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(54) Title: SYNTHESIS OF (+) AND (-) 1 -(5,5-DIPHENYLTETRAHYDROFURAN-3- YL)-N,N-DIMETHYLMETHANAMINE, (+) AND (-) 1-(2,2-DIPHENYLTETRAHYDROFURAN-3-YL)-N,N- DIMETHYLMETHANAMINE AND (+) AND (-) 1-(2,2- DFFHENYLTETRAHYDROFURAN-3-YL)-N-METIHYLMETHANAMINE

(57) Abstract: The current invention covers the synthesis of (+) and (-) 1-(5,5-diphenyltetrahydrofuran-3- yl)-N,N-dimethylmethanamine [(±)1] and [(-)1] respectively, including their pharmacologically acceptable acid addition salts. The new products can be synthesized starting from 5,5-diphenyltetrahydrofuran-2(3H)-one (4) after insertion of an aldehyde group in the α-position, reduction to the prochiral 3-(hydroxymethyl)-1, 1-diphenylbutane-1,4-diol (6), chemoenzymatic desymmetrization using the enzyme Amano Lipase PS30, tosylation, intramolecular nucleophilic attack, hydrolysis, reaction with trifluoromethanesulfonic anhydride and substitution by dimethylamine, thus producing (+) 1-(5,5-diphenyl- tetrahydrofuran-3-yl)-N,N-dimethylmethanamine [(+)1]. Protection of the product of the chemoenzymatic desymmetrization with tert-butyldimethylsilyl chloride, hydrolysis, tosylation, intramolecular nucleophilic attack, removal of tert-butyldimethylsilyl group, reaction with trifluoromethanesulfonic anhydride and substitution by dimethylamine produces (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine [(-)1]. It also covers the synthesis of (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N- dimethylmethanamine [(+)2] and [(-)2] respectively and (+) and (-) 1-(2,2-diphenyl- tetrahydrofuran-3-yl)-N-methylmethanamine \(+)3] and [(-)3] respectively, including their pharmacologically acceptable acid addition salts. The new products can be synthesized either starting from the reduction of 5-oxo-2,2-diphenyltetrahydrofuran-3-carboxylic acid (13) with $LiA1H_4$, followed by the cyclization of the obtained triol (14) under acidic conditions, reaction with 1S-(-) or1R-(+)camphanic chloride, recrystallization, hydrolysis, reaction with trifluoromethanesulfonic anhydride and substitution by dimethylamine or methylamine, or by the reaction of R-(-) or S-(+) Mandelic acid and acetic acid with racemic 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine (2), recrystallization, followed by reaction with an aqueous solution of NaOH. The compounds mentioned in the invention present neuroprotective, antiepileptic and antidepressant activity and can be used as therapeutic agents.

SYNTHESIS OF (+) AND (-) 1-(5,5 DIPHENYLTETRAHYDROFURAN-3-YL)-*N*,*N*-DIMETHYLMETHANAMINE, (+) AND (-) 1-(2,2-DIPHENYLTETRAHYDROFURAN-3-YL)-*N*,*N*-DIMETHYLMETHANAMINE AND (+) AND (-) 1-(2,2-DIPHENYLTETRAHYDROFURAN-3-YL)-*N*-METHYLMETHANAMINE.

The current invention covers the synthesis of the optically active (+) and (-) compounds of the following categories , including their pharmacologically acceptable acid addition salts:

Category A

1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine of the type (+)1 and (-)1 (SCHEME 1).

Category B

1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine of the type (+)2 and (-)2 (SCHEME 2).

Category C

1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine of the type (+)3 and (-)3 (SCHEME 3).

The above mentioned compounds present neuroprotective, antiepileptic and antidepressant activity.

The compounds of category A are synthesized according to the reactions of scheme 4, the compounds of category B are synthesized according to the reactions of scheme 5 or 6, while the compounds of category C are synthesized according to the reactions of scheme 5.

The synthesis of (+) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+) 1] is described in the following reactions (SCHEME 4). Lactone 4 is used as starting material, which after insertion of an aldehyde group in α-position is converted to aldehyde 5. Reduction to the prochiral 3-(hydroxymethyl)-1,1-diphenylbutane-1,4-diol (6), followed by enantioselective chemoenzymatic desymmetrization using the enzyme Amano Lipase PS30 leads to the synthesis of the (+) enantiomer of ester 7. After formation of p-toluenesulfonic ester of the primary alcohol and intramolecular attack from the tertiary hydroxyl group under basic conditions, the tetrahydrofuranyl analogue [(+) 8] is

synthesized. Hydrolysis of the ester leads to alcohol [(+) 9], which reacts with trifluoromethanesulfonic anhydride and then with a solution of dimethylamine to the formation of amine (+) 1.

For the formation of enantiomeric amine (-) 1 first the primary hydroxyl group of alcohol (+) 7 is protected as a *tert*-butyldimethylsilyl ether [(+) 10]. Hydrolysis of the ester to the alcohol [(-) 11], followed by the synthesis of p-toluolsulfonic ester of the primary alcohol and intramolecular attack from the tertiary hydroxyl group under basic conditions leads to the synthesis of the tetrahydrofuranyl product [(-) 12]. After removal of *tert*-butyldimethylsilyl group and reaction of the obtained alcohol [(-) 9] with trifluoromethanesulfonic anhydride and then with a solution of dimethylamine, amine (-) 1 is synthesized.

The preparation of the compounds of Category B and C is described in the following reactions (SCHEME 5). First, acid 13 is reduced with $LiAlH_4$ to the triol 14, which after cyclization under acidic conditions is transformed to the racemic alcohol 15. Reaction of alcohol 15 with 1S-(-)camphanic chloride produces a diastereomeric mixture of esters, from which one of the two possible diastereomers [(-) 16] is isolated in pure form after recrystallizations with ethanol 95% till constant a_D. Finally, after hydrolysis to the alcohol (-) 15, reaction with trifluoromethanesulfonic anhydride and then with a solution of dimethylamine or methylamine, amine (-) 2, or amine (-) 3 is formed respectively. Following the same synthetic route, amine (+) 2 and amine (+) 3 is formed after reaction of 1R-(+) camphanic chloride with racemic alcohol 15.

The compounds of Category B can alternatively be prepared according to the following reactions (SCHEME 6). The racemic tetrahydrofuranyl amine 2 forms diastereomeric mixtures of salts with R-(-)-Mandelic acid and acetic acid. After recrystallization with a mixture of isopropanol/diethyl ether till constant a_D the diastereomeric salt (+)18 is obtained in pure form, which reacts with 10% NaOH aqueous solution, thus providing the chiral amine (+) 2. Following the same synthetic route, reaction of the racemic amine 2 with S-(+)- Mandelic acid and acetic acid produces amine (-) 2.

The preparation of the salts of the products that are mentioned in the invention can be accomplished based on known methods.

All the reactions took place under Argon atmosphere, unless otherwise indicated. The Specific Rotation was recorded on a Perkin-Elmer 241 polarimeter using CH_2Cl_2 as a solvent. ^1H NMR spectra were recorded on a Brüker MSL 400 MHz spectrometer using

deuterated chloroform ($CDCl_3$) as solvent and TMS as internal standard. The measurement of the enantiomeric excess of the intermediates was performed using a Shimadzu LC-20AD High-Performance Liquid Chromatography (HPLC) spectrometer, detection at 210 and 254 nm wavelength, equipped with a Chiralpak IA chiral column and a mixture of n-hexane/isopropanol as mobile phase. The measurement of the enantiomeric excess of the final chiral amines was performed by obtaining their NMR spectra in the presence of equimolar quantities of (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid [(+) Mosher acid].

Camphanic chloride: 3-oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carbonyl chloride.

Mandelic acid: α-hydroxyphenylacetic acid.

Examples:

2-oxo-5,5-diphenyltetrahydrofuran-3-carbaldehyde (5)

To a stirred dispersion of sodium hydride (60% dispersion in mineral oil) (1.1g, 27mmol) in anhydrous toluene (20mL), a solution of 5,5-diphenyltetrahydrofuran-2(3*H*)-one 4 (4.4g, 18.47mmol) and ethyl formate (3.7mL, 45.17mmol) in anhydrous toluene (20mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 8h and then decanted into an aqueous solution of HCl 2N at 0°C. The two layers were separated and the aqueous phase was washed with diethyl ether. The organic phases were combined and washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The product of the reaction was obtained as a colorless oil (5.4g), which was used without further purification.

3-(hydroxymethyl)-1,1-diphenylbutane-1,4-diol (6)

To a stirred solution of 2-oxo-5,5-diphenyltetrahydrofuran-3-carbaldehyde (5) (5.1g, 19.15mmol) in absolute ethanol (190mL) at 0°C, $NaBH_4$ (10.9g, 130.2mmol) was added portionwise and then stirred at room temperature for 24h. The reaction mixture was carefully decanted into an aqueous solution of HCl 1N at 0°C, warmed to room temperature and stirred for 30min. After extraction with AcOEt, the organic phase was washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The product of the reaction was obtained as a wax-like solid (5.3g), which was used without further purification.

(+) 4-hydroxy-2-(hydroxymethyl)-4,4-diphenylbutyl acetate [(+) 7]

To a stirred solution of 3-(hydroxymethyl)-1,1-diphenylbutane-1,4-diol (6) (1.92g, 7.05mmol) in 1,4-dioxane (19mL) at 0°C, vinyl acetate (975μl, 10.58mmol) and enzyme PS30 (480mg) were added. The reaction mixture was stirred at 0°C for 4.5 days, filtered from Celite, washed with acetone and the solvent was evaporated, providing a white amorphous solid. The reaction mixture was subjected to flash column chromatographic using a mixture of cyclohexane:ethyl acetate (70:30-60:40) as eluent for the isolation of the chiral acetylated product (2.1g, 6.68mmol) and 50:50 for the isolation of the starting material that remained unreacted (100mg, 0.37mmol).

(a_D=+12.3°, c=1.1, CH_2Cl_2)

(+) (5,5-diphenyltetrahydrofuran-3-yl)methyl acetate [(+) 8].

To a stirred solution of (+) 4-hydroxy-2-(hydroxymethyl)-4,4-diphenylbutyl acetate [(+) 7] (1.07g, 3.4mmol) in CH_2Cl_2 (14mL), Et_3N (0.57mL, 4.08mmol), DMAP (41.5mg, 0.34mmol) and TsCl (713mg, 3.74mmol) were added at room temperature and the reaction mixture was stirred for 1.5h. Et_3N (0.5mL) was added then and the reaction mixture was heated to reflux for 24h. The solvent was evaporated in vacuo, AcOEt was added and extracted with water. The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane:ethyl acetate (90:10-80:20) as eluent. The product was obtained as a white solid (720mg, 2.43mmol, yield: 71.5%).

(a_D=+26°, c=1, CH_2Cl_2)

(+) (5,5-diphenyltetrahydrofuran-3-yl)methanol [(+) 9].

To a stirred solution of (+) (5,5-diphenyltetrahydrofuran-3-yl)methyl acetate [(+)8] (434mg, 1.46mmol) in a mixture of MeOH/THF 1:1 (20mL), a solution of LiOH (112mg, 4.69mmol) in H_2O (1.5mL) at 0°C was added dropwise and then the reaction mixture was left to warm to room temperarure. After 1h the solvent was evaporated in vacuo, AcOEt was added and extracted with water. The organic phase was dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane:ethyl acetate (70:30-50:50) as eluent and the product was obtained as a white solid (371mg, 1.46mmol, yield: 100%).

(95.1%ee, a_D=+32°, c=1, CH_2Cl_2)

(+) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+) 1].

To a stirred solution of (+) (5,5-diphenyltetrahydrofuran-3-yl)methanol [(+) 9] (52mg, 0.20mmol) in anhydrous CH_2Cl_2 (2.6 mL) at -10°C, 2,6-lutidine (35.7μL, 0.31mmol) and trifluoromethane sulfonic anhydride (50.3μL, 0.31mmol) were added dropwise. After stirring for 1h at -10°C, CH_2Cl_2 was evaporated and Et_2O was added. The organic phase was washed quickly with cold water and dried with Na_2SO_4. After evaporation of the solvent in vacuo without heating, the corresponding trifluoromethanesulfonate was obtained, which was dissolved with stirring in THF (0.5mL) at 0°C. A solution of Me_2NH in THF (4.95M, 412μL) was added, the reaction mixture was warmed to room temperature and stirred for 8h. The solvent was then evaporated in vacuo, Et_2O was added, the organic layer was washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2:MeOH (95:5) as eluent and the product was obtained as a white solid (54mg, 0.19mmol, yield:94%).

(a_D=+15°, c=1, CH_2Cl_2).

(+) 2-[(*tert*-butyldimethylsilyloxy)methyl]-4-hydroxy-4,4-diphenylbutyl acetate [(+) 10]

To a stirred solution of (+) 4-hydroxy-2-(hydroxymethyl)-4,4-diphenylbutyl acetate [(+) 7] (0.69g, 2.19mmol) in DMF (3mL) at room temperature, imidazole (224mg, 3.29mmol) and TBSCl (397mg, 2.63mmol) were added and the reaction mixture was stirred for 2.5h. Et_2O was added then, the organic layer was washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane:ethyl acetate (90:10-80:20) as eluent and the product was obtained as a white amorphous solid (801mg, 1.87mmol, yield:85%).

(a_D=+13.6°, c=1, CH_2Cl_2)

(-) 3-[(*tert*-butyldimethylsilyloxy)methyl]-1,1-diphenylbutane-1,4-diol [(-) 11].

It was synthesized according to (+) (5,5-diphenyltetrahydrofuran-3-yl)methanol [(+)9] using ester (+) 10 as starting material.

(a_D=-2.4°, c=1, CH_2Cl_2)

(-) *tert*-butyl[(5,5-diphenyltetrahydrofuran-3-yl)methoxy]dimethylsilane [(-) 12].

It was synthesized according to (+) (5,5-diphenyltetrahydrofuran-3-yl)methyl acetate [(+)8] using diol (-) 11 as starting material.

(a_D=-22°, c=1, CH_2Cl_2)

(-) (5,5-diphenyltetrahydrofuran-3-yl)methanol [(-) 9].

To a stirred solution of (-) *tert*-butyl[(5,5-diphenyltetrahydrofuran-3-yl)methoxy] dimethylsilane [(-)12] (93mg, 0.25mmol) in THF (2mL) at 0°C, TBAF (1M in THF, 0.5mL) was added and the reaction mixture was stirred for 2.5h at room temperature. NH_4Cl (aqueous saturated solution) and Et_2O were added, the organic layer was washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane:ethyl acetate (80:20-50:50) as eluent and the product was obtained as a white amorphous solid (59mg, 0.23mmol, yield: 92%).

(94.8%ee, a_D=-32°, c=1, CH_2Cl_2)

(-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-) 1].

It was synthesized according to (+) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+) 1] using alcohol [(-) 9] as starting material.

(a_D=-15°, c=1, CH_2Cl_2)

2-(hydroxymethyl)-1,1-diphenylbutane-1,4-diol (14).

To a stirred dispersion of $LiAlH_4$ (3.70g, 97.50mmol) in anhydrous THF (110mL) at 0°C, 5-oxo-2,2-diphenyltetrahydrofuran-3-carboxylic acid (13) (4.0g, 14.17mmol) was added portionwise and then the reaction mixture was heated to reflux for 10h. After that time it was carefully decanted portionwise into water at 0°C, NaOH 40% aqueous solution (100mL) was added and stirred at 0°C for 30min. The solvent was evaporated in vacuo and the residue was filtered from Celite and washed with AcOEt. The two layers were separated and the aqueous phase was washed with AcOEt. The organic phases were combined and washed with water, dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was obtained as a colorless oil that solidified on standing. After trituration with n-pentane, the product was obtained as white solid (3.51g, 12.89mmol, yield:91%).

(2,2-diphenyltetrahydrofuran-3-yl)methanol (15).

To a stirred solution of triol 14 (3.5g, 12.85mmol) in anhydrous CH_2Cl_2 (150mL) at room temperature, anhydrous p-toluenesulfonic acid was added (0.5g, 2.9mmol) and the reaction mixture was heated to reflux for 5h. The solvent was evaporated in vacuo, Et_2O was added and the mixture was extracted with Na_2CO_3 (saturated aqueous solution) and water, dried with Na_2SO_4, filtered and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of cyclohexane:ethyl acetate (80:20-60:40) as eluent. A white amorphous solid was obtained (2.3g, 9.04mmol, yield:70%).

(-) (2,2-diphenyltetrahydrofuran-3-yl)methyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo [2.2.1] heptane-1-carboxylate [(-)16].

To a stirred suspension of (1S)-(-)-camphanic chloride (2.53g, 11.68mmol), DMAP (2.60g, 21.23mmol), and Na_2SO_4 (200 mg) in anhydrous CH_2Cl_2 (100mL) at 0°C, a solution of (2,2-diphenyltetrahydrofuran-3-yl)methanol (15) (2.70g, 10.61mmol) in anhydrous CH_2Cl_2 (62mL) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 8h and after evaporation of CH_2Cl_2 in vacuo it was extracted with AcOEt and HCl 1N. The organic layer was washed with water and $NaHCO_3$ (1N aqueous solution), dried with Na_2SO_4, filtered and evaporated in vacuo, thus providing a nearly white solid (4.7g), which was recrystallized with EtOH 95%. After each recrystallization the diastereomeric excess of the obtained solid was checked with chiral HPLC. After three recrystallizations, 1.60g of a white crystalline solid was obtained. (99.6%ee, a_D=-144°, c=1, CH_2Cl_2).

(+) (2,2-diphenyltetrahydrofuran-3-yl)methyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo [2.2.1] heptane-1-carboxylate [(+)16].

It was obtained starting with (1R)-(+)-camphanic chloride and racemic (2,2-diphenyltetrahydrofuran-3-yl)methanol (15) and following the aforementioned procedure. (99.8%ee, a_D=+144°, c=1, CH_2Cl_2)

(-) (2,2-diphenyltetrahydrofuran-3-yl)methanol [(-)15].

To a stirred solution of (-)-camphanic ester [(-)16] (1.6g, 3.68mmol) in a mixture of MeOH/THF 1:1 (52mL), a solution of LiOH (282mg, 11.8mmol) in H_2O (3.7mL) was

added slowly. The resulting mixture was stirred for 1h, the solvents were evaporated in vacuo, AcOEt was added, the organic layer was washed with water, dried with Na_2SO_4, filtered and evaporated under vacuum. The residue was triturated with petroleum ether, filtered and dried, providing a white crystalline solid (0.93g, 3.67mmol).

(a_D=-229°, c=1, CH_2Cl_2).

(+) (2,2-diphenyltetrahydrofuran-3-yl)methanol [(+)15].

It was obtained starting with camphanic ester [(+)16] and following the previous procedure.

(a_D=+229°, c=1, CH_2Cl_2)

(-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)2].

To a stirred solution of (-) (2,2-diphenyltetrahydrofuran-3-yl)methanol [(-)15] (450mg, 1.77mmol) in anhydrous CH_2Cl_2 (23 mL) at -10°C, 2,6-lutidine (0.31mL, 2.65mmol) and trifluoromethanesulfonic anhydride (0.435mL, 2.65mmol) were added dropwise. After stirring at -10°C for 1h, the solvent was evaporated and Et_2O was added. The organic layer was washed very quickly with cold water and dried with Na_2SO_4. Evaporation of the solvent in vacuo without heating led to the crude triflate [(-)17]), which was dissolved in THF (5mL) at 0°C and a solution of Me_2NH in THF (4.95M, 3.6mL) was added with stirring. The reaction mixture was warmed to room temperature and stirred for 8h. The solvent was then evaporated, Et_2O was added, the organic layer was washed with water and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2:MeOH (95:5) as eluent and the product was obtained as a white amorphous solid (473mg, 1.68mmol, yield:95%).

(a_D=-215°, c=1, CH_2Cl_2)

(+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2].

It was obtained starting with alcohol [(+)15] and following the preceding procedure.

(a_D=+215°, c=1, CH_2Cl_2)

(-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(-)3].

To a stirred solution of (-) (2,2-diphenyltetrahydrofuran-3-yl)methanol [(-)15] (740mg, 2.91mmol) in anhydrous CH_2Cl_2 (37 mL) at -10°C, 2,6-lutidine (0.51mL, 4.36mmol) and

trifluoromethanesulfonic anhydride (0.72mL, 4.36mmol) was added dropwise. After stirring for 1h at -10°C, the solvent was evaporated and Et_2O was added. The organic layer was washed very quickly with cold water and dried with Na_2SO_4. Evaporation of the solvent in vacuo without heating led to the crude triflate [(-)17], which was dissolved in THF (22mL) at 0°C and a solution of $MeNH_2$ (41% in water, 22mL) was added with stirring. The reaction mixture was warmed to room temperature and stirred for 8h. The solvent was then evaporated, Et_2O was added, the organic layer was washed with water and evaporated in vacuo. The residue was purified by flash column chromatography using a mixture of CH_2Cl_2:MeOH (95:5 - 90:10) as eluent and the product was obtained as a white amorphous solid (2.89mmol, yield:99%).

(a_D=-208°, c=1, CH_2Cl_2)

(+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(+)3].

It was obtained starting with alcohol [(+)15] and following the previous procedure.

(a_D=+208°, c=1, CH_2Cl_2)

Salt of (+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N,N*-dimethylmethanamine with R-(-)-Mandelic acid [(+)18].

To a stirred solution of racemic 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N,N*-dimethylmethanamine (2) (1.95g, 6.93mmol) in EtOH 95% (15mL), R-(-)-Mandelic acid (527mg, 3.47mmol) was added at room temperature and the mixture was stirred for 1h. The solvent was then evaporated in vacuo and the obtained residue was dissolved in H_2O (1.7mL) and AcOH (0.4mL) with heating and stirred at room temperature for 30 min. Toluene was then added and the solvents were evaporated under vacuum. The azeotropic removal of H_2O and AcOH with toluene was repeated two more times, thus providing a white solid, which was recrystallized from iPrOH/Et_2O (x 3), followed by filtration. The product was obtained as white crystals (800mg).

(a_D=+108°, c=1, CH_2Cl_2)

Salt of (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N,N*-dimethylmethanamine with S-(+)- Mandelic acid [(-)18].

It was obtained starting with S-(+)-Mandelic acid and the racemic 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N,N*-dimethylmethanamine (2), following the aforementioned procedure.

(a_D=-108°, c=1, CH_2Cl_2)

(+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2].

To a stirred solution of the salt of (+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine with R-(-)-Mandelic acid [(+)18] (1,39g, 3.21mmol) in H_2O (10mL) at 0°C, a 10% aqueous solution of NaOH (7.0mL) and Et_2O (20mL) were added. The reaction mixture was warmed to room temperature and stirred for 20min. The two layers were separated and the organic phase was washed with water, dried with Na_2SO_4 and evaporated in vacuo, providing the product as a white solid (897mg, 3.19mmol, yield: 99.5%).

(a_D=+215°, c=1, CH_2Cl_2)

(-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)2].

It was obtained starting with the salt of (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine with S-(+)- Mandelic acid [(-)18], following the preceding procedure.

(a_D=-215°, c=1, CH_2Cl_2)

References

1. Ann. Pharmaceutiques françaises (1985), 43 (3), 257-264, N. Kolokouris et al, "New aminoethers and aminolactones. Synthesis and pharmacological approach".
2. WO9730983 Vamvakides et al, "Tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanemethanamine, its enantiomers, and their pharmaceutically acceptable acid addition salts".
3. Il Farmaco (1996), 51 (1), 19-26, G. B. Foscolos et al, "Synthesis and pharmacological study of some new beta-(dialkylaminomethyl)- gamma-butyrolactones and their tetrahydrofuran analogues".

CLAIMS

1. (+) and (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)1] and [(-)1] respectively, including their pharmaceutically acceptable acid addition salts.
2. (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2] and [(-)2] respectively, including their pharmaceutically acceptable acid addition salts.
3. (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(+)3] and [(-)3] respectively, including their pharmaceutically acceptable acid addition salts.
4. Every pharmaceutical synthesis consisted of the products of claim 1: (+) and (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)1] and [(-)1] respectively or of claim 2: (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2] and [(-)2] respectively or of claim 3: (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(+)3] and [(-)3] respectively, their pharmaceutically acceptable acid addition salts and pharmaceutically acceptable excipient or solvent.
5. The process for the preparation of the products of claim 1 which involves the synthesis of (+) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)1] starting from 5,5-diphenyltetrahydrofuran-2(3*H*)-one (4), which after insertion of an aldehyde group in the α-position, followed by reduction, is converted to the prochiral 3-(hydroxymethyl)-1,1-diphenylbutane-1,4-diol (6). After chemoenzymatic desymmetrization using the enzyme Amano Lipase PS30, reaction with p-toluenesulfonyl chloride and intramolecular nucleophilic attack, the tetrahydrofuranyl derivative [(+)8] is obtained. Hydrolysis of the ester group, followed by reaction with trifluoromethanesulfonic anhydride and then with a solution of dimethylamine produces (+) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)1]. Protection of alcohol [(+)7], which results from the chemoenzymatic desymmetrization, with *tert*-butyldimethylsilyl chloride, hydrolysis of the ester group, synthesis of p-toluenesulfonate and intramolecular nucleophilic attack leads to the synthesis of the tetrahydrofuranyl derivative [(-)12]. Removal of *tert*- butyldimethylsilyl group, followed by reaction with trifluoromethanesulfonic anhydride and then with a solution of dimethylamine produces (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)1]. (+) and (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmetha-

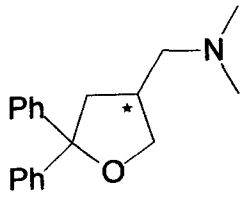
pharmaceutically acceptable acid.

6. The process for the preparation of the products of claims 2 and 3 which involves the synthesis of (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)2] starting from the effect of $LiAlH_4$ on 5-oxo-2,2-diphenyltetrahydrofuran-3-carboxylic acid (13), followed by the cyclization of the obtained triol (14) under acidic conditions and reaction of 1S-(-)camphanic chloride with (2,2-diphenyltetrahydrofuran-3-yl) methanol (15). After recrystallization of the diastereomeric mixture with EtOH 95%, hydrolysis of the camphanic ester [(-)16], reaction with trifluoromethanesulfonic anhydride followed by a solution of dimethylamine or methylamine, (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)2] or (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(-)3] are obtained respectively, which can be converted to salts under the effect of a pharmaceutically acceptable acid. Following the same synthetic route reaction of 1R-(+)camphanic chloride with (2,2-diphenyltetrahydrofuran-3-yl)methanol (15) leads to the synthesis of either (+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2] or (+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(+)3], which can be converted to salts under the effect of a pharmaceutically acceptable acid.

7. The process for the preparation of the products of claim 2 which involves the synthesis of (+) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2] after the reaction of R-(-)-Mandelic acid and acetic acid with racemic 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine (2), isolation of the diastereomerically pure salt after recrystallizations, followed by reaction with an aqueous solution of NaOH. Following the same synthetic route, reaction of S-(+)-Mandelic acid and acetic acid with racemic 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine (2) produces (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(-)2].

8. Use of (+) and (-) 1-(5,5-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)1] and [(-)1] respectively, (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*,*N*-dimethylmethanamine [(+)2] and [(-)2] respectively, (+) and (-) 1-(2,2-diphenyltetrahydrofuran-3-yl)-*N*-methylmethanamine [(+)3] and [(-)3] respectively and their salts for the preparation of pharmaceutical products with neuroprotective, antiepileptic and antidepressant activity.

SCHEME 1



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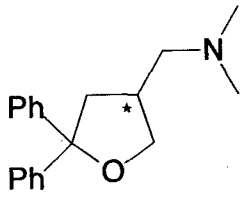
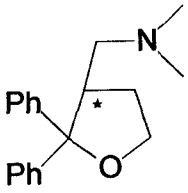


(+) **1**

SCHEME 2



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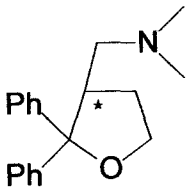
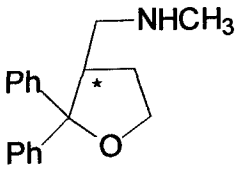
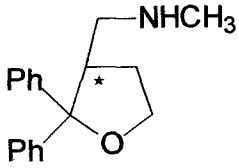


(+) **2**

SCHEME 3



(-) **3**



(+) **3**

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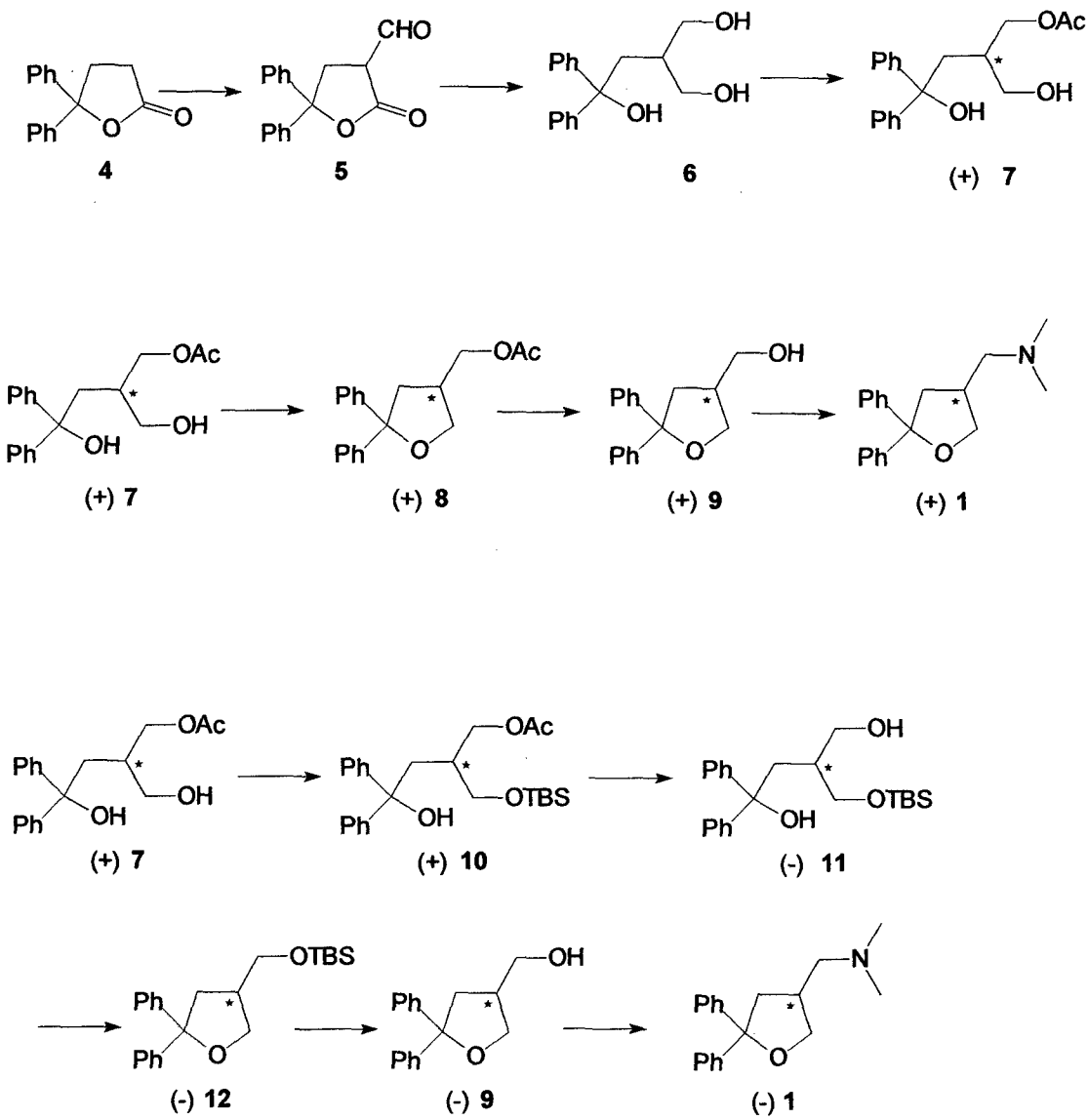

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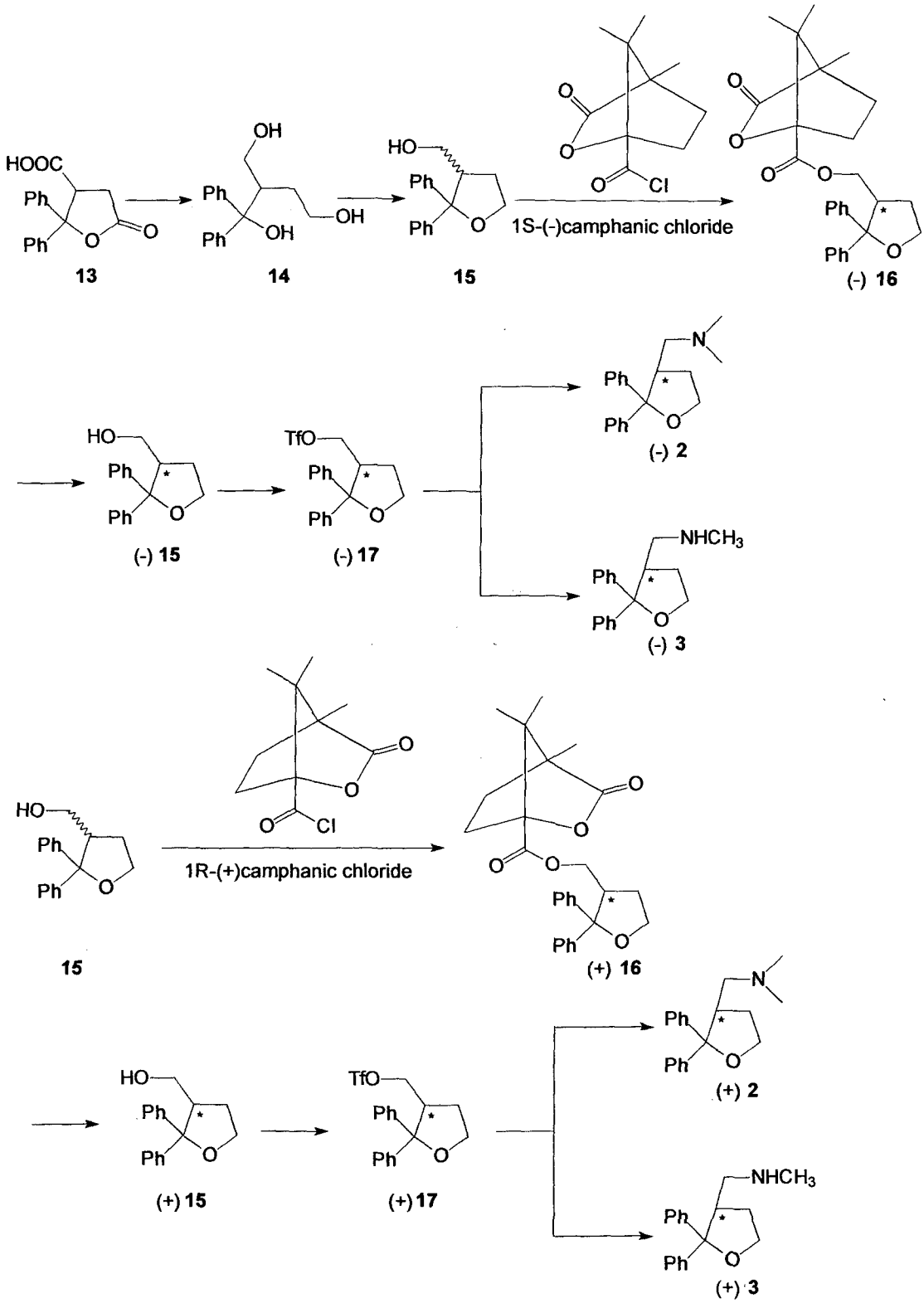
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Ph
O
O
13
OH
Ph
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OH
OH
14
HO
Ph
Ph
O
15
1S-(-)camphanic chloride
O
O
O
Cl
O
O
O
Ph
Ph
O
(-) 16
HO
Ph
Ph
O
(-) 15
TfO
Ph
Ph
O
(-) 17
N
Ph
Ph
O
(-) 2
NHCH3
Ph
Ph
O
(-) 3
HO
Ph
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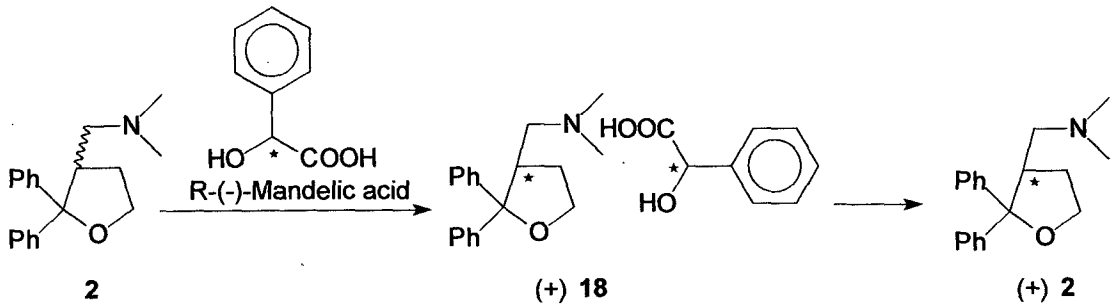
O
(+) 3

SCHEME 6


HO * COOH
R-(-)-Mandelic acid
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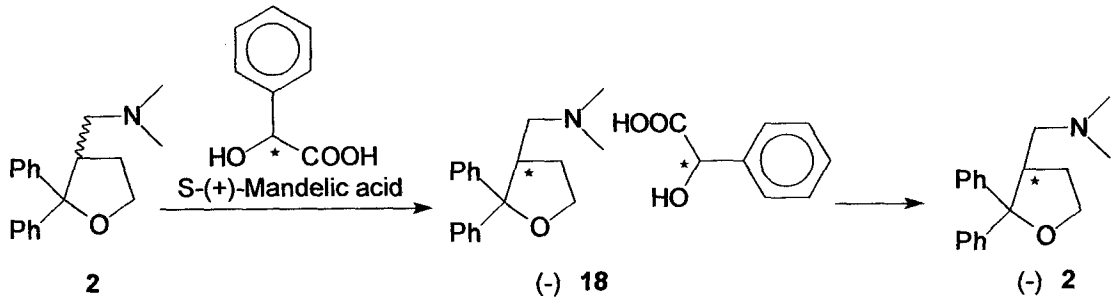
Ph
O
N
HOOC
HO
2
(+) 18
(+) 2


HO * COOH
S-(+)-Mandelic acid
Ph
Ph
O
N
HOOC
HO
2
(-) 18
(-) 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/GR2012/000030

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/14 A61K31/341 A61P25/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/30983 A1 (VAMVAKIDES ALEXANDRE [GR]; COLOCOURIS NIKOLAOS [GR]; FOSCOLOS GEORGE []) 28 August 1997 (1997-08-28) cited in the application claims 1-5; figure 1; example 2; compound 7	2,4,8
X	WO 2010/097641 A1 (VAMVAKIDES ALEXANDRE [GR]) 2 September 2010 (2010-09-02) page 10/12 - page 11/12; compounds AE14, AE37, AE37Met	1,2,4
X	FR 2 897 535 A1 (VAMVAKIDES ALEXANDRE [FR]) 24 August 2007 (2007-08-24) claims 4, 5; compounds AE14, AE37	1,2,4,8

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2012	11/09/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Moriggi, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/GR2012/000030

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WILEN S H: "RESOLVING AGENTS AND RESOLUTIONS IN ORGANIC CHEMISTRY", TOPICS IN STEREOCHEMISTRY, WILEY, NEW YORK, NY, US, vol. 6, 1 January 1971 (1971-01-01), pages 107-171, XP009034961, ISSN: 0082-500X pages 138, 145, paragraphs VII.B., VII.C. -----	6,7
A	ASHRAF GHANEM ET AL: "Application of lipases in kinetic resolution of racemates", CHIRALITY, vol. 17, no. 1, 1 January 2004 (2004-01-01), pages 1-15, XP055026099, ISSN: 0899-0042, DOI: 10.1002/chir.20089 the whole document -----	5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GR2012/000030

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730983 A1	28-08-1997	AU 1614097 A	10-09-1997
		GR 1002616 B	20-02-1997
		WO 9730983 A1	28-08-1997
WO 2010097641 A1	02-09-2010	CN 102325529 A	18-01-2012
		EP 2400965 A1	04-01-2012
		US 2011301154 A1	08-12-2011
		WO 2010097641 A1	02-09-2010
FR 2897535 A1	24-08-2007	NONE	