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A convenient synthesis of 2-fluoro-α-methyl[1,1′-biphenyl]-4-acetic acid via rearrangement of aryl ketones

A V Pol, A Sudalai* & H R. Sonawane

Division of Organic Chemistry, National Chemical Laboratory, Pune 411 008, India

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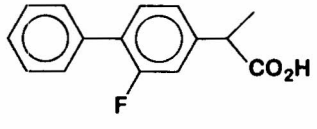
The rearrangement of various *meta*-substituted *p*-cyclohexyl aryl ketones has been investigated with the objective to develop a convenient route for the synthesis of 2-fluoro-α-methyl [1,1′-biphenyl-4-acetic acid [(±) -flurbiprofen], a potent anti-inflammatory agent of current importance.

2-Arylpropanoic acids, a type of non-steroidal antiinflammatory drug currently used for controlling the pain and inflammation of rheumatic disease[1], inhibit cyclooxygenase system and thus stop the arachidonic acid cascade to prostaglandins and thromboxane A_2. They are also effective as analgesics and antipyretics and marketed and consumed as racemic mixtures except (+) - (*S*) - naproxen and (+) - (*S*) - flunoxaprofen. Among the various methods reported[2] so far to prepare 2-arylpropanoic acids, the aryl migration methods of propiophenones seemed attractive due to their improved yield, specificity and easy working. The synthesis of flubiprofen [2-fluoro-α-methyl-(1,1′-biphenyl)-4-acetic acid] **1**, yet another potent antiinflammatory agent of current importance has attracted considerable attention[3] due to its unique structural features providing opportunities for development of novel strategies.



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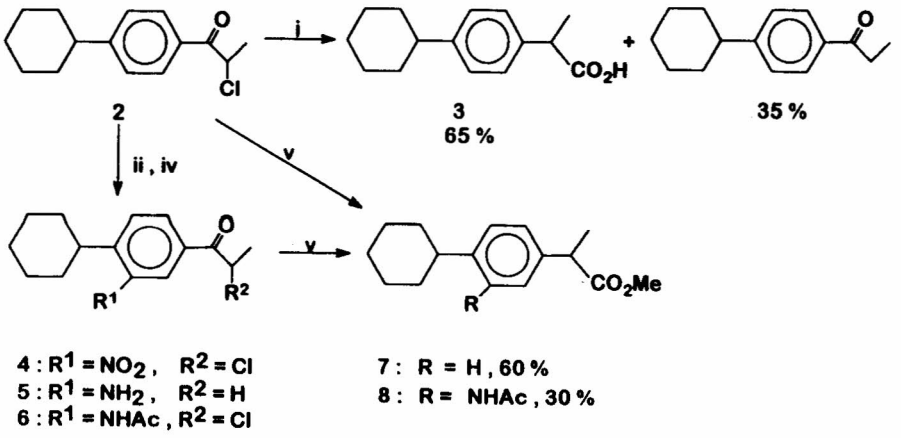
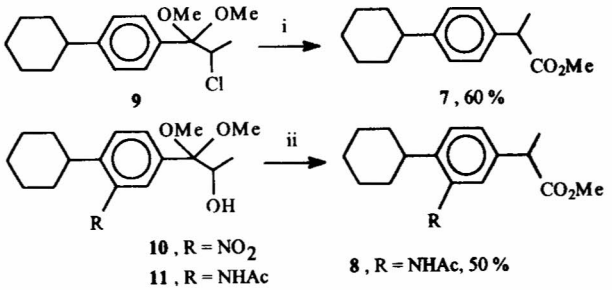
It is observed that most of the information available on the synthesis of flubiprofen is in the form of patents[4]. Moreover, the various synthetic strategies disclosed in the patent literature reveal that an expensive meta fluoro aromatic derivative has been chosen as the starting material which is transformed through multi step sequence of reactions into the target molecule[5]. The key step generally consists of classical aryl coupling via Meerwein reaction of aryl diazo compounds wherein generally the yields are not satisfactory[6]. Herein, we wish to report a short and an efficient synthesis of **1** via lead tetraacetate-mediated rearrangement of aryl ketones from the easily available starting materials.

Results and Discussion

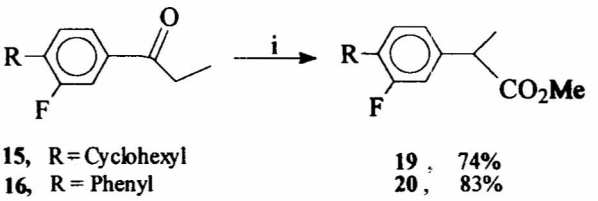
We have recently reported[7] an interesting photochemical transformation of α-chloropropiophenone into 2-arylpropanoic acid as a single step, convenient protocol which has been found to be extremely useful for the preparation of ibuprofen. As a logical extension of this technique, 4-cyclohexyl-α-chloropropiophenone **2** prepared by the Friedel-Crafts acylation of cyclohexylbenzene with α-chloropropionyl chloride (60% yield), was subjected to photochemical rearrangement both in aq. acetone and MeOH as solvent to afford the required acid **3** and ester **7** respectively in 65% and 60% yield along with propiophenone formed by the reductive cleavage of C-Cl bond. This result has prompted us to study the photochemical behaviour of certain *meta*-substituted *p*-cyclohexyl α-chloropropiophenones with the objective to obtain **1**. The desired photosubstrate **6** was prepared in a straight-forward manner viz. nitration of **2** to give the nitroderivative **4** followed by its reduction with Raney alloy[8] to give aminopropiophenone **5**. It may



Scheme I : i) hv, 300 nm, acetone : H_2O (9:1); ii) Fuming HNO_3, AcOH; iii) Raney alloy, AcOH; Ac_2O, Zn; LiCl, CuCl, DMF; v) hv, 300 nm, MeOH.



Scheme II: i) $ZnCl_2$, Tol., Δ; ii) SO_2Cl_2, Et_3N, CH_2Cl_2



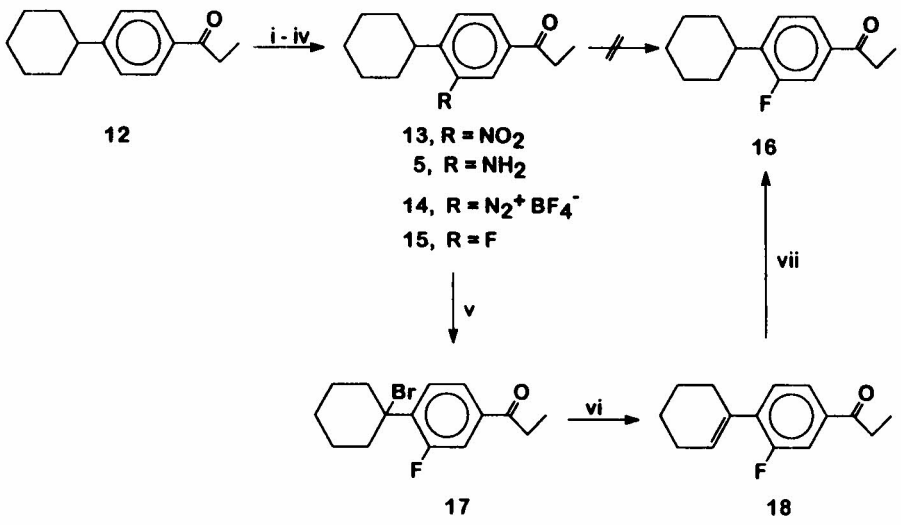
Scheme III: i) $Pb(OAc)_4$, $CH)OMe)_3$, $HClO_4$, 50°C

be noted that during treatment with Raney alloy, simultaneous reduction of C-Cl bond was also observed. Hence, the aminopropiophenone **5** was *N*-acetylated with Ac_2O in the presence of catalytic amount of Zn dust and the *N*-acetate **5a** was subjected to α-chlorination[9] using LiCl and CuCl in DMF to give **6**. Compound **6** was then subjected to photochemical rearrangement at 300 nm in MeOH. It was observed that while the unsubstituted α-chloro-propiophenone **2** gave the rearranged product photochemically in good yield, the corresponding *meta*-substituted (R=NHAc) compound **6** produced the rearranged ester **8** in low yields (30%) along with complex mixtures of other products **(Scheme I)**.

Lewis acid-catalyzed rearrangement of α-arylpropanoic acids has been established as one of the practical methods for their large scale production[10]. ZnX_2(X=Br, Cl) has been found to be an excellent catalyst in bringing about the rearrangement of α-haloketals. Accordingly, the chloroketal **9** prepared by the ketalizagtion of **2** with MeOH, was subjected to $ZnCl_2$ mediated rearrangement to produce the rearranged ester **7** in 60% yield. Further, the α-hydroxy ketal such as **11** (R=NHAc), prepared in two steps of reduction of nitrocompound **10** with Raney alloy[8] followed by its acetylation, underwent rearrangement with SO_2Cl_2 - Et_3N conditions[11] to afford the ester **8** in 50% yield **(Scheme II)**.

Since both the photochemical and Lewis acid mediated rearrangement routes gave the esters **7** and **8** in moderate yields, we turned our attention to another attractive methodology[12] explored to bring about the desired rearrangement based upon the reaction of propiophenones with lead tetraacetate and trimethyl orthoformate **(Scheme III)**

Accordingly, ketone **12**, obtained by the Friedel-Crafts acylation of cyclohexylbenzene with propionyl chloride, was nitrated with fuming HNO_3 to produce the *meta*-nitro derivative **13** in 76% yield, followed by its reduction with Raney alloy[8] in aq.AcOH to afford the corresponding amine **5**. On diazotization with 40% HBF_4, the amino derivative **5** gave a diazofluoroborate salt **14** in 79% yield



Scheme IV: i) Fuming HNO_3, AcOH; ii) Raney alloy, AcOH; iii) 40% HBF_4, $NaNO_2$; iv) Tol., Δ; v) NBS, CCl_4; vi) LiBr, Li_2CO_3, DMF, 150°C; vii) 5% Pd/C, 200°C, N_2

(m.p. 75°C). It was then decomposed by refluxing with toluene to produce the fluoro derivative **15** in 44% yield. Direct aromatization of **15** with either S or Pd/C at elevated temperature (250-280°C) did not furnish the corresponding biphenyl derivative **16**. Therefore, a recourse to two-step protocol was employed. It consists of benzylic bromination with NBS followed by dehydrobromination[13] with LiBr-Li_2CO_3 to give **18** almost in quantitative yield. The aromatization was then accomplished by heating the olefinic compound **18** with Pd/C (5%, w/w) in N_2 atmosphere to afford the fluorobiphenylketone **16** in 60% yield **(Scheme IV)**.

The transformation of the ketones **15** and **16** was smoothly brought about by reacting with lead tetraacetate in trimethyl orthoformate catalyzed by perchloric acid[12] to produce the methyl esters **19** and **20** in 74% and 83% yield respectively **(Scheme III)**. Finally, alkaline hydrolysis of ester **20** furnished flurbiprofen **1**. The synthetic material was in complete agreement in its m.p. with the reported values[14] of the flurbiprofen.

In summary, we have shown that among the four rearrangement methods employed here, the lead tetraacetate-mediated 1,2-aryl shift of 2-fluorobiphenylpropanone **16** as well as its corresponding hexahydroderivative **15** was quite successful and resulted in excellent yields of the corresponding rearranged esters, thereby providing an excellent method for the straight-forward synthesis of flurbiprofen **1**.

Experimental Section

All mps reported are uncorrected. IR spectra were recorded as neat or nujol mulls (in the case of solid samples) on Perkin-Elmer Infrared model 137-E, ^1H NMR spectra on a Varian FT 80A, T-60, Bruker FT 90, 200 MHz instruments, ^{13}C NMR on a Bruker 50.3 MHz instrument (chemical shifts in δ, ppm using TMS as internal standard) and mass spectra (MS) on an automated Finnigan MAT 1020 C mass spectrometer using ionization energy of 70 eV.

2-Chloro-1-[4-(cyclohexylphenyl)]-1-propanone 2. To a stirred mixture of anhyd. aluminium chloride (40 g; 0.3 mol) and ethylene dichloride (EDC) (70 mL) was added a mixture of cyclohexylbenzene (40 g; 0.25 mol) and α-chloropropionyl chloride (35 g; 0.28 mol) in EDC (70 mL) at 0-5°C during 1 hr. The mixture was stirred for 2 hr more at 5-10°C and poured into ice water, extracted with chloroform (200 mL × 3). The organic layer was washed with water, brine and dried over Na_2SO_4. The crude product weighed 39 g. It was recrystallized from pet. ether, m.p. 74-75°C; IR (nujol) : 1700, 1615, 1580, 1460, 1390, 1270, 970 and 850 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.63 (3H, d, *J*=10 Hz, CH_3), 1.25-1.9 (10H, m, cyclohexyl), 2.5 (1H, bs benzylic-H), 5.2 (1H, q, *J*=6 Hz, CH), 7.2 (2H, d, *J*=10 Hz, Ar-H), 7.9 (2H, d, *J*=10 Hz, Ar-H) (Found: C, 71.30; H, 7.44. $C_{15}H_{19}ClO$ requires C, 71.85; H, 7.58%).

Photochemical reaction of 2-chloro-1-[4-(cyclohexylphenyl)]-1-propanone 2. Compound **2** (1.095 g) was subjected to irradiation in 90% acetone : water mixture (50 mL), at 300 nm for 20 hr till no further change using propylene oxide as acid scavenger. The acetone was removed and the residue was extracted with ethyl acetate. The ethyl acetate extract was washed with bicarbonate sol. which was acidified to furnish the acid **3** (0.660 g; 65%). The acid **3** was recrystallized from aq. MeOH, m.p. 98-102°C; IR (nujol) : 1710 (C=O), 1447, 1380, 1230 and 950 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.60(3H, d, *J*=8 Hz, CH_3), 1.46-1.91 (10H, m, cyclohexyl), 2.55 (1H, bs, benzylic-H), 3.8 (1H, q, *J*=4 Hz, CH), 7.38 (5H, m, Ar-H). (Found : C, 71.3; H, 7.42. $C_{15}H_{19}ClO$ requires: C, 71.8; H, 7.58%)

When compound **2** was subjected to photochemical rearrangement(300 nm, for 20 hr) in MeOH as solvent, the corresponding ester **7** was obtained in 60% yield. IR (nujol) : 1720, 1447, 1380, 1230 and 950 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.6(3H, d, *J*=8 Hz, CH_3), 1.46-1.91 (10H, m, cyclohexyl), 2.55 (1H, brs, benzylic H), 3.60 (3H, s, OMe), 3.80 (1H, q, *J*=4 Hz, CH), 7.38 (5H, m, ArH).

2-Chloro-1-(3-nitro-4- cyclohexylphenyl)-1-propanone 4. To a stirred mixture of **2** (15 g; 0.06 mol) in gl. acetic acid (35 mL) was added fuming nitric acid (d 1.5 mL) at −5 to 0°C in 1.5 hr. The mixture was stirred for 2h more at 0°C and poured onto icewater. The crude mass was then passed through a short column of celite + silica gel and eluted with pet. ether to yield a syrupy liquid (11.8 g; 67%); IR (neat) : 1700, 1620, 1540 (NO_2) 1450, 1350 (NO_2), 1250, 1200, 1070 and 750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) : δ 1.73 (3H, d, *J*=10 Hz, CH_3), 1.3-1.8 (10 H, m, cyclohexyl), 3.0 (1H, bs, benzylic-H), 5.15 (1H, q, *J*=6 Hz, CH), 7.6 (1H, d, J=10 Hz, Ar-H), 8.15 (1H, dd, *J*=10 and 2 Hz, Ar-H), 8.3 (1H, d, *J*=2 Hz, Ar-H) (Found: C, 60.82; H, 6.12. $C_{15}H_{18}ClNO_3$ requires C, 60.91; H, 6.09%).

1-(3-Amino-4- cyclohexylphenyl)-1-propanone 5. A mixture of nitro compound **4** (6.19 g; 0.02 mol) and Raney alloy (18.5 g) in AcOH-H_2O (1:1, 90 mL) was gently refluxed for 5 hr, cooled and filtered to remove the alloy which was washed with EtOH. The combined filtrate and washings were concentrated at reduced temperature and pressure. The residue was then extracted with ethyl acetate (50 mL × 3). Evaporation of solvent gave a dehalogenated amino product **5** (4.70 g, 97%), m.p. 80-81°C; IR (nujol) : 3550 and 3450 (N-H), 1690 (C=O), 1620, 1480 and 1380 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.2 (3H, t, *J*=7 Hz, CH_3), 1.37-1.86 (10H, m, cyclohexyl), 2.46 (1H, bs, benzylic-H), 2.91 (2H, q, *J*=6 Hz, CH_2), 3.6 (2H, bs, NH_2 exchangeable with D_2O), 7.06-7.33 (3H, m, Ar-H); MS : m/z (rel. intensity): 232 (M^+ + 1,8), 231(M^+, 56), 216 (4), 202 (100), 187 (37), 175 (8), 132 (17), 106 (9) and 91 (7) (Found: 77.42; H, 8.92. $C_{15}H_{21}NO$ requires C, 77.92; H, 9.09%).

The above amino compound **5** (2.73 g; 0.0118 mol) was acetylated with Ac_2O in the presence of catalytic amount of Zn dust to give a crude *N*-acetate **5a**. It was crystallized from EtOH, m.p. 162-65°C (1.72 g; 53%); IR (nujol) : 3250 (NH), 1690 (C=O), 1665, 1610, 1460, 800 and 620 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.22(3H, t, *J*=7 Hz CH_3), 1.28-1.51 (5H, m, cyclohexyl), 1.62-2 (5H, m, cyclohexyl), 2.22 (3H, s, $COCH_3$), 2.58 (1H, bs, benzylic -H), 2.91 (2H, q, *J*=6 Hz, CH_2), 7.27 (1H, d, *J*=10 Hz, Ar-H), 7.76 (1H, dd, *J*=10 Hz and 2Hz), 8.11 (1H, d, *J*=2 Hz, Ar-H). MS : m/z (rel. intensity): 273 (M^+, 28), 258 (8), 245 (14), 244 (84), 231 (15), 217 (14), 216 (15), 202 (37), 188 (17), 187 (100), 132 (19), 121 (27), 91 (19).

2-Chloro-1(3-acetamido-4-cyclohexylphenyl)-1-propanone 6. A mixture of *N*-acetate **5a** (1.5 g; 0.005 mol), lithium chloride (0.4 g) and cupric chloride (2.41 g) in dry dimethyl formamide (15 mL) was heated at 100-105°C for 5 hr. It was then cooled, acidified with 2 *N* HCl (30 ml) and extracted with ethyl acetate (25 mL × 3). On evaporation gave the crude mass, which was purified by passing through a column of silica gel and eluting with pet. ether and $CHCl_3$ mixture to get chloro compound **6** (1.30 g; 84%), m.p. 164-65°C; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.73 (3H, d, J=10 Hz, CH_3), 1.24-1.55 (5H, m, cyclohexyl), 1.64-1.93 (5H, m, cyclohexyl), 2.2 (3H, s, $COCH_3$), 2.6 (1H, bs, benzylic-H), 5.18 (1H, q, *J*=6 Hz, CH), 7.31 (1H, d, *J*=10 Hz, Ar-H), 7.73 (1H, dd, *J*=10 Hz and 2 Hz, Ar-H), 8.11 (1H, d, *J*=2 Hz, Ar-H) (Found: C, 66.01; H, 7.01. $C_{17}H_{22}ClNO_2$ requires C, 66.34; H, 7.15%).

Photolysis of 2-chloro-1-(3-acetamido-4-cy-

clohexyl)-1-propanone 6. Compound **6** (1.2 g; 0.003 mol) was subjected to photolysis in a Ryonate chamber at 254 nm in methanol (100 mL) using propylene oxide (5 mL) as an acid scavanger, for 11 hr till no further change. The solvent was stripped off and the crude product was extracted with ethyl acetate. After drying over Na_2SO_4 and passing through column chromatography yielded the corresponding ester of aryl propionic acid **8** (0.310 g; 30%) as a syrupy liquid; IR (neat) : 3240 (NH), 1740 (ester C=O), 1680 ($NHCOCH_3$), 1540, 1220 and 780 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) : δ 1.46 (3H, d, *J*=10 Hz, CH_3), 1.15-1.51 (5H, m, cyclohexyl-H), 1.55-1.91 (5H, m, cyclohexyl-H), 2.16 (3H, s, $COCH_3$), 2.55 (1H, bs, benzylic-H), 3.6 (3H, s, OCH_3), 3.61 (1H, q, *J*=3 Hz, CH), 7.04-7.53 (4H, m, Ar-H and NH); MS: m/z (rel. intensity): 304 (M^++ 1, 17), 303 (M^+, 84), 288 (45), 261 (26), 260 (56), 244(53), 243 (53), 216 (41), 201 (34), 200 (100), 192 (62), 185 (56), 176 (36), 174 (48), 158 (82), 146 (59), 144 (85), 132 (62), 130 (62), 120 (62), 89 (81), 69 (63).

Chloroketal of 2-chloro-1-(4-cyclohexylphenyl)-1-propanone 9. A mixture of 2-chloroketone **2** (2.5 g, 0.01 mol), trimethyl orthoformate (3 mL, 0.03 mol) and methanesulphonic acid (0.1 g) in dry methanol (15 mL) was stirred at reflux temperature for 24 hr. It was then poured with stirring into a saturated aqueous solution of sodium carbonate (25 mL) and extracted with ether (30 mL × 3). The combined ether extract was washed with sodium bicarbonate solution and dried (Na_2SO_4). The solvent was distilled off and the residue (3 g) was passed through a column of neutral alumina using pet. ether for elution to yield chloroketal **9** (2.55 g, 87%), m.p. 71-73°C; IR (nujol) : 1620, 1530, 1460, 1390, 1350, 1190, 1140, 1100, 980 and 840 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.29 (3H, d, *J*=10 Hz, CH_3), 1.24-1.44 (5H, m, cyclohexyl), 1.60-2.00 (5H, m, cyclohexyl), 3.18 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 4.33 (1H, q, *J*=7 Hz, CH), 7.24 (2H, d, *J*=10 Hz, Ar-H), 7.44 (2H, d, *J*=10 Hz, Ar-H).

Zinc chloride catalyzed reaction of chloroketal 9. A mixture of the chloroketal **9** (1 g; 0.0033 mol) and freshly fused zinc chloride (1 g) in toluene (10 mL) was refluxed under nitrogen atmosphere for 6 hr. After cooling to room temperature, the reaction mixture was poured into ice water (75 mL) and extracted with ether (30 mL × 3). After work-up, crude ester was distilled to give **7** as a colourless liquid, b.p. 180°/15 mm (0.67 g; 60%) (*vide supra* photochemical reaction).

Hydroxyketal of 2-chloro-1-(3-nitro-4-cyclohexylphenyl)-1-propanone 10. A mixture of nitro compound **4** (2.64 g; 0.009 mol), trimethyl orthoformate (3 mL) and methane sulphonic acid (0.1 mL) in dry methanol (10 mL) was refluxed for 48 hr. It was then poured into saturated sodium bicarbonate solution (35 mL) and extracted with ether (50 mL × 3). The crude product after work-up and purification by column chromatography on neutral alumina and eluting with pet. ether afforded nitrochloroketal **4a** (1.010 g; 29%), m.p. 90-92°C; IR (nujol) : 1540 (NO_2), 1475, 1460, 1395 (NO_2), 1070 and 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (3H, d, *J*=8 Hz, CH_3), 3.05 (1H, m, benzylic-H) 3.25 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 4.45 (1H, q, *J*=7 Hz, CH), 7.4 (1H, d, *J*=8 Hz, Ar-H), 7.7 (1H, dd, *J*=8 Hz and 2 Hz, Ar-H), 7.85 (1H, d, *J*=2 Hz, Ar-H).

A mixture of nitro compound **4** (0.997 g; 0.0033 mol) and sodium methoxide [prepared from Na (0.15 g) and MeOH (8 mL)] in methanol (10 mL) was refluxed with stirring for 8 hr. The solvent was removed and the residue was extracted with CH_2Cl_2. On distillation, hydroxyketal **10** was obtained as a syrupy liquid (0.805 g; 73%); IR (neat) : 3450 (OH), 1460, 1010, 950 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 0.96 (3H, d, J=10 Hz, CH_3), 1.17-1.55 (5H, m, cyclohexyl), 1.68-2.08 (5H, m, cyclohexyl), 2.36 (1H, bs, benzylic-H), 3.24 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 4.11 (1H, q, *J*=6 Hz, CH), 7.34 (1H, d, *J*=10 Hz, Ar-H), 7.57 (1H, dd, *J*=10 Hz and 2 Hz, Ar-H), 7.8 (1H, d, *J*=2 Hz, Ar-H).

Hydroxyketal of 2-chloro-1-(3-acetamido-4-cyclohexylphenyl)-1-propanone 11. To a solution of sodium methoxide [prepared from Na (0.3 g) and MeOH (10 mL)] in methanol (10 mL) was added a methanolic solution of **6** (1.5 g; 0.0045 mol) in 15 min at room temperature and stirred for 16 hr. After the reaction was complete (TLC), the methanol was distilled off *in vacuo* and the residue was extracted with CH_2Cl_2. After evaporation of solvent pure hydroxyketal **11** was obtained (1.27 g; 77%). m.p. 105-7°C; IR (nujol) : 3260 (NH), 1670, 1050, 900, 835 and 740 cm^{-1}; ^1H NMR (80 MHz,

$CDCl_3$): δ 0.98 (3H, d, *J*=10 Hz, CH_3), 1.24-1.55 (5H, m, cyclohexyl), 1.66-2.00 (5H, m, cyclohexyl), 2.18 (3H, s, $COCH_3$), 2.62 (1H, bs, benzylic-H), 3.22 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 4.06 (1H, q, *J*=2 Hz, CH), 7.04-7.62 (3H, m, Ar-H).

Sulphuryl chloride-triethylamine mediated reaction of hydroxyketal 11. To a mixture of hydroxyketal **11** (1.27 g; 0.0038 mol) and triethylamine (8 mL) in dry CH_2Cl_2 (10 mL) was added a solution of sulphuryl chloride (0.8 g; 0.01 mol) in CH_2Cl_2 (10 ml) at 0-5°C with stirring. The mixture was stirred at room temperature for 16 hr. Saturated sodium bicarbonate solution (25 mL) was added to above mixture and extracted with CH_2Cl_2. The crude product (1.72 g) was purified by column chromatography (SiO_2 gel, EtOAc as eluent), to afford **8** as a syrupy liquid (0.477 g; 44%) (*vide supra*, photochemical reaction).

1-(4-Cyclohexylphenyl)-1-propanone 12. Cyclohexylbenzene (40 g; 0.25 mol) and propionyl chloride (25 g; 0.28 mol) in EDC (200 mL) was added to a stirring solution of $AlCl_3$ (35 g; 0.26 mol) in EDC (250 mL) in 1 hr at 0°C, stirred at 0-5°C for 2 hr more and quenched with ice water and extracted with CH_2Cl_2. On evaporation gave a crude product (50 g) which on crystallization weighed 40 g (75%), m.p. 54-55°C; IR (nujol) : 1690, 1610, 1450, 1420, 1350, 1230, 1190, 1010, 950 and 800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) : δ 1.25 (3H, t, J=6 Hz, CH_3), 1.3-1.6 (5H, m, cyclohexyl-H), 1.62-2.0 (5H, m, cyclohexyl-H), 3.00 (2H, q, *J*=7 Hz, CH_2), 7.3 (2H, d, J=8 Hz, Ar-H) and 7.9 (2H, d, J=8 Hz, Ar-H); MS: m/z (rel. intensity) 216 (M^+, 16), 187 (100), 131 (13), 115 (14), 105 (7), 103 (8), 91 (14), 77 (8) (Found: C, 83.10; H, 9.34. $C_{15}H_{20}O$ requires C, 83.28; H, 9.32%).

1-(3-Nitro-4-cyclohexylphenyl)-1-propanone 13. To a stirring mixture of the ketone **12** (13 g, 0.06 mol) in gl. acetic acid (45 mL) was added fuming nitric acid (108 mL, d=1.5) at -5-0°C during 2 hr. After stirring for another 2 hr at 0°C, the mixture was poured onto ice-water and extracted with CH_2Cl_2 (100 mL × 3). After evaporation of solvent a crude product (20 g) was passed through a short column of silica gel and celite to give nitro compound **13** as a syrupy liquid (12 g; 76%); IR (neat) : 1700, 1620, 1540, (NO_2), 1450, 1350 (NO_2), 1220 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) : δ 1.38 (3H, t, *J*=6 Hz, CH_3), 1.51-1.84, (10 H, m, cyclohexyl CH_2), 2.50 (1H, bs, benzylic-H), 3.0 (2H, q, *J*=7 Hz, CH_2), 7.44 (1H, d, *J*=8 Hz, Ar-H), 8.1-8.25 (2H, m, Ar-H) (Found: C, 68.67; H, 7.0; N, 5.25. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%).

1-(3-Fluoro-⌒4⌒-cyclohexylphenyl)-1-propanone 15. To a solution of aminoketone **5** (0.5 g; 0.002 mol) in THF (1 mL) was added a 40% solution of fluoroboric acid (2.2 mL) at 0°C. Sodium nitrite solution (0.3 g in 2 mL H_2O) was added with stirring, to get a pink coloured solid. The reaction mixture was stirred for 0.5 hr more at 0°C, filtered, the solid was washed with 4% HBF_4 sol. (5 mL), 90:10 :: ether : MeOH sol. (10 mL), finally with ehter (10 mL), dried in a dessicator over KOH pellets to give diazofluoroborate salt **14** (0.570 g; 80%), m.p. 75°C. The solid diazosalt **14** was then added slowly to boiling toluene (10 mL) with stirring when a lot of effervescence was observed, cooled, washed with water, dried (Na_2SO_4), the solvent was removed to yield a crude product (0.420 g). This was then subjected to silica gel column chromatography. A fraction eluted with pet. ether gave almost pure fluoroketone derivative **15** (0.220 g; 44%), b.p. 150°/2-3 mm Hg; IR (neat) : 1690, 1570, 1450, 1430, 1350, 1250 and 800 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) : δ 1.13 (3H, t, *J*=7 Hz, CH_3), 1.21-1.86 (10H, m, cyclohexyl-H), 2.76 (2H, q, *J*=8 Hz, CH_2), 6.83-7.56 (3H, m, Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) : δ 8.1 (CH_3), 26.0, 26.7, 31.7 (all CH_2), 32.8 ($COCH_2$), 37.5 (CH), 114.3, 114.8, 123.8, 123.9, 127.8, 127.9, 136.3, 136.4, 139.7, 140.0, 158.1, 163.0 (all Ar-C), 199.1 (C=O). MS : m/z (rel. intensity): 234 (M^+, 7), 206 (17), 205 (100), 149 (10), 133 (9), 123 (10), 109 (7) (Found : C, 77.06; H, 8.09. $C_{15}H_{19}FO$ requires C, 76.92; H, 8.12%).

1-(3-Fluoro-1′- bromocyclohexylphenyl)-1-propanone 17. A mixture of fluoroketone **15** (0.240 g; 0.001 mol) and *N*-bromo succinimide (0.18 g; 0.001 mol) in carbon tetrachloride (20 mL) was refluxed for 2.5 hr, with catalytic amount of benzoyl peroxide. The reaction mixture was filtered to remove succinimide solids and washed with CCl_4. The filtrate and washings were combined and the solvent distilled off to yield a crude syrupy product which was used further without purification (0.300 g, quantitative); IR (nujol) : 1695, 1570, 1420, 1250, 810 and 720 cm^{-1}; ^1H

NMR (80 MHz, $CDCl_3$): δ 1.2 (3H, t, *J*=6 Hz, CH_3), 1.2-1.8 (10H, m, cyclohexyl-H), 2.9 (2H, q, *J*=7 Hz, CH_2), 7.5 (3H, m, Ar-H); MS : m/z (rel. intensity), M^+ not observed, 233 (24), 232 (24), 205 (71), 204 (23), 203 (100), 175 (19), 165 (20), 146 (20), 133 (25), 122 (15), 105 (16).

1(3-Fluoro-1, 1'-dehydrocyclohexylphenyl)-1-propanone 18. A mixture of bromofluoroketone **17** (0.3 g; 0.001 mol), lithium bromide (0.25 g; 0.0028 mol) and lithium carbonate (0.26 g; 0.0035 mol) in dry dimethylformamide (15 mL) was refluxed under N_2 for 1 hr with stirring. The reaction mixture was then cooled and diluted with water (80 mL) containing AcOH (5 mL). The work-up with ether furnished a crude product 18 (0.320 g; quantitative) as a viscous liquid which was used without purification; IR (neat) : 1690, 1620, 1570, 1500, 1420, 1350, 1250, 1110, 980, 870 and 800 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.09 (3H, t, *J*=7 Hz, CH_3), 1.37-2.37 (10H, m, cyclohexyl-H), 2.81 (2H, q, *J*=6 Hz, CH_2), 5.87 (1H, t, *J*=1 Hz, olefinic-H), 7-7.9 (3H, m, Ar-H); MS : m/z (rel. intensity): 232 (M^+, 26), 205 (43), 204 (20), 203 (100), 175 (20), 146 (16), 133 (14) (Found : C, 77.51; H, 7.28. $C_{15}H_{17}FO$ requires C, 77.58; H, 7.32%).

1-[3-Fluoro-(1, 1'-biphenyl)]-4-yl-1-propanone 16. The dehydrocyclohexyl fluoroketone **18** (0.300 g; 0.00013 mol) and 5% Pd/C catalyst (50 mg) were mixed and heated in oil bath at 180°C for 2 hr under a slow stream of dry N_2, cooled and taken in CH_2Cl_2. The mixture was filtered to remove catalyst and the filtrate was concentrated to dryness to yield a crude product **16** (0.190 g). This was purified by passing through a column of silica gel and eluting with pet. ether to yield a liquid (0.180 g; 60%), b.p. 160°/3-4 mm Hg; ^1H NMR (80 MHz, $CDCl_3$): δ 1.19 (3H, t, *J*=6 Hz, CH_3), 2.9 (2H, q, J=7 Hz, CH_2), 7.12-7.81 (8H, m, Ar-H); MS: m/z (rel. intensity): 228 (M^+, 33), 205 (10), 199 (100), 171 (26), 170 (37); (Found: C, 78.38; H, 5.51. $C_{15}H_{13}FO$ requires C, 78.94; H, 5.70%).

Methyl 2-(3-fluoro-4-cyclohexylphenyl) propionate 19. A mixture of fluoroketone **15** (0.2 g; 0.00085 mol), lead tetraacetate (0.6 g; 0.00135 mol) and 70% perchloric acid (0.2 mL) in trimethyl orthoformate (5 mL) was stirred at room temperature for 24 hr. After removing the trimethyl orthoformate at 100°C *in vacuo*, chloroform (20 mL) was added when a white precipitate of lead diacetate was thrown out. It was removed by filtration, filtrate washed with water, dried and solvent evaporated to yield the corresponding crude aryl propionic ester **19** (0.220 g). This was purified by column chromatography (SiO_2 gel). The compound eluted in a mixture of pet. ether and benzene was pure **19** (0.165 g; 74%), b.p. 160°/2-3 mm Hg; IR (neat): 1750 (COOMe), 1630, 1580, 1510, 1460, 1440, 1260 and 940 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 1.5 (3H, d, *J*=10 Hz, CH_3), 1.2-2 (10H, m, cyclohexyl-H), 2.8 (1H, b, benzylic-H), 3.6 (3H, s, OCH_3), 3.5 (1H, q, J=4 Hz, CH), 6.9 (3H, m, Ar-H); MS : m/z (rel. intensity) 264 (M^+, 24), 236 (9), 205 (100), 180 (20), 161 (23), 149 (40), 138 (15), 135 (18), 133 (16), 123 (39), 109 (18).

Methyl [2-(2-fluorobiphenyl)-4yl]-propionate 20. A mixture of biphenylfluoroketone **16** (0.120 g; 0.0003 mol), lead tetraacetate (0.3 g; 0.006 mol) and 70% perchloric acid (0.1 mL) in trimethyl orthoformate (10 mL) was stirred for 48 hr at room temperature. The excess reagent was removed *in vacuo* at 100°C. To the residue, chloroform (20 mL) was added and the solid lead diacetate was removed by filtration. The filtrate was washed with water till neutral, dried (Na_2SO_4) and the solvent was removed to get a crude product (0.130 g). This was purified (SiO_2 gel column; pet. ether as eluent) (0.113 g; 83%), b.p. 150-160°/4-5 mm Hg; IR (neat) : 1745 (COOMe), 1600, 1420, 1180, 780 and 710 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 1.50 (3H, d, *J*=8 Hz, CH_3), 3.68 (3H, s, OCH_3), 3.69 (1H, q, *J*=4 Hz, CH), 6.94-7.5 (8H, m, Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) : 18.6 (CH_3), 45.1 (CH), 52.3 (OCH_3), 115.2, 115.6, 123.70, 123.75, 127.8, 128.2, 128.6, 129.1, 130.9, 131.0, 135.7, 141.9, 142.1, 157.4 (all Ar-C), 174.6 (C=O); MS : m/z (rel. intensity), 258 (M^+, 18), 228 (8), 205 (8), 200 (14), 199 (100), 183 (10), 178 (12), 170 (20).

2[2-Fluoro-4-biphenyl)-4-yl] propionic acid 1. The biphenylfluoroester **20** (0.04 g; 0.15 mmol) was saponified with alcoholic KOH sol. [KOH (50 mg) in ethanol (10 mL)] for 1 hr on water-bath, ethanol was removed, diluted with water and extracted with ether to remove any neutral material (negligible). The aq. layer was acidified with 6 *N* HCl (*p*H 2) and extracted with ether to give a crude material (0.040 g) which was crystallized from pet. ether to afford a white crystalline com-

pound 1 (0.028 g; 75%), m.p. 104-7°C (lit.[14] m.p. 110°C); IR (nujol) : 1710, 1620, 1580, 1410, 1250, 1070 and 750 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) : δ 1.44 (3H, d, *J*=6 Hz, CH_3), 3.69 (1H, q, *J*=7 Hz, CH), 7-7.5 (8H, m, Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 18.2 (CH_3), 45.1 (CH), 115.4, 123.90, 123.96, 127.9, 128.2, 128.7, 129.18, 129.2, 131.0, 131.1, 135.6, 141.1, 141.3, 157.5, 162.4 (all Ar-C), 186.4 (C=O) (Found : C, 72.78; H, 5.36. $C_{15}H_{13}FO_2$ requires C, 73.77; H, 5.32%).

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