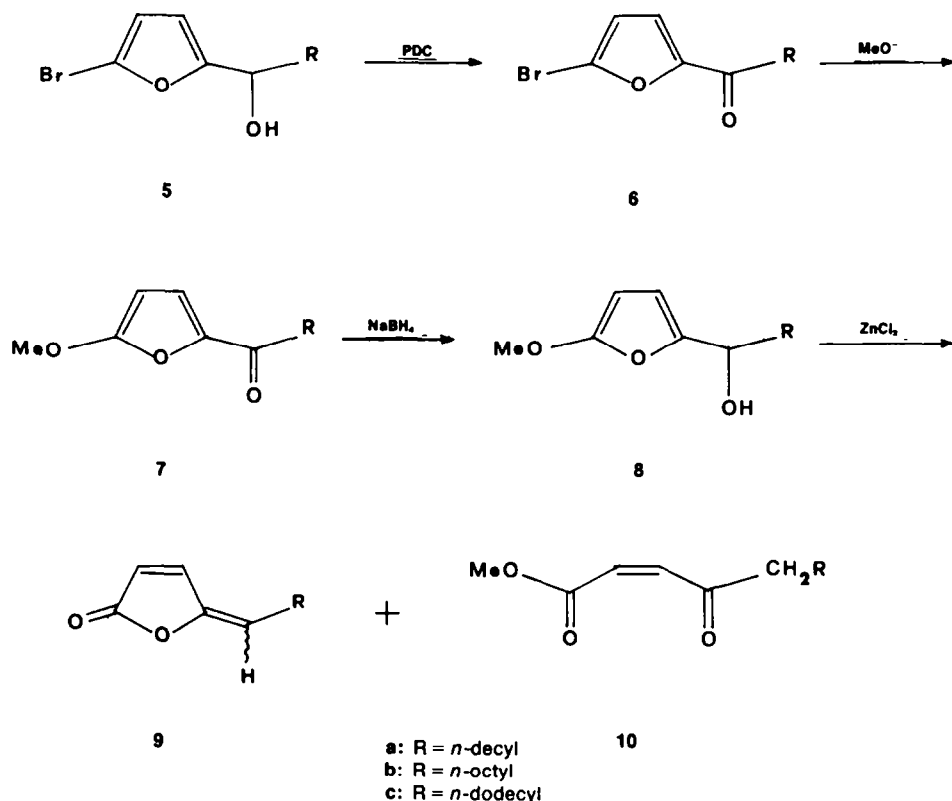
Since compounds **8** belong to an unknown class of furan derivatives, we carried out a simple effective method of synthesis (Scheme 1).

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 alkyl-magnesium 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 I), 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}





Scheme 1.

Table 1. Reaction times and yields of the rearrangements*

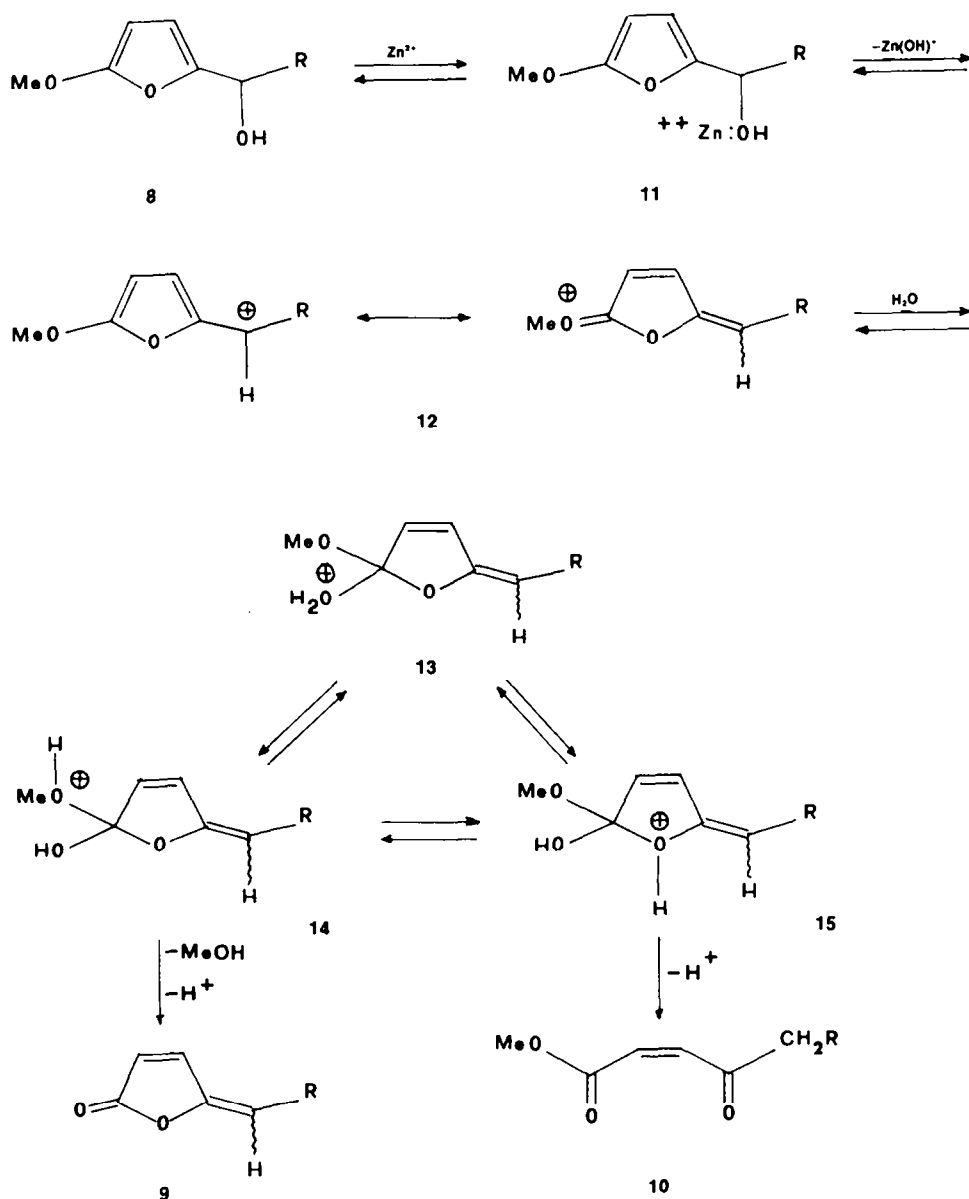
R	R'	T°C	Reaction times, h	yields (%)
CH ₃	allyl	70	72	35 ²
CH ₃	<i>n</i> -butyl	70	72	18 ²
CH ₃	phenyl	70	24	70 ²
CH ₃	2-thienyl	70	4	85 ²
CH ₃	<i>p</i> -tolyl	70	4	65 ²
CH ₃ O	<i>n</i> -decyl	20	0.25	90
CH ₃ O	<i>n</i> -octyl	20	0.25	89
CH ₃ O	<i>n</i> -dodecyl	20	0.25	85

* - 5-bromo-2-furyl carbinols and 5-nitro-2-furyl carbinols³ were tested too. As expected, they did not react under the same conditions as **1b** and **8**.

cm⁻¹): 1782, 1667. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1730, 1707, 1625, 1393, 1210. ¹H NMR (CCl₄, 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.

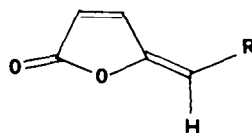
5-Methoxy-2-furyl carbinols (8) reacted much faster than the corresponding 5-Me derivatives 1b (Table 1): thus the MeO-group on the furan ring increased the stability of 12 by dispersion of the positive charge. The reaction rate and yield enhancement could be attributed to the powerful electron donor 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.p.s were determined on a Kofler block and are uncorrected. ¹H NMR spectra were taken with a Perkin-Elmer R32 spectrometer, using CCl₄ 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 H₂SO₄ 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 CH₂Cl₂. The mixture was refluxed at 55° for 2 hr. Then, the mixture was diluted with Et₂O and filtered. The removal of the solvent gave a crude product which was chromatographed on SiO₂: elution with n-hexane-Et₂O 9:1 yielded pure **6**.

1-(5-Bromo-2-furyl)-n-undecyl-1-one 6a, (80%), plates from MeOH, m.p. 77°. ¹H NMR (CCl₄, 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% CCl₄, 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 C₁₅H₂₃BrO₂: C, 77.15; H, 7.87%.

1-(5-Bromo-2-furyl)-n-nonyl-1-one 6b, (82%), plates from MeOH, m.p. 78–79°. ¹H NMR (CCl₄, δ): 7.00 (d, 1 H, J = 4 Hz), 6.42 (d, 1 H, 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% CCl₄, 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 C₁₃H₁₉BrO₂: C, 54.37; H, 6.67%.

1-(5-Bromo-2-furyl)-n-tridecyl-1-one 6c, (79%), plates from MeOH, m.p. 76–78°. ¹H NMR (CCl₄, δ): 6.98 (d, 1 H, J = 4 Hz), 6.39 (d, 1 H, 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% CCl₄, 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 C₁₇H₂₇BrO₂: 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 Et₂O. The neutral extracts were dried over Na₂SO₄. The removal of the solvent yielded the crude product that was chromatographed on SiO₂. The elution with n-hexane-Et₂O 4:1 gave pure **7**.

1-(5-Methoxy-2-furyl)-n-undecyl-1-one 7a, (71%), prisms from MeOH, m.p. 55–57°. ¹H NMR (CCl₄, δ): 6.99 (d, 1 H, J = 4 Hz), 5.30 (d, 1 H, J = 4 Hz), 3.96 (s, 3 H), 2.60 (t, 2 H, J = 8 Hz), 1.65 (m, 2 H), 1.28 (s, 14 H), 0.90 (t, 3 H). IR (1% CCl₄, 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 C₁₆H₂₆O₃: C, 72.14; H, 9.84%.

1-(5-Methoxy-2-furyl)-n-nonyl-1-one 7b, (69%), prisms from MeOH, m.p. 56–57°. ¹H NMR (CCl₄, 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, 2 H, J = 8 Hz), 1.65 (m, 2 H), 1.32 (s, 10 H), 0.90 (t, 3 H). IR (1% CCl₄, 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 C₁₄H₂₂O₃: C, 70.56; H, 9.30%.

1-(5-Methoxy-2-furyl)-n-tridecyl-1-one 7c, (67%), needles from MeOH, m.p. 56–57°. ¹H NMR (CCl₄, 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% CCl₄, 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 C₁₈H₃₀O₃: C, 73.43; H, 10.27%.

Compounds 8—general procedure

NaBH₄ (1.2 g) were added to a soln of 5 mmoles of **7**, 24 ml MeOH, 24 ml diethylenedioxiide, 2.1 ml H₂O, at 20°. The mixture was poured in H₂O, satd with NaCl, and extracted with Et₂O. The neutral extracts were dried over Na₂SO₄. The removal of the solvent yielded pure **8**.

1-(5-Methoxy-2-furyl)-n-undecyl-1-ol 8a, (100%), oil. ¹H NMR (CCl₄, 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. ¹H NMR (CCl₄, 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. ¹H NMR (CCl₄, 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

ZnCl₂ (2 g) were added to a soln of **8** (5 mmoles) in 135 ml of Me₂CO and 5.4 ml H₂O, at 20°. After 15 min the mixture was diluted with Et₂O and washed with H₂O, satd with NaCl. The neutral organic layer was dried over Na₂SO₄. The removal of the solvent yielded the crude product that was chromatographed on SiO₂: elution with C₆H₆ gave pure **9** (E + Z stereoisomers) and then **10**.

(E + Z)-2(5H)-Furanone-5-(n-decylmethylene) 9a, (65%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1782, 1667. MS (*m/e*): 236 (M⁺). Found: C, 76.35; H, 10.32. Calc. for C₁₅H₂₄O₂: C, 76.23; H, 10.21%.

cis-2-Pentadecenoic acid-4-oxo-methyl ester 10a, (25%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1730, 1707, 1625, 1393, 1210. MS (*m/e*): 268 (M⁺). Found: C, 71.68; H, 10.63. Calc. for C₁₆H₂₈O₃: C, 71.60; H, 10.52%.

(E + Z)-2(5H)-Furanone-5-(n-octylmethylene) 9b, (66%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1785, 1668. MS (*m/e*): 208 (M⁺). Found: C, 75.05; H, 9.74. Calc. for C₁₃H₂₀O₂: C, 74.96; H, 9.68%.

cis-2-Tridecenoic acid-4-oxo-methyl ester 10b, (23%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1730, 1710, 1630, 1212. MS (*m/e*): 240 (M⁺). Found: C, 70.08; H, 10.15. Calc. for C₁₄H₂₄O₃: C, 69.96; H, 10.07%.

(E + Z)-2(5H)-Furanone-5-(n-dodecylmethylene) 9c, (55%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1786, 1670, 1470, 1287, 1120, 877. MS (*m/e*): 264 (M⁺). Found: C, 77.42; H, 10.57. Calc. for C₁₇H₂₈O₂: C, 77.22; H, 10.67%.

cis-2-Heptadecenoic acid-4-oxo-methyl ester 10c, (30%), oil. ¹H NMR (CCl₄, 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% CCl₄, ν_{max} cm⁻¹): 1742, 1710, 1630, 1388, 1216. MS (*m/e*): 296 (M⁺). Found: C, 73.00; H, 10.96. Calc. for C₁₈H₃₂O₃: C, 72.93; H, 10.88%.

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