Abstract: The invention relates to a method of preparation of 2-amino-2-[(4-octylphenyl)ethyl]propane-1,3-diol (I), comprising opening of the aziridine ring of the intermediates (LVD by the treatment with organometallic compounds, preferably the Grignard reagents (LVII), producing the key intermediates (LVIII) or (LK). Another object of the invention is use of the compounds (LVIII) and (LLX) for preparation of fingolimod.
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A method for the preparation of fingolimod

Technical Field

The invention relates to a new method of producing 2-amino-2-[2-(4-octylphenyl)ethyl]-propane-1,3-diol (I), known under the corporate code FTY 720 or generic name fingolimod, which is, in the hydrochloride form, the active substance of the Gilenya drug (Novartis), used for treatment of multiple sclerosis.

Background Art

The first mention of preparation of fingolimod I, as shown in Scheme 1, was published in 1995 (Adachi K., Kohara T., Nakao N., Arifa M., Chiba K., Mishina T., Sasaki S., Fujita T.: Bioorg. Med. Chem. Lett. 1995, 5, 853-856). It starts from halo derivatives IIa (X = Br) or lib (X = I), which react with the acetamido malonate III to provide the corresponding intermediate IV, further processing of which provides fingolimod I. The article does not mention any details of the preparation or yields.
The first complete preparation was described in the Japanese patent of the company Yoshitomi Pharmaceutical (Mishina T., Obara T.: JPl 1310556, 1998), which describes two preparation methods of fingolimod. The first one is an analogy of the synthesis shown in Scheme 1, but it also describes the synthesis of the corresponding iodo derivative lib. The synthesis starts from a derivative V, which provides a ketone VI by Friedel-Crafts acylation with a corresponding acyl chloride in the presence of AlCl₃. The ketone is subsequently reduced by means of triethylsilane to the respective acetate VII. The next step is hydrolysis of the acetate producing an alcohol VIII, which is converted to a mesylate IX, which reacts with NaI to provide an iodide lib (Scheme 2). A different synthesis of the iodide lib from 4-(2-hydroxyethyl)phenol was published in 2004 (Seidel G., Laurich D., Furstner A.: J. Org. Chem. 2004, 69, 3950-3952).
According to the above mentioned patent the iodide lib can be transformed to the final product using two methods. The first method consists in reaction of the iodide with diethyl-acetamido malonate III in the presence of sodium ethoxide, producing an ester IV. The latter is then reduced with L1AIH4 to provide a diol X, which is subsequently acylated with acetanhydride to provide an acetate XI. Its hydrolysis provides fmgolimid I (Scheme 3). A disadvantage of this method includes difficulty in obtaining the starting halo derivatives (see the previous paragraph). Another disadvantage consists in the necessity of relatively lengthy conversion of ester groups to hydroxyl groups (reduction, protection and deprotection).
Scheme 3: Synthesis of fingolimod from the iodide \( \text{lib} \)

An alternative way of preparation of fingolimod from the iodide \( \text{lib} \) (Scheme 4) consists in reaction of the iodide with diethyl malonate \( \text{XII} \) in the presence of sodium ethoxide. The resulting ester \( \text{XIII} \) is converted to an amino ester \( \text{XV} \) by reaction with an amination agent \( \text{XIV} \). The last step is reduction of the ester groups with sodium borohydride. Again, this method starts from the difficult-to-prepare iodide \( \text{lib} \), which is an obvious disadvantage of this method. Again, ester groups have to be reduced to hydroxyl groups.
Scheme 4: Synthesis of fingolimod

The other possibility described in the above mentioned patent JP1 1310556 starts from diethyl acetamido malonate III again, which reacts with 2-haloethyl benzene XVI producing an ester XVII. The diol XVIII, obtained by subsequent reduction of the ester, is then acylated to an intermediate XIX. The intermediate is then converted to a ketone XX by Friedel-Crafts acylation with octanoic acid chloride in the presence of AlCl₃ (Scheme 5).

Scheme 5: Synthesis of the intermediate XX
The ketone \( \text{XX} \) can be transformed to fingolimod \( \text{I} \) in accordance with the above mentioned patent JPl 1310556 in three ways indicated in Scheme 6. The first way consists in reduction of the keto group in the intermediate \( \text{XX} \), which provides a compound \( \text{XI} \), the conversion of which to fingolimod \( \text{I} \) is illustrated in Scheme 3. Another described possibility is deacetylation of the hydroxyl groups of the compound \( \text{XX} \), providing a diol \( \text{XXI} \), the keto group of which is then reduced to produce a compound \( \text{XXII} \), the subsequent \( N \)-deacetylation providing fingolimod \( \text{I} \). The last possibility shown in Scheme 6 then consists in complete deacetylation of the compound \( \text{XX} \) to a compound \( \text{XXIII} \), the reduction of which then yields fingolimod \( \text{I} \). The method indicated in Schemes 5 and 6 principally keeps the disadvantages of the method shown in Schemes 2 and 3; it only changes the sequence of individual steps.

Scheme 6: Synthesis of fingolimod from the ketone \( \text{XX} \)

Another method of preparation of fingolimod \( \text{I} \) was described in an article published in 2000 (Durand F., Peralba P., Sierra F., Renaut P.: Synthesis. **2000**, 505-506) (Scheme 7). The starting compound is octylbenzene, which provides a bromoacetophenone derivative \( \text{XXIV} \) by Friedel-Crafts acylation with bromoacetyl chloride in the presence of aluminium chloride.
This reaction is followed by condensation with the sodium salt of diethyl-acetamido malonate III, producing a keto-derivative XXV, the reduction of which produces an intermediate IV. Synthesis of fingolimod I from this substance is illustrated in Scheme 3. This method retains the disadvantages of the method shown in Scheme 3 again.

Another preparation method was described in a publication issued in 2001 (Kalita B., Barua N., Bezbarua M., Bez G.: Synlett. 2001, 9, 1411-1414). A substituted benzaldehyde XXVI was prepared by Negishi reaction of n-octyl zinc iodide with p-chlorobenzaldehyde in the presence of Ni°. The thus obtained aldehyde subsequently reacts with vinylmagnesium bromide, yielding an allyl alcohol XXVII. Epoxidation of the double bond by means of m-CPBA provides an epoxide XXVIII, the reaction of which with MgSO₄-NaNO₂ provides a nitrodiol XXIX. The latter is converted to an unsaturated nitro derivative XXX by means of chlorotrimethylsilane and sodium iodide. The subsequent reduction of the double bond is carried out by hydrogenation on Pd/C and the resulting nitro derivative XXXII is further reacted with formaldehyde to provide a nitrodiol XXXII. Fingolimod I is then obtained by reduction of the nitro group on Ra-Ni (Scheme 8). This method, though it does not require conversion of the ester function to the hydroxyl group any more, nevertheless represents a linear and relatively lengthy procedure.
Scheme 8: Synthesis of fingolimod from 4-chlorobenzaldehyde

A different way of using the octylbenzaldehyde XXVI is described in literature dating back to 2005 (Sugiyama S., Arai S., Kiriyama M., Ishii K.: Chem. Pharm. Bull. 2005, 53, 100-102). 4-Octylbenzaldehyde XXVI first provides a dibromide XXXIII by reaction with triphenylphosphine and tetrabromomethane, which dibromide is converted to an alkyne XXXIV by treatment with butyllithium. Addition of catecholborane to the triple bond provides, after processing of the reaction mixture with water, boronic acid XXXV. The next step is Petasis reaction with dihydroxyacetone and benzylamine providing an unsaturated intermediate XXXVI. This is converted to fingolimod I by hydrogenation on Pd/C (Scheme 9). A disadvantage of this method includes the use of the expensive catecholborane.
Another published (Kim S., Lee H., Lee M., Lee T.: *Synthesis*. 2006, 5, 753-755) method starts from 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris) XXXVII, which is first protected in the form of acetonide and, on the nitrogen, in the form of a Boc-derivative XXXVIIIA, which is subsequently converted to an aldehyde XXXIX by Swern oxidation. This aldehyde then provides an alkyne XL by reaction with dimethyl 2-oxopropylphosphonate and />-toluene-sulfonylazide. The subsequent Sonogashira reaction with 1-iodo-4-octylbenzene then leads to an intermediate XLI, and Boc-amine XLII, obtained by reduction of the latter intermediate, is converted to fingolimod (I) by acidic hydrolysis (Scheme 10). This method starts from a logical starting substance - the cheap 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris). Thus, disadvantages may be the Swern oxidation of the alcohol XXXVIIIA to the corresponding aldehyde (malodorous side products) and the use of the potentially dangerous tosyl azide.

Scheme 9: Synthesis of fingolimod
A Chinese magazine published a synthesis of fingolimod (I) (Liang, T.: *Jilin Daxue Xuebao, Lixueban,* 2008, 46, 139-142), which rather represents a summary of well-known reactions. The first step is Friedel-Crafts acylation of benzene with octanoic acid chloride. Reduction of the ketone obtained this way provides octylbenzene, the conversion of which to fingolimod (I) is only a modification of the procedure shown in Schemes 7 and 3.

The method described in a Novartis patent application (Sedelmeier G.: WO 20091 15534) starts from 2,4'-dibromoacetophenone XLIII, which provides a diester XLIV by reaction with diethyl-acetamidomalonate HI. Then, Sonogashira reaction with 1-octyne follows, providing an alkyne VL. The latter is subsequently hydrogenated on palladium to an intermediate IV, the conversion of which to fingolimod I has been described in several previous methods already (Scheme 11).
Another procedure leading to fmgolimod I is described in a Chinese patent of Xuzhou Normal University (Wang Y., Ji G., Gu S., Zhang X., Li L., Chen Y.: CN1814583. CN100548968). The synthesis starts from styrene, which is first acylated with octanoic acid chloride to an intermediate VLI, which then provides an intermediate VLII by reaction with diethyl-acetamidomalonate III. Reduction of the keto group in compound VLII provides the well-known intermediate IV, the conversion of which to fmgolimod I has already been described in several previous methods.

The latest method of preparation of fmgolimod I, based on Julia olefimation, is described in a Chinese patent application of Growingchem (Feng X., Feng H: CN 102120720). The starting sulfide VLIII, prepared by reaction of 4-octylbenzylbromide with 2-mercaptobenzothiazole, is first oxidized to a sulfone IL, which is used in the next step for olefimation of an aldehyde L. The unsaturated derivative LI is further hydrogenated on Pd and the resulting
fingolimod acetonide LII is then subjected to acidic hydrolysis providing fingolimod in the hydrochloride form (Scheme 13). A similar approach coming from the same institute consists in Wittig olefination of the aldehyde L 4-with octylbenzyltriphenylphosphonium bromide, providing the unsaturated derivative LI (Feng X., Mei Y., Luo Y.: *Monatsh. Chem.* 2012, 143, 161-164). Similarly to the method described in Scheme 10, this method uses the aldehyde L, obtained by Swern oxidation of the alcohol XXXVIIIa again (malodorous side products).

It is known that some aziridine derivatives can be regioselectively opened by reaction with suitable nucleophilic agents to provide the corresponding amino derivatives. An example may be nucleophilic opening of substituted aziridines LIII by organometallic derivatives of the R₂CuLi type in the presence of BF₃·Et₂O, providing secondary amines LIV (Eis M. J., Ganem B.: *Tetrahedron Lett.* 1985, 26, 1153-6). Another option consists in opening of aziridines with 3-methoxyphenyl magnesium bromide in the presence of CuBr-Me₂S, described by Bringmann et al. (Bringmann G., Bischof S. K. Mueller S., Gulder T., Winter C., Stich A., Heidrun M., Kaiser M., Brun R., Dreher J., Baumann, K.: *Eur. J. Med. Chem.* 2010, 45, 5370-5383) (Scheme 14).
Disclosure of Invention

This invention provides an efficient method of synthesizing fingolimod. The invention is based on the finding that compounds of the general formula LVI can be regioselectively opened to the corresponding amino derivatives by treatment with Grignard reagents of the general formula LVII. This reaction provides the corresponding monocyclic derivatives LVIII and LIX, which can be converted to fingolimod (Scheme 15). The main advantage of this fingolimod synthesis method with regard to the state of the art is easy availability of the starting derivative LVI from the cheap and commercially well available 2-amino-2-(hydroxymethyl)propane-1,3-diol (Tris). Similarly, compounds of the general formula LVII are easily available as well.

Detailed description of the invention

Spirocyclic compounds of the general formula LVI, wherein R¹, R² is H, C₄ (un)substituted alkyl, or wherein R¹, R² is (CH₂)ₙ-A-(CH₂)ₘ, n, m is 1-3 and A is either a heteroatom, e.g. O, S, NR¹, or wherein A is CR¹R², wherein R¹ and R² are as described above, and wherein R³ is a protecting group, e.g. (un)substituted benzyl, or a COOR⁵ group wherein R⁵ is an (un)branched C₆ alkyl, (un)substituted aryl, or (un)substituted benzyl, can, in accordance with the invention, be opened by means of benzyl magnesium halides - Grignard reagents of the general formula LVII, wherein R⁴ is 1-octyl, Cl, Br, or I, and wherein X is Cl, Br, or I, under catalysis of salts and complexes of transition metals, especially Cu compounds (e.g. Cul, CuBr-Me₂S, CuCl),
to the corresponding monocyclic derivatives LVIII and LIX (Scheme 15).

Scheme 15: Nucleophilic opening of the aziridine LVI with benzylmagnesium halides

In the case of the compounds LVIII (R^4 is 1-octyl), wherein R^3 is the protecting COOR^5 group, these compounds can be directly converted to fingolimod I by acidic hydrolysis. As regards the compounds LVIII wherein R^3 is a protecting group of the benzyl type the conversion to fingolimod I is carried out in two stages, wherein hydrogenolytic deprotection of the amino group is performed either before or after acidic deprotection of the diol grouping.

In the case of the compounds LVIII wherein R^3 is the protecting COOR^5 group wherein R^5 is an (un)substituted benzyl, it is possible to carry out deprotection of the amino group first and then the diol grouping can be deprotected by acidic hydrolysis to produce fingolimod.

As regards the compounds LIX, wherein R^4 is Cl, Br, or I, these primarily formed halo derivatives are further converted to octyl derivatives LVIII either directly by reaction with organometallic reagents LX or in two steps making use of the Sonogashira reaction, wherein the aryl halide LIX first reacts with 1-octyne LXI and the resulting alkyne LXII is then hydrogenated to provide protected fingolimod LVIII (Scheme 16). Fingolimod is again obtained after removal of the protecting groups as described above.
Scheme 16: Preparation of fingolimod from the aryl halides LIX

For direct transformation of the aryl halides LIX to the octyl derivatives LVIII it is especially suitable to use the Negishi reaction of the organozinc compounds LX, wherein M is ZnX or ZnX-LiY, X is or is not identical with Y and they represent Cl, Br or I. The reaction takes place under catalysis with salts and complexes of transition metals - especially Pd and Ni - and possibly also in the presence of ligands, such as especially phosphines PR³SR²SR¹ and phosphites P(OR⁶)(OR⁷)(OR⁸), heterocyclic carbene ligands and tridentate (so-called pincer) ligands on the basis of amines and phosphines. R⁶, R⁷ and R⁸ may be (un)substituted alkyl, cycloalkyl, bicyclic or (hetero)aromatic groups and, especially preferably if R⁶≠R⁷=R⁸ wherein R⁶ is an (un)substituted biphenyl. The course of the reaction can further be influenced with other additives such as LiX and ZnX₂ (X=Cl, Br, I), alkenes and dienes, or tertiary and heterocyclic amines.

In the latter case the reaction of the aryl halides LIX with 1-octyne LXI takes place under catalysis with transition metals or their salts and complexes, especially Pd and Cu, or possibly both at the same time. Ligands that are identical with the above mentioned ones are used as co-catalysts, especially phosphines PR³SR²SR¹ wherein R³≠R²=R¹, wherein R³ is an (un)substituted biphenyl. The reaction can be carried out in polar as well as non-polar, aprotic and protic solvents in the presence of bases such as alkali metal carbonates or amines. The best results have been achieved with the use of the last mentioned biphenyl ligands, preferably
XPhos, in the presence of Pd° or Pd^{2+} complexes (Pd(MeCN)_{2}Cl_{2}, Pd_{2}(dba)_{3}), or preferably directly in the presence of Pd/C, wherein the less reactive aryl chloride LIX (R^{1}=R^{2}=Me, R^{3}=Boc, R^{4}=Cl) can also be used.

The Grignard reagents LVII, used for regioselective opening of the aziridines LVI, can easily be prepared from the corresponding benzyl halides by reaction with an excess of metallic magnesium.

Benzyl halides containing Cl, Br or I in position 4 are generally commercially available. In our synthesis of 4-octyl benzyl halides we have started from methyl 4-chlorobenzoate, which provided methyl 4-octylbenzoate by reaction with octyl magnesium chloride or octyl magnesium bromide catalyzed with a salt of iron. In optimizing this particular reaction we have managed to substantially reduce the quantity of the used solvent, making the reaction more attractive for possible commercial use. Reduction of methyl 4-octylbenzoate with Synhydride or LAH provided 4-octyl benzyl alcohol in high yields. Conversion of 4-octyl benzyl alcohol to 4-octyl benzyl chloride was carried out by the known method using thionyl chloride. Similarly, 4-octyl benzyl alcohol was converted to 4-octyl benzyl bromide by treatment with PBr_{3}.

In preparing a Grignard reagent from benzyl halides, selection of a suitable solvent is also important, besides the control of temperature, in order to suppress formation of diaryl side products and to achieve a high conversion rate. The reaction runs best in ethers - preferably in diethyl ether, methyl tert-butyl ether, 2-methyltetrahydrofuran or tetrahydrofuran - and in mixtures thereof with aromatic hydrocarbons, preferably with toluene. The thus prepared solution of a Grignard reagent is used for regioselective opening of the aziridines LVI.

The aziridine derivatives LVI were synthesized again in accordance with the described procedures, or analogously. The starting tris(hydroxymethyl)aminomethane XXXVII was first substituted on N by means of a suitable protecting group, then the two hydroxyl groups were protected in the acetal or ketal form (preferably in the form of an acetonide), and the remaining hydroxyl group was activated as a mesylate, tosylate, or other benzene sulfonate.

By the action of a strong base, preferably NaHMDS, the corresponding 5,7-dioxa-1-azaspiro[2.5]octane derivative was then produced.

In this manner, derivatives LVIa (R^{*}=R^{2}=Me, R^{3}=Boc) and LVIb (R^{*}=R^{2}=Me, R^{3}=BnOCO), which are especially suitable for the preparation of fingolimod, were prepared.
Examples

Example 1

Methyl 4-octylbenzoate

A 2M solution of octyl magnesium chloride in THF (35 ml, 70 mmol) was added dropwise using a linear dispenser to a solution of methyl 4-chlorobenzoate (10 g; 58.6 mmol) and Fe(acac)$_3$ (1 g) in a mixture of dry THF (90 ml) and NMP (10 ml) with stirring under Ar within 1 hour and the mixture was stirred for another 1 hour at room temperature. Then, the mixture was poured onto a mixture of water (90 ml), cone. HCl (10 ml) and diethyl ether (200 ml), the mixture was shaken, layers separated and the aqueous layer was further extracted with 2 x 50 ml of diethyl ether. The combined organic extracts were washed with water (2 x 100 ml) and dried with MgSO$_4$. Distillation of the crude product provided 11.7 g (80 %) of an oily liquid (HPLC content 99.7 %) with the boiling point of 120-122 °C/1.99 Pa (0.09 torr).

Example 2

Methyl 4-octylbenzoate

A 2M solution of octyl magnesium bromide in diethyl ether (35 ml, 70 mmol) was added dropwise using a linear dispenser to a solution of methyl 4-chlorobenzoate (10 g; 58.6 mmol) and Fe(acac)$_3$ (1 g) in a mixture of dry THF (90 ml) and NMP (10 ml) with stirring under Ar within 1 hour. After adding of 25 ml, a solution of further Fe(acac)$_3$ (0.3 g) in NMP (3 ml) was simultaneously continuously added with another dispenser in such a manner that adding of the two components was completed at the same time. After stirring at room temperature for
another 1 hour the mixture was poured onto a mixture of water (90 ml), cone. HCl (10 ml) and diethyl ether (200 ml). The mixture was shaken, layers separated and the aqueous layer was further extracted with 2 x 50 ml of diethyl ether. The combined organic extracts were washed with water (2 x 100 ml) and dried with MgSO₄. Distillation of the crude product provided 13.6 g (93 %) of an oily liquid (HPLC content 99.3 %) with the boiling point of 118-122 °C/10.66 - 11.99 Pa (0.08-0.09 torr).

Example 3

4-Octyl benzyl alcohol

A 65% solution of Synhydride was added dropwise using a linear dispenser to a stirred solution of methyl 4-octylbenzoate (24.8 g; 10 mmol) in toluene (200 ml) under nitrogen at a temperature of 2-5 °C within 1 hour and the mixture was stirred at room temperature overnight. The mixture was decomposed by addition of a solution of sodium potassium tartrate (150 g) in water (300) - caution, froths heavily at the beginning. The aqueous layer was extracted with 4 x 50 ml of toluene, the combined organic layers were washed with 2 x 50 ml of brine and dried with MgSO₄. After evaporation, 18.4 g (83 %) of an evaporation residue with the HPLC content of 96.5 % was obtained, which was used for the next reaction without further purification.

Example 4

4-Octyl benzyl alcohol

A solution of LiAlH₄ (20 ml, 1M in THF) was added dropwise using a linear dispenser to a stirred solution of methyl 4-octylbenzoate (2.5 g; 10 mmol) in THF (50 ml) under nitrogen at a temperature of 2-5 °C within 1 hour and the mixture was stirred at room temperature overnight. The mixture was decomposed by gradual addition of water (15 ml), a 15% solution of NaOH (15 ml) and water (45 ml). The thus resulting mixture was stirred at room temperature for 30 minutes, the insoluble fraction was aspirated and washed with ethyl acetate (5 ml). The aqueous layer was further extracted with ethyl acetate (4 x 25 ml), the combined organic extracts were thoroughly washed with brine and dried with MgSO₄. After evaporation,
2.1 g of an evaporation residue (95 %) was obtained with the HPLC content of 98.9 %, which
was used for the next reaction without any other purification.

Example 5

4-Octyl benzyl chloride

Thionyl chloride (6.5 ml) was added to a stirred solution of 4-octyl benzyl alcohol (14.2 g; 64 mmol) in acetonitrile (350 ml) and the mixture was stirred in a bath at 90°C for 1 hour. After cooling the mixture was diluted with diethyl ether (700 ml), washed with brine (4 x 100 ml) and then with water (2 x 100 ml). After drying with MgSO₄ the residue was distilled in vacuo. 12.5 g (81 %) was obtained; boiling point 110-115 °C/23.99 Pa (0.18 torr).

Example 6

4-Octyl benzyl bromide

PBr₃ (25 ml) was added dropwise using a linear dispenser to a stirred solution of 4-octyl benzyl alcohol (14.2 g; 64 mmol) in diethyl ether (400 ml) within 1 hour and the mixture was stirred in a bath at 90°C for 1 hour. After cooling the mixture was diluted with diethyl ether (700 ml), washed with brine (4 x 100 ml) and then with water (2 x 100 ml). After drying with MgSO₄ the residue was distilled in vacuo. 14.3 g (79 %) was obtained; boiling point 132-141 °C/79.99 - 106.67 Pa (0.6-0.8 torr).

Example 7

(5-i-Butyloxycarbonylamino-2,2-dimethyl[1,3]dioxan-5-yl)ethanol (XXXVIIIa)

Boc₂0 (120 g, 0.55 mol) was added to a suspension of tris(hydroxymethyl)aminomethane (XXXVII) (60.6 g; 0.5 mol) in DMF (450 ml) under stirring at room temperature and the mixture was stirred at room temperature for another 2 hours. 2,2-Dimethoxypropane (74 ml; 0.6 mol) and p-toluenesulfonic acid monohydrate (4.8 g, 25 mmol) were then added and the homogeneous reaction mixture was stirred at room temperature for 18 hours. After dilution
with diethyl ether (1000 ml) the mixture was extracted with a saturated solution of NaHCO₃ (3 x 100 ml) and brine (100 ml). The organic phase was dried with Na₂SO₄ and, after evaporation, a crude product (135 g) was obtained, which was crystallized from a hexane-MTBE 9:1 mixture. Together with the fraction obtained after concentration of the mother liquor, a total amount of 115.6 g (88 %) of the product XXXVIIIa was obtained in the form of colourless, needle-shaped crystals with the melt, point of 99-101 °C. 1H NMR (250 MHz, CDCl₃): δ = 1.43 (s, 3H), 1.46 (2x s, 12H), 3.73 (d, 2H, J = 6.5 Hz), 3.80 (m, 2H), 3.86 (m, 2H), 4.18 (bs, 1H), 5.31 (bs, 1H). 13C NMR (62.5 MHz, CDCl₃): δ = 20.38; 26.72; 28.31 (3C); 53.69; 64.38; 64.69; 80.43; 98.75; 156.41.

Example 8

(5-ieri-Butyloxycarbonylamino-2,2-dimethyl[1,3]dioxan-5-yl)methyl methanesulfonate

LXIIIaa

Methanesulfonyl chloride (2.55 ml; 33 mmol) was slowly added dropwise to a solution of XXXVIIIa (7.84 g; 30 mmol) and Et₃N (10.5 ml; 75 mmol) in dichloromethane (60 ml) at -5 °C, during which the temperature in the reaction mixture increased to 3 °C. Then, the reaction mixture was slowly heated up to room temperature and, after 3 hours, processed by pouring into MTBE (150 ml) and subsequent extraction with water (2 x 50 ml), 10% aqueous solution of citric acid (2 x 50 ml) and a saturated solution of NaHCO₃ (50 ml). The organic fraction was dried with Na₂SO₄ and, after evaporation, 9.73 g (96 %) of the mesylate LXIIIaa was obtained in the form of slightly yellowish crystals. For analytic purposes the product was recrystallized from MTBE; the melt, point of the obtained crystals was 97-99 °C. 1H NMR (250 MHz, CDCl₃): δ = 1.41 (s, 3H), 1.44 (s, 9H), 1.48 (s, 3H), 3.04 (s, 2H), 3.85 (d, 2H, J = 12.0 Hz), 3.99 (d, 2H, J = 12.0 Hz), 4.58 (s, 2H), 4.77 (bs, 1H). 13C NMR (62.5 MHz, CDCl₃): δ = 22.19; 24.60; 28.20 (3C); 36.93; 51.36; 62.79; 62.84 (2C); 68.38; 98.89; 154.57. HRMS (APCI-MS, positive mode): calculated for C₁₃H₂₆N₀₇S [M+H]+: 340.142449 Da, found: 340.1425.
Example 9

(5-½ri-Butyloxykarbonylamino-2,2-dimethyl[1,3]dioxan-5-yl)methyl p-toluenesulfonate

LXIIIab

jt?-Toluensulfonyl chloride (2.0 g; 10.5 mmol) was added to a solution of XXXVIIIa (2.6 g; 10.5 mmol) and Et3N (1.5 ml; 10.5 mmol) in dichloromethane (20 ml), followed by DMAP (120 mg) and the mixture was stirred at room temperature for 4 hours. Then, a saturated solution of NH₄Cl (15 ml) and water (5 ml) were added, the organic phase was separated and the aqueous phase was extracted with dichloromethane (2 x 10 ml). The combined organic fractions were washed with a 10% aqueous solution of citric acid and a saturated solution of NaHCO₃. The organic fraction was dried with Na₂SO₄ and the product obtained after evaporation was dissolved in a hexane-EtOAc 9:1 mixture; the resulting solution was filtered through a silica gel column (50 g) and washed with the same mixture of solvents (500 ml). After evaporation and crystallization from MTBE, 2.6 g (62 %) of the tosylate LXIIIab with the melt. point of 106-107 °C was obtained.

1H NMR (250 MHz, CDC1₃): δ = 1.40 (s, 9H), 1.42 (s, 3H), 1.43 (s, 3H), 2.44 (s, 3H), 3.79 (d, 2H, J = 12.0 Hz), 3.98 (d, 2H, J = 12.0 Hz), 4.34 (s, 2H), 7.33-7.38 (m, 2H), 7.77-7.81 (m, 2H). 13C NMR (62.5 MHz, CDC1₃): δ = 21.54; 22.07; 24.59; 28.17 (3C); 51.37; 62.68 (2C); 63.11; 68.66; 98.71; 127.95 (2C); 129.86 (2C); 132.41; 144.94; 154.41. HRMS (APCI-MS, positive mode): calculated for C₁₉H₃₀N₇O₇ [M+H]+: 416.173749 Da, found: 416.1742.

Example 10

L-(½ri-Butyloxycarbonyl)-6,6-dimethyl-5,7-dioxa-l-azaspiro[2.5]octane (LVla, R¹=R²=Me, R³=Boc)

LVla

A solution of NaHMDS (17 ml; 2M in THF; 34 mmol) was added dropwise to a solution of the mesylate LXIIIaa (9.72 g; 28.64 mmol) in dry THF (150 ml), cooled to -8°C, within 5
The temperature of the reaction mixture increased to -2 °C during the addition of NaHMDS. During another 2 hours, the mixture was left to heat up to room temperature, then a saturated solution of NH₄Cl (150 ml), water (50 ml) and MTBE (150 ml) were gradually added. The aqueous phase was separated and extracted with MTBE (2 x 50 ml). The combined organic fractions were washed with a 10% aqueous solution of citric acid (1 x 50 ml) and a saturated solution of NaHCO₃ (1 x 50 ml). After evaporation, 6.8 g (98%) of the aziridine LVIa was obtained in the form of light beige crystalline matter. Crystallization of the sample from hexane provided a sample with the melt point of 49-52 °C.

**Example 11**

1-(3′ri-Butoxycarbonyl)-6,6-dimethyl-5,7-dioxo-1-azaspiro[2.5]octane (LVIa, R¹=R²=Me, R³=Boc)

A solution of NaHMDS (0.6 ml; 2M v THF; 1.2 mmol) was slowly added dropwise to a solution of p-toluenesulfonate LXIIIab (416 mg; 1 mmol) in dry THF (10 ml), cooled to 0 °C, and then the mixture was left to heat up to room temperature. After another 4 hours a saturated solution of NH₄Cl (50 ml) and water (2 ml) were gradually added and the mixture was extracted with ethyl acetate (3 x 5 ml). After drying with anhydrous Na₂SO₄ and evaporation, 226 mg (93%) of the aziridine LVIa was obtained with the NMR purity of 95%.

**Example 12**

Benzyl 1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl carbamate

Benzyl chloroformate (14.5 ml, 100 mmol) was added dropwise using a linear dispenser to a suspension of tris(hydroxymethyl)aminomethane (XXXVII) (12.1 g; 100 mmol) and NaHCO₃ (10.6 g, 125 mmol) in a mixture of water (50 ml) and ethyl acetate (100 ml) under stirring at room temperature within 1 hour and the mixture was stirred at room temperature for another 5
The mixture was diluted with ethyl acetate (100 ml) and washed with water (2 x 50 ml). The organic layer was then evaporated to dryness and toluene (50 ml) was added, which was then evaporated in an evaporator. This was repeated 2 more times. 18.1 g of an evaporation residue (71 %) was obtained, which was used for the next reaction without any other purification.

Example 13

(5-Benzylxycarbonylamino-2,2-dimethyl[1,3]dioxan-5-yl)methanol (XXXVIIIb)

A mixture of benzyl 1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl carbamate (5.1 g, 20 mmol), 2,2-dimethoxypropane (3.0 g, 28 mmol), p-toluenesulfonic acid monohydrate (0.5 g) mmol) and DMF (15 ml) was stirred for 10 days at room temperature. After dilution with diethylether (50 ml), the mixture was extracted with a saturated solution of NaHCO₃ (3 x 10 ml) and brine (10 ml). The organic phase was dried with Na₂SO₄ and, after evaporation, a crude product XXXVIIIb; (4.3 g) was obtained, which was used for the next reaction.

Example 14

1-(Benzyloxycarbonyl)-6,6-dimethyl-5,7-dioxa-1-azaspiro[2.5]octane (LVib, R¹=R²=Me, R³=BzOCO)

Using the procedure described in Example 11 the aziridine LVib was obtained in the yield of 88 % and HPLC purity of 95-97 %.
Example 15

5-\textit{tert}-Butyloxycarbonylamino-2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxane
\textit{tert}-Butyl 2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxan-5-yl carbamate \textbf{LVIIIa}

A) Magnesium (0.4 g), covered with a layer of dry diethyl ether (2 ml), was activated with 1,2-dibromoethane (25 \textmu l) under nitrogen. Before elapsing of the reaction a solution of 4-o chloride (0.4 g) in dry diethylether (2 ml) was added at once. Then, the reaction was maintained by gradual dropwise addition of a solution of 4-octyl benzyl chloride (2.0 g) in a mixture of dry diethyl ether (8 ml) and toluene (5 ml). After completion of the dropwise addition the mixture was stirred at room temperature under nitrogen for another 1 hour. A solution of the Grignard salt was then drawn into a syringe and used in step B).

B) The Grignard salt solution obtained according to A) was added dropwise to a stirred suspension of the aziridine \textbf{LVIa} (1.2 g; 5 mmol) and CuBr-Me$_2$S (0.5 g; 2.4 mmol) in dry diethyl ether (25 ml) at -70 °C within one hour. After completion of the dropwise addition the mixture was stirred at the above mentioned temperature for 1 hour and then stirred under nitrogen without cooling overnight. The mixture was decomposed by addition of a saturated solution of ammonium chloride (7 ml). The undissolved fraction was aspirated through kieselguhr and washed with diethyl ether. The filtrate was then divided; the aqueous layer was extracted with diethyl ether (2 x 5 ml). The combined organic fractions were washed with brine (2 x 3 ml) and dried with magnesium sulfate. The evaporation residue was distilled by means of Kugelrohr distillation in a vacuum of 6.67 Pa (0.05 torr). 0.65 g (72 \% calculated on \textbf{LVIa}) of a solid product with the HPLC purity of 93.5 \% was obtained. Crystallization of a sample from pentane provided colourless crystals with the HPLC purity of 97.6 \% and the melt, point 61-65 °C.

Example 16

5-\textit{tert}-Butyloxycarbonylamino-2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxane
\textit{tert}-Butyl 2,2-dimethyl-5-(4-octylphenethyl)-1,3-dioxan-5-yl carbamate \textbf{LVIIIa}

Using the procedure described in Example 15 with the use of 2-methyltetrahydrofuran provided 83 \% of the product \textbf{LVIIIa}. 
Example 17

5-(ieri-Butyloxycarbonylamino)-5-[2-(4-chlorophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXa, R′=R^2=Me, R^3=Boc, R^4=Cl)

A) Magnesium (3.2 g; 132 mmol), covered with a layer of dry diethyl ether (25 ml), was activated with 150 μl of 1,2-dibromoethane (≈1.5 mol%) under nitrogen. After elapsing of the reaction the mixture was cooled to 15 °C and a solution of p-chlorobenzyl chloride (10.6 g; 66 mmol) in dry diethyl ether (110 ml) was added dropwise within 1 hour, while the mixture was cooled such that the temperature be maintained in the range of 15-25 °C. After adding of all the chloride the mixture was stirred at room temperature under nitrogen for another 30 minutes. The solution of the Grignard salt was then drawn into a syringe and used in step B).

B) The Grignard salt solution obtained according to A) was added dropwise to a stirred suspension of the aziridine LVla (4.9 g; 20 mmol) and CuBr·Me2S (2.5 g; 12 mmol) in dry diethyl ether (80 ml) at -65 °C in such a manner that the temperature does not exceed -60 °C. After completion the mixture was left to slowly heat up to -10 °C (15 hours) and then it was decomposed by addition of a saturated aqueous solution of NH4Cl (60 ml) and water (20 ml). The organic phase was separated and the aqueous phase was also extracted with MTBE (2 x 25 ml). The combined organic fractions were washed with brine (50 ml), filtered through kieselguhr and evaporated. Heptane with 5 % vol. of MTBE (40 ml) was added to the oily evaporation residue, the mixture was cooled to 30 °C and after seeding with ca. 20 mg of the product it was left for a few hours at 5 °C. This procedure provided 5.9 g (79 %) of the pure chloride LIXa in the form of colourless needle-shaped crystals with the melt, point of 94-95 °C. In a similar way, another 0.9 g of the product can be obtained from the mother liquors.

Accordingly, the total yield was 6.8 g (92 %) of LIXa.

1H NMR (250 MHz, CDCl3): δ = 1.41 (s, 3H), 1.43 (s, 3H), 1.47 (s, 9H), 1.96 (m, 2H), 2.54 (m, 2H), 3.67 (d, 2H, J = 11.7 Hz), 3.88 (d, 2H, J = 11.7 Hz), 4. (bs, 1H), 7.07-7.14 (m, 2H), 7.18-7.27 (m, 2H). 13C NMR (62.5 MHz, CDCl3): δ = 19.80; 27.33; 28.42 (3C); 28.51; 33.52; 51.68; 66.35 (2C); 79.46; 98.43; 128.51 (2C); 129.71 (2C); 131.65; 140.45; 154.90. HRMS (APCI-MS, positive mode: calculated for C_{9}H_{29}N_{0}·^{35}Cl [M+H]^+: 370.1780 Da, found: 370.1788 Da.
Example 18

5-(\(\frac{1}{2}\)-Butyloxycarbonylamino)-5-[2-(4-chlorophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXa, \(R^1=R^2=\text{Me}, R^3=\text{Boc}, R^4=\text{Cl}\))

The procedure described in Example 17 with the use of Cul (15 mol\%) instead of CuBr-Me\(_2\)S provided 88\% of the product LIXa.

Example 19

5-(\(\frac{1}{2}\)-Butyloxycarbonylamino)-5-[2-(4-chlorophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXa, \(R^1=R^2=\text{Me}, R^3=\text{Boc}, R^4=\text{Cl}\))

By means of the procedure described in Example 17, using CuCl (20 mol\%) instead of CuBr-Me\(_2\)S, 69\% of the product LIXa was obtained after chromatography on silica gel (2-10\% of EtOAc/\(n\)-hexane) from 2 mmol of the aziridine LVI.

Example 20

5-(\(\frac{1}{2}\)-Butyloxycarbonylamino)-5-[2-(4-chlorophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXa, \(R^1=R^2=\text{Me}, R^3=\text{Boc}, R^4=\text{Cl}\))

By means of the procedure described in Example 17, using Li\(_2\)CuCl\(_4\) (5 mol\%) instead of CuBr-Me\(_2\)S and a mixture of THF-Et\(_2\)O 1:2 as the solvent, 34\% of the product LIXa was obtained after chromatography on silica gel (2-10\% EtOAc/\(n\)-hexane) from 2 mmol of the aziridine LVIIa.
Example 2 1

5-(reri-Butyloxycarbonylamino)-5-[2-(4-bromophenyl)ethyl]-2,2-dimethyl[1,3]dioxane

\( \text{LIX}_b, \ R^3=R^4=\text{Me}, \ R^3=\text{Boc}, \ R^4=\text{Br} \)

A) By means of the procedure described in Example 17, a 0.5M solution of p-bromobenzyl magnesium bromide in diethyl ether was prepared from magnesium (1.5 g; 60 mmol) and p-bromobenzyl bromide (7.5 g; 30 mmol).

B) By means of the procedure described in Example 17, 3.1 g (74 %) of the pure bromide \( \text{LIX}_b \) was obtained from the aziridine \( \text{LVII}_a \) (2.43 g; 10 mmol), CuBr-Me_2S (1.23 g; 6 mmol) and 30 mmol of the above mentioned Grignard reagent solution after crystallization from heptane with 5 % vol. of MTBE, namely in the form of colourless crystals with the melt point of 84-87 °C. ^1H NMR (250 MHz, CDCl_3): \( \delta = 1.42 \ (s, \ 3H), \ 1.43 \ (s, \ 3H), \ 1.47 \ (s, \ 9H), \ 1.95 \ (m, \ 2H), \ 2.52 \ (m, \ 2H), \ 3.67 \ (d, \ 2H, \ J = 11.6 \ Hz), \ 3.88 \ (d, \ 2H, \ J = 11.6 \ Hz), \ 4.97 \ (bs, \ 1H), \ 7.02-7.11 \ (m, \ 2H), \ 7.33-7.42 \ (m, \ 2H). \ )^13C NMR (62.5 MHz, CDCl_3): \( \delta = 19.64; \ 27.33; \ 28.34 \ (3C); \ 28.49; \ 33.35; \ 51.56; \ 66.26 \ (2C); \ 79.35; \ 98.36; \ 119.57; \ 130.06 \ (2C); \ 131.39 \ (2C); \ 140.88; \ 154.83. \) HRMS (APCI-MS, positive mode): calculated for C\(_{19}\)H\(_{29}\)NO\(_4\)\(^{79}\)Br [M+H]^+: 414,1274 Da, found: 414,1280 Da.

Example 2 2

5-(læri-Butyloxycarbonylamino)-5-[2-(4-bromophenyl)ethyl]-2,2-dimethyl[1,3]dioxane

\( \text{LIX}_b, \ R^2=\text{Me}, \ R^3=\text{Boc}, \ R^4=\text{Br} \)

A) By means of the procedure described in Example 17, a 0.5M solution of p-bromobenzyl magnesium bromide in 2-methyltetrahydrofuran was prepared from magnesium (1.9 g; 79 mmol) and p-bromobenzyl bromide (9.0 g; 36 mmol).

B) By means of the procedure described in Example 17, 2.86 g (69 %) of the pure bromide \( \text{LIX}_b \) was obtained from the aziridine \( \text{LVII}_a \) (2.43 g; 10 mmol), CuBr-Me_2S (1.23 g; 6 mmol) and 30 mmol of the above mentioned Grignard reagent solution after crystallization from heptane with 5 % vol. of MTBE.
Example 23

5-(ter/-Butyloxycarbonylamino)-5-[2-(4-bromophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXb, R₁=R²=Me, R³=Boc, R⁴=Br)

A) By means of the procedure described in Example 17, a 0.5M solution of j?-bromobenzyl magnesium bromide in a mixture of toluene-MTBE 1:2 was prepared from magnesium (730 mg; 30 mmol) and p-bromobenzyl bromide (3.75 g; 15 mmol).

B) By means of the procedure described in Example 17, 71 % of the product LIXb was obtained from 2 mmol of the aziridine LVIa and 6 mmol of the above mentioned Grignard reagent solution after chromatography on silica gel (2-10 % of EtOAc/ n-hexane).

Example 24

5-(ter/-Butyloxycarbonylamino)-5-[2-(4-bromophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXb, R₁=R²=Me, R³=Boc, R⁴=Br)

A) By means of the procedure described in Example 17, a 0.5M solution of p-bromobenzyl magnesium bromide in a mixture of toluene-Et₂O 1:2 was prepared from magnesium (730 mg; 30 mmol) and j?-bromobenzyl bromide (3.75 g; 15 mmol).

B) By means of the procedure described in Example 17, 90 % of the product LIXb was obtained from 2 mmol of the aziridine LVIa and 6 mmol of the above mentioned Grignard reagent solution after chromatography on silica gel (2-10 % of EtOAc/ rc-hexane).

Example 25

5-(ter/-Butyloxycarbonylamino)-5-[2-(4-bromophenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LIXb, R₁=R²=Me, R³=Boc, R⁴=Br)

By means of the procedure described in Example 22, with the use of CuCl (20 mol%) instead of CuBr-Me₂S, 58 % of the product LIXb was obtained from 2 mmol of the aziridine LVIa after chromatography on silica gel (2-10 % of EtOAc/ n-hexane).
Example 26

5-(tert-Butyloxycarbonylamino)-5-[2-[4-[(1-octyn-1-yl)phenyl]ethyl]-2,2-dimethyl[1,3]dioxane (LXII, $R'=R=\text{Me}$, $R^2=\text{Boc}$)

Dry dimethyl acetamide (2 ml) and 1-octyne (LXI, 550 µl) were added into a flask containing the aryl chloride LIXa (555 mg, 1.5 mmol), $K_2\text{CO}_3$ (311 mg, 2.25 mmol), XPhos (14 mg, 2 mol%) and 10% Pd/C (32 mg, 2 mol%) after degasification and filling with argon. The reaction mixture was heated in an oil bath at 110 °C for 24 hours. After cooling to room temperature the mixture was diluted with MTBE (5 ml) and rc-hexane (5 ml), filtered through kieselguhr and washed with 10% citric acid (1 x 5 ml), saturated NaHCO$_3$ (1 x 5 ml), and brine (1 x 5 ml). After evaporation the mixture was partitioned by column chromatography on silica gel (2-10 % of EtOAc/rc-hexane). 351 mg (53 %) of the pure alkyne LXII was obtained in the form of light yellow crystalline matter.

Example 27

5-(tert-Butyloxycarbonylamino)-5-[2-[4-[(1-octyn-1-yl)phenyl]ethyl]-2,2-dimethyl[1,3]dioxane (LXII, $R'=R^2=\text{Me}$, $R^3=\text{Boc}$)

The procedure described in Example 26 with the use of 1 mol% of Pd$_2$(dba)$_3$ instead of 10% Pd/C provided the product LXII in the yield of 34 %.

Example 28

5-(terti-Butyloxycarbonylamino)-5-[2-[4-[(1-octyn-1-yl)phenyl]ethyl]-2,2-dimethyl[1,3]dioxane (LXII, $R'=R^2=\text{Me}$, $R^3=\text{Boc}$)

The procedure described in Example 26 with the use of the aryl bromide LIXb instead of the chloride LIXa provided the product LXII in the yield of 27 %.
Example 29

5-(rer-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LVIIIa, R = R2 = Me, R3 = Boc)

166 mg of the aryl bromide LIXb (0.4 mmol), 6.5 mg of SPhos (4 mol%) and 1.8 mg of Pd(OAc)2 (2 mol%) were dissolved in 2 ml of dry THF in a Schlenk flask after degasification. A 0.5M solution of n-CgHnZnBr in THF (1.2 ml) was added using a linear dispenser at room temperature within 30 min. After 30 min the reaction mixture was decomposed by addition of 4 ml of a 0.5M aqueous solution of Na2EDTA and extracted with 3×4 ml of a mixture of n-hexane/MTBE 2:1. After evaporation the crude mixture was chromatographically purified on silica gel (2-10 % of EtOAc/ re-hexane). This procedure provided 113 mg (63 %) of the pure product LVIIIa as colourless crystals with the melt. point of 63-65 °C.

Example 30

5-(rer-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LVIIIa, R’ = R2 = Me, R3 = Boc)

148 mg of the aryl chloride LIXa (0.4 mmol), 7.5 mg of RuPhos (4 mol%) and 1.8 mg of Pd(OAc)2 (2 mol%) were dissolved in 2 ml of dry THF in a Schlenk flask after degasification. The mixture was heated up in a bath at 60 °C and 1.8 ml of a 0.5M solution of n-C8H17ZnBr in THF was added at this temperature within 90 min. The reaction mixture was heated at the same temperature for another 20 hours. After cooling to room temperature it was processed using the procedure described in Example 29. 93 mg (52 %) of the pure product LVIIIa was obtained.
Example 31

5-(½rr-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LVIIIa, R'=R ²=Me, R³=Boc)

A) A solution of \( n \)-C₈H₁₆ZnBr (0.67M in DMAc) was prepared from 0.98 g of powdered zinc (15 mmol) and 1.93 g of \( n \)-octyl bromide (10 mmol) using a procedure described in literature (Huo, S.: *Org.Lett.* 2003, 5, 423).

B) 332 mg of the aryl bromide LIXb (0.8 mmol), 13 mg of SPhos (4 mol%) and 3.6 mg of Pd(OAc)₂ (2 mol%) were dissolved in 4 ml of dry THF in a Schlenk flask after degasification. 1.8 ml of the above mentioned solution of \( n \)-C₈H₁₇ZnBr (1.2 mmol) was added dropwise with a linear dispenser at room temperature within 30 min. After another 30 min the reaction mixture was processed using the procedure described in Example 29. 217 mg (61%) of the pure product LVIIIa was obtained.

Example 32

5-(rrr-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LVIIIa, R*=R ²=Me, R³=Boc)

166 mg of the aryl bromide LIXb (0.4 mmol) and 4 mg of Pd(i-Bu₃P)₂ (2 mol%) were dissolved in 0.5 ml of dry THF and 1.5 ml of NMP in a Schlenk flask after degasification. A 0.5M solution of \( n \)-C₈H₁₇ZnBr in THF (1.2 ml) was added after cooling to 0 °C and the reaction mixture was stirred at room temperature for another 1.5 hours. The processing method described in Example 29 provided 65 mg (36%) of the pure product LVIIIa.

Example 33

5-(rrr-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane
(LVIIIa, R'=R ²=Me, R³=Boc)

166 mg of the aryl bromide LIXb (0.4 mmol) and 5.5 mg of PEPPSI-IPr (2 mol%) were dissolved in 2 ml of dry NMP in a Schlenk flask after degasification. A 0.5M solution of \( n \)-
C₈H₁₇ZnBr in THF (1.3 ml) was added at room temperature and then the reaction mixture was heated at 40 °C. After 4 hours the mixture was processed using the method described in Example 29. 52 mg (29 %) of the pure product LVHIA were obtained.

Example 34

5-(ferf-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane (LVHIA, R'=R²=Me, R³=Boc)

The procedure described in Example 33 was modified by addition of 3.2 equiv. of LiBr to the reaction mixture. This way, the pure product LVHIA was obtained in the yield of 41 %.

Example 35

5-(ferf-Butyloxycarbonylamino)-5-[2-(4-octylphenyl)ethyl]-2,2-dimethyl[1,3]dioxane (LVilla, R'=R²=Me, R³=Boc)

The procedure described in Example 34 with the use of the aryl chloride LIXa instead of the bromide LIXb provided 22 % of the pure product LVHIA.
CLAIMS

1. A method for the preparation of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol I,

![Chemical Structure](image)

(I)

classified in that it comprises opening of the aziridine ring of the intermediates LVI,

![Chemical Structure](image)

(LVI)

wherein each of \( R^1 \) and \( R^2 \) independently means \( H \), \( \text{Ci}_4 \) (un)substituted alkyl, or wherein each of \( R^1 \) and \( R^2 \) independently \( (\text{CH}_2)_n \)-\( -A-(\text{CH}_2)_m \), wherein \( n \) and \( m \) are independently from 1 to 3 and \( A \) is either a heteroatom, e.g. O, S, NR\(^1\), or \( A \) is CR\(^1\)R\(^2\), wherein \( R^1 \) and \( R^2 \) are as defined above,

and wherein \( R^3 \) is a protecting group, e.g. an (un)substituted benzyl or a COOR\(^5\) group, wherein \( R^5 \) is an (un)substituted \( \text{Ci}_{6} \) alkyl, (un)substituted aryl or (un)substituted benzyl,

by treatment with organometallic compounds, preferably the Grignard reagents LVII,
wherein $R^4$ is 1-octyl, Cl, Br, or I and wherein $X$ is Cl, Br, or I,
producing the intermediates LVIII or LIX

![Chemical Structures](LVIII) ![Chemical Structures](LIX)

wherein $R^1$, $R^2$, $R^3$ are as defined above and $R^4$ is Cl, Br, or I.

2. The method according to claim 1, characterized in that the opening of the aziridine ring of the compounds LVI by the treatment the Grignard reagents LVII is performed under catalysis by salts and complexes of transition metals, especially compounds of Cu.

3. The method according to claims 1 or 2, characterized in that the opening of the aziridine ring of the compounds LVI is carried out with a Grignard reagent LVII, wherein $R^4$ is 1-octyl and the products are directly the key intermediates LVIII, wherein $R^1$, $R^2$, $R^3$ are as defined in claim 1.

![Chemical Structure](LVIII)

4. The method according to claims 1 or 2, characterized in that the opening of the aziridine ring of the compounds LVI is carried out with the Grignard reagents LVII, wherein $R^4$ is Cl, Br, or I and the products are the less advanced intermediates LIX, wherein $R^1$, $R^2$, and $R^3$ are as defined in claim 1.
5. The method according to claim 4, characterized in that the intermediates LIX are further converted to the advanced intermediates LVIII by reaction with organometallic reagents derived from 1-octyl halides, preferably organozinc reagents of the general formula \( n-C_8H_{17}ZnX \), wherein \( X = Cl, Br, \) or \( I \), under catalysis of transition metals, preferably Pd.

6. The method according to claim 4, characterized in that the intermediates LIX are further converted, by reaction with 1-octyne under Pd catalysis, to compounds of the general formula LXII,

\[
\text{LXII)
\]

wherein \( R^1, R^2 \) and \( R^3 \) are as defined in claim 1,

which are converted to the advanced intermediates LVIII in the next stage.

7. The method according to any one of claims 1 to 6, characterized in that both \( R^1 \) and \( R^2 \) is the methyl group and \( R^3 \) is \( COOR^5 \), wherein \( R^5 \) is tert-butyl or benzyl, and \( R^4 \) is 1-octyl, Cl, Br, or I.
8. A compound of formula LVIII, obtainable by a method according to any one of the preceding claims 1 to 7, wherein both $R^1$ and $R^2$ is the methyl group and $R^3$ is COOR$^5$, wherein $R^5$ is benzyl.

9. Compounds of the general formula LIX, obtainable by a method according to any one of the preceding claims 1 to 7, wherein both $R^1$ and $R^2$ is the methyl group and $R^3$ is COOR$^5$, wherein $R^5$ is tert-butyll or benzyl, and $R^4$ is Cl, Br, or I.

10. Compounds of the general formula LXII, obtainable by a method according to any one of the preceding claims 1 to 7, wherein both $R^1$ and $R^2$ is the methyl group and $R^3$ is COOR$^5$, wherein $R^5$ is tert-butyll or benzyl.

11. Use of a compound according to any one of claims 8 to 10 for the preparation of fingolimod.
INTERNATIONAL SEARCH REPORT

PCT/CZ2013/000075

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D319/06 C07C213/08

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 C07C

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

EPO-Internal, WPI Data, BEI LSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>X</td>
<td>WO 2012/056458 A2 (MAPI PHARMA LTD [IL]; MAROM EHUD [IL]; MIZHI RITSKI I MICHAEL [IL]; RUBN) 3 May 2012 (2012-05-03)</td>
<td>8-11</td>
</tr>
<tr>
<td>A</td>
<td>claims 25-40; example 17</td>
<td>1-7</td>
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Date of the actual completion of the international search: 6 September 2013

Date of mailing of the international search report: 19/09/2013

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Authorized officer:

Zervas, Brigitte
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