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Lewis Acids Catalysed Fries Rearrangement of Isopropylcresol Esters

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Summary. In the course of the Fries rearrangement, aluminium chloride frequently induces migration or elimination of alkyl groups. The results obtained with titanium tetrachloride for the synthesis of vicinal *o*-hydroxyketones are compared with those obtained with aluminium chloride for some aliphatic and aromatic esters of isopropylcresols. In order to understand the migration and elimination processes occurring, the stabilities of the *o*-hydroxyketones are studied in the presence of aluminium chloride at different temperatures. Furthermore, all-vicinal *o*-hydroxyketones were prepared by the Fries rearrangement of 6-*tert*-butyl-*p*-thymol with titanium tetrachloride.

Keywords. Fries rearrangement; Titanium tetrachloride; Thymols; *o*-Hydroxyketones; Dealkylation.

Lewis-Säure-katalysierte Fries-Umlagerung von Isopropylkresolestern

Zusammenfassung. Im Verlauf der Fries-Umlagerung induziert Aluminiumchlorid des öfteren eine Wanderung oder Eliminierung von Alkylgruppen. Die Resultate mit Titantetrachlorid bei der Synthese von vicinalen *o*-Hydroxyketonen werden mit denen mit Aluminiumchlorid für einige aliphatische und aromatische Ester des Isopropylkresols verglichen. Um zu einem Verständnis der auftretenden Wanderungs- und Eliminierungsprozesse zu gelangen, wurden die Stabilitäten von *o*-Hydroxyketonen bei verschiedenen Temperaturen in der Gegenwart von Aluminiumchlorid untersucht. Außerdem wurden all-vicinale *o*-Hydroxyketone mittels Fries-Umlagerung von 6-*tert*-Butyl-*p*-thymol mit Titantetrachlorid hergestellt.

Introduction

In the course of research on the Fries rearrangement of phenyl, cresyl and chlorophenyl propionates, one of us proposed the use of titanium tetrachloride as catalyst for their *ortho* rearrangement [1–2]. Later on, a Japanese patent [3] described the preparation of *o*-hydroxypropiophenone by this catalyst. Recently, we used the properties of titanium tetrachloride as soft catalyst to carry out the synthesis of six original vicinally polysubstituted *o*-hydroxyketones derived from various xylenol and thymol propionates [4]. Thus the preparation of these ketones was made possible, as titanium tetrachloride does not induce migrations and/or cleavages of the isopropyl and methyl groups during the Fries reaction – contrary to what occurs with aluminium chloride.

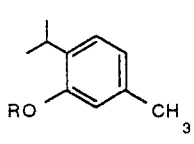
Hindered *o*-hydroxyketones are interesting synthons for the synthesis of analogues of pharmacologically active compounds; it appeared useful to further develop these preliminary results. Thus, we undertook:

- to compare the results of the Fries rearrangement of the four isopropyl-*m*-cresol propionates **1–4** (*n*-thymol, *p*-thymol, *m*-thymol and *vic*-thymol) at 20°C in nitromethane and at 100°C without solvent, with either titanium tetrachloride or aluminium chloride;
- to study the stability of the *o*-hydroxypropiophenones **5–8** in the presence of aluminium chloride at 50 and 100°C;
- to examine the behaviour, with titanium tetrachloride, of the esters of *p*-thymol and 6-*tert*-butyl-*p*-thymol other than the propionates for the synthesis of vicinal and non-vicinal *o*-hydroxyketones.

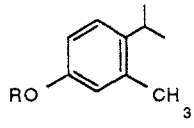
Results and Discussion

Fries Rearrangement of Esters **1–4**

When submitted to the Fries reaction for 170 hours, the propionates **1–4**, in nitromethane solution at 20°C (in the presence of $AlCl_3$ or of $TiCl_4$) gave similar proportions of the *o*- and *p*-hydroxyketones according to the electronic and/or steric effects of their substituents.



1



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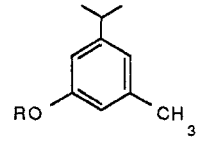

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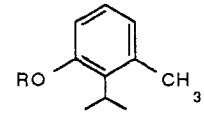
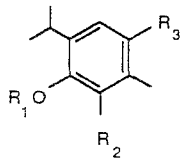


4

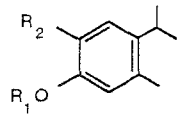
R = COEt

The Fries rearrangement of the esters **1–4** lead respectively to the *o*-hydroxyketones **5** (10%), **6** (95%), **7** (80%), and **8** (95%). The propionates **1** and **4** also furnish the *p*-hydroxyketones **9** (60%), and **10** as traces ($\approx$ 1%). The total yields are less than 100%, the differences (5–30%) are due to unreacted ester and to isopropyl-*m*-cresol resulting from the heterolysis of the ester.

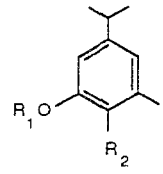
In a precedent paper [4] we reported that whereas the Fries rearrangement of the *n*-thymyl propionate **1** by $AlCl_3$ without solvent at 100°C gave eight compounds resulting from rearragements and/or cleavages, in the presence of $TiCl_4$ only the ketone **5**, in 80% yield, was obtained under the same conditions. We extended the comparison here to the esters **2**, **3**, and **4** in order to define the influence of the substitution pattern on the rearrangements occurring at 100°C without solvent with $AlCl_3$ or $TiCl_4$. The reaction with $TiCl_4$ at 100°C gives the expected ketone without alkyl migration; however, under the same conditions with $AlCl_3$ extensive migration and degradation were observed.



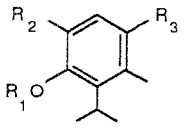
1 : R_1 = COEt, R_2 = R_3 = H
5 : R_1 = R_3 = H, R_2 = COEt
9 : R_1 = R_2 = H, R_3 = COEt



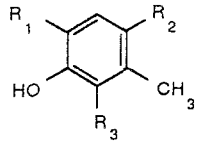
2 : R_1 = COEt, R_2 = H
6 : R_1 = H, R_2 = COEt



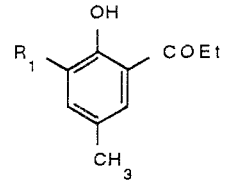
3 : R_1 = COEt, R_2 = H
7 : R_1 = H, R_2 = COEt



4 : R_1 = COEt, R_2 = R_3 = H
8 : R_1 = R_3 = H, R_2 = COEt
10 : R_1 = R_2 = H, R_3 = COEt



11 : R_1 = COEt, R_2 = R_3 = H
12 : R_1 = R_3 = H, R_2 = COEt
15 : R_1 = R_2 = H, R_3 = COEt



13 : R_1 = H
14 : R_1 = C_3H_7 (iso)

Table 1. Hydroxyketones obtained from thymol esters **1–4**[a]

Starting esters	Ketones obtained (%)[b]						
	6	**7**	**9**	**11**	**12**	**13**	**14**
1	14	9	35	14		6	16
2	44		17[c]		11		8
3	6	76					
4	17	53	7[c]		1		6

[a] Without solvent for 2 hours at 100°C with $AlCl_3$ (1.4 equiv.); the mixtures were analysed by G. C., column temp. 240°C

[b] The sums of the yields indicated here are less than 100%: the difference (6–17%) is due to unreacted ester and to traces of various phenols resulting from the cleavage of the acyl group

[c] *p*-Hydroxyketone resulting from a migration of the isopropyl group on the phenoxy anion before acylation [5]

From the results indicated in Table 1, it can be noted that:

- no *o*-hydroxyketone is produced from *n*-thymol and *vic*-thymol;
- by rearrangement, all the *n*-thymol, *m*-thymol, and *vic*-thymol propionates lead to the ketones derived from the *m*- and *p*-thymol structures;

- the three isomeric esters **1**, **2**, and **4** equally furnish a fair proportion of the ketone **14** resulting from a rearrangement to the *iso*-thymol structure due to the migration of the methyl group;
- to establish the structure of the novel ketone **14** we performed a four-step unambiguous synthesis from the commercial *o*-isopropylphenol;
- apart from *m*-thymyl propionate **3**, all the other isomers **1**, **2**, and **4** lead to hydroxyketones resulting from the cleavage of the isopropyl group.

Stability of the Hydroxyketones **5–8**

For a better understanding of the processes generating the formation of the hydroxyketones listed in Table 1, it appeared useful to study the stability of the *o*-hydroxyketones **5–8**, prepared with $TiCl_4$ as catalyst. Effectively, it can be conceived that these ketones are formed in the presence of $AlCl_3$ but they are not stable in the harsh experimental conditions leading to isomerisations and/or dealkylations.

Thus, we determined the nature and quantities of products resulting from the reaction of the ketones **5–8** in the presence of $AlCl_3$ at 50°C (4 h) in chlorobenzene and at 100°C (2 h) with and without chlorobenzene.

The results presented in Table 2 give a comprehensive account of the transformations undergone by these ketones.

From these results it appears that most of the ketones **5–8** cannot survive in the presence of aluminium chloride at 100°C. In the harshest conditions, the *o*-hydroxyketone **5** undergoes a Whitmore rearrangement [7] transforming it into

Table 2. Compounds obtained using $AlCl_3$ on the four *o*-hydroxyketones **5–8**

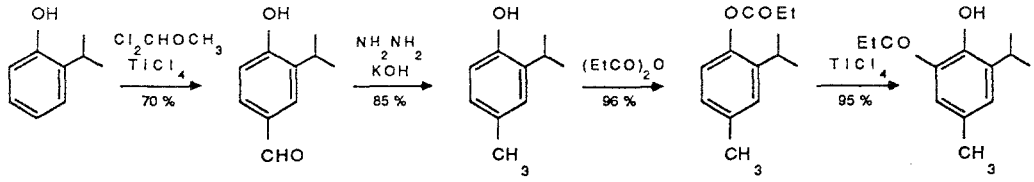
Starting ketones	Experimental conditions[a]	*o*-Hydroxyketones obtained (%)							
		5	**6**	**7**	**8**	**11**	**13**	**14**	**15**
5	I	45					25	28	
	II		10	5		16			28[b]
	III		5			37			40[b]
6	I		68			32			
	II		48			52			
	III					85[c]			
7	I			99					
	II			99					
	III			58		22[b]			
8	I				60	40			
	II					99			
	III					100			

[a] I: 1.4 equiv. of $AlCl_3$ for 2 h at 100°C, without solvent. II: 5.2 equiv. of $AlCl_3$ for 20 h at 20°C, then 4 h at 50°C, in solution of chlorobenzene as reported by John and Beetz [6]; III: identical to II. except heated at 100°C for 2 h; the mixtures were analysed by G.C., column temp. 240°C

[b] 39, 17 and 19% of *m*-cresol was also identified, resulting from the degradation of the ketones **5** and **7**

[c] With 6% *p*-thymol resulting from the deacylation of the ketone **6**

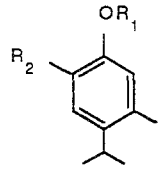
the ketone **14**. In all the other cases, migration or cleavage of the isopropyl group is observed, as well as the elimination of the acyl group. The *o*-hydroxyketone **7** is more stable than its isomers **5**, **6**, **8** (see Table 2), this stability is most likely due to the symmetrical structure of *m*-thymol [8].

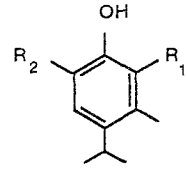


16 **17** **18** **14**

Preparation of the Vicinal Ketones **31–32** *Derived from p-Thymol*

In order to evaluate the scope and limits of $TiCl_4$ as soft inductor of the Fries reaction, we studied the acetate, heptanoate and *p*-methoxy benzoate esters of *p*-thymol **19**, **20**, and **21** and of 6-*tert*-butyl-*p*-thymol **22**, **23**, and **24**. The propionate of this latter phenol had previously [4] enabled us to synthesize the vicinal *o*-hydroxyketone derived from *p*-thymol by sequential use of Lewis acid catalysts: $TiCl_4$ as soft catalyst for the rearrangement, followed by $AlCl_3$ to eliminate the *t*-butyl protecting the non-vicinal *o*-position.





19: $R_1 = COCH_3$, $R_2 = H$
20: $R_1 = COC_6H_{13}(n)$, $R_2 = H$
21: $R_1 = CO\text{-}C_6H_4\text{-}OCH_3(p)$, $R_2 = H$
22: $R_1 = COCH_3$, $R_2 = t\text{-}Bu$
23: $R_1 = COC_6H_{13}(n)$, $R_2 = t\text{-}Bu$
24: $R_1 = CO\text{-}C_6H_4\text{-}OCH_3(p)$, $R_2 = t\text{-}Bu$

25: $R_1 = H$, $R_2 = COCH_3$
26: $R_1 = H$, $R_2 = COC_6H_{13}(n)$
27: $R_1 = H$, $R_2 = COC_6H_4OCH_3(p)$
28: $R_1 = COCH_3$, $R_2 = t\text{-}Bu$
29: $R_1 = COC_6H_{13}(n)$, $R_2 = t\text{-}Bu$
30: $R_1 = CO\text{-}C_6H_4\text{-}OCH_3(p)$, $R_2 = t\text{-}Bu$
31: $R_1 = COCH_3$, $R_2 = H$
32: $R_1 = COC_6H_{13}(n)$, $R_2 = H$
33: $R_1 = CO\text{-}C_6H_4\text{-}OCH_3(p)$, $R_2 = H$

With $TiCl_4$ or $AlCl_3$ as catalyst at 20°C, the acetate **19** and heptanoate **20** lead to the non-vicinal *o*-hydroxyketones **25** and **26** in nearly quantitative yields, as for the propionate **2**. The anisoate **21** also gives a non-vicinal diarylketone **27**, but in yields not exceeding 66%, with as much as 44% of *p*-thymol due to heterolysis.

The orientation of the rearrangement is a consequence of steric hindrance, which is greater at the 2-position than at the 6-position. As we have already proposed

for the propionate [4], the rearrangement can be modified by protecting the 6-position by a *t*-butyl group (esters **22**–**24**). Thus, with $TiCl_4$ at 100°C, we obtained the vicinal *tert*-butyl ketones **28** (23%) and **29** (67%), easily separable from their respective non-vicinal ketones **25** (65%) and **26** (20%) resulting from detertiobutylation during the reaction. The 6-position was detertiobutylated by $AlCl_3$, thus affording the vicinal *o*-hydroxyketones **31** and **32**, respectively, in yields close to 85%.

The anisoate **24** behaves differently, as it yields only 4% of the nonvicinal ketone **27** with 64% of unreacted ester **24** and 32% of heterolysis of the ester. Consequently, the synthesis of vicinal benzophenones by this method does not appear to be extendible to the benzoates.

Experimental

Melting points were determined on a Kofler-apparatus ($t \geqslant 60$°C) or in capillary tube ($t < 60$°C). The IR spectra were recorded on a Perkin-Elmer 1710 spectrometer, the UV spectra on a Varian Techtron 635 spectrometer and the ^{1}H-NMR spectra on a Varian EM 390 spectrometer. Mass spectra were determined on a Ribermag R-10-10-C apparatus (70 eV). GC analyses were performed with a Girdel 30 apparatus fitted with a catharometer (15% OV 17 on chromosorb GHP, length 4 m, 200–300°C; eluent He). The elementary analyses were carried out by CNRS (Service Central de Microanalyse, Solaise).

The four "thymols" (**1**–**4**, R=H) are available commercially and were used without further purification. The three esters **1**–**3** and the 2-(1,1-dimethylethyl)-5-methyl-4-(1-methylethyl)phenol were prepared according to [4]. The esters **4**, **18**, **19**, and **22** were prepared by the same method with the corresponding acid anhydride and are characterized below.

3-Methyl-2-(1-methylethyl)phenyl Propanoate (**4**)

Yield: 98%, colourless oil, b.p. 137°C/16 Torr. For $C_{13}H_{18}O_2$ (206.3). Calc. C 75.69, H 8.80; found C 75.59, H 8.83. ^{1}H-NMR ($CDCl_3$): 1.27 [d, 6 H, $(CH_3)_2CH-$], 1.27 (t, 3 H, $-CH_2CH_3$), 2.35 (s, 3 H, CH_3), 2.60 (q, 2 H, $-CH_2CH_3$), 3.25 (m, 1 H, $>CH-$), 6.63 (m, 3 H, $H_{4'}$, $H_{5'}$, $H_{6'}$). IR (CH_2Cl_2): 1 757 cm^{-1} (C=O). MS: m/z (%) = 206 (M^+, 61), 135 (100).

4-Methyl-2-(1-methylethyl)phenyl Propanoate (**18**)

a) *4-Hydroxy-3-(1-methylethyl)benzaldehyde* (**16**). To a solution containing titanium tetrachloride (0.64 mol, 70 ml), and dichloromethyl methyl ether (0.33 mol, 30 ml) in dichloromethane (400 ml) cooled at −15°C, 2-isopropylphenol (0.25 mol, 34 ml) is added with stirring. After leaving for 4 h between −5°C and 0°C with stirring, the solution is poured onto a slurry of 170 ml 1 *N* HCl and 700 g of ice. After work-up, the crude product obtained (37.7 g) is purified by column chromatography on silica gel, eluted with benzene-petroleum ether (3 : 7). The aldehyde thus obtained is recrystallized from benzene-cyclohexane (7 : 3), colourless microcrystals 29.9 g (72%), m.p. 71°C. For $C_{10}H_{12}O_2$ (164.2). Calc. C 73.14, H 7.37; found C 73.00, H 7.45. ^{1}H-NMR ($CDCl_3$): 1.28 [d, 6 H, $-CH(CH_3)_2$], 3.28 (m, 1 H, $>CH-$), 6.87 (s, 1 H, OH), 6.93 (d, 1 H, H_5, J_0 = 8.4), 7.63 (dd, 1 H, H_6), 7.78 (d, 1 H, H_2), 9.80 (s, 1 H, $-CHO$). IR (CH_2Cl_2): 3 575 cm^{-1} (OH), 1 690 cm^{-1} (C=O). MS: m/z (%) = 164 (M^+, 76), 149 (100).

b) *4-Methyl-2-(1-methylethyl)phenol ("isothymol")* (**17**) A mixture of 4-hydroxy-3-(1-methylethyl)benzaldehyde (0.08 mol, 13.6 g), diethylene glycol (200 ml) and hydrazine hydrate (0.34 mol, 17 g) is heated at 165°C for 30 min. After cooling to about 150°C, potassium hydroxide pellets (0.37 mol, 20 g) are added fractionwise over 20 min, then heated at 210°C for 1 hour. After work-up, the reaction

product (14.1 g) is distilled under reduced pressure, b.p. 117°C/18 Torr (Lit. [8]: 82°C/3 Torr, [9]: 140°C/50 Torr), then recrystallized from pentane. Colourless microcrystals 10.2 g (82%), m.p. 35°C (Lit. [10, 11]: 35°C, [8]: 36–37°C). For $C_{10}H_{14}O$ (150.2). Calc. C 79.96, H 9.39; found C 80.00, H 9.54. ^{1}H-NMR ($CDCl_3$): 1.26 [d, 6 H, $-CH(CH_3)_2$, $J = 6.7$], 2.3 (s, 3 H, CH_3), 3.2 (m, 1 H, $-CH<$), 4.6 (s, 1 H, OH), 6.60 (d, 1 H, H_6, $J = 8$), 6.82 (dd, 1 H, H_5), 6.97 (d, 1 H, H_3, $J = 2.7$). IR (CH_2Cl_2): 3 587 cm^{-1} and 3 450 cm^{-1} (OH). MS: m/z (%) = 150 (M^+, 61), 135 (100).

c) *4-Methyl-2-(1-methylethyl)phenyl Propanoate* (**18**). Yield: 96%, colourless oil, b.p. 141–142°C/23 Torr. For $C_{13}H_{18}O_2$ (206.3). Calc. C 75.69, H 8.80; found C 75.68, H 8.80. ^{1}H-NMR ($CDCl_3$): 1.24 [d, 6 H, $(CH_3)_2CH-$], 1.30 (t, 3 H, $-CH_2CH_3$), 2.30 (s, 3 H, CH_3), 2.55 (q, 2 H, $-CH_2CH_3$), 2.96 (m, 1 H, $>CH-$), 6.78 (d, 1 H, H_6), 6.88 (dd, 1 H, H_5, $J_0 = 8$). IR (CH_2Cl_2): 1 752 cm^{-1} (C=O). MS: m/z (%) = 206 (M^+, 40), 150 (100).

3-Methyl-4-(1-methylethyl)phenyl Ethanoate (**19**)

Yield: 93%, colourless oil, b.p. 135°C/16 Torr. (Lit. [12]: 135°C/12 Torr.). ^{1}H-NMR ($CDCl_3$): 1.17 [d, 6 H, $(CH_3)_2CH-$], 2.18 (s, 3 H, $COCH_3$), 2.27 (s, 3 H, CH_3), 3.1 (m, 1 H, $>CH-$), 6.82 (d, 1 H, H_2), 6.87 (dd, 1 H, H_6, $J_0 = 8.5$), 7.13 (dd, 1 H, H_5). IR (CH_2Cl_2): 1 757 cm^{-1} (C=O). MS: m/z (%) = 192 (M^+, 8), 135 (100).

2-(1,1-Dimethylethyl)-5-methyl-4-(1-methylethyl)phenyl Ethanoate (**22**)

Yield: 97%, colourless crystals from ethanol, m.p. 44°C, b.p. 159–160°C/17 Torr. For $C_{16}H_{24}O_2$ (248.4). Calc. C 77.38, H 9.74; found C 77.54, H 10.07. ^{1}H-NMR ($CDCl_3$): 1.17 [d, 6 H, $(CH_3)_2CH-$], 1.32 [s, 9 H, $(CH_3)_3C-$], 2.23–2.27 (2 s, 6 H, CH_3 and $COCH_3$), 3.00 (m, 1 H, $>CH-$), 6.70 (s, 1 H, H_3), 7.20 (s, 1 H, H_6). IR (CH_2Cl_2): 1 755 cm^{-1} (C=O). MS: m/z (%) = 248 (M^+, 16), 191 (100).

The following esters **20**, **21**, **23**, and **24** were prepared by condensation of the corresponding acid chloride and phenol in the presence of pyridine. After work-up, the pure products were purified by distillation or recrystallization, and are characterized below.

3-Methyl-4-(1-methylethyl)phenyl Heptanoate (**20**)

Yield: 91%, colourless oil, b.p. 197°C/18 Torr. For $C_{17}H_{26}O_2$ (262.4). Calc. C 77.82, H 9.99; found C 77.60, H 10.00. ^{1}H-NMR ($CDCl_3$): 0.87 [m, 3 H, $CH_3(CH_2)_5-$], 1.17 [d, 6 H, $(CH_3)_2CH-$], 1.47 [m, 8 H, $(CH_2)_4CH_3$], 2.28 (s, 3 H, CH_3), 2.48 (t, 2 H, $COCH_2$), 3.07 (m, 1 H, $>CH-$), 6.8 (d, 1 H, H_2), 6.85 (dd, 1 H, H_6, $J_0 = 8.5$), 7.16 (dd, 1 H, H_5). IR (CH_2Cl_2): 1 752 cm^{-1} (C=O). MS: m/z (%) = 262 (M^+, 20), 150 (100).

3-Methyl-4-(1-methylethyl)phenyl 4-Methoxybenzoate (**21**)

Yield: 74%, colourless crystals from methanol, m.p. 92°C. For $C_{18}H_{20}O_3$ (284.1). Calc. C 76.03, H 7.09; found C 75.89, H 7.11. ^{1}H-NMR ($CDCl_3$): 1.23 [d, 6 H, $(CH_3)_2CH-$], 2.33 (s, 3 H, CH_3), 3.13 (m, 1 H, $>CH-$), 3.87 (s, 3 H, OCH_3), 6.95 (m, 4 H, H_2, $H_{3'}$, $H_{5'}$, H_6, $J_0 = 9$), 7.23 (d, 1 H, H_5), 8.12 (d, 2 H, $H_{2'}$, $H_{6'}$). IR (CH_2Cl_2): 1 728 cm^{-1} (C=O). MS: m/z (%) = 284 (M^+, 12), 135 (100).

2-(1,1-Dimethylethyl)-5-methyl-4-(1-methylethyl)phenyl Heptanoate (**23**)

Yield: 97%, colourless oil, b.p. 139–141°C/0.06 Torr. For $C_{21}H_{34}O_2$ (318.5). Calc. C 79.19, H 10.76; found C 79.21, H 10.95. ^{1}H-NMR ($CDCl_3$): 0.87 [m, 3 H, $CH_3(CH_2)_5-$], 1.23 [d, 6 H, $(CH_3)_2CH-$], 1.3 [s, 9 H, $(CH_3)_3C-$], 1.57 [m, 8 H, $(CH_2)_4CH_3$], 2.23 (s, 3 H, CH_3), 2.55 (t, 2 H, $COCH_2$), 3.07

(m, 1 H, >CH−), 6.70 (s, 1 H, H_3), 7.20 (s, 1 H, H_6). IR (CH_2Cl_2): 1 750 cm^{-1} (C=O). MS: *m/z* (%) = 318 (M^+, 12), 191 (100).

2-(1,1-Dimethylethyl)-5-methyl-4-(1-methylethyl)phenyl 4-Methoxybenzoate (**24**)

Yield: 95%, colourless crystals from methanol, m.p. 93°C. For $C_{22}H_{28}O_3$ (340.4). Calc. C 77.61, H 8.29; found C 77.70, H 8.48. ^{1}H-NMR ($CDCl_3$): 1.25 [d, 6 H, $(CH_3)_2CH-$], 1.38 [s, 9 H, $(CH_3)_3C-$], 2.30 (s, 3 H, CH_3), 3.13 (m, 1 H, >CH−), 3.90 (s, 3 H, OCH_3), 6.82 (s, 1 H, H_3), 6.97 (d, 2 H, $H_{3'}$, $H_{5'}$, J_0 = 9), 7.27 (s, 1 H, H_6), 8.17 (d, 2 H, $H_{2'}$, $H_{6'}$). IR (CH_2Cl_2): 1 726 cm^{-1} (C=O). MS: *m/z* (%) = 340 (M^+, 4), 135 (100).

Fries Rearrangements (General Procedures)

Method A (*Esters* **1–4**, **19–21**). To a solution of ester (10 mmol) in nitromethane (6 ml), previously cooled at 0°C, $TiCl_4$ (14 mmol, 1.5 ml) or $AlCl_3$ (14 mmol, 1.9 g) is added while stirring. This solution is stirred at 20°C for 170 hours. After usual work-up (addition of 4 *N* HCl, extraction by ether, etc.) the ketones are purified as indicated below.

Method B (*Esters* **1–4**, **18**). A mixture of ester (10 mmol) and $TiCl_4$ (14 mmol, 1.5 ml) or $AlCl_3$ (14 mmol, 1.9 g) is heated with stirring at 100°C for 2 hours. After cooling to 80°C, the complex is hydrolysed with 4 *N* hydrochloric acid (100 ml) and treated as usual. The products obtained by this method are purified as indicated below.

Method C (*Esters* **22–24**). To a solution of ester (10 mmol) in chlorobenzene (10 ml), $TiCl_4$ (12 mmol, 1.3 ml) is added. The resulting solution is heated at 100°C for 2 h with stirring, then treated as usual. The products thus obtained are described below.

1-[2-Hydroxy-4-methyl-3-(1-methylethyl)phenyl]-1-propanone (**8**) *and 1-[4-Hydroxy-2-methyl-3-(1-methylethyl)phenyl]-1-propanone* (**10**)
(Method A, $AlCl_3$; starting from ester **4**)

After elimination of the solvent, the crude product is distilled (98%), b.p. 143–144°C/11 Torr, then recrystallized from ethanol (3 ml/g), furnishing the ketone **8** as pale yellow crystals, m.p. 47–48°C. For $C_{13}H_{18}O_2$ (206.3). Calc. C 75.69, H 8.80; found C 75.80, H 8.80. ^{1}H-NMR ($CDCl_3$): 1.20 (t, 3 H, CH_3CH_2-), 1.37 [d, 6 H, $(CH_3)_2CH$], 2.35 (s, 3 H, CH_3), 2.97 (q, 2 H, CH_3CH_2-), 3.30 (m, 1 H, >CH−), 6.63 (d, 1 H, H_5, J = 7.5), 7.47 (d, 1 H, H_6), 12.85 (s, 1 H, OH). IR (CH_2Cl_2): 1 631 cm^{-1} (C=O). MS: *m/z* (%) = 206 (M^+, 43), 177 (100). UV (ethanol): nm (log ε): 225 (4.36), 260 (4.12), 335 (3.64).

The mother liquors of **8** are evaporated and the residue is chromatographed on preparative silica gel plate, using benzene-ethyle acetate (9 : 1). The ketone **10** is so obtained (yield: 1%) from cyclohexane as colourless crystals, m.p. 91°C. For $C_{13}H_{18}O_2$ (206.3). Calc. C 75.69, H 8.80; found C 75.65, H 9.07. ^{1}H-NMR ($CDCl_3$): 1.17 (t, 3 H, $-CH_2-CH_3$), 1.35 [d, 6 H, $(CH_3)_2CH$], 2.37 (s, 3 H, CH_3), 2.87 (q, 2 H, $-CH_2-$), 3.42 (m, 1 H, >CH−), 5.77 (s, 1 H, OH), 6.57 (d, 1 H, H_6, J_0 = 8), 7.22 (d, 1 H, H_5). IR (CH_2Cl_2): 1 680 cm^{-1} (C=O). MS: *m/z* (%) = 206 (M^+, 16), 177 (100). UV (ethanol): nm (log ε): 203 (4.17), 227 (4.02), 275 (4.99).

1-[2-Hydroxy-5-methyl-3-(1-methylethyl)phenyl]-1-propanone (**14**)
(Method B, $TiCl_4$; starting from ester **18**)

Yield 95%, b.p. 148–149°C/15 Torr. Pale yellow crystals from ethanol, m.p. 28–29°C. For $C_{13}H_{18}O_2$ (206.3). Calc. C 75.69, H 8.80; found C 75.33, H 8.49. ^{1}H-NMR ($CDCl_3$): 1.25 [d, 6 H, $(CH_3)_2CH$], 1.25 (t, 3 H, CH_3CH_2-), 2.32 (s, 3 H, CH_3), 3.05 (q, 2 H, $-CH_2-$), 3.38 (m, 1 H, >CH−), 7.20

(d, 1 H, H_4), 7.38 (d, 1 H, H_6), 12.60 (s, 1 H, OH). IR (CH_2Cl_2): 1 636 cm^{-1}. MS: *m/z* (%) = 206 (M^+, 39), 177 (100). UV (ethanol): nm (log ε): 219 (4.32), 259 (3.99), 345 (3.61).

1-[2-Hydroxy-4-methyl-5-(1-methylethyl)phenyl]-ethanone (**25**)
(Method A, $TiCl_4$; starting from ester **19**)

Yield 95%, b.p. 153°C/17 Torr, pale yellow crystals from ethanol, m.p. 29°C. For $C_{12}H_{16}O_2$ (192.3). Calc. C 75.03, H 8.39; found C 74.85, H 8.53. ^{1}H-NMR ($CDCl_3$): 1.23 [d, 6 H, $(CH_3)_2CH$], 2.32 (s, 3 H, CH_3), 2.60 (s, 3 H, $COCH_3$), 3.05 (m, 1 H, >CH−), 6.73 (s, 1 H, H_3), 7.53 (s, 1 H, H_6), 12.07 (s, 1 H, OH). IR (CH_2Cl_2): 1 641 cm^{-1} (C=O). MS: *m/z* (%) = 192 (M^+, 37), 177 (100). UV (ethanol): nm (log ε): 217 (4.34), 263 (4.11), 334 (3.60).

1-[2-Hydroxy-4-methyl-5-(1-methylethyl)phenyl]-1-heptanone (**26**)
(Method A, $TiCl_4$; starting from ester **20**)

Yield 95%. Pale yellow crystals from ethanol, m.p. 38°C. For $C_{17}H_{26}O_2$ (262.4). Calc. C 77.82, H 9.99; found C 77.57, H 9.85. ^{1}H-NMR ($CDCl_3$): 0.87 [m, 3 H, $(CH_2)_5CH_3$], 1.25 [d, 6 H, $(CH_3)_2CH$], 1.50 [m, 8 H, $(CH_2)_4CH_3$], 2.33 (s, 3 H, CH_3), 2.97 (t, 2 H, CH_2CO), 3.03 (m, 1 H, >CH−), 6.73 (s, 1 H, H_3), 7.57 (s, 1 H, H_6), 12.17 (s, 1 H, OH). IR (CH_2Cl_2): 1 641 cm^{-1} (C=O). MS: *m/z* (%) = 262 (M^+, 32), 177 (100). UV (ethanol): nm (log ε): 217 (4.33), 263 (4.12), 335 (3.65).

[2-Hydroxy-4-methyl-5-(1-methylethyl)phenyl] (4-methoxyphenyl) methanone (**27**)
(Method A, $TiCl_4$; starting from ester **21**)

Purification is achieved by column chromatography on silica gel using CH_2Cl_2. Yield 66%. Yellow crystals from pentane, m.p. 100°C. For $C_{18}H_{20}O_3$ (284.4). Calc. C 76.03, H 7.09; found C 75.78, H 7.10. ^{1}H-NMR ($CDCl_3$): 1.17 [d, 6 H, $(CH_3)_2CH$], 2.37 (s, 3 H, CH_3), 3.05 (m, 1 H, >CH−), 3.90 (s, 3 H, OCH_3), 6.83 (s, 1 H, H_3), 7.00 (dd, 2 H, $H_{3'}$, $H_{5'}$), 7.45 (s, 1 H, H_6), 7.77 (dd, 2 H, $H_{2'}$, $H_{6'}$), 11.77 (s, 1 H, OH). IR (CH_2Cl_2): 1 633 cm^{-1} (C=O). MS: *m/z* (%) = 284 (M^+, 61), 161 (100). UV (ethanol): nm (log ε): 202 (4.41), 221 (4.28), 279 (4.12), 292 (4.15), 345 (3.81).

1-[3-(1,1-Dimethylethyl)-2-hydroxy-6-methyl-5-(1-methylethyl)phenyl]-ethanone (**28**)
(Method C, starting from ester **22**)

The crude product is column-chromatographed on silica gel, using benzene-petroleum ether, b.p. 40–65°C (3 : 7). Yield 23%. Yellow crystals from ethanol, m.p. 44°C. For $C_{16}H_{24}O_2$ (248.4). Calc. C 77.38, H 9.74; found C 77.64, H 10.00. ^{1}H-NMR ($CDCl_3$): 1.22 [d, 6 H, $(CH_3)_2CH$], 1.38 [s, 9 H, $(CH_3)_3C$], 2.38 (s, 3 H, CH_3), 2.60 (s, 3 H, $COCH_3$), 3.12 (m, 1 H, >CH−), 7.32 (s, 1 H, H_4), 10.88 (s, 1 H, OH). IR (CH_2Cl_2): 1 626 cm^{-1} (C=O). MS: *m/z* (%) = 248 (M^+, 38), 233 (100). UV (ethanol): nm (log ε): 202 (4.25), 220 (4.13), 272 (3.66), 345 (3.24).

1-[3-(1,1-Dimethylethyl)-2-hydroxy-6-methyl-5-(1-methylethyl)phenyl]-1-heptanone (**29**)
(Method C, starting from ester **23**)

Purification is achieved by column chromatography on silica gel, using benzene-petroleum ether, b.p. 40–65°C (3 : 7). Yield 67%. Pale yellow oil, b.p. 156–157°C/0.2 Torr. For $C_{21}H_{34}O_2$ (318.5). Calc. C 79.19, H 10.76; found C 79.21, H 10.95. ^{1}H-NMR ($CDCl_3$): 0.87 [t, 3 H, $(CH_2)_5CH_3$], 1.22 [d, 6 H, $(CH_3)_2CH$], 1.40 [s, 9 H, $(CH_3)_3C$], 1.62 [m, 8 H, $(CH_2)_4CH_3$], 2.37 (s, 3 H, CH_3), 2.87 (t, 2 H, $COCH_3$), 3.10 (m, 1 H, >CH−), 7.28 (s, 1 H, H_3), 9.75 (s, 1 H, OH). IR (CH_2Cl_2): 1 631 cm^{-1} (C=O). MS: *m/z* (%) = 318 (M^+, 20), 233 (100). UV (ethanol): nm (log ε): 202 (4.34), 218 (4.15), 273 (3.54).

Detertiobutylation of the Ketones **28** *and* **29**

To a solution of ketone (10 mmol) in nitromethane (10 ml) cooled at 0°C, aluminum chloride (15 mmol, 2 g) is added while stirring. After 24 h at 20°C under agitation, the mixture is hydrolysed using 1 *N* hydrochloric acid (20 ml) and treated as usual. Purification is performed by column chromatography on silica gel, using CH_2Cl_2, to give the ketones **31** and **32**.

1-[6-Hydroxy-2-methyl-3-(1-methylethyl)phenyl]-ethanone (**31**)

Yield 84%, colourless crystals from pentane, m.p. 70°C. For $C_{12}H_{16}O_2$ (192.3). Calc. C 75.03, H 8.39; found C 74.81, H 8.30. ^{1}H-NMR ($CDCl_3$): 1.20 [d, 6 H, $(CH_3)_2CH-$], 2.45 (s, 3 H, CH_3), 2.58 (s, 3 H, $COCH_3$), 3.13 (m, 1 H, $>CH-$), 6.80 (d, 1 H, H_5, $J = 9$), 7.3 (d, 1 H, H_4, $J = 9$), 10.00 (s, 1 H, OH). IR (CH_2Cl_2): 1 635 cm^{-1} and 1 698 cm^{-1} (C=O). MS: *m/z* (%) = 192 (M^+, 36), 177 (100). UV (ethanol): nm (log ε): 202 (4.16), 217 (4.10), 287 (3.24).

1-[6-Hydroxy-2-methyl-3-(1-methylethyl)phenyl]-1-heptanone (**32**)

Yield 82%, colourless crystals from pentane, m.p. 65°C. For $C_{17}H_{26}O_2$ (262.4). Calc. C 77.82, H 9.99; found C 78.09, H 9.79. ^{1}H-NMR ($CDCl_3$): 0.85 [m, 3 H, $(CH_2)_5CH_3$], 1.20 [d, 6 H, $(CH_3)_2CH$], 1.53 [m, 8 H, $(CH_2)_4CH_3$], 2.33 (s, 3 H, CH_3), 2.80 (t, 2 H, $COCH_2$), 3.08 (m, 1 H, $>CH-$), 6.73 (d, 1 H, H_5, $J = 9$), 7.20 (d, 1 H, H_4, $J = 9$), 8.77 (s, 1 H, OH). IR (CH_2Cl_2): 1 636 cm^{-1} and 1 697 cm^{-1} (C=O). MS: *m/z* (%) = 262 (M^+, 12), 177 (100). UV (ethanol): nm (log ε): 202 (4.19), 217 (4.10), 287 (3.27).

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