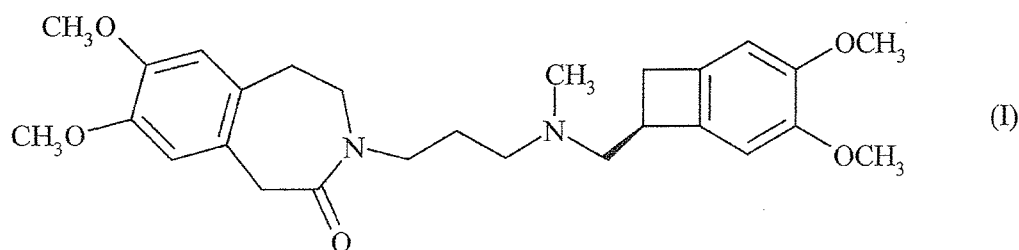


New process for the preparation of functionalised benzocyclobutenes, and application in the synthesis of ivabradine and addition salts thereof with a pharmaceutically acceptable acid

The present invention relates to a process for the preparation of functionalised benzocyclobutenes, and to their application in the synthesis of ivabradine, addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

Ivabradine of formula (I) :



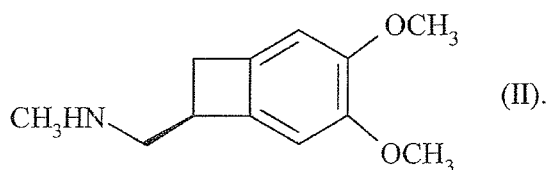
5

or 3-{3-[{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]-propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one,

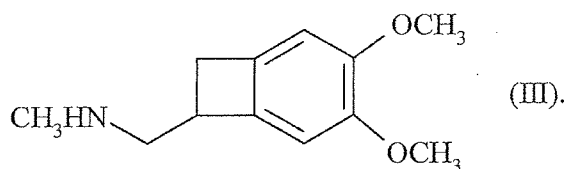
and also addition salts thereof with a pharmaceutically acceptable acid, and more especially the hydrochloride thereof, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, which render those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia, such as angina pectoris, myocardial infarction and associated rhythm disorders, as well as in various pathologies involving rhythm disorders, especially supraventricular rhythm disorders, and in heart failure.

The preparation and therapeutic use of ivabradine and addition salts thereof with a pharmaceutically acceptable acid, and more especially the hydrochloride thereof, have been described in European patent specification EP 0 534 859.

10 That patent specification describes the synthesis of ivabradine using as starting material a compound of formula (II) :



The compound of formula (II) is obtained by resolving, with the aid of camphorsulphonic acid, the compound of formula (III) :



5

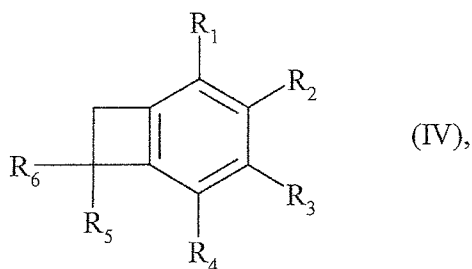
The compound of formula (II) is an important intermediate in the synthesis of ivabradine.

The present invention relates to a process for the preparation of functionalised benzocyclobutenes and to their application in the synthesis of ivabradine, addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof *via* the compound of formula (II).

The preparation of functionalised benzocyclobutenes has been described in *Angewandte Chemie, International Edition* **2003**, 42, 5736-5740. This publication describes the possibility of applying C(sp³)-H bond activation to the preparation of functionalised benzocyclobutenes using a palladium catalyst system.

15

More specifically, the present invention relates to a process for the preparation of the compounds of formula (IV) :

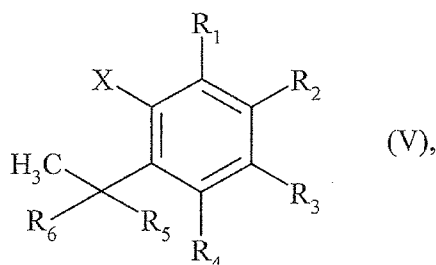


wherein R_1 , R_2 , R_3 and R_4 , which may be identical or different, each represent a hydrogen atom, a linear or branched (C_1 - C_6)alkyl group, a linear or branched (C_1 - C_6)alkoxy group, a fluorine atom, a chlorine atom, a protected amine group, a protected hydroxyl group, an alkoxy carbonyl group in which the alkoxy group is linear or branched (C_1 - C_6), or a CF_3 group, or $R_1=R_4=H$ and R_2 and R_3 together with the carbon atoms carrying them form a 1,3-dioxolane group,

R_5 represents a saturated or unsaturated, linear or branched (C_1 - C_6)alkyl group, a linear or branched (C_1 - C_6)hydroxyalkyl group in which the hydroxyl function is protected, or a CO_2R_7 group in which R_7 is a linear or branched (C_1 - C_6)alkyl group,

R_6 represents a cyano group or a CO_2R_8 group in which R_8 is a linear or branched (C_1 - C_6)alkyl group,

which process is characterised in that a compound of formula (V) :



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 are as defined hereinbefore and X represents a halogen atom, preferably a bromine atom, or a triflate group,

is subjected to a cyclisation reaction in the presence of a catalyst/ligand system comprising a palladium catalyst and an organic phosphine selected from tri-*tert*-butylphosphine, 2-biphenyl-di-*tert*-butylphosphine, 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)-ferrocene and tris(4-methoxy-2-methylphenyl)phosphine, or a phosphonium salt of the said phosphines,

in the presence of a base,

in an organic solvent.

Protected hydroxyl group or protected hydroxyl function means a hydroxyl function substituted by a protecting group customary for that function. Among those protecting groups there may be mentioned, without implying any limitation, silyl-containing groups

such as triisopropylsilyl and *tert*-butyldimethylsilyl, and the groups tetrahydropyran, benzyl, para-methoxybenzyl, trityl, acetyl and pivaloyl.

A protected amine group means an amine function substituted by a protecting group customary for that function. Among those protecting groups there may be mentioned,
5 without implying any limitation, the groups nosyl, tosyl, mesyl, acetyl, *tert*-butoxycarbonyl, benzyl and phthalimide.

Among the palladium catalyst that can be used there may be mentioned, without implying any limitation, Pd(OAc)₂, Pd(dba)₂, Pd₂(dba)₃, PdCl₂, PdCl₂(CH₃CN)₂, PdBr₂, or *trans*-di-(μ-acetate)bis[*o*-(di-*o*-tolylphosphine)benzyl]dipalladium (Herrmann's catalyst).

10 The palladium catalyst preferably used is Pd(OAc)₂.

The organic phosphine preferably used is tri-*tert*-butylphosphine.

Among the phosphonium salts that can be used there may be mentioned, without implying any limitation, phosphonium tetrafluoroborates, hexafluorophosphates and hexafluoroantimonates.

15 The phosphonium salt preferably used is tri-*tert*-butylphosphonium tetrafluoroborate.

Among the bases that can be used there may be mentioned, without implying any limitation, K₂CO₃, Cs₂CO₃, Na₂CO₃, K₃PO₄, KHCO₃, *t*-BuCO₂Na, *t*-BuCO₂K and *t*-BuCO₂Cs.

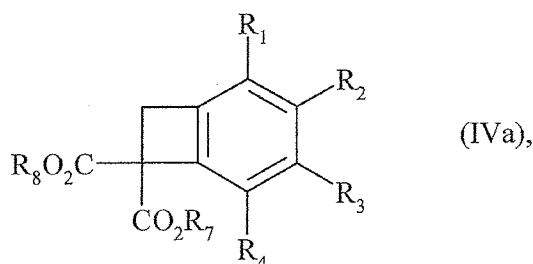
The base preferably used is K₂CO₃.

20 Among the solvents that can be used there may be mentioned, without implying any limitation, DMF, *N,N*-dimethylacetamide, *N*-methylpyrrolidine, xylene and mesitylene.

The solvent preferably used is DMF.

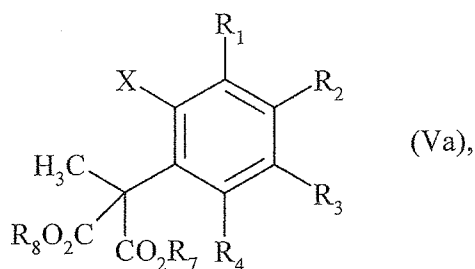
The temperature of the reaction is preferably from 100°C to 150°C.

According to a preferred embodiment, the present invention relates to a process for the preparation of compounds of formula (IVa), particular cases of the compounds of formula (IV) wherein $R_5=CO_2R_7$ and $R_6=CO_2R_8$:



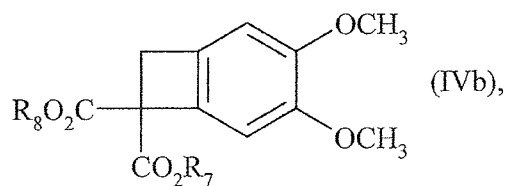
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wherein R_1 , R_2 , R_3 , R_4 , R_7 and R_8 are as defined hereinbefore, starting from compounds of formula (Va), particular cases of the compounds of formula (V) wherein $R_5=CO_2R_7$ and $R_6=CO_2R_8$:



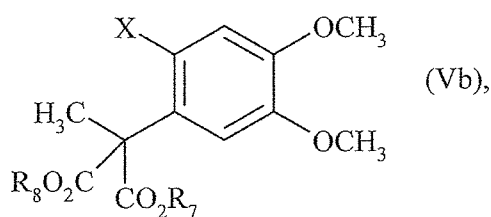
10 wherein R_1 , R_2 , R_3 , R_4 , R_7 , R_8 and X are as defined hereinbefore.

According to another preferred embodiment, the present invention relates to a process for the preparation of compounds of formula (IVb), particular cases of the compounds of formula (IVa) wherein $R_1=R_4=H$ and $R_2=R_3=OCH_3$:



wherein R_7 and R_8 are as defined hereinbefore,

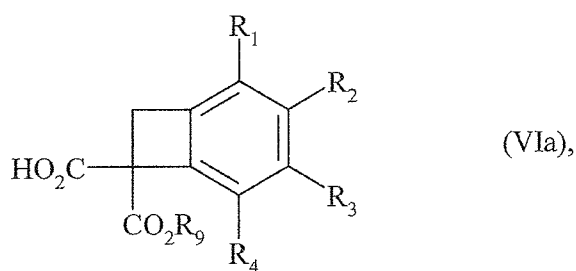
starting from compounds of formula (Vb), particular cases of the compounds of formula (Va) wherein $R_1=R_4=H$ and $R_2=R_3=OCH_3$:



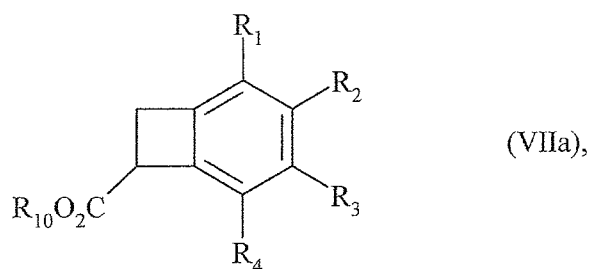
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wherein R_7 , R_8 and X are as defined hereinbefore.

The compounds of formula (IVa) obtained according to the process of the invention can lead to compounds of formula (VIa) :

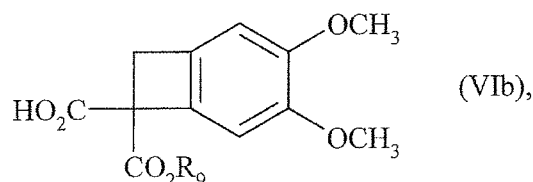


- 10 wherein R_1 , R_2 , R_3 and R_4 are as defined hereinbefore
and R_9 is a linear or branched (C_1 - C_6)alkyl group,
by an ester saponification or hydrolysis reaction,
then the compounds of formula (VIa) lead to compounds of formula (VIIa) :



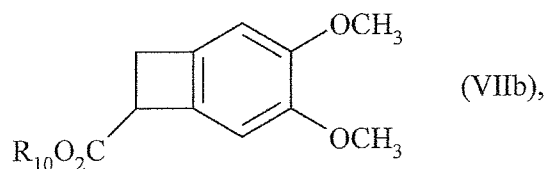
wherein R_1 , R_2 , R_3 and R_4 are as defined hereinbefore
and R_{10} is a hydrogen atom or a linear or branched (C_1 - C_6)alkyl group,
by a decarboxylation reaction.

- 5 The hydrolysis or the saponification of an ester function of the compounds of formula (IVb) results in compounds of formula (VIb), particular cases of the compounds of formula (VIa) wherein $R_1=R_4=H$ and $R_2=R_3=OCH_3$:



wherein R_9 is as defined hereinbefore.

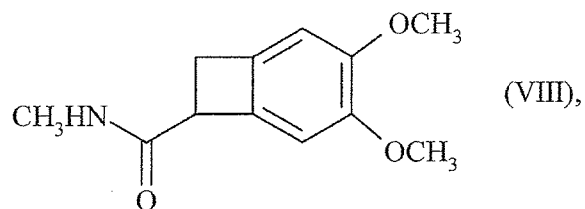
- 10 The decarboxylation of the compounds of formula (VIb) then results in compounds of formula (VIIb), particular cases of the compounds of formula (VIIa) wherein $R_1=R_4=H$ and $R_2=R_3=OCH_3$:



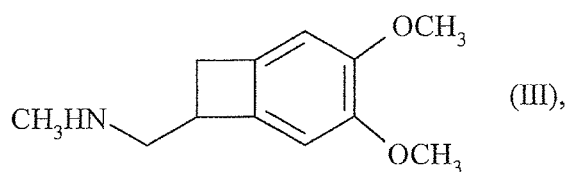
wherein R_{10} is as defined hereinbefore.

- 15 The compounds of formula (VIIb) obtained according to the process of the invention are useful in the synthesis of ivabradine, addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

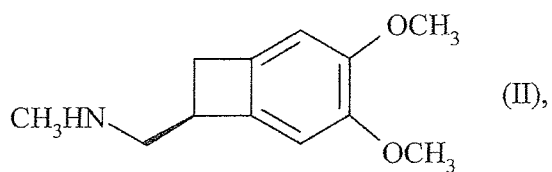
By way of example, their reaction with methylamine results in the compound of formula (VIII) :



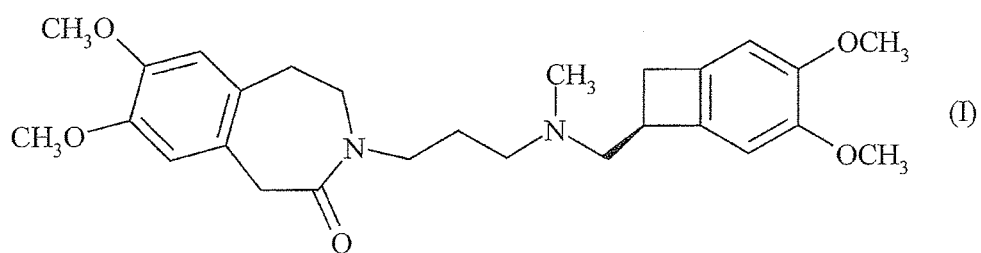
5 the reduction of which results in the compound of formula (III) :



the resolution of which, using camphorsulphonic acid, results in the compound of formula (II) :



10 which is converted into ivabradine of formula (I)



or 3-{3-[[[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]-propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one,

which may optionally be converted into its addition salts with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and into its hydrates.

Among the methods known for carrying out the conversion of the compound of formula (II) to ivabradine, those described in the European patent specifications EP 0 534 859 and EP 1 589 005 may be mentioned.

Obtaining compounds of formula (IVb) in good yields is thus especially useful in the synthesis of ivabradine, addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof.

The compounds of formula (IVa), which are particular cases of the compounds of formula (IV) wherein $R_5=CO_2R_7$ and $R_6=CO_2R_8$, and also the compounds of formula (VIb), as well as the compounds of formula (VIIc), which are particular cases of the compounds of formula (VIIb) wherein R_{10} represents a linear or branched (C_1-C_6)alkyl group, are new products which are useful as synthesis intermediates in the chemical or pharmaceutical industry, especially in the synthesis of ivabradine, addition salts thereof with a pharmaceutically acceptable acid and hydrates thereof and, as such, constitute an integral part of the present invention.

List of the abbreviations used:

dba : dibenzylidene acetone

DMF : *N,N*-dimethylformamide

DMSO : dimethyl sulphoxide

eq. : equivalent

THF : tetrahydrofuran

The Examples hereinbelow illustrate the invention.

General procedure A for the formation of benzocyclobutenes by C-H bond activation

5 Introduce aryl bromide (1 mmol), Pd(OAc)₂ (0.1 eq.), P(*t*-Bu)₃.HBF₄ (0.2 eq.) and anhydrous K₂CO₃ (1.3 eq.) into a dry and hermetically sealable Schlenk tube provided with a bar magnet. The Schlenk tube is purged and placed under argon. 4 ml of anhydrous DMF are added under argon, and the Schlenk tube is hermetically sealed and then subjected to stirring in an oil bath preheated to 140°C until complete disappearance of the aryl bromide
10 in GC/MS. After returning to ambient temperature, the reaction mixture is diluted with diethyl ether and filtered over Celite[®]. The organic solution is washed with saturated aqueous NaCl solution and dried over MgSO₄ and the residual solvent is evaporated off under reduced pressure. The crude reaction product is purified by flash chromatography to yield the benzocyclobutene.

15 **General procedure B for the formation of benzocyclobutenes by C-H bond activation**

Introduce aryl bromide (1 mmol), Pd₂(dba)₃ (0.05 eq.), P(*t*-Bu)₃.HBF₄ (0.1 eq.) and anhydrous K₂CO₃ (1.3 eq.) into a dry and hermetically sealable Schlenk tube provided with a bar magnet. The Schlenk tube is purged and placed under argon. 4 ml of anhydrous DMF are added under argon, and the Schlenk tube is hermetically sealed and then subjected to
20 stirring in an oil bath preheated to 120°C until complete disappearance of the aryl bromide in GC/MS. After returning to ambient temperature, the reaction mixture is diluted with diethyl ether and filtered over Celite[®]. The organic solution is extracted with saturated aqueous NaCl solution and dried over MgSO₄ and the residual solvent is evaporated off under reduced pressure. The crude reaction product is purified by flash chromatography to
25 yield the benzocyclobutene.

Example 1 : Dimethyl 7-methylbicyclo[4.2.0]octa-1,3,5-triene-3,7-dicarboxylate

Following general procedure A and using methyl 3-bromo-4-(2-methoxy-1,1-dimethyl-2-oxoethyl)benzoate as starting material, the title compound is obtained in a yield of 92%.

IR (film) : $\nu = 2952, 1714, 1433, 1275, 1146, 1079, 768 \text{ cm}^{-1}$.

5 **Example 2 : Methyl 7-methyl-4-(trifluoromethyl)bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate**

Following general procedure A and using methyl 2-[2-bromo-5-(trifluoromethyl)phenyl]-2-methylpropanoate as starting material, the title compound is obtained in a yield of 81%.

IR (film) : $\nu = 2955, 1731, 1315, 1143, 1113, 826, 685 \text{ cm}^{-1}$.

10 **Example 3 : 7-Isopropylbicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile**

Following general procedure A and using 2-(2-bromophenyl)-2,3-dimethylbutanenitrile as starting material, the title compound is obtained in a yield of 72%.

IR (film) : $\nu = 2964, 1458, 748, 715 \text{ cm}^{-1}$.

Example 4 : Dimethyl 3-methylbicyclo[4.2.0]octa-1,3,5-triene-7,7-dicarboxylate

15 Following general procedure A and using dimethyl 2-(2-bromo-4-methylphenyl)-2-methylmalonate as starting material, the title compound is obtained in a yield of 87%.

IR (film) : $\nu = 2952, 1731 \text{ cm}^{-1}$.

Example 5 : Dimethyl 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7,7-dicarboxylate

20 The title compound is obtained according to general procedure A using dimethyl 2-(2-bromo-4,5-dimethoxyphenyl)-2-methylmalonate as starting material.

IR (pure) : $\nu = 3007, 2960, 1730, 1591, 1239, 1116, 1090, 878, 758 \text{ cm}^{-1}$.

Example 6 : *tert*-Butyl methyl 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7,7-dicarboxylate

Following general procedure A and using *tert*-butyl methyl 2-(2-bromo-4,5-dimethoxyphenyl)-2-methylmalonate as starting material, the title compound is obtained in
5 a yield of 69%.

IR (pure) : ν = 2977, 2936, 1728, 1591, 1464, 1249, 1115, 840 cm^{-1} .

Example 7 : Methyl 7-{4-[(triisopropylsilyl)oxy]butyl}bicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate

Following general procedure A and using methyl 2-(2-bromophenyl)-2-methyl-6-
10 [(triisopropylsilyl)oxy]hexanoate as starting material, the title compound is obtained in a yield of 82%.

IR (film) : ν = 2940, 2863, 1731, 1457, 1253, 1103, 881, 678 cm^{-1} .

Example 8 : Methyl 7-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate

Following general procedure B and using methyl 2-(2-bromophenyl)-2-methylpropanoate
15 as starting material, the title compound is obtained in a yield of 81%.

IR (pure) : ν = 2972, 2952, 2930, 1729, 1457, 1433, 1277, 1140, 740, 711 cm^{-1} .

Example 9 : (*R,S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid

638 mg (2.28 mmol) of dimethyl 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7,7-dicarboxylate obtained in Example 5 are dissolved in 18 ml of DMSO and 445 mg
20 (6.84 mmol) of KCN are added in one go. The mixture is stirred under an argon atmosphere at 130°C for 12 h. After returning to ambient temperature, 25 ml of aqueous 1N HCl solution and 20 ml of diethyl ether are cautiously added to the reaction mixture
(**ATTENTION** : HCN formation) and the mixture is stirred for 1 h. The organic phase is washed with aqueous 1N NaOH solution (3 x 10 ml). The aqueous phases are combined,
25 then acidified to pH 2 using aqueous 6N HCl solution at ambient temperature and extracted

with diethyl ether (3 x 15 ml). The organic phases are dried over MgSO₄ and the residual solvents are evaporated off under reduced pressure. The crude reaction product is purified by flash chromatography (hexane/ethyl acetate : 85/15) to yield the title compound.

IR (pure) : ν = 3227, 2842, 2835, 1725, 1593, 1486, 1302, 1160, 1140, 970, 753 cm⁻¹.

5 **Example 10 : Methyl (*R,S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carboxylate**

424 mg (1.31 mmol) of *tert*-butyl methyl 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7,7-dicarboxylate obtained in Example 6 are dissolved in 2.1 ml of trifluoroacetic acid (99%) and the mixture is refluxed for 1.5 h. After returning to ambient temperature, the mixture is evaporated under reduced pressure to yield the monocarboxylic acid methyl
10 monoester.

The crude compound is dissolved in 4.34 ml of a 30 :1 DMF/pyridine mixture and the solution is heated at 120°C for 2 h under an argon atmosphere and then brought to ambient temperature. The reaction mixture is hydrolysed with saturated aqueous NH₄Cl solution and the aqueous phase is extracted with ethyl acetate (3 x 10 ml). The organic phases are
15 combined, washed with saturated aqueous NaCl solution (20 ml), dried over MgSO₄ and evaporated under reduced pressure. The crude reaction product is purified by flash chromatography (hexane/AcOEt : 8/2) to yield the title product.

IR (pure) : ν = 2950, 2834, 1729, 1464, 1207, 1068, 729 cm⁻¹.

20 **Example 11 : (*R,S*)-3,4-Dimethoxy-N-methylbicyclo[4.2.0]octa-1,3,5-triene-7-carboxamide**

0.05 ml of sulphuric acid ($d = 1.83$) is added to a solution of 2.5 g (12 mmol) of (*R,S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carboxylic acid obtained in Example 9 in 40 ml of methanol. The mixture is refluxed for 2 h and then cooled to 10°C. 40 ml of a 40% solution of methylamine in water are added in the course of 15 min. and the mixture
25 is stirred for 2 h. The methanol is evaporated off under reduced pressure and 40 ml of water are added. After extraction with CH₂Cl₂, the combined organic phases are washed in succession with water, 1N HCl and saturated NaCl solution and then dried over MgSO₄.

After evaporating off the solvents under reduced pressure, 2.2 g of the title product are obtained in the form of a beige solid (Yield : 83%).

Melting point : 142-147°C

Example 12 : *(R,S)*-1-(3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)-N-methyl-methanamine hydrochloride

20 ml of a molar solution of BH_3 in THF are added at ambient temperature to a mixture of 2.2 g (10 mmol) of the product obtained in Example 11 in 45 ml of THF. After stirring for 1 h, 10 ml of the solution of BH_3 in THF are added. After stirring overnight at ambient temperature, 20 ml of ethanol are added dropwise and the mixture is stirred until the evolution of gas ceases (about 1 h). 20 ml of a solution of HCl in ethanol are then added dropwise. After stirring for 4 h, the precipitate obtained (1.2 g of the title product) is filtered off. The filtrate is concentrated and a further 0.65 g of title product is obtained by solidifying in an 80:20 AcOEt/ethanol mixture.

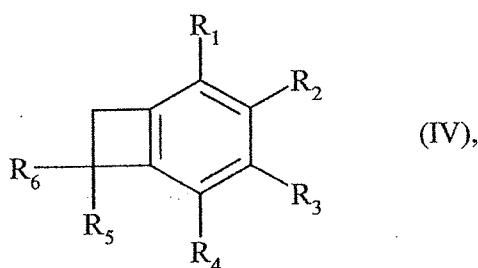
The two precipitates are combined to yield 1.85 g of the title product (Yield 77%).

Melting point : 174-177°C

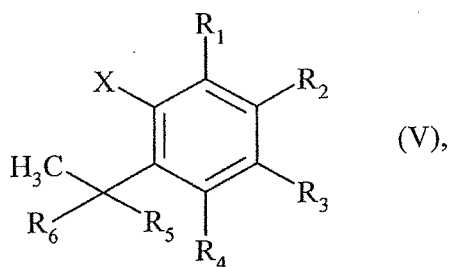
CLAIMS

The invention claimed is:

1. A process for the preparation of a compound selected from those of formula (IV):



wherein R_1 , R_2 , R_3 and R_4 , which may be identical or different, each represent a hydrogen atom, a linear or branched (C_1 - C_6)alkyl group, a linear or branched (C_1 - C_6)alkoxy group, a fluorine atom, a chlorine atom, a protected amine group, a protected hydroxyl group, an alkoxycarbonyl group in which the alkoxy group is linear or branched (C_1 - C_6), or a CF_3 group, or R_1 and R_4 represent hydrogen and R_2 and R_3 together with the carbon atoms carrying them form a 1,3-dioxolane group, R_5 represents a saturated or unsaturated, linear or branched (C_1 - C_6)alkyl group, a linear or branched (C_1 - C_6)hydroxyalkyl group in which the hydroxyl function is protected, or a CO_2R_7 group in which R_7 is a linear or branched (C_1 - C_6)alkyl group, R_6 represents a cyano group or a CO_2R_8 group in which R_8 is a linear or branched (C_1 - C_6)-alkyl group, wherein a compound of formula (V)



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 are as defined hereinbefore and X represents a halogen atom or a triflate group, is subjected to a cyclisation reaction in the presence of a catalyst/ligand system comprising a palladium catalyst and an organic phosphine selected from tri-tert-butylphosphine, 2-biphenyl-di-tert-butylphosphine, 1,2,3,4,5-pentaphenyl-1'-(di-tert-butylphosphino)-ferrocene and tris(4-methoxy-2-methylphenyl)phosphine, or a phosphonium salt of the said phosphines, in the presence of a base, in an organic solvent.

2. The process of claim 1, wherein the palladium catalyst is selected from $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{dba})_2$, $\text{Pd}_2(\text{dba})_3$, PdCl_2 , $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, PdBr_2 and trans-di-(μ -acetate)bis[o-(di-o-tolylphosphine)benzyl]dipalladium.
3. The process of claim 1, wherein the palladium catalyst is $\text{Pd}(\text{OAc})_2$.
4. The process of claim 1, wherein the organic phosphine is tri-tert-butylphosphine.
5. The process of claim 1, wherein the phosphonium salt is a phosphonium tetrafluoroborate, hexafluorophosphate or hexafluoroantimonate.
6. The process of claim 5, wherein the phosphonium salt is tri-tert-butylphosphonium tetrafluoroborate.
7. The process of claim 1, wherein the base is selected from K_2CO_3 , Cs_2CO_3 , Na_2CO_3 , K_3PO_4 , KHCO_3 , t-BuCO₂Na, t-BuCO₂K and t-BuCO₂Cs.
8. The process of claim 7, wherein the base is K_2CO_3 .
9. The process of claim 1, wherein the organic solvent is selected from DMF, N,N-dimethylacetamide, N-methylpyrrolidine, xylene and mesitylene.
10. The process of claim 9, wherein the organic solvent is DMF.
11. The process of claim 1, wherein the temperature of the reaction is from 100.degree. C. to 150.degree. C.
12. The process of claim 1, wherein X represents a bromine atom.