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A NEW SIMPLE PROCEDURE FOR THE ISOMERIZATION OF 2-FURYLCARBINOLS TO CYCLOPENTENONES

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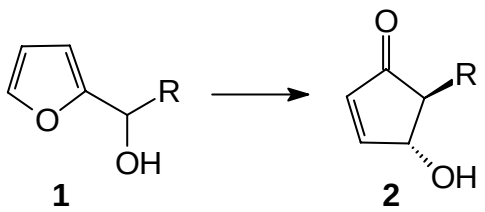
Abstract – The previously reported acid catalyzed isomerization of 2-furylcarbinols to 5-alkyl-4-hydroxycyclopent-2-enones was performed in boiling water in the absence of any acid catalyst. In this case the reaction led to the formation of more stable isomer 2-alkyl- or 2-aryl-4-hydroxycyclopent-2-enones. The reaction of chiral 2-furylcarbinol in the presence of zinc chloride gave a racemic cyclopentenone while 2-furylcarbinol did not undergo racemization. A new mechanism for the conversion of 2-furylcarbinols into cyclopentenone is proposed.

Twenty-two years ago the first isomerization reaction of 2-furylcarbinols (**1**) to cyclopentenones (**2**) has been described (Scheme 1).[1]

Scheme 1

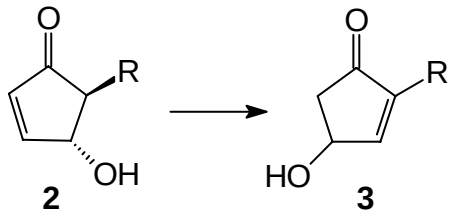


In this paper the conversion of 2-furylcarbinols to 4-hydroxy-5-alkylcyclopent-2-en-1-ones was performed in an acetone-water mixture in the presence of an acid catalyst. In the following papers in this field acetone can be substituted by DME or dioxane.[2] Interestingly, when 5-methyl-2-furylcarbinols were used as substrates protic acid catalysis should be substituted by Lewis acid such as zinc chloride.[3] After this pioneer work most of the research activity in this field have be carried out by researchers of

Sumitomo Chemical Co., Ltd. They found that the same reaction can be carried out only in water at 100 °C in the presence of buffer solution at pH 5.5.[4]

From a synthetic point of view it is important to note that 4-hydroxy-5-alkylcyclopent-2-en-1-ones (**2**) can be converted into 2-alkyl-4-hydroxycyclopent-2-en-1-ones (**3**) in the presence of basic or neutral alumina[5] or adjusting the pH at basic value (Scheme 2).[6] Alternatively, the same reaction can be obtained in acidic conditions.[7-9]

Scheme 2



In this paper we report our results in this field showing that neutral conditions can be used for the conversion of 2-furylcarbinols to cyclopentenones. Furthermore, on the basis of these results and on the use of a chiral cyclopentenone we present a new mechanistic hypothesis.

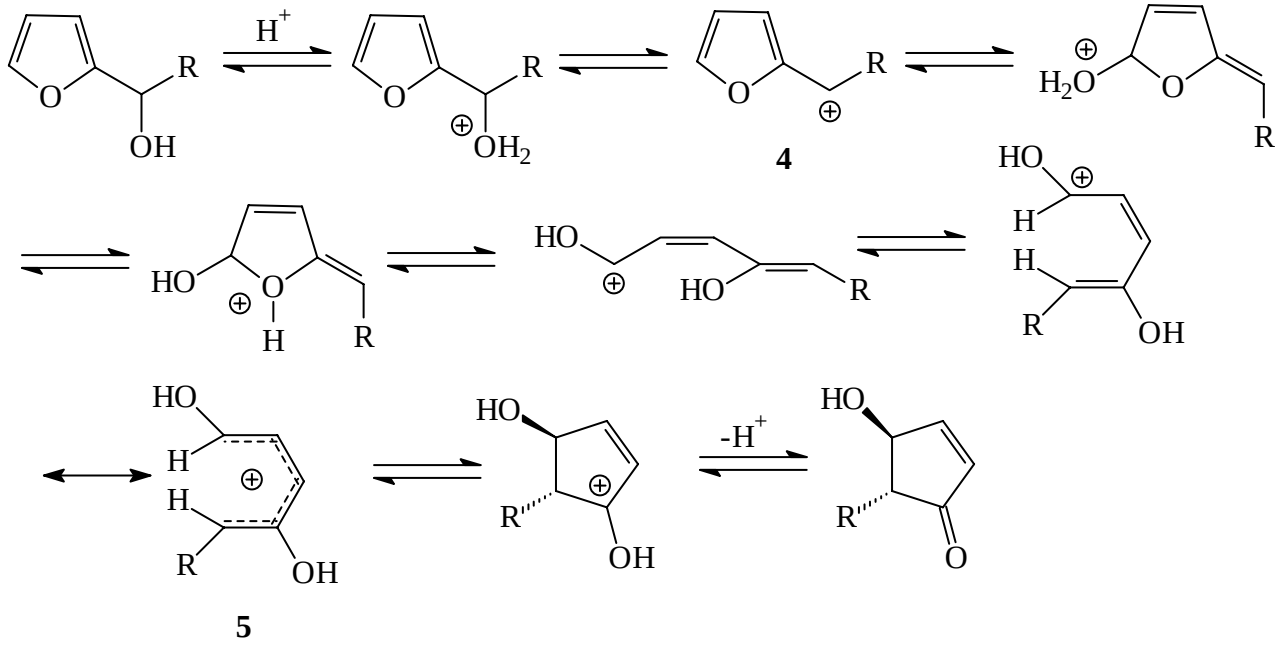
RESULTS AND DISCUSSION

The role of pH in this reaction is critical. In fact, the decrease of the pH induced a decrease of the yield in cyclopentenone and the increase of by-product formations. In fact, Japanese researchers found a relationship between reaction rate and kinetic constant (eq. 1):[2] this equation shows the kinetic constant decreases at acid pH values.

$$\ln k = -0.60\left[pH\right] + 2.1 \qquad (1)$$

On the basis of the equation 1 the best reaction conditions for this reaction should be the absence of any acid catalyst. This statement is not in agreement with the proposed mechanism for the conversion **1** → **2**.[10] In fact, this hypothesis involved the formation of the carbocation (**4**) that, then, underwent the attack of water on five position on the furan ring. Prototropic shifts gave the ring opening intermediate (**5**). This intermediate was cyclized through a 4 π electron thermal conrotatory electrocyclic reaction to give **2** (Scheme 3).

Scheme 3



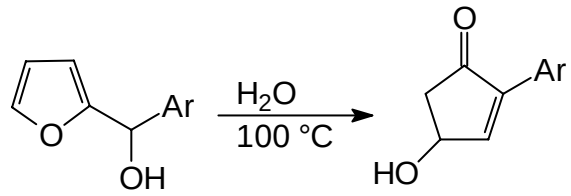
We tested the behavior of some 2-furylcarbinols in absence of acid catalyst in order to solve this apparent incongruity. The furylcarbinol (**1a**) was suspended in redistilled water under argon and the mixture was stirred at 100 °C for 24 h. At the end we obtained in almost quantitatively yield the isomeric cyclopentenone (**3a**) (Scheme 4, Table 1).

The same behavior was observed using as substrate the 2-thienyl derivative (**1b**) (Scheme 4, Table 1). On the contrary, when the compound (**1c**), bearing an alkyl group as substituent on the 2-furylcarbinol, was treated under the same reaction condition only 57% conversion of the substrate was observed. Furthermore, the reaction led to a 5:2 mixture of the cyclopentenone (**2c**) and the isomeric one (**3c**) (Scheme 4, Table 1). The cyclopentenone (**2c**) was not obtained stereospecifically as reported above. We obtained a 4:1 mixture of isomers at C4.

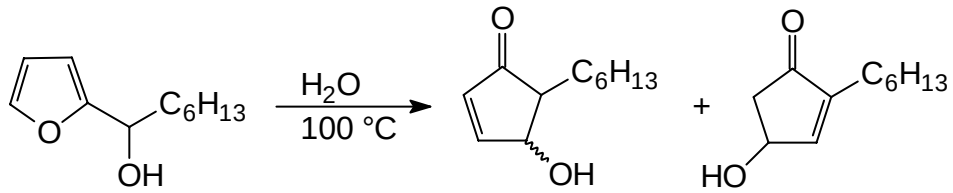
When the reaction was carried out for seven days under the same conditions, we obtained a quantitative conversion of the furylcarbinol (**1c**) and a mixture of products where **3c** was the main product and **2c** a by-product (Table 1).

As reported above, the conversion **1** → **2** was carried out also using 5-methyl-2-furylcarbinols (**6**). These substrates, in comparison with **1**, showed a more pronounced instability. All the reactions with this type of substrates were accompanied with the presence of some by-products.[2] We used 5-methyl-2-furyl-phenylcarbinol (**6a**) and the corresponding 2-thienyl derivative (**6b**) (Scheme 5). The treatment of **6a** in boiling water for 15 h gave a mixture of the cyclopentenone (**7a**) and the isomeric cyclopentenone (**8a**) (Scheme 5, Table 1).

Scheme 4

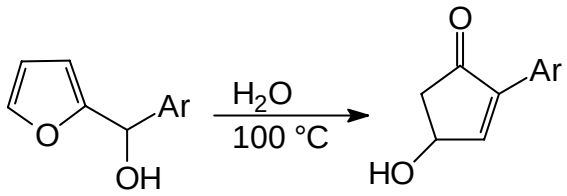


1a: Ar = Ph **3a**
1b: Ar = 2-Thienyl **3b**

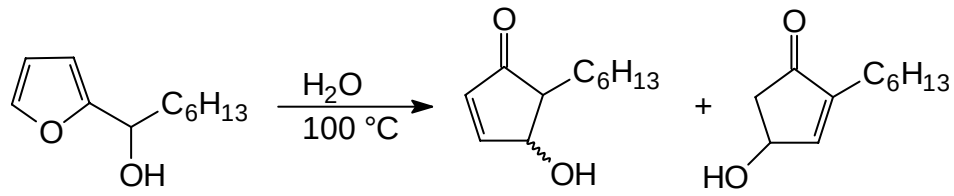


1c **2c** **3c**

Scheme 5



1a: Ar = Ph **3a**
1b: Ar = 2-Thienyl **3b**



1c **2c** **3c**

Also in this case the cyclopentenone (**7a**) was not obtained stereospecifically as reported in a previous paper,[3] but as a 3:2 mixture of isomers at C4. When the reaction was carried out for 48 h we obtained, almost quantitatively, the isomeric cyclopentenone (**8a**) (Scheme 5, Table 1).

Using as substrate the 2-thienyl derivative (**6b**), after 36 h treatment of the substrate in boiling water, we obtained only the cyclopentenone (**8b**) (Scheme 5, Table 1).

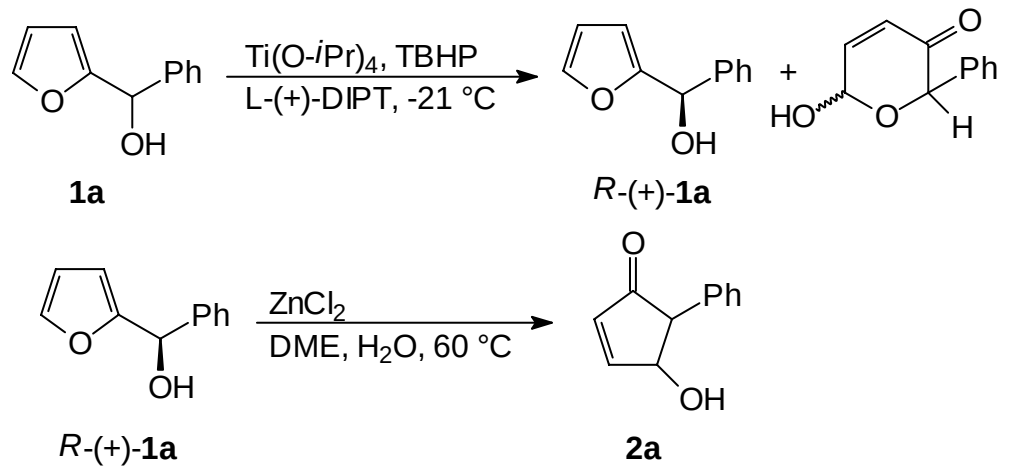
We have to note that the above-described procedure is very simple and clean. In fact we did not obtain by-product and the reaction mixture after the reaction did not show to need chromatographic purification.

Table 1 – Conversion of 2-furylcarbinols into cyclopentenones

Substrate	R	Reaction time (h)	Conversion (%)	Product	Yields (%)
1a	phenyl	24	100	**3a**	99
1b	2-thienyl	24	100	**3b**	95
1c	*n*-hexyl	24	57	**2c**	40
				3c	15
		168	100	**2c**	32
				3c	65
6a	phenyl	15	100	**7a**	22
				8a	77
		36	100	**8a**	96
6b	2-thienyl	36	100	**8b**	95

Finally, we used as substrate in the conversion **1** → **2** a chiral 2-furylcarbinol. *R*-(+)-**1a** was obtained through kinetic resolution of (±)-**1a** in the presence of Ti(O-*i*Pr)$_4$, TBHP and L-(+)-DIPT.[11,12] *R*-(+)-**1a** was dissolved in 2:1 DME-water mixture in the presence of $ZnCl_2$ at 60 °C. After four days only 34% conversion of the substrate was observed. It is noteworthy that, while the cyclopentenone (**2a**) was a racemic mixture, the recovered **1a** was optically pure (Scheme 6).

Scheme 6



The above reported data are not in agreement with the proposed mechanism: 1. we have shown that the conversion **1** → **2** can occur without acid catalyst, while the mechanism outlined in the Scheme 3 needs

an acid catalyst; 2. we have shown that we can obtain mixtures of stereoisomeric (**2**) and that the conversion **1** → **2** was not stereospecific as described previously and as required by the mechanism of the Scheme 3; 3. the mechanism proposed in the Scheme 3 needs an equilibrium between all the species: the recovery of chiral (+)-**1a** is not in agreement with this hypothesis.

On the basis of experimental results we can formulate a new hypothesis for the mechanism of the conversion **1** → **2**. The mechanism is outlined in the Scheme 7. The thermal reaction of water in five position on the furan ring in an irreversible reaction allows to the formation of **9**. Prototropic equilibrium gives **10** and, then, to the ring opening intermediate (**11**). This compound spontaneously cyclizes to the cyclopentenone (**2**).

Scheme 7

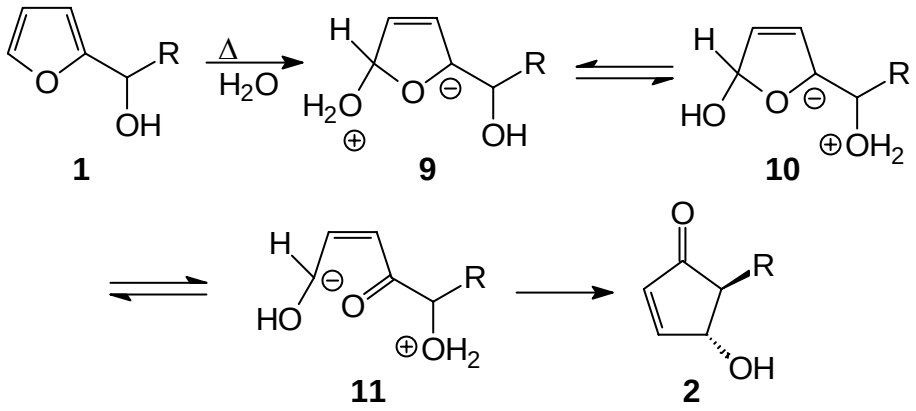
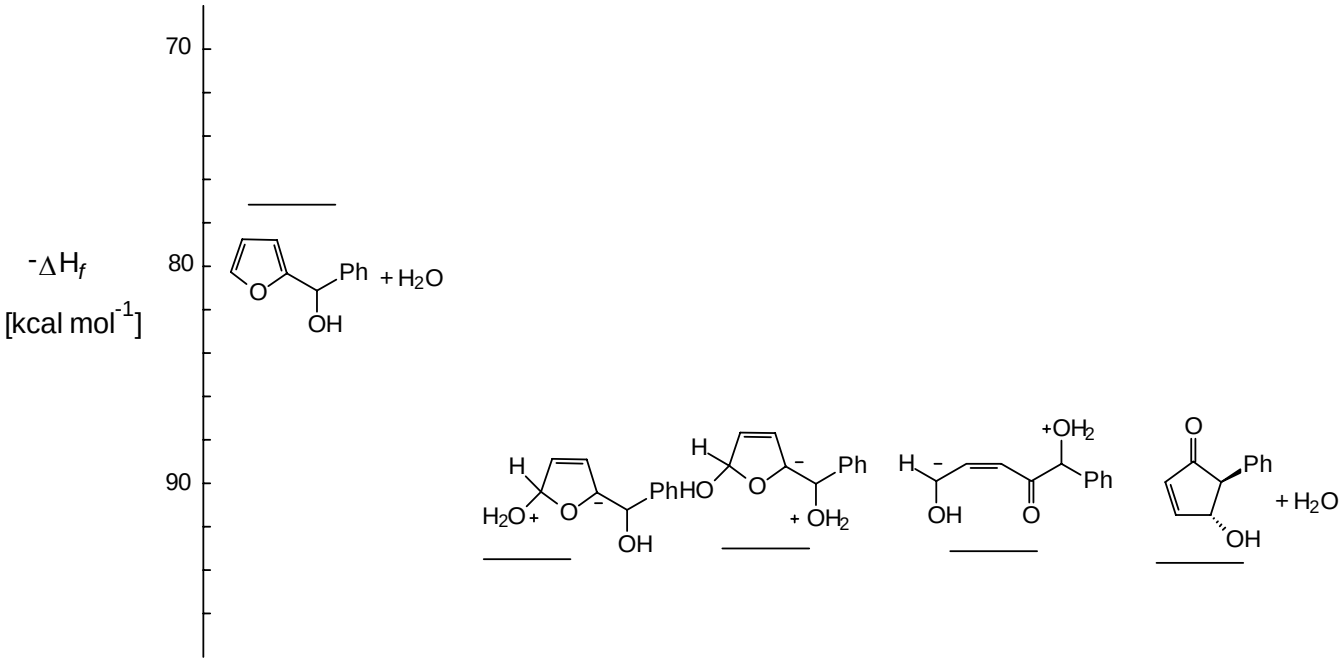
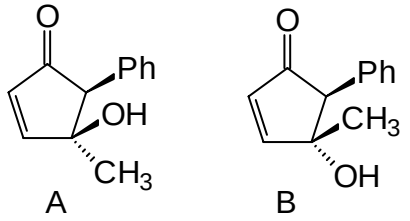


Figure 1



This hypothesis was tested performing theoretical calculations on the possible intermediates. The results (obtained by using PM3 semiempirical method) are collected in the Figure 1 and are completely in agreement with the proposed mechanism. In Figure 1 we have reported ΔH_f values of the reagents, the products and all the proposed intermediate. Clearly, whatever the value of the activation energy is, the reaction is completely irreversible and it can evolve only to the formation of more stable cyclopentenone.
In the case of 5-methyl substituted furylcarbinols, calculations are in agreement with the formation of an isomeric mixture. We compared ΔH_f values for the isomers A and B of **7a** (Figure 2). Isomer A showed ΔHf = -44.1 kcal mol^{-1} while B showed a value of –43.5 kcal mol^{-1}.

Figure 2



EXPERIMENTAL

MS spectra were obtained with a Hewlett-Packard 5971 mass-selective detector on a Hewlett-Packard 5890 gas chromatograph [OV-1 capillary column between 70-250 °C (20 °C min^{-1})]. NMR spectra were recorded on a Bruker 300 AM instrument. Melting points were detemined on a Kofler block and are uncorrected. Elemental analyses were obtained with a Carlo Erba elemental analyser 1106.
2-Furylcarbinols were obtained through reaction of 2-furancarbaldehyde or 5-methyl-2-furancarbaldehyde with Grignard reagents.

2-Furylbenzylic alcohol (**1a**) – Oil. ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 6 H), 6.31 (d, 1 H, J = 3.2 Hz), 6.10 (d, 1 H, J = 3.2 Hz), 5.78 (m, 1 H), and 2.69 ppm (s, 1 H). IR ($CHCl_3$) ν_{max}: 3620, 3410, 1590, 1492, 1453, 1225, 1200, 1184, 1127, 1032, 1018, 945, 920, and 699 cm^{-1}.

2-Furyl-2-thienylmethanol (**1b**) – Oil. ^{1}H-NMR ($CDCl_3$) δ: 7.07 (m, 1 H), 6.90 (m, 2 H), 6.12 (m, 1 H), 6.08 (m, 1 H), 5.80 (m, 2 H),and 2.88 ppm (s, 1 H).

1-(2-Furyl)heptanol (**1c**) – Oil. ^{1}H-NMR ($CDCl_3$) δ: 7.38 (m, 1 H), 6.33 (m, 1 H), 6.20 (m, 1 H), 4.64 (t, 1 H, J = 7 Hz), 2.05 (br s, 1 H), 1.80 (m, 2 H), 1.23 (m, 8 H), and 0.86 ppm (t, 3 H, J = 7 Hz).

5-Methyl-2-furylbenzyl alcohol (**6a**) – Oil. ^{1}H-NMR (CCl_4) δ: 7.22 (m, 5 H), 5.76 (m, 2 H), 5.50 (s, 1 H), 3.30 (br s, 1 H), 2.18 (s, 3 H). IR (film) ν_{max}: 3600, 3012, 1584, and 1560 cm^{-1}.

5-Methyl-2-furyl-2-thienylmethanol (**6b**) – Oil. ^{1}H-NMR (CCl_4) δ: 7.05 (m, 1 H), 6.75 (m, 2 H), 5.93 (m, 1 H), 5.72 (m, 2 H), 2.98 (br s, 1 H), 2.22 (s, 3 H). IR (film) ν_{max}: 3390 and 1560 cm^{-1}.

Thermal isomerization of 2-furylcarbinols in water – General procedure.
2-Furylcarbinol (100 mg) was suspended in redistilled water (50 mL) and the mixture was stirred at reflux temperature (Table 1). After the reaction was completed the reaction mixture was extracted many times with ether and the extracts were then dried (Na_2SO_4). Evaporation of the solvent yielded a crude product which was chromatographed on silica gel eluting with 4:1 *n*-hexane/ethyl acetate.

2-Phenyl-4-hydroxycyclopent-2-en-1-one (**3a**). mp 58-59 °C (lit.,[5] 58-59 °C). Calcd for $C_{11}H_{10}O_2$: C 75.84, H 5.79; Found C 75.90, H 5.71. ^{1}H-NMR ($CDCl_3$) δ: 7.67 (m, 2 H), 7.65 (m, 1 H), 7.38 (m, 3 H), 5.01 (m, 1 H), 2.96 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 6.1 Hz), 2.8 (br s, 1 H), and 2.48 ppm (dd, 1 H, J_1 = 18.5 Hz, J_2 = 2 Hz). MS, m/z: 175 (7%), 174 (55), 146 (23), 145 (26), 131 (18), 129 (14), 128 (19), 127 (14), 117 (18), 115 (16), 105 (12), 104 (100), 103 (25), 102 (34), 78 (10), 77 (22), 76 (12).

2-(2-Thienyl)-4-hydroxycyclopent-2-en-1-one (**3b**) – Oil. Calcd. for $C_9H_8O_2S$: C 59.98, H 4.47, S 17.79; Found C 60.1, H 4.4, S 17.9. ^{1}H-NMR ($CDCl_3$) δ: 7.46 (m, 1 H), 6.94 (m, 1 H), 6.70 (m, 2 H), 4.87 (m, 1 H), 3.6 (br s, 1 H), 2.28 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 6.1 Hz), and 2.32 ppm (dd, 1H, J_1 = 18.5 Hz, J_2 = 2 Hz). MS, *m/z*: 181 (16%), 180 (100), 179 (12), 152 (35), 151 (53), 137 (28), 136 (12), 135 (47), 134 (15), 124 (13), 123 (23), 111 (21), 110 (47), 109 (27), 108 (37), 97 (21), 91 (33), 84 (17), 82 (14), 69 (30), 65 (20), 63 (18).

5-n-Hexyl-4-hydroxycyclopent-2-en-1-one (**2c**) – Oil. Calcd for $C_{11}H_{18}O_2$: C 72.49, H 9.95; Found C 72.40, H 10.03. ^{1}H-NMR ($CDCl_3$) δ: 7.50 (dd, 1H, J_1 = 5.7 Hz, J_2= 2.3 Hz), 6.16 (dd, 1 H, J_1 = 5.7 Hz, J_2 = 1.3 Hz), 4.66 (m, 1 H), 3.0 (br s, 1H), 2.20 (m, 1 H), 1.80 (m, 2 H), 1.27 (m, 8 H), and 0.86 ppm (t, 3 H, J = 6.8 Hz). MS, m/z: 182 (10%), 153 (18), 139 (20), 138 (100%), 135 (13), 121 (10), 113 (20), 112 (14), 111 (30), 109 (20), 107 (10), 97 (18), 96 (20), 95 (24), 93 (10), 83 (16), 81 (12), 79 (12), 69 (26), 67 (18).

2-n-Hexyl-4-hydroxycyclopent-2-en-1-one (**3c**) - Oil. Calcd for $C_{11}H_{18}O_2$: C 72.49, H 9.95; Found C 72.38, H 10.05. ^{1}H-NMR ($CDCl_3$) δ: 7.15 (m, 1 H), 4.92 (m, 1 H), 3.0 (br s, 1 H), 2.78 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 6 Hz), 2.28 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 2 Hz), 2.17 (dt, 2H, J_1 = 6.8 Hz, J_2 = 1.3 Hz), 1.27 m, 8 H), and 0.86 ppm (t, 3 H, J = 6.8 Hz). MS, *m*/*z*: 182 (7%), 126 (10), 111 (21), 98 (100), 97 (14), 80 (30).

4-Methyl-4-hydroxy-5-phenylclopent-2-en-1-one (**7a**) - Oil. Calcd for $C_{12}H_{12}O_2$: C 76.57, H 6.43; Found C 76.63, H 6.35. ^{1}H-NMR ($CDCl_3$) d: 7.55 (δ, 0.5 H, J = 5.7 Hz), 7.47 (d, 0.5 H, J = 5.7 Hz), 7.45-7.25 (m, 5 H), 6.34 (d, 0.5 H, J = 5.7 Hz), 6.22 (d, 0.5 H, J = 5.7 Hz), 3.78 (s, 0.5 H), 3.58 (s, 0.5 H), 2.9 (br s, 1 H), 1.60 (s, 1.5 H), and 1.01 ppm (s, 1.5 H). MS, m/z: 188 (10%).

2-Phenyl-3-methyl-4-hydroxycyclopent-2-en-1-one (**8a**) - mp. 102-104 °C (lit. ,[5] 102-104 °C). Calcd for $C_{12}H_{12}O_2$: C 76.57, H 6.43; Found C 76.51, H 6.40, ^{1}H-NMR ($CDCl_3$) δ: 7.40-7-20 (m, 5H), 4.77 (m, 1 H), 3.1 (br s, 1 H), 2.87 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 6 Hz), 2.42 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 2 Hz), 2.17 (s, 3 H). MS, m/z: 188 (6%).

2-(2-Thienyl)-3-methyl-4-hydroxycyclopent-2-en-1-one (**8b**) - mp. 89-90 °C (lit.,[5] 89-90 °C). Calcd for $C_{10}H_{10}O_2S$: C 61.83, H 5.19, S 16.50; Found C 61.89, H 5.23, S 16.44, ^{1}H-NMR ($CDCl_3$) δ: 7.30-7.10 (m, 3 H), 4.69 (m, 1 H), 3.0 (br s, 1 H), 2.88 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 6 Hz), 2.33 (dd, 1 H, J_1 = 18.5 Hz, J_2 = 2 Hz), 2.28 (s, 3 H). MS, *m/z*: 196 (2%), 194 (12).

R-(+)-Phenyl-(2-furyl)methanol [*R*-(+)-**1a**] – A solution of Ti(O-*i*Pr)$_4$ (6.84 mL, 46 mmol) in CH_2Cl_2 (112 mL) was treated at –20 °C with L-(+)-DIPT (5.77 mL, 55 mmol). After 10 min at –30 °C phenyl(2-furyl)methanol (4 g, 46 mmol) dissolved in CH_2Cl_2 (5.5 mL) and *t*-butylhydroperoxide (4.6 mL) were added. The solution was stirred at –21 °C for 40 h and then poured into a mixture of 10% tartaric acid (0.94 mL), ether (37.4 mL), and NaF (5.6 g). The mixture was stirred for 3 h at rt. The mixture was filtered on Celite. The organic phase was concentrated to give an oil which was dissolved in ether (187 mL) and treated with 1 *N* NaOH (93.5 mL) for 30 min at 0 °C. The ethereal phase was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave an oil that was chromatographed on silica gel to give pure *R*-(+)-**1a** as oil: ^{1}H-NMR ($CDCl_3$) δ: 7.30 (m, 6 H), 6.31 (d, 1 H, J = 3.2 Hz), 6.10 (d, 1 H, J = 3.2 Hz), 5.78 (s, 1 H), 2.69 (s, 1 H). α_D^{25} = + 8.0 ° (c = 1.10, $CHCl_3$) [lit.,[11] + 6.9 ° (c = 1.10, $CHCl_3$)].

*The reaction of R-(+)-**1a*** - *R-(+)*-Phenyl(2-furyl)methanol (405 mg, 2.33 mmol), dissolved in 2:1 DME/water mixture (40 mL), was treated with $ZnCl_2$ (300 mg, 2.20 mmol) and then stirred at 60 °C for 96 h. The mixture was poured into water and extracted with ether. The ethereal phase was washed with brine and dried (Na_2SO_4). The evaporation of the solvent gave a crude product which was chromatographed on silica gel. Elution with 2:1 ether/*n*-hexane mixture gave 5-phenyl-4-hydroxycyclopent-2-en-1-one (115 mg, 28%) (oil) as a racemic mixture and *R*-(+)-phenyl(2-furyl)methanol (267 mg, 66%) with α_D^{25} = + 8.0 ° (c = 1.10, $CHCl_3$).

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