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Recent Progress on the Iterative Construction of 4-Substituted-3-Hydroxy Benzoic Acids from Unsaturated Aldehydes and Dimethyl Succinate

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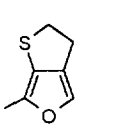
Abstract: An improvement of a known two step cyclization procedure, affording 4-aryl-3-hydroxy benzoic acid derivatives from 3-aryl-2,3-unsaturated aldehydes and dimethyl succinate, is described. The high versatility of the synthetic procedure is shown, as the aryl substituent can be a benzene or naphthalene moiety, or an heteroaromatic ring. It can be applied iteratively to prepare p,p'-oligophenyl derivatives. © 1997 Elsevier Science Ltd.

INTRODUCTION

During a work[1] aimed to the synthesis of the C_7 coffee aroma component *Kahweofuran* **1**, we were interested in preparing the carbinol intermediate **2**, containing all the carbon atoms of the skeleton of **1** into the brackets, by a selective sodium borohydride reduction of the mixed anhydride **6a** (R = Ph, R' = Me).



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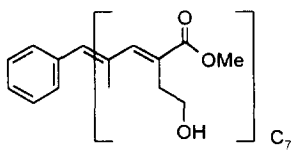
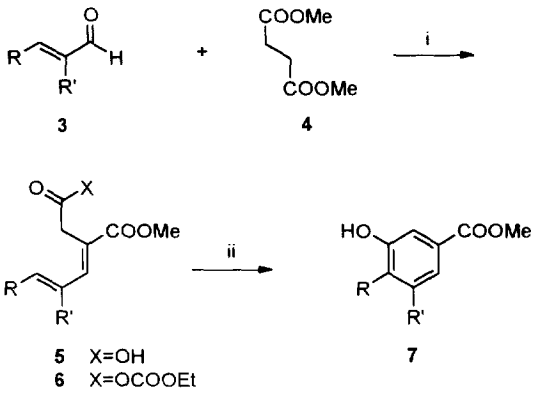


2

Stobbe condensation[2] between unsaturated aldehyde **3a** and dimethyl succinate **4** afforded the mono ester mono acid derivative **5a**, which was then treated with ethyl chloroformate and triethylamine to obtain **6a**. Unexpectedly, compound **6a** resulted to be unstable in basic conditions towards a cyclization process affording the aromatic derivative **7a**, so that its isolation required a careful control on the equivalents of triethylamine to be added. We observed that a slight excess of base allowed the complete conversion of the starting substrate **5a** into the 3-hydroxy benzoic acid methyl ester **7a** (Scheme 1), *via* the suitably activated form **6a**, in a few minutes.

We found that this synthetic method was of general applicability for the preparation of aryl substituted C-7 benzoic acid derivatives **7** from unsaturated aldehydes **3** and dimethyl succinate.



Scheme 1: Reagents and conditions: (i) MeONa, MeOH; (ii) ClCOOEt, Et_3N, THF

We assumed that the key cyclization step possibly proceeded through a 1,6-electrocyclic reaction[3,4] involving a ketene intermediate,[5] as in the case of the annulation reaction of phosphinic-carboxylic mixed anhydrides described by Ramage *et al.*[6]

Thus, our finding could be considered an improvement of a known cyclization procedure, and we decided to investigate its applicability to the synthesis of relevant biaryl, oligoaryl and heteroaromatic derivatives. The results of our study are reported herein.

RESULTS AND DISCUSSION

In a typical experiment, cinnamaldehyde **3b** was condensed with dimethyl succinate **4** to afford acid **5b** in 50 % yield.[7] This latter derivative reacted at 0°C in methylene chloride solution with 1.1 mol. eq. of ethyl chloroformate, followed by the dropwise addition of 1.2 mol. eq. of triethylamine at the same temperature. Column chromatography of the residue obtained upon evaporation of the reaction mixture, which had been washed with diluted HCl and water, afforded ester **7b** in 77 % yield. The identity of this product was confirmed by comparison of the corresponding acid, recovered upon basic hydrolysis, with an authentic sample prepared through a different way.[8]

The general applicability of the process is clearly demonstrated by the examples of Table 1. The reported values are non optimised yields for the conversion of aldehydes **3a-f** in mono acid mono ester derivatives **5a-f**, and for the cyclization of these latter substrates to **7a-f**.

The Stobbe condensation, providing **5a-f**, proceeded with moderate yields. This classic synthetic approach to mono ester mono acid derivatives was preferred to the use of triphenyl-(α-carbomethoxy-β-*t*-

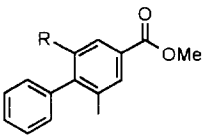
butoxycarbonyl-methyl) phosphonium betaine[6] in the case of these aromatic and heteroaromatic unsaturated aldehydes, being the reagents (dimethyl succinate, sodium methylate) more easily available and the reaction step of *t*-butyl ester hydrolysis thus avoided. Furthermore, we improved the cyclization step by using ethyl chloroformate as the activating agent. This latter resulted to be less dangerous to handle, less expensive, and more effective than diphenylphosphinic chloride, thus allowing to increase the isolation yields of the aromatic derivative **7a** from 47%[6] to 81% (see Experimental).

Table 1. Isolation Yields for the Stobbe Condensation of Dimethyl Succinate with Aldehydes **3a-f** Affording **5a-f**, and for the Cyclization Reaction of Acids **5a-f** to Esters **7a-f**.

Aldehyde 3	R	R'	Acid 5	yield (%)	Ester 7	yield (%)
3a	C_6H_5	CH_3	**5a**	55	**7a**	81
3b	C_6H_5	H	**5b**	50	**7b**	77
3c	4-F-C_6H_4	H	**5c**	48	**7c**	90
3d	2-Furyl	H	**5d**	60	**7d**	80
3e	2-Furyl	CH_3	**5e**	69	**7e**	87
3f	2-Thienyl	H	**5f**	45	**7f**	82

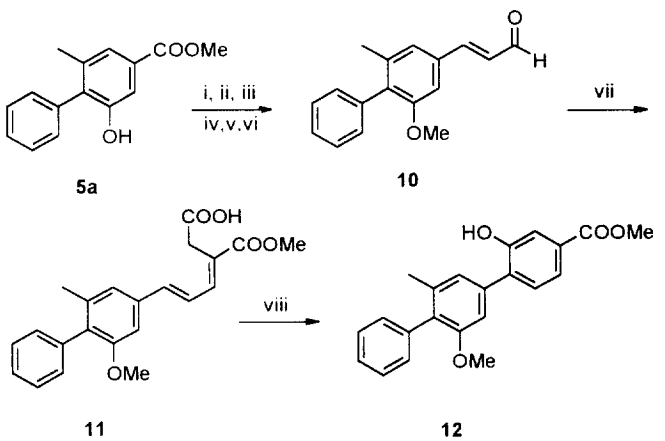
Examination of the substitution pattern of the unsaturated aldehydes **3**, used as starting materials together with dimethyl succinate in the two step synthesis of methyl 4-aryl-benzoates **7**, shows the flexibility of the synthesis (Table 1). The overall process can be regarded as an "arylation" procedure of aromatic and heteroaromatic substrates, formally alternative to the well known processes of oxidative coupling of suitably activated ring systems, mediated by transition metals.[9] The mixed anhydride cyclization method offers the following advantages: i) the conversion of the substrate to be arylated into the effectively reacting unsaturated aldehyde can be achieved through a wide variety of synthetic methods; ii) three of the six carbon atoms of the new benzene ring are offered by the easily available dimethyl succinate; iii) the mild basic catalysis promoting the cyclization step can be considered environmental friendly, as it affords triethylammonium chloride, ethanol and carbon dioxide as the only by-products; iv) the reaction can be performed at room temperature without any particular care, except for anhydrous conditions.

An additional feature of the method is represented by the fact that it allows the insertion onto a certain substrate of a benzene substituent bearing an hydroxylic group and a carboxylic moiety in position ortho and para, respectively. The presence of an hydroxyl moiety in position 3 of the resulting benzoic acid derivatives is not a limitation. Indeed, product **7a**, produced from α-methylcinnamaldehyde **3a**, was easily deoxygenated to methyl 3-methyl-4-phenylbenzoate **9** upon hydrogenolysis[10] of the corresponding phenyltetrazolyl derivative **8** in 87% overall yield.



8 R= O-5-Phenyl tetrazolyl
9 R= H

The arylation procedure of Scheme 1 can be applied iteratively. According to the sequence reported in Scheme 2, C-6--C-6--C-1 derivative **5a** afforded product **12**, in which two of the three differently substituted aromatic rings were obtained by this new cyclization process. The ester **5a** was converted into the corresponding phenolic methyl ether and homologated through unexceptional steps to the C-6--C-6--C-3 aldehyde **10**. This latter derivative underwent Stobbe condensation to afford acid **11**, embodying all the necessary carbon atoms for the subsequent cyclization to product **12** by reaction with ethyl chloroformate/triethylamine. Thus, starting from benzaldehyde, which provided the initial C-6--C-1 portion of the molecule, product **12** was obtained with the use of two moles of C-4 dimethyl succinate and one mole of C-3 and C-2 moieties, which are synthetic equivalents of propionaldehyde and acetaldehyde, respectively. This iterative cyclization procedure can be considered as an useful method for the regioselective synthesis of functionalized p,p'-oligophenyls, whose study is now in progress in the field of material science because of their outstanding optical non linear properties.[11]

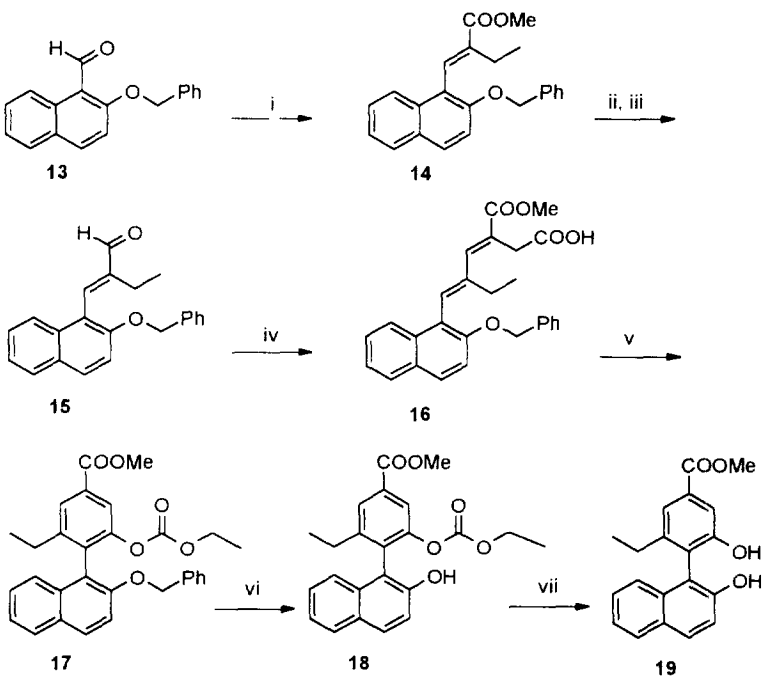


Scheme 2: Reagents and conditions: (i) MeI, K_2CO_3, acetone. 89% ; (ii) $LiAlH_4$, Et_2O, 96%; (iii) MnO_2, $CHCl_3$, 74%; (iv) $Ph_3PCHCOOEt$, CH_2Cl_2, 85%; (v) $LiAlH_4$, Et_2O, 98%; (vi) MnO_2, $CHCl_3$, 65%; (vii) dimethyl succinate, MeONa, MeOH, 50%; (viii) ClCOOEt, Et_3N, THF, 67%

Another significant application of this benzene ring synthesis is outlined in Scheme 3. Starting from 2-benzyloxy-1-naphtaldehyde **13**, the α-ethyl unsaturated ester **14** was obtained through an Emmons reaction.[12] Reduction/oxidation procedures converted **14** into aldehyde **15**. Stobbe condensation of **15** and ethyl

chloroformate/triethylamine treatment of the condensation product **16**, using a large excess of reagents, gave substrate **17**, in which the phenolic groups adjacent to the bond interconnecting the two aromatic fragments were protected in different ways. The benzyl group was first removed by hydrogenolysis to provide **18**, yielding, in turn, ester **19** upon NaOMe/MeOH treatment. This latter compound showed hindered rotation around the interanular single bond. The two enantiomers of the axially dissymmetric biaryl (±)-**19** could be separated by HPLC analysis on a chiral column,[13] thus resulting to be configurationally stable at room temperature.

It is well known that chiral atropisomeric biaryls of this kind play a key role in a variety of chiral recognition phenomena:[14] diphosphine ligands, such as binap,[15] are widely used in transition metal catalysed stereoselective reactions;[16] titanium complexes of 1,1'-binaphthol derivatives have been employed for enantioselective addition of nucleophiles to carbonyl groups,[17] and for catalytic asymmetric Diels-Alder reactions.[18]



Scheme 3: (i) $(EtO)_2POCHEtCOOEt$, NaH, DME, 85%; (ii) $LiAlH_4$, Et_2O, 96%;(iii) MnO_2, $CHCl_3$,76%; (iv) dimethyl succinate, MeONa, MeOH, 69%, (v) ClCOOEt, Et_3N, THF, 78%; (vi) H_2, Pd/C, 66%, (vii) MeONa, MeOH, 96%

1-Phenyl naphthalenes, prepared following our procedure, can be manipulated in order to obtain new ligands for asymmetric synthesis, either functionalizing the two hydroxylic groups, or condensing another benzene ring,

according for example to the method recently reported by Katritzky.[19] Moreover, the presence of the carboxylic moiety could be of some help for the resolution step of the chiral biaryl, and it could be used as an anchor to link the substrate to a polymeric matrix.[20]

Work is now in progress on the use of unsaturated aldehydes showing the double bond as a part of an aliphatic cyclic skeleton. The study is aimed to apply this kind of procedure as an "aromatic annulation method", in order to synthesise ring fused structures.[21] These results will be conveniently compared with those obtained by Paquette *et al.*, proposing an annulation route of analogous mono acid derivatives mediated by oxalyl chloride in methylene chloride[22]

Apart from the mechanistic interest, the present procedure for the selective construction of functionalized 4-substituted-benzoic acids holds preparative significance. In fact, it is possible to synthesise a variety of highly functionalized aromatic compounds, not easily accessible through the available methods, by a selected choice i) of the aromatic aldehyde used as a "starter", and ii) of the equivalents of aliphatic aldehyde required to prepare the reacting α,β-unsaturated aldehyde of type **3**.

Acknowledgement. We thank Progetto Strategico CNR Tecnologie Chimiche Innovative for the partial financial support.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^{1}H). The chemical shift scale is based on internal tetramethylsilane.. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. Unsaturated aldehydes **3a**, **3b**, **3d**, **3e** were commercially available. Aldehyde **3f** were prepared according to the literature procedure.[23]

3-(4-Fluorophenyl)-2-propenal (3c)

Aldolic condensation between 4-fluorobenzaldehyde and acetaldehyde (NaOH, aqueous ethanol, 0°C) afforded derivative **3c** (62 %): ^{1}H NMR δ 6.65 (dd, 1H), 7.10 (t, 2H), 7.45 (d, 1H), 7.55 (dd, 2H), 9.70 (d, 1H). Anal. Calcd for C_9H_7FO: C, 71.99; H, 4.70; F, 12.65. Found: C, 71.96; H, 4.66, F, 12.58.

3-[4-(2-Methoxy-6-methyl-1,1'-biphenyl)]-2-propenal (10)

Unsaturated aldehyde **10** was obtained from **5a**, according to the reaction steps reported in Scheme 2, as a crystalline solid (ethanol) (35% five steps) : mp 126-128°C; ^{1}H NMR δ 2.12 (s, 3H), 3.75 (s, 3H), 6.75 (dd, 1H), 6.98 (s, 1H), 7.13 (s, 1H), 7.22 (m, 2H), 7.31 - 7.54 (m, 4H), 9.72 (d, 1H); IR (Nujol): 1668, 1623 cm^{-1}; MS *m z* (EI): 252 (M$^+$), 237 (M$^+$-Me), 221 (M$^+$ - OMe), 178, 165, 152, 115. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.61; H, 6.27.

2-(Benzyloxy)-1-naphthaldehyde (13)

Benzylation of 2-hydroxy-1-naphthaldehyde according to the common procedure gave **13** as a crystalline solid (ethanol) (86%): mp 119-120°C; ^{1}H NMR δ 5.35 (s, 2H), 7.30-7.50 (m, 6H), 7.62 (dd, 1H), 7.68 (d, 1H), 8.05 (d, 1H), 9.28 (d, 1H), 10.98 (s, 1H); IR (nujol): 1664 cm^{-1}; MS *m/z* (EI): 262 (M^+), 115, 91. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.51; H, 5.33.

Methyl 3-[2-(benzyloxy)-1-naphthyl]-2-ethyl-2-propenoate (14)

A dispersion of sodium hydride 80% in mineral oil (6.7 g, 0.22 mol) was added to a solution of ethyl α–ethyl-diethylphosphonoacetate (56 g, 0.22 mol) in dimethoxyethane (100 mL). After stirring 1 h at room temperature, a solution of compound **13** (59 g, 0.22 mol) in dimethoxyethane (50 mL) was added dropwise. The reaction mixture was heated at 50°C for 3 h, then diluted with water and extracted with diethyl ether. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure. This derivative was purified by conversion into the corresponding alcohol upon lithium aluminium hydride reduction and chromatographed on a silica gel column, using hexane - ethyl acetate 2:1 as eluent. The alcohol **15** (55g, 80 % two steps) showed the following analytical and spectroscopic data: ^{1}H NMR δ 0.85 (t, 3H), 2.00 (q, 2H), 4.35 (s, 2H), 4.8 (broad s, 1H), 5.15 (s, 2H), 6.55 (s, 1H), 7.2 - 7.5 (m, 8H), 7.65 - 7.9 (m, 3H); IR (neat) 3447 cm^{-1}; MS *m/z* (EI): 318 (M^+), 301 (M^+ -1), 256, 227, 209, 197, 181. Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 83.07; H, 6.91.

3-[2-(Benzyloxy)-1-naphthyl]-2-ethyl-2-propenal (15)

Unsaturated aldehyde **15** was prepared from **14** according to the sequence reported in Scheme 3 (73% two steps): ^{1}H NMR δ 0.85 (t, 3H), 2.18 (q, 2H), 5.22 (s, 2H), 7.2-7.8 (m, 12H), 9.82 (s, 1H); IR (neat): 1685 cm^{-1}; MS *m/z* (EI): 316 (M^+), 225 (M^+ -$PhCH_2$), 209 (M^+-$PhCH_2O$), 181, 165, 152, 141, 115, 91. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.47; H, 6.32.

General procedure for Stobbe condensation[2]

A 2.0 M solution of sodium methylate (1.1 eq) in methanol was added to a mixture of the suitable α,β-unsaturated aldehyde **3a-f** (1 eq) and dimethyl succinate (1.1 eq). The homogeneous solution was concentrated under reduced pressure in 30 min at 40°C. The residue was treated with 5% HCl, and extracted with diethyl ether. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure, to give the desired mono acid mono ester derivatives.

3-(Methoxycarbonyl)-5-methyl-6-phenyl-3,5-hexadienoic acid (5a)

Obtained as a crystalline solid from hexane-ethyl acetate (55%): mp 160-163°C; ^{1}H NMR δ 2.1 (s, 3H), 3.65 (s, 2H), 3.80 (s, 3H), 6.70 (s, 1H), 7.30 (m, 5H), 7.5 (s, 1H); IR (Nujol) 1622, 1709 cm^{-1}; MS *m/z* (EI) 260 (M^+, 100), 228 (M - MeOH, 50), 200 (M^+ -HCOOMe, 84), 183 (M^+ -Ph, 18), 155 (90);. Anal. Calcd for

$C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.32; H, 6.50.

3-(Methoxycarbonyl)-6-phenyl-3,5-hexadienoic acid (5b)

Obtained as a pure compound by column chromatography using hexane-ethyl acetate (3:1-1:1) as eluent (50%): ^{1}H NMR δ 3.58 (s, 2H), 3.82 (s, 3H), 7.00 (m, 2H), 7.2-7.6 (m, 6H); IR (Nujol) 1695, 1628 cm^{-1}; MS *m/z* (EI): 246 (M^+), 215 (M^+-OMe), 202 (M^+-CO_2), 187 (M^+ - COOMe), 169, 141, 115. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.15; H, 5.81.

6-(4-Fluorophenyl)-3-(methoxycarbonyl)- 3,5-hexadienoic acid (5c)

Obtained as a pure compound by column chromatography, eluting with hexane - ethyl acetate (3:1 - 1:1) (48%): ^{1}H NMR δ 3.55 (s, 2H), 3.80 (s, 3H), 6.90 (m, 2H), 7.05 (t, 2H), 7.50 (m, 3H); 3448, 1720, 1698, 1625 cm^{-1}, MS *m/z* (EI) 264 (M^+), 220 (M^+ -CO_2), 159, 133. Anal. Calcd for $C_{14}H_{13}FO_4$: C, 63.63; H, 4.96; F, 7.19. Found: C, 63.50; H, 5.01; F, 7.03.

6-(2-Furyl)-3-(methoxycarbonyl)- 3,5-hexadienoic acid (5d)

Obtained as a crystalline solid from hexane-ethyl acetate (60%): mp. 143-145°C; ^{1}H NMR δ 3.55 (s, 2H), 3.80 (s, 3H), 6.4-6.5 (m, 2H), 6.70 (d, 1H), 6.85 (dd, 1H), 7.50 (m, 2H); IR (Nujol) 3448, 1717, 1618 cm^{-1}, MS *m/z* (EI): 236 (M^+), 205 (M^+-OMe), 192 (M^+ - CO_2), 159, 132, 131. Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.11; H, 5.04.

6-(2-Furyl)-3-(methoxycarbonyl)-5-methyl-3,5-hexadienoic acid (5e)

Obtained as a pure compound by column chromatography, eluting with hexane - ethyl acetate (3:1 - 1:1) (69%), ^{1}H NMR δ 2.20 (s, 3H), 3.65 (s, 2H), 3.80 (s, 3H), 6.45 (m, 3H), 7.45 (s, 2H); IR (Nujol) 1712, 1618 cm^{-1}; MS *m/z* (EI): 250 (M^+), 219 (M^+-OMe), 191, 173, 145. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.29; H, 5.72.

3-(Methoxycarbonyl)-6-(2-thienyl)- 3,5-hexadienoic acid (5f)

This derivative was recovered by extraction of the Stobbe condensation's residue with a saturated solution of sodium hydrogen carbonate. The aqueous phase was acidified with HCl 15%, and extracted with diethyl ether. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure, to give **5f** as an amorphous solid (45%): ^{1}H NMR δ 3.55 (s, 2H), 3.80 (s, 3H), 6.75 (dd, 1H), 7.10 (m, 2H), 7.3 (d, 1H), 7.5 (1H, d), 11.8 (broad s, 1H); IR (Nujol) 3450, 1697, 1624 cm^{-1}; MS *m/z* (EI): 252 (M^+), 211 (M^+-OMe), 208 (M^+-CO_2), 193, 175, 147. Anal. Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.79; S, 12.71. Found: C, 57.29; H, 4.78; S, 12.86.

3-(Methoxycarbonyl)-6-[4-(2-methoxy-6-methyl-1,1'-biphenyl)]-3,5-hexadienoic acid (11)

Obtained by column chromatography, eluting with hexane-ethyl acetate (5:1 - 1:1) (50 %): ^{1} H

NMR δ 2.08 (s, 3H), 3.70 (s, 2H), 3.75 (s, 3H), 3.81 (s, 3H), 6.87-7.48 (m, 10H). Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.06; H, 6.15.

6-[2-(Benzyloxy)-1-naphthyl]-5-ethyl-3-(methoxycarbonyl)-3,5-hexadienoic acid (16)

Obtained by column chromatography, eluting with hexane-ethyl acetate (5:1 - 1:1) (69%): ^{1}H NMR δ 0.85 (t, 3H), 2.02 (q, 2H), 3.70 (s, 2H), 3.78 (s, 3H), 5.15 (s, 2H), 7.20-7.8 (m, 13H); IR (neat): 1712 cm^{-1}; MS *m z* (EI): 430 (M^+), 339 (M^+ - $PhCH_2$), 307, 289, 261, 181, 165, 152. Anal. Calcd for $C_{27}H_{26}O_5$: C, 75.33; H, 6.09. Found: C, 75.59; H, 6.13.

General procedure for the cyclization reaction to give 4-aryl and 4-heteroaryl-3-hydroxy-benzoic acid methyl esters 7a-f, and 12

Ethyl chloroformate (1.1 eq) was added to a 1.0 M solution of the suitable mono acid mono ester derivative **5a-f**, **11** (1 eq) in THF; then, triethylamine (1.2 eq) was added dropwise, keeping the temperature under 20°C. The reaction mixture was stirred at room temperature for 15 min, then treated with HCl 5%, and extracted with diethyl ether. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure, to give derivatives **7a-f**, and **12**.

3-Hydroxy-5-methyl-4-phenyl benzoic acid methyl ester(7a)

Obtained as a crystalline solid from petroleum ether (81%): mp. 127-128°C; ^{1}H NMR δ 2.1 (s, 3H), 3.9 (s, 3H), 4.9 (bs, 1H) 7.2-7.6 (m, 7H); IR (Nujol) 1700, 3415 cm^{-1}; MS *m z* (EI) 242 (M^+), 211 (M^+-OMe), 183, 165 (M -Ph), 155, 115, 77. Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.48; H, 5.92.

3-Hydroxy-4-phenyl benzoic acid methyl ester (7b)

Obtained as a pure compound by column chromatography using hexane-ethyl acetate (5:1-2:1) as eluent (77%): ^{1}H NMR δ 3.85 (s, 3H), 7.3-7.7 (m, 8H), 8.25 (s, 1H); IR (Nujol) 1703, 3420 cm^{-1}; MS *m z* (EI) 228 (M^+), 197 (M^+-OMe), 141, 115, 98. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.43; H, 5.19.

4-(4-Fluorophenyl)-3-hydroxy benzoic acid methyl ester(7c)

Obtained as a crystalline solid from methylene chloride (90%): mp. 181°C; ^{1}H NMR (DMSO - d_6) δ 3.85 (s, 3H), 7.25 (t,2H), 7.4 (d, 1H), 7.45 (dd, 1H), 7.55 (d, 1H), 7.65 (dd, 2H), 10.1 (s, 1H); IR (Nujol) 1706, 3408 cm^{-1}; MS *m z* (EI) 246 (M^+), 215 (M^+-OMe), 181, 133, 111. Anal. Calcd for $C_{14}H_{11}FO_3$: C, 68.29; H, 4.50; F, 7.72. Found: C, 68.11; H, 4.42; F, 7.83.

4-(2-Furyl)-3-hydroxy benzoic acid methyl ester (7d)

Obtained as a pure compound by column chromatography using hexane-ethyl acetate (5:1-2:1) as eluent (80%): ^{1}H NMR δ 3.9 (s, 3H),6.64 (dd, 1H), 6.93 (d, 1H), 7.52 (broad s, 1H), 7.85-8 (m, 3H); IR (Nujol) 1721, 3449 cm^{-1}; MS *m/z* (EI) 218 (M$^+$), 189, 159(M$^+$-COOMe). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.23; H, 4.73.

4-(2-Furyl)-3-hydroxy-5-methyl benzoic acid methyl ester (7e)

Obtained as a pure compound by column chromatography using hexane-ethyl acetate (5:1-2:1) as eluent (87%): ^{1}H NMR δ 2.4 (s, 3H), 3.95 (s, 3H), 4.8 (broad s, 1H), 6.6 (m, 2H), 7.5 (s, 2H), 7.6 (s, 1H); IR (Nujol) 1686, 3430 cm^{-1}; MS *m/z* (EI) 232 (M$^+$), 203, 173(M$^+$-COOMe), 144, 115. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.24; H, 5.21. Found: C, 67.35; H, 5.17.

3-Hydroxy-4-(2-thienyl) benzoic acid methyl ester(7f)

This compound was purified by hydrolysis to the corresponding carboxylic acid, followed by crystallisation from hexane-ethyl acetate (82%): mp 210°C (dec.). Analytical data of the acid derivative are: ^{1}H NMR (acetone - d_6) δ 7-7.9 (m, 6H), 9.5 (broad s, 1H); IR (Nujol) 1686, 3430 cm^{-1}; MS *m z* (EI) 220 (M$^+$), 203, 175(M$^+$-COOH), 147, 115. Anal. Calcd for $C_{11}H_8O_3S$: C, 59.99; H, 3.66; S, 14.56. Found: C, 60.11; H, 3.70; S, 14.41.

2''-Hydroxy-2'-methoxy-6'-methyl-[1,1';4',1'']terphenyl-4''-carboxylic acid methyl ester (12)

Obtained as a crystalline solid from isopropyl ether (67 %): mp. 192-195°C; ^{1}H NMR δ 2.13 (s, 3H), 3.74 (s, 3H), 3.94 (s, 3H), 6.90 (s, 1H), 7.03 (s, 1H), 7.25 (m, 2H), 7.3-7.5 (m, 4H), 7.68 (m, 2H); IR (nujol) 1686, 3412 cm^{-1}; MS *m z* (EI) 348 (M$^+$), 317 (M$^+$-OMe), 202, 165, 159, 151, 115. Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.85; H, 5.79. Found: C, 75.42; H, 5.83.

Experimental procedure for the cyclization reaction of mono acid mono ester derivative 16 to give methyl 4-[2-(benzyloxy)-1-naphthyl]-3-[(ethoxycarbonyl)oxy]-5-ethyl benzoate (17)

Ethyl chloroformate (2.2 eq) was added to a 1.0 M solution of mono acid mono ester derivative **16** (1 eq) in THF; then, triethylamine (5 eq) was added dropwise, keeping the temperature under 20°C. The reaction mixture was stirred at room temperature for 30 min, then treated with HCl 5%, and extracted with diethyl ether. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluting with hexane-ethyl acetate (5:1-2:1), to give derivative **17** (78 %), ^{1}H NMR δ 0.90 (t, 3H), 1.00 (t, 3H), 2.32 (q, 2H), 3.82 (q, 2H), 3.95 (s, 3H), 5.15 (2H, s), 7.1-8.1 (m, 13H); IR (neat): 1762, 1724 cm^{-1}; MS *m/z* (EI): 484 (M$^+$), 422, 289, 261. Anal. Calcd for $C_{30}H_{28}O_6$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.79.

Methyl 3-[(ethoxycarbonyl)oxy]-5-ethyl-4-(2-hydroxy-1-naphthyl)benzoate (18)

Hydrogenolysis (H_2, Pd/C, rt, toluene) of substrate **17** afforded derivative **18** (66%): ^{1}H NMR δ 1.00 (m, 6H), 2.32 (q, 2H), 3.98 (s + q, 5H), 5.30 (broad s, 1H), 7.02 (m, 1H), 7.2-7.4 (m, 3H), 7.7 - 7.9 (m, 3H), 8.05 (s, 1H); IR (neat) 3432, 1760, 1727 cm^{-1}; MS *m/z* (EI) 395 (M^++1), 322, 161. Anal. Calcd for $C_{23}H_{22}O_6$: C, 70.04; H, 5.62. Found: C, 70.13; H, 5.51

Methyl 3-ethyl-5-hydroxy-4-(2-hydroxy-1-naphthyl)benzoate(19)

Saponification (2 eq. MeONa, methanol, rt) of compound **18** gave derivative **19** (96%): ^{1}H NMR δ 0.95 (t, 3H), 2.32 (q, 2H), 3.94 (s, 3H), 4.90 (broad s, 1H), 5.30 (broad s, 1H), 7.1-7.4 (m, 4H), 7.62 (d, 1H), 7.71 (d, 1H), 7.8-7.95 (m, 2H); IR (Nujol) 3422, 1710 cm^{-1}; MS *m/z* (EI): 322 (M^+), 291 (M^+-OMe), 215, 202, 189.Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.37; H, 5.71.

Methyl 3-methyl-4-phenyl-5-[(1-phenyl-1*H*-1,2,3,4-tetraazol-5-yl)oxy] benzoate (8)

A mixture of compound **7a** (5 g, 0.022 mol), potassium carbonate (16g, 0.11 mol), and 5-chloro-1-phenyl-1*H*-tetrazole (6 g, 0.033 mol) in acetone (100 mL) was refluxed for 10 h. The solvent was removed under reduced pressure; the residue was treated with water, and extracted with methylene chloride. The organic phase was dried over sodium sulphate, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluting with hexane - ethyl acetate 2:1, to give derivative **8** (8.1 g, 95%): ^{1}H NMR δ 2.20 (s, 3H), 3.90 (s, 3H), 7.15-7.55 (m, 10H), 7.95 (s, 1H), 8.15 (s, 1H); IR (nujol) 1716 cm^{-1}; MS *m/z* (EI): 387 (M^+ + 1), 386 (M^+), 358, 299, 240, 182. Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50. Found: C, 68.41; H, 4.66; N, 14.55.

5-Methyl-4-phenyl benzoic acid methyl ester (9)

Hydrogenolysis (H_2, Pd/C, 3 atm, rt, 3 days) of derivative **8** gave compound **9** (92%): ^{1}H NMR δ 2.30 (s, 3H), 3.93 (s, 3H), 7.24 - 7.48 (m, 6H), 7.90 (dd, 1H), 7.96 (d, 1H); IR (neat) 1721 cm^{-1}; MS *m/z* (EI): 226 (M^+), 195 (M^+-OMe), 167 (M^+-COOMe), 165, 152, 115. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.81, H, 6.31

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