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(54) Title: THERAPEUTIC COMPOUNDS FOR PAIN AND SYNTHESIS THEREOF

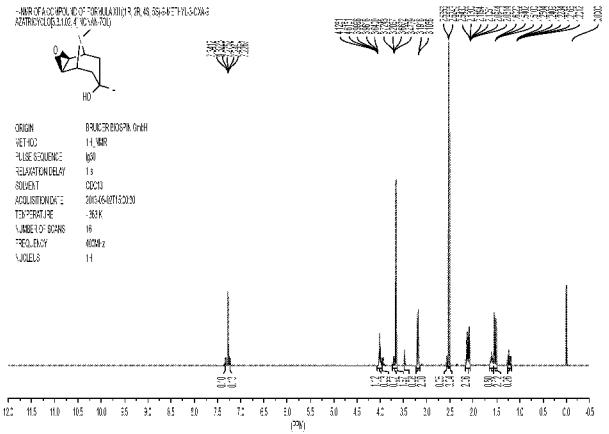
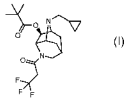


FIG. 1



(I)

(57) Abstract: The invention provides compounds of Formula (1): and stereoisomers, pharmaceutically acceptable salts and derivatives thereof; and methods of making and using such compounds. The invention includes pharmaceutical compositions containing such compounds, and the use of such compounds in methods of treating conditions, diseases, or disorders.

WO 2017/040770 A1

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# THERAPEUTIC COMPOUNDS FOR PAIN AND SYNTHESIS THEREOF

## Related Applications

**[0001]** This patent application claims the benefit of U.S. Provisional Application Ser. No. 62/214,727, filed September 4, 2015, and U.S. Provisional Application Ser. No. 62/214,734, filed September 4, 2015, each of which is incorporated by reference herein in its entirety.

## Field of the Invention

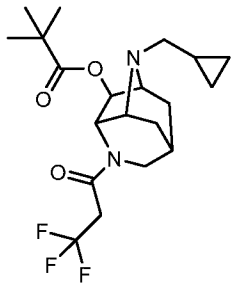
**[0002]** The invention provides new pharmaceutically active chemical compounds, which can be used for treating conditions and disorders in animals, mammals, and humans.

## Background

**[0003]** New chemical compounds having pharmaceutical activity can be indicated for the treatment of previously untreatable conditions, better treatment of conditions than can be achieved with conventional pharmaceutical compounds, and treatment of conditions that were previously treatable with conventional pharmaceutical compounds, but now are no longer effectively treatable. For example, such compounds can be useful in the case of bacterial or viral infectious agents that have evolved to become drug resistant.

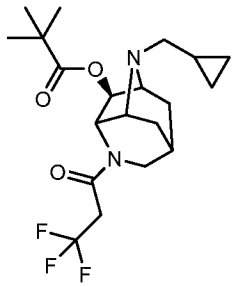
## SUMMARY OF THE INVENTION

**[0004]** The invention provides a compound of Formula 1:



1-(cyclopropylmethyl)-4-(3,3,3-trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate, or a stereoisomer, pharmaceutically acceptable salt, or mixture thereof.

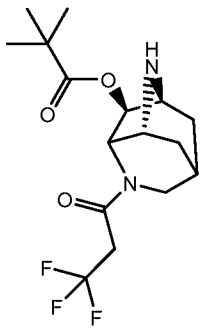
**[0005]** In certain embodiments, Formula 1 is



(2S,3S,6R,7aR)-1-(cyclopropylmethyl)-4-(3,3,3-trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate.

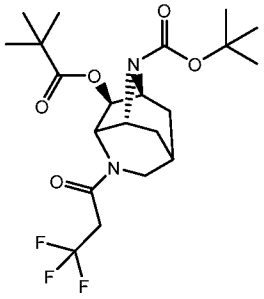
**[0006]** In certain embodiments, the invention includes a pharmaceutical composition containing a compound of Formula 1 and/or a derivative thereof. In one embodiment, the invention includes a pharmaceutical composition comprising a compound of Formula 1 and/or derivative thereof and a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention provides a method for treating a subject (a human or an animal) suffering from a condition, disease, or disorder, comprising administering to the subject an effective amount of a compound of Formula 1 and/or derivative thereof. In one embodiment, the compound is administered to effect localized delivery to the subject. In another embodiment, the compound is administered to effect systemic delivery to the subject. In a further embodiment, a compound of Formula 1, and/or derivative thereof is used as a medicament, or used in the manufacture of a medicament. In some embodiments, the condition or disorder is neuropathic pain or chronic pain.

**[0007]** In other embodiments, the method includes making the compound of Formula 1. In one such embodiment, the method of making the compound of Formula 1 includes reacting a compound of Formula 2:



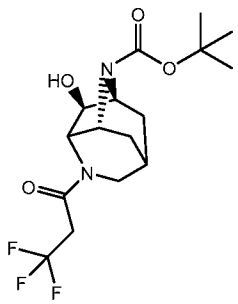

(2S*,3S*,3aS*,6R*,7aR*)-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate with cyclopropylcarboxaldehyde in the presence of a reducing agent. In some embodiments the cyclopropylcarboxaldehyde was added before the reducing agent. In certain embodiments the reducing agent is sodium triacetoxyborohydride. In some embodiments the compound of Formula 1 is chirally separated.

**[0008]** In some embodiments, the method can also include making the compound of Formula 2. In an embodiment, the method of making the compound of Formula 2 includes reacting a compound of Formula 3:



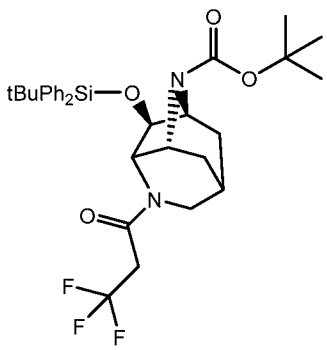
(2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-(pivaloyloxy)-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with an acid. In certain embodiments, the acid is trifluoroacetic acid.

**[0009]** In some embodiments, the method can also include making the compound of Formula 3. In an embodiment, the method of making the compound of Formula 3 includes reacting a compound of Formula 4:



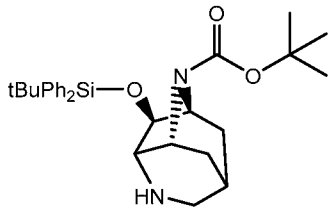
(2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-hydroxy-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with dimethylaminopyridine (DMAP).

**[0010]** In some embodiments, the method can also include making the compound of Formula 4. In an embodiment, the method of making the compound of Formula 4 includes reacting a compound of Formula 5:

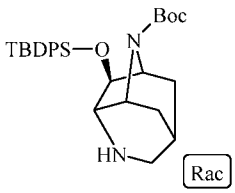


(2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-((tertbutyldiphenylsilyl)oxy)-4-(3,3,3 trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with tert-butyldiphenylchlorosilane. In some embodiments the reaction further comprises pyridine.

**[0011]** In some embodiments, the method can also include making the compound of Formula 5. In an embodiment, the method of making the compound of Formula 5 includes reacting a compound of Formula 6.b:

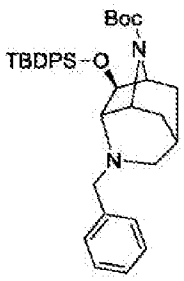



(2S*,3R*,3aS*,6R*,7aR*)-tert-butyl 3-((tertbutyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with 3,3,3-trifluoropropanoic acid. In some embodiments, the reaction further comprises N-N-Diisopropylethylamine. In certain embodiments, the reaction further comprises (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) sodium triacetoxyborohydride. In some embodiments, the method includes chirally separating a compound of Formula 7:



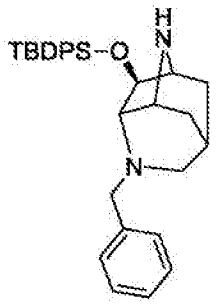

rac-(2S*,3R*,3aS*,6R*,7aR*)-tert-butyl 3-((tertbutyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate.

**[0012]** In other embodiments, the method includes making the compound of Formula 7. In one such embodiment, the method of making the compound of Formula 7 includes reacting a compound of Formula 8:



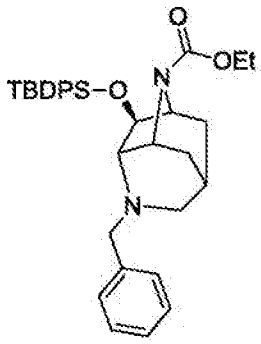
rac-(2R,3R,6S,7aS)-tert-butyl 4-benzyl-3- ((tert-butyldiphenylsilyl)oxy)octahydro-1H- 2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with hydrogen. The reaction may be performed in the presence of a catalyst. In a preferred embodiment, the catalyst includes palladium. For example, the catalyst can be palladium on carbon.

**[0013]** In other embodiments, the method includes making the compound of Formula 8. In one such embodiment, the method of making the compound of Formula 8 includes reacting a compound of Formula 9:



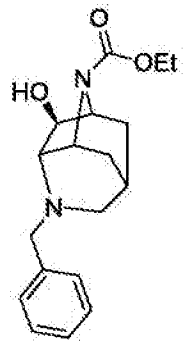

rac-(2R,3R,6S,7aS)-4-benzyl-3-((tert-butyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine with di-tert-butyl dicarbonate ($Boc_2O$) to add a tert-butyloxycarbonyl (Boc) protecting group. In a preferred embodiment the reaction further comprises triethylamine ($Et_3N$).

**[0014]** In other embodiments, the method also includes making the compound of Formula 9. In one such embodiment, the method of making the compound of Formula 9 includes reacting a compound of Formula 10:



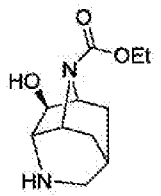

(2R,3R,6S,7aS)-ethyl 4-benzyl-3-((tert-butyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with iodotrimethylsilane.

**[0015]** In other embodiments, the method also includes making the compound of Formula 10. In one such embodiment, the method of making the compound of Formula 10 includes reacting a compound of Formula 11:



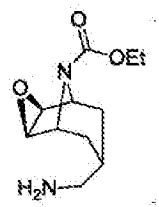

(2R,3S,6S,7aS)-ethyl-4-benzyl-3-hydroxyoctahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with TBDPS. In a preferred embodiment the reaction further comprises imidazole.

**[0016]** In other embodiments, the method also includes making the compound of Formula 11. In one such embodiment, the method of making the compound of Formula 11 includes reacting a compound of Formula 12:



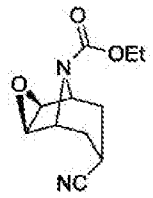

(2R,3S,6S,7aS)-ethyl 3-hydroxyoctahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate with benzaldehyde. In a preferred embodiment the reaction further comprises sodium triacetoxyborohydride (STAB).

**[0017]** In other embodiments, the method also includes making the compound of Formula 12. In one such embodiment, the method of making the compound of Formula 12 includes cyclizing a compound of Formula 12.a:



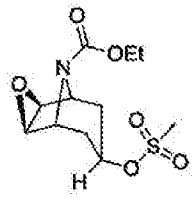
(1R,2R,4S,5S,7s)-ethyl 7-(aminomethyl)-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate in a solvent. The solvent can be ethanol (EtOH).

**[0018]** In other embodiments, the method also includes making the compound of Formula 12.a. In one such embodiment, the method of making the compound of Formula 12.a includes reacting a compound of Formula 13:



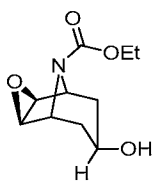

(1R,2R,4S,5S,7s)-ethyl 7-cyano-3-oxa-9- azatricyclo[3.3.1.02,4]nonane-9-carboxylate with hydrogen. The reaction may be performed in the presence of a catalyst. In one embodiment, the catalyst includes nickel. For example, the catalyst can be Raney-nickel.

**[0019]** In other embodiments, the method also includes making the compound of Formula 13. In one such embodiment, the method of making the compound of Formula 13 includes reacting a compound of Formula 14:



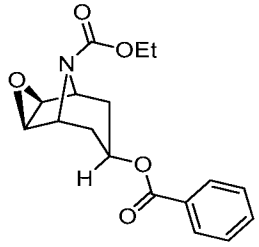

(1R,2R,4S,5S,7r)-ethyl 7-((methylsulfonyl)oxy)-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate with potassium cyanide. In other embodiments the reaction further comprises 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane).

**[0020]** In other embodiments, the method also includes making the compound of Formula 14. In one such embodiment, the method of making the compound of Formula 14 includes reacting a compound of Formula 15:



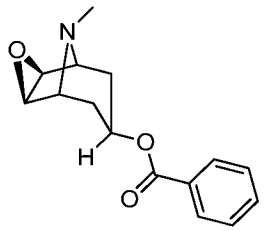

(1R,2R,4S,5S,7r)-ethyl 7-hydroxy-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate with mesyl chloride. In a preferred embodiment the reaction further comprises triethylamine ($ET_3N$).

**[0021]** In other embodiments, the method also includes making the compound of Formula 15. In one such embodiment, the method of making the compound of Formula 15 includes reacting a compound of Formula 16:



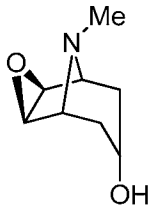
(1R,2R,4S,5S,7r)-ethyl 7-(benzoyloxy)-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate with a reducing agent. The reducing agent can be sodium borohydride.

**[0022]** In other embodiments, the method also includes making the compound of Formula 16. In one such embodiment, the method of making the compound of Formula 16 includes reacting a compound of Formula 17:



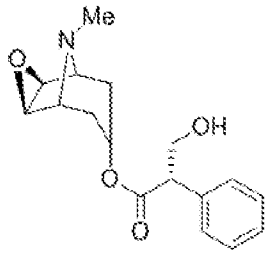
(1R,2R,4S,5S,7r)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl benzoate with ethyl chloroformate. In a preferred embodiment the reaction further comprises a base. The base can be potassium carbonate.

**[0023]** In other embodiments, the method also includes making the compound of Formula 17. In one such embodiment, the method of making the compound of Formula 17 includes reacting a compound of Formula 18:



(1R,2R,4S,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-ol) with benzoic acid in the presence of an activating agent. The activating agent can be diethylazodicaroxylate (DEAD) with triphenylphosphine ($PPh_3$) or diisopropyl azodicarboxylate (DIAD) with $PPh_3$.

**[0024]** In other embodiments, the method also includes making the compound of Formula 18. In one such embodiment, the method of making the compound of Formula 18 includes reacting a compound of Formula 19:




(2S)-(1R,2R,4S,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl-3-hydroxy-2-phenylpropanoate hydrobromide trihydrate (scopolamine) with a reducing agent. The reducing agent can be sodium borohydride. In a preferred embodiment the reaction further comprises HCl in isopropyl alcohol.

**[0025]** In some embodiments, the compounds described herein are used in the treatment or prevention of neuropathic pain in a subject in need. In other embodiments the compounds described herein are useful in the treatment or prevention of chronic pain in a subject in need.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0026]** The preceding Summary, as well as the following Detailed Description of the invention, can be better understood when read in conjunction with the appended Figures. For the purpose of illustrating the invention, the Figures demonstrate embodiments of the present invention. However, it should be understood that the invention is not limited to the precise arrangements, examples, and instrumentalities shown.

**[0027]** Figure 1 shows the results of a $^{1H}$NMR ($CDCl_3$) analysis of the compound of Formula 18, according to one embodiment of the invention.

**[0028]** Figure 2 shows the results of a MS analysis of the compound of Formula 17, according to one embodiment of the invention.

**[0029]** Figures 3A and 3B show the results of a structural analysis of the compound of Formula 16. Figure 3A shows the results of a $^{1H}$NMR analysis of the compound of Formula 16. Figure 3B shows the results of a MS analysis of the compound of Formula 16.

**[0030]** Figure 4 shows the results of a $^{1H}$NMR analysis of the compound of Formula 15.

**[0031]** Figure 5 shows the results of a $^{1H}$NMR analysis of the compound of Formula 14.

**[0032]** Figure 6 shows the results of a $^{1H}$NMR analysis of the compound of Formula 13.

**[0033]** Figure 7 shows the results of a $^{1H}$NMR analysis of the compound of Formula 12.

**[0034]** Figures 8A and 8B show the results of a structural analysis of the compound of Formula 11. Figure 8A shows the results of a MS analysis of the compound of Formula 11. Figure 8B shows the results of a $^{1H}$NMR analysis of the compound of Formula 11.

**[0035]** Figures 9A and 9B show the results of a structural analysis of the compound of Formula 10. Figure 9A shows the results of a LCMS analysis of the compound of Formula 10. Figure 9B shows the results of a $^{1H}$NMR analysis of the compound of Formula 10.

**[0036]** Figure 10 shows the results of a LCMS analysis of the compound of Formula 9.

**[0037]** Figures 11A and 11B show the results of a structural analysis of the compound of Formula 8. Figure 11A shows the results of a $^{1H}$NMR analysis of the compound of Formula 8. Figure 11B shows the results of a LCMS analysis of the compound of Formula 8.

**[0038]** Figures 12A and 12B show the results of a structural analysis of the compound of Formula 7. Figure 12A shows the results of a LCMS analysis of the compound of Formula 7. Figure 12B shows the results of a $^{1H}$NMR analysis of the compound of Formula 7.

**[0039]** Figure 13 shows the results of a $^{1H}$NMR analysis of the compound of Formula 2.

## Detailed Description

Embodiments of the invention are discussed in detail below. In describing these embodiments, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology selected. A person skilled in the relevant art will recognize that other equivalent parts can be employed and other methods developed without

## Certain Definitions

**[0040]** The term "alkyl" refers to branched or unbranched hydrocarbon chains, in for example, hydrocarbon chains having from 1 to 12 carbon atoms in the chain. In some embodiments, an alkyl group is a $C_1$-$C_6$ alkyl group. In some embodiments, an alkyl group is a $C_1$-$C_4$ alkyl group. Examples of alkyl groups include methyl (Me) ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

**[0041]** The term "haloalkyl" refers to a straight- or branched-chain alkyl group having from 1 to

12 carbon atoms in the chain and having at least one of the hydrogens replaced with a halogen. In some embodiments, a haloalkyl group is a $C_1$-$C_6$ haloalkyl group. In some embodiments, a haloalkyl group is a $C_1$-$C_4$ haloalkyl group. One exemplary substitutent is fluoro. Preferred substituted alkyl groups of the invention include trihalogenated alkyl groups such as trifluoromethyl groups. Haloalkyl includes and is not limited to $CF_3$, $CH_2F$, -$CHF_2$, -$CH_2Cl$, -$CH_2$-$CF_3$, and the like.

**[0042]** "Cycloalkyl" refers to monocyclic, non-aromatic hydrocarbon groups having from 3 to 7 carbon atoms. Examples of cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

**[0043]** The term "alkoxy" includes a straight chain or branched alkyl group with a terminal oxygen linking the alkyl group to the rest of the molecule. In some embodiments, an alkoxy group is a $C_1$-$C_6$ alkoxy group. In some embodiments, an alkoxy group is a $C_1$-$C_4$ alkoxy group. Alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and so on.

**[0044]** The term "heterocycle" represents" a mono- or bi-cyclic hydrocarbon ring structure optionally containing heteroatoms selected from O, S, and N. Heterocyclyl rings can have 2 to 10 carbon atoms in the ring.

**[0045]** The term "halogen" represents chlorine, fluorine, bromine, or iodine. The term "halo" represents chloro, fluoro, bromo, or iodo.

**[0046]** A wavy line "§" indicates the point of attachment to the rest of the molecule.

**[0047]** "Benzyl" and –$CH_2$-phenyl are used interchangeably.

**[0048]** "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

**[0049]** "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid,

succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

**[0050]** "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered. A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

**[0051]** "Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

**[0052]** "Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or

"treatment" refers to delaying the onset of the disease or disorder.

**[0053]** In treatment methods according to the invention, a therapeutically effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. A "therapeutically effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment for the designated disease, disorder, or condition.

**[0054]** Effective amounts or doses of the compounds of the present invention may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

**[0055]** "Compounds of the present invention," and equivalent expressions, are meant to embrace compounds of the Formula as described herein, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

**[0056]** As used herein, the term "isotopic variant" refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more non-radioactive or radioactive isotopes, such as for example, deuterium ($^{2}$H or D), carbon-13 ($^{13}$C), nitrogen-15 ($^{15}$N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be $^{2}$H/D, any carbon may be $^{13}$C, or any nitrogen may be $^{15}$N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance

for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. Radiolabeled compounds of the invention can be used in diagnostic methods such as single-photon emission computed tomography (SPECT). The radioactive isotopes tritium, i.e. $^{3}H$, and carbon-14, i.e. $^{14}C$, are particularly useful for their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as $^{11}C$, $^{18}F$, $^{15}O$ and $^{13}N$, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

**[0057]** All isotopic variants of the compounds of the invention, radioactive or not, are intended to be encompassed within the scope of the invention. In one aspect, provided herein are deuterated or tritiated analogs of compounds described.

**[0058]** It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers."

**[0059]** Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture."

**[0060]** "Tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of $\pi$ electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

**[0061]** Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

**[0062]** Compounds of the invention may also exist as "rotamers," that is, conformational isomers that occur when the rotation leading to different conformations is hindered, resulting a rotational energy barrier to be overcome to convert from one conformational isomer to another.

**[0063]** The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)-or (S)-stereoisomers or as mixtures thereof.

**[0064]** Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

**[0065]** As used herein, the term "localized delivery" denotes delivery of a pharmaceutical or therapeutic agent to a specific, limited region of the body.

**[0066]** As used herein, the term "systemic delivery" denotes delivery of a pharmaceutical or therapeutic agent throughout the body, for example, through administration to the circulatory system.

**[0067]** As used herein, the term "mass spectrometry (MS)" denotes an analytic technique that ionizes a chemical compound to generate charged molecules or molecule fragments and measures their abundance as a function of mass-to-charge (m/z) ratio (the mass spectrum). From the mass spectrum, conclusions as to the structure of the chemical compound can be drawn.

**[0068]** As used herein, the term "liquid chromatography – mass spectrometry (LCMS)" denotes an analytic technique that combines the physical separation capability of liquid chromatography with the analytic capability of mass spectrometry. In the liquid chromatography step, the sample is introduced into a column packed with a stationary phase, separating the chemical compounds of the sample by their retention time (Rt) in the column. The chemical compound or compounds associated with a retention time interval are then directed to a mass spectrometer, to obtain a mass spectrum that allows conclusions as to the structure of this chemical compound or compounds to be drawn.

**[0069]** As used herein, the term "thin-layer chromatography (TLC)" denotes an analytic technique that separates chemical compounds in a sample by the different rates in which they are drawn up a plate coated with a stationary phase material.

**[0070]** As used herein, the term "nuclear magnetic resonance spectroscopy (NMR)" denotes an

analytic technique that measures the intensity of a resonance response of a set of nuclei to a radio frequency pulse to allow information as to the electronic environment of the nuclei to be obtained. From this, conclusions can be drawn as to the chemical structure of the compound in which the nuclei reside. A nuclear magnetic resonance spectroscopy technique that uses hydrogen nuclei (protons) is termed proton nuclear magnetic resonance spectroscopy ($^{1H}$NMR).

**[0071]** The term "ester" is used herein as is conventional in the field of organic chemistry. For example, the term "ester" can denote a carbonyl group with a bonded oxygen and alkyl or an oxygen with a bonded carbonyl and alkyl.

**[0072]** As used herein, the term "metabolic syndrome" denotes a medical or biological disorder of energy utilization and storage in an animal or human, which can be characterized by abdominal obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and/or low high-density cholesterol levels.

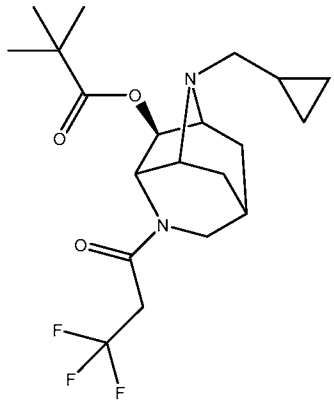
**[0073]** As used herein, the term "polymerase chain reaction" denotes a biomedical technique for generating many copies of a particular DNA sequence.

**[0074]** As used herein, the term "triturate" denotes a method of purifying a material in which the crude material is washed with a solvent. The solvent can be selected, so that the desired product is insoluble and the impurities are soluble, in which case, the purified product is left in solid form and the impurities are removed with the solvent. Conversely, the solvent can be selected, so that the desired product is soluble and the impurities are insoluble, in which case, the purified product is in solution and the impurities are removed as solids. The solvent can then be removed, for example, through evaporation, to obtain the purified product.

**[0075]** As used herein, the term "Boc-protection" denotes functionalization of a chemical compound with a tert-butyloxycarbonyl (Boc) group as a protecting group. This allows the chemical compound as a whole to be treated with reagents that would otherwise undesirably attack the unprotected group. The protected group can thereafter be deprotected to yield the desired original group.

## Exemplary Compounds

**[0076]** The present invention, provides a molecule having the structure of a compound of the structure of Formula 1:



Formula 1

(2S,3S,6R,7aR)-1-(cyclopropylmethyl)-4-(3,3,3-trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate, and stereoisomers thereof. This compound can be prepared by the reaction sequences described in the Schemes set forth in Example 1.

## Pharmaceutical Compositions and Administration

**[0077]** The compounds of the present invention are useful as pharmaceutical agents and can be incorporated into pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention, as defined herein, and a pharmaceutically acceptable carrier or diluent.

**[0078]** The compounds of the invention can also be used in the manufacture of derivative compounds that are useful as pharmaceutical agents, and which can likewise be incorporated into pharmaceutical compositions prepared with a therapeutically effective amount of such a derivative compound and a pharmaceutically acceptable carrier or diluent.

**[0079]** The compounds of the invention, and such derivatives thereof, can be useful in the treatment of conditions, diseases, and disorders in humans and animals. Such compounds can be formulated as pharmaceutical compositions and administered to a subject in need of treatment, for example a mammal, such as a human patient, in a variety of forms adapted to the chosen route of administration. For example compounds of the invention may be formulated for administration, orally, nasally, intraperitoneally, or parenterally, by intravenous, intramuscular, topical, or subcutaneous routes, or by injection into tissue.

**[0080]** Thus, compounds of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable

edible carrier, or by inhalation or insufflation. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the compounds may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The compounds may be combined with an inert powdered carrier and inhaled by the subject or insufflated. Such compositions and preparations should contain at least 0.1% of a compound of the present invention. The percentage of the compound of the invention present in such compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of the compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

**[0081]** The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose, or aspartame, or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or for otherwise modifying the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac, or sugar, and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the compounds may be incorporated into sustained-release preparations and devices. For example, the compounds may be incorporated into time release capsules, time release tablets, time release pills, and time release polymers or nanoparticles.

**[0082]** The compounds may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the compounds can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols,

triacetin, and mixtures thereof, and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

**[0083]** The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the compounds which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid, and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions, or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers, or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

**[0084]** Sterile injectable solutions are prepared by incorporating the compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, preferably followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

**[0085]** For topical administration, the compounds may be applied in pure form. However, it may be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

**[0086]** Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina, and the like. Other solid carriers include nontoxic polymeric nanoparticles or microparticles. Useful liquid carriers include water, alcohols, or glycols, or water/alcohol/glycol blends, in which the compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and

additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

**[0087]** Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses, or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

**[0088]** Examples of useful dermatological compositions which can be used to deliver the compounds to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508), all of which are hereby incorporated by reference.

**[0089]** The concentration of the therapeutic compounds of the invention in such formulations can vary widely depending on the nature of the formulation and intended route of administration. For example, the concentration of the compounds in a liquid composition, such as a lotion, can preferably be from about 0.1 - 25% by weight, or, more preferably, from about 0.5 - 10% by weight. The concentration in a semi-solid or solid composition such as a gel or a powder can preferably be about 0.1 - 5% by weight, or, more preferably, about 0.5 - 2.5% by weight.

**[0090]** Effective dosages and routes of administration of agents of the invention are conventional. The exact amount (effective dose) of the agent will vary from subject to subject, depending on, for example, the species, age, weight, and general or clinical condition of the subject, the severity or mechanism of any disorder being treated, the particular agent or vehicle used, the method and scheduling of administration, and the like. A therapeutically effective dose can be determined empirically, by conventional procedures known to those of skill in the art. See, e.g., The Pharmacological Basis of Therapeutics, Goodman and Gilman, eds., Macmillan Publishing Co., New York. For example, an effective dose can be estimated initially either in cell culture assays or in suitable animal models. The animal model may also be used to determine the appropriate concentration ranges and routes of administration. Such information can then be used to determine useful doses and routes for administration in humans. Methods for the extrapolation of effective dosages in mice and other animals to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is hereby incorporated by reference. A therapeutic dose can also be selected by analogy to dosages for comparable therapeutic agents.

**[0091]** The particular mode of administration and the dosage regimen will be selected by the attending clinician, taking into account the particulars of the case (e.g., the subject, the disease, the disease state involved, and whether the treatment is prophylactic). Treatment may involve daily or multi-daily doses of compound(s) over a period of a few days to months, or even years.

**[0092]** In general, however, a suitable dose will be in the range of from about 0.001 to about 100 mg/kg of body weight per day, preferably from about 0.01 to about 100 mg/kg of body weight per day, more preferably, from about 0.1 to about 50 mg/kg of body weight per day, or even more preferred, in a range of from about 1 to about 10 mg/kg of body weight per day. For example, a suitable dose may be about 1 mg/kg, 10 mg/kg, or 50 mg/kg of body weight per day.

**[0093]** The compounds are conveniently administered in unit dosage form; for example, containing about 0.05 to about 10000 mg, about 0.5 to about 10000 mg, about 5 to about 1000 mg, or about 50 to about 500 mg of active ingredient per unit dosage form.

**[0094]** The compounds can be administered to achieve peak plasma concentrations of, for example, from about 0.25 to about 200 μM, about 0.5 to about 75 μM, about 1 to about 50 μM, about 2 to about 30 μM, or about 5 to about 25 μM. Exemplary desirable plasma concentrations include at least 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 or 200 μM. For example, plasma levels may be from about 1 to about 100 micromolar or from about 10 to about 25 micromolar. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the compounds, optionally in saline, or orally administered as a bolus containing about 1 to about 100 mg of the compounds. Desirable blood levels may be maintained by continuous or intermittent infusion.

**[0095]** The compounds may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as one dose per day or as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator.

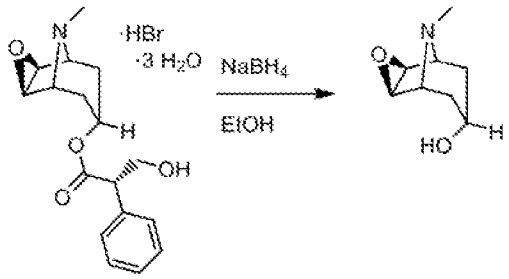
**[0096]** All documents, references, and information, including, but not limited to, journal articles, patent applications, and patents, that are mentioned, cited, or referred to in this application are hereby incorporated by reference in their entirety as if each had been individually incorporated.

## Example 1: Synthesis of a Compound of Formula I

**[0097]** A compound of Formula 1 was synthesized, from the compound of Formula 19

(Scopolamine [51-34-3]) ((2S)-(1R,2R,4S,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl-3-hydroxy-2-phenylpropanoate hydrobromide trihydrate) by the steps described below in Schemes 1 through 18.

**[0098]** A first step is illustrated in Scheme 1.




Formula 19 Formula 18

Scheme 1

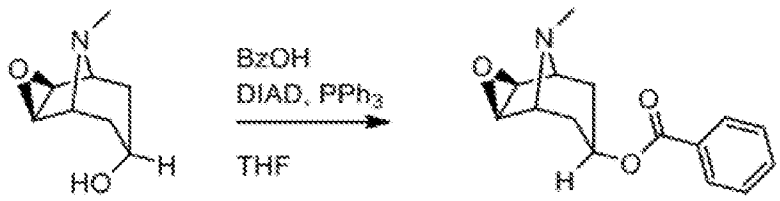
**[0099]** Inside a 10 liter four necked round bottom flask, sodium borohydride (172 g, 4558 mmol) was added portion wise over about 2 hours to a mechanically stirred suspension of a compound of Formula 19 (333 g, 760 mmol) in 3 liters of absolute ethanol in an ice bath. During this time, gas formation occurred and the suspension was stirred while being warmed to ambient temperature overnight. While being heated, at approximately 10 °C, sudden additional gas formation and foaming occurred.

**[00100]** The milky suspension was then concentrated to about half of its original volume (*i.e.* from about 3 L to 1.5 L) with additional precipitate observed, which yielded the batch. 5 M HCl in isopropyl alcohol (IPA) (5318 mmol, 1.064 L) was then diluted with 2 L of technical diethyl ether ($Et_2O$). The obtained hydrochloric acid (HCl) solution was then added drop wise to the ice-chilled batch, while being stirred. The white suspension was allowed to be mechanically stirred overnight to allow for full hydrolysis of the borate salts.

**[00101]** The reaction mixture was filtered and the resulting solid was rinsed twice with 500 mL portions of $Et_2O$. The dried solid (which contained some $Et_2O$) was dissolved in a minimum amount of 10% aqueous potassium carbonate ($K_2CO_3$) solution (~1.5 L) until just a clear solution was obtained. 200 mL of brine and ~50 g solid NaCl was added to the solution. The aqueous phase was then thoroughly extracted with chloroform / methanol (MeOH) / [7N $NH_3$ in MeOH] (85:14:1). This procedure was performed 5 times with 1.0 L portions of this solvent mixture each.

**[00102]** The combined organic extracts were dried (sodium sulphate ($Na_2SO_4$)), filtered and the solvent was removed under reduced pressure to give 102.2 g (659 mmol) of a compound of Formula 18 ((1R,2R,4S,5S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-ol) as a slightly tan oil at 87% yield. $^{1H}$NMR ($CDCl_3$) (Figure 1) showed structural agreement with the compound of Formula 18 with minor amounts of impurities. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 4.03-4.00 (m, 1H), 3.67 (s, 2H), 3.20-3.18 (m, 2H), 2.52 (s, 3H), 2.14-2.08 (m, 2H), 1.69 – 1.37 (m, 3H).

**[00103]** The next step proceeded as illustrated by Scheme 2.




Formula 18 Formula 17

Scheme 2

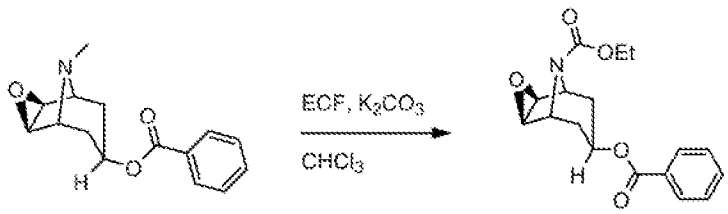
**[00104]** To a solution of the compound of Formula 18 (102.2 g, 659 mmol), benzoic acid (BzOH) (97 g, 790 mmol) and triphenylphosphine ($PPh_3$) (207 g, 790 mmol) in 1000 mL of dry tetrahydrofuran (THF) a solution of diisopropyl azodicaboxylate (DIAD) (160 g, 790 mmol, 154 mL) in 100mL of dry THF was added drop wise over a period of 4 hours. During the addition the solution was kept between -35 and -25 °C using acetone/dry ice. The clear, colorless solution was then removed from the ice bath and stirred at room temperature overnight.

**[00105]** Samples were taken and analyzed, and the analysis showed the reaction went to completion. The reaction mixture was concentrated, dissolved in 1 L of ethyl acetate (EtOAc), extracted with 1 L of saturated sodium bicarbonate ($NaHCO_3$), and subsequently with aqueous 2 M HCl (1x1 L, 2x0.5 L). The combined acidic aqueous fractions were washed once more with 1 L of EtOAc. Approximately 400 g of potassium carbonate ($K_2CO_3$) was added portion wise to the acidic aqueous layer, while being stirred, until no more gas formation was observed. The pH of the resulting solution was slightly basic and slightly turbid and yellow.

**[00106]** The aqueous phase was then extracted with a dichloromethane (DCM) / MeOH 9:1 (3x, 1 L each) solution and the combined organic fractions were dried with sodium sulfate ($Na_2SO_4$), filtered and concentrated to afford 118.3 g (447 mmol) of a compound of Formula 17 ((1R,2R,4S,5S,7r)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]nonan-7-yl benzoate), which was

then confirmed by MS (Figure 2) to have 98% purity at 67.9% yield. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.93 (m, 2H), 7.59 – 7.48 (m, 1H), 7.44 – 7.40 (m, 2H), 5.39 – 5.30 (m, 1H), 3.63 (s, 2H), 3.42 – 3.25 (m, 2H), 2.57 (s, 3H), 2.10 – 2.04 (m, 2H), 1.92 – 1.86 (m, 2H).

**[00107]** The next step proceeded as illustrated in Scheme 3.




Formula 17 Formula 16

Scheme 3

**[00108]** To a solution of the compound of Formula 17 (201.9 g, 779 mmol) in chloroform (350 mL) under a nitrogen atmosphere (not a stream), $K_2CO_3$ (452 g, 3270 mmol) and ethyl chloroformate (279 g, 2569 mmol, 247 mL) were added to form a light yellow suspension which was then stirred under reflux overnight.

**[00109]** A sample was then taken and analyzed to show that the reaction had reached a 74% conversion to the product, a compound of Formula 16 (1R,2R,4S,5S,7r)-ethyl 7-(benzoyloxy)-3-oxa-9-azatricyclo[3.3.1.02,4] nonane-9-carboxylate). The mixture was further stirred at reflux temperature for another 24 hours.

**[00110]** Another sample was then taken and analyzed which showed that the reaction had reached a 75% conversion to product. In order to drive the reaction toward completion, additional $K_2CO_3$ (53.8 g, 389 mmol) and ethyl chloroformate (85 g, 779 mmol, 74.8 mL) were added to the reaction solution and the mixture was stirred at reflux temperature overnight.

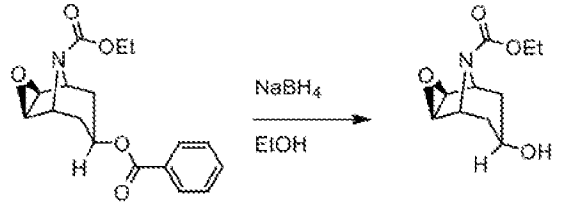
**[00111]** After being stirred and refluxed overnight, another sample was taken which was analyzed to show that the reaction had reached 81% conversion to the compound of Formula 16.

**[00112]** The reaction mixture was then diluted with 500 mL of DCM and the organic layer was washed with 750 mL of a half saturated aqueous $NaHCO_3$ solution, 750 mL of 0.4 M aqueous HCl, and 750 mL of brine. The mixture next dried over $Na_2SO_4$, then filtered and concentrated under reduced pressure which then afforded a yellow oil. 300 mL of Heptane was added and the mixture was vigorously stirred overnight.

**[00113]** A white suspension had formed which contained big white lumps which were crushed with a spatula. The suspension was filtered over a glass filter, rinsed with approximately 250 mL

of heptane and approximately 200 mL of pentane. The suspension was then dried using a vacuum oven for 3 hours yielding the compound of Formula 16 as a white solid (219.6 g, 692 mmol, 89% yield). LCMS of the product showed a percent yield greater than 95%, with a mass and structure agreement with the desired product as shown in the MS(Figure 3B) and $^{1H}$NMR (Figure 3A)). $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.97 (m, 2H), 7.61 – 7.53 (m, 1H), 7.48 – 7.42 (m, 2H), 5.48 – 5.39 (m, 1H), 4.58 (m, 1H), 4.48 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.53 (m, 2H), 2.34 – 2.21 (m, 2H), 1.98 – 1.86 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

**[00114]** The next step proceeded as illustrated in Scheme 4.




Formula 16 Formula 15

Scheme 4

**[00115]** In a 6 L three necked flask, sodium borohydride (157 g, 4152 mmol) was added to a suspension of the compound of Formula 16 (219.6 g, 692 mmol) in 1.5 L of absolute ethanol at room temperature. The reaction was exothermic, and had an internal temperature greater than 60 °C over a period of approximately 4 hours, during the reaction extreme gas/foam formation was observed. The suspension was magnetically stirred at 50 °C overnight.

**[00116]** A sample was then taken and analyzed by TLC to show that the reaction had gone to completion. The resulting product was a white solid which stopped the magnetic stirrer during the night. The mixture was concentrated under reduced pressure and the white solid residue was partitioned between 1 L of chloroform and 3.5 L of half-saturated aqueous $NaHCO_3$ solution. The layers were next separated and the aqueous layer was extracted with additional chloroform (2x, 1 L each). The combined organic layers were washed with 1 L of brine, dried over $Na_2SO_4$, and filtered and concentrated under reduced pressure to afford approximately 220 g of the product as a white solid which was stirred in 0.6 L of heptane overnight with a magnetic stirrer.

**[00117]** The mixture was then filtered off, the product had formed spheres which were crushed and had 500 mL of heptane added to them. The mixture was stirred vigorously overnight with a magnetic stirrer.

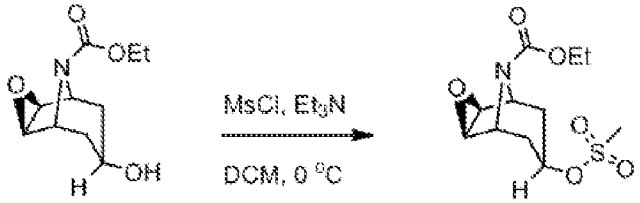
**[00118]** After stirring the mixture overnight, the off-white suspension still contained spheres

which then were crushed with a spatula. The suspension was filtered and the residue was rinsed with approximately 300 mL heptane and dried by vacuum which yielded approximately 148 g of the product.

**[00119]** A sample was taken and analysed by $^{1H}$NMR to show the structure was in agreement with the compound of Formula 15 (1R,2R,4S,5S,7r)-ethyl 7-hydroxy-3-oxa-9-azatricyclo [3.3.1.02,4]nonane-9-carboxylate), (Figure 4).

**[00120]** The residue was then stirred in approximately 300 mL of $Et_2O$ for 1 hour. The white suspension was filtered; and the residue was rinsed again with approximately 300 mL of $Et_2O$ and then dried by vacuum (under $N_2$-flow) to yield the compound of Formula 15 (122 g, 572 mmol, 82% yield). $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 4.50 (m, 1H), 4.41 (m, 1H), 4.23 – 4.09 (m, 3H), 3.42 – 3.39 (m, 2H), 2.15 – 2.08 (m, 2H), 1.73 – 1.62 (m, 2H), 1.44 (d, *J* = 5.9 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

**[00121]** The next step proceeded as illustrated in Scheme 5.




Formula 15 Formula 14

Scheme 5

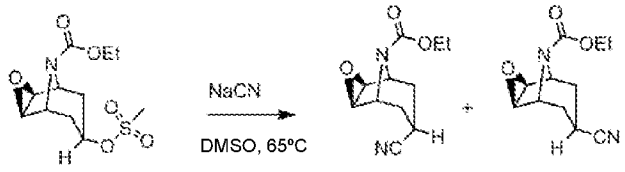
**[00122]** Triethylamine (22.78 g, 225 mmol, 31.4 mL) and mesyl-Cl (23.64 g, 206 mmol, 16.08 mL) was added drop wise to a solution of the compound of Formula 15 (40 g, 188 mmol) in DCM (500 mL) at 0 °C. Once the addition was complete, the ice bath was removed and the slightly milky suspension was stirred while warming to room temperature.

**[00123]** After 1 hour a sample was taken and analyzed by TLC which showed full conversion had occurred. The reaction mixture was then washed twice with 500 mL of water. The DCM layer appeared milky and was dried over $Na_2SO_4$ (which made the layer clearer), and then filtered and concentrated under reduced pressure to afford a thick oil. The oil was stripped twice with toluene to afford 54.2 g of a light tan solid which contained 21 w% toluene.

**[00124]** The solid was further dried under vacuum at 50 °C until the weight remained constant at 43.2 g (148 mmol; 78.9% yield) yielding a compound of Formula 14 ((1R,2R,4S,5S,7r)-ethyl 7-((methylsulfonyl)oxy)-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate). A sample was

taken and the structure was confirmed by $^{1H}$NMR (Figure 5). $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 5.11 – 5.02 (m, 1H), 4.54 – 4.53 (m, 1H), 4.44 – 4.43 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.47 – 3.45 (m, 2H), 3.00 (s, 3H), 2.28 – 2.23 (m, 2H), 2.00 – 1.90 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

**[00125]** The next step proceeded as illustrated in Scheme 6.




Formula 14 Formula 13 Formula 13.a

Scheme 6

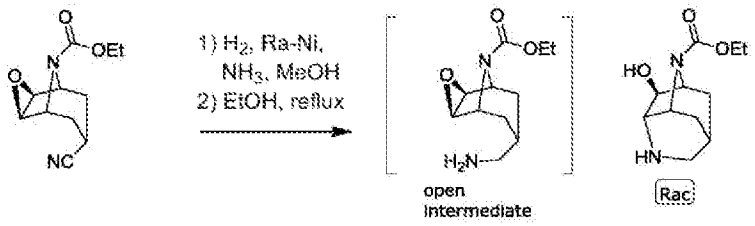
**[00126]** Potassium cyanide (12.14 g, 186 mmol) and 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) (0.493 g, 1.864 mmol) were added to a solution of the compound of Formula 14 (19.89 g, 62.1 mmol, 91 %) in 300 mL of dry Dimethyl sulfoxide to form a pale yellow solution which was stirred at 65 °C for two and a half days, or approximately 65 hours, to yield a light brown solution.

**[00127]** A sample was taken and analyzed by TLC (heptane / DME 1:1, molybdate staining required), which showed a clean conversion to the desired product (no exo-epimeric sideproduct observed). However, at this time, it was found that the reaction had not run to completion as starting material was also observed. The stirring was continued for a total of 118 hours, after which the brown solution was allowed to cool to room temperature, and combined with an additional batch before being partitioned between 2 L of EtOAc and 2 L of water.

**[00128]** The layers were separated and the organic layer was washed twice with 1 L of brine, dried over $Na_2SO_4$, and filtered and concentrated under reduced pressure to afford the crude product, a compound of Formula 13 ((1R,2R,4S,5S,7s)-ethyl 7-cyano-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate). The product was purified by gravity column chromatography (750 g silica, heptane / [5->50% EtOAc]) to afford 15.1 g of a white solid, or a compound of Formula 13. A sample was taken and analyzed by $^{1H}$NMR (Figure 6) which demonstrated the product was in agreement with the structure of Formula 13, although the product did contain 10 w% of the exo-sideproduct (which was not problematic for the follow-up reactions) and 7.5 w% of heptane. The combined yield from all experiments was 7.55 g, or 45% yield, after correction for solvent and side product content. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ

4.53 – 4.52 (m, 1H), 4.43 – 4.41 (m, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 3.70 – 3.68 (m, 2H), 2.93 – 2.89 (m, 1H), 2.22 – 2.12 (m, 2H), 2.04 – 1.98 (m, 2H), 1.24 (t, $J$ = 7.1 Hz, 3H).

**[00129]** The next step proceeded as illustrated in Scheme 7.




Formula 13 Formula 12.a Formula 12

Scheme 7

**[00130]** A 50% slurry of Raney-nickel in water was added to a solution of the compound of Formula 13 (18.20 g, 82 mmol) in 350 mL of MeOH / 200 mL of ammonia (7N in MeOH). The solution was kept under a nitrogen atmosphere and the Raney-nickel slurry was added until a dark black suspension was obtained while being stirred vigorously.

**[00131]** The reaction vessel was evacuated and refilled with $H_2$ balloons, which was repeated twice, and then stirred at 45 $^{o}$C under a $H_2$ atmosphere created by the balloons. After 3 hours, a sample was taken and analyzed by TLC using heptane / dimethoxyethane (DME) 1:1, which demonstrated the reaction was complete. The reaction mixture was filtered over a short pad of celite which was pre-rinsed with MeOH. The residue was also rinsed with additional MeOH.

**[00132]** The filtrate was then concentrated under reduced pressure to give a light yellow oil. This crude product consisted mainly of the open amines of a compound of Formula 12.a (1R,2R,4S,5S,7s)-ethyl 7-(aminomethyl)-3-oxa-9-azatricyclo[3.3.1.02,4]nonane-9-carboxylate and to a lesser extent the (desired) cyclized amine a compound of Formula 12 (rac-(2R,3S,6S,7aS)-ethyl 3-hydroxyoctahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate).

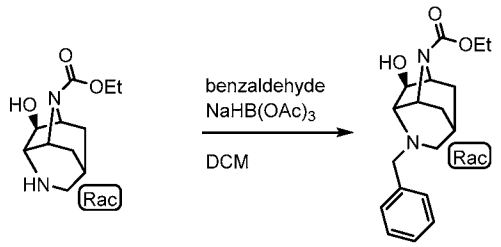
**[00133]** To drive cyclization of the main endo-isomer to completion, the intermediate was dissolved in 500 mL of absolute ethanol, which created a light yellow solution, which was then stirred and refluxed overnight.

**[00134]** A sample was taken, concentrated under reduced pressure, dissolved in $CDCl_3$, and analyzed by $^{1H}$NMR (Figure 7) which showed the intermediate, open endo-isomer, had cyclized. It was further shown that approximately 9% of the product was open exo-amine, and some solvent

remained. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 4.46 – 4.01 (m, 5H), 3.50 – 3.44 (m, 1H), 3.16 – 3.11 (m, 1H), 3.96 – 2.93 (m, 1H), 2.10 – 1.66 (m, 5H), 1.47 (d, *J* = 13.3 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

**[00135]** The main batch, a yellow solution, was concentrated under reduced pressure and the residue was redissolved in 500 mL of $CHCl_3$ and dried over $Na_2SO_4$. The solution was filtered and concentrated to give 21.7 g of a compound of Formula 12 as a thick yellow oil which contained solvent and the open exo-amine which was used in the next step.

**[00136]** The next step proceeded as illustrated in Scheme 8.




Formula 12 Formula 11

Scheme 8

**[00137]** Benzaldehyde (22.74 g, 214 mmol, 21.72 mL) was added to a solution of the compound of Formula 12 (37.3 g, 165 mmol) in 1000 mL of dichloromethane. After 15 minutes STAB (55.9 g, 264 mmol) was added. The suspension was then stirred at room temperature overnight.

**[00138]** The reaction mixture was washed with 1 L of water and 1 L $NaHCO_3$. The organic layer was dried with $Na_2SO4_2$ and concentrated to dryness to afford 55 g of the reacted product, which was next purified by gravity column chromatography (600 g, Hep/5-60% ETOAc) affording: 2.2 g of exo-Bn2N-adduct; and 35.3 g of a compound of Formula 11 (rac-(2R,3S,6S,7aS)-ethyl 3-hydroxyoctahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) as analyzed and confirmed by $^{1H}$ NMR (Figure 8B) and MS (Figure 8A). $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.30 (m, 4H), 7.26 – 7.22 (m, 2H), 4.41 – 4.02 (m, 5H), 3.83 – 3.78 (m, 1H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.30 – 3.26 (m, 1H), 3.11 – 3.06 (m, 1H), 2.35 – 2.31 (m, 1H), 2.07 – 1.88 (m, 3H), 1.77 – 1.65 (m, 2H), 1.44 (d, *J* = 13.9 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

**[00139]** The next step proceeded as illustrated in Scheme 9.




Formula 11 Formula 10

Scheme 9

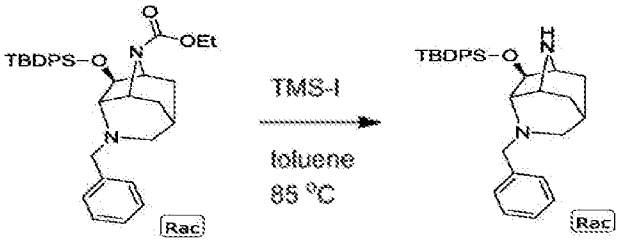
**[00140]** Imidazole (15.19 g, 223 mmol) and tert-butyldiphenylchlorosilane (30.7 g, 112 mmol, 28.7 mL) were added to a solution of the compound of Formula 11 (35.3 g, 112 mmol) in 100 mL of dry N,N-dimethylformamide to form a pale yellow solution which was stirred at room temperature overnight.

**[00141]** After the stirring was complete a sample was taken and analyzed by LCMS which showed the reaction was complete.

**[00142]** The solution was then concentrated under reduced pressure to yield an oily residue which was diluted with 750 mL of DCM and washed with 750 mL of 1:1 saturated aqueous $NaHCO_3$ solution and water. Next the solution was washed with 750 mL of brine. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated to afford approximately 65 g of the reacted product as confirmed by TLC.

**[00143]** The reacted product was purified by gravity column chromatography (approximately 600 g, Hep/5-15% EtOAc) which afforded 59.5 g, or a 90% yield, of a compound of Formula 10 (rac-(2R,3R,6S,7aS)-ethyl 4-benzyl-3-((tert-butyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) as a very thick colorless oil. A sample was taken and analyzed by $^{1H}$NMR (Figure 9B) and LCMS (Figure 9A), which showed the product was in agreement with the structure of Formula 10 and contained 6 w/w% heptane. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 7.72 – 7.66 (m, 4H), 7.47 – 7.36 (m, 6H), 7.26 – 7.16 (m, 3H), 7.12 – 7.09 (m, 2H), 4.62 – 4.48 (m, 1H), 4.26 (s, 1H), 4.22 – 4.03 (m, 3H), 3.40 – 3.29 (m, 2H), 2.89 – 2.78 (m, 2H), 1.92 – 1.76 (m, 4H), 1.62 – 1.52 (m, 1H), 1.31 – 1.23 (m, 3H), 1.17 – 1.11 (m, 1H), 1.02 (s, 9H).

**[00144]** The next step proceeded as illustrated in Scheme 10.



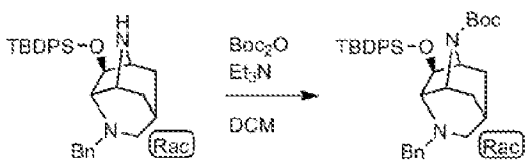

Formula 10 Formula 9

Scheme 10

**[00145]** Iodotrimethylsilane (75.0 g, 375 mmol, 51 ml) was added to a solution of the compound of Formula 10 (73.9 g, 124 mmol, 93 %) in 1.2 L of dry toluene to create a yellow reaction mixture which was stirred at 85 °C overnight.

**[00146]** A sample taken then taken and analyzed by TLC, which showed the reaction had gone to completion. The resulting reaction mixture was a dark solution, and was allowed to cool to room temperature (suspension) and quenched with 250 mL of MeOH. The mixture was next concentrated to approximately 250 mL. After which 750 mL of DCM was added and the mixture was washed with 750 mL of 1:1 saturated aqueous $NaHCO_3$ solution/$H_2O$. The organic layer was then washed with 750 mL of brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford approximately 72 g, or a 92% yield, of a compound of Formula 9 (rac-(2R,3R,6S,7aS)-4-benzyl-3-((tert-butyldiphenylsilyl)oxy) octahydro-1H-2,6-methanopyrrolo [3,2-b]pyridine) as a dark yellow/orange oil. A sample was taken and analyzed by LCMS (Figure 10) which showed the correct mass, and that the product had a purity of about 80%, with the peak at 0.448 being toluene. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.63 (m, 4H), 7.47 – 7.37 (m, 6H), 7.26 – 7.12 (m, 5H), 4.36 (s, 1H), 3.73 – 3.70 (m, 1H), 3.39 (d, $J$ = 13.7 Hz, 1H), 3.26 (d, $J$ = 7.6 Hz, 1H), 3.06 (s, 1H), 2.90 (d, $J$ = 13.7 Hz, 1H), 2.79 – 2.74 (m, 1H), 2.41 (bs, 1H), 1.90 – 1.80 (m, 4H), 1.67 – 1.64 (m, 1H), 1.11– 0.99 (m, 10H).

**[00147]** The next step proceeded as illustrated in Scheme 11.




Formula 9 Formula 8

Scheme 11

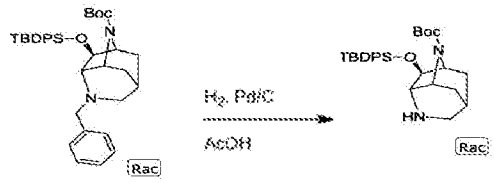
**[00148]** $Et_3N$ (48.3 g, 477 mmol, 0.067 L) and di-tert-butyl dicarbonate ($Boc_2O$) (39.1 g, 179 mmol) was added to a solution of the compound of Formula 9 (72 g, 119 mmol, 80 %) in 1 L of dichloromethane to form a light yellow solution which was stirred at room temperature over weekend.

**[00149]** A sample taken and analyzed by TLC which showed the reaction was complete. The solution was diluted with 250 mL of DCM and washed with 1 L of saturated aqueous $NaHCO_3$ solution and 1 L of brine. The organic layer was then dried over $Na_2SO_4$, filtered, and concentrated to afford approximately 80 g of the crude product.

**[00150]** Purification by gravity column chromatography (800 g, heptane / [EtOAc 1->10%]) afforded 68.4 g, or a 94% yield, of a compound of the Formula 8 (rac-(2R,3R,6S,7aS)-tert-butyl 4-benzyl-3- ((tert-butyldiphenylsilyl)oxy)octahydro-1H-2, 6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) as a colorless glass.

**[00151]** A sample was taken and analyzed by $^{1H}$NMR (Figure 11A) and LCMS (Figure 11B) which showed agreement between the product and the structure of Formula 8, and further showing that the product contained 4 w/w% heptane. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.65 (m, 4H), 7.47 – 7.35 (m, 6H), 7.24 – 7.10 (m, 5H), 4.53 – 4.40 (m, 1H), 4.24 (d, $J$ = 3.8 Hz, 1H), 4.10 – 3.92 (m, 1H), 3.44 – 3.32 (m, 2H), 2.87 (d, $J$ = 13.6 Hz, 1H), 2.33 – 2.77 (m, 1H), 1.93 – 1.72 (m, 4H), 1.65 – 1.54 (m, 1H), 1.50 – 1.47 (m, 9H), 1.10 – 1.02 (m, 10H).

**[00152]** The next step proceeded as illustrated in Scheme 12.




Formula 8 Formula 7

Scheme 12

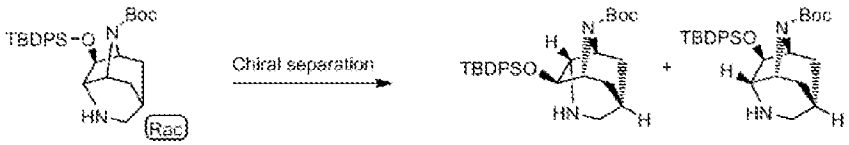
**[00153]** Under a nitrogen flow, Palladium, 10% on activated carbon (7 g, 125 mmol) was added to a solution of the compound of Formula 8 (72.9 g, 125 mmol) in 600 mL of acetic acid. The vessel was closed and the resulting mixture was stirred at 50 °C for 2 hours under a hydrogen atmosphere created by a balloon.

**[00154]** The mixture was then stirred at 50 °C overnight. The black suspension was filtered over EtOH rinsed celite and the filtrate was concentrated under reduced pressure. The residue was stripped twice with 0.5 L of toluene, after which it was dissolved in 1 L of diethyl ether.

**[00155]** The organic layer was then washed with 1 L of 10% (w/v) aqueous $K_2CO_3$ solution, 1 L of brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure before being stripped again with pentane to afford 58.5 g of a thick tan syrup, a compound of Formula 7 (rac-(2R,3S,6S,7aS)-tert-butyl 3-((tert- butyldiphenylsilyl)oxy)octahydro-1H-2,6-methanopyrrolo [3,2-b]pyridine-1-carboxylate).

**[00156]** A sample was taken and analyzed by $^{1H}$NMR (Figure 12B) and LCMS (Figure 12A) which showed the product was in agreement with structure of Formula 7 and contained 5.1 weight% of toluene and 1.3 weight% of *n*-pentane. $^{1H}$NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.63 (m, 4H), 7.45 – 7.35 (m, 6H), 4.40 – 4.25 (m, 1H), 4.13 – 3.93 (m, 2H), 3.41 – 3.36 (m, 1H), 2.97 – 2.92 (m, 1H), 2.62 (d, *J* = 11.5 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.67 (s, 1H), 1.64 – 1.56 (m, 1H), 1.49 – 1.47 (m, 9H), 1.16 – 1.13 (m, 1H), 1.05 – 1.04 (m, 9H).

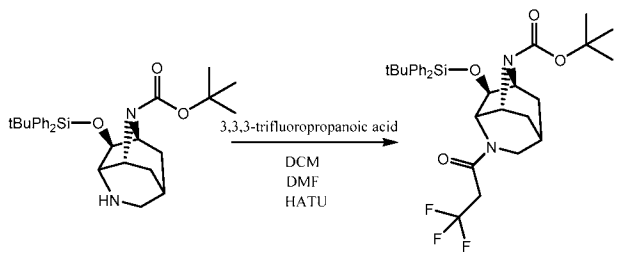
**[00157]** The compound of Formula 7 was separated into its respective enantiomers via supercritical fluid chromatography (SFC) on a Welkho-1 column with 90/10 $scCO_2$/iPrOH + 0.2% isopropylamine eluent as as illustrated in Scheme 13.




Formula 7 Formula 6.a Formula 6.b

Scheme 13

**[00158]** The next step proceeded as illustrated in Scheme 14.




Formula 6.b Formula 5

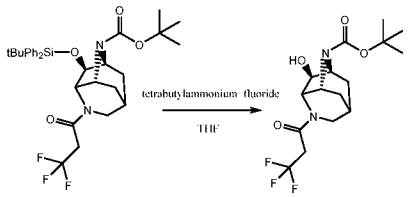
Scheme 14

**[00159]** 3,3,3-trifluoropropanoic acid (3.629 mL, 41.1 mmol, 1.5 eq) was dissolved in DCM (120 mL) and dry DMF (10 mL). DIPEA (7.16 mL, 41.1 mmol, 1.5 eq) and HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxidhexafluorophosphate) (15.63 g, 41.1 mmol, 1.5 eq) were added and the mixture was stirred at room temperature for 1.5 hours. This resulted in the formation of a clear red-brown solution.

**[00160]** To that solution, a solution of the compound of Formula 6.b (13.5g, 27.4 mmol) in DCM (100 mL) was added and the solution was stirred for at room temperature for 4 hours.

**[00161]** The reaction mixture was diluted with DCM (250 mL), washed with aqueous 1 M $KHSO_4$ (400 mL), saturated aqueous $NaHCO_3$ (400 mL), water (400 mL), brine (250 mL), dried over $Na_2SO_4$ and concentrated in vacuo to afford 22.74 g (> 100%) a compound of Formula 5 ((2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-((tertbutyldiphenylsilyl)oxy)-4-(3,3,3 trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) as a brown oil.

**[00162]** The next step proceeded as illustrated in Scheme 15.




Formula 5 Formula 4

Scheme 15

**[00163]** The compound of Formula 5 (max 27.4 mmol) was dissolved in dry THF (115 mL).

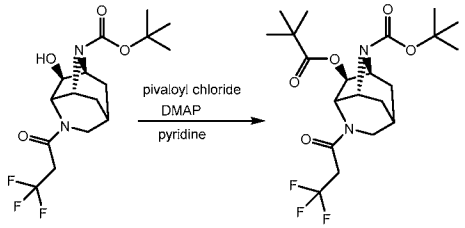
**[00164]** A solution of tetrabutylammonium fluoride in THF (1 M, 82 mL, 82 mmol) was added and the reaction mixture was stirred at 50 °C overnight. LCMS analysis revealed complete conversion to desired material.

**[00165]** The solution was concentrated in vacuo and co-evaporated twice with 50% EtOAc/heptane (2 x, each 100 mL) to afford 38.66 g of crude material as a brown oil. The material was dissolved in 25% EtOAc/$Et_2O$ (800 mL) and washed with water (2 x, each 600 mL). The aqueous layers were combined and extracted with 25% EtOAc/Et2O (400 mL). The organic layers were combined, washed with brine (400 mL), dried over $Na_2SO_4$ and concentrated in vacuo to afford 15.14 g of material as a brown oil.

**[00166]** Purification by gravitation column chromatography (gradient 50% EtOAc/heptane to 100% EtOAc) yielded 5.85 g of a compound of Formula 4 ((2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-

hydroxy-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) (58% over 2 steps) as a white foam.

**[00167]** The next step proceeded as illustrated in Scheme 16,




Formula 4 Formula 3

Scheme 16

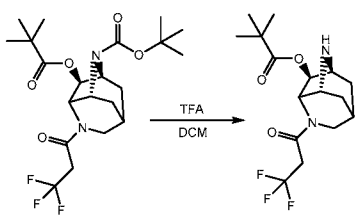
**[00168]** The compound of Formula 4 (5.85 g, 16 mmol) was dissolved in pyridine (50 mL), followed by the addition of DMAP (dimethylaminopyridine) (1.96 g, 16.06 mmol) and pivaloyl chloride (3.95 mL, 32.1 mmol).

**[00169]** The reaction mixture was stirred overnight at 60°C. LCMS analysis revealed complete conversion to desired material. The reaction mixture was allowed to cool to room temperature (a light brown suspension formed) and concentrated in vacuo.

**[00170]** The residue was diluted with EtOAc (250 mL) and washed with aqueous 0.5 M $KHSO_4$ (200 mL) and saturated aqueous $NaHCO_3$ (250 mL). Each time the aqueous layer was extracted with additional EtOAc (50 mL).

**[00171]** The combined organic layers were washed with brine (200 mL), dried with sodium sulfate, filtered and evaporated to dryness to yield 6.8 g of crude material. Purification by flash column chromatography (EtOAc/heptane gradient) afforded 5.49 g (76%) of a compound of Formula 3 ((2S*,3S*,3aS*,6R*,7aR*)-tert-butyl 3-(pivaloyloxy)-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridine-1-carboxylate) as a white foam. LCMS analysis: purity > 95%, found 449.3 [M+H]+ & 393.2 (M-(C4H8)+H]+).

**[00172]** The next step proceeded as illustrated in Scheme 17.




Formula 3 Formula 2

Scheme 17

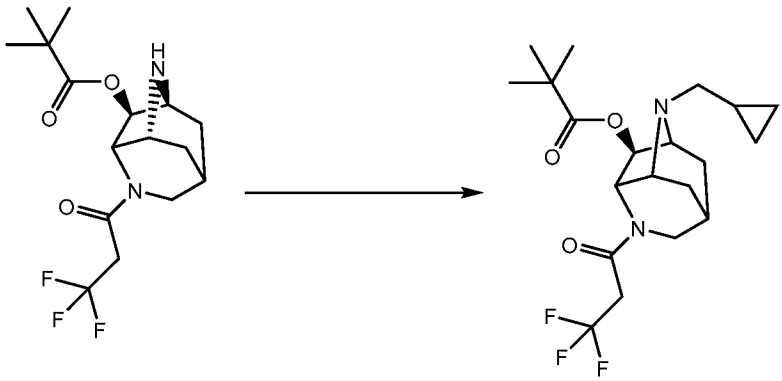
**[00173]** The compound of Formula 3 (1 g, 2.23 mmol) was dissolved in DCM (20 mL).

**[00174]** TFA (trifluoroacetic acid) (8.54 mL, 111 mmol) was added and the mixture was stirred at room temperature for 1 h. LCMS analysis revealed complete conversion to desired material.

**[00175]** The reaction mixture was concentrated in vacuo and co-evaporated with toluene (2 x, each 20 mL). The residue was dissolved in chloroform (40 mL) and washed with aqueous saturated $Na_2CO_3$ solution (40 mL). The aqueous phase was extracted with chloroform (3 x, each 20 mL).

**[00176]** The organic layers were combined, washed with brine (70 mL), dried ($Na_2SO_4$), filtered and evaporated under reduced pressure to afford 769.9 mg (99%) of a compound of Formula 2 ((2S*,3S*,3aS*,6R*,7aR*)-4-(3,3,3- trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate) as an off-white solid. The structure was confirmed by $^{1H}$NMR as shown in Figure 13.

**[00177]** The next step proceeded as illustrated in Scheme 18,



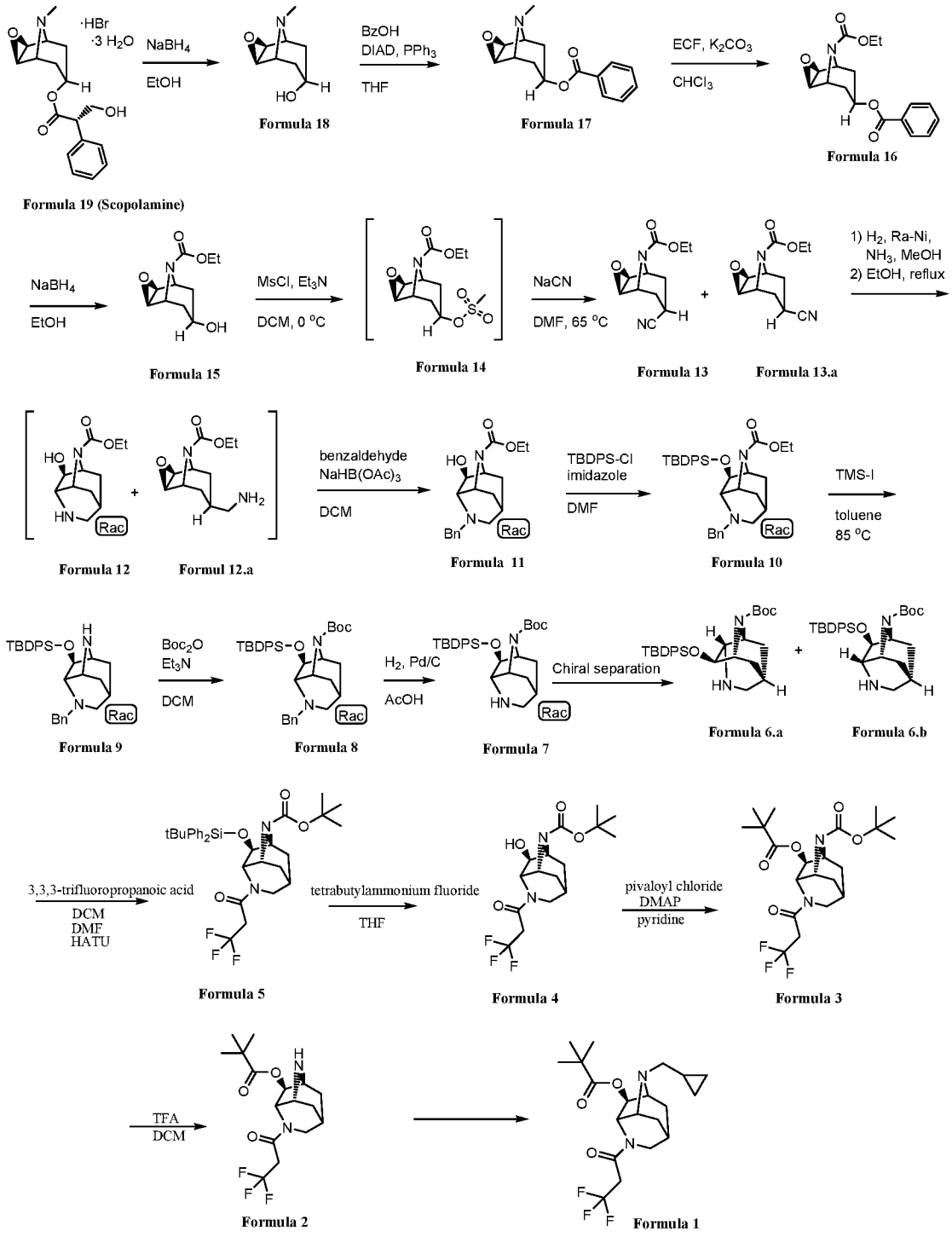
Formula 2 Formula 1

Scheme 18

**[00178]** To the compound of Formula 2 (199.8 mg; 0.574 mmol) in dichloromethane (2 mL), cyclopropylcarboxaldehyde (55.7 uL; 0.523 mmol) was added, and the reaction mixture was stirred for 2 hours at room temperature. Next sodium triacetoxyborohydride (200.7 mg; 0.947 mmol) was added to the reaction mixture, and the reaction mixture was stirred at room temperature overnight. The reaction mixtures were evaporated to dryness under reduced pressure. Purification by prep LCMS followed by evaporation of the solvents under reduced pressure (Genevac) afforded a compound of Formula 1 ((2S,3S,6R,7aR)-1-(cyclopropylmethyl)-4-(3,3,3-trifluoropropanoyl)octahydro-1H-2,6-methanopyrrolo[3,2-b]pyridin-3-yl pivalate). (MH+ = 403.1).

**[00179]** An overview of these synthetic steps to transform the starting reactant into a compound

of Formula 1 is provided in Scheme 19, below.




Scheme 19

**Example 2: In Vivo Activity of the Compound of Formula 1**

**[00180]** Table 7 summarizes the activity of Formula 1 in mice models of neuropathic pain following repeated daily administration using different routes of administration.

**Table 7: Summary of the activity of Formula 1 in animal models for neuropathic pain in mice.**

| TI | Model | Route | Doses Tested (mg/kg) | Level of activity (% of maximum effect- baseline) | Duration of activity at maximum effect | Peak of activity (T) | Dose of maximum activity (mg/kg) |
|---|---|---|---|---|---|---|---|
| Gabapentin | CCI | IP | 150 | 66% | 4-6H | 2-3H | 150 |
| | | SC | 150 | 64% | 4-6H | 2-3H | 150 |
| | | SC | 150 | >100% | 4-6H | 2-3H | 150 |
| Gabapentin | Taxol | SC | 150 | 100% | 4 H | 2-4H | 150 |
| Formula 1 | Taxol | SC | 1,3,10 | 100% | 3 day | 1H-3 days | 1 |
| Gabapentin | Taxol | PO | 150 | 100% | 4 H | 2-4H | 150 |
| Formula 1 | Taxol | PO | 30 | 100% | 3 days | 1-24 H | <30 |

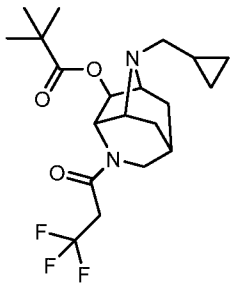
**[00181]** The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. The above-described embodiments of the invention may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

**[00182]** It should be understood that although the compounds of Formulas 1-18 may be drawn with specific chirality for the sake of simplicity, one skilled in the art would recognize how to create and separate these various isomers. Accordingly, all isomers of the compounds of Formulas 1-18 may be understood to be within the scope of the present application.

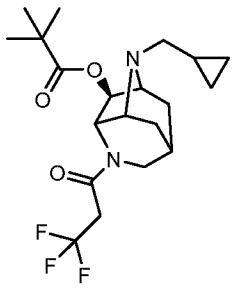
## CLAIMS

What is claimed is:

1. A compound of Formula 1:



or a stereoisomer, pharmaceutically acceptable salt, or mixture thereof.

2. The compound of claim 1, wherein Formula 1 is:  or a stereoisomer, pharmaceutically acceptable salt, or mixture thereof.

3. A pharmaceutical composition comprising a compound of claim 2, and a pharmaceutically acceptable carrier or diluent.

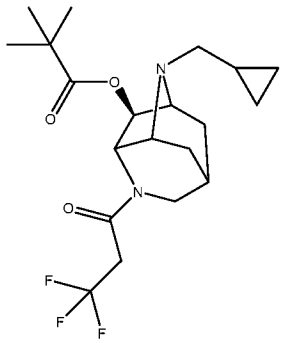
4. A method for treating a subject (a human or an animal) suffering from a condition, disease, or disorder, comprising administering to the subject an effective amount of the compound of claim 2.

5. The method of claim 4, wherein the compound is administered to effect localized delivery to the subject.

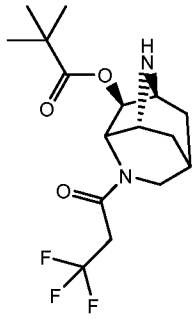
6. The method of claim 4, wherein the compound is administered to effect systemic delivery to the subject.

7. The method of claim 4, wherein the condition or disorder is neuropathic pain or chronic pain.

8. A method of making a compound of Formula 1:



comprising reacting a compound of Formula 2:

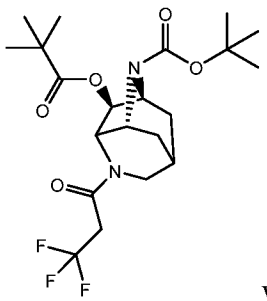


with cyclopropylcarboxaldehyde in the presence of a reducing agent.

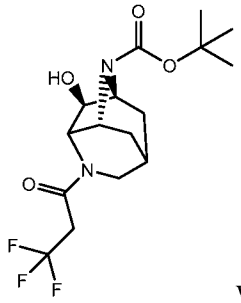
9. The method of claim 8, wherein the cyclopropylcarboxaldehyde was added before the reducing agent.

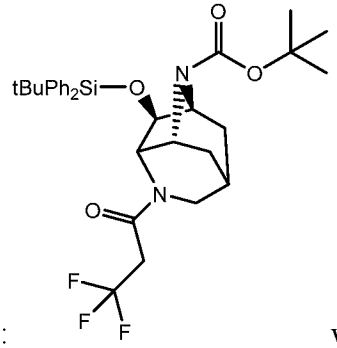
10. The method of claim 8, wherein the reducing agent is sodium triacetoxyborohydride.

11. The method of claim 8, wherein the compound of Formula 1 is chirally separated.

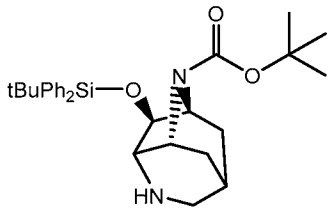
12. The method of claim 8, further comprising making the compound of Formula 2 by reacting a compound of Formula 3:  with an acid.

13. The method of claim 12, wherein the acid is trifluoroacetic acid.

14. The method of claim 12, further comprising making the compound of Formula 3 by reacting a compound of Formula 4:  with dimethylaminopyridine (DMAP).

15. The method of claim 14, further comprising making the compound of Formula 4 by reacting a compound of Formula 5:  with tert-butyldiphenylchlorosilane.

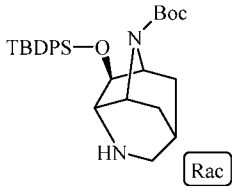
16. The method of claim 15, wherein the reaction further comprises pyridine.

17. The method of claim 15, further comprising making the compound of Formula 5 by reacting a compound of Formula 6.b:  with 3,3,3-trifluoropropanoic acid.

18. The method of claim 17, wherein the reaction further comprises N-N-Diisopropylethylamine.

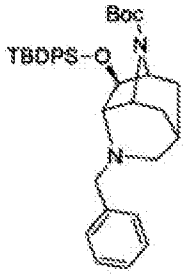
19. The method of claim 18, wherein the reaction further comprises (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) sodium triacetoxyborohydride.

20. The method of claim 17, further comprising making the compound of Formula 6.b by

chirally separating a compound of Formula 7: 

.

21. The method of claim 20, further comprising making the compound of Formula 7 by

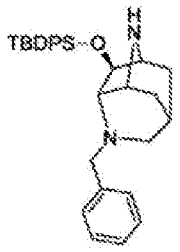
reacting a compound of Formula 8: 

with hydrogen in the presence of a catalyst.

22. The method of claim 21, wherein the catalyst comprises palladium.

23. The method of claim 22, wherein the catalyst is palladium on carbon.

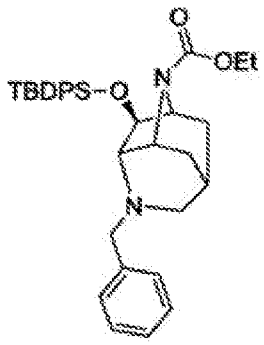
24. The method of claim 21, further comprising making the compound of Formula 8 by

reacting a compound of Formula 9: 

with $Boc_2O$.

25. The method of claim 24, wherein the reaction further comprises triethylamine ($Et_3N$).

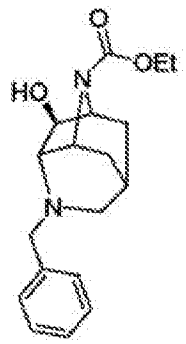
26. The method of claim 24, further comprising making the compound of Formula 9 by

reacting a compound of Formula 10: 

with iodotrimethylsilane.

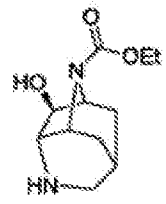
27. The method of claim 26, wherein the reaction takes place at a temperature above 60 °C.

28. The method of claim 26, further comprising making the compound of Formula 9 by

reacting a compound of Formula 11:  with tert-butyldiphenylchlorosilane.

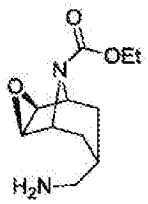
29. The method of claim 28, wherein the reaction further comprises imidazole.

30. The method of claim 28, further comprising making the compound of Formula 11 by

reacting a compound of Formula 12:  with benzaldehyde.

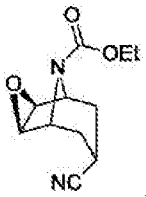
31. The method of claim 30, wherein the reaction further comprises sodium triacetoxyborohydride.

32. The method of claim 30, further comprising making the compound of Formula 11 by

cyclizing a compound of Formula 12.a:  in a solvent.

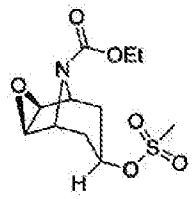
33. The method of claim 32, wherein the solvent is ethanol.

34. The method of claim 30, further comprising making the compound of Formula 12.a by

reacting a compound of Formula 13:  with hydrogen in the presence of a catalyst.

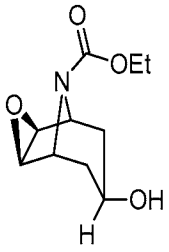
35. The method of claim 34, wherein the catalyst is Raney-nickel.

36. The method of claim 34, further comprising making the compound of Formula 13 by

reacting a compound of Formula 14:  with potassium cyanide.

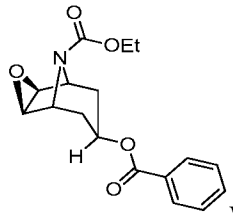
37. The method of claim 36, wherein the reaction further comprises 18-crown-6.

38. The method of claim 36, further comprising making the compound of Formula 14 by

reacting a compound of Formula 15:  with mesyl chloride.

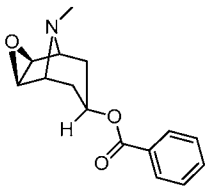
39. The method of claim 38, wherein the reaction further comprises triethylamine ($Et_3N$).

40. The method of claim 38, further comprising making the compound of Formula 15 by

reacting a compound of Formula 16:  with a reducing agent.

41. The method of claim 40, wherein the reducing agent is sodium borohydride.

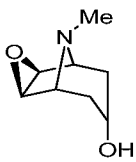
42. The method of claim 40, further comprising making the compound of Formula 16 by

reacting a compound of Formula 17:  with ethyl chloroformate.

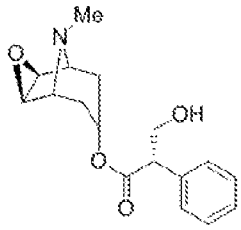
43. The method of claim 42, wherein the reaction further comprises a base.

44. The method of claim 43, wherein the base is potassium carbonate.

45. The method of claim 42, further comprising making the compound of Formula 17 by

reacting a compound of Formula 18:  with benzoic acid in the presence of an activating agent.

46. The method of claim 45, wherein the activating agent is diethylazodicaroxylate (DEAD) with triphenylphosphine or diisopropyl azodicarboxylate (DIAD) with triphenylphosphine.

47. The method of claim 48, further comprising making the compound of Formula 18 by reacting a compound of Formula 19:  with a reducing agent.

48. The method of claim 47, wherein the reducing agent is sodium borohydride.

49. The method of claim 47, wherein the reaction further comprises HCl in isopropyl alcohol.

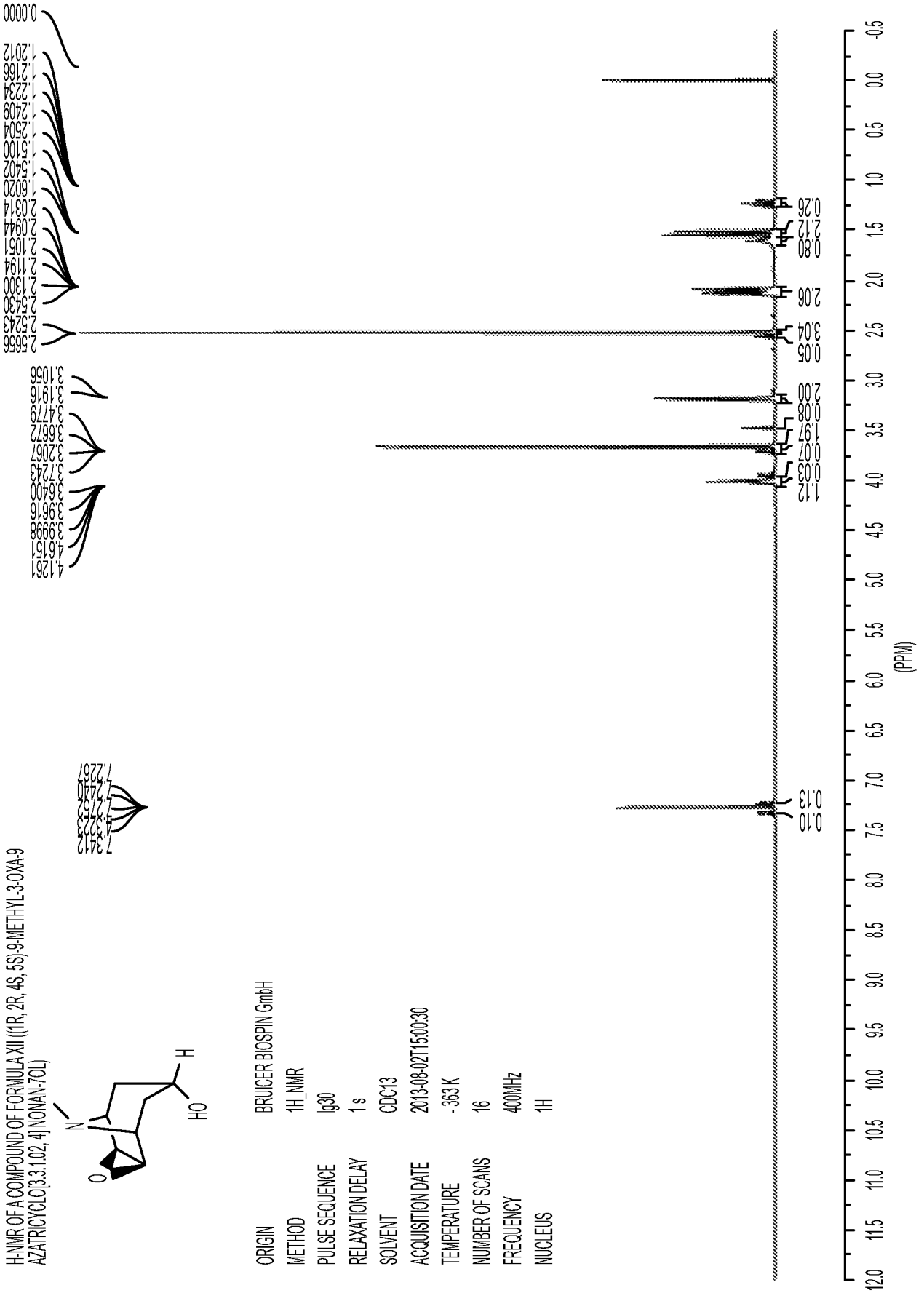

1H-NMR OF A COMPOUND OF FORMULA XII ((1R, 2R, 4S, 5S)-9-METHYL-3-OXA-9-AZATRICYCLO[3.3.1.02, 4]NONAN-7OL)
ORIGIN BRUICER BIOSPIN GmbH
METHOD 1H_NMR
PULSE SEQUENCE lg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-08-02T15:00:30
TEMPERATURE -363 K
NUMBER OF SCANS 16
FREQUENCY 400MHz
NUCLEUS 1H
(PPM)

FIG. 1

MASS SPECTRUM OF A COMPOUND OF FORMULA XI ((1R,2R,4S,5S,7r)-9-METHYL-3-OXA-9-AZATRICYCLO[3.3.1.02,4]NONAN-7-YL BENZOATE)

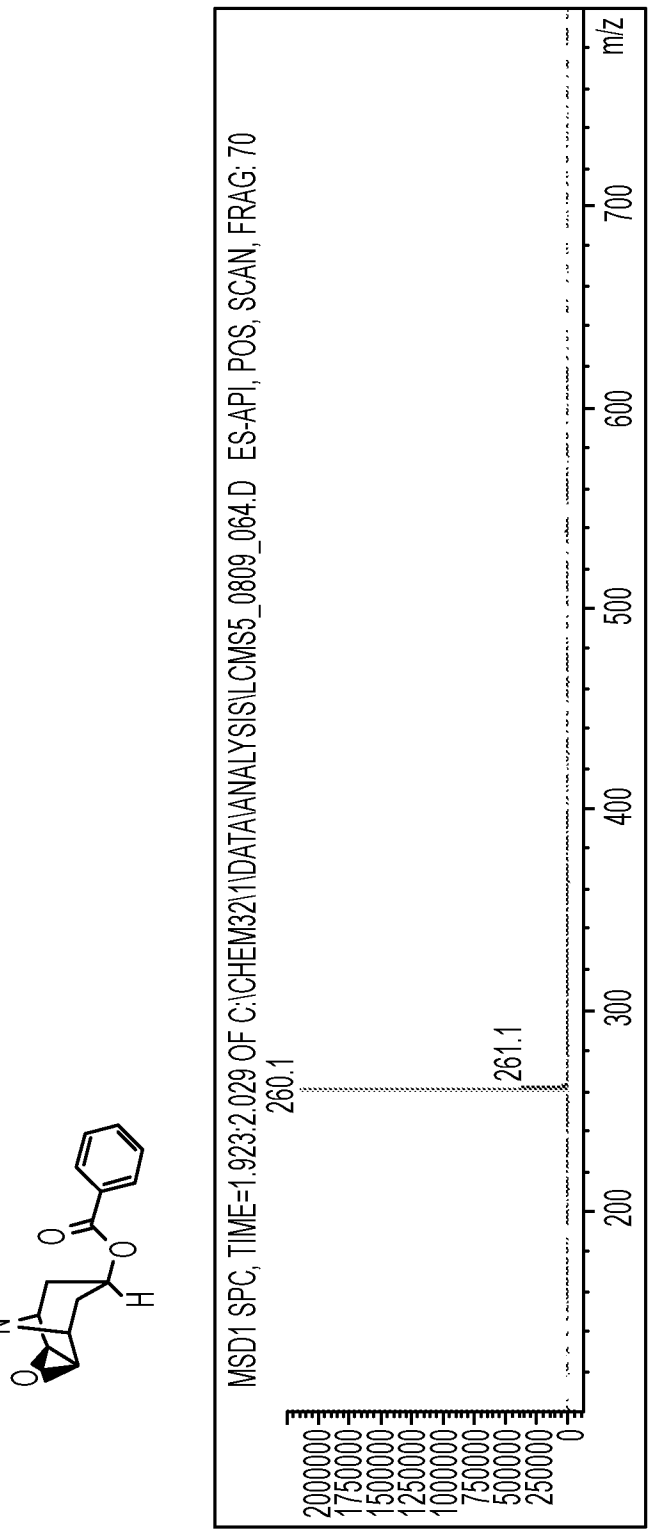



FIG. 2

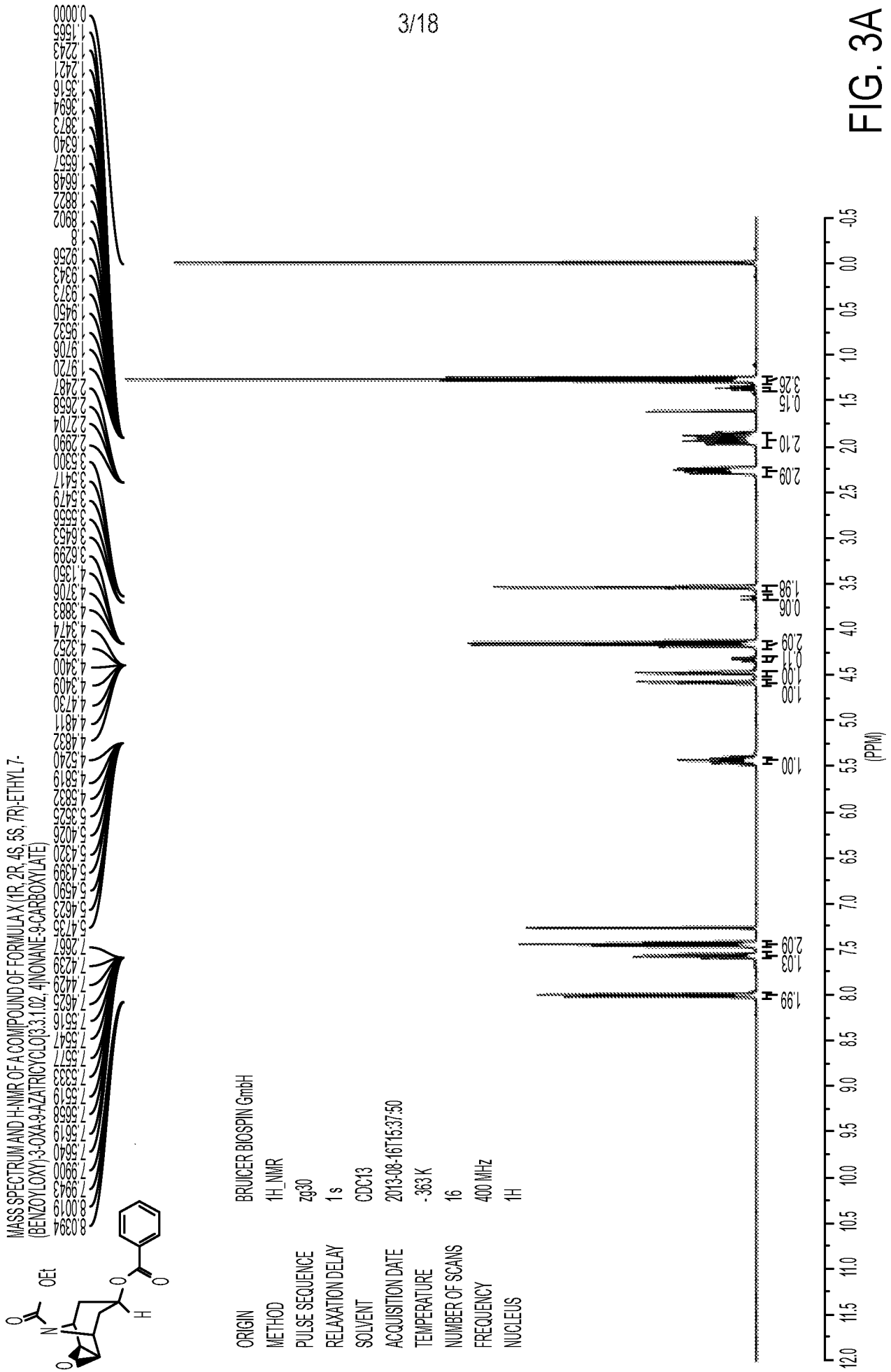

MASS SPECTRUM AND H-NMR OF A COMPOUND OF FORMULA X (1R, 2R, 4S, 5S, 7R)-ETHYL 7-(BENZOYLOXY)-3-OXA-9-AZATRICYCLO[3.3.1.02, 4]NONANE-9-CARBOXYLATE)
ORIGIN BRUCER BIOSPIN GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDC13
ACQUISITION DATE 2013-08-16T15:37:50
TEMPERATURE -363 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
1.99
1.03
2.09
1.00
1.00
1.09
0.11
2.09
0.06
1.98
2.09
2.10
0.15
3.26
(PPM)

FIG. 3A

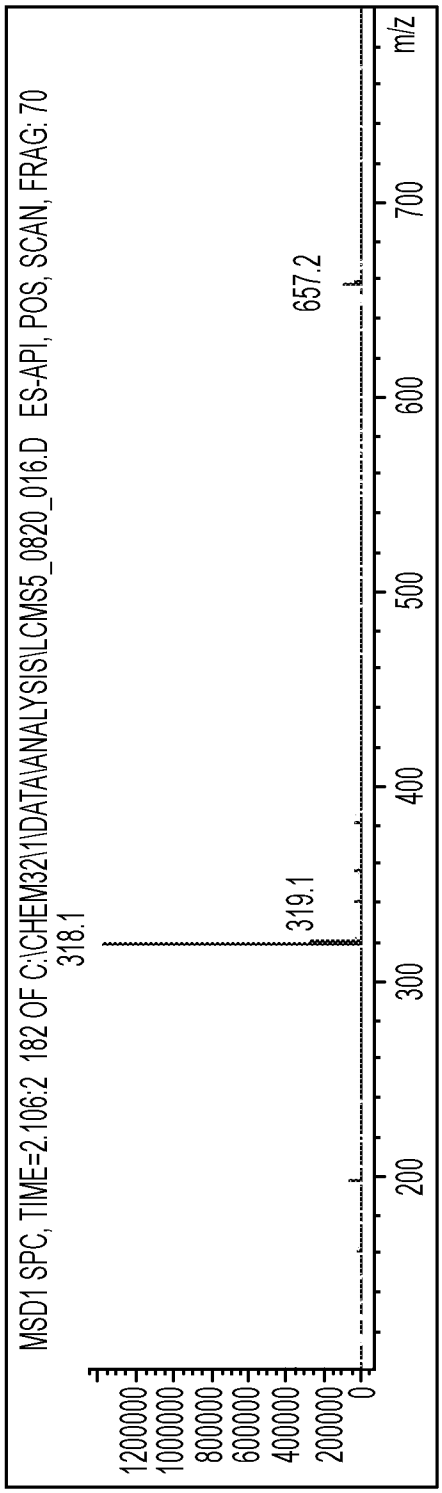

MSD1 SPC, TIME=2.106:2 182 OF C:\CHEM32\1\DATA\ANALYSIS\LCMS5_0820_016.D ES-API, POS, SCAN, FRAG: 70
318.1
319.1
657.2
1200000
1000000
800000
600000
400000
200000
0
200
300
400
500
600
700
m/z

FIG. 3B

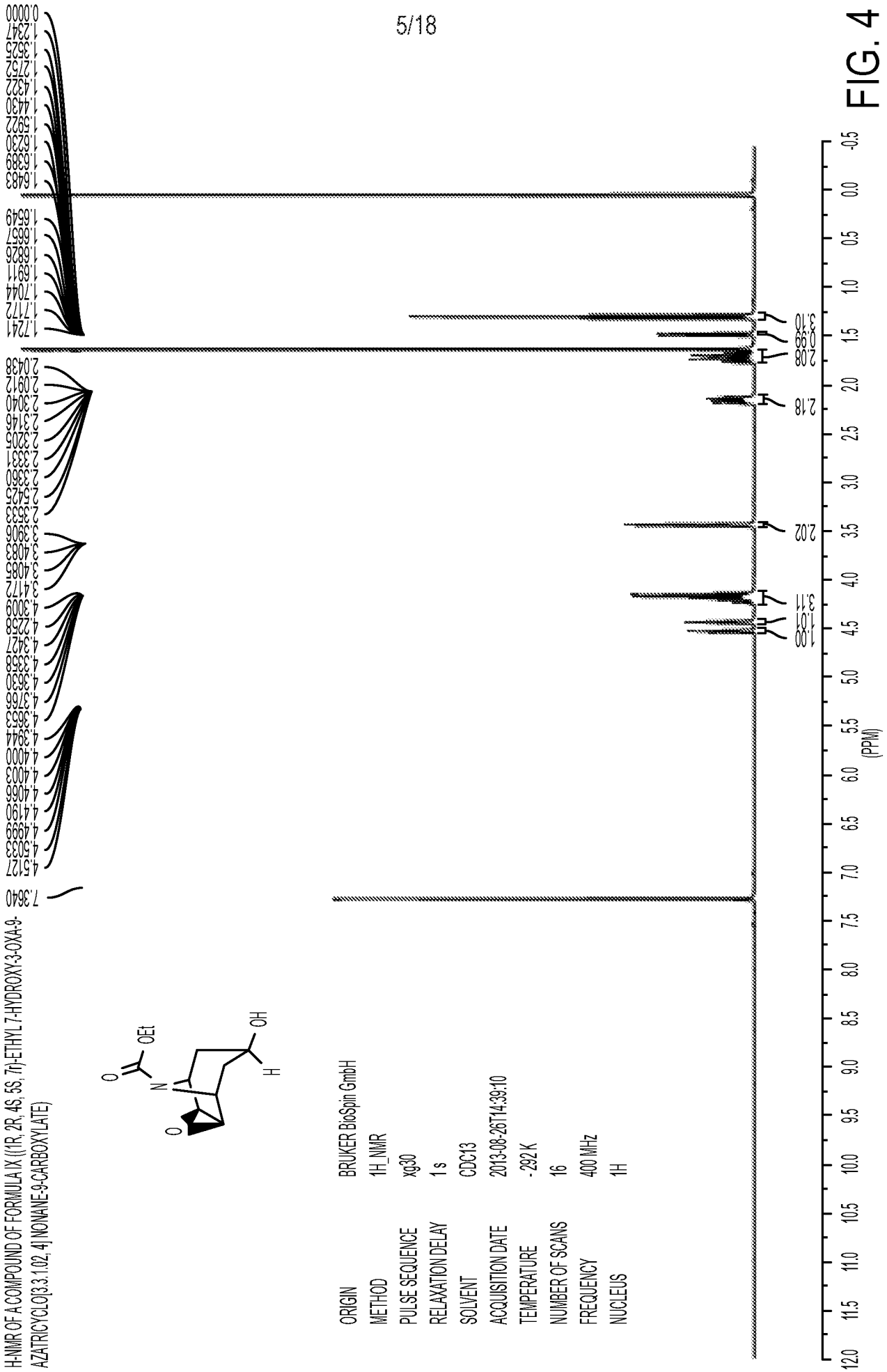

H-NMR OF A COMPOUND OF FORMULA IX ((1R, 2R, 4S, 5S, 7r)-ETHYL 7-HYDROXY-3-OXA-9-AZATRICYCLO[3.3.1.02, 4] NONANE-9-CARBOXYLATE)
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE xg30
RELAXATION DELAY 1 s
SOLVENT CDC13
ACQUISITION DATE 2013-08-26T14:39:10
TEMPERATURE -292 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
(PPM)

FIG. 4

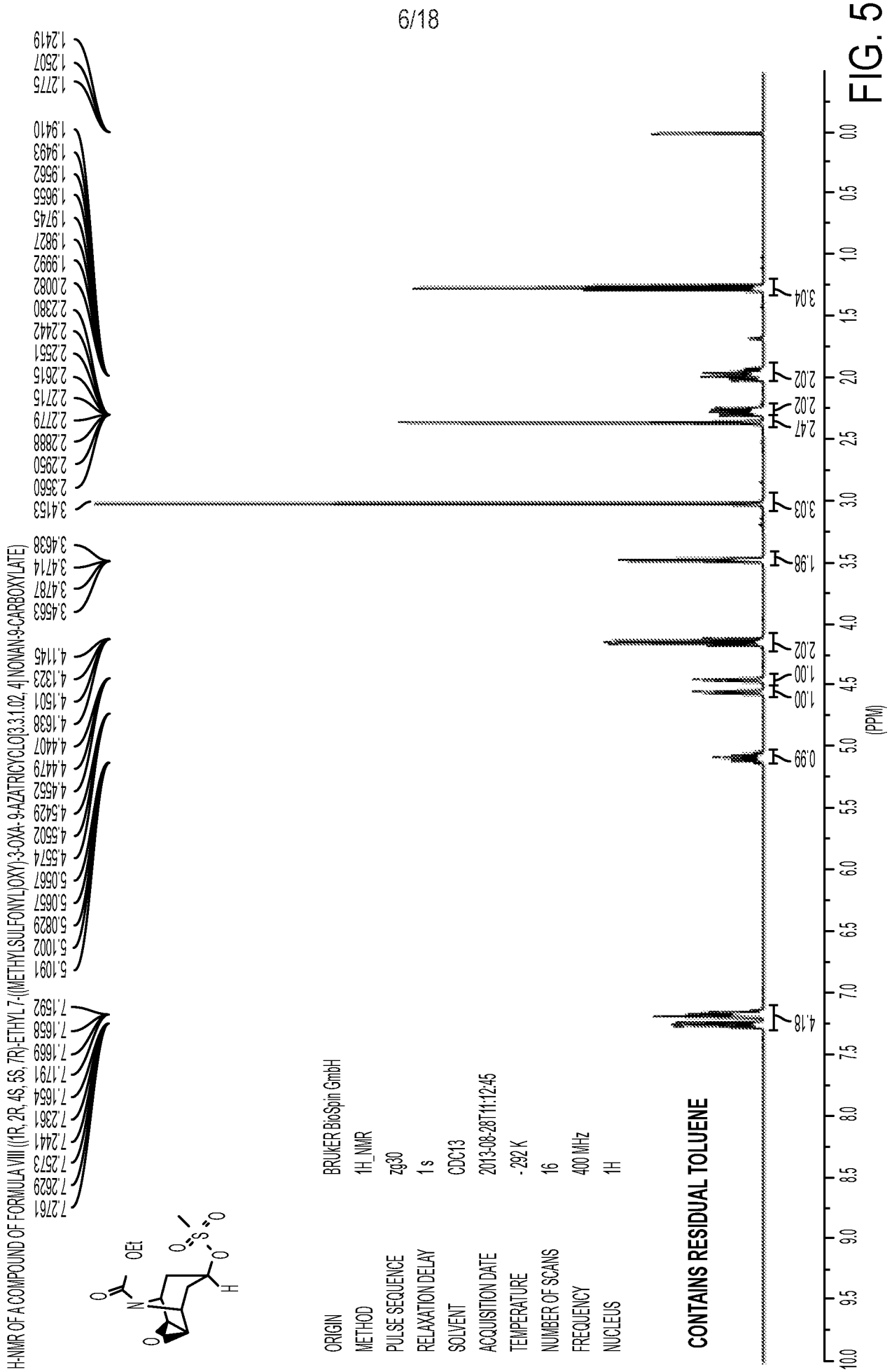

1H-NMR OF A COMPOUND OF FORMULA VIII ((1R, 2R, 4S, 5S, 7R)-ETHYL 7-(((METHYLSULFONYL)OXY)-3-OXA- 9-AZATRICYCLO[3.3.1.02, 4]NONAN-9-CARBOXYLATE)
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-08-28T11:12:45
TEMPERATURE -292 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
CONTAINS RESIDUAL TOLUENE
(PPM)

FIG. 5

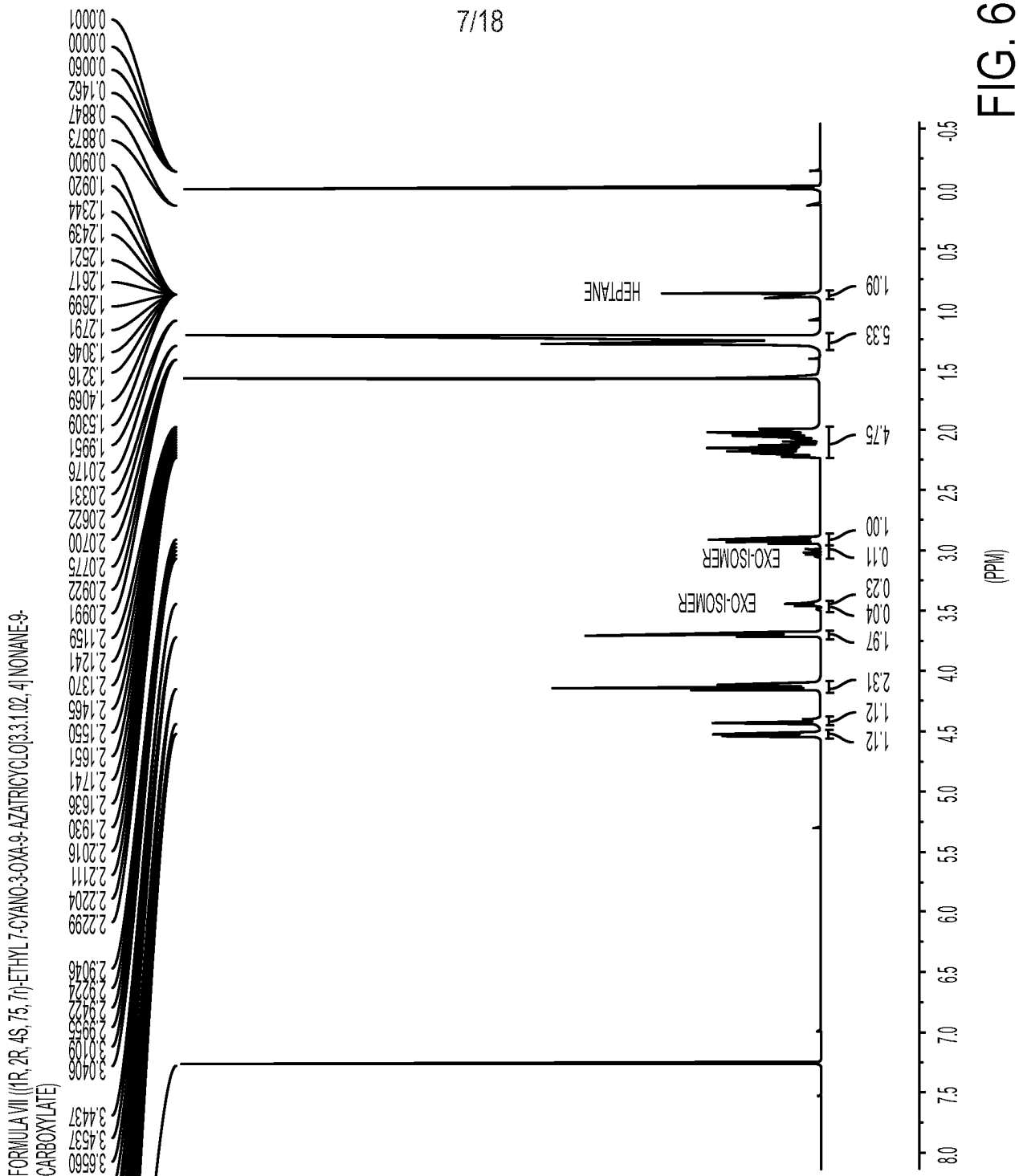

FORMULA VII ((1R, 2R, 4S, 7S, 7r)-ETHYL 7-CYANO-3-OXA-9- AZATRICYCLO[3.3.1.02, 4] NONANE-9-CARBOXYLATE)
TITLE JARUS45-140-B
DATA FILE NAME 1004_54D
ORIGIN BURKER BioSpin GmbH
METHOD iH_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-10-04-T15:19:56
TEMPERATURE -298 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
HEPTANE
EXO-ISOMER
EXO-ISOMER
EXO-ISOMER
1.09
5.33
4.75
1.00
0.11
0.23
0.04
1.97
2.31
1.12
1.12
(PPM)

FIG. 6

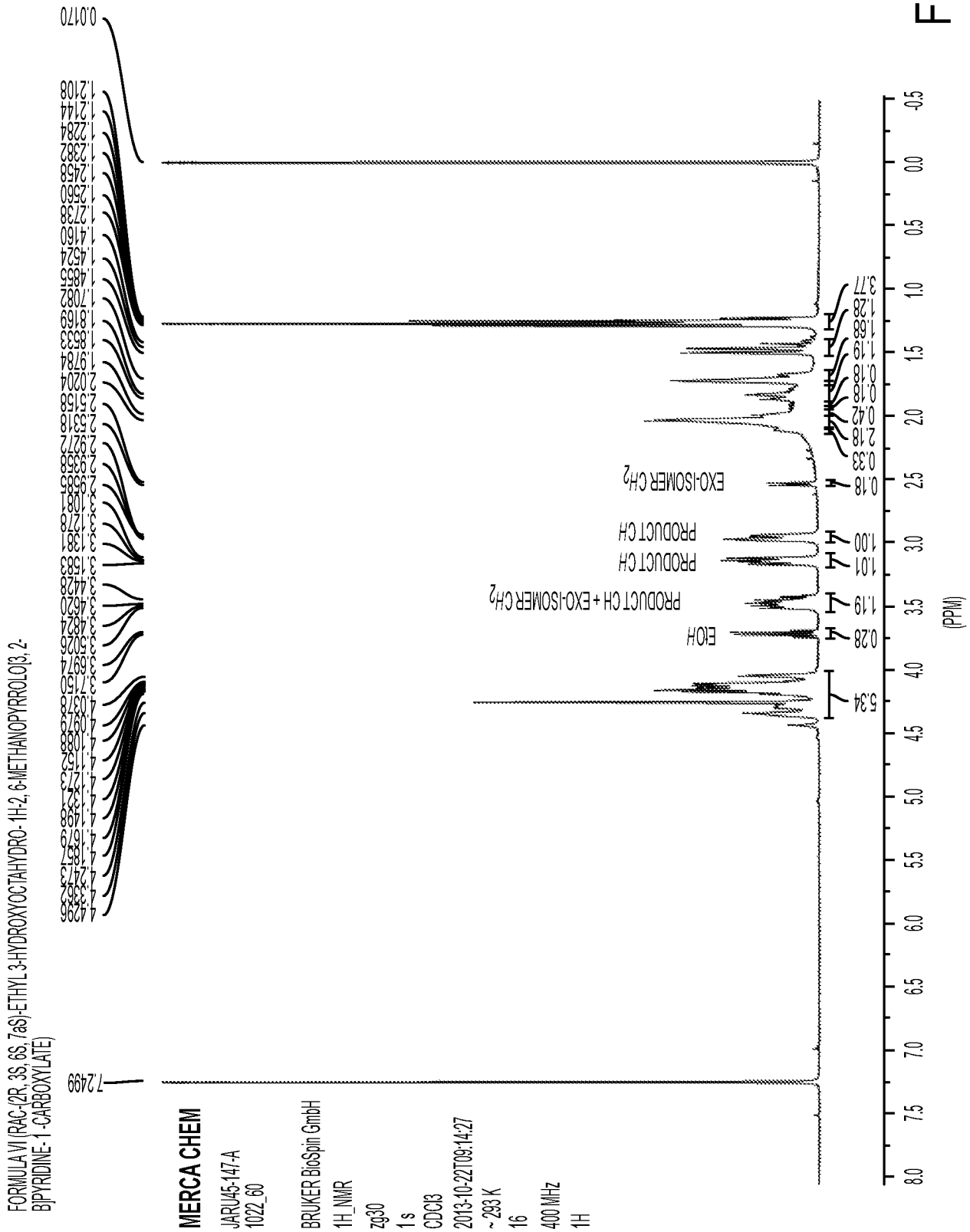

FORMULA VI (RAC-(2R, 3S, 6S, 7aS)-ETHYL 3-HYDROXYOCTAHYDRO- 1H-2, 6-METHANOPYRROLO[3, 2-B]PYRIDINE-1 -CARBOXYLATE)
MERCA CHEM
TITLE
DATA FILE NAME
JARU45-147-A
1022_60
ORIGIN
METHOD
PULSE SEQUENCE
RELAXATION DELAY
SOLVENT
ACQUISITION DATE
TEMPERATURE
NUMBER OF SCANS
FREQUENCY
NUDEUS
BRUKER BioSpin GmbH
1H_NMR
zg30
1 s
CDCl3
2013-10-22T09:14:27
~ 293 K
16
400 MHz
1H
EtOH
PRODUCT CH + EXO-ISOMER CH2
PRODUCT CH
PRODUCT CH
EXO-ISOMER CH2
(PPM)

FIG. 7

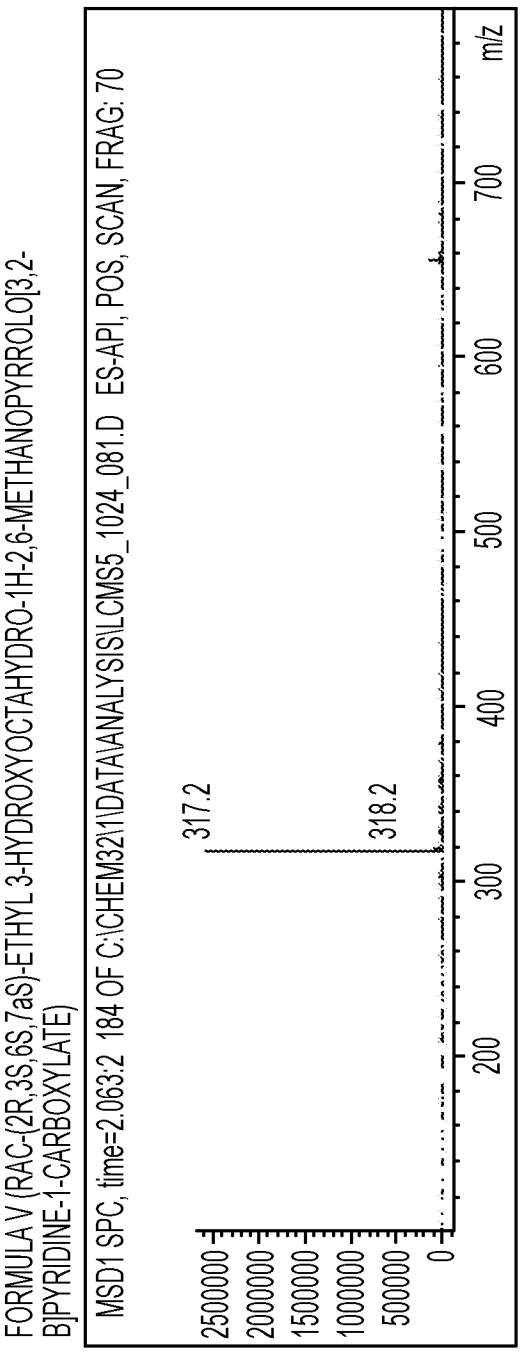

FORMULA V (RAC-(2R,3S,6S,7aS)-ETHYL 3-HYDROXYOCTAHYDRO-1H-2,6-METHANOPYRROLO[3,2-B]PYRIDINE-1-CARBOXYLATE)
MSD1 SPC, time=2.063:2 184 OF C:\CHEM32\1\DATA\ANALYSIS\LCMS5_1024_081.D ES-API, POS, SCAN, FRAG: 70
317.2
318.2
2500000
2000000
1500000
1000000
500000
0
200
300
400
500
600
700
m/z

FIG. 8A

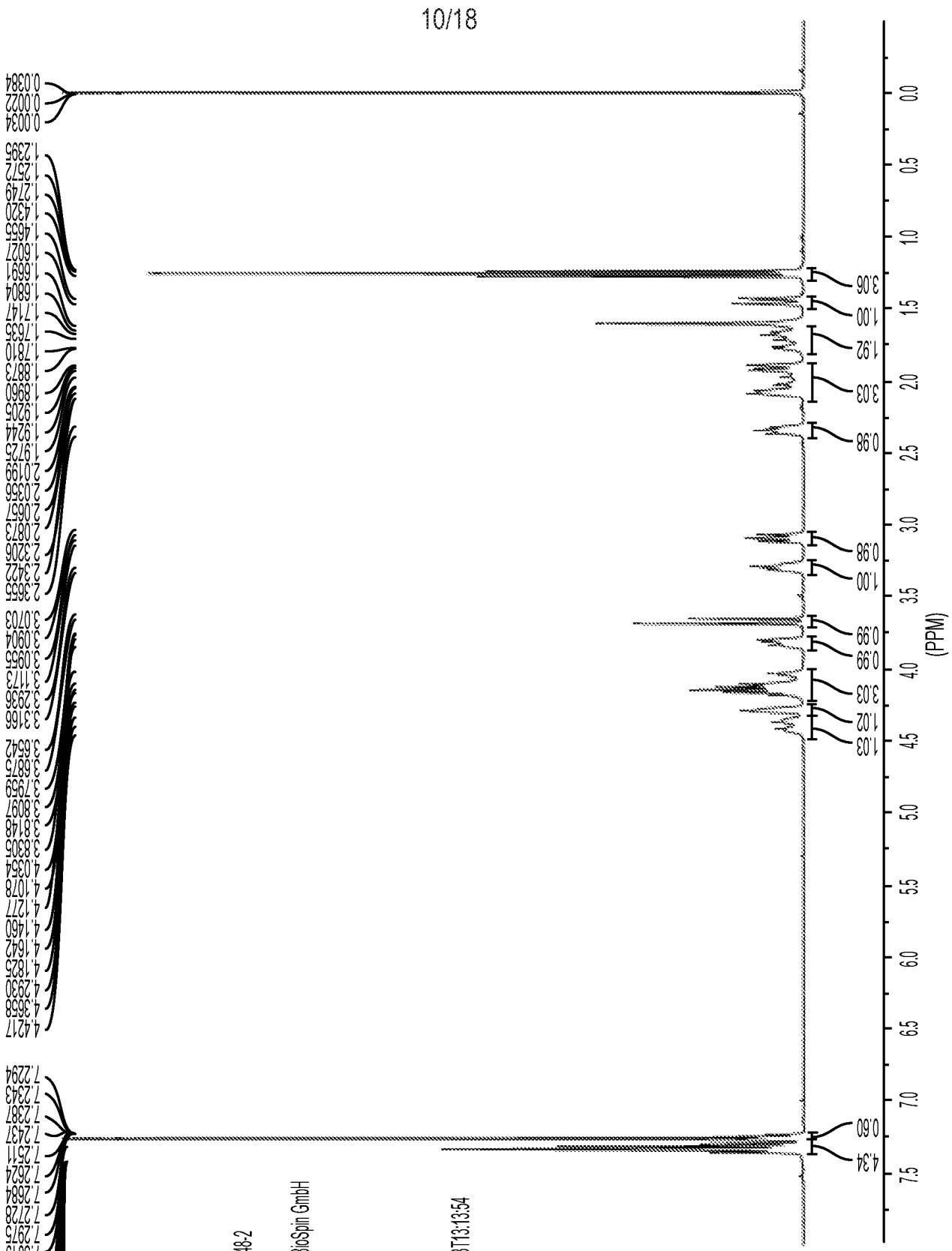

TITLE WOGR34-48-2
DATA FILE NAME 1028_290
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-10-28T13:13:54
TEMPERATURE ~372 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
(PPM)

FIG. 8B

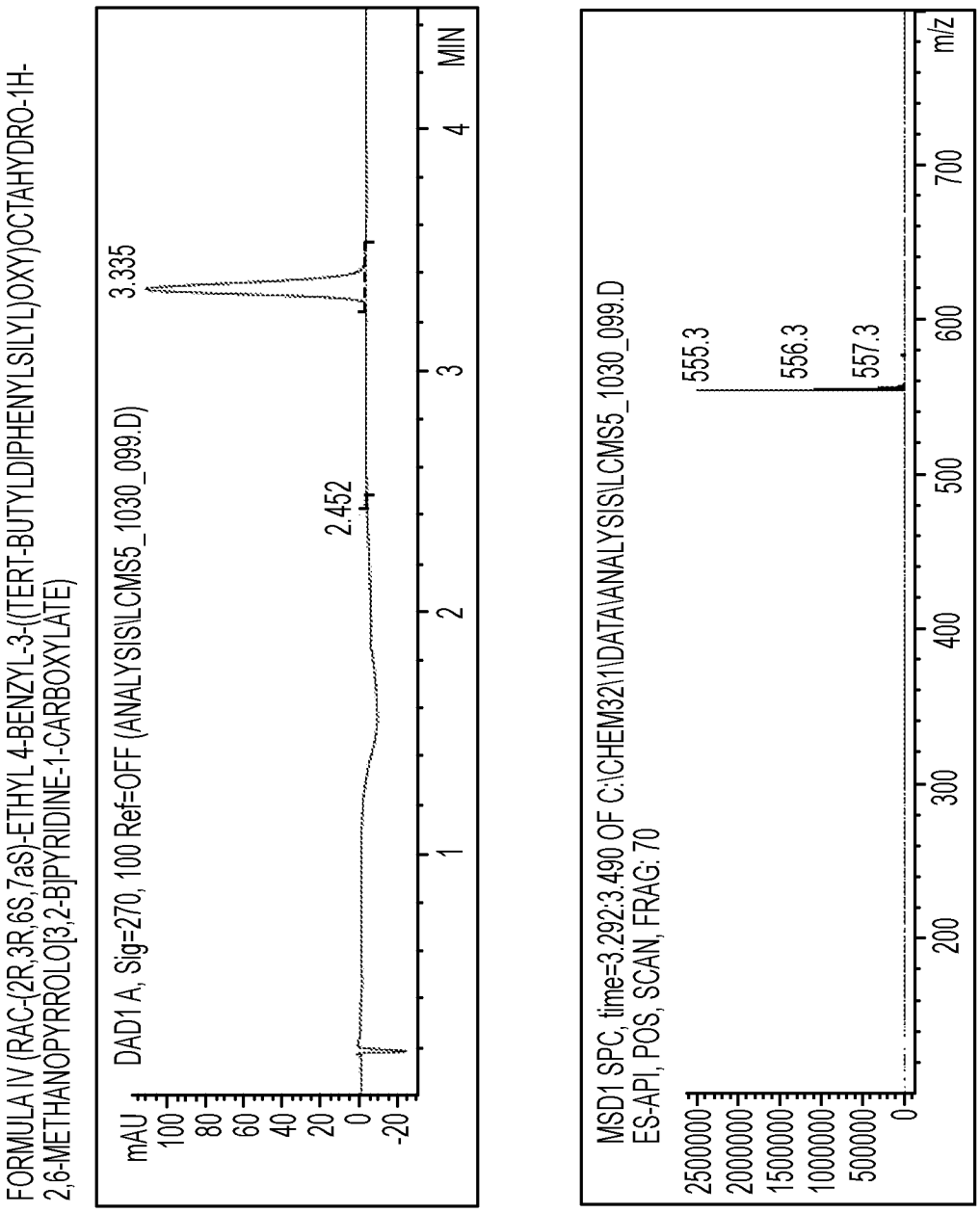

FORMULA IV (RAC-(2R,3R,6S,7aS)-ETHYL 4-BENZYL-3-((TERT-BUTYLDIPHENYLSILYL)OXY)OCTAHYDRO-1H-2,6-METHANOPYRROLO[3,2-B]PYRIDINE-1-CARBOXYLATE)
DAD1 A, Sig=270, 100 Ref=OFF (ANALYSIS\LCMS5_1030_099.D)
mAU
MIN
3.335
2.452
MSD1 SPC, time=3.292:3.490 OF C:\CHEM32\1\DATA\ANALYSIS\LCMS5_1030_099.D
ES-API, POS, SCAN, FRAG: 70
555.3
556.3
557.3
m/z

FIG. 9A

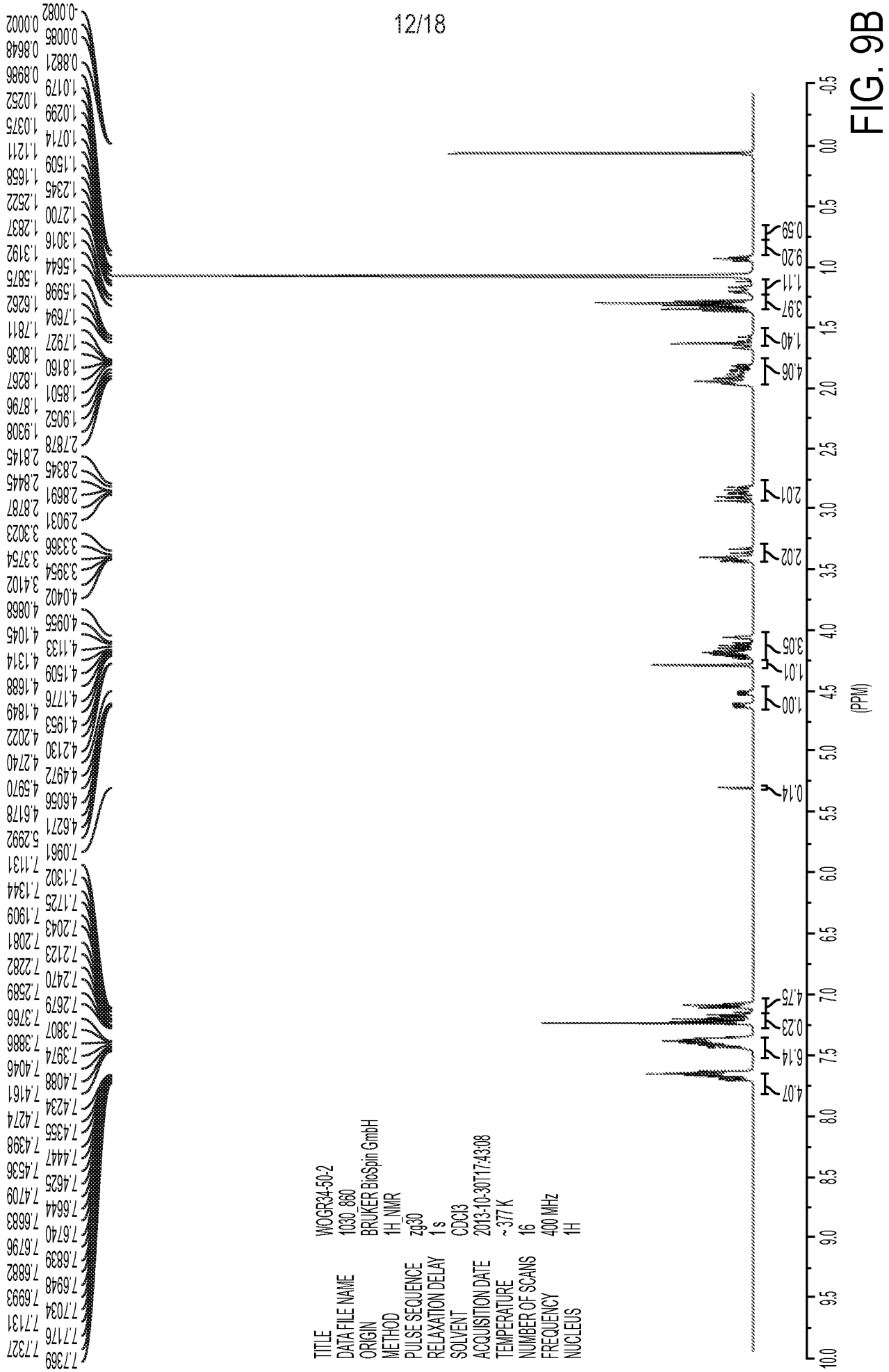

TITLE WOGR34-50-2
DATA FILE NAME 1030_860
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-10-30T17:43:08
TEMPERATURE ~ 377 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
4.07
6.14
0.23
4.75
0.14
1.00
1.01
3.05
2.02
2.01
4.06
1.40
3.97
1.11
9.20
0.59
(PPM)

FIG. 9B

FORMULA III (RAC-(2R,3R,6S,7aS)-4-BENZYL-3-((TERT-BUTYLDIPHENYLSILYL)OXY) OCTAHYDRO-1H-2,6-METHANOPYRROLO[3,2-b]PYRIDINE)

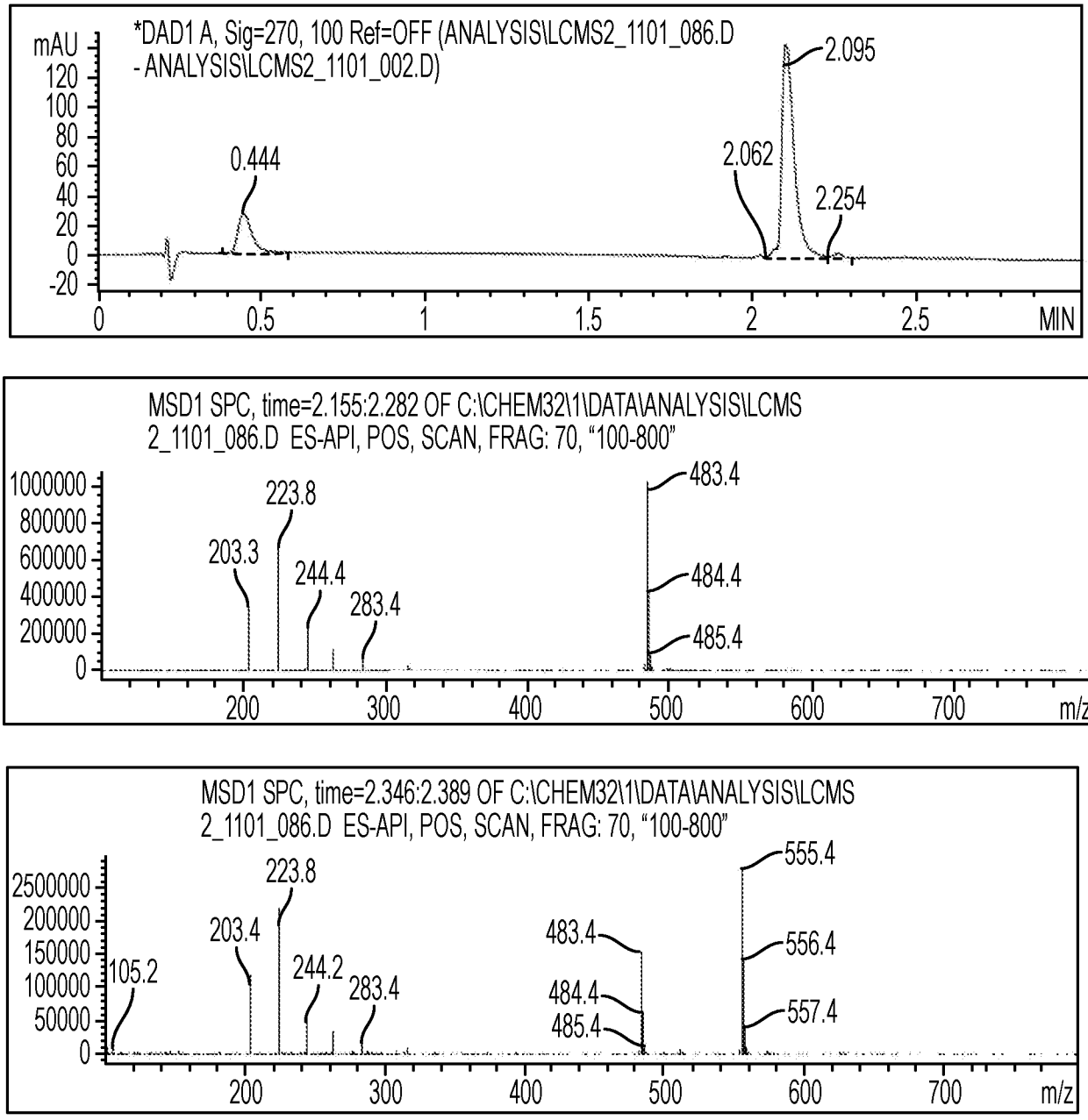



FIG. 10

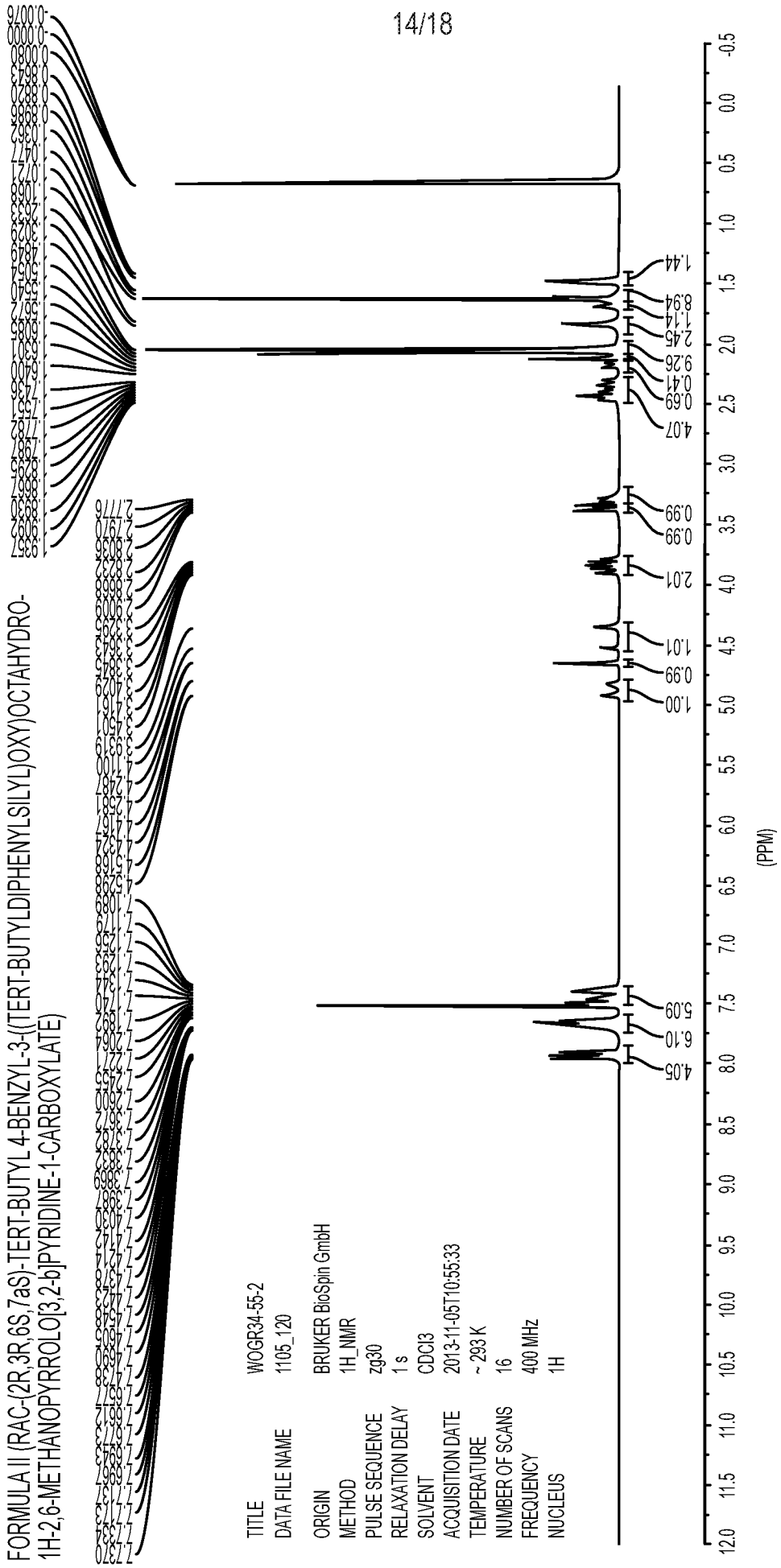

FORMULA II (RAC-(2R,3R,6S,7aS)-TERT-BUTYL 4-BENZYL-3-((TERT-BUTYLDIPHENYLSILYL)OXY)OCTAHYDRO-1H-2,6-METHANOPYRROLO[3,2-b]PYRIDINE-1-CARBOXYLATE)
TITLE WOGR34-55-2
DATA FILE NAME 1105_120
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-11-05T10:55:33
TEMPERATURE ~293 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
4.05
6.10
5.09
1.00
0.99
1.01
2.01
0.99
0.99
4.07
0.69
0.41
9.26
2.45
1.14
8.94
1.44
(PPM)

FIG. 11A

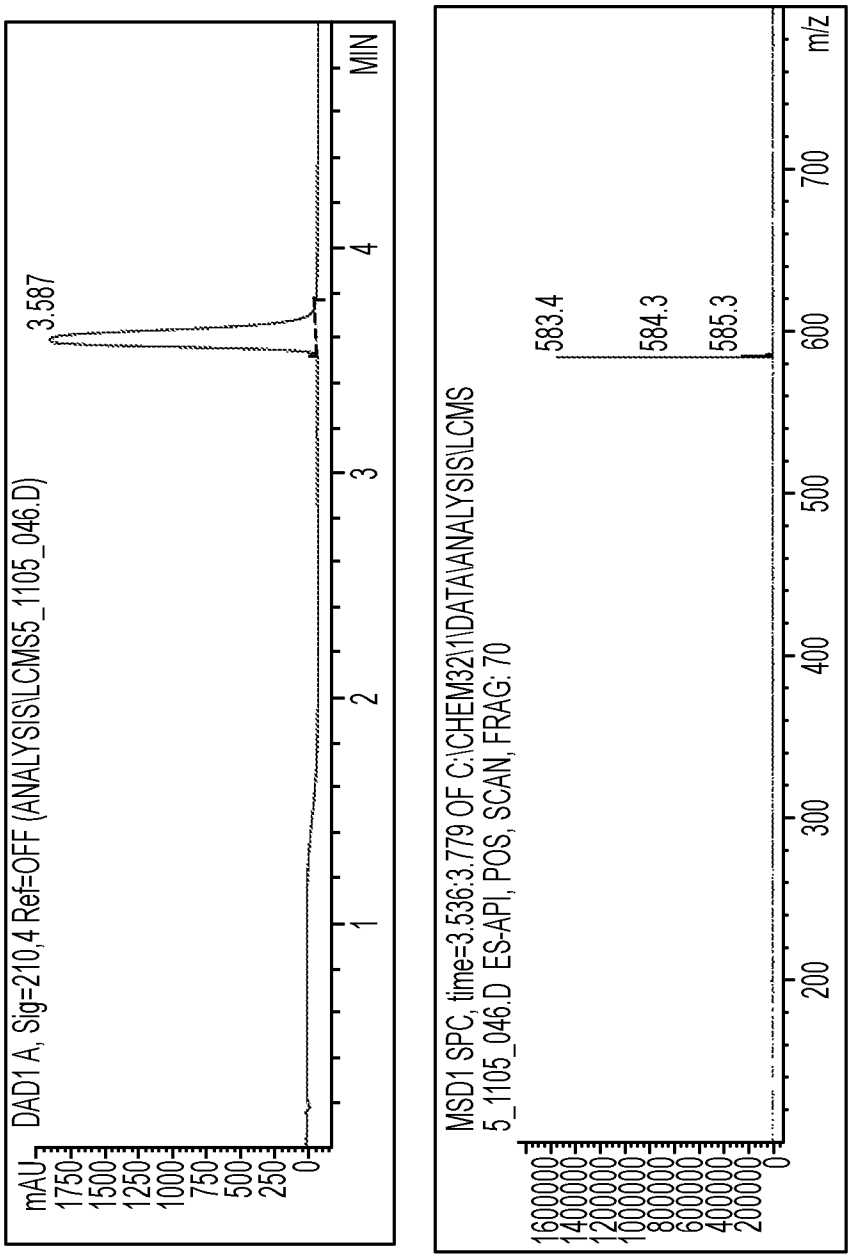

DAD1 A, Sig=210,4 Ref=OFF (ANALYSIS\LCMS5_1105_046.D)
mAU
1750
1500
1250
1000
750
500
250
0
3.587
1
2
3
4
MIN
MSD1 SPC, time=3.536:3.779 OF C:\CHEM32\1\DATA\ANALYSIS\LCMS
5_1105_046.D ES-API, POS, SCAN, FRAG: 70
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
583.4
584.3
585.3
200
300
400
500
600
700
m/z

FIG. 11B

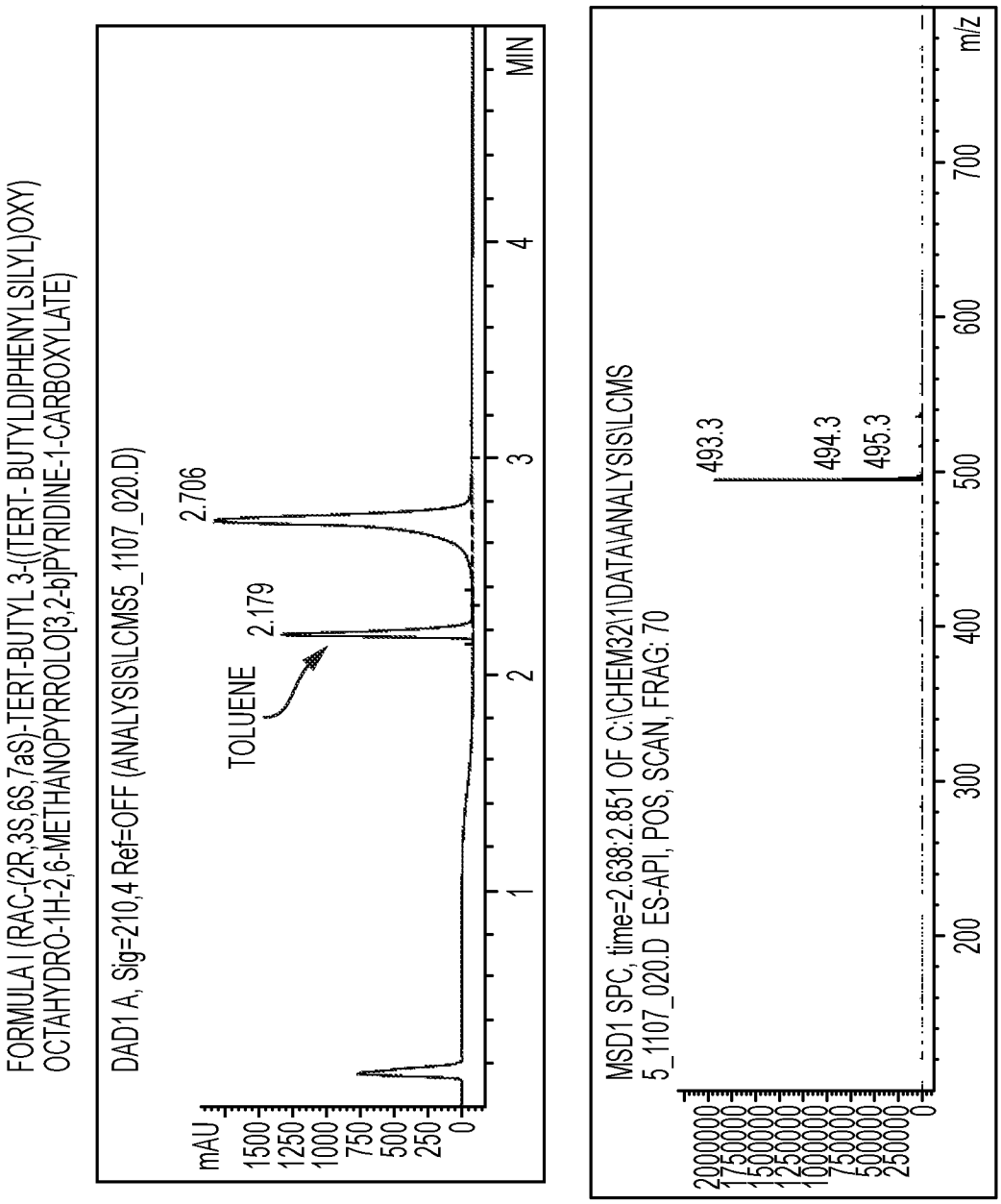

FORMULA I (RAC-(2R,3S,6S,7aS)-TERT-BUTYL 3-((TERT- BUTYLDIPHENYLSILYL)OXY)
OCTAHYDRO-1H-2,6-METHANOPYRROLO[3,2-b]PYRIDINE-1-CARBOXYLATE)
DAD1 A, Sig=210,4 Ref=OFF (ANALYSIS\LCMS5_1107_020.D)
mAU
1500
1250
1000
750
500
250
0
TOLUENE
2.179
2.706
1
2
3
4
MIN
MSD1 SPC, time=2.638:2.851 OF C:\CHEM32\1\DATA\ANALYSIS\LCMS
5_1107_020.D ES-API, POS, SCAN, FRAG: 70
493.3
494.3
495.3
2000000
1750000
1500000
1250000
1000000
750000
500000
250000
0
200
300
400
500
600
700
m/z

FIG. 12A

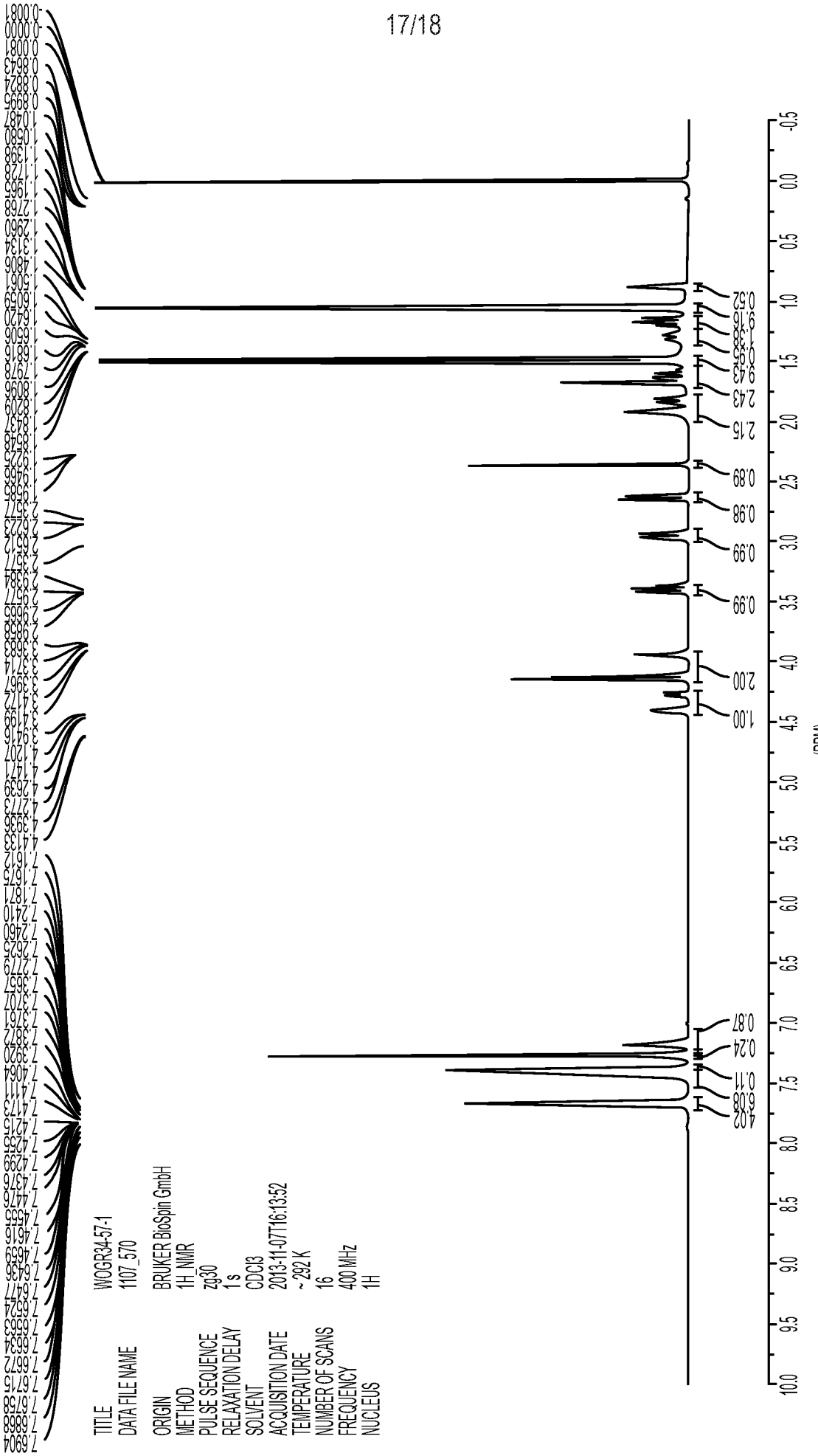

TITLE WOGR34-57-1
DATA FILE NAME 1107_570
ORIGIN BRUKER BioSpin GmbH
METHOD 1H_NMR
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT CDCl3
ACQUISITION DATE 2013-11-07T16:13:52
TEMPERATURE ~ 292 K
NUMBER OF SCANS 16
FREQUENCY 400 MHz
NUCLEUS 1H
4.02
6.08
0.11
0.24
0.87
1.00
2.00
0.99
0.98
0.89
2.15
2.43
9.43
9.16
0.52
(PPM)

FIG. 12B

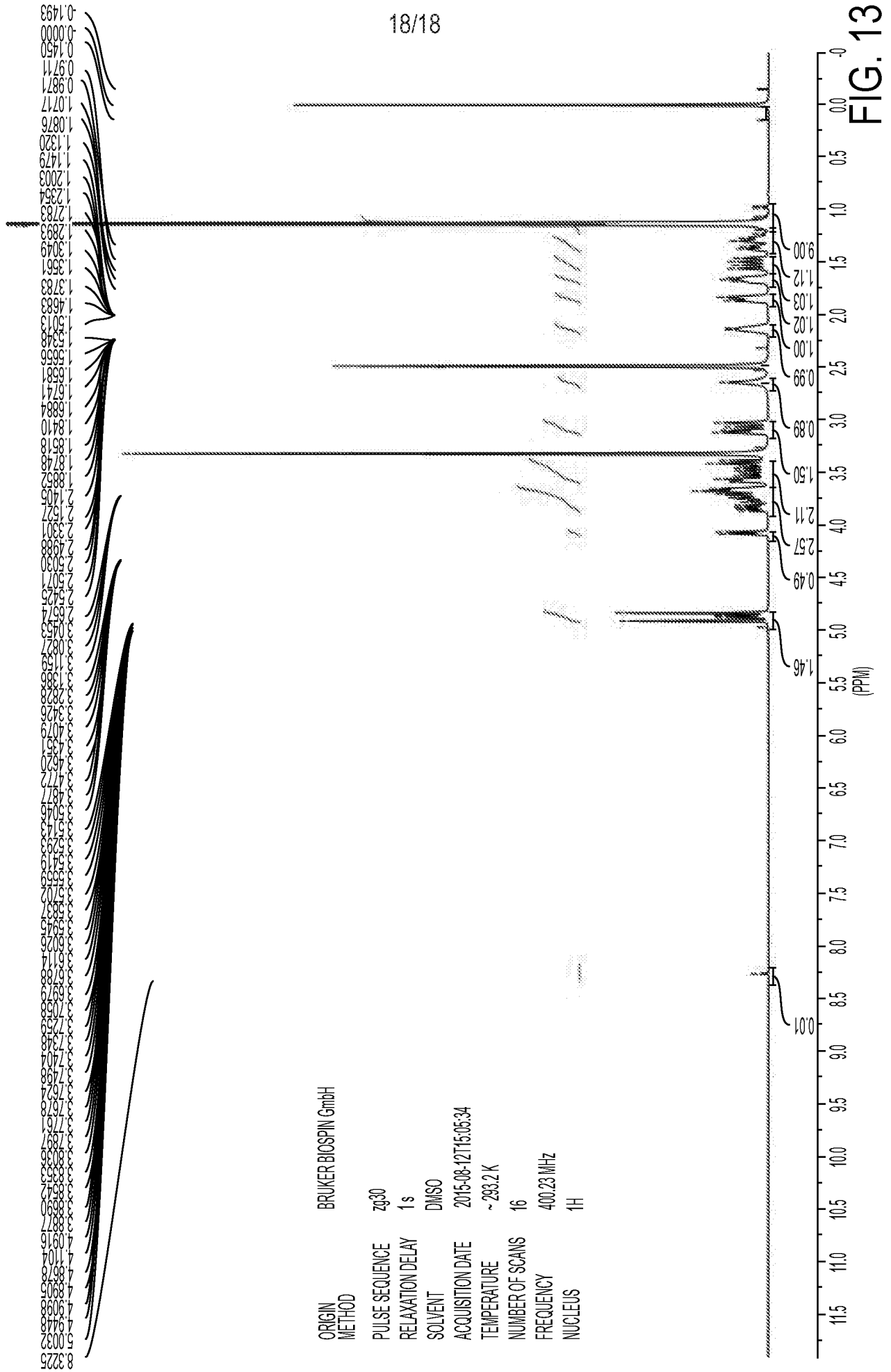

ORIGIN BRUKER BIOSPIN GmbH
METHOD
PULSE SEQUENCE zg30
RELAXATION DELAY 1 s
SOLVENT DMSO
ACQUISITION DATE 2015-08-12T15:05:34
TEMPERATURE ~ 293.2 K
NUMBER OF SCANS 16
FREQUENCY 400.23 MHz
NUCLEUS 1H
0.01
1.46
0.49
2.57
2.11
1.50
0.89
0.99
1.00
1.02
1.03
1.12
9.00
(PPM)

FIG. 13

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2016/049881**

**A. CLASSIFICATION OF SUBJECT MATTER**

**C07D 471/12(2006.01)i, C07D 471/18(2006.01)i, A61K 31/437(2006.01)i, A61K 31/4375(2006.01)i**

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 471/12; A61K 31/573; A61K 31/517; A61P 35/00; A61P 9/14; C07D 471/18; A61K 31/437; A61K 31/4375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(Kipo internal), STN (Registry, Caplus, Marpat), Google & Keywords: octahydro-pyrrolo[3,2-b]pyridin-3-yl, pain

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CN 102579458 A (JIZHONG ENERGY FENGFENG GROUP CO., LTD. GENERAL HOSPITAL) 18 July 2012<br>See abstract. | 1-3,8-49 |
| A | US 2008-0188452 A1 (ALTENBACH, R. J. et al.) 07 August 2008<br>See abstract; and claim 1. | 1-3,8-49 |
| A | MACOR, J. E. et al., "The 5-HT3 antagonist tropisetron (ICS 205-930) is a potent and selective α7 nicotinic receptor partial agonist", Bioorganic & Medicinal chemistry Letters, 2001, Vol. 11, No. 3, pp. 319-321<br>See the whole document. | 1-3,8-49 |
| A | WESSIG, P. et al., "Photochemical preparation of tricyclic hydroxyketones by transanular cyclization of bridged 4-benzoylcyclohexanones", Monatshefte fur Chemie/Chemical Monthly, 1997, Vol. 128, No. 8, pp. 849-862<br>See the whole document. | 1-3,8-49 |

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"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 |
|---|---|
| 19 December 2016 (19.12.2016) | **20 December 2016 (20.12.2016)** |

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
PARK, Jung Min
Telephone No. +82-42-481-3516

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2016/049881**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4-7
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 4-7 pertain to a method for treating a human body, and thus relate to a subject matter not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2016/049881**

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | TANAKA, K. et al., "Synthetic studies on a picrotoxane sesquiterpene, coriamyrtin. II. An effective stereocontrolled synthesis of the picrotoxane skeleton except for a C1 unit at the C9 position and functionalization of the five-membered ring", Chemical and Pharmaceutical Bulletin, 1983, Vol. 31, No 6, pp. 1958-1971<br>See the whole document. | 1-3,8-49 |

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2016/049881**

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| CN 102579458 A | 18/07/2012 | None | |
| US 2008-0188452 A1 | 07/08/2008 | TW 2008-31508 A | 01/08/2008 |
| | | US 8735411 B2 | 27/05/2014 |
| | | WO 2008-060767 A2 | 22/05/2008 |
| | | WO 2008-060767 A3 | 17/07/2008 |