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A Comparative Study on the Photo-induced Arylation of β-Dicarbonyl Compounds by Arylazosulfides and its Use in the Synthesis of Methyl Labeled 2-Arylpropionic Acids

Mercè Tona, Francisco Sánchez-Baeza and Angel Messeguer *

Dpt. of Biological Organic Chemistry, CID (CSIC). J. Girona, 18. 08034 Barcelona, Spain.

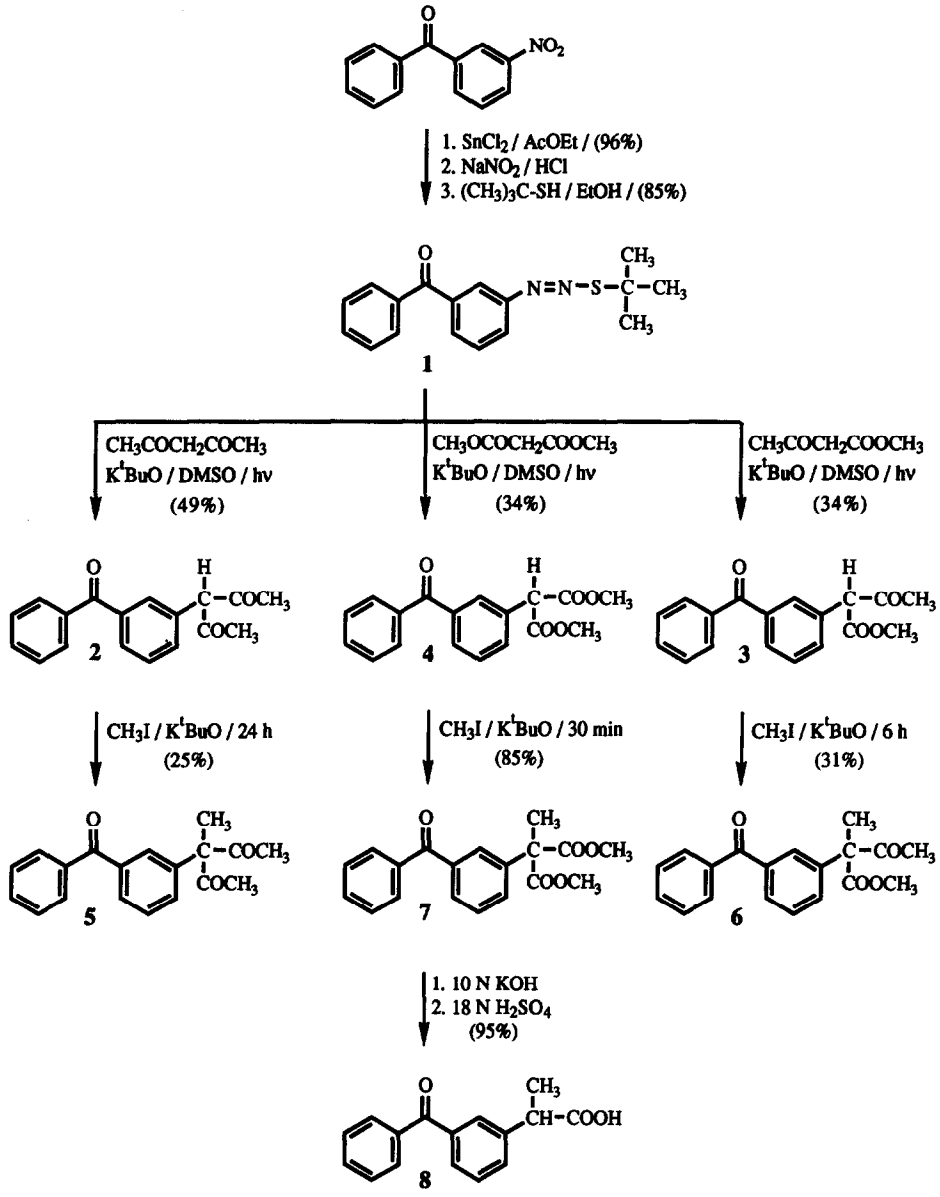
Abstract: A comparative study on the arylation of β-dicarbonyl derivatives (acetylacetone, methyl acetoacetate and dimethyl malonate) by using the photo-induced decomposition of arylazosulfides is presented. The arylazosulfides used contained the aryl moieties related to Ketoprofen or Ibuprofen and the reaction was performed following the procedure reported by Dell'Erba et al. (*Tetrahedron*, **1991**, *47*, 333). From the arylazosulfides assayed, only those bearing a carbonyl group attached to the benzene ring, i.e., **1** and **11**, afforded the corresponding arylation adducts in satisfactory yields. Concerning the β-dicarbonyl derivatives, condensation of acetylacetone in the case of **1** and of dimethyl malonate in that of **11** gave the best results. However, the further methylation of the aryl β-dicarbonyl adduct was clearly advantageous for the case of the 2-arylmalonate derivatives. The use of this synthetic strategy for the convenient preparation of Ketoprofen (23% overall yield, 7 steps from 3-nitrobenzophenone) and Ibuprofen (34% overall yield, 8 steps from 4-isobutyrylbenzene) isotopomers labeled at the methyl group at C-2 is also reported.

2-Arylpropionic acids constitute an important group of non-steroidal anti inflammatory drugs and their therapeutic value has been demonstrated by the introduction and extensive use of several compounds in the pharmaceutical market. Ketoprofen (**8**) and Ibuprofen (**20**) can be considered as representative examples of this class of drugs. Recently, evidence showing that the pharmacological activity of these compounds is mainly due to the enantiomer with the (*S*) configuration, and that a bioconversion from the (*R*) into the (*S*) enantiomer takes place to a certain extent, has raised considerably the interest in these compounds.[1] Therefore, intense research for developing synthetic methods for the preparation of racemic and non-racemic 2-arylpropionic acid derivatives has been carried out by numerous laboratories, [2,3] and the increasing number of patents filed by pharmaceutical industries corroborate these efforts.

Another consequence of the above interest is the need for synthetic routes for preparing labeled 2-arylpropionic acids for metabolism and pharmacokinetic studies. To this aim, labeling at the methyl group of the propionic acid chain and introduction of this methyl labeled moiety at the final stages of the synthesis would constitute an attractive strategy. From this point of view, the arylation of β-dicarbonyl compounds appeared to be the key step for attaching the aryl fragment of the respective drug to an activated moiety, which then could be methylated and easily processed to render the desired 2-arylpropionic acid. The arylation of β-dicarbonyl compounds, particularly acetylacetone derivatives, has been subject of different studies. In our hands, however, the procedures based on the condensation of acetylacetonates with aryl halides in the presence of copper catalysts [4] or on the radical-mediated decomposition of aryldiazonium tetrafluoroborates in the presence of copper complexes of β-diketones [5], by using the 3-benzoylphenyl moiety corresponding to Ketoprofen as aryl

fragment, afforded poor yields of the corresponding adduct (i.e. **2** in Scheme I) or led to a complex mixture of compounds.

Scheme I



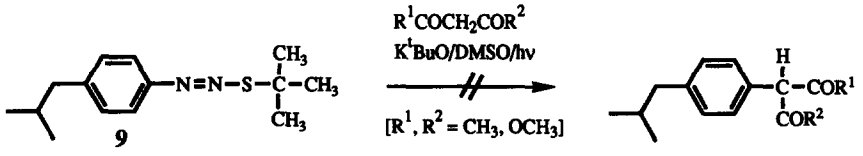
Then we turned our attention to the procedure recently reported by Dell'Erba et al., which is based on the photochemically induced decomposition of arylazosulfides in the presence of potassium 2,4-pentanedionate .[6]

In the present study, the extension of this arylation reaction to other β-dicarbonyl compounds (*i.e.*, acetoacetate and malonate derivatives) has been explored and the results obtained have been used for developing convenient preparations of isotopomers of Ketoprofen and Ibuprofen labeled at the methyl group of the propionic acid chain.

Results and Discussion

In the first instance the synthetic sequence directed towards racemic Ketoprofen (**8**) was attempted and results obtained are shown in Scheme I. Thus, reduction of 3-nitrobenzophenone with $SnCl_2$, followed by diazotation of the amine and reaction with 2-methylpropanethiol led to the arylazosulfide **1**.[7] When this compound was subjected to a photochemically induced decomposition in the presence of the potassium salt of acetylacetone, methyl acetoacetate or dimethyl malonate, under the conditions reported by Dell'Erba et al. for the case of acetylacetone,[6] the starting arylazosulfide was consumed (HPLC monitoring), and the corresponding arylated adducts **2**, **3** and **4** were isolated in 45, 34 and 38% yields, respectively. Compound **2** was 100% enolized in solution (NMR analysis), whereas a partial enolization was observed for the case of acetoacetate **3**. On the other hand, substantial amounts of benzophenone and *tert*-butyl 3-benzoylphenyl sulfide were formed in all cases, which accounted for the rest of the reacted arylazosulfide. The formation of these side-products through competing paths for the intermediate aryl radicals generated in the reaction medium is documented in the literature [6].

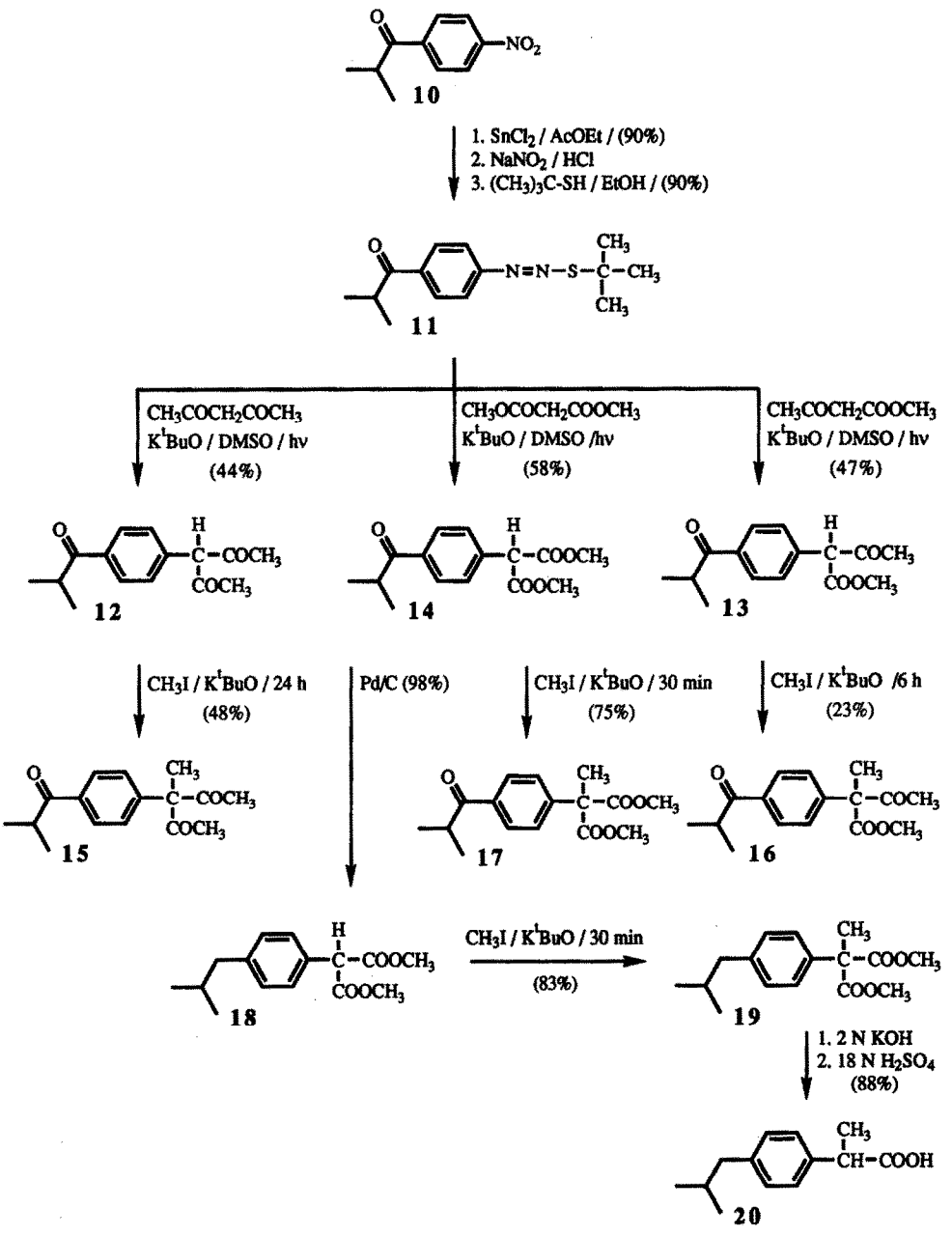
When the photochemical decomposition was assayed with the arylazosulfide **9**, which contains the isobutylphenyl fragment present in Ibuprofen (**20**), only traces of the corresponding adducts with either acetylacetone, methyl acetoacetate or dimethyl malonate were detected by GC/MS analysis. In fact, the major products obtained from the different assays were isobutylbenzene and 4-isobutylphenyl *tert*-butyl sulfide. This result is in agreement with those reported by Dell'Erba et al. for the case of acetylacetone condensations, where the absence of electron withdrawing substituents in the aromatic ring dropped the yields of the desired arylation reaction [6].



However, when the photochemical decomposition was assayed on the arylazosulfide **11** (Scheme II), the formation of the corresponding adducts **12-14** in satisfactory yields was observed. These yields were also higher than those obtained for the case of the decomposition of arylazosulfide **1**. In fact, decomposition of arylazosulfide **11** in the presence of the anion of dimethyl malonate afforded the highest arylation yield within the different derivatives assayed. These results confirmed that under the reaction conditions assayed, arylation of a β-dicarbonyl substrate not easily enolizable such as malonate, depends mainly on the nature of the substituents present in the aromatic ring. On the other hand, as it occurred with the case of the 3-benzoylphenyl compounds, the acetylacetone **12** was completely enolized in solution at room temperature, whereas the adduct derived from acetoacetate **13** was partially enolized working under the same conditions. In these cases, similarly to that observed for the case of the photo-induced decomposition of arylazosulfide **1**, the formation of

isobutyrophenone and *tert*-butyl 4-isobutyrylphenyl sulfide accounted for the rest of the decomposed starting material.

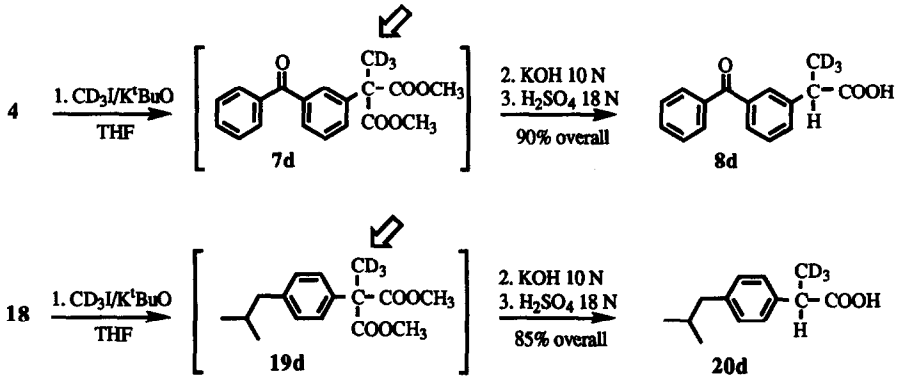
Scheme II



The results obtained in the photochemical induced condensation made somewhat difficult the selection of the best synthetic route for obtaining the desired profens, particularly for the case of Ketoprofen. However, the ensuing C-methylation reaction was decisive to clarify this question. As shown in Schemes I and II, the C-methylation took place with the highest yields and under the mildest conditions using the malonate adducts **4**, **14** and **18** as substrates. In this respect, both malonate derivatives structurally related to Ibuprofen (i.e., **14** and **18**) afforded the methylation product in good yields. Nevertheless, since the catalytic hydrogenation of **14** gave **18** in quantitative yield, this synthetic route, which also involved the labeling step at a later stage, was selected for the preparation of the corresponding labeled isotopomer (see below).

On the other hand, as it is also shown in Schemes I and II, the methylation of the adducts containing either acetylacetone or acetoacetate moities was less satisfactory. Thus, the reaction on the acetylacetone derivatives **2** required long reaction times and an important excess of both the base and the methylating agent, and still the conversion was not complete. For diketone **12**, the above excess could not be used due to the competitive methylation at the isobutyryl CH residue, and conversion was also incomplete. Likewise, the methylation of acetoacetates **3** or **13** needed long reaction times; in addition, different side-products were also formed in these cases, which dropped the yields in the respective 2-methyl derivatives **6** and **16**, and made difficult the purification of the crude reaction mixtures. These results indicate that the C-methylation reaction of these arylated β-dicarbonyl adducts is somewhat prevented in those structures susceptible of enolization.

Scheme III



As consequence of the results obtained in the route involving the malonate derivatives, the preparation of Ketoprofen (**8**) in 7 steps and 23% overall yield from 3-nitrobenzophenone, and of Ibuprofen (**20**) in 8 steps and 34% overall yield from 4-isobutyrylbenzene, was achieved. In addition, a convenient application for the synthesis of isotopomers of these profens labeled at the methyl substituent of the propionic acid chain could be developed. These derivatives are important tools for pharmacokinetic and metabolism studies, and references related to their preparation are scarce in the literature [8]. On the other hand, the strategy of incorporating the labeled moiety at the methyl group at C-2 is particularly attractive, since metabolism at this point is much less important in comparison with that occurring at the COOH or at the aryl fragment [9]. As shown in Scheme III, the respective malonates **4** or **18** were subjected to a one-pot operation involving the methylation with the appropriate labeled reagent ([$^2H_3$-methyl] iodide was used as model), followed by basic hydrolysis and further acidification to render highly pure samples of the deuterated profens **8d** or **20d**, in excellent overall yields. The

experimental procedure is simple enough to facilitate the synthesis of methyl radiolabeled acids. Finally, the fact that this method affords racemic mixtures of profens does not represent a serious drawback, due to the variety of efficient procedures for the resolution of these compounds that have been recently reported [1a], particularly at the scale used in the work with isotopically labeled drugs.

In conclusion, results reported herein show that photochemical decomposition of arylazosulfides containing electron withdrawing groups in the presence of the anion of dimethyl malonate, constitutes a suitable method for the preparation of 2-arylmalonate derivatives. As exemplified in the cases of Ketoprofen and Ibuprofen, the former adducts can be easily transformed into the respective profens, and the process could be used for a convenient synthesis of isotopomers of these acids specifically labeled at the methyl group of the propionic acid chain.

Experimental Section

Melting points were obtained with a Koffler apparatus and are uncorrected. The IR spectra were recorded with a Bomen model MB120 apparatus. The NMR spectra (^1H, ^{13}C) were recorded on a Varian Gemini 200 or a Varian Unity 300 spectrometer. All NMR spectra were performed in neutralized $CDCl_3$ solutions; chemical shifts are given in ppm using tetramethylsilane as internal reference. The GC-MS-EI spectra (70 eV) were obtained using a Fisons model MD 800 mass spectrometer coupled to a Fisons GC 8000 apparatus, which was equipped with a 25 m HP-5 capillary column. The HPLC-TSP-MS analyses were performed with a Hewlett Packard HP-5988A quadrupole apparatus (direct flow injection with 50 mM ammonium formate / acetonitrile (50:50) at 1 mL/min, positive mode). Elemental analyses were performed on a Carlo Erba 1108 instrument (Microanalysis Service, CID).

Reagents were used as received from commercial sources. DMSO and THF were dried, distilled and stored over molecular sieves. The photochemical reactions were performed with a Heraeus apparatus provided by an immersion mercurium lamp TQ-150 and a Pyrex filter. Unless otherwise stated, organic extracts coming from crude reaction mixtures were routinely washed with water, brine and dried over $MgSO_4$, and silica gel was used for the flash chromatography purifications. Likewise, unless indicated, all new compounds reported herein were isolated as colorless or pale yellow oils.

Preparation of arylazosulfides: (3-benzoyl)phenylazo *tert*-butyl sulfide (1). A soln. of 3-nitrobenzophenone (prepared in 90% yield from benzene, 3-nitrobenzoyl chloride and $AlCl_3$, 5.0 g, 22 mmol) in AcOEt (50 mL), was treated with $SnCl_2.2H_2O$ (24 g, 110 mmol) [10] and the mixture was stirred under reflux for 1 h. The crude reaction mixture was poured into ice, basified with $NaHCO_3$ soln., extracted with ^{t}BuOMe and dried. The residue obtained after elimination of solvent was identified as 3-aminobenzophenone (4.2 g, 97% yield), mp 87-8 °C (lit. 87 °C [11]), (^1H NMR δ: 7.80 (br. d, 2 H, J = 7.5 Hz, H-2', H-6'), 7.57 (t, 1 H, J = 7 Hz, H-4'), 7.45 (t, 2 H, J = 7 Hz, H-3', H-5'), 7.24 (t, 1 H, J = 8 Hz, H-5), 7.15-7.08 (2 H, H-2, H-6), 6.88 (d, 1 H, J = 8 Hz, H-4); ^{13}C NMR δ: 196.9 (CO), 146.4 (C-3), 138.5 (C-1), 137.6 (C-1'), 132.2 (C-4'), 129.9 (C-2', C-6'), 129.0 (C-5), 128.1 (C-3', C-5'), 120.5 (C-6), 118.9 (C-4), 115.8 (C-2); MS, m/z: 197 (M^+, 100), 120, 105, 92). Following the procedure described by Sakla et al. [7], a cold soln. of the diazonium chloride from the above amine (prepared from 6.1 g, 30 mmol) and buffered with 25% NaOAc, was added to a soln. of 2-methylpropanethiol (3.5 mL, 30 mmol) in EtOH (70 mL), and the mixture was stirred at 0 °C for 30 min. The crude reaction mixture was poured into water, extracted with ^{t}BuOMe, washed and dried. The residue obtained after elimination of solvent was purified by flash chromatography (4:1 hexane:^{t}BuOMe), to give the expected arylazosulfide 1 (7.3 g, 80% yield), which was identified by comparison with the spectral data reported elsewhere [12]. 1: ^1H NMR δ: 7.86-7.78 (3 H, H-2', H-6', H-4), 7.64–7.55 (2 H, H-4', H-2), 7.53-7.42 (3 H, H-3', H-5', H-5), 7.30 (ddd, 1 H, J_1 = 8 Hz, J_2 = 1.5 Hz, J_3 = 1 Hz, H-6), 1.63 (s, 9 H, CH_3); ^{13}C NMR δ: 195.3 (CO), 155.6 (C-1), 138.5 (C-3), 136.9 (C-1'), 132.6 (C-4'), 130.1 (C-2', C-6'), 129.4 (C-4, C-5), 128.3 (C-3', C-5'), 122.1 (C-6), 119.3 (C-2), 49.4 (C-^{t}Bu), 30.0 (CH_3); HPLC-TSP-MS, m/z: 340 (M^++41+1, 31), 316 (M^++18, 2), 299 (M^++1, 100), 242 (41), 180 (61).

-(4-Isobutyryl)phenylazo *tert*-butyl sulfide (11). Similarly, the reduction of 4-nitroisobutyrophenone (**10**, 10.0 g, 52 mmol, prepared as described elsewhere [13]), with $SnCl_2.2H_2O$ (58.4 g, 0.26 mol) afforded the expected 4-aminoisobutyrophenone (7.5 g, 90% yield), mp 105-106 °C, (^1H NMR: δ 7.82 (d, 2 H J = 8 Hz, H-2', H-6'), 6.64 (d, 2 H, J = 10 Hz, H-3', H-5'), 4.22 (2 H, NH_2), 3.48 (hp, 1H, J

= 7 Hz, CH), 1.18 (d, 6 H, J = 7 Hz, CH_3); ^{13}C NMR: δ 202.8 (CO), 151.1 (C-4'), 130.6 (C-2', C-6'), 126.3 (C-1'), 113.7 (C-3', C-5'), 34.4 (CH), 19.3 (CH_3)). Then, the addition of a cold soln. of the corresponding diazonium chloride (prepared from 3.3 g, 20 mmol of the above amine) to a soln. of 2-methylpropanethiol (2.5 mL, 22 mmol) in 10 % NaOH (200 mL), led to a crude reaction mixture which was purified by flash chromatography (10:1 hexane:^{t}BuOMe), to give the expected arylazosulfide **11** (4.7 g, 90% yield). IR: 2968, 1683, 1222, 979 cm^{-1}; ^1H NMR: δ 8.08 (d, 2 H, J = 8 Hz, H-2', H-6'), 7.12 (d, 2 H, J = 8.5 Hz, H-3' H-5'), 3.56 (hp, 1 H, J = 7 Hz, CH), 1.61 (s, 9 H, CH_3), 1.24 (d, 6 H, J = 7 Hz, CH_3); ^{13}C NMR: δ 203.2 (CO), 159.0 (C-4') 135.2 (C-1'), 129.7 (C-2', C-6), 118.1 (C-3', C-5'), 49.6 (C, ^{t}Bu), 35.4 (CH), 30.1 (CH_3, ^{t}Bu), 19.1 (CH_3, i-Bu). Anal. calcd. for $C_{14}H_{20}N_2SO$: C, 63.61, H, 7.64, N, 10.60, S, 12.12. Found: C, 63.69, H, 7.63, N, 10.58, S, 12.17.

(4-Isobutyl)phenylazo *tert*-butyl sulfide (9). Following the same procedure described above, from the diazonium salt of 4-isobutylaniline (prepared from 1.5 g, 10 mmol of this amine) and 2-methylpropanethiol (1.2 mL, 11 mmol), it was isolated the arylazosulfide **9** (2.13 g, 85% yield). IR (film): 2958, 1456, 1383, 1166 cm^{-1}; ^1H NMR: δ 7.23 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 7.07 (d, 2 H, J = 8.5 Hz, H-2', H-6', 2.50 (d, 2 H, J = 7.5 Hz, CH_2), 1.88 (n, 1 H, J = 7 Hz, CH), 1.59 (s, 9 H, CH_3), 0.91 (d, 6 H, J = 7 Hz, CH_3); ^{13}C NMR: δ 153.4 (C-4'), 142.0 (C-1'), 129.6 (C-3', C-5'), 118.2 (C-2', C-6'), 48.8 (C, ^{t}Bu), 45.1 (CH_2), 30.1 30.0 (CH, CH_3-^{t}Bu), 22.3 (CH_3); HPLC-TSP-MS, m/z: 292 (M^++41+1, 26), 251 (M^++1, 100), 242 (12), 191 (16), 161 (29). Anal. calcd. for $C_{14}H_{22}N_2S$: C, 67.14, H, 8.87, N, 11.20, S, 12.80. Found: C, 67.24, H, 8.90, N, 11.33, S, 13.02.

Arylation of β-dicarbonyl derivatives. General procedure: Following the procedure reported by Dell'Erba et al. [6] with minor modifications, a soln. of the corresponding arylazosulfide (**1** or **11**, 6 mmol) in DMSO (35 mL) was added to a soln. of the potassium salt of the respective β-dicarbonyl compound (acetylacetone, methyl acetoacetate or dimethyl malonate, prepared from 60 mmol of these substrates and 60 mmol of K^{t}BuO in 55 mL DMSO). The mixture was irradiated at 350 nm until reaction was completed (HPLC monitoring). The crude reaction mixture was poured into ice and 1N HCl, extracted with ^{t}BuOMe and dried. The residue obtained after elimination of solvent was purified by flash chromatography eluting with hexane:^{t}BuOMe mixtures to obtain the expected arylated adduct.

3-(3'-Benzoyl)phenylpentane-1,3-dione (2). This compound was obtained as a colorless solid from diazosulfide **1** (1.8 g, 6 mmol) and acetylacetone in 45 % yield (0.76 g), and it was identified by comparison with spectral data reported elsewhere [6]. **2**: mp 113-115 °C; ^1H NMR: δ 16.72 (s, 1 H, OH), 7.82-7.78 (3 H, H-2", H-6", H-4'), 7.65-7.40 (6 H, H_{Ar}), 1.93 (s, 6 H, CH_3); ^{13}C NMR: δ 196.3 (COAr), 190.8 ($COCH_3$), 138.2 (C-3'), 137.3 (C-1"), 137.1 (C-1'), 135.1 (C-4"), 132.6, 132.5 (C-6', C-2'), 129.9 (C-2", C-6"), 129.2 (C-4'), 128.9 (C-5'), 128.3 (C-3", C-5"), 114.3 (C-3), 24.2 (CH_3); MS, m/z: 280 (M^+, 22), 238 (14), 105 (100), 77 (73).

Methyl 3-oxo-2-(3'-benzoyl)phenylbutanoate (3). This compound was obtained as a colorless solid from diazosulfide **1** (1.2 g, 4 mmol) and methyl acetoacetate in 34 % yield (0.40 g). **3**: mp 97-99 °C; IR (film): 1726, 1658, 1654 1253, 717 cm^{-1}; ^1H NMR: δ 13.05 (s, 1 H, OH), 7.90-7.33 (9 H, H_{Ar}), 4.81 (s, 1 H, H-2, keto), 3.77 (s, 3H, OCH_3, keto), 3.71 (s, 3 H, OCH_3, enol), 2.24 (s, 3 H, $COCH_3$, keto), 1.90 (s, 3 H, $COCH_3$, enol); ^{13}C NMR: δ 196.3 (COAr), 174.4 (CO), 172.5 (COO), 137.6 (C-3'), 137.5 (C-1"), 135.3 (C-1'), 135.2 (C-4"), 132.9, 132.4 (C-6', C-2'), 130.0 (C-2", C-6"), 128.7 (C-4'), 128.2 (C-3", C-5"), 128.1 (C -5'), 103.4 (C-2), 65.1 (C-2, keto), 52.6 (OCH_3), 51.8 (OCH_3, keto), 28.9 (C-4), 19.8 (C-4, keto); MS, m/z: 281 (M^+-15, 1), 221 (2), 196 (100), 165 (11), 118 (17), 105 (88), 77 (50). Anal. calcd. for $C_{18}H_{16}O_4$: C, 72.96, H, 5.45. Found: C, 73.01, H, 5.50.

Dimethyl 2-(3'-benzoyl)phenylpropanedioate (4). This compound was obtained as a colorless solid from diazosulfide **1** (1.2 g, 4 mmol) and dimethyl malonate in 38 % yield (0.45 g). **4**: mp 94-95 °C; IR (film): 3066, 2952, 1753, 1737, 1656, 1311, 1288, 713 cm^{-1}. ^1H NMR: δ 7.9-7.4 (9 H, H_{Ar}), 4.73 (s, 1 H, CH), 3.76 (s, 6 H, CH_3); ^{13}C NMR: δ 195.8 (COAr), 161.1 (COO), 137.9 (C-3'), 137.3 (C-1"), 133.1 (C-4"), 132.9 (C-1'), 132.4 (C-6'), 130.9 (C-2'), 130.0 (C-2", C-6"), 129.9 (C-4'), 128.5 (C-5'), 128.2 (C-3", C-5"), 57.3 (C-2), 52.8 (CH_3); MS, m/z: 312 (M^+, 19), 253 (12), 235 (27), 210 (13), 105 (100), 77 (54). Anal Calcd for $C_{18}H_{16}O_5$: C, 69.24, H, 5.17; Found: C, 69.30, H, 5.19.

3-(4'-Isobutyryl)phenylpentane-1,3-dione (12). This compound was obtained from diazosulfide **11** (1.05 g, 4 mmol) and acetylacetone in 44 % yield (0.40 g). **12**: IR (film): 2972, 1681, 1602, 1222, 981 cm^{-1}; ^1H NMR (enol form): δ 16.74 (s, 1 H, OH), 8.01 (d, 2 H, J = 8 Hz, H-3', H-5'), 7.31 (d, 2 H, J = 8

Hz, H-2', H-6'), 3.59 (hp, 1 H, J = 7 Hz, H-2"), 1.91 (s, 6 H, $COCH_3$), 1.25 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 203.8 (COAr), 190.5 ($COCH_3$), 141.6 (C-1'), 135.2 (C-4'), 131.3 (C-2', C-6'), 128.7 (C-3', C-5'), 114.4 (C-3), 35.3 (C-2"), 24.1 ($COCH_3$), 19.1 (C-3"); MS, m/z: 246 (M^+, 24), 203 (100), 185 (63), 161 (57). Anal. calcd. for $C_{15}H_{18}O_3$: C, 73.13, H, 7.42. Found: C, 73.11, H, 7.48.

Methyl 3-oxo-2-(4'-isobutyryl)phenylbutanoate (13). This compound was obtained from diazosulfide **11** (1.05 g, 4 mmol) and methyl acetoacetate in 47 % yield (0.47 g). **13**: mp 57-59 °C; IR (film): 2972, 1749, 1720, 1681, 1647, 1604, 1267, 1224, 981 cm^{-1}; ^1H NMR: δ 13.09 (s, 1 H, OH), 7.98 (d, 1 H, J = 8.5 Hz, H-3', H-5', keto), 7.95 (d, 1 H, J = 8 Hz, H-3', H-5'), 7.47 (d, 1 H, J = 8.5 Hz, H-2', H-6', keto), 7.28 (d, 1 H, J = 8 Hz, H-2', H-6'), 4.81 (s, 1 H, H-2, keto), 3.77 (s, 3 H, OCH_3, keto), 3.70 (s, 3 H, OCH_3), 3.70-3.44 (1 H, H-2", keto + enol), 2.22 (s, 3 H, CH_3CO, keto), 1.88 (s, 3 H, CH_3CO), 1.24 (d, 3 H, J = 7 Hz, H-3"), 1.22 (d, 3 H, J = 7 Hz, H-3", keto); ^{13}C NMR (keto form): δ 203.9 (COAr), 200.3 ($COCH_3$), 172.3 (OCH_3), 137.1 (C-4'), 135.9 (C-1'), 129.6 (C-3', C-5'), 128.1 (C-2', C-6'), 65.1 (C-2), 52.6 (OCH_3), 35.3 (C-2"), 28.9 ($COCH_3$), 18.9 (C-3"); enol form: δ 203.7 (COAr), 174.2 (OCH_3), 168.3 ($COCH_3$), 139.8 (C-1'), 134.7 (C-4'), 131.4 (C-2', C-6'), 128.7 (C-3', C-5'), 103.3 (C-2), 51.8 (OCH_3), 35.2 (C-2"), 19.8 ($COCH_3$), 19.1 (C-3"); MS, m/z: 204 (M^+-58, 7), 162 (69), 161 (100), 133 (28), 119 (83), 91 (66). Anal calcd. for $C_{15}H_{18}O_4$: C, 68.67, H 6.93. Found: C, 68.56, H, 6.98.

Dimethyl 3-(4'-isobutyryl)phenylpropanedioate (14). This compound was obtained from diazosulfide **11** (1.05 g, 4 mmol) and dimethyl malonate in 58 % yield (0.63 g). **14**: mp 50-52 °C °C; IR (film): 2976, 1753, 1737, 1681, 1226 cm^{-1}; ^1H NMR: δ 7.96 (d, 2 H, J = 8 Hz, H-3', H-5'), 7.51 (d, 2 H, J = 8 Hz, H-2', H-6'), 4.72 (s, 1 H, H-2), 3.77 (s, 6 H, OCH_3), 3.54 (hp, 1 H, J = 7 Hz, H-2"), 1.21 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR : δ 203.8 (COAr), 167.9 (COO), 137.1 (C-4'), 135.9 (C-1'), 129.5 (C-3', C-5'), 128.5 (C-2', C-6'), 57.3 (C-2), 52.9 (OCH_3), 35.3 (C-2"), 19.0 (C-3"); MS, m/z: 278 (M^+, 1), 235 (100), 145 (14). Anal. calcd. for $C_{15}H_{18}O_5$: C, 64.72, H 6.53. Found: C, 64.97, H, 6.60.

Dimethyl 3-(4'-isobutyl)phenylpropanedioate (18). A soln. of diester **14** (1.08 g, 3.9 mmol) in ethanol (15 mL), which contained 50 μL of $HClO_4$, was hydrogenated under pressure (4 bar) at 25 °C, in the presence of 10% Pd/C as catalyst. When the reaction was completed (6 h, GC monitoring), ethanol was removed under vacuum, the residue was redissolved in ^{t}BuOMe and filtered over Celite®. The residue obtained after elimination of solvent was characterized as diester **18** (1.0 g, 98% yield). **18**: IR film: 2954, 1758, 1739, 1147 cm^{-1}; ^1H NMR: δ 7.29 (d, 2 H, J = 8 Hz, H-2', H-6'), 7.13 (d, 2 H, J = 8 Hz, H-3', H-5'), 4.62 (s, 1 H, H-2), 3.74 (s, 6 H, OCH_3), 2.45 (d, 2 H, J = 7 Hz, CH_2), 1.85 (n, 1 H, J = 7 Hz, H-2"), 0.89 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR : δ 168.6 (COO), 141.8 (C-4'), 129.7 (C-1'), 129.3, 128.8 (C-2', C-3', C-5', C-6'), 57.1 (C-2), 52.7 (OCH_3), 45.0 (CH_2), 30.1 (C-2"), 22.3 (C-3"); MS, m/z: 264 (M^+, 58), 221 (82), 205 (61), 177 (81), 162 (90), 131 (100). Anal. calcd. for $C_{15}H_{20}O_4$: C, 68.15, H, 7.64. Found: C, 68.39, H, 7.77.

Methylation of arylated β-dicarbonyl derivatives. General procedure: A soln. of the appropriate arylated β-dicarbonyl derivative (**2-4, 12-14**) in anhydrous THF was added to a suspension of potassium *tert*-butoxide (40% molar excess) in the same solvent and the mixture was stirred for 15 min at 25 °C in an inert atmosphere. Then methyl iodide (10% molar excess) was added to the mixture and stirring was prolonged under the same conditions until maximum conversion of the starting compound was achieved (GC monitoring). The crude reaction mixture was poured into 1 N HCl soln., extracted with ^{t}BuOMe and dried. The residue obtained after elimination of solvent was purified by flash chromatography with hexane:^{t}BuOMe mixtures to obtain the corresponding methylated product.

3-Methyl-3-(3'-benzoyl)phenylpentane-1,3-dione (5). This compound was obtained from **2** (0.200 g, 0.7 mmol) in 26% yield (0.051 g). A 25% of unreacted **2** was also isolated. **5**: IR (film): 3075, 2975, 1716, 1702, 1660, 1280, 717 cm^{-1}; ^1H NMR: δ 7.86 - 7.40 (9 H, H_{Ar}); 2.16 (s, 6 H, $COCH_3$), 1.85 (s, 3 H, C-CH_3); ^{13}C NMR: δ 206.2 ($COCH_3$), 195.9 (COAr), 138.2, 138.1 (C-1', C-3'), 137.2 (C-1"), 132.6 (C-4"), 131.6 (C-6'), 129.9 (C-2", C-6"), 129.5 (C-2'), 128.7, 128.6 (C-4', C-5'), 128.3 (C-3", C-5"), 70.1 (C-CH_3), 27.2 ($COCH_3$), 19.6 (C-$\underline{C}H_3$); MS, m/z: 252 (M^+-42, 64), 147 (42), 105 (100), 77 (77). Anal. calcd. for $C_{19}H_{18}O_3$: C, 77.52, H, 6.17. Found: C, 77.55, H, 6.18.

Methyl 2-methyl-3-oxo-2-(3'-benzoyl)phenylbutanoate (6). This compound was obtained from **3** (0.100 g, 0.33 mmol) in 35% yield (0.035 g). A 20% of unreacted **3** and a 10% of a product which was identified as the methyl ester of ketoprofen by comparison with a standard, were also isolated. **6**: IR (film): 3065, 2953, 1741, 1716, 1660, 1282, 1253, 714 cm^{-1}; ^1H NMR δ 7.90-7.40 (9 H, H_{Ar}), 3.79 (s, 3 H,

OCH_3), 2.14 (s, 3 H, $COCH_3$), 1.83 (s, 3 H, C-CH_3); ^{13}C NMR: δ 203.9 ($COCH_3$), 196.1 (COAr), 172.0 (COO), 138.6 (C-1'), 137.9 (C-3'), 137.3 (C-1"), 132.6 (C-4"), 131.5 (C-6'), 130.0 (C-2", C-6"), 129.4 (C-2'), 128.9 (C-4'), 128.5 (C-5'), 128.3 (C-3", C-5"), 64.6 (C-CH_3), 52.7 (OCH_3), 26.9 ($COCH_3$), 21.1 (C-CH_3); MS, m/z: 268 (M^+-42, 61), 236 (99), 131 (27), 105 (100), 77 (56). Anal. calcd. for $C_{19}H_{18}O_4$: C, 73.52, H, 5.86. Found: C, 73.47, H, 5.97.

Dimethyl 2-methyl-2-(3'-benzoyl)phenylpropanedioate (7). This compound was obtained from **4** (0.100 g, 0.32 mmol) in 80% yield (0.080 g). **7**: IR (film): 3100, 2952, 1731, 1660, 1282, 1259, 715 cm^{-1}; ^1H NMR: δ 7.90-7.30 (9 H, H_{Ar}), 3.77 (s, 6 H, CH_3), 1.91 (s, 3 H, C-CH_3); ^{13}C NMR: δ 196.1 (COAr), 171.5 (COO), 138.5 (C-1'), 137.5 (C-3'), 137.4 (C-1"), 132.4 (C-4"), 131.5 (C-6'), 130.1 (C-2'), 130.0 (C-2", C-6"), 129.4 (C-4'), 128.4 (C-5'), 128.2 (C-3", C-5"), 58.8 (C-CH_3), 52.9 (OCH_3), 22,2 (C-CH_3); MS, m/z: 326 (M^+, 17), 282 (26), 267 (23), 239 (25), 207 (31), 105 (100), 77 (63). Anal. calcd. for $C_{19}H_{18}O_5$: C, 69.92, H, 5.57. Found: C, 70.04, H, 5.63.

3-Methyl-3-(4'-isobutyryl)phenylpentane-1,3-dione (15). This compound was obtained from **12** (0.120 g, 0.48 mmol) in 48% yield (0.058 g). **15**: IR (film): 2974, 1718, 1703, 1681, 1353, 1226, 981 cm^{-1}; ^1H NMR: δ 7.99 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 7.35 (d, 2 H, J = 8.5, Hz, H-2', H-6'), 3.55 (hp, 1 H, J = 7 Hz, CH), 2.14 (s, 6 H, $COCH_3$), 1.83 (s, 3 H, C-CH_3), 1.22 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 206.2 ($COCH_3$), 203.6 (COAr), 142.5 (C-1'), 135.5 (C-4'), 128.7, 127.8 (C-2', C-3', C-5', C-6'), 70.1 (C-CH_3), 35.5 (CH), 27.3 ($COCH_3$), 19.5 (C-CH_3), 19.0 (C-3"); MS, m/z: 218 (M^+-42, 32), 175 (100); Anal calcd. for $C_{16}H_{20}O_3$: C, 73.82, H, 7.76. Found: C, 73.70, H, 7.80.

Methyl 2-methyl-3-oxo-2-(4'-isobutyryl)phenylbutanoate (16). This compound was obtained from **13** (0.120 g, 0.45 mmol) in 23% yield (0.027 g). **16**: IR (film): 2972, 1741, 1716, 1683, 1251, 1228, 981 cm^{-1}; ^1H NMR: δ 7.96 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 7.39 (d, 2 H, J = 8.5 Hz, H-2', H-6'), 3.80 (s, 3 H, OCH_3), 3.54 (hp, 1 H, J = 7 Hz, CH), 2.13 (s, 3 H, $COCH_3$), 1.81 (s, 3 H, C-CH_3), 1.21 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 203.9, 203.7 (COAr, $COCH_3$), 171.8 (COO), 142.9 (C-1'), 135.4 (C-4'), 128.5, 127.7 (C-2', C-3', C-5', C-6'), 64.7 (C-CH_3), 52.8 (OCH_3), 35.4 (CH), 27.1 ($COCH_3$), 21.1 (C-CH_3), 19.0 (C-3"); MS, m/z: 234 (M^+-42, 59), 191 (100), 159 (41). Anal. calcd. for $C_{16}H_{20}O_4$: C, 69.55, H, 7.30. Found: C, 69.43, H, 7.39.

Dimethyl 3-methyl-3-(4'-isobutyryl)phenylpropanedioate (17). This compound was obtained from **14** (0.200 g, 0.71 mmol) in 75% yield (0.150 g). **17**: IR (film): 2972, 1735, 1683, 1257, 1228, 1112, 981 cm^{-1}; ^1H NMR: δ 7.94 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 7.45 (d, 2 H, J = 8.5 Hz, H-2', H-6'), 3.78 (s, 6 H, OCH_3), 3.54 (hp, 1 H, J = 7 Hz, CH), 1.90 (s, 3 H, C-CH_3), 1.21 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 203.8, (COAr), 171.3 (COO), 142.8 (C-1'), 135.3 (C-4'), 128.1, 127.6 (C-2', C-3', C-5', C-6'), 58.8 (C-CH_3), 53.0 (OCH_3), 35.3 (CH), 22.2 (C-CH_3), 19.0 (C-3"); MS, m/z: 249 (M^+-42, 100), 190 (18). Anal. calcd. for $C_{16}H_{20}O_5$: C, 65.73, H, 6.91. Found: C, 65.77, H, 6.97.

Dimethyl 3-methyl-3-(4'-isobutyl)phenylpropanedioate (19). This compound was obtained as an oil from **18** (0.100 g, 0.37 mmol) in 83% yield (0.083 g). **19**: IR (film): 2952, 1737, 1257, 1110 cm^{-1}; ^1H NMR: δ 7.24 (d, 2 H, J = 8.5 Hz, H-2', H-6'), 7.11 (d, 2 H, J = 8.5 Hz, H-3', H-5'), 3.75 (s, 6 H, OCH_3), 2.45 (d, 2 H, J = 7 Hz, CH_2), 1.86 (s, 3 H, C-CH_3), 1.86 (n, 1 H, J = 7 Hz, CH), 0.90 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 172.1 (COO), 141.4 (C-4'), 135.3 (C-1'), 128.9, 126.9 (C-2', C-3', C-5', C-6'), 58.4 (C-CH_3), 52.7 (OCH_3), 44.9 (CH_2), 30.1 (CH), 22.3 (C-CH_3), 22.3 (C-3"); MS, m/z: 278 (M^+, 23), 219 (100), 191 (40), 159 (70). Anal. calcd. for $C_{16}H_{22}O_4$: C, 69.02, H, 7.98. Found: C, 69.11, H, 8.02.

Ketoprofen (8). A soln. of diester **7** (25 mg, 76 μmol) in THF (100 μL) was treated with 10 N KOH (200 μL) for 24 h at 25 °C. The crude reaction mixture was acidified with 18 N H_2SO_4, stirred for 5 min, diluted with H_2O and extracted with AcOEt. The residue obtained after the elimination of solvents afforded pure racemic acid **8** (18 mg, 95% yield), which was identified by comparison with an authentic standard.

Ibuprofen (20). By using the same procedure described above for acid **8**, diester **19** (10 mg, 35 μmol) was hydrolyzed and decarboxylated to give pure racemic acid **20** (6.5 mg, 88%), which was identified by comparison with an authentic standard.

[2-$^2H_3$]Ketoprofen (8d): one pot operation from diester 4. Following the methylation procedure described above, [$^2H_3$-methyl] iodide (48 μL, 0.76 mmol) was added to a suspension of diester **4** (0.20 g, 0.64 mmol) and potassium *tert*-butoxide (0.14 g, 1,28 mmol) in THF (2 mL), and the mixture was stirred under an inert atmosphere for 30 min at 25 °C. Then, the mixture was treated with 10 N KOH (3 mL) for

20 h at the same temperature, followed by acidification with 18 N H_2SO_4 (1.5 mL). After 5 min of stirring, the crude reaction mixture was basified with Na_2CO_3 satd. soln. and washed with AcOEt. The aqueous phase was acidified with 1N HCl, extracted with AcOEt and dried. The residue obtained after elimination of solvent contained the expected deuterated acid **8d** as a pure colorless solid (0.145 g, 90% overall yield). **8d**: IR (film): 3163, 3075, 2925, 1706, 1658, 1284 717 cm^{-1}; ^1H NMR: δ 11.22 (br.s, 1 H, COOH), 7.90-7.40 (9 H, H_{Ar}), 3.81 (s, 1 H, CH); ^{13}C NMR: δ 196.4 (COAr), 180.1 (COOH), 140.0 (C-1'), 137.7 (C-3'), 137.2 (C-1"), 132.5 (C-4"), 131.6 (C-2'), 130.0 (C-2", C-6"), 129.3 (C-4'), 129.2 (C-6'), 128.5 (C-5'), 128.2 (C-3", C-5"), 45.1 (CH); MS, m/z: (as methyl ester): 271 (M^+, 31), 212 (100), 194 (36), 105 (82), 77 (63).

[2-$^2H_3$]Ibuprofen (20d): one pot operation from diester 18. Following the procedure described above for acid **8d**, diester **18** (0.10 g, 0.37 mmol) was methylated with [$^2H_3$-methyl] iodide, saponified and decarboxylated to give the pure acid **20d** (0.085 g, 85% overall yield) as a colorless solid. **20d**: IR (film): 2954, 2638, 1706 cm^{-1}; ^1H NMR: δ 7,21 (d, 2 H, J = 8 Hz, H-2', H-6'), 7.09 (d, 2 H, J = 8 Hz, H-3', H-5'), 3.68 (s, 1 H, H-2), 2.43 (d, 2 H, J = 7 Hz, CH_2), 1.84 (n, 1 H, J = 7 Hz, H-2"), 0.88 (d, 6 H, J = 7 Hz, H-3"); ^{13}C NMR: δ 181.1 (COOH), 140.8 (C-1'), 136.8 (C-4'), 129.3 (C-2', C-6'), 127.2 (C-3', C-5'), 45.0 (C-2), 44.7 (CH_2), 30.1 (C-2"), 22.3 (C-3"); MS, m/z: (as methyl ester): 223 (M^+, 30), 180 (23), 164 (100), 121 (18).

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