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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
**C07C 57/30, 59/68, 59/84, 51/16, 309/00, 49/76, 211/43**

**A1**

(11) International Publication Number: **WO 98/05623**

(43) International Publication Date: 12 February 1998 (12.02.98)

(21) International Application Number: PCT/EP97/04050

(22) International Filing Date: 25 July 1997 (25.07.97)

(30) Priority Data:
MI96A001683 2 August 1996 (02.08.96) IT

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: A PROCESS FOR THE PREPARATION OF 2-ARYL-PROPIONIC AND 2-ARYL-ACETIC ACIDS STARTING FROM ARYL-OLEFINS

(57) Abstract

A process for the preparation of meta-substituted arylalkanoic acids starting from m-aryl-olefins followed by the Claisen rearrangement and an oxidative cleavage of the formed compound.

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# A PROCESS FOR THE PREPARATION OF 2-ARYL-PROPIONIC AND 2-ARYL-ACETIC ACIDS STARTING FROM ARYL-OLEFINS

The present invention relates to a process for the preparation of meta-substituted arylalkanoic acids starting from m-aryl-olefins.

A number of meta-substituted arylalkanoic acids are known, being pharmaceutically interesting as analgesic, antipyretic and antiinflammatory agents, such as: 2-amino-3-benzoyl-phenylacetic acid (amfenac), 2-(3-phenoxy-phenyl)-propionic acid (fenoprofen), 2-(3-benzoyl-phenyl)-propionic acid (ketoprofen), 2-(2-hydroxy-5-benzoyl-phenyl)-propionic acid, 2-(2-hydroxy-3-benzoyl-phenyl)-propionic acid, 2-(2-amino-5-benzoyl-phenyl)-propionic acid, 2-(4-hydroxybenzoyl-phenyl)-propionic acid, 2-(3-hydroxybenzoyl-phenyl)-propionic acid, 3-(2-hydroxybenzoyl-phenyl)-propionic acid, 2-(4-benzoylamino-phenyl)-propionic acid, 2-(3-benzoyl-4-amino-phenyl-propionic acid), 2-(4-benzoyloxy-phenyl)-propionic acid.

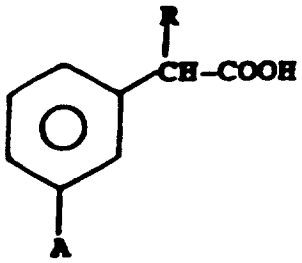
Some of these compounds have a well-established use in therapy; other compounds, such as 2-(2-hydroxy-5-benzoyl-phenyl)-propionic, 2-(2-hydroxy-3-benzoyl-phenyl)-propionic, 2-(4-hydroxy-benzoyl-phenyl)-propionic, 2-(3-hydroxybenzoyl-phenyl)-propionic acids, are examples of non-steroidal antiinflammatories which are metabolites or potential metabolites of ketoprofen.

Ketoprofen is one of the most widely used non-steroidal antiinflammatory agents, with a consumption in the region of hundreds of thousands tons a year. The arrangement of meta-substituents to the aryl-aliphatic residue makes the processes for the total synthesis of

these compounds rather expensive and complex, so that up to now no general procedures suitable for their preparation are known.

The available, more established synthetic procedures involve usually reagents (bromine, cyanides, benzene) and/or carboxylation and alkylation reactions which, although formerly usual, are now undesirable in terms of safety of the workers as well as environmental impact, which is nowadays an exceedingly serious problem.

Now a process has been found for the preparation of meta-substituted arylalkanoic acids of formula

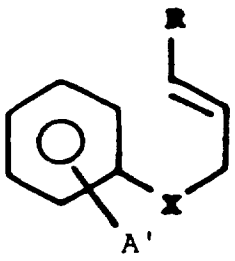



(I)

wherein R is hydrogen or $C_1$-$C_6$ alkyl, A is a $C_1$-$C_4$ alkyl group or aryl, aryloxy or aroyl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy substituents;

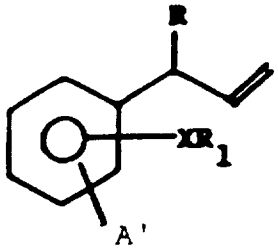
which comprises:

a) Claisen rearrangement of compounds of formula (II):




(II)

in which A' is $C_1$-$C_4$ alkyl group or benzyl, aryl, aryloxy or aroyl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkoxy substituents, and R is as defined above, X is O, S or NH and the A' group is at the ortho or para position to the X-alkylene group, to give a compound of formula




(III)

wherein A' and R are as defined above, $XR_1$ is at the ortho position to the allyl chain and is a OH, $NH_2$ or S($C_3$-$C_{10}$) acyl group;

b) optional elimination of the $-XR_1$ group be means of a dehydroxylation, deamination or desulfuration reaction;

c) oxidative cleavage of the compound (III);

d) elimination of the $-XR_1$, OH or $NH_2$ groups by dehydroxylation or deamination reactions, when not already carried out in step b).

Claisen rearrangement of the compounds of formula II in step a) is effected using conventional conditions, for example using solvents such as hydrocarbons, aromatic hydrocarbons, halo hydrocarbons or mixtures thereof, at a temperature ranging from about 50°C to the solvent's reflux temperature, for times from about 2 to about 10 hours.

The compounds of formula II are known or they can be prepared according to known methods, starting from

suitable phenols, anilines or thiophenols, by reaction with suitable allyl or crotyl halides, in the presence of strong bases and of solvents such as halo hydrocarbons, ethers, aromatic hydrocarbons or mixtures thereof.

The OH or $NH_2$ groups resulting from the Claisen rearrangement at the ortho position to the allyl chain can be removed with conventional methods: in case of amino groups, nitrosation reactions with alkali nitrites will for example be used, followed by decomposition of the diazonium salt in the presence of copper sulfate catalytic amounts. The OH groups, on the other hand, can be removed treating the corresponding trifluoromesylate with formic acid and triethylamine in the presence of palladium acetate/triphenylphosphine complex. Said reactions can be indifferently carried out before or after the double bond degradation reaction to give the carboxylic acid (step c).

The oxidative cleavage of the double bond can be carried out either by means of ozonolysis or using potassium permanganate in phase transfer conditions. During the oxidative cleavage of the double bond in phase transfer conditions with $KMnO_4$, the benzyl group linked to the aromatic ring is oxidized at the same time into the benzoyl group.

On the other hand, when the $XR_1$ group is an S-acyl group, known desulfuration reactions can be effected, for example by means of Raney nickel, but such reactions have to be carried out before the oxidative cleavage of the double bond. The desulfuration reaction can be carried out directly on the S-acyl group, or on the SH

group, resulting from the hydrolysis of the S-acyl group.

Claisen rearrangement of the compounds of formula II in which X is sulfur takes place in the presence of $C_3$-$C_{10}$ fatty acid anhydrides, for example butyric anhydride or higher ones, as described in Tetrahedron Letters 1971, 1969, to give directly the compounds of formula III wherein $R_1$ is an acyl group having 3 to 10 carbon atoms.

Of course, the synthesis of the compound known as amfenac (see above) requires no elimination of the amino group at the ortho position to the allyl chain.

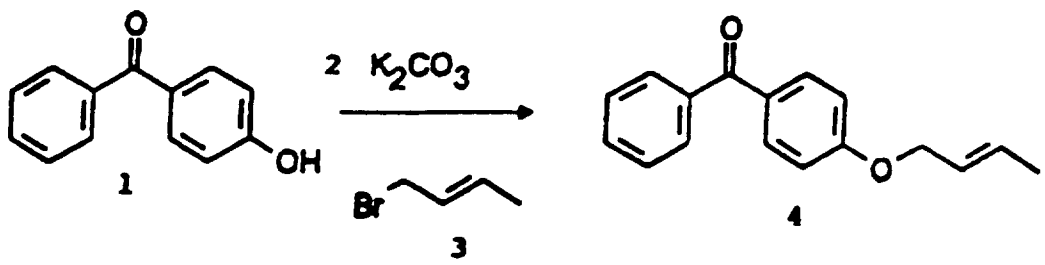
The process of the invention is particularly advantageous from the environmental point of view, allows to obtain the products in very high yields and provides a versatile synthetic procedure, adaptable to a number of meta-substituted arylacetic or arylpropionic acid derivatives of pharmaceutical interest.

The following examples further illustrate the invention.

## EXAMPLE 1

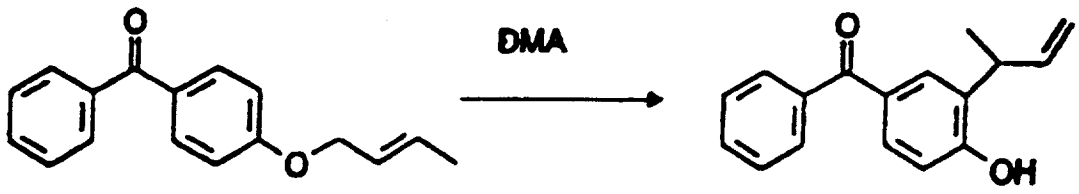
### Preparation of Ketoprofen

a) from 4-hydroxy-benzofenone




Compound 1 (3 g, 15.1 mmoles) was dissolved in 30 ml of acetone, 2 (4.2 g, 30 mmoles) was added

keeping the mixture under stirring. Compound 3 (1.6 ml, 15.5 mmoles) dissolved in 15 ml of acetone was dropped into the mixture, which was kept under stirring at room temperature for 12 hours and subsequently at 40°C for 3 hours. The reaction was complete (TLC control Hexane/EtOAc 8:2). Acetone was evaporated off, the residue was taken up with water (20 ml) and extracted with EtOAc (50 ml). The organic extracts were washed with brine and dried over $Na_2SO_4$, then filtered and the solvent was evaporated off. 3.8 g (15 mmoles) of the product were recovered (pale yellow oil, solid at + 4°C) sufficiently pure to be used in the subsequent reaction. Hexane/EtOAc 7:3. Rf = 0.38.

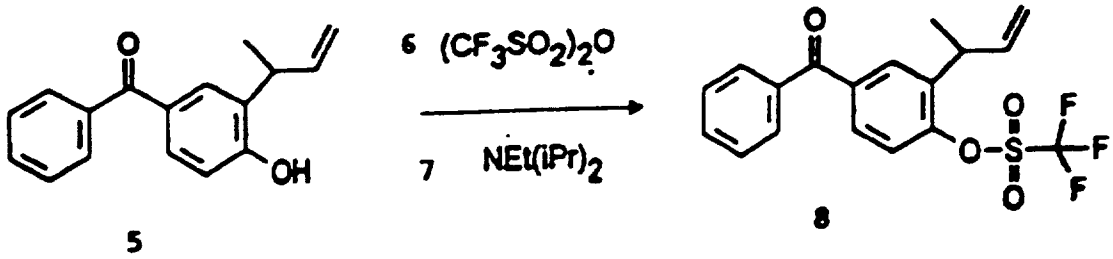



4 5

2.8 g of compound 4 (11.1 mmoles) were dissolved in DMA (dimethylaniline), heating to a temperature of 210° (temperature of the outer oil bath) for 10 hours (2 x 5 hours). The progress of the reaction was controlled by TLC (Hexane/Etoac 7:3) on a sample taken from the mixture and poured into a 2N HCl solution and extracted with EtOAc.

At the end of 10 hours the starting product had almost disappeared; the mixture was worked up as the control samples. The organic extracts were washed first with 2N HCl to remove completely DMA,

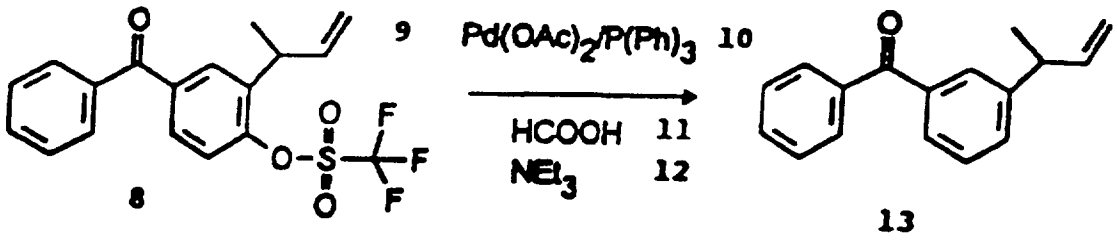
then with brine and dried over $Na_2SO_4$, filtered and the solvent was evaporated off. A crude weighing 2.55 g was obtained, which was purified on a chromatographic column (Hexane/EtOAc 8:2). The resulting product had still a slightly yellow colour which disappeared upon washing with Hexane:EtOAc 7:3. 1.97 g (7.8 mmoles) of a white solid 5 were obtained. Hexane/EtOAc 7:3. Rf = 0.14.



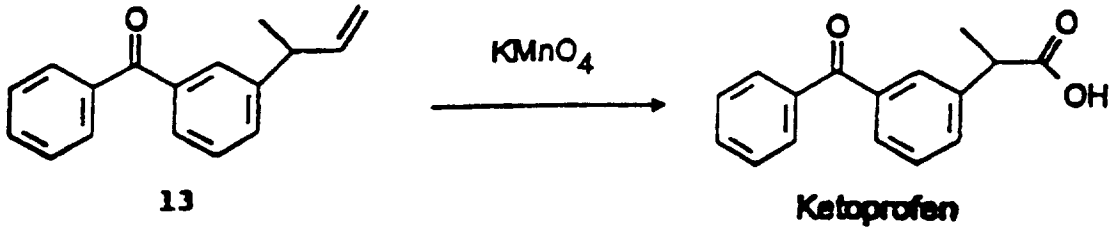

5 8

Compound 5 (1.8 g 7.15 mmoles) was dissolved in 18 ml of dry $CH_2Cl_2$ under argon atmosphere. The mixture was cooled to a temperature of -25°C with an acetone/dry ice mixture. Compound 7 (1.27 ml, 7.3 mmoles) was added, stirring for 30 minutes, then 6 (1.17 ml, 7.15 mmoles) was added in small portions, checking the temperature. The mixture was kept under stirring at -25°C for a further hour, then it was left to warm at room temperature, diluted with ethyl ether and washed with 2N HCl (3 x 10 ml) and with brine (2 x 10 ml). The mixture was then dried over $Na_2SO_4$, filtered and the solvent was evaporated off. 2.5 g of a pale yellow oil 8 were obtained, which was used in the subsequent reaction.

Hexane/EtOAc 95:5, Rf = 0.59




Compound 8 (2.5 g, 6.52 mmoles) was dissolved in 18 ml of DMF, 12 (19.4 ml, 2.7 ml) was added at room temperature and subsequently compounds 9 (57 mg, 0.255 mmoles) and 10 (134 mg, 0.511 mmoles) were added under an argon stream. After that, compound 11 (0.6 g, 13.1 moles) was added in small amounts. Temperature was raised to 60°C for 1 hour. The solution changed colour to black. An amount of the mixture was taken with a capillary tube for the control, the content was shaken in 2N HCl and extracted with $CH_2Cl_2$. The TLC control showed the completion of the reaction. The cooled mixture was poured into 2N HCl and extracted repeatedly with ethyl ether. The organic phase was washed with 2N HCl, sat. $NaHCO_3$ and brine, then dried over $Na_2SO_4$ and the solvent was evaporated off. Compound 13 was obtained as a yellow oil (1.45 g, 6.2 mmoles). Hexane/EtOAc 95:5 - Rf = 0.65.

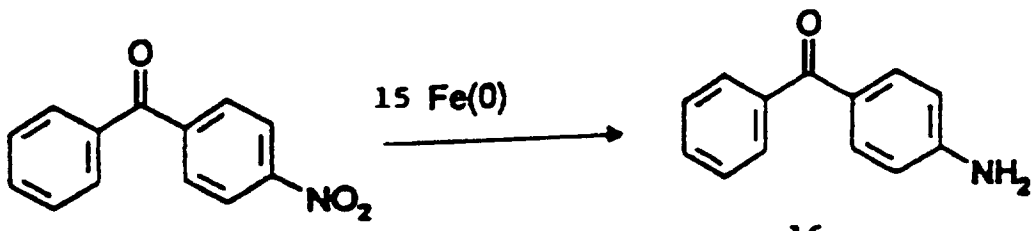


Compound 13 (1.4 g, 5.93 mmoles) was dissolved in $CH_2Cl_2$ (35 ml), then water (35 ml), conc. $H_2SO_4$ (1.89 ml), glacial acetic acid (0.7 ml) and a small amount of Aliquat were added. The mixture was stirred vigorously at room temperature and $KMnO_4$ (2.7 g, 17 mmoles) was added in small amounts, stirring for 48 hours. A TLC control of the organic phase evidenced the disappearance of the starting product. The mixture was added with $Na_2S_2O_5$ until the brown colour due to manganese dioxide disappears completely, then it was diluted with $CH_2Cl_2$ and the phases were separated. The organic phase was extracted with sat. $NaHCO_3$, the aqueous phase was acidified with 2N HCl and extracted with EtOAc. The organic phase was dried over $Na_2SO_4$ and evaporated. The crude (950 mg) was taken up into a benzene/petroleum ether 6:20 mixture to crystallize pure Ketoprofen (white solid) (725 mg, 2.85 mmoles). $CH_2Cl_2/CH_3OH$ 95:5 Rf = 0.14.

## EXAMPLE 2

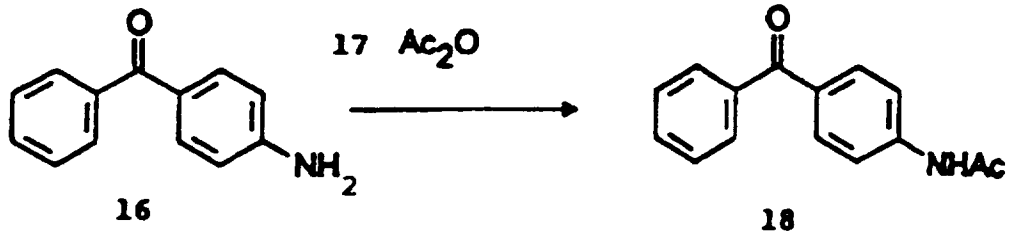
### Preparation of Ketoprofen (see example 1)

b) from 4-nitro-benzofenone



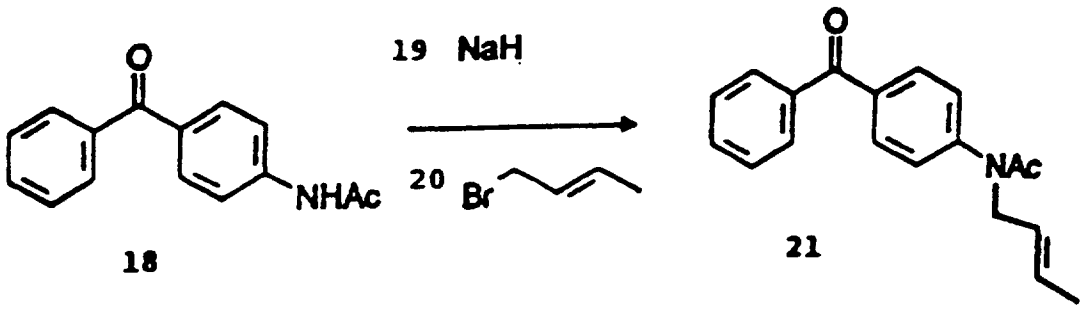

14 16

Compound 15 (13 g, 0.23 moles) was suspended in 50 ml of $H_2O$, 8 drops of conc. HCl were added and the mixture was heated to ebullition. After 1/2 hour compound 14 (10.4 g, 0.045 moles) dissolved in 50 ml of 95% EtOH was dropped therein. The mixture was heated again to ebullition, keeping reflux for 2 hours. A TLC control (Hexane/EtOAc 7:3) showed the reaction was complete. EtOH was evaporated off, the mixture was alkalinized with 2N NaOH, extracted with EtOAc (2x100 ml), dried over $Na_2SO_4$ and the solvent was evaporated off. A pale yellow solid was obtained, which was washed with an hexane/EtOAc mixture. Compound 16 was obtained as a white solid (7.1 g, 0.036). Hexane/EtOAc 7:3 Rf = 0.3.

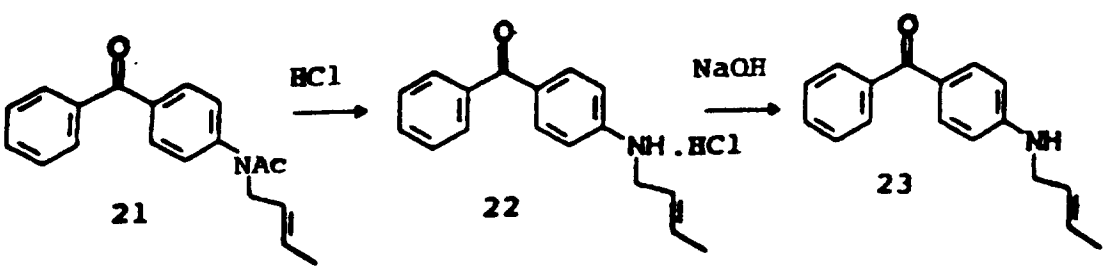



16 18

Compound 16 (7.1 g, 0.036 moles) was dissolved in dry $CH_2Cl_2$ (50 ml), 17 (3.46 ml, 0.036 moles) was added at room temperature, stirring for 12 hours. A TLC control (Hexane: EtOAc 7:3) evidenced the disappearance of the starting product. Solvent was evaporated off and the formed acetic acid was removed by evaporation (azeotropic mixture with toluene). 8.3 g (0.035 moles) of 18 as a white solid were obtained. Hexane/EtOAc 7:3 Rf = 0.1.

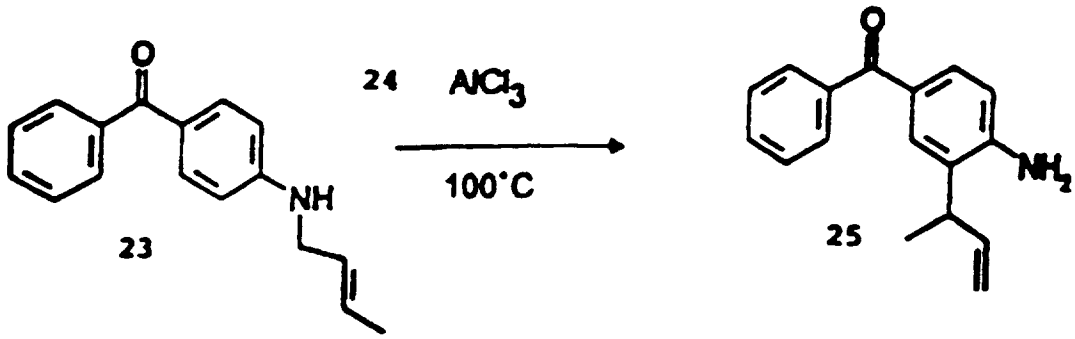



Compound 18 (8.2 g, 0.035 moles) was dissolved in hot $CH_2Cl_2$ (80 ml) (50°C), the solution was left to cool slightly and 19 (2.1 g of a 60% mineral oil dispersion, 0.052 moles) was added. The mixture was heated to 50°C, stirring for 30 minutes. The abundant precipitate formed was added with compound 20 (4.23 ml, 0.042 moles) dissolved in 20 ml of dry $CH_2Cl_2$. The mixture was kept overnight at room temperature and at 50°C for 8 hours. The starting product had almost disappeared, the mixture was diluted with $CH_2Cl_2$, washed with a 5% $NaH_2PO_4$ solution, then with brine. The organic phase was dried over $Na_2SO_4$ and the solvent was evaporated off. Compound 21 was obtained as a pale yellow solid, which was sufficiently pure to be used in the subsequent reaction (8.6 g 0,029 moles). Hexane/EtOAc 7:3 Rf = 0.44.



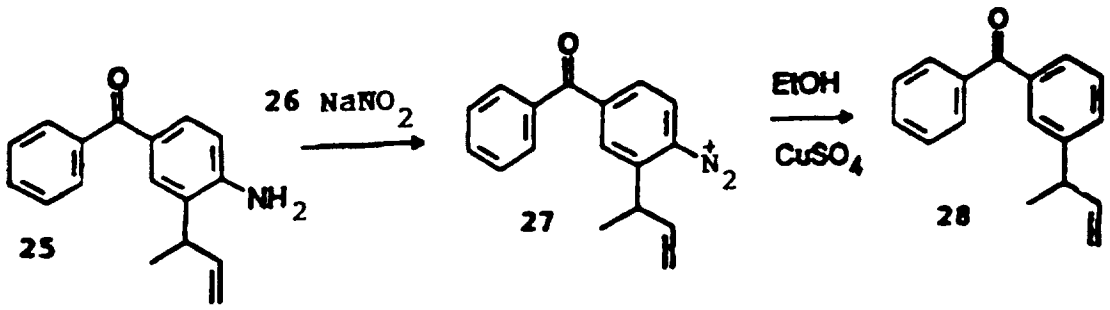

Compound 21 (8.6 g, 0.029 moles) was dissolved in

95% EtOH (15 ml), conc. HCl (15 ml) was added and the mixture was heated to ebullition for 3 hours. The TLC control (Hexane/EtOAc 1:1) evidenced the formation of a UV active spot with Rf = 0. 21 had not completely disappeared. EtOH was evaporated off, the acid solution was washed with EtOAc to remove the residual starting product, the solution was alkalinized with 5% NaOH and extracted again with EtOAc, dried over $Na_2SO_4$, filtered and the solvent was evaporated off. The resulting yellow oil was washed with Hexane/EtOAc 7:3, to precipitate compound 23 as a powdery yellowish solid (5.5 g, 0.022 moles). Hexane/EtOAc 7:3 Rf = 0.64.




Compound 23 (0.2 g, 0.8 mmoles) was dissolved in toluene, 24 (0.1 g, 0.8 mmoles) was added and temperature was raised to 100°C for 5 hours. After a night at room temperature, heating was maintained for a further 5 hours. TLC (Hexane/EtOAc 8:2) showed no increases in the desired product. The mixture was left to cool, poured into 2N HCl (5 ml), alkalinized with 2N NaOH and extracted with EtOAc. The extracts were dried over $Na_2SO_4$ and filtered. The solvent was evaporated off. A crude of about 200 mg was obtained, 150 mg of which were purified on

chromatographic column (Hexane: EtOAc 9:1). 18 mg of 25 were obtained (0.07 mmoles). Hexane: EtOAc 8:2 Rf = 0.4




Compound 25 (30 mg, 0.12 mmoles) was dissolved in 4 ml of $H_2O$ added with 15 µl of conc. HCl. The mixture was boiled for 5 minutes, then cooled on ice to 15°C and added with a further 15 µl of conc. HCl. After stirring for 15 minutes at 10°C, 8.8 mg of 26 (0.127 mmoles) dissolved in 0.4 ml of $H_2O$ were added, stirring for 20 minutes. EtOH (3 ml) added with a spatula tip of $CuSO_4$ was heated to 60°C in another flask. This solution was added with the mixture containing the diazonium salt in small amounts (slight gas evolution), keeping for 30 minutes at 60°C. EtOH was evaporated off, the residue was extracted with EtOAc and dried over $Na_2SO_4$. The solvent was evaporated off. The crude (30 mg) was purified on preparative TLC Hexane: EtOAc 8:2. 10 mg of compound 28 (pale yellow oil) were obtained. Hexane:EtOAc 8:2 Rf = 0.72.

## EXAMPLE 3

## 4-(perfluoro-1-butanesulfonate)-3-(1'-methyl-2'-propen-1-yl)benzophenone.

To a solution of 3-(1'-methyl-2'-propen-1-yl)-4-hydroxybenzophenone (5 g, 0.02 mol) in acetone (25 ml),

potassium carbonate (5.5 g, 0.04 mol) and the mixture was left stirring at room temperature for 15'. Then perfluoro-1-butanesulfonyl fluoride (6.6 g, 0.021 mol) was dropped and the solution refluxed for 3 hours. After cooling the inorganic salts were filtered off and the filtrate evaporated under vacuum to give a residue that was diluted with EtOAc (50 ml) and washed with brine (2x50 ml). After drying over $Na_2SO_4$ the solvent was evaporated to give 4-(perfluoro-1-butanesulfonate)-3-(1'-methyl-2'-propen-1-yl) benzophenone as yellowish oil (10.15 g, 0.019 mol). Yield 95%.

TLC (n-Hexane:EtOAc 9:1) Rf= 0.43.

$^1$H-NMR ($CDCl_3$) d 7.9-7.82 (dd, 3H, J= 8 Hz), 7.75-7.65 (m, 2H), 7.49 (t, 2H, J= 8Hz), 7.35 (d, 1H, J=8Hz), 6.05-5.92 (m, 1H), 5.21-5.03 (m, 2H), 3.95 (m, 1H), 1.41 (d, 3H, J= 8Hz).

## EXAMPLE 4

## 3-(1'-methyl-2'-propen-1-yl)benzophenone

To a solution of 4-(perfluoro-1-butanesulfonate)-3-(1'-methyl-2'-propen-1-yl)-benzophenone (6.13 g, 0.0115 mol) in dioxane (50 ml), triethylamine (4.96 ml, 0.036 mol) was added and then, under Ar, palladium acetate (0.108 g, $4.8x10^{-4}$ mol) and triphenylphosphine (0.25 g, $9.6x10^{-4}$ mol). Formic acid (1.1 g, 0.024 mol) was then added portionwise and the mixture was warmed at 60°C and left at the temperature for 1.5 h. After cooling the mixture was evaporated under vacuum; the residue was diluted with diethyl ether (50 ml), the formed precipitate was filtered off and the filtrate washed with 2N HCl (2x15 ml), 1N NaOH (2x8 ml), dried over $Na_2SO_4$ and evaporated under vacuum to give pure 3-(1'-

methyl-2'-propen-1-yl)benzophenone (2.6 g 0.011 mol) as yellow oil. Yield =95%

Perfluorobutanesulfonic acid (3.21 g, 0.0107 mol) was recovered from basic aqueous layer (1N NaOH) by acidification (conc. HCl) and extraction with ethyl acetate (2x 20 ml). Recovering yield= 93%.

TLC (n-Hexane/EtOAc 9:1) Rf=0.8

$^1$H-NMR ($CDCl_3$) d 7.79-7.71 (d, 3H), 7.70-7.65 (m, 2H), 7.55-7.35 (m, 4H), 6.09-5.89 (m, 1H), 5.15-5.02 (m, 2H), 3.55 (m, 1H), 1.42 (d, 3H, J= 8Hz).

## EXAMPLE 5

## 4-(benzenesulfonate)-3-(1'-methyl-2'-propen-1-yl)benzophenone.

To a solution of 3-(1'-methyl-2'-propen-1-yl)-4-hydroxybenzophenone (0.9 g, 0.0036 mol) in acetone (10 ml), potassium carbonate (0.99 g, 0.0076 mol) was added and the mixture was left stirring at room temperature for 15'. Then benzenesulfonyl chloride (0.633 g, 0.0036 mol) was dropped and the solution was stirred at room temperature for 3 hours and then refluxed for 1 hour. After cooling inorganic salts were filtered off and the filtrate evaporated under vacuum to give a residue that was diluted with EtOAc (10 ml) and washed with brine (2x10 ml). After drying over $Na_2SO_4$ the solvent was evaporated to give 4-(benzenesulfonate)-3-(1'-methyl-2'-propen-1-yl)benzophenone as yellowish oil (1.4 g, 0.0036 mol). Quantitative yield.

TLC (n-Hexane:EtOAc 9:1) Rf= 0.4.

$^1$H-NMR ($CDCl_3$) d 7.79-7.71 (dd, 2H, J=8Hz), 7.70-7.4 (m, 10H), 7.25 (d, 1H), 5.9-5.72 (m, 1H), 5.15-4.9 (m, 2H), 3.65 (m, 1H), 1.15 (d, 3H, J= 8Hz).

## EXAMPLE 6

### 3-(1'-methyl-2'-propen-1-yl)benzophenone

To a solution of 4-(benzenesulfonate)-3-(1'-methyl-2'-propen-1-yl)-benzophenone (0.31 g, 0.0008 mol) in DMF (5.5 ml), triethylamine (0.325 mg, 0.0032 mol) was added and then, under Ar, palladium acetate ($9x10^{-3}$ g, $4x10^{-5}$ mol) and 1,3-Bis(diphenylphosphino)propane ($1.8x10^{-4}$ g, $4.4x10^{-5}$ mol). Formic acid (0.147 g, 0.0032 mol) was then added portionwise and the mixture was warmed at 90°C and left at the temperature for 3 h. After cooling the mixture was poured in 2N HCl (10 ml) and extracted with EtOAc (2x10 ml). The organic layer was washed with brine (10 ml), dried over $Na_2SO_4$ and evaporated under vacuum to give a crude oil (0.21 g). Pure 3-(1'-methyl-2'-propen-1-yl)benzophenone (0.085 g $3.5x10^{-4}$ mol) was obtained as colourless oil by chromatographic purification (silica gel; n-Hexane/EtOAc 8:2). Yield =44%

The saturated compound was isolated in traces as side product.

TLC (n-Hexane/EtOAc 9:1) Rf=0.8

$^1$H-NMR ($CDCl_3$) d 7.79-7.71 (d, 3H), 7.70-7.65 (m, 2H), 7.55-7.35 (m, 4H), 6.09-5.89 (m, 1H), 5.15-5.02 (m, 2H), 3.55 (m, 1H), 1.42 (d, 3H, J = 8Hz).

## EXAMPLE 7

### 2-(2'-benzenesulfonate-5'-benzoylphenyl)propionic acid

To a solution of 4-(benzenesulfonate)-3-(1'-methyl-2'-propen-1-yl)-benzophenone (1 g, $2.55x10^{-3}$ mol) in $CH_2Cl_2$ (15 ml) an equal volume of $H_2O$, glacial acetic acid (0.3 ml), conc. $H_2SO_4$ (0.8 ml) and a catalytic

amount of Aliquat 336 were added. Then potassium permanganate (1.2 g, $7.6x10^{-3}$ mol) was added to the mixture portionwise. The mixture was stirred 24 hours at room temperature until disappearence of starting material (TLC). An aqueous solution of sodium metabisulfite was added under stirring until disappearence of the dark brown colour of the solution. $CH_2Cl_2$ (5 ml) was added and the two phases separated; the organic layer was washed with water (2x 10 ml), dried over $Na_2SO_4$ and evaporated under vacuum to give a crude residue (1.05 g). The pure 2-(2'-benzenesulfonate-3'-benzoylphenyl)propionic acid (0.8 g, $1.9x10^{-3}$) was obtained by chromatographic purification (silica gel, $CH_2Cl_2$/MeOH 95:5). Yield 76%.

TLC ($CH_2Cl_2$/MeOH 9:1) Rf=0.45

$^1$H-NMR ($CDCl_3$) d 8.0-7.15 (m, 13H), 4.15-3.95 (q, 1H,J=7Hz), 1.35 (d, 3H, J= 7Hz).

## EXAMPLE 8

## 2-(2'-perfluorobutanesulfonate-5'-benzoylphenyl)propionic acid

To a solution of 4-(perfluorobutanesulfonate)-3-(1'-methyl-2'-propen-1-yl)benzophenone (0.2 g.,$0.37x10^{-3}$ mol) in $CH_2Cl_2$ (2.5 ml) an equal volume of $H_2O$, glacial acetic acid (0.046 ml), conc. $H_2SO_4$ (0.12 ml) and a catalytic amount of Aliquat 336 were added. Then potassium permanganate (0.173 g, $1.09x10^{-3}$ mol) was added to the mixture portionwise. The mixture was stirred 24 hours at room temperature until disappearence of starting material (TLC). An aqueous solution of sodium metabisulfite (0.115 g, 1 ml) was added under stirring until disappearence of the dark brown colour of

the solution. $CH_2Cl_2$ (3 ml) was added and the two phases were separated; the organic layer was washed with water (2x 5 ml), dried over $Na_2SO_4$ and evaporated under vacuum to give a crude residue (0.25 g). 2-(2'-Perfluoro-butanesulfonate-5'-benzoylphenyl)propionic acid (0.17 g, $0.3x10^{-3}$ mol) was obtained by chromatographic purification (silica gel, $CH_2Cl_2$/MeOH 95:5). Yield 83%. The isolated product was contaminated by traces of Aliquat 336 (4%, NMR).

TLC ($CH_2Cl_2$/MeOH 9:1) Rf=0.5.

$^1$H-NMR ($CDCl_3$) d 8.0-7.41 (m, 8H), 4.25-4.1 (q, 1H,J=7Hz), 1.55 (d, 3H, J= 7Hz).

**EXAMPLE 9**

**3-(1'-methyl-2'-propen-1'-yl)-2-trifluoromethanesulfonate-diphenylmethane**

**3-(1'-methyl-2'-propen-1'-yl)-2-(perfluoro-1-butanesulfonate)-diphenylmethane**

A solution of crotyl bromide (1, 65 mL) in acetone ( 18 mL) was added to a stirred mixture of $K_2CO_3$ (4,5 g) and 2-hydroxydiphenylmethane (2,8 g) in acetone (30 mL)., The mixture was kept at room temperature.for 8 hrs and then heated for 4 hrs at. 45°C.

After the usual work-up (filtration of the inorganic material, solvent evaporation and water/AcOEt extraction) 3,46 g of the 2-crotyloxy-diphenylmethane were recovered.

A solution of 2-crotyloxy-diphenylmethane (2,8 g) in dimethylaniline (30 mL) was warmed for 12 hrs at 210°C (temperature of the outer oil bath).

The solvent was removed by vapour stream; the aqueous phase was extracted with AcOEt to give after the

usual work-up 2,24 g of 3-(1'-methyl-2'- -propen-1'-yl) -2-hydroxy-diphenylmethane that (according to the procedure of the example 1) when treated with trifluoromethanesulfonic anhydride in methylene chloride in the presence of diisopropyl-ethylamine gave 3-(1'-methyl-2'-propen-1'-yl) -2-trifluoromethanesulfonate-diphenylmethane. By reaction with perfluoro- 1-butanesulforyl fluoride (according to the procedure of the example 3), the same product gave 3-(1'-methyl-2'-propen-1'-yl)-2-(perfluoro-1-butanesulfonate)-diphenylmethane.

**EXAMPLE 10**

**4-(perfluoro-1-butanesulfonate)-3-(1'-methyl-2'-propen-1'-yl)-diphenylmethane**

The use of the 4-hydroxydiphenylmethane [obtained by Paternò reaction between phenol and benzyl alcohol; $^1$H-NMR δ 7.3-6.5 (m, 9H), 4.9 (s, OH), 3.9 (s, 2H) TLC (n-Hexane/EtOAc 8:2 Rf=0.50)] in the procedure of the example 9 instead of commercially available 2-hydroxydiphenylmethane [$^1$H-NMR δ 7.3-6.5 (m, 9H), 4.65 (s, OH), 3.95 (s, 2H) TLC (n-Hexane/EtOAc 8:2 Rf=0.55)] gave the 4-crotyloxy-diphenylmethane.

By Claisen rearrangement of 3,2 g of 4-crotyloxy-diphenylmethane in the dimetylaniline 2,87 g of 3-(1'-methyl-2'-propen-1'-yl)-4-hydroxy-diphenylmethane were obtained. In the presence of finely powdered $K_2CO_3$ (3g), a solution of perfluoro-1-butanesulfonyl fluoride (3,3 g) in acetone (6mL) was dropwise added to a solution of 2,5 g of this material in acetone (10 ml).

The mixture was refluxed for 3 hrs, the inorganic salts were filtered off to obtain after the usual work-

up 5,3 g of 4-(perfluoro-1-butanesulfonate)-3-(1'-methyl-2'-propen- 1'-yl)-diphenylmethane.

**EXAMPLE 11**

Using in the procedure of example 8 a diphenylmethane-sulfonate consisting of:
3-(1'-methyl-2'-propen-1'-yl)-2-trifluoromethanesulfonate-diphenylmethane, 3-(1'-methyl-2'-propen-1'-yl)-4-(perfluoro-1-butanesulfonate)-diphenylmethane;
3-(1'-methyl-2'-propen-1'-yl)-2-(perfluoro-1-butanesulfonate)-diphenylmethane;
after potassium permanganate phase transfer oxidation, the following acids:
2-(2'-trifluoromethanesulfonate-3'-benzoylphenyl)-propionic acid;
2-(2'-perfluorobutanesulfonate-3'-benzoylphenyl)-propionic acid;
2-(2'-perfluorobutanesulfonate-5'-benzoylphenyl)-propionic acid were obtained.

Using the above sulfonates in the procedure of the examples 1, 4, and 6, by reductive removal of the sulfonate group with formic acid in the presence of Pd acetate and a suitable phosphine (triphenylphosphine and 1,3-bis-(diphenyl- phosphine)propane], the same 2-(3-benzoylphenyl)-propionic acid (ketoprofen) was obtained.

**EXAMPLE 12**

Methyl esters of 2-(2'-benzenesulfonate-3'-benzoylphenyl)propionic acid and 2-(2'-perfluorobutane sulfonate -3'-benzoylphenyl) propionic acid were easily obtained starting from the acids according to the usual esterification methods (diazomethane/ether; dry MeOH/ and catalytic amounts of $H_2SO_4$, benzensulfonic or p-

toluensulfonic acids).

By hydrogenolysis of the following esters:

2-(2'-perfluorobutane sulfonate-5'-benzoylphenyl) propionic acid methyl ester.

$^1$H-NMR ($CDCl_3$) δ 7.8-7.4 (m, 8H), 4.25-4.1 (q, 1H,J=7Hz), 3.95 (s,3H) 1.55 (d, 3H, J= 7Hz).

2-(2'-benzenesulfonate-5'-benzoylphenyl)propionic acid methyl ester.

$^1$H-NMR ($CDCl_3$) δ 8.1-7.9 (d, 1H),7.9-7.5 (m, 11H), 7.33 (d,1H J=8Hz), 4.15-3.95 (q, 1H,J=7Hz),3.75 (s, 3H), 1.35 (d, 3H, J= 7Hz).

The 2-(3'-benzoylphenyl)propionic acid methyl ester (methyl ketoprofenate) was obtained according the following procedure.

To a solution of 2-(2'-perfluorobutane sulfonate - 5'-benzoylphenyl) propionic acid methyl ester (6.8 g, 0.012 mol) in dioxane (50 ml), triethylamine (4.96 mL, 0.036 mol) was added and then, under Ar, palladium acetate (0.108 g, $4.8x10^{-4}$ mol) and triphenylphosphine (0.25 g, $9.6x10^{-4}$ mol). Formic acid (1.1 g, 0.024 mol) was then added portionwise and the mixture was warmed at T=60 °C for 1.5 h. After cooling the mixture was evaporated under vacuum; the residue was diluted with diethyl ether (50 ml), the formed precipitate was filtered off. The filtrate was washed with 2N HCl (2x15 ml), 1N NaOH (2x8 mL), dried over $Na_2SO_4$ and evaporated under vacuum to give pure 2-(3'-benzoylphenyl)propionic acid methyl ester (2.14 g 0.008 mol) as yellow oil. Yield =67%; TLC (n-Hexane/EtOAc 9:1) Rf=0.53. $^1$H-NMR ($CDCl_3$) δ 7.85-7.3 (m, 9H), 3.85 (q, 1H, J=8Hz), 3.65 (s, 3H), 1.5 (d, 3H, J=

8Hz).

Perfluoro-1-butansulfonic acid (3.21 g, 0.0107 mol) was recovered from basic aqueous layer (NaOH 1N) by acidification (HCl conc.) and extraction with ethyl acetate (2x 20 ml).

**EXAMPLE 13**

**3-(1'-methyl-2'-propen-1-yl)-2-aminodiphenylmethane**

**3-(1'-methyl-2'-propen-1-yl)-4-aminodiphenylmethane**

Using in the procedure of the example 2 both 2-amino-diphenylmethane and 4-amino-diphenylmethane, the following amines

3-(1'-methyl-2'-propen-1-yl)-2-aminodiphenylmethane

$^1$H-NMR δ 7.5-7.2 (m, 5H), 7.17 (d, 1H J= 9 Hz), 7.0 (d, 1H J= 9Hz); 6.85 (t, 1H J=9Hz); 6.1-5.9 (m, 1H); 5.2-5.0 (m, 2H); 3.96 (s, 2H); 3.6 (bs, $NH_2$); 3.5 (m, 1H),1.35 (d, 3H, J= 7 Hz) TLC (n-Hexane/EtOAc 9:1 Rf=0.2).

3-(1'-methyl-2'-propen-1-yl)-4-aminodiphenylmethane

$^1$H-NMR δ 7.5-7.1 (m, 5H), 6.85-6.7 (m, 3H ); 6.1-5.9 (m, 1H); 5.2-5.0 (m, 2H); 4.3 (s, 2H); 4.2 (bs, $NH_2$); 3.5 (m, 1H), 1.35 (d, 3H, J= 7 Hz) TLC (n-Hexane/EtOAc 9:1 were obtained.

**EXAMPLE 14**

**3-(1'-methyl-2'-propen-1-yl)-2-hydroxy-diphenylmethane**

**3-(1'-methyl-2'-propen-1-yl)-4-hydroxy-diphenylmethane**

A mixture of 3-(1'-methyl-2'-propen-1-yl)-2-aminodiphenylmethane (0.3 g, 1.26 mmol), water (3 ml) and conc HCl (0.114 ml 1.38 mmol.) was heated at the reflux temperature for 5 min. After cooling at room temperature, an equal amount of conc. HCl was added to the mixture, that is cooled at 4 °C and treated with an aqueous solution of sodium nitrite (0.096 g,

1.38 mmol. in 1 mL), maintaining the temperature of the mixture below 5 °C. The subsequent addition of hypophosphorous acid (1.3 ml 50% sol., 12.6 mmol) gave 3-(1'-methyl-2'-propen-1-yl)-2-hydroxy-diphenylmethane.

$^1$H-NMR δ 7.4-7.15 (m, 5H), 7.1-6.95 (m, 2H), 6.9-6.8 (m, 1H); 6.2-6.0 (m,1H); 5.2-5.0 (m, 2H); 4.1 (s, 2H); 3.8 (m, 1H); 1.35 (d, 3H, J= 7 Hz) TLC (n-Hexane/EtOAc 9:1 Rf=0.39).

Starting from the 4-amine-diphenyl-methane-propenyl derivate, the 3-(1'-methyl- 2'-propen-1-yl)-4-hydroxy-diphenylmethane was prepared.

**EXAMPLE 15**

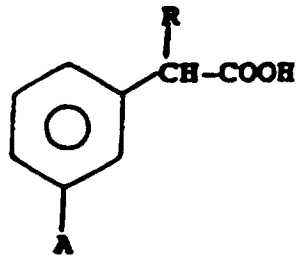
Starting from 3-(1'-methyl-2'-propen-1-yl)-2-amino-diphenylmethane and making use of well-known acylation procedures 3-(1'-methyl-2'-propen-1-yl)-2-acetylamino-diphenylmethane and 3-(1'-methyl-2'-propen-1-yl)-2-tert-butoxycarbonylamino-diphenyl methane are prepared.

According the procedure of example 1, the following potassium permanganate phase transer oxidation of the above N-acylamino compounds affords respectively:
2-(2'-acetylamino-3'-benzoylphenyl)-propionic acid,
2-(2'-tertbutoxycarbonylamino-3'-benzoylphenyl)-propionic acid.

The treatment of 2-(2'-tertbutoxycarbonylamino-3'-benzoylphenyl)-propionic acid in $CH_2Cl_2$, at 5-10 °C, with an excess of trifluoroacetic acid allows to recover the 2-(2-amino-3-benzoylphenyl)propionic acid as trifluoroacetic acid salt.

CLAIMS

1. A process for the preparation of meta-substituted arylalkanoic acids of formula

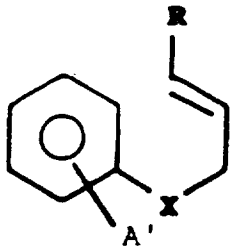


(I)

wherein R is hydrogen or $C_1$-$C_6$ alkyl, A is a $C_1$-$C_4$ alkyl group or aryl, aryloxy or aroyl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkyl, haloalkoxy substituents;

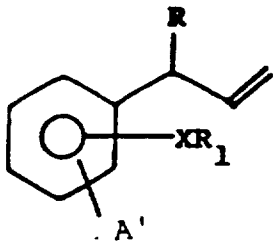
which comprises:

a) Claisen rearrangement of compounds of formula (II):



(II)

in which A' is $C_1$-$C_4$ alkyl group or benzyl, aryl, aryloxy or aroyl optionally substituted with one or more alkyl, hydroxy, amino, cyano, nitro, alkoxy, haloalkoxy substituents and R is as defined above, X is O, S or NH and the A' group is at the ortho or para position to the X-alkylene group, to give a compound of formula




(III)

wherein A' and R are as defined above, $XR_1$ is at the ortho position to the allyl chain and is a OH, $NH_2$ or $S(C_3-C_{10})$ acyl group;

b) optional elimination of the $-XR_1$ group by means of a dehydroxylation, deamination or desulfuration reaction;

c) oxidative cleavage of the compound (III);

d) elimination of the $-XR_1$, OH or $NH_2$ groups by dehydroxylation or deamination reactions, when not already carried out in step b).

2. A process according to claim 1, for the preparation of the compound of formula I in which R is methyl and A is benzoyl.

3. A process according to claim 1 or 2, wherein compounds of formula II in which X is 0 are used.

4. A process according to claim 1 or 2, wherein compounds of formula II in which X is NH are used.

5. A process according to claim 1 or 2, wherein compounds of formula II in which X is S are used.

6. A process according to any one of the above claims, wherein step c) is effected with $KMnO_4$ in phase transfer conditions.

7. Compounds of formula II wherein R, X and A are as defined above.

# INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 97/04050

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6 C07C57/30 C07C59/68 C07C59/84 C07C51/16 C07C309/00
C07C49/76 C07C211/43

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
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