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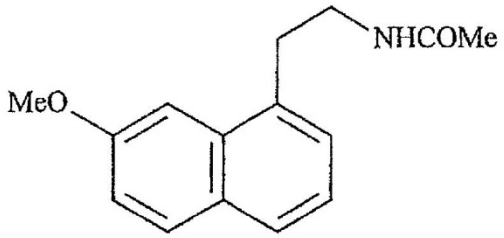
(54) Benevnelse **NOVEL METHOD FOR THE SYNTHESIS OF AGOMELATINE**

(56) Anførte publikasjoner EP-A1- 0 447 285, EP-A1- 1 564 202, LI P-K ET AL: "The development of a charged melatonin receptor ligand", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 7, no. 18, 23 septembre 1997 (1997-09-23), pages 2409-2414, XP004136454, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(97)00444-7, EP-A1- 2 322 508, EP-A1- 2 151 427

Description

The present invention relates to a new process for the industrial synthesis of agomelatine or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide of formula (I):



(I)

Agomelatine or *N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide has valuable pharmacological properties.

It has the double feature of being on the one hand an agonist of the receptors of the melatoninergic system and on the other hand an antagonist of the 5-HT_{2C} receptor. These properties impart thereto an activity in the central nervous system and more especially in the treatment of major depression, seasonal affective disorder, sleep disorders, cardiovascular pathologies, pathologies of the digestive system, insomnia and fatigue due to jet-lag, appetite disorders and obesity.

Agomelatine, its preparation and its use in therapeutics have been described in European patents EP 0 447 285 and EP 1 564 202.

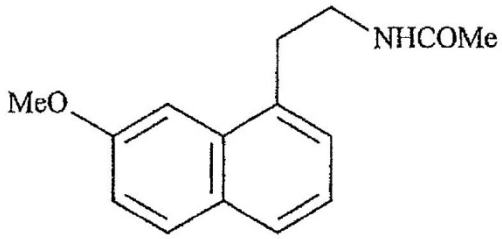
In view of the pharmaceutical value of this compound, it was essential to be able to obtain it by means of an efficient industrial synthesis process which can easily be transposed to the industrial scale and yields agomelatine with a good yield and excellent purity.

Patent EP 0 447 285 describes access to agomelatine in eight steps starting from 7-methoxy-1-tetralone. In patent EP 1 564 202, the applicant has developed a new synthesis route which is much more efficient and industrialisable, in only four steps starting from 7-methoxy-1-tetralone, and which allows agomelatine to be obtained in a

highly reproducible manner in a well defined crystalline form. However, the search for new synthesis routes, especially starting from less expensive starting materials than 7-methoxy-1-tetralone, is still current.

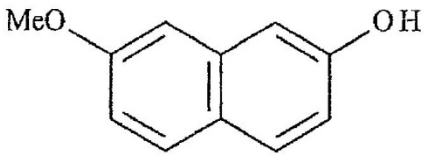
The applicant has continued his investigations and has developed a new process for the synthesis of agomelatine starting from 7-methoxy-naphthalen-2-ol: this new starting material has the advantage of being simple and readily obtainable in large quantities at lower costs. 7-Methoxy-naphthalen-2-ol also has the advantage of having a naphthalene nucleus in its structure, which avoids the inclusion of an aromatisation step in the synthesis, which is always tricky from an industrial point of view.
This new process additionally allows agomelatine to be obtained in a reproducible manner and without the need for laborious purification, with a purity which is compatible with its use as a pharmaceutical active ingredient.

More specifically, the present invention relates to a process for the industrial synthesis of the compound of formula (I):



(I)

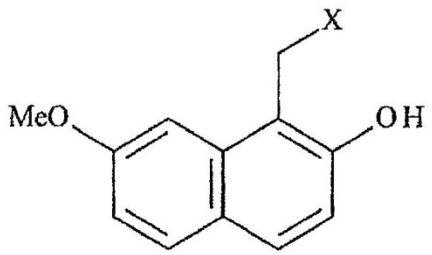
characterised in that 7-methoxy-naphthalen-2-ol of formula (II):



(II)

is reacted, wherein there is introduced in position 1 of the compound of formula (II) the group $–CH_2X$ wherein X represents a group $–N(CH_3)_2$, $-CO-N(CH_2-Ph)_2$, $-CH_2-OH$, $-CH=CH_2$ or $–CO-NH_2$,

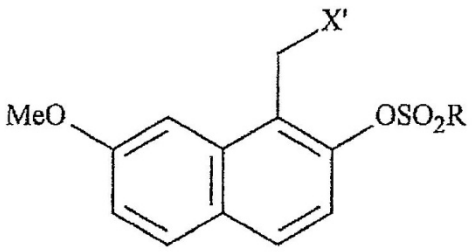
to yield the compound of formula (III):



(III)

wherein X represents a group $–N(CH_3)_2$, $-CO-N(CH_2-Ph)_2$, $-CH_2-OH$, $-CH=CH_2$ or $-CO-NH_2$;

which compound of formula (III) is subjected to a sulfonylation reaction on the aromatic alcohol and the substituent X of which is modified, before or after the step of sulfonylation of the aromatic alcohol, by means of conventional chemical reactions to yield the compound of formula (IV):

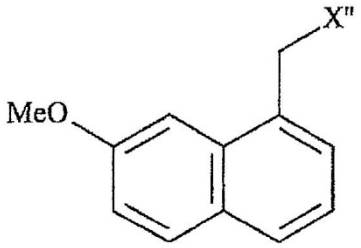


(IV)

wherein X' represents a group –CN, $-CO-NH_2$, $-CH_2-OH$, $-CH_2-N(CH_2-Ph)_2$, $-CH_2-NH-CO-CH_3$, $-CH(OH)-CH_2-OH$, -CHO or (2,5-dioxopyrrolidin-1-yl)methyl and R represents a group $–CH_3$, $-(CH_2)_2-CH_3$, $-CF_3$ or toluyl;

which compound of formula (IV) is subjected to a deoxygenation reaction in the presence of a transition metal and a reducing agent to yield:

- either, when X' represents the group $–CH_2-NH-CO-CH_3$, the compound of formula (I) directly, which is isolated in the form of a solid;
- or the compound of formula (V):



(V)

wherein X" represents a group –CN, -CH_2-N(CH_2-Ph)$_2$, -CH_2-OH, -CO-NH_2, -CH(OH)-CH_2-OH or (2,5-dioxopyrrolidin-1-yl)methyl;

which compound of formula (V) is then subjected to conventional chemical reactions to yield the compound of formula (I), which is isolated in the form of a solid.

In a variant of the process of industrial synthesis, the group X is not modified in the conversion of the compound of formula (III) into the compound of formula (IV). The resulting compound sulfonylated on its aromatic alcohol then undergoes a deoxygenation reaction by the action of a transition metal and a reducing agent. The group X is modified subsequently by means of conventional chemical reactions to yield the compound of formula (I), which is isolated in the form of a solid.

The compound of formula (II) is commercially available or readily accessible to the person skilled in the art by conventional chemical reactions or chemical reactions described in the literature.

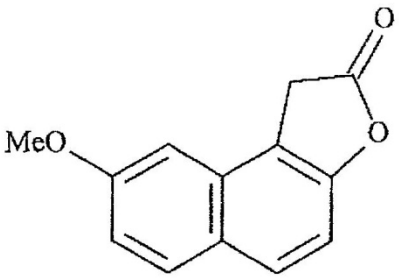
In the process according to the invention, the conversion of the compound of formula (II) into the compound of formula (III) wherein X represents the group -N(CH_3)$_2$ is carried out in accordance with the Mannich reaction by the action of formaldehyde in the presence of dimethylamine.

In the process according to the invention, the conversion of the compound of formula (II) into the compound of formula (III) wherein X represents the group -CH_2-OH consists in that the compound of formula (II) is subjected to the action of glyoxal (or ethane-1,2-dione) followed by the action of a reducing agent. Advantageously, the reducing agent is lithium aluminium hydride, diisobutylaluminium

hydride, lithium triethylborohydride or borane dimethylsulfide. Preferably, the reducing agent is lithium aluminium hydride.

In the process according to the invention, the conversion of the compound of formula (II) into the compound of formula (III) wherein X represents the group -CO-NH_2 or –CO-$N(CH_2\text{-}Ph)_2$ is carried out by the action of glyoxal followed by the action, in a heated medium, of the compound of formula NHR'R' wherein R' represents H or a group –CH_2-Ph.

Said reaction with glyoxal which results in the formation of the lactone intermediate of formula (VI):



(VI)

is preferably carried out in two steps.

In the first step, the compound of formula (II) is dissolved in a basic medium in the presence of glyoxal. The base is preferably sodium hydroxide or potassium hydroxide and more especially potassium hydroxide.

In the second step, the intermediate product, namely 8-methoxy-1,2-dihydronaphtho-[2,1-*b*]furan-1,2-diol, is dissolved directly in an acidic medium, preferably hydrochloric acid, in order to yield the lactone intermediate of formula (VI).

In the process according to the invention, the conversion of the compound of formula (II) into the compound of formula (III) wherein X represents the group -CH=CH_2 is carried out in accordance with the Claisen sigmatropic rearrangement by the action of allyl bromide in a basic medium followed by a thermal rearrangement. The action of allyl bromide is carried out in the presence of a base such as sodium hydride, potassium *tert*-butylate, sodium methanolate, potassium hydroxide, sodium hydroxide, potassium carbonate or sodium carbonate. An advantageous

embodiment consists in using potassium carbonate as the base in the step of reaction with allyl bromide.

In the process according to the invention, the conversion of the compound of formula (III) into the compound of formula (IV) consists of a step of sulfonylation of the aromatic alcohol followed by modification of the group X by means of conventional chemical reactions, X being as defined hereinbefore. According to another advantageous embodiment, the conversion of the compound of formula (III) into the compound of formula (IV) consists in modifying the group X by means of conventional chemical reactions followed by a step of sulfonylation of the aromatic alcohol, X being as defined hereinbefore.

Said sulfonylation step is carried out by virtue of the action of a sulfonyl chloride, a sulfonic anhydride or a sulfonimide. According to a preferred embodiment, the sulfonylation step is carried out by virtue of the action of tosyl chloride, *n*-propylsulfonyl chloride, triflic anhydride or phenyl triflimide (or *N,N*-bis(trifluoromethylsulfonyl)aniline).

In the process according to the invention, the conversion of the compound of formula (IV) into the compound of formula (V) consists of a step of deoxygenation in the presence of a transition metal and a reducing agent.

Preferably, the transition metal is nickel, palladium or platinum. The transition metal may either be in the form of a salt or in the form of an element. Preferably, the transition metal salt is a nickel salt or a palladium salt, more preferably a nickel salt.

Advantageously, the reducing agent is either a hydride such as sodium borohydride or lithium aluminium hydride; or an aminoborane such as dimethylamineborane; or an alkoxysilane such as dimethoxymethylsilane; or an alkylsilane such as triethylsilane; or an alkaline earth metal such as magnesium; or dihydrogen. According to another preferred embodiment, the conversion of the compound of formula (IV) into the compound of formula (V) consists of a step of deoxygenation in the presence of nickel, in particular a nickel salt, and a hydride, preferably sodium borohydride.

According to another preferred embodiment, the conversion of the compound of formula (IV) into the compound of formula (V) consists of a step of deoxygenation in

the presence of palladium and dihydrogen. Dihydrogen is used directly in its gaseous form or is obtained indirectly by decomposition of an ammonium formate.

According to another preferred embodiment, the conversion of the compound of formula (IV) into the compound of formula (V) consists of a step of deoxygenation in the presence of palladium and an alkaline earth metal, preferably magnesium.

According to another preferred embodiment, the conversion of the compound of formula (IV) into the compound of formula (V) consists of a step of deoxygenation in the presence of a transition metal, a reducing agent and a ligand. The ligand is preferably a phosphine ligand and, more especially, triphenylphosphine.

According to a particular embodiment, the step of deoxygenation of the compound of formula (IV) wherein X' represents the group $–CH_2$-NH-CO-CH_3, which is carried out:

- either in the presence of nickel, especially a nickel salt, and a hydride, preferably sodium borohydride;
- or in the presence of palladium and dihydrogen;
- or in the presence of palladium and an alkaline earth metal;

results directly in the formation of the compound of formula (I).

This process is especially valuable for the following reasons:

- it allows the compound of formula (I) to be obtained on an industrial scale with good yields starting from a starting material that is simple and inexpensive;
- it allows an aromatisation reaction to be avoided, a step which is always tricky from an industrial point of view, since the naphthalene nucleus is present in the starting substrate;
- it allows agomelatine to be obtained starting from 7-methoxy-naphthalen-2-ol with a reduced number of steps.

The compounds of formulae (III), (IV) and (VI) obtained in accordance with the process of the invention are new and can be used as an intermediate for the synthesis of agomelatine.

The compounds of formula (V) obtained in accordance with the process of the invention can be used as an intermediate for the synthesis of agomelatine. The compounds of formula (V) obtained in accordance with the process of the invention are new, except for (7-methoxynaphthalen-1-yl)acetonitrile, *N,N*-dibenzyl-2-(7-methoxynaphthalen-1-yl)ethanamine, 2-(7-methoxynaphthalen-1-yl)ethanol and 2-(7-methoxynaphthalen-1-yl)acetamide.

The preferred compounds of formula (III) are the following:

- 1-[(dimethylamino)methyl]-7-methoxynaphthalen-2-ol;
- *N,N*-dibenzyl-2-(2-hydroxy-7-methoxynaphthalen-1-yl)acetamide;
- 1-(2-hydroxyethyl)-7-methoxynaphthalen-2-ol;
- 2-(2-hydroxy-7-methoxynaphthalen-1-yl)acetamide;
- 7-methoxy-1-(prop-2-en-1-yl)naphthalen-2-ol.

The preferred compounds of formula (IV) are the following:

- 1-(cyanomethyl)-7-methoxynaphthalen-2-yl trifluoromethanesulfonate;
- 1-[2-(acetylamino)ethyl]-7-methoxynaphthalen-2-yl 4-methylbenzene-sulfonate;
- 1-[2-(dibenzylamino)ethyl]-7-methoxynaphthalen-2-yl trifluoromethane-sulfonate;
- 1-[2-(acetylamino)ethyl]-7-methoxynaphthalen-2-yl propane-1-sulfonate;
- 1-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]-7-methoxynaphthalen-2-yl propane-1-sulfonate;
- 1-(2-hydroxyethyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate;
- 1-(2-amino-2-oxoethyl)-7-methoxynaphthalen-2-yl 4-methylbenzene-sulfonate;
- 7-methoxy-1-(2-oxoethyl)naphthalen-2-yl 4-methylbenzenesulfonate;
- 1-(2,3-dihydroxypropyl)-7-methoxynaphthalen-2-yl 4-methylbenzene-sulfonate.

(2-Hydroxy-7-methoxynaphthalen-1-yl)acetonitrile, 7-methoxy-1-(2-{[(4-methyl-phenyl)sulfonyl]oxy}ethyl)naphthalen-2-yl 4-methylbenzenesulfonate, 7-methoxy-1-{2-[(propylsulfonyl)oxy]ethyl}naphthalen-2-yl propane-1-sulfonate and 1-[2-

(acetylamino)ethyl]-7-methoxynaphthalen-2-yl acetate are new and can be used as an intermediate for the synthesis of agomelatine.

The examples below illustrate the invention but do not limit it in any way.

In order to validate the reaction routes, the synthesis intermediates were systematically isolated and characterised. However, it is possible to optimise the processes considerably by limiting the number of intermediates isolated.

The structures of the described compounds were confirmed by the usual spectroscopic techniques: proton NMR (s = singlet, bs = broad singlet; d = doublet; t = triplet; dd = doublet of doublets; m = multiplet); carbon NMR (s = singlet; d = doublet; t = triplet; q = quadruplet); electrospray ionisation (ESI) mass spectrometry.

EXAMPLE 1: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-[(Dimethylamino)methyl]-7-methoxynaphthalen-2-ol

To a solution of 7-methoxy-naphthalen-2-ol (1.74 g; 10 mmol) in ethanol (10 mL) there are added at ambient temperature dimethylamine (40 % in water; 1.52 mL; 12 mmol) and then formaldehyde (37 % in water; 0.78 mL; 10.5 mmol). After one hour's stirring, the solvent is evaporated off. The crude product obtained (quantitative yield) is used directly in the following step without further purification.

^{1}H NMR spectroscopic analysis (DMSO-d_6, 300.13 MHz, δ in ppm): 11.18 (bs, 1H); 7.68 (d, J = 8.8 Hz, 1H); 7.6 (d, J = 8.8 Hz, 1H); 7.23 (d, J = 2.3 Hz, 1H); 6.93 (dd, J = 8.8 and 2.3 Hz, 1H); 6.89 (d, J = 8.8 Hz, 1H); 3.96 (s, 2H); 3.86 (s, 3H); 2.3 (s, 6H).

^{13}C NMR spectroscopic analysis (DMSO-d_6, 75.5 MHz, δ in ppm): 157.7 (s); 156.1 (s); 134.3 (s); 129.9 (d); 128.5 (d); 123.3 (s); 116.0 (d); 114.2 (d); 112.0 (s); 101.6 (d); 55.8 (t); 55.0 (q); 44.3 (2 x q).

Step B: (2-Hydroxy-7-methoxynaphthalen-1-yl)acetonitrile

A solution of the product of the preceding Step A (1.155 g; 5 mmol) in dimethylformamide (5 mL) in the presence of potassium cyanide (390 mg; 6 mmol) is heated at 80°C for 30 hours. After dilution in ethyl acetate, 2 M aqueous HCl solution

(5 mL) is added. The mixture is stirred and then neutralised by the addition of dilute $NaHCO_3$ solution. The two phases are separated and the organic fraction is washed three times with brine, dried over sodium sulfate and filtered. Evaporation of the solvent yields a crude product which is then purified by chromatography on a silica gel column (eluant: ether/petroleum ether 40/60) to yield the expected product.

^{1}H NMR spectroscopic analysis (acetone-d_6, 300.13 MHz, δ in ppm): 9.25 (bs, 1H, OH); 7.74 (d, J = 9.1 Hz, 1H); 7.71 (d, J = 8.9 Hz, 1H); 7.31 (d, J = 2.5 Hz, 1H); 7.13 (d, J = 8.9 Hz, 1H); 7.03 (dd, J = 9.1 and 2.5 Hz, 1H); 4.21 (s, 2H); 3.96 (s, 3H).

^{13}C NMR spectroscopic analysis (acetone-d_6, 75.5 MHz, δ in ppm): 159.9 (s); 154.1 (s); 135.1 (s); 131.1 (d); 130.4 (d); 124.9 (s); 119.1 (s); 116.2 (d); 115.7 (d); 108.7 (s); 102.1 (d); 55.6 (q); 13.6 (t).

Step C: 1-(Cyanomethyl)-7-methoxynaphthalen-2-yl trifluoromethanesulfonate

To a solution of the product of the preceding Step B (120 mg; 0.52 mmol) in dichloromethane (5 mL) there are added *N,N*-bis(trifluoromethylsulfonyl)aniline (204 mg; 0.571 mmol) and triethylamine (72 µL; 0.52 mmol). After stirring for 16 hours, the solvents are evaporated off and the residue is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether, gradient from 10/90 to 20/80) to give the title product (125 mg; 70 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.85-7.78 (m, 2H); 7.3-7.22 (m, 3H); 4.13 (s, 2H); 3.98 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 159.9 (s); 145.6 (s); 133.2 (s); 131.2 (d); 130.8 (d); 128.0 (s); 125.0 (s); 120.3 (d); 118.6 (s, J = 318 Hz); 116.9 (s); 116.8 (d); 116.0 (s); 102.3 (d); 55.6 (q); 15.2 (t).

Mass spectrometry (ESI; m/z(%)): 345(45) $[M]^{+\bullet}$; 212(100); 184(15); 169(34); 140(18).

Step D: (7-Methoxynaphthalen-1-yl)acetonitrile

A solution of the product of the preceding Step C (73 mg; 0.212 mmol) in absolute ethanol (4 mL) in the presence of 10 % palladium on carbon (4.5 mg; 0.004 mmol) and triethylamine (150 µL) is hydrogenated (4 bar) at ambient temperature for 20 hours.

After filtration over Celite, washing with ethyl acetate and evaporation of the solvents, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 15/85) to give the title product (28 mg; 67 %).

Melting point: *86-87°C*

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.78 (d, J = 8.9 Hz, 1H); 7.77 (d, J = 7.8 Hz, 1H); 7.52 (d, J = 7.1 Hz, 1H); 7.32 (dd, J = 7.8 and 7.1 Hz, 1H); 7.21 (dd, J = 8.9 and 2.4 Hz, 1H); 7.03 (d, J = 2.4 Hz, 1H); 4.0 (s, 2H); 3.94 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.5 (s); 132.0 (s); 130.6 (d); 129.1 (s); 128.8 (d); 127.1 (d); 124.4 (s); 123.2 (d); 118.8 (d); 117.7 (s); 101.3 (d); 55.4 (q); 21.9 (t).

Step E: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

136 g of Raney nickel, 2.06 litres of ethanol and 0.23 litre of water are introduced into an 8-litre reactor. While stirring at 70°C and under 30 bar of hydrogen, the compound obtained in the preceding Step D (0.8 kg) in solution in acetic anhydride (2.4 L) is added slowly. At the end of the addition, the reaction mixture is stirred for one hour under 30 bar of hydrogen and then the reactor is decompressed and the liquors are filtered off. After concentration of the mixture, the residue is crystallised from an ethanol/water mixture 35/65 to yield the title product with a yield of 89 % and a chemical purity greater than 99 %.

Melting point: *108°C*

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 2: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-[(Dimethylamino)methyl]-7-methoxynaphthalen-2-yl 4-methylbenzene-sulfonate

To a solution of the product obtained in Step A of Example 1 (2.042 g; 8.84 mmol) in dimethylformamide (8 mL) there are added potassium *tert*-butylate (1.091 g; 9.724 mmol) and then, at the end of 5 minutes, tosyl chloride (1.684 g; 8.84 mmol). After 6 hours' stirring, the solution is diluted in ethyl acetate and washed twice with water and then with brine. The organic phase is dried over sodium sulfate and filtered, and the solvent is evaporated off. The crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether, gradient from 30/70 to 70/30) to give the expected product in the form of a solid (1.94 g; 57 %).

Melting point: 115-118°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.78 (d, J = 8.1 Hz, 2H); 7.7 (d, J = 9.0 Hz, 1H); 7.62 (d, J = 8.8 Hz, 1H); 7.53 (d, J = 2.3 Hz, 1H); 7.34 (d, J = 8.1 Hz, 2H); 7.14 (dd, J = 9.0 and 2.3 Hz, 1H); 6.96 (d, J = 8.8 Hz, 1H); 3.93 (s, 3H); 3.67 (s, 2H); 2.47 (s, 3H); 2.24 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.4 (s); 146.9 (s); 145.5 (s); 135.1 (s); 133.2 (s); 130.0 (2 x d); 129.9 (d); 129.1 (d); 128.6 (2 x d); 127.8 (s); 125.7 (s); 118.5 (d); 117.9 (d); 104.5 (d); 55.3 (q); 54.2 (t); 45.6 (2 x q); 21.9 (q).

Step B: 1-(Cyanomethyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

Iodomethane (267 µL; 4.29 mmol) is added to a solution of the product of the preceding Step A (1.5 g; 9.9 mmol) in dimethylformamide (8 mL). After 4 hours' stirring at ambient temperature, potassium cyanide (304 mg; 4.68 mmol) is added. The solution is stirred for a further 16 hours and is then diluted in ethyl acetate, washed with water and three times with brine, dried over sodium sulfate and filtered. Evaporation of the solvent gives a crude product which is then purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 40/60) to give the expected product (1.276 g; 89 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.77 (d, J = 8.3 Hz, 2H); 7.75 (d, J = 8.9 Hz, 1H); 7.69 (d, J = 8.9 Hz, 1H); 7.35 (d, J = 8.3 Hz, 2H); 7.22-7.15 (m, 2H); 7.01 (d, J = 8.9 Hz, 1H); 3.98 (s, 2H); 3.95 (s, 3H); 2.45 (s, 3H).

Step C: *1-[2-(Acetylamino)ethyl]-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate*

The product of the preceding Step B (54 mg; 0.147 mmol), nickel chloride hexahydrate (35 mg; 0.147 mmol), dichloromethane (1.5 mL) and methanol (1.5 mL) are introduced into a sealed bottle. Argon is then bubbled into the solution for 5 minutes, and then sodium borohydride (100 mg; 2.94 mmol) is added carefully in small portions. After stirring for 30 minutes under argon and at ambient temperature, water is added. At the end of 15 minutes' stirring, the mixture is filtered over Celite and then washed with dichloromethane. The organic fraction is dried over sodium sulfate and then filtered. After evaporation of the solvents, the crude product obtained is placed in the presence of acetic anhydride (1 mL) and sodium acetate (50 mg) with stirring at ambient temperature for 30 minutes. The mixture is poured into dilute Na_2CO_3 solution and the product is extracted three times with ethyl acetate. The organic fractions are washed with brine, dried over sodium sulfate and filtered. Evaporation of the solvent gives a crude product, which is then purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the expected product in the form of a solid (24 mg; 40 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.81 (d, J = 8.2 Hz, 2H); 7.68 (d, J = 8.9 Hz, 1H); 7.62 (d, J = 2.4 Hz, 1H); 7.55 (d, J = 8.9 Hz, 1H); 7.36 (d, J = 8.2 Hz, 2H); 7.14 (dd, J = 8.9 and 2.4 Hz, 1H); 6.89 (d, J = 8.9 Hz, 1H); 5.97 (m, 1H); 4.01 (s, 3H); 3.53-3.46 (m, 2H); 3.22-3.17 (m, 2H); 2.46 (s, 3H); 1.95 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 170.9 (s); 158.9 (s); 146.4 (s); 145.7 (s); 134.6 (s); 133.3 (s); 130.1 (2 x d); 130.0 (d); 128.5 (2 x d); 128.2 (d); 127.7 (s); 126.2 (s); 119.2 (d); 117.8 (d); 103.3 (d); 55.8 (q); 39.4 (t); 26.4 (t); 23.4 (q); 21.9 (q).

Step D: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The product of the preceding Step C (83 mg; 0.2 mmol), nickel chloride (26 mg; 0.2 mmol) and methanol (4 mL) are introduced into a sealed bottle. Argon is then

bubbled into the solution for 5 minutes, and then sodium borohydride (136 mg; 4 mmol) is added carefully in small portions. After stirring for 30 minutes under argon and at ambient temperature, the mixture is filtered over Celite and then washed with ethyl acetate, and the solvents are evaporated off. The crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the expected product (39 mg; 80 %).

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 3: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

*Step A: 8-Methoxynaphtho[2,1-*b*]furan-2(1*H*)-one*

An 85 % aqueous solution of potassium hydroxide (2.76 g; 40 mmol) and 7-methoxy-naphthalen-2-ol (6.96 g; 40 mmol) in water (80 mL) is added dropwise at ambient temperature to a solution of glyoxal (40 % in water; 28 mL; 240 mmol). After 3 hours' stirring, the white precipitate is collected by filtration and washed with water. The solid (8-methoxy-1,2-dihydronaphtho[2,1-*b*]furan-1,2-diol) obtained is dissolved in 1,2-dichloroethane (160 mL), and 3 M aqueous HCl solution (300 mL) is then added. The heterogeneous mixture is heated to 50°C with vigorous stirring. At the end of 1.5 hours, all the solid has dissolved and the two phases are separated. The organic phase is collected and the solvents are evaporated off. The crude product is dried by azeotropy with toluene to give the title product (8.69 g), which will be used directly for the following step without further purification.

^{1}H NMR spectroscopic analysis (DMSO-d_6, 300.13 MHz, δ in ppm): 7.88 (d, J = 8.8 Hz, 1H); 7.85 (d, J = 8.6 Hz, 1H); 7.28 (d, J = 8.8 Hz, 1H); 7.12-7.06 (m, 2H); 4.15 (s, 2H); 3.89 (s, 3H).

Step B: N,N-*Dibenzyl-2-(2-hydroxy-7-methoxynaphthalen-1-yl)acetamide*

The product of the preceding Step A (1.976 g; 9.23 mmol) and dibenzylamine (4 mL; 20.3 mmol) are introduced into a flask and then heated at 120°C for 2 hours. After cooling, the residue is diluted with ethyl acetate (200 mL). The addition of 2 M aqueous HCl solution precipitates the dibenzylamine hydrochloride salt, which is then filtered over Celite. The organic phase is washed with 2 M aqueous HCl solution and is then washed with brine, dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 30/70) to give the expected product in the form of a solid (2.88 g; 76 %).

Melting point: *155-157°C*

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 9.85 (bs, 1H); 7.66 (d, J = 8.7 Hz, 1H); 7.62 (d, J = 8.7 Hz, 1H); 7.4-7.24 (m, 6H); 7.18-7.14 (m, 4H); 7.08 (d, J = 8.7 Hz, 1H); 6.95-6.91 (m, 2H); 4.72 (s, 2H); 4.64 (s, 2H); 4.21 (s, 2H); 3.55 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 174.6 (s); 158.6 (s); 155.8 (s); 136.4 (s); 135.5 (s); 134.1 (s); 130.6 (d); 129.3 (d); 129.2 (2 x d); 128.9 (2 x d); 128.4 (2 x d); 128.1 (d); 127.8 (d); 126.4 (2 x d); 124.6 (s); 117.5 (d); 114.9 (d); 111.5 (s); 101.2 (d); 55.9 (q); 50.8 (t); 49.0 (t); 31.5 (t).

Step C: 1-[2-(Dibenzylamino)ethyl]-7-methoxynaphthalen-2-ol

To a solution of the product of the preceding Step B (230 mg; 0.56 mmol) in tetrahydrofuran (10 mL) there is added a 1 M solution of borane-tetrahydrofuran complex in tetrahydrofuran (1.7 mL; 1.7 mmol). The mixture is heated at reflux for 2 hours, and 2 M aqueous HCl solution (10 mL) is then added. After stirring overnight, saturated $NaHCO_3$ solution is added until a neutral pH is reached, and the product is extracted three times with ethyl acetate. The organic fractions are dried over sodium sulfate and filtered, and the solvent is evaporated off. The crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 30/70) to give the expected product (150 mg; 72 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 12.09 (bs, 1H); 7.69 (d, J = 8.9 Hz, 1H); 7.61 (d, J = 8.8 Hz, 1H); 7.44-7.26 (m, 10H); 7.14 (d, J = 8.8 Hz, 1H); 7.12 (d, J = 2.4 Hz, 1H); 7.0 (dd, J = 8.8 and 2.4 Hz, 1H); 3.93 (s, 3H); 3.79 (s, 4H); 3.21-3.18 (m, 2H); 3.01-2.98 (m, 2H).

Step D: 1-[2-(Dibenzoylamino)ethyl]-7-methoxynaphthalen-2-yl trifluoromethanesulfonate

Triflic anhydride (135 µL; 0.801 mmol) is added at 0°C to a solution of the product of the preceding Step C (303 mg; 0.763 mmol) in dichloromethane (10 mL). At the end of 2 hours' stirring at that temperature, the solvent is evaporated off. The residue is taken up in a mixture of diethyl ether/semi-saturated aqueous $NaHCO_3$ solution. After separation, the organic phase is dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 10/90) to give the expected product (306 mg; 76 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.73 (d, J = 8.9 Hz, 1H); 7.69 (d, J = 8.9 Hz, 1H); 7.44-7.4 (m, 4H); 7.35-7.22 (m, 7H); 7.15 (dd, J = 8.9 and 2.3 Hz, 1H); 6.99 (d, J = 2.3 Hz, 1H); 3.78 (s, 4H); 3.6 (s, 3H); 3.43-3.37 (m, 2H); 2.91-2.86 (m, 2H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.9 (s); 146.1 (s); 139.8 (2 x s); 134.3 (s); 130.3 (d); 128.7 (4 x d); 128.6 (d); 128.3 (4 x d); 128.1 (s); 127.4 (s); 127.0 (2 x d); 119.5 (d); 118.7 (s, J_{C-F} = 318 Hz); 116.8 (d); 102.8 (d); 58.3 (2 x t); 55.3 (q); 52.5 (t); 24.6 (t).

Step E: N,N-*Dibenzyl-2-(7-methoxynaphthalen-1-yl)ethanamine*

The product of the preceding Step D (130 mg; 0.25 mmol), palladium acetate (5.6 mg; 0.025 mmol), triphenylphosphine (20 mg; 0.075 mmol), ammonium formate (142 mg; 2.25 mmol) and dimethylformamide (1 mL) are introduced into a flask. After 16 hours' stirring at 60°C, the solution is diluted in ethyl acetate, washed with water, washed twice with brine, dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product obtained is purified by chromatography on a silica gel

column (eluant: ethyl acetate/petroleum ether 10/90) to give the title product in the form of a white solid (93 mg; 98 %).

Melting point: 92-93°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.74 (d, J = 8.9 Hz, 1H); 7.65 (m, 1H); 7.43-7.39 (m, 4H); 7.35-7.22 (m, 8H); 7.11 (dd, J = 8.9 and 2.4 Hz, 1H); 7.05 (d, J = 2.4 Hz, 1H); 3.76 (s, 4H); 3.67 (s, 3H); 3.29-3.23 (m, 2H); 2.92-2.86 (m, 2H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 157.6 (s); 139.9 (2 x s); 135.3 (s); 133.2 (s); 130.3 (d); 129.3 (s); 128.7 (4 x d); 128.3 (4 x d); 127.3 (d); 127.0 (2 x d); 126.5 (d); 123.3 (d); 118.2 (d); 102.2 (d); 58.6 (2 t); 55.2 (q); 54.2 (t); 31.5 (t).

Step F: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The product of the preceding Step E (66 mg; 0.173 mmol), palladium hydroxide on carbon (20 % Pd, 60 % humidity; 10 mg), ethanol (2 mL) and ethyl acetate (2 mL) are introduced into a flask placed in an autoclave. The autoclave is filled with hydrogen under pressure (5 bar) and the mixture is stirred for 30 hours. The solution is then filtered over Celite and washed with ethanol, and the solvents are evaporated off. Acetic anhydride (500 µL) and sodium acetate (100 mg) are added to the crude reaction product. At the end of 4 hours' stirring, the mixture is diluted in ethyl acetate. The organic phase is washed twice with 2 M saturated aqueous sodium hydroxide solution, with brine, dried over sodium sulfate and filtered. After evaporation of the solvents, the expected product is obtained in pure form (41 mg; 98 %).

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 4: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-(2-Hydroxyethyl)-7-methoxynaphthalen-2-ol

The product obtained in Step A of Example 3 (8.96 g; 40 mmol) is dissolved in tetrahydrofuran (160 mL), and then lithium aluminium hydride (1.52; 40 mmol) is added in portions at 0°C under a stream of nitrogen. The mixture is stirred for 16 hours at ambient temperature and then the reaction is stopped at 0°C with the addition of ethyl acetate and then water. 1 M aqueous sulfuric acid solution (80 mL) is added. At the end of one hour's stirring, the heterogeneous mixture is filtered over Celite and washed with ethyl acetate. After decantation and separation, the organic phase is washed with water and then with brine. The solution is again filtered through a fine layer of silica and the solvents are evaporated off to yield the title product without further purification (8.21 g; 94 % starting from 7-methoxy-naphthalen-2-ol).

^{1}H NMR spectroscopic analysis (DMSO-d_6, 300.13 MHz, δ in ppm): 7.6 (d, J = 8.8 Hz, 1H); 7.49 (d, J = 8.8 Hz, 1H); 7.25 (d, J = 2.4 Hz, 1H); 6.94 (d, J = 8.8 Hz, 1H); 6.9 (dd, J = 8.8 and 2.4 Hz, 1H); 3.9 (s, 3H); 3.79-3.73 (m, 2H); 3.31-3.25 (m, 2H).

Step B: 7-Methoxy-1-(2-{[(4-methylphenyl)sulfonyl]oxy}ethyl)naphthalen-2-yl 4-methylbenzenesulfonate

The product of the preceding Step A (436 mg; 2 mmol), dichloromethane (10 mL), triethylamine (670 µL; 4.8 mmol) and 4-dimethylaminopyridine (12 mg; 0.1 mmol) are introduced into a flask. After cooling to 0°C, tosyl chloride (800 mg; 4 mmol) is added in a single batch and the solution is stirred for 2 hours at 0°C and then for 14 hours at ambient temperature. After evaporation of the solvent, the residue is taken up in ethyl acetate and water. The organic fraction is washed with water and with brine, dried over sodium sulfate and filtered. Once the solvent has evaporated, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether, gradient from 20/80 to 30/70) to give the title product (728 mg; 69 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.78 (d, J = 8.3 Hz, 2H); 7.69 (d, J = 9.1 Hz, 1H); 7.66 (d, J = 8.3 Hz, 2H); 7.59 (d, J = 8.9 Hz, 1H); 7.35 (d, J = 8.3 Hz, 2H); 7.26 (d, J = 2.4 Hz, 1H); 7.23 (d, J = 8.3 Hz, 2H); 7.15 (dd, J = 8.9

and 2.4 Hz, 1H); 7.03 (d, J = 9.1 Hz, 1H); 4.2 (t, J = 7.7 Hz, 2H); 3.94 (s, 3H); 3.34 (d, J = 7.7 Hz, 2H); 2.47 (s, 3H); 2.39 (s, 3H).

Step C: 1-[2-(Acetylamino)ethyl]-7-methoxy-naphthalen-2-yl 4-methylbenzenesulfonate

The product of the preceding Step B (124 mg; 0.236 mmol), acetonitrile (1 mL) and 35 % aqueous ammonia solution (1 mL) are introduced into a sealed bottle. The flask is placed in a bath heated at 110°C and the solution is stirred for 3.5 hours. After cooling, the solution is diluted in ethyl acetate, washed with dilute $NaHCO_3$ solution, washed with brine, dried over sodium sulfate and filtered. Once the solvents have evaporated, the crude product is dissolved in acetic anhydride (1 mL), and sodium acetate (300 mg) is then added. After 14 hours' stirring, the mixture is poured into dilute $NaHCO_3$ solution. At the end of 30 minutes' stirring, the product is extracted three times with ethyl acetate. The organic phase is washed with water and with brine, dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (84 mg; 86 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.81 (d, J = 8.2 Hz, 2H); 7.68 (d, J = 8.9 Hz, 1H); 7.62 (d, J = 2.4 Hz, 1H); 7.55 (d, J = 8.9 Hz, 1H); 7.36 (d, J = 8.2 Hz, 2H); 7.14 (dd, J = 8.9 and 2.4 Hz, 1H); 6.89 (d, 8.9 Hz, 1H); 5.97 (m, 1H); 4.01 (s, 3H); 3.53-3.46 (m, 2H); 3.22-3.17 (m, 2H); 2.46 (s, 3H); 1.95 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 170.9 (s); 158.9 (s); 146.4 (s); 145.7 (s); 134.6 (s); 133.3 (s); 130.1 (2 x d); 130.0 (d); 128.5 (2 x d); 128.2 (d); 127.7 (s); 126.2 (s); 119.2 (d); 117.8 (d); 103.3 (d); 55.8 (q); 39.4 (t); 26.4 (t); 23.4 (q); 21.9 (q).

Step D: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The title product is obtained in accordance with the process described in Step D of Example 2 using the product of the preceding Step C as the starting reagent.

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.20 (m,

2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 5: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 7-Methoxy-1-{2-[(propylsulfonyl)oxy]ethyl}naphthalen-2-yl propane-1-sulfonate

The product obtained in Step A of Example 4 (2.45 g; 11.238 mmol) is dissolved in dichloromethane (60 mL), and triethylamine (3.7 mL; 26.4 mmol) is then added. After cooling to 0°C, *n*-propylsulfonyl chloride (2.8 mL; 24.6 mmol) is added dropwise. At the end of 2 hours' stirring at ambient temperature, the solvent is evaporated off. The residue obtained is taken up in diethyl ether and water. After separation, the organic phase is washed with dilute aqueous HCl solution, with water and with brine, dried over sodium sulfate and filtered. Once the solvent has evaporated, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 20/80) to give the title product in the form of a solid (3.335 g; 66 % over 3 steps starting from 7-methoxy-naphthalen-2-ol).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (m, 2H); 7.37 (d, J = 2.4 Hz, 1H); 7.31 (d, J = 9.0 Hz, 1H); 7.17 (dd, J = 9.0 and 2.4 Hz, 1H); 4.48 (t, J = 8.0 Hz, 2H); 3.96 (s, 3H); 3.6 (t, J = 8.0 Hz, 2H); 3.45-3.4 (m, 2H); 3.04-2.98 (m, 2H); 2.1 (m, 2H); 1.8 (m, 2H); 1.17 (t, J = 7.3 Hz, 3H); 0.99 (t, J = 7.3 Hz, 3H).

Step B: 1-[2-(Acetylamino)ethyl]-7-methoxynaphthalen-2-yl propane-1-sulfonate

The product of the preceding Step A (532 mg; 1.237 mmol), acetonitrile (18 mL) and 35 % aqueous ammonia solution (18 mL) are introduced into a sealed bottle. The mixture is then placed in a bath heated at 110°C for 3 hours. The solvents are then evaporated off under reduced pressure, producing an azeotrope with ethanol. The crude product is dissolved in acetic anhydride (5 mL) and, in a second stage, sodium acetate (500 mg) is

added. At the end of one hour's stirring, the solution is diluted with ethyl acetate and is then poured carefully into saturated aqueous $NaHCO_3$ solution. After 15 minutes' stirring, the two phases are separated and the aqueous phase is extracted twice with ethyl acetate. The organic fractions are combined, washed with water and then with brine, dried over sodium sulfate and filtered. Once the solvent has evaporated, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (289 mg; 64 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.73 (d, J = 8.9 Hz, 1H); 7.68 (d, J = 8.9 Hz, 1H); 7.62 (d, J = 2.5 Hz, 1H); 7.27 (d, J = 8.9 Hz, 1H); 7.16 (dd, J = 8.9 and 2.5 Hz, 1H); 5.95 (m, 1H); 4.02 (s, 3H); 3.62-3.54 (m, 2H); 3.43-3.32 (m, 2H); 2.09 (m, 2H); 1.17 (t, J = 7.4 Hz, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 170.9 (s); 159.0 (s); 145.6 (s); 134.7 (s); 130.2 (d); 128.6 (d); 127.7 (s); 126.0 (s); 119.2 (d); 118.1 (d); 103.3 (d); 55.9 (q); 53.6 (t); 39.4 (t); 26.5 (t); 23.4 (q); 17.6 (t); 13.1 (q).

Step C: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The product of the preceding Step B (327 mg; 0.896 mmol), ammonium acetate (1.19 g; 15.54 mmol), 10 % palladium on carbon (95 mg; 0.09 mmol), ethanol (3 mL) and magnesium powder (83 mg; 3.584 mmol) are introduced into a flask. At the end of 16 hours' stirring, the heterogeneous mixture is filtered over Celite and washed with ethyl acetate. After evaporation of the solvents, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (190 mg; 87 %).

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs; 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 6: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-[2-(2,5-Dioxopyrrolidin-1-yl)ethyl]-7-methoxynaphthalen-2-yl propane-1-sulfonate

The product obtained in Step A of Example 5 (240 mg; 0.558 mmol), potassium carbonate (231 mg; 1.674 mmol), succinimide (66 mg; 0.67 mmol) and dimethylformamide (2 mL) are introduced into a flask. After stirring for 16 hours at 100°C, the solution is diluted in ethyl acetate, washed with dilute aqueous HCl solution, with water and with brine, and then dried over sodium sulfate and filtered. Once the solvent has evaporated, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 70/30) to yield the title product (123 mg; 57 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.74 (d, J = 9.0 Hz, 1H); 7.7 (d, J = 8.9 Hz, 1H); 7.6 (d, J = 2.4 Hz, 1H); 7.38 (d, J = 9.0 Hz, 1H); 7.16 (dd, J = 8.9 and 2.4 Hz, 1H); 4.05 (s, 3H); 3.86-3.8 (m, 2H); 3.58-3.52 (m, 2H); 3.33-3.27 (m, 2H); 2.72 (s, 4H); 2.14 (m, 2H); 1.2 (t, J = 7.5 Hz, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 177.3 (2 x s); 159.1 (s); 145.3 (s); 134.4 (s); 130.4 (d); 128.8 (d); 127.7 (s); 124.2 (s); 119.2 (d); 118.4 (d); 102.4 (d); 55.8 (q); 53.5 (t); 37.7 (t); 28.4 (2 x t); 24.7 (t); 17.5 (t); 13.1 (q).

Step B: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The product of the preceding Step A (65 mg; 0.16 mmol), ammonium acetate (240 mg; 3.12 mmol), 10 % palladium on carbon (16.5 mg; 0.016 mmol), methanol (0.7 mL) and magnesium powder (8 mg; 0.36 mmol) are introduced into a flask in a single portion. After stirring for 12 hours at 30°C, the heterogeneous mixture is filtered over Celite and then washed with ethyl acetate. After evaporation of the solvents, the crude product is dissolved in ethanol (2 mL) in a sealed tube, and then aqueous sodium hydroxide solution (180 mg; 4.5 mmol in 1 mL of water) is added. The mixture is then diluted in acetic anhydride (5 mL), and sodium acetate (500 mg) is introduced. At the end of one hour's stirring, the solution is diluted in ethyl acetate and then poured carefully into saturated aqueous $NaHCO_3$ solution. After 15 minutes' stirring, the two phases are

separated and the aqueous phase is extracted twice with ethyl acetate. The organic fractions are combined, washed with water and with brine, dried over sodium sulfate and filtered. Once the solvent has evaporated, the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (14.4 mg; 37 %).

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 7: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-(2-Hydroxyethyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

To a solution of the product obtained in Step A of Example 4 (109 mg; 0.5 mmol) in tetrahydrofuran (2.5 mL) there are added at 0°C potassium *tert*-butylate (56.4 mg; 0.5 mmol) and then, at the end of 5 minutes, tosyl chloride (95 mg; 0.5 mmol). At the end of 3 hours' stirring, the solution is allowed to return to ambient temperature and is stirred for a further 15 hours. The solvent is evaporated off and the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 50/50) to give a mixture of two diastereoisomers (116 mg; 62 %) in a ratio of 88:12. The mixture is used as such without further purification.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.83 (d, J = 8.2 Hz, 2H); 7.71 (d, J = 9.1 Hz, 1H); 7.59 (d, J = 8.9 Hz, 1H); 7.35 (d, J = 8.2 Hz, 2H); 7.29 (d, J = 2.4 Hz, 1H); 7.15 (dd, J = 8.9 and 2.4 Hz, 1H); 7.04 (d, J = 9.1 Hz, 1H); 3.91 (s, 3H); 3.87 (t, J = 7.1 Hz, 2H); 3.23 (t, J = 7.1 Hz, 2H); 2.46 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.6 (s); 146.7 (s); 145.7 (s); 134.5 (s); 133.3 (s); 130.3 (d); 130.1 (2 x d); 128.5 (2 x d); 128.2 (d); 127.8 (s); 125.7 (s); 118.5 (d); 118.3 (d); 103.4 (d); 62.1 (t); 55.5 (q); 29.7 (t); 21.9 (q).

Step B: 2-(7-Methoxynaphthalen-1-yl)ethanol

The mixture of diastereoisomers obtained in the preceding Step A (80 mg; 0.176 mmol of the correct isomer), nickel chloride hexahydrate (51 mg; 0.215 mmol), dichloromethane (2 mL) and methanol (2 mL) are introduced into a sealed bottle. Argon is then bubbled into the solution for 5 minutes, and then sodium borohydride (146 mg; 4.3 mmol) is added carefully in small portions. At the end of one hour's stirring at ambient temperature under argon, dilute aqueous HCl solution is added. After 4 hours' stirring, the mixture is filtered over Celite and washed with ethanol. The solvent is evaporated off and the crude product obtained is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 40/60) to give the title product (22 mg; 62 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.63 (d, J = 8.1 Hz, 1H); 7.3-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.6 Hz, 1H); 3.93 (t, J = 6.7 Hz, 2H); 3.88 (s, 3H); 3.24 (d, J = 6.7 Hz, 2H); 1.99 (bs, 1H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 157.8 (s); 133.2 (s); 133.0 (s); 130.4 (d); 129.4 (s); 127.7 (d); 127.1 (d); 123.3 (d); 118.1 (d); 102.5 (d); 62.7 (t); 55.4 (q); 36.4 (t).

Mass spectrometry (ESI; m/z(%)): 202(29) $[M]^{+\bullet}$; 171(100).

Step C: 2-(7-Methoxynaphthalen-1-yl)ethyl methanesulfonate

To a solution of the product of the preceding Step B (275 mg; 1.361 mmol) in dichloromethane (7 mL) there are added at 0°C triethylamine (227 µL; 1.633 mmol) and methanesulfonyl chloride (116 µL; 1.498 mmol). At the end of one hour's stirring, the solvents are evaporated off and the residue is taken up in diethyl ether and water. After separation, the organic phase is washed three times with water and with brine, dried over sodium sulfate and filtered. Evaporation of the solvent provides the clean expected product without additional purification (356 mg; 93 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.66 (d, J = 8.9 Hz, 1H); 7.31-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.5 Hz, 1H); 4.47 (t, J = 7.4 Hz, 2H); 3.92 (s, 3H); 3.45 (d, J = 7.4 Hz, 2H); 2.77 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.2 (s); 133.0 (s); 133.0 (s); 130.6 (s); 130.4 (d); 129.3 (s); 128.0 (d); 127.7 (d); 123.2 (d); 118.4 (d); 101.9 (d); 67.9 (t); 55.5 (q); 37.4 (q); 33.3 (t).

Step D: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The product of the preceding Step C (356 mg; 1.271 mmol), acetonitrile (7 mL) and 35 % aqueous ammonia solution (5 mL) are introduced into a flask. The flask is placed in a bath heated at 110°C and the solution is stirred for 3 hours. The solution is diluted with ethyl acetate and washed with 2 M aqueous sodium hydroxide solution, water and brine and is then dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is dissolved in acetic anhydride (2 mL) in the presence of sodium acetate (500 mg). At the end of one hour's stirring, water and ethyl acetate are added and, after 15 minutes' stirring, the organic phase is washed twice with 2 M aqueous sodium hydroxide solution, washed with water and brine, dried over sodium sulfate and filtered. The solvent is evaporated off and the crude product obtained is then purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (230 mg; 74 %).

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 8: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 2-(2-Hydroxy-7-methoxynaphthalen-1-yl)acetamide

7 N ammonia solution in methanol (10 mL; 70 mmol) and the product obtained in Step A of Example 3 (1.5 g; 7 mmol) are introduced into a sealed bottle. At the end of 18

hours' stirring at 100°C, the solvent is evaporated off to give the crude title product (1.58 g; 98 %), which is used directly without any additional purification.

^{1}H NMR spectroscopic analysis (DMSO-d_6, 300.13 MHz, δ in ppm): 9.87 (bs, 1H); 7.68 (d, J = 9.0 Hz, 1H); 7.59 (d, J = 8.7 Hz, 1H); 7.36 (bs, 1H); 7.18 (d, J = 2.4 Hz, 1H); 7.01 (d, J = 8.7 Hz, 1H); 7.01 (bs, 1H); 6.94 (dd, J = 9.0 and 2.4 Hz, 1H); 3.84 (s, 3H); 3.79 (s, 2H).

Step B: 1-[2-(Acetylamino)ethyl]-7-methoxynaphthalen-2-yl acetate

Lithium aluminium hydride (396 mg; 10.432 mmol) is added to a suspension of the product of the preceding Step A (1.205 g; 5.216 mmol) in tetrahydrofuran (25 mL). After stirring at reflux for 8 hours, the mixture is cooled to 0°C and water (40 mL) and then citric acid (10 g) are added. At the end of 14 hours' stirring, the mixture is neutralised using saturated aqueous $NaHCO_3$ solution and the product is extracted three times with ethyl acetate. The organic phases are combined, washed with water and with brine and then dried over sodium sulfate and filtered. After evaporation, the crude product (802 mg) is dissolved in acetic anhydride (3 mL) in the presence of sodium acetate (500 mg). The mixture is stirred for 16 hours and is then poured into dilute aqueous $NaHCO_3$ solution. The product is extracted three times with ethyl acetate and the organic phases are combined, washed with water and with brine, dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/methanol, gradient from 100/0 to 95/5) to give the title product in the form of a white solid (337 mg; 21 %).

Melting point: 149-151°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.73 (d, J = 8.9 Hz, 1H); 7.68 (d, J = 8.8 Hz, 1H); 7.42 (d, J = 2.2 Hz, 1H); 7.14 (dd, J = 8.8 and 2.2 Hz, 1H); 7.01 (d, J = 8.9 Hz, 1H); 5.75 (bs, 1H); 3.97 (s, 3H); 3.52 (m, 2H); 3.19 (t, J = 6.7 Hz, 2H); 2.39 (s, 3H); 1.9 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 170.7 (s); 170.6 (s); 158.6 (s); 147.5 (s); 134.3 (s); 130.3 (d); 128.2 (d); 127.5 (s); 124.1 (s); 119.0 (d); 118.2 (d); 102.9 (d); 55.6 (q); 39.1 (t); 25.9 (t); 23.4 (q); 21.1 (q).

Step C: 1-[2-(Acetylamino)ethyl]-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

The product of the preceding Step B (230 mg; 0.764 mmol) is added to a solution of sodium hydroxide (61 mg; 1.528 mmol) in absolute ethanol (10 mL). After stirring for one hour, the solvent is evaporated off. The residue is taken up in a mixture of ethyl acetate/dilute aqueous hydrochloric acid solution. After separation, the organic phase is washed with water and with brine and then dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is dissolved in dichloromethane (4 mL) in the presence of triethylamine (150 μL; 2.47 mmol) and tosyl chloride (174 mg; 0.917 mmol). At the end of 16 hours' stirring at ambient temperature, the solvent is evaporated off. The residue is taken up in ethyl acetate and water. After separation, the organic phase is washed with water and with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (261 mg; 83 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.81 (d, J = 8.2 Hz, 2H); 7.68 (d, J = 8.9 Hz, 1H); 7.62 (d, J = 2.4 Hz, 1H); 7.55 (d, J = 8.9 Hz, 1H); 7.36 (d, J = 8.2 Hz, 2H); 7.14 (dd, J = 8.9 and 2.4 Hz, 1H); 6.89 (d, 8.9 Hz, 1H); 5.97 (m, 1H); 4.01 (s, 3H); 3.53-3.46 (m, 2H); 3.22-3.17 (m, 2H); 2.46 (s, 3H); 1.95 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 170.9 (s); 158.9 (s); 146.4 (s); 145.7 (s); 134.6 (s); 133.3 (s); 130.1 (2 x d); 130.0 (d); 128.5 (2 x d); 128.2 (d); 127.7 (s); 126.2 (s); 119.2 (d); 117.8 (d); 103.3 (d); 55.8 (q); 39.4 (t); 26.4 (t); 23.4 (q); 21.9 (q).

Step D: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The title product is obtained in accordance with the process described in Step D of Example 2 using the product of the preceding Step C as the starting reagent.

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 9: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 1-(2-Amino-2-oxoethyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

Sodium hydride (60 % in mineral oil; 78 mg; 1.953 mmol) is added at 0°C to a solution of the product obtained in Step A of Example 8 (376 mg; 1.628 mmol) in dimethylformamide (3 mL). At the end of 30 minutes' stirring, tosyl chloride (341 mg; 1.79 mmol) is introduced in one portion. After 2 hours' stirring, the reaction mixture is diluted in ethyl acetate and then washed twice with water and twice with brine. The organic phase is dried over sodium sulfate and filtered. After evaporation of the solvents, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/dichloromethane 30/70) to give the title product in the form of a white solid (260 mg; 40 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.89 (d, J = 7.9 Hz, 2H); 7.72 (d, J = 9.0 Hz, 1H); 7.66 (d, J = 9.0 Hz, 1H); 7.4 (d, J = 7.9 Hz, 2H); 7.37 (d, J = 2.4 Hz, 1H); 7.17 (dd, J = 9.0 and 2.4 Hz, 1H); 7.01 (d, J = 9.0 Hz, 1H); 6.02 (bs, 1H); 5.48 (bs, 1H); 3.93 (s, 2H); 3.91 (s, 3H); 2.50 (s, 3H).

Step B: 2-(7-Methoxynaphthalen-1-yl)acetamide

The product obtained in the preceding Step A (50 mg; 0.13 mmol), nickel chloride hexahydrate (31 mg; 0.13 mmol), dichloromethane (1.3 mL) and methanol (1.3 mL) are introduced into a sealed bottle. Argon is then bubbled into the solution for 5 minutes, and then sodium borohydride (88 mg; 2.6 mmol) is added carefully in small portions. After stirring for one hour under argon and at ambient temperature, water is added. At the end of 15 minutes' stirring, the mixture is filtered over Celite and then washed with dichloromethane and ethyl acetate. The organic fraction is dried over sodium sulfate and then filtered. After evaporation of the solvents, the crude product is purified by

chromatography on a silica gel column (eluant: ethyl acetate) to give the title product (8 mg; 29 %).

^{1}H NMR spectroscopic analysis (DMSO-d_6, 300.13 MHz, δ in ppm): 7.84 (d, J = 9.0 Hz, 1H); 7.73 (d, J = 8.0 Hz, 1H); 7.62 (bs, 1H); 7.41-7.36 (m, 2H); 7.28 (dd, J = 8.0 and 7.1 Hz, 1H); 7.18 (dd, J = 9.0 and 2.4 Hz, 1H); 7.02 (bs, 1H); 3.88 (s, 3H); 3.82 (s, 2H).

^{13}C NMR spectroscopic analysis (DMSO-d_6, 75.5 MHz, δ in ppm): 172.3 (s); 157.3 (s); 133.2 (s); 131.8 (s); 130.0 (d); 128.7 (s); 128.4 (d); 126.7 (d); 123.1 (d); 117.7 (d); 103.4 (d); 55.2 (q); 40.2 (t).

Step C: *(7-Methoxynaphthalen-1-yl)acetonitrile*

The title product is obtained in accordance with the protocol described in Step F of Preparation 1 of patent EP 0 447 285 using the product of the preceding Step B as the starting reagent.

Melting point: 86-87°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.78 (d, J = 8.9 Hz, 1H); 7.77 (d, J = 7.8 Hz, 1H); 7.52 (d, J = 7.1 Hz, 1H); 7.32 (dd, J = 7.8 and 7.1 Hz, 1H); 7.21 (dd, J = 8.9 and 2.4 Hz, 1H); 7.03 (d, J = 2.4 Hz, 1H); 4.0 (s, 2H); 3.94 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.5 (s); 132.0 (s); 130.6 (d); 129.1 (s); 128.8 (d); 127.1 (d); 124.4 (s); 123.2 (d); 118.8 (d); 117.7 (s); 101.3 (d); 55.4 (q); 21.9 (t).

Step D: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The title product is obtained in accordance with the process described in Step E of Example 1 using the product of the preceding Step C.

Melting point: 108°C

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 10: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 2-Methoxy-7-(prop-2-en-1-yloxy)naphthalene

Allyl bromide (4.4 mL; 50.56 mmol) is added to a solution of 7-methoxy-naphthalen-2-ol (5.865 g; 33.71 mmol) and potassium carbonate (13.96 g; 101.12 mmol) in acetone (33 mL). After stirring at 65°C for 16 hours, the mixture is cooled to ambient temperature and water is added (60 mL). After stirring for 3 hours, the product is extracted three times with ethyl acetate. The organic fractions are combined, washed twice with water and then with brine, dried over sodium sulfate and filtered. Evaporation of the solvents provides a crude product (7.963 g) which is used directly in the following step without further purification.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.68 (d, J = 8.9 Hz, 1H); 7.67 (d, J = 8.9 Hz, 1H); 7.08-6.99 (m, 3H); 6.13 (m, 1H); 5.48 (m, 1H); 5.34 (m, 1H); 4.65 (m, 1H); 3.92 (s, 3H).

Step B: 7-Methoxy-1-(prop-2-en-1-yl)naphthalen-2-ol

In a flask, the product of the preceding Step A (7.963 g; 33.71 mmol) is placed in a bath heated at 200°C for 2.5 hours. After cooling, the crude product is used directly in the following step without further purification.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.69 (d, J = 8.9 Hz, 1H); 7.6 (d, J = 8.7 Hz, 1H); 7.2 (d, J = 2.4 Hz, 1H); 7.03 (dd, J = 8.9 and 2.4 Hz, 1H); 6.95 (d, J = 8.7 Hz, 1H); 6.08 (m, 1H); 5.28 (s, 1H); 5.14 (m, 1H); 5.1 (m, 1H); 3.93 (s, 3H); 3.8 (m, 1H).

Step C: 7-Methoxy-1-(prop-2-en-1-yl)naphthalen-2-yl 4-methylbenzenesulfonate

Triethylamine (1.95 mL; 14.02 mmol) and tosyl chloride (2.23 g; 11.68 mmol) are added to a solution of the product of the preceding Step B (2.5 g; 11.68 mmol) in dichloromethane (22 mL). After stirring for 16 hours at ambient temperature, the solvent is evaporated off and the residue is taken up in ethyl acetate and water. After separation, the organic phase is washed with water and with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether, gradient from 10/90 to 20/80) to give the title product (3.79 g; 88 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.9 (d, J = 8.3 Hz, 2H); 7.71 (d, J = 8.9 H\, 1H); 7.6 (d, J = 8.9 Hz, 1H); 7.33 (d, J = 8.3 Hz, 2H); 7.24 (d, J = 2.5 Hz, 1H); 7.14 (dd, J = 8.9 and 2.5 Hz); 7.1 (d, J = 8.9 Hz, 1H); 5.79 (m, 1H); 5.02-4.95 (m, 2H); 3.88 (s, 3H); 3.68 (d, J = 5.9 Hz, 2H); 2.46 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.3 (s); 146.1 (s); 145.5 (s); 135.5 (d); 134.4 (s); 133.3 (s); 130.1 (d); 130.0 (2 x d); 128.5 (2 x d); 128.0 (d); 127.7 (s); 126.6 (s); 118.5 (d); 118.4 (d); 116.1 (t); 103.9 (d); 55.4 (q); 30.5 (t); 21.8 (q).

Step D: 1-(2,3-Dihydroxypropyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate

Hydrated 4-methylmorpholine *N*-oxide (1.666 g; 12.35 mmol) and osmium tetroxide (4 % in water; 653 µL; 0.01 mmol) are added to a solution of the product of the preceding Step C (3.786 g; 10.29 mmol) in acetone (40 mL) and deionised water (10 mL). After stirring at ambient temperature for 20 hours, sodium thiosulfate pentahydrate is added (1 g). At the end of a further hour's stirring, the solvents are evaporated off. The residue is taken up in ethyl acetate and the organic phase is washed with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate) to give the title product in the form of a white solid (3.617 g; 87 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.81 (d, J = 8.3 Hz, 2H); 7.69 (d, J = 9.0 Hz, 1H); 7.58 (d, J = 9.0 Hz, 1H); 7.33 (d, J = 8.3 Hz, 2H); 7.13

(dd, J = 9.0 and 2.4, 1H); 7.02 (d, J = 9.0 Hz, 1H); 4.01 (m, 1H); 3.88 (s, 3H); 3.63-3.47 (m, 2H); 3.11 (d, J = 7.0 Hz, 2H); 2.9 (bs, 1H); 2.62 (bs, 1H); 2.44 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.6 (s); 146.8 (s); 145.8 (s); 134.6 (s); 133.1 (s); 130.2 (d); 130.1 (2 x d); 128.4 (2 x d); 128.3 (d); 127.7 (s); 125.4 (s); 118.6 (d); 118.0 (d); 103.6 (d); 72.0 (d); 65.8 (t); 55.5 (q); 30.1 (t); 21.8 (q).

Step E: 7-Methoxy-1-(2-oxoethyl)naphthalen-2-yl 4-methylbenzenesulfonate

Sodium periodate (785 mg; 3.671 mmol) and 2 M aqueous HCl solution (1.8 mL) are added to a solution of the product of the preceding Step D (1.23 g; 3.06 mmol) in tetrahydrofuran (12 mL) and water (3 mL). At the end of 30 minutes, the mixture is neutralised with dilute aqueous $NaHCO_3$ solution and the product is then extracted with ethyl acetate. The organic fractions are combined, dried over sodium sulfate and filtered. Evaporation of the solvent provides the title compound in the form of a clean white solid (1.13 g; 100 %), which is used directly in the following step.

Melting point: 101-103°C

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 9.43 (t, J = 2.6 Hz, 1H); 7.78 (d, J = 8.3 Hz, 2H); 7.74 (d, J = 8.9 Hz, 1H); 7.68 (d, J = 8.9 Hz, 1H); 7.35 (d, J = 8.3 Hz, 2H); 7.17 (dd, J = 8.9 and 2.4 Hz, 1H); 7.04 (d, J = 8.9 Hz, 1H); 6.97 (d, J = 2.4 Hz, 1H); 3.98 (d, J = 2.6 Hz, 2H); 3.88 (s, 3H); 2.46 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 199.2 (d); 159.1 (s); 146.8 (s); 146.0 (s); 134.7 (s); 132.7 (s); 130.4 (d); 130.2 (2 x d); 129.4 (d); 128.6 (2 x d); 127.6 (s); 120.1 (s); 119.1 (d); 118.6 (d); 102.9 (d); 55.5 (q); 41.7 (t); 21.9 (q).

Step F: 2-(7-Methoxynaphthalen-1-yl)ethanol

To a solution of the product of the preceding Step E (950 mg; 2.567 mmol) in methanol (13 mL) there are added under argon nickel chloride (366 mg; 2.824 mmol) and sodium borohydride (1.3 g; 38.2 mmol) in small portions. At the end of one hour's stirring, the mixture is hydrolysed with 2 M aqueous HCl solution (80 mL) and is then stirred for 30 minutes in the presence of ethyl acetate. The heterogeneous solution is filtered over Celite and washed with ethyl acetate. The two phases are separated and the organic

fraction is washed with brine, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 40/60) to give the title product in the form of a white solid (442 mg; 85 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.63 (d, J = 8.1 Hz, 1H); 7.3-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.6 Hz, 1H); 3.93 (t, J = 6.7 Hz, 2H); 3.88 (s, 3H); 3.24 (d, J = 6.7 Hz, 2H); 1.99 (bs, 1H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 157.8 (s); 133.2 (s); 133.0 (s); 130.4 (d); 129.4 (s); 127.7 (d); 127.1 (d); 123.3 (d); 118.1 (d); 102.5 (d); 62.7 (t); 55.4 (q); 36.4 (t).

Mass spectrometry (ESI; m/z(%)): 202(29) $[M]^{+\bullet}$; 171(100).

Step G: 2-(7-Methoxynaphthalen-1-yl)ethyl methanesulfonate

The title product is obtained in accordance with the process described in Step C of Example 7 using the product of the preceding Step F as the starting reagent.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.66 (d, J = 8.9 Hz, 1H); 7.31-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.5 Hz, 1H); 4.47 (t, J = 7.4 Hz, 2H); 3.92 (s, 3H); 3.45 (d, J = 7.4 Hz, 2H); 2.77 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.2 (s); 133.0 (s); 133.0 (s); 130.6 (s); 130.4 (d); 129.3 (s); 128.0 (d); 127.7 (d); 123.2 (d); 118.4 (d); 101.9 (d); 67.9 (t); 55.5 (q); 37.4 (q); 33.3 (t).

Step H: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

The title product is obtained in accordance with the process described in Step D of Example 7 using the product of the preceding Step G as the starting reagent.

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

EXAMPLE 11: *N*-[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide

Step A: 3-(7-Methoxynaphthalen-1-yl)propane-1,2-diol

The product obtained in Step D of Example 10 (44 mg; 0.11 mmol), nickel chloride (16 mg; 0.12 mmol) and methanol (1 mL) are introduced, under argon, into a sealed bottle. Sodium borohydride (74 mg; 2.19 mmol) is then added carefully in small portions. At the end of 2 hours' stirring, water (1 mL) and then hydrogen peroxide (35 % in water; 1 mL) are added and the mixture is stirred for 2 hours. Brine is then added and the aqueous phase is extracted three times with ethyl acetate. The organic phases are combined, dried over sodium sulfate and filtered. Evaporation of the solvents gives a clean product (22 mg; 86 %) without the need for additional purification.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.75 (d, J = 9.1 Hz, 1H); 7.68 (d, J = 8.1 Hz, 1H); 7.32-7.23 (m, 3H); 7.16 (dd, J = 9.1 and 2.4 Hz, 1H); 4.11 (m, 1H); 3.92 (s, 3H); 3.72-3.55 (m, 2H); 3.25-3.1 (m, 2H); 2.54 (bs, 2H, OH).

Step B: (7-Methoxynaphthalen-1-yl)acetaldehyde

The title product is obtained in accordance with the process described in Step E of Example 10 using the product of the preceding Step A instead of 1-(2,3-dihydroxypropyl)-7-methoxynaphthalen-2-yl 4-methylbenzenesulfonate.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 9.74 (t, J = 2.6 Hz, 1H); 7.74-7.84 (m, 2H); 7.38 (d, J = 6.0 Hz, 1H); 7.32 (t, J = 7.5 Hz, 1H); 7.19 (dd, J = 9.0 Hz and 2.4 Hz, 1H); 7.1 (d, J = 2.4 Hz, 1H); 4.05 (d, J = 2.6 Hz, 2H); 3.92 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 199.85; 158.29; 133.54; 130.44; 129.32; 129.07; 128.23; 126.83; 123.36; 118.63; 102.12; 55.36; 48.83.

Step C: 2-(7-Methoxynaphthalen-1-yl)ethanol

Sodium borohydride (38 mg; 1 mmol) is added to a solution of the product of the preceding Step B (20 mg; 0.1 mmol) in ethanol (1 mL). At the end of 2 hours' stirring at ambient temperature, the mixture is hydrolysed with 2 M aqueous HCl solution (2 mL) and is then stirred for 30 minutes in the presence of ethyl acetate (1 mL). The solution is extracted 4 times with ethyl acetate. The organic fractions are combined, dried over sodium sulfate and filtered. After evaporation of the solvent, the crude product is purified by chromatography on a silica gel column (eluant: ethyl acetate/petroleum ether 20/80) to give the title product in the form of a white solid (19.8 mg; 98 %).

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.63 (d, J = 8.1 Hz, 1H); 7.3-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.6 Hz, 1H); 3.93 (t, J = 6.7 Hz, 2H); 3.88 (s, 3H); 3.24 (d, J = 6.7 Hz, 2H); 1.99 (bs, 1H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 157.8 (s); 133.2 (s); 133.0 (s); 130.4 (d); 129.4 (s); 127.7 (d); 127.1 (d); 123.3 (d); 118.1 (d); 102.5 (d); 62.7 (t); 55.4 (q); 36.4 (t).

Mass spectrometry (ESI: m/z(%)): 202(29) $[M]^{+\bullet}$; 171(100).

Step D: 2-(7-Methoxynaphthalen-1-yl)ethyl methanesulfonate

The title product is obtained in accordance with the process described in Step C of Example 7 using the product of the preceding Step C as the starting reagent.

^{1}H NMR spectroscopic analysis ($CDCl_3$, 300.13 MHz, δ in ppm): 7.72 (d, J = 9.1 Hz, 1H); 7.66 (d, J = 8.9 Hz, 1H); 7.31-7.21 (m, 3H); 7.13 (dd, J = 9.1 and 2.5 Hz, 1H); 4.47 (t, J = 7.4 Hz, 2H); 3.92 (s, 3H); 3.45 (d, J = 7.4 Hz, 2H); 2.77 (s, 3H).

^{13}C NMR spectroscopic analysis ($CDCl_3$, 75.5 MHz, δ in ppm): 158.2 (s); 133.0 (s); 133.0 (s); 130.6 (s); 130.4 (d); 129.3 (s); 128.0 (d); 127.7 (d); 123.2 (d); 118.4 (d); 101.9 (d); 67.9 (t); 55.5 (q); 37.4 (q); 33.3 (t).

Step E: N-*[2-(7-Methoxynaphthalen-1-yl)ethyl]acetamide*

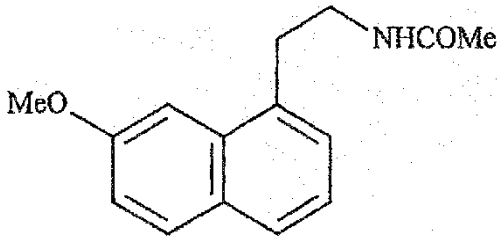
The title product is obtained in accordance with the process described in Step D of Example 7 using the product of the preceding Step D as the starting reagent.

^{1}H NMR spectroscopic analysis (CD_3OD, 300.13 MHz, δ in ppm): 8.21 (bs, 1H); 7.74 (d, J = 8.9 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H); 7.52 (d, J = 2.5 Hz, 1H); 7.31-7.2 (m, 2H); 7.11 (dd, J = 8.9 and 2.5 Hz, 1H); 3.96 (s, 3H); 3.52-3.44 (m, 2H); 3.23-3.18 (m, 2H); 1.94 (s, 3H).

^{13}C NMR spectroscopic analysis (CD_3OD, 75.5 MHz, δ in ppm): 173.4 (s); 159.4 (s); 135.1 (s); 134.6 (s); 131.2 (d); 130.8 (s); 128.2 (d); 127.9 (d); 124.2 (d); 119.3 (d); 103.2 (d); 55.9 (q); 41.4 (t); 34.2 (t); 22.6 (q).

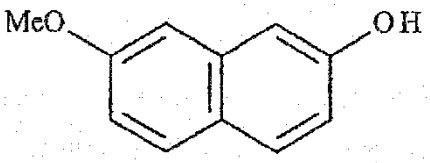
Patentkrav

1. Fremgangsmåte for industriell syntese av forbindelsen med formel (I):



(I)

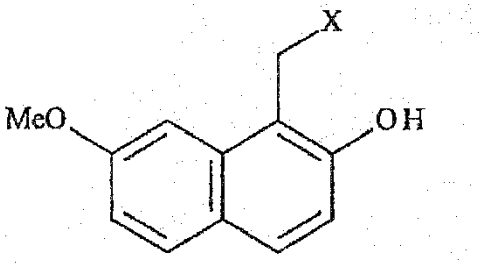
karakterisert ved at 7-metoksynaftalen-2-ol med formel (II):



(II)

omsettes, hvor det i posisjon 1 av forbindelsen med formel (II) innføres en gruppe $-CH_2X$ hvor X representerer en gruppe $-N(CH_3)_2$, $-CON(CH_2-Ph)_2$, $-CH_2-OH$, $-CH=CH_2$ eller $-CO-NH_2$,

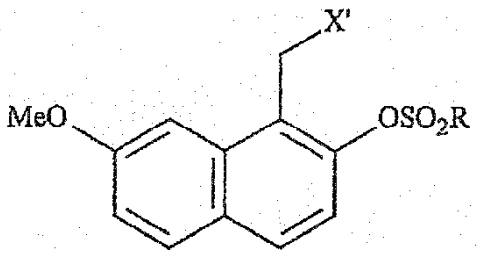
for å gi en forbindelse med formel (III):



(III)

hvor X representerer en gruppe $-N(CH_3)_2$, $-CO-N(CH_2-Ph)_2$, $-CH_2-OH$, $-CH=CH_2$ eller $-CO-NH_2$;

hvilken forbindelse med formel (III) underkastes en sulfonyleringsreaksjon på den aromatiske alkohol og hvis substituent X modifiseres, før eller etter trinnet hvor den aromatiske alkohol sulfonyleres, ved hjelp av konvensjonelle kjemiske reaksjoner for å gi en forbindelse med formel (IV):



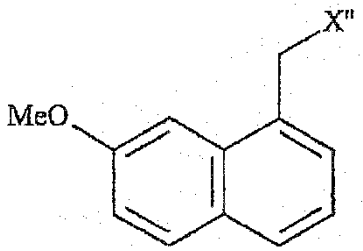
(IV)

hvor X' representerer en gruppe -CN, -CO-NH_2, -CH_2-OH, -CHO, -CH_2-N(CH_2-Ph)$_2$, -CH_2-NH-CO-CH_3, -CH(OH)-CH_2-OH eller (2,5-dioksopyrrolidin-1-yl)metyl og R representerer en gruppe -CH_3, -$(CH_2)_2$-CH_3, -CF_3 eller toluyl;

hvilken forbindelse med formel (IV) underkastes en deoksygeneringsreaksjon i nærvær av et overgangsmetall og et reduksjonsmiddel for å gi:

- enten, når X' representerer gruppen -CH_2-NH-CO-CH_3, forbindelsen med formel (I) direkte, som isoleres i form av et fast stoff;

- eller en forbindelse med formel (V):



(V)

hvor X" representerer en gruppe -CN, -CH_2-N(CH_2-Ph)$_2$, -CH_2OH, -CH(OH)-CH_2-OH, -CO-NH_2 eller (2,5-dioksopyrrolidin-1-yl)metyl;

hvilken forbindelse med formel (V) underkastes konvensjonelle kjemiske reaksjoner for å gi forbindelsen med formel (I), som isoleres i form av et fast stoff.

2. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (II) til forbindelsen med formel (III) utføres ved innvirkning av formaldehyd og dimetylamin for å gi en forbindelse med formel (III) hvor X representerer -N(CH_3)$_2$.

3. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (II) til forbindelsen med formel (III) utføres ved innvirkning av glyoksal fulgt av

innvirkning av et reduksjonsmiddel for å gi en forbindelse med formel (III) hvor X representerer -CH_2-OH.

4. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (II) til forbindelsen med formel (III) utføres ved innvirkning av glyoksal fulgt av innvirkning av en forbindelse med formel NHR'R' hvor R' representerer H eller en gruppe -CH_2-Ph, for å gi en forbindelse med formel (III) hvor X representerer -CO-NH_2 eller -CO-N(CH_2-Ph)$_2$.

5. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (II) til forbindelsen med formel (III) utføres ved innvirkning av allylbromid fulgt av en termisk omlegging for å gi en forbindelse med formel (III) hvor X representerer -CH=CH_2.

6. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at, ved omvandling av forbindelsen med formel (III) til forbindelsen med formel (IV), utføres sulfonyleringstrinnet ved hjelp av innvirkning av et sulfonylklorid, et sulfonsyreanhydrid eller et sulfonimid.

7. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (III) til forbindelsen med formel (IV) består av et trinn med sulfonylering av den aromatiske alkohol fulgt av modifikasjon av gruppen X ved hjelp av konvensjonelle kjemiske reaksjoner, hvor X har betydningen angitt for formel (III).

8. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (III) til forbindelsen med formel (IV) består av å modifisere gruppen X ved hjelp av konvensjonelle kjemiske reaksjoner, fulgt av et trinn med sulfonylering av den aromatiske alkohol, hvor X har betydningen angitt for formel (III).

9. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) til forbindelsen med formel (V) utføres i nærvær av nikkel og et hydrid.

10. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) til forbindelsen med formel (V) utføres i nærvær av palladium og dihydrogen.

11. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) til forbindelsen med formel (V) utføres i nærvær av palladium og et alkalijordmetall.

12. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) hvor X' representerer gruppen $-CH_2-NH-CO-CH_3$ til forbindelsen med formel (I) utføres i nærvær av nikkel og et hydrid.

13. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) hvor X' representerer gruppen $-CH_2-NH-CO-CH_3$ til forbindelsen med formel (I) utføres i nærvær av palladium og dihydrogen.

14. Fremgangsmåte for industriell syntese av forbindelsen med formel (I) ifølge krav 1, **karakterisert ved** at omvandlingen av forbindelsen med formel (IV) hvor X' representerer gruppen $-CH_2-NH-CO-CH_3$ til forbindelsen med formel (I) utføres i nærvær av palladium og et alkalijordmetall.

15. Forbindelse med formel (III) ifølge krav 1 for anvendelse som et mellomprodukt for syntese av agomelatin med formel (I).

16. Forbindelse med formel (III) ifølge krav 15, valgt fra de følgende forbindelser:

- 1-[(dimetylamino)metyl]-7-metoksynaftalen-2-ol;
- *N,N*-dibenzyl-2-(2-hydroksy-7-metoksynaftalen-1-yl)acetamid;
- 1-(2-hydroksyetyl)-7-metoksynaftalen-2-ol;
- 2-(2-hydroksy-7-metoksynaftalen-1-yl)acetamid;
- 7-metoksy-1-(prop-2-en-1-yl)naftalen-2-ol.

17. Anvendelse av en forbindelse med formel (III) ifølge krav 15 eller 16 ved syntese av agomelatin med formel (I).

18. Forbindelse med formel (IV) ifølge krav 1 for anvendelse som et mellomprodukt for syntese av agomelatin med formel (I).

19. Forbindelse med formel (IV) ifølge krav 18, valgt fra de følgende forbindelser:

- 1-(cyanometyl)-7-metoksynaftalen-2-yltrifluorometansulfonat;
- 1-[2-(acetylamino)etyl]-7-metoksynaftalen-2-yl-4-metylbenzensulfonat;
- 1-[2-(dibenzylamino)etyl]-7-metoksynaftalen-2-yltrifluorometansulfonat;
- 1-[2-(acetylamino)etyl]-7-metoksynaftalen-2-ylpropan-1-sulfonat;
- 1-[2-(2,5-dioksopyrrolidin-1-yl)etyl]-7-metoksynaftalen-2-ylpropan-1-sulfonat;
- 1-(2-hydroksyetyl)-7-metoksynaftalen-2-yl-4-metylbenzensulfonat;
- 1-(2-amino-2-oksoetyl)-7-metoksynaftalen-2-yl-4-metylbenzensulfonat;
- 7-metoksy-1-(2-oksoetyl)naftalen-2-yl-4-metylbenzensulfonat;
- 1-(2,3-dihydroksypropyl)-7-metoksynaftalen-2-yl-4-metylbenzensulfonat.

20. Anvendelse av en forbindelse med formel (IV) ifølge krav 18 eller 19 ved syntese av agomelatin med formel (I).

21. Forbindelse med formel (V) ifølge krav 1, valgt fra de følgende forbindelser:

- 1-[2-(7-metoksynaftalen-1-yl)etyl]pyrrolidin-2,5-dion;
- 3-(7-metoksynaftalen-1-yl)propan-1,2-diol;

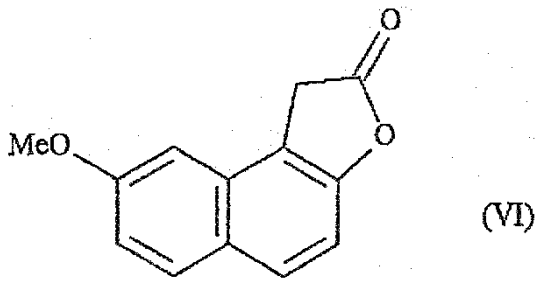
for anvendelse som mellomprodukter for syntese av agomelatin med formel (I).

22. Anvendelse av en forbindelse med formel (V) ifølge krav 21 ved syntese av agomelatin med formel (I).

23. (2-Hydroksy-7-metoksynaftalen-1-yl)acetonitril, 7-metoksy-1-(2-{[(4-metylfenyl)sulfonyl]oksy}etyl)naftalen-2-yl-4-metylbenzensulfonat, 7-metoksy-1-{2-[(propylsulfonyl)oksy]etyl}naftalen-2-ylpropan-1-sulfonat og 1-[2-(acetylamino)etyl]-7-metoksynaftalen-2-ylacetat for anvendelse som mellomprodukter for syntese av agomelatin med formel (I).

24. Anvendelse av (2-hydroksy-7-metoksynaftalen-1-yl)acetonitril, 7-metoksy-1-(2-{[(4-metylfenyl)sulfonyl]oksy}etyl)naftalen-2-yl-4-metylbenzensulfonat, 7-metoksy-1-{2-[(propylsulfonyl)oksy]etyl}naftalen-2-ylpropan-1-sulfonat og 1-[2-(acetylamino)etyl]-7-metoksynaftalen-2-ylacetat ifølge krav 23 ved syntese av agomelatin med formel (I).

25. Forbindelse med formel (VI):



(VI)

for anvendelse som et mellomprodukt for syntese av agomelatin med formel (I).

26. Anvendelse av en forbindelse med formel (VI) ifølge krav 25 ved syntese av agomelatin med formel (I).

27. Anvendelse av en forbindelse med formel (II) ifølge krav 1 ved syntese av agomelatin med formel (I).

28. Fremgangsmåte for syntese av agomelatin ifølge krav 1 utgående fra en forbindelse med formel (III), **karakterisert ved** at forbindelsen med formel (III) erholdes ved en synteseprosess ifølge et hvilket som helst av kravene 1 til 5.

29. Fremgangsmåte for syntese av agomelatin ifølge krav 1 utgående fra en forbindelse med formel (IV), **karakterisert ved** at forbindelsen med formel (IV) erholdes ved en synteseprosess ifølge et hvilket som helst av kravene 1 til 8.