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(54) Benævnelse: **FREMGANGSMÅDE TIL SYNTESE AF (S)-3-AMINO-4-(DIFLUORMETHYLENYL)CYCLOPENT-1-EN-1-CARBOXYLSYRE**

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DESCRIPTION

Description

TECHNICAL FIELD

Synthesis of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid.

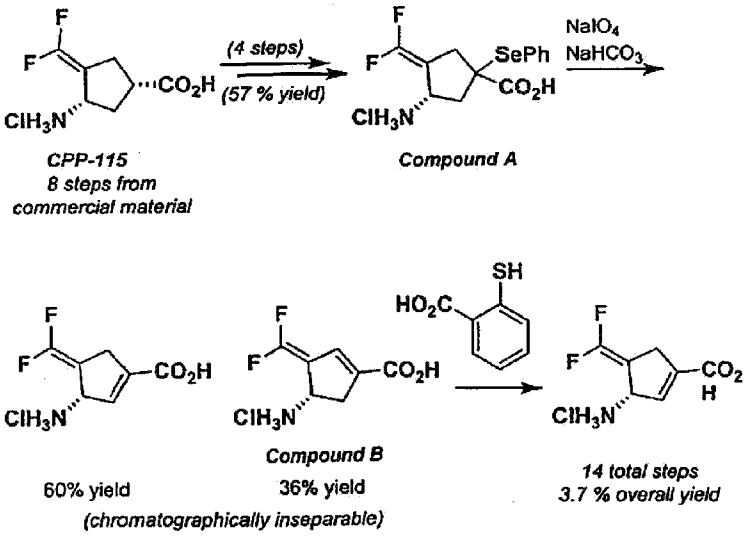
BACKGROUND

[0001] (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid is an inhibitor of γ-aminobutyric acid aminotransferase (GABA-AT) and has been shown as a possible treatment of epilepsy, addiction and hepatocellular carcinoma. See, e.g., US Patent No. 9,670,141 and Juncosa et al., J. Am. Chem. Soc. 2018, 140, 2151-2164. GABA is an inhibitory neurotransmitter in the central nervous system (CNS). When GABA concentrations in the brain drop below a threshold level, convulsions can occur. Increasing GABA levels has been shown to stop convulsions. Additionally, increased concentrations of GABA antagonize the release of dopamine from the nucleus accumbens, a region of the hypothalamus associated with reward and motivation, and have been suggested as a possible treatment of addiction. Unfortunately, direct administration of GABA is not viable as GABA does not cross the blood brain barrier. GABA concentrations, however, can be increased by inhibiting GABA aminotransferase (GABA-AT). 4-Aminohex-5-enoic acid, also known as vigabatrin (marketed as Sabril®), currently is the only FDA approved inhibitor of GABA-AT for the treatment of infantile spasms and has been shown as a possible treatment of addiction. Vigabatrin, however, requires a large dose (1-3 g/day), inhibits multiple GABA receptors, and, with prolonged use, causes retinal damage in 25-40% of patients.

[0002] *In vivo* studies in rats indicate that (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid is superior to previous inhibitors of GABA-AT at suppressing the release of dopamine in the corpus striatum after exposure to cocaine or nicotine. (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid does not inhibit off-target aminotransferase enzymes like alanine aminotransferase and aspartate aminotransferase. It additionally does not inhibit the hERG potassium ion channel or various microsomal cytochrome P450 enzymes.

[0003] According existing techniques, (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid has been synthesized in six steps from (1S,3S)-3-amino-4-

(difluoromethylidene)cyclopentane-1-carboxylic acid (also known as CPP-115).



[0004] See also, e.g., Juncosa et al., J. Am. Chem. Soc., *supra,* and US Patent Nos. 7,381,748, 6,794,413 and 9,670,141.

[0005] CPP-115 is an inhibitor of GABA-AT and currently in clinical trials for the treatment of epilepsy. It has been determined that (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid is 9.8 times more efficient as an activator of GABA-AT than CPP-115. Since synthesis of CPP-115 takes 8-steps, the total synthetic step count from commercial starting material to (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid is fourteen with an overall yield of 3.7%. The synthesis of CPP-115 involves the use of the highly flammable *tert*-butyl lithium (on gram scale) to install the 1,1'-difluoroolefin, which limits the scale at which the reaction can be run. Furthermore, the existing synthesis relies of the introduction of the cyclopentene through selenoxide elimination. Protected CPP-115 is selenated in 70% yield, although yields can vary depending on scale. α-Elimination of Compound A yields a mixture of chromatographically inseparable isomers in a 5:3 ratio favoring (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid. Compound B is selectively degraded using thiosalicylic acid to produce solely (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid in an overall yield of 36% from Compound A. Only small batches of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid can be obtained using the existing technique. Additionally, since selenium is toxic and regulated by the FDA to levels below 80-150 µg/day, the production of selenol in the penultimate step complicates the synthesis and purification of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid.

[0006] Accordingly, there is a need for processes that are better suited for larger scale preparation of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid that will reduce costs, decrease the number of manufacturing steps, decrease hazardous environmental waste, and increase efficiency of manufacture.

SUMMARY

[0007] A process for preparing (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) or salt thereof is provided which includes converting ((1*R*,4*S*)-2-Azabicyclo[2.2.1]hept-5-en-3-one) (2) to (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3). (1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) is converted to (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4). (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is converted to (1R,4R,6S,7R)-7-Bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[22.1.]heptan-3-one (25). (1R,4R,6S,7R)-7-Bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1.]heptan-3-one (25) is converted to (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5). *(1R,4R,7R)-7*-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) is converted to (1R,4R,7R)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (6) is converted to *(1R,4R,7R)-7*-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) is converted to methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9). Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) is converted to (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

[0008] (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) is made by a process described herein. Compositions including (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) are described herein. Pharmaceutical compositions including (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) are described herein.

[0009] (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is provided herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (6) are provided herein. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is made by a process described herein.

[0010] (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) is provided herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) are provided herein. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) is made by a process described herein.

[0011] (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-

azabicyclo[2.2.1]heptan-3-one (8) is provided herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) are provided herein. 1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[22.1]heptan-3-one (8) is made by a process described herein.

[0012] Methyl (*S*)-3-((tert-Butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) is provided herein. Compositions including methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) are provided herein. Methyl (*S*)-3-((tert-Butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) is made by a process described herein.

[0013] (*S*)-3-((tert-Butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1 -ene-1 -carboxylic acid (19) is provided herein. Compositions including (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) are provided herein. (*S*)-3-((tert-Butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) is made by a process described herein.

BRIEF DESCRIPTION OF DRAWINGS

[0014]

FIG. 1 is a 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo [2.2.1]heptan-3 -one (6).

FIG. 2 is a ^{13}C NMR spectrum ($CDCl_3$; 126 MHz) of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo [2.2.1]heptan-3 -one (6).

FIG. 3 is a 127.5 MHz ^{19}F NMR spectrum ($CDCl_3$) of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo [2.2.1]heptan-3-one (6).

FIG. 4 is a 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7).

FIG. 5 is a ^{13}C NMR spectrum ($CDCl_3$; 126 MHz) of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7).

FIG. 6 is a 127.5 MHz ^{19}F NMR spectrum of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) ($CDCl_3$).

FIG. 7 is a 500 MHz ^{1}H NMR spectrum ($CDCl_3$) of methyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9).

FIG. 8 is a ^{13}C NMR spectrum ($CDCl_3$; 126 MHz) of methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9).

FIG. 9 is a 127.5 MHz ^{19}F NMR spectrum of methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9).

FIG. 10 is a 500 MHz ^{1}H NMR spectrum ($CDCl_3$) (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

FIG. 11 is a ^{13}C NMR spectrum ($CDCl_3$; 126 MHz) of (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

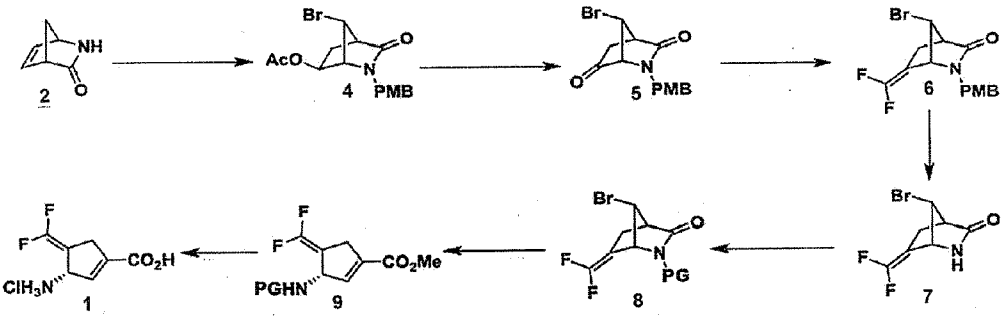
FIG. 12 is a 127.5 MHz ^{19}F NMR spectrum of (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

DETAILED DESCRIPTION

[0015] Provided herein are processes, compounds and compositions for making (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1). The processes herein are scalable and high yielding as compared to the existing technique, avoid the use of selenium and *tert*-butyllithium, and avoid forming multiple isomers from an α-elimination. In embodiments, the present process incorporates elimination of a leaving group from the β-position, precludes a resulting mixture of isomers, reduces the number of synthesis steps from fourteen to nine as compared to the existing technique, and increases yield from 3.7% to 8.1%.

[0016] In embodiments, synthesis of (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) is shown in Scheme 1 starting with ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2).

Scheme 1



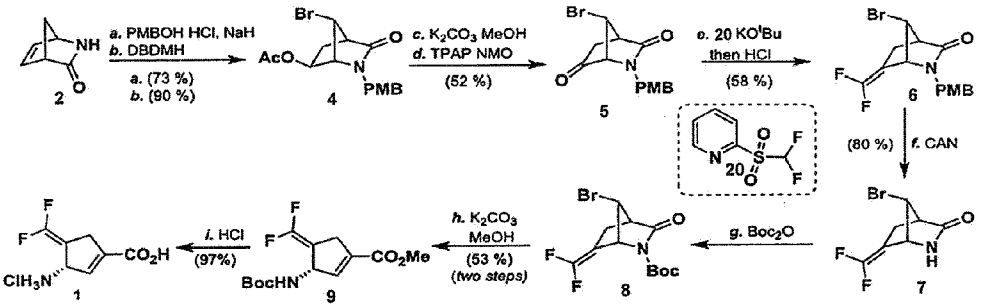
AC=Acetyl, PMB= 4-Methoxybenzyl, PG= Protecting Group

[0017] According to Scheme 1, a process for preparing (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) or salt thereof is provided which

includes converting ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2) to (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2. 1]hept-5-en-3-one (3). (1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) is converted to (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4). (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is converted to (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5). (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3 -one (6). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene) -2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[22.1]heptan-3-one (7). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) is converted to methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9). Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) is converted to (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

[0018] In embodiments, synthesis of (*S*)-3-amino-4-(dif|uoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) is shown in Scheme 1A.

Scheme 1A



Abbreviations: PMBOH: 4-methoxybenzyl alcohol; DMF: *N*-*N*-dimethylformamide; DBDMH: 1,3-dibromo-5,5- dimethylhydantoin; TPAP: tetrapropylammonium perruthenate; NMO: N-methylmorpholine *N*-oxide; CAN: ceric ammonium nitrite; DMAP: *N*,*N*-dimethylaminopyridine

[0019] In embodiments, starting from ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2) (also known as the Vince lactam) and following a modification of literature steps such as the use of PMBOH/HCl, (See, Qiu, J.; Silverman, R. B. J. Med. Chem. 2000, 43, 706-720), (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is obtained on a multi-gram scale (Scheme 1A): a. PMBOH, HCl, NaH, THF/DMF; b. DBDMH, AcOH. Alcoholysis of the acetate and oxidation yields ketone (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5): c. K_2CO_3, alcohol; d. TPAP, NMO, 4 Å MS, CH_2Cl_2, over two steps. The foregoing allows difluoro-Horner-Wadsworth-Emmons olefination of ketone 5. When 2-((difluoromethyl)sulfmyl)pyridine (20) (also known as Hu's reagent) is employed with KO^{t}Bu as base, (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-

methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is obtained: e. 2-((difluoromethyl)sulfmyl)pyridine (20), KO^{t}Bu, DMF, then NH4Cl, then HCl. Alternatively, e. can be *tert-BuLi* and $F_2CHP(O)(OEt)_2$ (See, Pan, Y.; Qiu, J.; Silverman, R. B. J. Med. Chem. 2003, 46, 5292-5293). The next step is alcoholysis of the lactam and elimination. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is deprotected to yield (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7): f. CAN, MeCN, H_2O. A small amount of 4-methoxybenzoyl protected lactam may also be isolated. Boc protection of the lactam (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one) (7) yields (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8): g. Boc_2O, DMAP, Et_3N, CH_2Cl_2. Alcoholysis of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[22.1]heptan-3-one (8) with K_2CO_3 and alcohol, leads to subsequent elimination of the bromide to yield methyl or ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9): h. K_2CO_3, alcohol, over two steps. Final deprotection in HCl yields (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) with no observable isomerization or degradation: i. HCl, dioxane. Although methanol is shown in the above schematic, it should be understood that alcohols such as ethanol or propanol may be utilized as an alcohol.

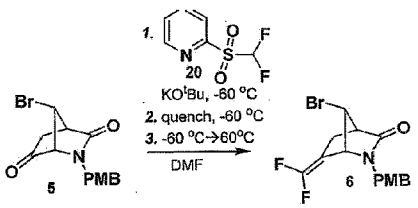
[0020] In embodiments, starting from ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2) (Vince lactam) and following a modification of literature steps (see, Qiu et al. *supra*), e.g., use of PMBOH/HCl, (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is obtained on a multi-gram scale (Scheme 1A): a. PMBOH (1-2 equiv.), HCl, NaH (0.8-1.5 equiv.) 0-5 °C, THF/DMF (0.75-1.5:0.75-1.5) , 4-8 h,; b. DBDMH (0.4-0.8 equiv), AcOH, 15-30°C, 4-8 h; Methanolysis of the acetate and oxidation yields ketone (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5): c. K_2CO_3 (2-4 equiv), MeOH 0.5-2 h; d. TPAP (0.001-0.2 equiv), NMO (1.0-3.0 equiv), 4 Å MS, CH_2Cl_2, 15-25 h, over two steps. The foregoing allows difluoro-Horner-Wadsworth-Emmons olefination of ketone 5. When 2-((difluoromethyl)sulfinyl)pyridine (20) (Hu's reagent) is employed with KO^{t}Bu as base, (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is obtained, e.g., infusion of base over 15 minutes to 2 hours with NH_4Cl/6 M HCl quench: e. 2-((difluoromethyl)sulfinyl)pyridine (20) (1.0-1.5 equiv), KO^{t}Bu (1.25-1.75 equiv), DMF, -80--40°C, 15-60 min, then NH4Cl, then HCl, then 15-30°C, then 40-80°C, 1 h. Alternatively, e. can be *tert-BuLi* and $F_2CHP(O)(OEt)_2$ (See, Pan, Y. et al. *supra*). The next step is methanolysis of the lactam and elimination. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is deprotected to yield (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7): f. CAN (2-4 equiv), MeCN, H_2O, -10 to 10°C, 0.75-2 h. A small amount of 4-methoxybenzoyl protected lactam may also be isolated. Boc protection of the lactam (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one) (7) yields (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8): g. Boc_2O (1.0-1.5 equiv), DMAP (0.01-0.5 equiv), Et_3N (1.0-2.0 equiv), CH_2Cl_2, 0.5-2.0 h. Methanolysis of (1*R*,4*R*,7*R*)-7-bromo-6-

(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) with K_2CO_3 and methanol, leads to subsequent elimination of the bromide to yield methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9): h. K_2CO_3 (2-4 equiv), MeOH, 4-8 h, over two steps. Final deprotection at 70-90°C in 6M HCl yields (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) with no observable isomerization or degradation: i. HCl (6 M), dioxane, 70-90°C, 1-3 h.

[0021] In embodiments, starting from ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2) (Vince lactam) and following a modification of literature steps such as the use of PMBOH/HCl, (See, Qiu, J., eta al. *supra*), (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is obtained on a multi-gram scale (Scheme 1A): a. PMBOH (1.5 equiv.), HCl, NaH (1.1 equiv.) 0 °C, THF/DMF (1:1), 6 h, 73%; b. DBDMH (0.6 equiv), AcOH, 23°C, 6 h, 90%; Methanolysis of the acetate and oxidation yields ketone (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5): c. K_2CO_3 (3 equiv), MeOH 1 h; d. TPAP (0.01 equiv), NMO (2.0 equiv), 4 Å MS, CH_2Cl_2, 18 h, 52% over two steps. The foregoing provides a modality to run these steps on multi-gram scale allowing difluoro-Horner-Wadsworth-Emmons olefination of ketone 5. When 2-((difluoromethyl)sulfinyl)pyridine (20) (Hu's reagent) is employed with KO^tBu as base, employing Hu's reported conditions (see, Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. Org. Lett. 2010, 12, 1444-1447), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is obtained in small amounts (<10% yield). Slow infusion of base over 30 minutes with NH_4Cl/6 M HCl quench dramatically increases the yield to 45%. Prolonging infusion of base to one hour increases the yield to 58%. See, Table 1, below. The reaction was not greatly affected by scale, allowing scale up to 3.5 g of (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) with no decrease in yield: e. 2-((difluoromethyl)sulfinyl)pyridine (20) (1.2 equiv), KO^tBu (1.5 equiv), DMF, -60 °C, 30 min, then NH4Cl, then 6 M HCl, then 23 °C, then 60 °C, 1 h. Alternatively, e. can be *tert-BuLi* and $F_2CHP(O)(OEt)_2$ (See, Pan, et al., *supra*). The next step is methanolysis of the lactam and elimination. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is deprotected to yield (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) in 80% yield: f. CAN (3 equiv), MeCN, H2O, 0°C, 1 h. A small amount of 4-methoxybenzoyl protected lactam may also be isolated. Boc protection of the lactam (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one) (7) yields (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8): g. Boc_2O (1.2 equiv), DMAP (0.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 1 h. Methanolysis of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) with K_2CO_3 and methanol, leads to subsequent elimination of the bromide to yield methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9): h. K_2CO_3 (3 equiv), MeOH, 6 h, 52% over two steps. Final deprotection at 80°C in 6M HCl yields (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) in 97% yield with no observable isomerization or degradation: i. HCl (6 M), dioxane, 80°C, 2 h. Overall, the yield from Vince

Lactam (2) to *S*)-3-amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (1) is 8.1%.

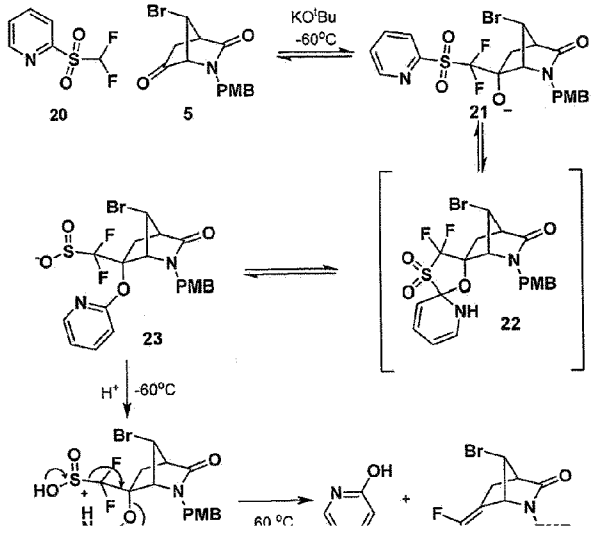
Table 1. Optimization of Fluorination[a]

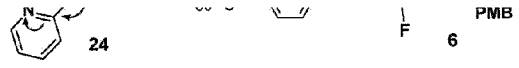


entry	scale (9)	base addition method	quench (time)[b]	yield[c]
1	0.05	dropwise over 5 min	6 M HCl (5 min)	0
2	0.05	dropwise over 5 min	6 M HCl (1 h)	9%
3	0.05	dropwise over 5 min	a. sat. NH_4Cl (1 h)	15%
			b. 6 M HCl (1 min)	
4	0.13	infusion over 30 min	a. sat. NH_4Cl (1 h)	45%
			b. 6 M HCl (2 min)	
5	1	infusion over 60 min	a. sat. NH_4Cl (1 h)	58%
			b. 6 M HCl (2 min)	
6	3.5	infusion over 90 min	a. sat. NH_4Cl (1 h)	50%
			b. 6 M HCl (2 min)	

[a]Conditions: **5** (1 equiv), **20** (1.2 equiv), DMF (0.3 M) -60 °C, then KO^{t}Bu (1.5 equiv) in DMF (0.5 M), then quench at -60 °C, then 23 °C, then 60 °C for 1 h; [b]time *before* quenching solution was added; [c]isolated yield after chromatography.

[0022] In embodiments, without wishing to be bound by any theory, the following is a proposed mechanism for fluorination of (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5):

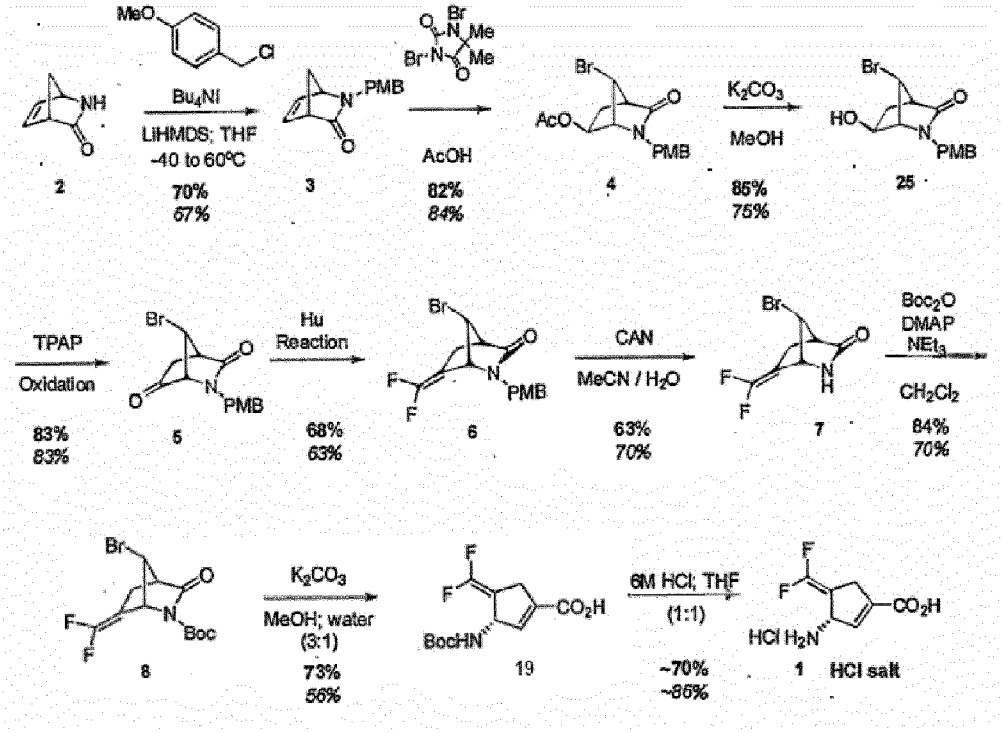




[0023] As shown above, multiple intermediates form during the course of the fluorination reaction. Intermediate **21,** which forms first, rearranges via cyclic intermediate **22** to form sulfonate **23,** which is then protonated, triggering elimination and formation of the olefin (see above). If the reaction were quenched at -60 °C with 6 M HCl five minutes after the addition of KO^{t}Bu to a mixture of **5** and **20,** then only **21** was observed by LC/MS (entry 1, Table 1). Addition of KO^{t}Bu followed by a 6 M HCl quench at -60 °C (entry 2, Table 1), and subsequent heating at 60 °C for 1 h provided 6 in 9% yield along with starting material and intermediate **21.** Quenching after 1 hour with a saturated NH_4Cl solution, followed by 6 M HCl, slightly improved the yield (entry 3, Table 1). Slow infusion of base with a syringe pump over 30 min with an NH_4Cl/6 M HCl quench dramatically increased the yield to 45%. Prolonging infusion of base to one hour increased the yield to 58%.

[0024] In embodiments, synthesis of (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) is shown in Scheme 2.

Scheme 2



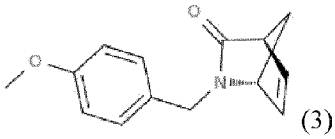
Racemic synthesis yield (%) is provided over the (s)-isomer yield (%).

Abbreviations: LiHMDS: lithium bis(trimethylsilyl) amide; THF: tetrahydrofuran; PMB: 4-methoxybenzyl; DBDMH: 1,3-dibromo-5,5- dimethylhydantoin; TPAP: tetrapropylammonium perruthenate; CAN: ceric ammonium nitrite; DMAP: *N,N*-dimethylaminopyridine

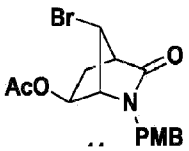
[0025] According to Scheme 2, a process for preparing (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) or salt thereof is provided which

includes converting ((1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one) (2) to (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3). (1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) is converted to (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4). (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) is converted to (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25). (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) is converted to (1R,4R,7R)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5). (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene) -2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) is converted to (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8). (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[22.1]heptan-3-one (8) is converted to (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19). (*S*)-3-((Tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) is converted to (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1).

[0026] In embodiments, the following compounds are provided:

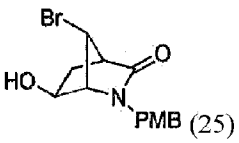

(3)

(1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5 -en-3 -one (3)



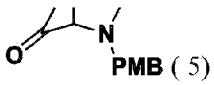
(4)

(1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2. 1]heptan-6-yl acetate (4)



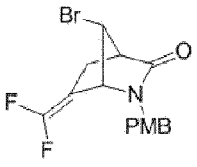
(25)

(1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25)



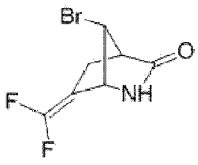
(5)

(1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5)



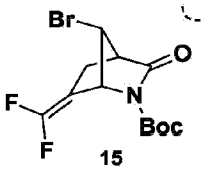
(6)

(1R,4R,7R)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6)



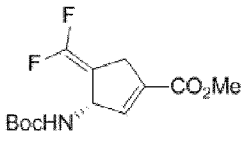
(7)

(1*R*,4*R*,7*R*)-1-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7)



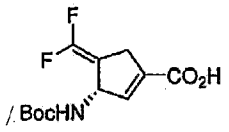
(8)

(1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[22.1]heptan-3-one (8)



(9)

Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9)



(19)

(*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19)

[0027] Described herein are compositions including (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2. 1]hept-5-en-3-one (3) or a salt thereof are provided herein. Such compositions

may include reaction mixtures such as those described herein. Compositions including (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0/.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0028] Described herein are compositions including (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[22.1]heptan-6-yl acetate (4) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9

mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg Described herein are compositions including (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1R,4R,6S,7R)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (25) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0029] Described herein are compositions including (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002

mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0030] Described herein are compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2. 1]heptan-3-one (6) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0031] Described herein are compositions (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-

azabicyclo[2.2.1]heptan-3-one (7) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0032] Described herein are compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition can include (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0033] Described herein are compositions including methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) or a salt

thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including m ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg, 0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0034] Described herein are compositions including (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) or a salt thereof are provided herein. Such compositions may include reaction mixtures such as those described herein. Compositions including (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) or a salt thereof may include polar solvents, e.g., aqueous, methanol, ethanol, DMF, acetic acid, etc. or non-polar solvents, e.g., diethyl ether, hexane, dichloromethane, ethyl acetate, etc. Compositions including (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) or a pharmaceutically acceptable salt thereof can be pharmaceutical compositions. Compositions can include (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) or a salt thereof in amounts of from 0.0001 mg to 50 mg or more. For example, a pharmaceutical composition may include (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) or a pharmaceutically acceptable salt thereof in amounts greater than 0.0001 mg, e.g., from 0.0001 mg to 0.0002 mg, 0.0001 mg to 0.0003 mg, 0.0002 mg to 0.0003 mg, 0.0003 mg to 0.0004 mg, 0.0004 mg to 0.0005 mg, 0.0005 mg to 0.0006 mg, 0.0006 mg to 0.0007 mg, 0.0007 mg to 0.0008 mg, 0.0008 mg to 0.0009 mg, 0.0009 mg to 0.001 mg, 0.001 mg to 0.002 mg, 0.002 mg to 0.003 mg, 0.003 mg to 0.004 mg, 0.004 mg to 0.005 mg, 0.005 mg to 0.006 mg, 0.006 mg to 0.007 mg, 0.007 mg to 0.008 mg, 0.008 mg to 0.009 mg, 0.009 mg to 0.01 mg, 0.01 mg to 0.02 mg, 0.02 mg to 0.03 mg, 0.03 mg to 0.04 mg, 0.04 mg to 0.05 mg, 0.05 mg to 0.06 mg, 0.06 mg to 0.07 mg,

0.07 mg to 0.08 mg, 0.08 mg to 0.09 mg, 0.09 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.3 mg, 0.3 mg to 0.4 mg, 0.4 mg to 0.5 mg, 0.5 mg to 0.6 mg, 0.6 mg to 0.7 mg, 0.7 mg to 0.8 mg, 0.8 mg to 0.9 mg, 0.9 mg to 1.0 mg, 1.0 mg to 2.0 mg, 2.0 mg to 3.0 mg, 3.0 mg to 4.0 mg, 4.0 mg to 5.0 mg, 5.0 mg to 6.0 mg, 6.0 mg to 7.0 mg, 7.0 mg to 8.0 mg, 8.0 mg to 9.0 mg, or 9.0 mg to 10 mg.

[0035] Pharmaceutical compositions obtainable by the process of the invention may include (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid or a pharmaceutically acceptable salt thereof in an amount of, e.g., about 0.001 to 500 mg, 0.01 to 500 mg, 0.01 to 450 mg, 0.01 to 300 mg, 0.01 to 250 mg, 0.01 to 200 mg, 0.01 to 175 mg, 0.01 to 150 mg, 0.01 to 125 mg, 0.01 to 100 mg, 0.01 to 75 mg, 0.01 to 50 mg, 0.01 to 30 mg, 0.01 to 25 mg, 0.01 to 20 mg, 0.01 to 15 mg, 0.01 to 10 mg, 0.01 to 5 mg, 0.01 to 1mg, 0.025 to 500 mg, 0.025 to 450 mg, 0.025 to 300 mg, 0.025 to 250 mg, 0.025 to 200 mg, 0.025 to 175 mg, 0.025 to 150 mg, 0.025 to 125 mg, 0.025 to 100 mg, 0.025 to 75 mg, 0.025 to 50 mg, 0.025 to 30 mg, 0.025 to 25 mg, 0.025 to 20 mg, 0.025 to 15 mg, 0.025 to 10 mg, 0.025 to 5 mg, 0.025 to 1mg, 0.05 to 500 mg, 0.05 to 450 mg, 0.05 to 300 mg, 0.05 to 250 mg, 0.05 to 200 mg, 0.05 to 175 mg, 0.05 to 150 mg, 0.05 to 125 mg, 0.05 to 100 mg, 0.05 to 75 mg, 0.05 to 50 mg, 0.05 to 30 mg, 0.05 to 25 mg, 0.05 to 20 mg, 0.05 to 15 mg, 0.05 to 10 mg, 0.05 to 5 mg, 0.05 to 1mg, 0.075 to 500 mg, 0.075 to 450 mg, 0.075 to 300 mg, 0.075 to 250 mg, 0.075 to 200 mg, 0.075 to 175 mg, 0.075 to 150 mg, 0.075 to 125 mg, 0.075 to 100 mg, 0.075 to 75 mg, 0.075 to 50 mg, 0.075 to 30 mg, 0.075 to 25 mg, 0.075 to 20 mg, 0.075 to 15 mg, 0.075 to 10 mg, 0.075 to 5 mg, 0.075 to 1mg, 0.1 to 500 mg, 0.1 to 450 mg, 0.1 to 300 mg, 0.1 to 250 mg, 0.1 to 200 mg, 0.1 to 175 mg, 0.1 to 150 mg, 0.1 to 125 mg, 0.1 to 100 mg, 0.1 to 75 mg, 0.1 to 50 mg, 0.1 to 30 mg, 0.1 to 25 mg, 0.1 to 20 mg, 0.1 to 15 mg, 0.1 to 10 mg, 0.1 to 5 mg, 0.1 to 1mg, 0.25 to 500 mg, 0.25 to 450 mg, 0.25 to 300 mg, 0.25 to 250 mg, 0.25 to 200 mg, 0.25 to 175 mg, 0.25 to 150 mg, 0.25 to 125 mg, 0.25 to 100 mg, 0.25 to 75 mg, 0.25 to 50 mg, 0.25 to 30 mg, 0.25 to 25 mg, 0.25 to 20 mg, 0.25 to 15 mg, 0.25 to 10 mg, 0.25 to 5 mg, 0.25 to 1mg, 0.05 to 500 mg, 0.5 to 450 mg, 0.5 to 300 mg, 0.5 to 250 mg, 0.5 to 200 mg, 0.5 to 175 mg, 0.5 to 150 mg, 0.5 to 125 mg, 0.5 to 100 mg, 0.5 to 75 mg, 0.5 to 50 mg, 0.5 to 30 mg, 0.5 to 25 mg, 0.5 to 20 mg, 0.5 to 15 mg, 0.5 to 10 mg, 0.5 to 5 mg, 0.5 to 1mg, 1 to 500 mg, 1 to 450 mg, 1 to 300 mg, 1 to 250 mg, 1 to 200 mg, 1 to 175 mg, 1 to 150 mg, 1 to 125 mg, 1 to 100 mg, 1 to 75 mg, 1 to 50 mg, 1 to 30 mg, 1 to 25 mg, 1 to 20 mg, 1 to 15 mg, 1 to 10 mg, 1 to 5 mg, 1 to 4 mg, 1 to 3 mg, 1 to 2 mg, 2 to 500 mg, 2 to 450 mg, 2 to 300 mg, 2 to 250 mg, 2 to 200 mg, 2 to 175 mg, 2 to 150 mg, 2 to 125 mg, 2 to 100 mg, 2 to 75 mg, 2 to 50 mg, 2 to 30 mg, 2 to 25 mg, 2 to 20 mg, 2 to 15 mg, 2 to 10 mg, 2 to 5 mg, 3 to 500 mg, 3 to 450 mg, 3 to 300 mg, 3 to 250 mg, 3 to 200 mg, 3 to 175 mg, 3 to 150 mg, 3 to 125 mg, 3 to 100 mg, 3 to 75 mg, 3 to 50 mg, 3 to 30 mg, 3 to 25 mg, 3 to 20 mg, 3 to 15 mg, 3 to 10 mg, 3 to 5 mg, 4 to 500 mg, 4 to 450 mg, 4 to 300 mg, 4 to 250 mg, 4 to 200 mg, 4 to 175 mg, 4 to 150 mg, 4 to 125 mg, 4 to 100 mg, 4 to 75 mg, 4 to 50 mg, 4 to 30 mg, 4 to 25 mg, 4 to 20 mg, 4 to 15 mg, 4 to 10 mg, 4 to 5 mg, 5 to 500 mg, 5 to 450 mg, 5 to 300 mg, 5 to 250 mg, 5 to 200 mg, 5 to 175 mg, 5 to 150 mg, 5 to 125 mg, 5 to 100 mg, 5 to 75 mg, 5 to 50 mg, 5 to 30 mg, 5 to 25 mg, 5 to 20 mg, 5 to 15 mg, 5 to 10 mg, 10 to 500 mg, 10 to 450 mg, 10 to 300 mg, 10 to 250 mg, 10 to 200 mg, 10 to 175 mg, 10 to 150 mg, 10 to 125 mg, 10 to 100 mg, 10 to 75 mg, 10 to 50 mg, 10 to 30 mg, 10 to 25 mg, 10 to 20 mg, 10 to 15 mg, 15 to 500 mg, 15 to 450 mg, 15

to 300 mg, 15 to 250 mg, 15 to 200 mg, 15 to 175 mg, 15 to 150 mg, 15 to 125 mg, 15 to 100 mg, 15 to 75 mg, 15 to 50 mg, 15 to 30 mg, 15 to 25 mg, 15 to 20 mg, 20 to 500 mg, 20 to 450 mg, 20 to 300 mg, 20 to 250 mg, 20 to 200 mg, 20 to 175 mg, 20 to 150 mg, 20 to 125 mg, 20 to 100 mg, 20 to 75 mg, 20 to 50 mg, 20 to 30 mg, 20 to 25 mg, 25 to 500 mg, 25 to 450 mg, 25 to 300 mg, 25 to 250 mg, 25 to 200 mg, 25 to 175 mg, 25 to 150 mg, 25 to 125 mg, 25 to 100 mg, 25 to 80 mg, 25 to 75 mg, 25 to 50 mg, 25 to 30 mg, 30 to 500 mg, 30 to 450 mg, 30 to 300 mg, 30 to 250 mg, 30 to 200 mg, 30 to 175 mg, 30 to 150 mg, 30 to 125 mg, 30 to 100 mg, 30 to 75 mg, 30 to 50 mg, 40 to 500 mg, 40 to 450 mg, 40 to 400 mg, 40 to 250 mg, 40 to 200 mg, 40 to 175 mg, 40 to 150 mg, 40 to 125 mg, 40 to 100 mg, 40 to 75 mg, 40 to 50 mg, 50 to 500 mg, 50 to 450 mg, 50 to 300 mg, 50 to 250 mg, 50 to 200 mg, 50 to 175 mg, 50 to 150 mg, 50 to 125 mg, 50 to 100 mg, 50 to 75 mg, 75 to 500 mg, 75 to 450 mg, 75 to 300 mg, 75 to 250 mg, 75 to 200 mg, 75 to 175 mg, 75 to 150 mg, 75 to 125 mg, 75 to 100 mg, 100 to 500 mg, 100 to 450 mg, 100 to 300 mg, 100 to 250 mg, 100 to 200 mg, 100 to 175 mg, 100 to 150 mg, 100 to 125 mg, 125 to 500 mg, 125 to 450 mg, 125 to 300 mg, 125 to 250 mg, 125 to 200 mg, 125 to 175 mg, 125 to 150 mg, 150 to 500 mg, 150 to 450 mg, 150 to 300 mg, 150 to 250 mg, 150 to 200 mg, 200 to 500 mg, 200 to 450 mg, 200 to 300 mg, 200 to 250 mg, 250 to 500 mg, 250 to 450 mg, 250 to 300 mg, 300 to 500 mg, 300 to 450 mg, 300 to 400 mg, 300 to 350 mg, 350 to 500 mg, 350 to 450 mg, 350 to 400 mg, 400 to 500 mg, 400 to 450 mg, with 0.01 mg, 0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 125 mg, 150 mg 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, and 500 mg being examples.

[0036] The pharmaceutical compositions may include (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) and one or more of (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3), (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4), (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (6), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8), or methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) are provided.

[0037] The pharmaceutical compositions may include (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid (1) and one or more of ethyl-cyclopent-3-ene-carboxylate (10), (3*R*,4*S*)-ethyl-3-((tert-butoxycarbonyl)amino)-4-(hydroxy)cyclopentane carboxylate (11), (3*R*)-ethyl-3-((tert-butoxycarbonyl)amino)-4-oxo-cyclopentane carboxylate (12), ethyl (9S)-9-(tert-butoxycarbonylamino)-1,4-dioxa-7-spiro[4.4]nonanecarboxylate (13), ethyl (S)-9-(tert-butoxycarbonylamino)-1,4-dioxa-7-spiro[4.4]nonene-7-carboxylate (14), or ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (15), are provided.

[0038] (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid may be an acid addition salt, a zwitter ion hydrate, zwitter ion anhydrate, hydrochloride or hydrobromide salt, or in the form of the zwitter ion monohydrate. Acid addition salts, include but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, pantothenic, p-amino-benzoic, glutamic, benzene sulfonic or theophylline acetic acid addition salts, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. In embodiments, inorganic acid addition salts, including but not limited to, hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric or nitric acid addition salts may be used.

[0039] In embodiments, (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3), (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4), (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (6), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7), (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8), or methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) may be provided as an acid addition salt, a zwitter ion hydrate, zwitter ion anhydrate, hydrochloride or hydrobromide salt, or in the form of the zwitter ion monohydrate. Acid addition salts, include but are not limited to, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethane-disulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, pantothenic, p-amino-benzoic, glutamic, benzene sulfonic or theophylline acetic acid addition salts, as well as the 8-halotheophyllines, for example 8-bromo-theophylline. In embodiments, inorganic acid addition salts, including but not limited to, hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric or nitric acid addition salts may be used.

[0040] Pharmaceutical compositions include various dosage forms including conventional formulations and modified release formulations. Such pharmaceutical compositions may be adapted for any suitable route of administration, e.g., oral, rectal, nasal, ophthalmic, pulmonary, vaginal, sublingual, transdermal, intravenous, intraarterial, intramuscular, intraperitoneal and subcutaneous routes. Suitable dosage forms include tablets, capsules, oral liquids, ophthalmic drops, ophthalmic ointments, ophthalmic gels, powders, aerosols, transdermal modalities such as topical liquids, patches, creams and ointments, parenteral formulations and suppositories.

[0041] Pharmaceutical compositions herein may be provided with conventional release or modified release profiles. Pharmaceutical compositions may be prepared using a pharmaceutically acceptable "carrier" composed of materials that are considered safe and effective. The "carrier" includes all components present in the pharmaceutical formulation other than the active ingredient or ingredients. The term "carrier" includes, but is not limited to, diluents, binders, lubricants, disintegrants, fillers, and coating compositions. Those with skill in the art are familiar with such pharmaceutical carriers and methods of compounding

pharmaceutical compositions using such carriers.

[0042] Pharmaceutical compositions herein are modified release dosage forms which provide modified release profiles. Modified release profiles may exhibit immediate release, delayed release, or extended release profiles. Conventional (or unmodified) release oral dosage forms such as tablets, capsules, suppositories, syrups, solutions and suspensions typically release medications into the mouth, stomach or intestines as the tablet, capsule shell or suppository dissolves, or, in the case of syrups, solutions and suspensions, when they are swallowed. The pattern of drug release from modified release (MR) dosage forms is deliberately changed from that of a conventional dosage form to achieve a desired therapeutic objective and/or better patient compliance. Types of MR drug products include orally disintegrating dosage forms (ODDFs) which provide immediate release, extended release dosage forms, delayed release dosage forms (e.g., enteric coated), and pulsatile release dosage forms.

[0043] An ODDF is a solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue. The disintegration time for ODDFs generally range from one or two seconds to about a minute. ODDFs are designed to disintegrate or dissolve rapidly on contact with saliva. This mode of administration can be beneficial to people who may have problems swallowing tablets whether it be from physical infirmity or psychiatric in nature. Some subjects with an eye disorder may exhibit such behavior. ODDF's can provide rapid delivery of medication to the blood stream through mucosa resulting in a rapid onset of action. Examples of ODDFs include orally disintegrating tablets, capsules and rapidly dissolving films and wafers.

[0044] Extended release dosage forms (ERDFs) have extended release profiles and are those that allow a reduction in dosing frequency as compared to that presented by a conventional dosage form, e.g., a solution or unmodified release dosage form. ERDFs provide a sustained duration of action of a drug. Suitable formulations which provide extended release profiles are well-known in the art. For example, coated slow release beads or granules ("beads" and "granules" are used interchangeably herein) in which any of the compounds described herein are applied to beads, e.g., confectioners nonpareil beads, and then coated with conventional release retarding materials such as waxes, enteric coatings and the like. In embodiments, beads can be formed in which any of the compounds described herein are mixed with a material to provide a mass from which the compound leaches out. In embodiments, the beads may be engineered to provide different rates of release by varying characteristics of the coating or mass, e.g., thickness, porosity, using different materials, etc. Beads having different rates of release may be combined into a single dosage form to provide variable or continuous release. The beads can be contained in capsules or compressed into tablets.

[0045] Modified dosage forms herein incorporate delayed release dosage forms having delayed release profiles. Delayed release dosage forms can include delayed release tablets or delayed release capsules. A delayed release tablet is a solid dosage form which releases a compound (or compounds) described herein are at a time other than promptly after administration. A delayed release capsule is a solid dosage form in which the drug is enclosed

within either a hard or soft soluble container made from a suitable form of gelatin, and which releases a drug (or drugs) at a time other than promptly after administration. For example, enteric-coated tablets, capsules, particles and beads are well-known examples of delayed release dosage forms. Enteric coated tablets, capsules and particles and beads pass through the stomach and release the drug in the intestine. In embodiments, a delayed release tablet is a solid dosage form containing a conglomerate of medicinal particles that releases a drug (or drugs) at a time other than promptly after administration. In embodiments, the conglomerate of medicinal particles are covered with a coating which delays release of the drug. In embodiments, a delayed release capsule is a solid dosage form containing a conglomerate of medicinal particles that releases a drug (or drugs) at a time other than promptly after administration. In embodiments, the conglomerate of medicinal particles are covered with a coating which delays release of the drug.

[0046] Delayed release dosage forms are known to those skilled in the art. For example, coated delayed release beads or granules in which any of the compounds described herein are applied to beads, e.g., confectioners nonpareil beads, and then coated with conventional release delaying materials such as waxes, enteric coatings and the like. In embodiments, beads can be formed in which any of the compounds described herein are mixed with a material to provide a mass from which the drug leaches out. In embodiments, the beads may be engineered to provide different rates of release by varying characteristics of the coating or mass, e.g., thickness, porosity, using different materials, etc. In embodiments, enteric coated granules of any of the compounds described herein can be contained in an enterically coated capsule or tablet which releases the granules in the small intestine. In embodiments, the granules have a coating which remains intact until the coated granules reach at least the ileum and thereafter provide a delayed release of the drug in the colon. Suitable enteric coating materials are well known in the art, e.g., Eudragit® coatings such methacrylic acid and methyl methacrylate polymers and others. The granules can be contained in capsules or compressed into tablets Any of the compounds described herein are incorporated into porous inert carriers that provide delayed release profiles. In embodiments, the porous inert carriers incorporate channels or passages from which the drug diffuses into surrounding fluids. In embodiments, any of the compounds described herein are incorporated into an ion-exchange resin to provide a delayed release profile. Delayed action may result from a predetermined rate of release of the drug from the resin when the drug-resin complex contacts gastrointestinal fluids and the ionic constituents dissolved therein. In embodiments, membranes are utilized to control rate of release from drug containing reservoirs. In embodiments, liquid preparations may also be utilized to provide a delayed release profile. For example, a liquid preparation consisting of solid particles dispersed throughout a liquid phase in which the particles are not soluble. The suspension is formulated to allow at least a reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form). For example, a suspension of ion-exchange resin constituents or microbeads.

[0047] Pharmaceutical compositions described herein are suitable for ophthalmic or parenteral administration, including, e.g., intramuscular (i.m.), intravenous (i.v.), subcutaneous (s.c.),

intraperitoneal (i.p.), or intrathecal (i.t.). Parenteral or ophthalmic compositions must be sterile for administration by injection, infusion, instillation or implantation into the body and may be packaged in either single-dose or multi-dose containers. In embodiments, liquid pharmaceutical compositions for ophthalmic or parenteral administration to a subject include an active substance, e.g., any of the compounds described herein are in any of the respective amounts described above. In embodiments, the pharmaceutical compositions for ophthalmic or parenteral administration are formulated as a total volume of about, e.g., 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 7.5 ml, 10 ml, 20 ml, 25 ml, 50 ml, 100 ml, 200 ml, 250 ml, or 500 ml. In embodiments, the compositions are contained in a bag, a glass vial, a plastic vial, or a bottle.

[0048] Pharmaceutical compositions for ophthalmic or parenteral administration include respective amounts described above for any of the compounds described herein. In embodiments, pharmaceutical compositions for ophthalmic or parenteral administration include about 0.0001 mg to about 500 mg of any of the compounds described herein. In embodiments, pharmaceutical compositions for ophthalmic or parenteral administration to a subject may include any of the compounds described herein, at a respective concentration of about 0.005 mg/ml to about 500 mg/ml. In embodiments, the pharmaceutical composition for ophthalmic or parenteral administration includes any of the compounds described herein at a respective concentration of, *e.g.,* about 0.05 mg/ml to about 50 mg/ml, about 0.1 mg/ml to about 50 mg/ml, about 0.1 mg/ml to about 10 mg/ml, about 0.05 mg/ml to about 25 mg/ml, about 0.05 mg/ml to about 10 mg/ml, about 0.05 mg/ml to about 5 mg/ml, or about 0.05 mg/ml to about 1 mg/ml. In embodiments, the pharmaceutical composition for ophthalmic or parenteral administration includes any of the compounds described herein at a respective concentration of, *e.g.,* about 0.05 mg/ml to about 15 mg/ml, about 0.5 mg/ml to about 10 mg/ml, about 0.25 mg/ml to about 5 mg/ml, about 0.5 mg/ml to about 7 mg/ml, about 1 mg/ml to about 10 mg/ml, about 5 mg/ml to about 10 mg/ml, or about 5 mg/ml to about 15 mg/ml.

[0049] A pharmaceutical composition for ophthalmic or parenteral administration is described wherein the pharmaceutical composition is stable for at least six months. In embodiments, the pharmaceutical compositions for ophthalmic or parenteral administration exhibit no more than about 5% decrease in active substance, *e.g.,* (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt of thereof, *e.g.,* 3 months or 6 months. In embodiments, the amount of ((*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof, degrades at no more than about, *e.g.,* 2.5%, 1%, 0.5% or 0.1%. In embodiments, the degradation is less than about, *e.g.,* 5%, 2.5%, 1%, 0.5%, 0.25%, 0.1%, for at least six months.

[0050] Pharmaceutical compositions for ophthalmic or parenteral administration are described wherein the pharmaceutical composition remains soluble. In embodiments, pharmaceutical compositions for ophthalmic or parenteral administration are provided that are stable, soluble, local site compatible and/or ready-to-use. In embodiments, the pharmaceutical compositions herein are ready-to-use for direct administration to a subject in need thereof.

[0051] The pharmaceutical compositions for ophthalmic or parenteral administration described

herein may include one or more excipients, e.g., solvents, solubility enhancers, suspending agents, buffering agents, isotonicity agents, stabilizers or antimicrobial preservatives. When used, the excipients of the ophthalmic or parenteral compositions will not adversely affect the stability, bioavailability, safety, and/or efficacy of any of the compounds described herein used in the composition. Thus, ophthalmic or parenteral compositions are provided wherein there is no incompatibility between any of the components of the dosage form.

[0052] Ophthalmic or parenteral compositions including any of the compounds described herein include a stabilizing amount of at least one excipient. For example, excipients may be selected from the group consisting of buffering agents, solubilizing agents, tonicity agents, antioxidants, chelating agents, antimicrobial agents, and preservatives. One skilled in the art will appreciate that an excipient may have more than one function and be classified in one or more defined group Ophthalmic or parenteral compositions any of the compounds described herein and an excipient wherein the excipient is present at a weight percent (w/v) of less than about, *e.g.,* 10%, 5%, 2.5%, 1%, or 0.5%. In embodiments, the excipient is present at a weight percent between about, e.g., 1.0% to 10%, 10% to 25%, 15% to 35%, 0.5% to 5%, 0.001% to 1%, 0.01% to 1%, 0.1% to 1%, or 0.5% to 1%. In embodiments, the excipient is present at a weight percent between about, *e.g.,* 0.001% to 1%, 0.01% to 1%, 1.0% to 5%, 10% to 15%, or 1% to 15%.

[0053] Ophthalmic or parenteral compositions of any of the compounds described herein are provided, wherein the pH of the composition is between about 4.0 to about 8.0. In embodiments, the pH of the compositions is between, *e.g.,* about 5.0 to about 8.0, about 6.0 to about 8.0, about 6.5 to about 8.0. In embodiments, the pH of the compositions is between, *e.g.,* about 6.5 to about 7.5, about 7.0 to about 7.8, about 7.2 to about 7.8, or about 7.3 to about 7.6. In embodiments, the pH of the aqueous solution is, *e.g.,* about 6.8, about 7.0, about 7.2, about 7.4, about 7.6, about 7.7, about 7.8, about 8.0, about 8.2, about 8.4, or about 8.6.

[0054] Pharmaceutical compositions including (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof, provide an *in vivo* plasma profile having a C_{max} of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid less than about, *e.g.,* 2000 ng/ml, 1000 ng/ml, 850 ng/ml, 800 ng/ml, 750 ng/ml, 700 ng/ml, 650 ng/ml, 600 ng/ml, 550 ng/ml, 450 ng/ml, 400 ng/ml 350 ng/ml, or 300 ng/ml. In embodiments, the pharmaceutical composition provides an *in vivo* plasma profile having a C_{max} less than about, *e.g.,* 250 ng/ml, 200 ng/ml 150 ng/ml, or 100 ng/ml.

[0055] In embodiments, provided herein are pharmaceutical compositions containing (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein, wherein the composition provides a consistent *in vivo* plasma profile of (S)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid having a $AUC_{0-\infty}$ of less than about 900 ng•hr/ml.

[0056] The T_{max} of pharmaceutical compositions containing (*S*)-3-amino-4-

(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein is less than 3 hours. In embodiments, the T_{max} of the pharmaceutical composition is less than 2.5 hours. In embodiments, the T_{max} of the pharmaceutical composition is less than 2 hours. In embodiments, the T_{max} of the pharmaceutical composition is less than 1.5 hours. In embodiments, the T_{max} of the pharmaceutical composition is less than 1 hour. In embodiments, the T_{max} of the pharmaceutical composition is less than 0.5 hour. In embodiments, the T_{max} of the pharmaceutical composition is less than 0.25 hour.

[0057] Described herein are pharmaceutical compositions containing (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein provide a dissolution of at least about 80% within the first 20 minutes of administration to a subject in need thereof. In embodiments, pharmaceutical compositions containing (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein provide a dissolution of at least about, *e.g.,* 85%, 90% or 95% within the first 20 minutes of administration to a subject in need thereof. In embodiments, pharmaceutical compositions containing (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein provide a dissolution of at least 80% within the first 10 minutes of administration to a subject in need thereof.

[0058] It should be understood that respective amounts of (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof and one or more of any of the compounds described herein are applicable to all the dosage forms described herein including conventional dosage forms, modified dosage forms, as well as the ophthalmic and parenteral formulations described herein. Those skilled in the art will determine appropriate amounts depending on criteria such as dosage form, route of administration, subject tolerance, efficacy, therapeutic goal and therapeutic benefit, among other pharmaceutically acceptable criteria.

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosure herein belongs.

[0060] The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, up to 10%, up to 5%, and/or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

[0061] "PK" refers to the pharmacokinetic profile. C_{max} is defined as the highest plasma drug concentration estimated during an experiment (ng/ml). T_{max} is defined as the time when C_{max} is estimated (min). $AUC_{0-\infty}$ is the total area under the plasma drug concentration-time curve, from drug administration until the drug is eliminated (ng·hr/ml). The area under the curve is governed by clearance. Clearance is defined as the volume of blood or plasma that is totally cleared of its content of drug per unit time (ml/min).

[0062] "Pharmaceutically acceptable" refers to molecular entities and compositions that are "generally regarded as safe"-e.g., that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset and the like, when administered to a human. In embodiments, this term refers to molecular entities and compositions approved by a regulatory agency of the federal or a state government, as the GRAS list under section 204(s) and 409 of the Federal Food, Drug and Cosmetic Act, that is subject to premarket review and approval by the FDA or similar lists, the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0063] "Effective amount" or "therapeutically effective amount" means a dosage sufficient to alleviate one or more symptoms of a disorder, disease, or condition being treated.

[0064] "Co-administered with", "co-therapy", "in combination with", "a combination of", "combined with" or "administered along with" may be used interchangeably and mean that two or more agents are administered in the course of therapy. The agents may be administered together at the same time or separately in spaced apart intervals. The agents may be administered in a single dosage form or in separate dosage forms.

[0065] "Patient in need thereof' includes individuals that have been diagnosed with a disease, condition or disorder for which treatment with (*S*)-3-amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic acid, or a pharmaceutically acceptable salt thereof is indicated. "Patient" and "subject" are used interchangeably herein.

EXAMPLES

[0066] The Examples provided herein are included solely for augmenting the disclosure herein and should not be considered to be limiting in any respect.

Methods In General

[0067] (1*R*,4*S*)-2-Azabicyclo[2.2.1]hept-5-en-3-one (2) was purchased from Acella Chembio, San Diego, CA 92121 or AK Scientific, Inc., Union City, CA 94587. 4-Methoxybenzyl chloride

was purchased from AK Scientific, Inc., Union City, CA 94587. 2-(difluoromethyl)sulfmyl)pyridine (20) was either purchased from Enamine Chemicals, Monmouth Jct., NJ 08852, Sigma-Aldrich Corp, St Louis, MO, or synthesized from diethyl bromodifluoromethylphosphonate and 2-mercaptopyridine. See, Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. Angew. Chem. Int. Ed. 2013, 52, 3949-3952. 1,3-dibromo-5,5-dimethylhydantoin was purchased from Acros Organics division of Thermo Fisher Scientific, Waltham, MA 02451. TPAP was purchased from Combi Blocks, Inc. San Diego, CA 92126. Cerium ammonium nitrate was purchased from Alfa Aesar, Ward Hill, MA 01835. All other reagents were purchased from Sigma-Aldrich, Fisher Scientific or Acros Organics and used without further purification. Anhydrous solvents (THF, CH_2Cl_2, DMF) were purified before use by passing through a column composed of activated alumina and a supported copper redox catalyst. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material. Analytical thin-layer chromatography (TLC) was performed using Merck Silica Gel 60 Å F-254 precoated plates (0.25 mm thickness), and components were visualized by ultraviolet light (254 nm) and/or ceric ammonium molybdate stain. Flash column chromatography was performed on a Teledyne Combiflash Rf Plus automated flash purification system with various Teledyne cartridges (4-80 g, 40-63 µm, 60 Å). Purifications were performed with hexanes and ethyl acetate unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III NMR spectrometer at 500 MHz and 126 MHz, respectively, in $CDCl_3$ or D_2O. Chemical shifts were reported in ppm, multiplicities are indicated by s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad resonance. Coupling constants were reported in Hz. High resolution mass spectral data were obtained on an Agilent 6210 LC-TOF spectrometer in the positive ion mode using electrospray ionization with an Agilent G1312A HPLC pump and an Agilent G1367B autoinjector at the Integrated Molecular Structure Education and Research Center (IMSERC), Northwestern University. Analytical HPLC was performed by using a reserved-phase Agilent Infinity 1260 HPLC with a Phenomenex Kintex C-18 column (50 x 2.1 mm, 2.6 µm), detecting with UV absorbance at 254 nm.

Example 1

Manufacture of (1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3)

Method A

[0068] 4-Methoxybenzyl alcohol (35.80 mL, 0.29 mol, 1.5 equiv) was added dropwise to concentrated HCl (300 mL) and stirred for 1 h. Water was added, and the liquid was extracted (2 x 100 mL) with diethyl ether. The diethyl ether was dried over Na_2SO_4 and concentrated to a

volume of about 50 mL. To a 2 L flask, equipped with an addition funnel, was added (1R,4S)-2-azabicyclo[2.2.1]hept-5-en-3-one (21.00 g, 0.19 mol), DMF (600 mL), and THF (600 mL), and the flask was cooled to 0 °C. NaH (8.45 g, 0.21 mol, 1.1 equiv, 60% dispersion in mineral oil) was added portionwise. The flask was placed under N2 and stirred for 30 min. The Et2O/PMBCl solution was transferred to the addition funnel and was added dropwise at 0 °C. The reaction was stirred for 6 h at room temperature. Upon completion, THF was removed *in vacuo,* and diethyl ether and water were added. Any solids were filtered, and the layers were separated. The aqueous layer was extracted (3 x 100 mL) with diethyl ether, and the organic layers were combined and washed with brine (2 x 200 mL). After drying over Na2SO4 and concentration, a yellow oil was obtained. The crude oil was purified by flash chromatography to yield 32.2 g (0.14 mol, 73% yield) of protected (1R,4S)-2-azabicyclo[2.2.1]hept-5-en-3-one (3). Spectra matched those in the literature. See, Qiu, J.; Silverman, R. B. J. Med. Chem. 2000, 43, 706-720.

Method B

[0069] A dry 2-liter 3-neck round bottom flask was fitted with an overhead stirrer/ Teflon® paddle, 500 ml dropping funnel, and a serum cap/Type-K thermocouple /N_2 needle. *(1R4S)*-(-)-2-Aza-bicyclo[2.2.1]hept-5-en-3-one, **(-)-2** (25 gm, 229 mmol, 1 equiv) was dissolved in anhydrous THF (600 ml) in the flask and the dropping funnel charged with the LiHMDS solution (1M soln. in toluene). The flask contents were cooled to -40 °C and the LiHMDS solution (252 ml, 252 mmol, 1.2 equiv) was added in drop by drop into the flask keeping the temperature around -35 to 40 °C. The flask content started to thicken and became a thin gel towards the end of the base addition. The reaction mixture was stirred for further 1 hour after the LiHMDS had all been added, and then the 500 ml dropping funnel was removed and replaced with a smaller 125 ml dropping funnel charged with 4-methoxybenzyl chloride (37.2 gm, 240.5 mmol, 1.05 equiv). The halide was added into the reaction flask dropwise. When approximately ¼ of the chloride had been added, tetrabutylammonium iodide powder (1.3 g, 3.44 mmol, 0.015 equiv) was added in a single portion. When all the 4-methoxybenzyl chloride was added the flask was warmed to room temperature initially and then warmed to 60 °C in an heating mantle. The progress of the benzylation reaction was followed over time by hplc and by lcms. The reaction was worked up after 2 days at 60 °C when the reaction had reached -85% conversion to lactam (-)(1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-one (3). The fine solid precipitate in the reaction solution was removed by filtering through a large 17 cm Buchner funnel/ filter paper under vacuum. The residues were washed with THF (200 ml) and also collected with the original filtrate and the combined golden yellow filtrates were concentrated (rotary evaporator/vacuum/ water bath at 40 °C). The residual golden oil was dissolved in EtOAc (350 ml) and washed with water (250 ml). After the phase split, the aqueous layer was back extracted with EtOAc (2 x 100 ml). The EtOAc layers were combined and dried over anhydrous Na_2SO_4 powder, filtered and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid. This crude product was purified by chromatography on the Biotage with a 340 g silica column and an EtOAc-hexanes gradient [15% (2 CV) 15-75% (8 CV)

100% (3 CV)] with fractions collected in 25 x 150 mm tubes. The product containing fractions were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid which was pumped down on the vacuum line for several hours.

Method C

[0070] NaH (40.3 g, 1.01 mol, 60% purity, 1.1 equiv) and Bu_4NI (16.9 g, 45.8 mmol, 0.05 equiv) were added to THF (300 mL), then a solution of (1R,4S)-2-azabicyclo[2.2.1]hept-5-en-3-one (100.0 g, 916.3 mmol, 1 equiv) in DMF (900 mL) was added dropwise to the mixture at 0°C. The mixture was stirred for 0.5 h, and para-methoxybenzyl chloride (215.2 g, 1.37 mol, 186.5 mL, 1.50 equiv) was added dropwise to the above mixture at 0 °C. The mixture was stirred at 25 °C for 1 h. TLC (petroleum ether: ethyl acetate = 1:1, R_f = 0.20) showed the reactants were consumed completely. The mixture was diluted with MTBE (2 L) and water (3.5 L) was added. Any solids were filtered, and the layers were separated. The aqueous layer was extracted with MTBE (800 mL x 2) and the organic layers were combined and washed with brine (1 L x 2). The combined organic layers were dried over anhydrous Na2SO4 and concentrated to give a residue as a yellow oil. The residue was purified by column chromatography on silica gel with petroleum ether: ethyl acetate (10:1~1:1) to give a yellow oil. The crude (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3) (89.5 g, 390.3 mmol, 42.6% yield) was obtained as a yellow oil, which was used in the next step without further purification.

Example 2

Manufacture of (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4)

Method A

[0071] To a solution of (1*R*,4*S*)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (3), (10.00 g, 43.62 mmol) in AcOH (110.0 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (7.48 g, 26.17 mmol, 0.6 equiv). The reaction was stirred for 6 h, and upon completion, water was added. The aqueous layer was extracted with diethyl ether (3 x 200 mL), and the organic layers were combined, washed with 1 M NaOH, dried over Na_2SO_4, and concentrated. Purification by flash chromatography yielded (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) (14.40 g, 39.25 mmol, 90% yield) as a thick oil. Spectra matched those in the literature. See, Qiu, J.; Silverman, R. B. J. Med. Chem. 2000, 43, 706-720.

Method B

[0072] (1*R*, 4*R*)-(-)-2-(4-Methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (15.5 g, 67.60 mmol, 1 equiv) was dissolved in glacial acetic acid (125 ml) in a 250 ml round bottom flask with a stir-bar. 1,3-Dibromo-5,5-di-methylhydantoin (9.7 g, 33.43 mmol, 0.5 equiv) was added to the acidic solution in multiple batches in 10 minutes at room temperature. A serum cap/nitrogen needle was placed in the neck of the flask and the reaction mixture was stirred overnight at room temperature. In 20 minutes, after all the dibromide was added, the initial cloudy yellow solution turned clear golden yellow. The progress of the reaction was monitored by hplc and by lcms. After stirring overnight the reaction solvent was removed (rotary evaporator/vacuum / water bath at 55 °C to afford a dark golden yellow liquid that was then dissolved in dichloromethane (200 ml). Water was added (100 ml), and the mixture transferred into a 1-L Erlenmeyer flask. 10% Sodium sulfite solution (75 ml) was added and stirred vigorously in the conical flask for a ½-hour to destroy unreacted dibromohydantoin. More water (100 ml) was added and this was followed by 3M sodium hydroxide, added slowly and swirled in the conical flask, to bring the aqueous layer to pH= 7 (pH paper). The flask contents were transferred into in a 1-L separatory funnel; the conical flask was rinsed with dichloromethane (100 ml) and the rinse was combined in the funnel. The dichloromethane layer from the phase split was saved, the aqueous layer was back extracted with dichloromethane (2 x 100 ml) and combined with the original saved extract which were washed with satd. $NaHCO_3$ (250 ml), water (250 ml) and brine (250 ml). The organic phase was dried with anhydrous Na_2SO_4 powder, filtered and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid. This crude product was purified by chromatography on the Biotage with a 340 g silica column and a EtOAc-hexanes gradient [15% (1 CV) 15-75% (7.5 CV) 100% (3 CV)], fractions collected in 25 x 150 mm tubes. The fractions containing the product were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to give a golden yellow liquid which was pumped down further on the vacuum line for several hours, thus yielding purified (1*R*,4*R*,6S,7*R*)-(+)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]-heptan-6-yl acetate (4) (23 g; 82%).

Example 3

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5)

Method A

[0073] (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl

acetate (4) (12.8 g, 34.7 mmol) was dissolved in MeOH (270 mL) and K_2CO_3 (14.40 g, 104.28 mmol, 3.0 equiv) was added. The reaction was stirred for 1 h, filtered, and then concentrated. Ethyl acetate and water were added, and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated to yield an off-white colored solid ((1*R*,4*R*,6*S*,7*R*)-7-Bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one) (25), which was used directly in the next step.

[0074] This compound was placed in a 500 mL flask and purged with argon. Dichloromethane (170 mL) was added followed by 4 Å molecular sieves (10 g). TPAP (122.2 mg, 0.35 mmol. 0.01 equiv) and NMO (8.14 g, 69.52 mmol, 2.0 equiv) were then added, and the reaction mixture was stirred overnight. The reaction mixture was then filtered and concentrated to a volume of 20 mL and loaded directly onto a flash chromatography column. The resulting yellowish solid can be recrystallized from hexanes/ethyl acetate to obtain a white powder (1R,4R,7R)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) (5.96 g, 18.38 mmol, 52% yield). Spectra matched those in the literature. See, Qiu, J.; Silverman, R. B. J. Med. Chem. 2000, 43, 706-720.

Method B

[0075] (1*R*,4*R*,6*S*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl acetate (4) (25.5 g, 69.2 mmol) was dissolved in MeOH (300 mL) and K_2CO_3 (30 g, 0.23 mol, 3 equiv) was added. The reaction was stirred for 1 h, filtered, and then concentrated. Ethyl acetate and water were added, and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated to yield an off-white colored solid ((1*R*,4*R*,6*S*,7*R*)-7-Bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one), which was used directly in the next step.

[0076] A three-neck flask was equipped with a vent line to a bubble, dropping funnel with nitrogen inlet, and septum. Dichloromethane (160 mL) was added, and the flask was purged with nitrogen. Oxalyl chloride (8.40 mL, 98.0 mmol, 1.4 equiv) was added, and the reaction was cooled to -78 °C. DMSO (11.60 mL, 0.16 mol, 2.3 equiv) was added to the addition funnel and then added dropwise slowly at a rate to control the vigorous gas evolution. After addition, the reaction was stirred at -78 °C for 10 min. The deacylated material was dissolved in dichloromethane (160 mL) and added slowly to the reaction via addition funnel. The reaction was stirred for 10 min at -78 °C. Triethylamine (68.3 mL, 0.49 mol, 7 equiv) was then added dropwise via addition funnel. Upon completion, the reaction was stirred at -78 °C for 10 min, warmed to room temp, and quenched with 1 M HCl. After separation, the organic layer was dried over Na2SO4 and concentrated in a fume hood. Purification via flash chromatography yielded (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) as a beige solid (13.5 g, 41.7 mmol, 60% yield).

Method C

[0077] To (1*R*,4*R*,6*S*,7*R*)-7-bromo-2-(4-methoxybenzyl)-3-oxo-2-zabicyclo[2.2.1]heptan-6-yl acetate (4) (96.5 g, 262.0 mmol, 1 equiv) in MeOH (680 mL) was added K_2CO_3 (108.6 g, 786.2 mmol, 3 equiv). The mixture was stirred at 25 °C for 1 h. TLC (petroleum ether: ethyl acetate = 1:1, R_f = 0.65) showed that the reaction was complete. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a black brown solid. MTBE (500 mL) was added to the brown solid, and the mixture was stirred for 3 h, then filtered to give a filtrate, which was concentrated under reduced pressure to give the crude product. The crude compound (76.5 g, 234.5 mmol, 89.5% yield) was obtained as an off-white solid, which was used in the next step without further purification.

[0078] The above crude compound (76.5 g, 234.5 mmol, 1 equiv) was added to MeCN (400 mL). IBX (65.6 g, 234.5 mmol, 1.0 equiv) was added in one portion to the above mixture at 20-30 °C for 0.5 h. The reaction mixture was stirred at 75-80 °C for 2 h after which time a TLC (petroleum ether: ethyl acetate = 3:1, R_f = 0.23) showed the reaction was completed. The mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel with petroleum ether: ethyl acetate (20:1~1:1) to give (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) (48.5 g, 149.6 mmol, 63.7% yield) as an off-white solid.

Example 3(a)

Manufacture of (1*R*,4*R*,6*S*,7*R*)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[22.1]heptan-3-one (25)

[0079] (1*R*,4*R*,6*S*,7*R*)-(+)-7-Bromo-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo-[2.2.1]-heptan-6-yl acetate (4) (22.25 g, 60.42 mmol, 1 equiv) was dissolved in a solvent mixture of methanol (120 ml) and water (15 ml) in a 500 ml round bottom flask. Potassium carbonate powder (12.5 g, 90.45 mmol, 1.5 equiv) was added into the golden yellow solution and the resulting cloudy reaction mixture was sealed with a serum cap/N_2 needle and stirred overnight at room temperature. The progress of the reaction was monitored by lcms and by hplc. The reaction was worked up by evaporating the volatiles (rotary evaporator/vacuum/water bath at 40 °C). Distilled water (200 ml) was added to the dark golden yellow oil obtained from the evaporation. The pH of the aqueous layer was adjusted to pH= 7 with 1M hydrochloric acid and the product extracted into dichloromethane (200 ml, then 2 x 150 ml). The dichloromethane extracts were combined and washed with water (200 ml), brine (250 ml), dried with Na2SO4 powder. The dried extract was filtered and the spent drying agent was rinsed with dichloromethane (2 x 50 ml) and the combined extracts were concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow oil. The golden yellow product was split into two roughly equal portions and each portion was purified by chromatography on the Biotage on a 100 g silica column, with

an EtOAchexanes gradient [20% (1 CV) 20-100% (7 CV) 100% (5 CV)], fractions collected in 25 x 150 mm tubes. The product fractions were combined and concentrated (rotary evaporator/vacuum/water bath at 40 °C) to a golden yellow liquid which was pumped down on the vacuum line for several hours. The two chromatography purified samples (20 g) were combined and crystallized from hexanes-EtOAc. A first crop of crystals was collected (17 g). The mother liquors were concentrated and crystallized from hexanes-EtOAc to provide a second crop of crystals (2 g). (1*R*,4*R*,6S,7*R*)-(+)-7-Bromo-6-hydroxy-2-(4-methoxybenzyl)-2-aza-bicyclo [2.2.1]heptan-3-one (25) was obtained as a white crystalline powder (total of -15 g; 75 %).

Example 3(b)

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) by Swern Oxidation

[0080] A 1-liter 3-neck round bottom flask, fitted with overhead stirrer, 50 ml dropping funnel and serum cap/thermocouple/Nz needle, was charged with a solution of oxalyl chloride (3.4 g (2.3 ml), 1.25 equiv) and dichloromethane (90 ml), and the stirred acid chloride solution was cooled in an acetone/CO_2 cooling bath to -60 °C. The dropping funnel was charged with a solution of DMSO (2.6 g(2.35 ml), 1.5 equiv) in dichloromethane (18 ml) which was added into the cold acid chloride solution in 3 minutes. The resulting mixture was stirred for 7 minutes at -60 °C and then to the solution, (1*R*,4*R*,6*S*,7*R*)-(+)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (25) (7.2 g, 22.1 mmol, 1 equiv) was added in 10 minutes. The reaction mixture was kept at -60 °C for 25 minutes and then neat trimethylamine (21.5 ml, 7 equiv) was placed in the dropping funnel and added into the flask. The resulting milky white solution was kept cold for 1 hour, the reaction checked by hplc/lcms and then the reaction was allowed to warm to room temperature in 2.5 hours before the work up. Saturated brine (125 ml) was added to the flask followed by diethyl ether (125 ml) in the work up The quenched reaction was transferred into a 1-L separating funnel. The upper layer was saved and the aqueous lower layer was extracted with diethyl ether (2 x 125 ml). These ethereal extracts were combined with the original extract and this was then washed with 1 M hydrochloric acid (125 ml), brine (125 ml) and water (50 ml). The organic phase was dried over anhydrous Na_2SO_4 powder, filtered and the filter cake washed with dichloromethane (2 x 50 ml) and the wash combined with the filtrate. The volatiles were removed (rotary evaporator/vacuum/ water bath at 40 °C) to afford a yellow liquid that solidified on standing. The solid was crystallized from EtOAchexanes and afforded a 1st crop (5.31 g). The mother liquors were concentrated and crystallized to give a 2nd crop (1.36 g). The mother liquors from the 2nd crystallization were purified on the Biotage with a 25g silica column eluted with EtOAc-hexanes gradient [20% (2 CV), 20-100% (8 CV), 100% (2 CV)] fractions collected in 16 x 150 mm tubes. From the chromatography 250 mg of product was obtained. The combined yield of (1*R*,4*R*,7*R*)-(+)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) was 6.8 g (94% yield).

Example 3(c)

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) by TPAP Oxidation

[0081] A 2-liter 3-neck round bottom flask fitted with overhead stirrer and serum cap/thermocouple/Nz needle was charged with (1*R*,4*R*,6*S*,7*R*)-(+)-7-bromo-6-hydroxy-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]-heptan-3-one (25) (12 g, 36.8 mmol, 1 equiv), 4-morpholine-N-oxide (12.9 g, 110 mmol, 3 equiv), and 4A molecular sieve powder in methylene chloride (400 ml). A catalytic amount of TPAP (25 mg, 0.07 mmol, 0.002 equiv) was then added. The solution was stirred under a nitrogen at room temperature as a green solution which darkened over time. The reaction was monitored daily by lc-ms. On day 2, the reaction had stalled and the reaction was filtered through Celite® pad using a filter flask and vacuum source. The solution was returned to the 2-liter 3-neck round bottom reaction flask and fresh 4-morpholine-N-oxide (5.5 g), 4A molecular sieve powder (10 g) and TPAP (25 mg). The reaction had stalled late on Day 3 and the reaction was filtered and restarted with fresh NMO (5.5 g), 4A-sieves (10 g) and TPAP (25 mg). At the end of Day 4 there was ~ 7% bromoalcohol left and so the TPAP oxidation reaction was worked up. The solids in the reaction solution were removed by filtering with a plastic sinter funnel packed with ½-cm sand, ½-cm anhydrous Na2SO4 powder and 1-cm depth of Celite using a Buchner flask and vacuum source. The filter cake was washed with dichloromethane (2 x 100 ml and 50 ml) until the filtrate stream was colorless. The filtrate was concentrated to a dark golden oil (rotary evaporator/vacuum/ water bath at 40 °C) which showed signs of solidifying on the glass surface. The crude product was split into half and each half underwent chromatography on the Biotage on silica gel (100 g) eluted with a EtOAc-hexanes gradient 20% (ICV), 20-100% (7.5 CV) and 100% (4CV) collecting fractions in 25 x 150 mm tubes. The product fractions from the two chromatographies were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to afford a white powder.

[0082] The powder was crystallized from EtOAc-hexanes affording a 1st crystal crop (8.5 g). The mother liquors were concentrated and crystallized to give a 2nd crop (1.5 g). The combined yield of (1*R*,4*R*,7*R*)-(+)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) was 10 g (80%).

Example 4

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6)

Method A

[0083] (1*R*,4*R*,7*R*)-7-Bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) (1.00 g, 3.09 mmol) and 2-((difluoromethyl)sulfinyl)pyridine (20), (715.10 mg, 3.70 mmol, 1.2 equiv) were added to a round bottom flask and purged with argon. DMF (15 mL) was added, and the reaction was cooled to between -55 and -65 °C. KO^{t}Bu (623.0 mg, 5.55 mmol, 1.8 equiv, 0.5 M in DMF) was added via syringe pump over 1 h. The temperature was maintained between -55 and -65 °C. After addition was complete, the reaction was further stirred for 30 min at -60 °C. Saturated NH_4Cl (5.00 mL) was added, and the reaction was stirred for 5 min at -60 °C before 6 M HCl (5.00 mL) was added. After 5 min of stirring at -60 °C, the reaction mixture was warmed to room temperature and then to 65 °C for 1 h. After being cooled, the reaction was diluted with brine, extracted with ethyl acetate (2 x 20 mL), and washed with brine (10 mL). Drying over Na_2SO_4 and concentration yielded a yellow oil, which was purified via flash chromatography to yield a white solid (620.0 mg, 1.73 mmol, 58% yield).
$[\alpha]_D^{23°C} = -46.64$
(c 0.80, $CHCl_3$); **m.p.** 85-87 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 (d, *J*= 8.4 Hz, 1H), 6.86 (d, *J*= 8.5 Hz, 1H), 4.60 (d, *J*= 14.6 Hz, 1H), 4.19 (s, 0H), 4.14 (s, 0H), 3.90 (d, *J*= 14.7 Hz, 1H), 3.79 (s, 1H), 3.00 (s, 0H), 2.83 (dq, *J*= 14.6, 3.0 Hz, 1H), 2.27 (d, *J*= 15.2 Hz, 1H). See, FIG. 1. 13C NMR (126 MHz, $CDCl_3$) δ 173.0, 159.5, 153.9 (dd, *J*= 287.5, 283.8 Hz), 129.7, 127.5, 114.3, 87.1 (dd, *J* = 24.9, 23.5 Hz), 63.4, 63.3, 55.3, 50.8 (d, *J* = 17.1 Hz), 44.6, 24.8. See, FIG. 2. 19F NMR (376 MHz, $CDCl_3$) δ -88.15 (dp, *J* = 55.1, 2.7 Hz), -88.88 (dq, *J* = 54.8, 2.8 Hz). See, FIG. 3. **IR** (film, cm^{-1}) 3013, 1785, 1683, 1551; **HMRS (ESI$^+$)** calc'd for $C_{15}H_{14}BrF_2NO_2$+Na^+: 380.0074; found 380.0075.

Method B

[0084] 2-(Difluoromethylsulfonyl)pyridine (20) (2.5 gm, 12.94 mmol, 1.2 equiv) and (1*R*,4*R*,7*R*)-(+)-7-Bromo-2-(4-methoxy-benzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) (3.5 gm, 10.8 mmol, 1 equiv) were combined in a round bottom flask with stir bar to which dimethylformamide (32 ml) was added. The resulting yellow solution was sealed with a serum cap/N_2 needle/thermocouple and cooled to -40 °C. Potassium bis(trimethylsilyl)amide (KHMDS) solution (15.1 ml, 15.1 mmol, 1.4 equiv) was added keeping the temperature between -40 °C and -35 °C. The reaction solution turned a dark orange color as the base was added. The resulting reaction mixture was stirred for l-hour at -40 °C and then allowed to warm to room temperature gradually. The reaction was quenched with saturated NH_4Cl solution (10 ml), stirred for 10 minutes, 3M hydrochloric acid (40 ml) was added, stirred for 10 minutes and then the flask contents were heated in a heating bath at 60 °C for 1.5 hours and then cooled to room temperature. Water (35 ml) was added and the reaction was extracted with tert-butyl

methyl ether (MTBE) (3 x 75 ml). The ethereal extracts were combined into one and washed with brine, dried with anhydrous Na2SO4 powder and filtered through a Chem-R-Us plastic sinter funnel to remove the spent drying agent. The filtrate was concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to afford a light brown colored oil. The crude product was purified by chromatography on the Biotage on a 100 g silica column, an EtOAc-hexanes gradient [15% (1 CV) 15-75% (7.5 CV) 100% (3 CV)] and fractions collected in 16 x 100 mm tubes. The product fractions were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid that was pumped down on the vacuum line for several hours, yielding (1*R*,4*R*,7*R*)-(+)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1] heptane-3-one (6) (2.5 g; 63 %).

Method C

[0085] To a solution of (1*R*,4*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptane-3,6-dione (5) (48.5 g, 149.6 mmol, 1 equiv) and 2-((difluoromethyl)sulfinyl)pyridine (20), (31.8 g, 164.6 mmol, 1.1 equiv) in DMF (800 mL) was added dropwise a solution of t-BuOK (30.2 g, 269.3 mmol, 1.8 equiv) in DMF (800 mL) very slowly at -57 to -52 °C. The reaction was stirred at -55 °C for 0.5 h, then a saturated NH_4Cl solution (400 mL) was slowly added dropwise to the reaction mixture at a temperature below -30 °C. After addition, 6 N HCl solution (360 mL) was added to the above mixture below -20 °C. The mixture was warmed to 10 °C and stirred at 65 °C for 1 h. TLC (petroleum ether: ethyl acetate = 3:1, R_f = 0.50) showed a new spot. The mixture was added to water (4 L) and extracted with MTBE (2 L x 2). The organic layer was separated and washed with brine (2 L), then dried with Na_2SO_4, concentrated under reduced pressure to give a residue as a red oil. The crude product was purified by column chromatography on silica gel with petroleum ether: ethyl acetate (20:1~1:1) to give (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) (32.5 g, 90.7 mmol, 60.6% yield) as a white solid.

Example 5

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7)

Method A

[0086] (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-one (6) (140 mg, 0.39 mmol) was added to MeCN (2.0 mL) and cooled to 0 °C. Ceric ammonium nitrate (643.5 mg, 1.17 mmol, 3 equiv) in H_2O (0.75 mL) was

added dropwise. The reaction was allowed to warm to room temperature and stirred for 1 h. After completion, water was added, and the solution was extracted with ethyl acetate (2 x 15 mL). The organic layers were dried over Na2SO4 and concentrated under reduced pressure. Flash chromatography yielded (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) as a white solid (75 mg, 0.315 mmol, 80% yield).
$[\alpha]_D^{23^\circ C} = +38.5$

(*c* 0.90, $CHCl_3$); **m.p.** 139-141 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 4.41 (s, 1H), 4.32 (s, 1H), 2.96 (s, 1H), 2.87 (dq, *J*= 15.4, 3.4 Hz, 1H), 2.32 (d, *J*= 15.2 Hz, 1H). See, FIG. 4. 13C NMR (126 MHz, $CDCl_3$) δ 174.9, 153.5 (t, *J*= 287.5 Hz), 88.7 (t, *J*= 24.1 Hz), 60.6, 51.5, 50.3, 24.3. See, FIG. 5. 19F NMR (376 MHz, $CDCl_3$) δ -88.60 (dq, *J*= 55.1, 2.8 Hz), -88.88 (dp, *J* = 54.6, 2.5 Hz). See, FIG. 6. **IR** (film, cm-1) 3249. 1788, 1678, 1397; **HMRS (ESI$^+$)** calc'd for $C_7H_6BrF_2NO+H^+$: 237.9679; found 237.9678.

Method B

[0087] An aqueous solution of Cerium (IV) ammonium nitrate (CAN) (6.4 g) 11.67 mmol, 2.94 equiv) in 20 ml distilled water was prepared 10 minutes prior to the running the oxidative cleavage reaction. (1*R*,4*R*, 7*R*)-(+)-7-Bromo-6-(difl uoromethylene)-2-(4-methoxybenzyl)-2-aza-bicyclo[2 .2 .1]heptane-3-one (1.4 g, 3.91 mmol, 1 eqiv) was dissolved in acetonitrile (70 ml) and stirred with a stir bar in a round bottom flask. The aqueous CAN solution was added to the flask drop by drop and the resulting mixture stirred at room temperature for hours, monitoring the progress of the reaction by hplc and lcms. The reaction was worked up by pouring the reaction into a 500 ml separatory funnel and then EtOAc (300 ml) was added, shaken and the upper layer was saved. The lower aqueous layer was extracted with more EtOAc (2 x 50 ml). The ethyl acetate extracts were combined into one and washed with water (4 x 10 ml) and with saturated brine (25 ml) then dried over anhydrous Na_2SO_4. After filtering through a plastic sinter funnel to remove the spent drying agent, the filtrate was concentrated (rotary evaporator/vacuum/water bath at 40 °C) to afford a light brown colored oil. The crude product was purified by chromatography on the Biotage on a 25 g silica column, an EtOAc-hexanes gradient [15% (1 CV) 15-75% (7.5 CV) 100% (3 CV)] and fractions collected in 16 x 100 mm tubes. The product containing fractions were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid that was pumped down on the vacuum line for several hours yielding purified *(1R,4R,7R)*-(+)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptane-3-one (7) (0.65 g; 70 %).

Example 6

Manufacture of (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) and Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9)

Method A

[0088] (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) (890.0 mg, 3.74 mmol) was added to dichloromethane (18.0 mL) followed by the sequential addition of Boc_2O (978.8 mg, 4.49 mmol, 1.2 equiv), DMAP (45.7 mg, 0.37 mmol, 0.1 equiv), and Et_3N (0.78 mL, 5.61 mmol, 1.5 equiv). The reaction was stirred for 1 h and then was washed with 1 M HCl (10 mL), dried over Na_2SO_4, and concentrated. The resulting oil containing (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) was dissolved in methanol (18.0 mL), then K_2CO_3 (1.55 g, 11.21 mmol, 3.0 equiv) was added, and the reaction was stirred for 6 h. After completion, as indicated by LC/MS (methanolysis of the lactam occurs in the first 10 min), the reaction was diluted with brine and extracted with ethyl acetate (3 x 200 mL). Upon drying over Na_2SO_4, concentrating, and purification by flash chromatography, methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) was obtained as a white solid (570 mg, 1.97 mmol, 52% yield).
$[\alpha]_D^{23^\circ C} = +104.8$
(*c* 0.50, $CHCl_3$); **m.p.** 95-97 **°C; ^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 5.50 (d, *J*= 9.1 Hz, 1H), 4.63 (d, *J*= 8.7 Hz, 1H), 3.75 (s, 3H), 3.33 (d, *J* = 20.4 Hz, 1H), 3.21 (dd, *J*= 20.3, 2.7 Hz, 1H), 1.42 (s, 9H). See, FIG. 7. 13C NMR (126 MHz, $CDCl_3$) δ 164.3, 154.7, 154.6, 152.4 (t, *J* = 288.5 Hz), 150.1, 140.6, 135.5, 88.9 (dd, *J*= 21.8, 20.2 Hz), 80.1, 55.3, 51.9, 31.1, 28.3. See, FIG. 8. 19F NMR (376 MHz, $CDCl_3$) δ -84.49 (d, *J* = 43.6 Hz), -85.91 (d, *J*= 43.4 Hz). See, FIG. 9. **IR** (film, cm^{-1}) 3347, 2987, 1773, 1681; **HMRS (ESI$^+$)** calc'd for $C_{13}H_{17}F_2NO4+Na^+$: 312.1023; found 312.1018.

Method B

[0089] To a solution of (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]heptan-3-one (7) (14.4 g, 60.5 mmol, 1 equiv) in DCM (150 mL) were added DMAP (739.0 mg, 6.05 mmol, 0.1 equiv) and TEA (9.18 g, 90.7 mmol, 12.6 mL, 1.5 equiv). Then $(Boc)_2O$ (15.8 g, 72.6 mmol, 16.6 mL, 1.2 equiv) was added slowly. After the addition, the mixture was stirred at 25 °C for 1 h. TLC (petroleum ether: ethyl acetate = 1: 1, R_f = 0.20) showed that the reaction was completed. The mixture was adjusted to pH = 3-4 with 1N HCl solution, then the organic layer was separated and washed with brine (100 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give (1*R*,4*R*,7*R*)-7-bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) (7.50 g, crude) as a black brown solid, which was used in the next step without further purification. (1*R*,4*R*,7*R*)-7-Bromo-6-(difluoromethylene)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-one (8) (7.50 g, 22.1

mmol, 1 equiv) was dissolved in MeOH (55 mL), then CH_3ONa (1.44 g, 26.6 mmol, 1.2 equiv) was added. The mixture was stirred at 0 °C for 1 h. TLC (petroleum ether: ethyl acetate = 1:1, R_f = 0.70) showed that the reaction was completed. Water (100 mL) was added to the reaction mixture, and the mixture was extracted with MTBE (200 mL x 2), washed with brine (150 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue as a red solid (crude). The crude product was purified by column chromatography on silica gel with petroleum ether: ethyl acetate (20:1~1:1) to give methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) (5.20 g, 17.9 mmol, 81.0% yield) as a white solid.

Example 7

Manufacture of *tert*-Butyl (1*R*,4*R*,7*R*)-(+)-7-bromo-6-(difluoromethylene)-3-oxo-2-azabicyclo[2.2.1]heptan-2-carboxylate (8)

[0090] Dichloromethane (30 ml) used in this reaction was deoxygenated with a gas dispersion tube and nitrogen just prior to use in the reaction. (1*R*,4*R*,7*R*)-(+)-7-Bromo-6-(difluoromethylene)-2-azabicyclo[2.2.1]-heptan-3-one (7) (1.4 g, 5.88 mmol, 1 equiv) and di-tert-butyl dicarbonate (2.56 g, 11.73 mmol, 2 equiv) were dissolved in dichloromethane (30 ml) in a 100 ml round bottom flask. 4-(Dimethylamino)-pyridine (DMAP) (0.3 g, 2.46 mmol, 7.3 equiv) was dissolved in triethylamine (6 ml, 43 mmol, 0.4 eqiv) and then the amines were added to the reaction drop by drop under a nitrogen atmosphere blanket. The resulting reaction mixture in the flask was sealed with a serum cap/N_2 needle and the contents was stirred for 1 hour at room temperature. A small aliquot was removed and the reaction progress was checked by hplc and lcms. In the work up, the volatiles were removed (rotary evaporator/vacuum/water bath at ambient temperature) to afford a dark golden yellow liquid. The liquid was taken up in dichloromethane (50 ml) and partitioned with I M hydrochloric acid (25 ml), washed with brine (50 ml). The extract was dried over anhydrous Na2SO4 powder, filtered and the filtrate concentrated (rotary evaporator/vacuum/water bath at ambient temperature) to afford a brown oil. The crude product was purified by chromatography on the Biotage on a 25 g silica column, an EtOAc-hexanes gradient [15% (1 CV) 15-75% (7.5 CV) 100% (3 CV)] and fractions collected in 16 x 100 mm tubes. The product containing fractions were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow liquid that was pumped down on the vacuum line for several hours yielding purified tert-butyl (1*R*,4*R*,7*R*)-(+)-7-Bromo-6-(difluoromethylene)-3-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (1.65 g; 82%).

Example 8

Manufacture of (S)-3-((*tert*-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-

ene-1-carboxylic acid (19)

[0091] The solvent methanol-water (3:1 v/v) used in this reaction was deoxygenated with a gas dispersion tube and nitrogen just prior to use in the reaction. *tert*-Butyl (1*R*, 4*R*,7*R*)-(+)-7-bromo-6-(difluoromethylene)-3-oxo-2-azabicyclo[2.2.1]-heptane-2-carboxylate (8) (1.6 g, 4.73 mmol, 1 equiv) was dissolved in the aqueous methanol (35 ml) and stirred with a stir bar under a nitrogen atmosphere, and potassium carbonate powder (1.96 g, 14.18 mmol, 3 equiv) was added into the solution in a single portion. The reaction flask was sealed with a serum cap and nitrogen needle and the mixture inside stirred for 12 hours. Dichloromethane (50 ml) was added and then the biphasic crude reaction mixture was acidified with 1 M hydrochloric acid to destroy the excess potassium carbonate and bring the pH to 7 (pH papers). The phases were split and then the volatiles were removed from the dichloromethane layer. The crude product was purified by chromatography on the Biotage on a 25 g silica column, a methanol-CH2Ch gradient [1 % (1 CV) 1-20% (7.5 CV) 20% (3 CV)] and fractions collected in 16 x 100 mm tubes. The product containing fractions were combined and concentrated (rotary evaporator/vacuum/ water bath at 40 °C) to a golden yellow solid that was pumped down on the vacuum line for several hours to yield purified (S)-3-((*tert*-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid (19) (0. 733 g; 56 %).

Example 9

Manufacture of (S)-3-Amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid hydrochloride (1)

Method A

[0092] Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) (570.0 mg, 1.97 mmol) was dissolved in dioxane (1.00 mL), and 6 M HCl (9 mL) was added. After heating at 80 °C for 2 h, the reaction was concentrated to yield (S)-3-Amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid hydrochloride (1) as a light brown powder (403.0 mg, 1.90 mmol, 97% yield). Crystallization from ethanol/diethyl ether increased purity to >99%.

$[\alpha]_D^{23°C} = +67.2$

(c 0.90, H2O); **m.p.** 207 °C (decomp.); **^{1}H NMR** (500 MHz, D_2O) δ 6.59 (s, 1H), 4.70 (s, 13H), 3.39 (d, *J*= 20.5 Hz, 1H), 3.33 (d, *J*= 20.8 Hz, 1H). See, FIG. 10. 13C NMR (126 MHz, D_2O) δ 167.2, 153.0 (dd, *J*= 290.1, 288.4 Hz), 141.8, 134.3, 86.1 (dd, *J* = 26.6, 21.2 Hz), 54.8 (d, *J* = 5.7 Hz), 31.1. See, FIG. 11. 19F NMR (470 MHz, D_2O) δ -83.1 (dq, *J* = 40.8, 2.8 Hz), -83.5

(dq, *J*= 40.4, 2.1 Hz). See, FIG. 12. **IR** (film, cm^{-1}) 3348, 3075, 2981, 2883, 2829, 2600, 2434, 1771, 1686; **HMRS (ESI$^-$)** calc'd for $C_7H_7F_2NO_2$-H: 174.0372; found 174.0369.

Method B

[0093] (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate (9) (5.20 g, 17.9 mmol, 1 equiv) was added to 4 M HCl(g)/EtOAc (100 mL), and the mixture was stirred at 20-30 °C for 2 h. TLC (petroleum ether : ethyl acetate = 5:1, R_f = 0) indicated the starting material was consumed completely. The mixture was concentrated under reduced pressure to give methyl (S)-3-amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylate hydrochloride (3.00 g, crude, HCl salt) as a yellow solid, which was used in the next step without further purification. The above compound (3.00 g, 13.3 mmol, 1.0 equiv) was added to MeOH (15 mL), and a solution of $LiOH·H_2O$ (1.39 g, 33.2 mmol, 2.5 equiv) in H_2O (10 mL) was added to the above mixture slowly at 20-30 °C. The mixture was stirred at 20-30 °C for 3 h. TLC (dichloromethane: methanol = 5:1 ,R_f= 0.40) indicated that the starting material was consumed completely. The mixture was adjusted to pH = 2-3 with 6 M HCl solution and concentrated to give the crude product, which was purified by reversed-phase HPLC (Agela C18 330 g; mobile phase: [water (0.1%HCl)-MeOH]; B%: 10%-20%, 20 min, 70 mL/min) to give (S)-3-amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid hydrochloride (1) (1.80 g, 8.46 mmol, 63.7% yield, 99.5% purity) as a white solid.

Example 10

Manufacture of (S)-3 -Amino-4-(difluoromethylene)cyclopent-1-ene-1-carboxylic acid hydrochloride (1)

[0094] 6N Hydrochloric acid was prepared from mixing conc. hydrochloric acid (10 ml) and water (10 ml). THF used in this reaction was deoxygenated with a gas dispersion tube and nitrogen just prior to use in the reaction. (S)-3-((tert-butoxycarbonyl)amino)-4-(difluoromethylene)-cyclopent-1-ene-1-carboxylic acid (19) was dissolved in THF (2 ml) and stirred in a 10 ml round bottom flask with a stir bar. 6M hydrochloric acid (2 ml) was added. The reaction mixture was stirred at room temperature for 2 hours and then the THF and water was removed with an active nitrogen gas flow overnight. The pink colored solid residue was pumped down on a vacuum line for several hours to remove any residual solvent yielding (S)-3-amino-4-(difluoromethylene)-1-cyclopentene-1-carboxylic acid hydrochloride salt (1) as a pink solid (-100 mg; 86%).

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

- US9670141B [0001] [0004]
- US7381748B [0004]
- US6794413B [0004]

Non-patent literature cited in the description

- **JUNCOSA et al.**J. Am. Chem. Soc., 2018, vol. 140, 2151-2164 [0001]
- **JUNCOSA et al.**J. Am. Chem. Soc., [0004]
- **QIU, J.SILVERMAN, R. B.**J. Med. Chem., 2000, vol. 43, 706-720 [0019] [0071] [0074]
- **PAN, YQIU, J.SILVERMAN, R. B**J. Med. Chem., 2003, vol. 46, 5292-5293 [0019]
- **ZHAO, Y.HUANG, W.ZHU, L.HU, J.**Org. Lett., 2010, vol. 12, 1444-1447 [0021]
- **ZHOU, Q.RUFFONI, A.GIANATASSIO, R.FUJIWARA, Y.SELLA, E.SHABAT, D.BARAN, P. S.**Angew. Chem. Int. Ed., 2013, vol. 52, 3949-3952 [0067]
- **QIU, J.SILVERMAN, R. B**J. Med. Chem., 2000, vol. 43, 706-720 [0068]

Patentkrav

1. Fremgangsmåde til fremstilling af (S)-3-amino-4-(difluormethylenyl)cyclopent-1-en-1-carboxylsyre (1) eller salt deraf omfattende:

omdannelse af (1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-on (2) til (1*R*,4*R*,6*S*,7*R*)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4);

omdannelse af (1*R*,4*R*,6*S*,7*R*)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4) til (1*R*,4*R*,7*R*)-7-brom-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3,6-dion (5), fortrinsvis ved omsætning med a. K_2CO_3, alkohol; og enten b. 2-iodoxybenzoesyre (IBX), MeCN; eller b. tetrapropylammoniumperruthenat (TPAP), N-methylmorpholin N-oxid (NMO);

omdannelse af (1*R*,4*R*,7*R*)-7-brom-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3,6-dion (5) til (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-on (6), fortrinsvis ved omsætning enten med 2-((difluormethyl)sulfinyl)pyridin (20), KO^{t}Bu, DMF, NH_4Cl, HCl; eller med *tert*-BuLi og $F_2CHP(O)(OEt)_2$;

omdannelse af (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-on (6) til (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-azabicyclo[2.2.1]heptan-3-on (7), fortrinsvis ved omsætning med ceriumammoniumnitrit (CAN), MeCN, H_2O;

omdannelse af (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-azabicyclo[2.2.1]heptan-3-on (7) til (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-on (8), fortrinsvis ved omsætning med Boc_2O, N,N-dimethylaminopyridin (DMAP), Et_3N, CH_2Cl_2;

omdannelse af (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-on (8) til methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat (9) eller (S)-3-((*tert*-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylsyre (19); og

omdannelse af methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat (9) eller (S)-3-((*tert*-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylsyre (19) til (*S*)-3-amino-4-(difluormethylenyl)cyclopent-1-en-1-carboxylsyre (1), eventuelt efterfulgt af forsuring for at tilvejebringe hydrochloridsaltet deraf.

2. Fremgangsmåde ifølge krav 1, hvor (1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-on (2) omdannes til (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-on (3), fortrinsvis ved omsætning med 4-methoxybenzylchlorid, tetrabutyl-ammoniumiodid og lithium-bis(trimethylsilyl)amid; og (1*R*,4*S*)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-on (3) omdannes til (1*R*,4*R*,6*S*,7*R*)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4), fortrinsvis ved omsætning med 1,3-dibrom-5,5-dimethylhydantoin.

3. Fremgangsmåde ifølge krav 1, hvor (1*R*,4*S*)-2-azabicyclo[2.2.1]hept-5-en-3-on (2) omsættes med a. 4-methoxybenzylalkohol (PMBOH), HCl, NaH, THF/DMF; og b. 1,3-dibrom-5,5-dimethylhydantoin (DBDMH), AcOH for at opnå (1*R*,4*R*,6*S*,7*R*)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4).

4. Fremgangsmåde ifølge krav 1, hvor (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-on (8) omsættes med K_2CO_3, methanol eller ethanol for at opnå methyl eller ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat.

5. Fremgangsmåde ifølge krav 1, hvor (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-on (8) omsættes med K_2CO_3, methanol, CH_3ONa for at opnå methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat (9).

6. Fremgangsmåde ifølge krav 1, hvor methyl eller ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat omsættes med HCl for at opnå (S)-3-amino-4-(difluormethylenyl)cyclopent-1-en-1-carboxylsyre (1) eller farmaceutisk acceptabelt salt deraf.

7. Fremgangsmåde ifølge krav 1, hvor omdannelse af (1*R*,4*R*,6*S*,7*R*)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4) til (1*R*,4*R*,7*R*)-7-brom-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3,6-dion (5) omfatter:

omdannelse af (1*R*,4*R*,6*S*,7*R*)-(+)-7-brom-2-(4-methoxybenzyl)-3-oxo-2-azabicyclo[2.2.1]heptan-6-yl-acetat (4) til (1*R*,4*R*,6S,7*R*)-(+)-7-brom-6-hydroxy-2-(4-

methoxybenzyl)-2-aza-bicyclo[2.2.1]heptan-3-on (25), fortrinsvis ved omsætning med kaliumcarbonat i methanol; og

omdannelse af (1*R*,4*R*,6S,7*R*)-(+)-7-brom-6-hydroxy-2-(4-methoxybenzyl)-2-aza-bicyclo [2.2.1]heptan-3-on (25) til (1*R*,4*R*,7*R*)-(+)-7-brom-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3,6-dion (5), fortrinsvis ved omsætning enten med oxalylchlorid i dichlormethan, DMSO og triethyamin; eller med 4-methylmorpholin-N-oxid i dichlormethan, og tetrapropylammoniumperruthinat.

8. Fremgangsmåde ifølge krav 1, hvor (1*R*,4*R*,7*R*)-(+)-7-brom-6-(difluormethylen)-2-(tert-butoxycarbonyl)-2-azabicyclo[2.2.1]heptan-3-on (8) omsættes med K_2CO_3, methanol eller ethanol for at opnå (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylsyre (19); eller hvor (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylsyre (19) omsættes med HCl for at opnå (*S*)-3-amino-4-(difluormethylenyl)cyclopent-1-en-1-carboxylsyre (1) eller farmaceutisk acceptabelt salt deraf.

9. (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]heptan-3-on (6) eller et farmaceutisk acceptabelt salt deraf.

10. (1*R*,4*R*,7*R*)-7-brom-6-(difluormethylen)-2-azabicyclo[2.2.1]heptan-3-on (7) eller et farmaceutisk acceptabelt salt deraf.

11. Methyl (S)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat (8) eller et farmaceutisk acceptabelt salt deraf.

12. Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylat (9) eller et farmaceutisk acceptabelt salt deraf.

13. (S)-3-((*tert*-butoxycarbonyl)amino)-4-(difluormethylen)cyclopent-1-en-1-carboxylsyre (19) eller et farmaceutisk acceptabelt salt deraf.

DRAWINGS

Drawing

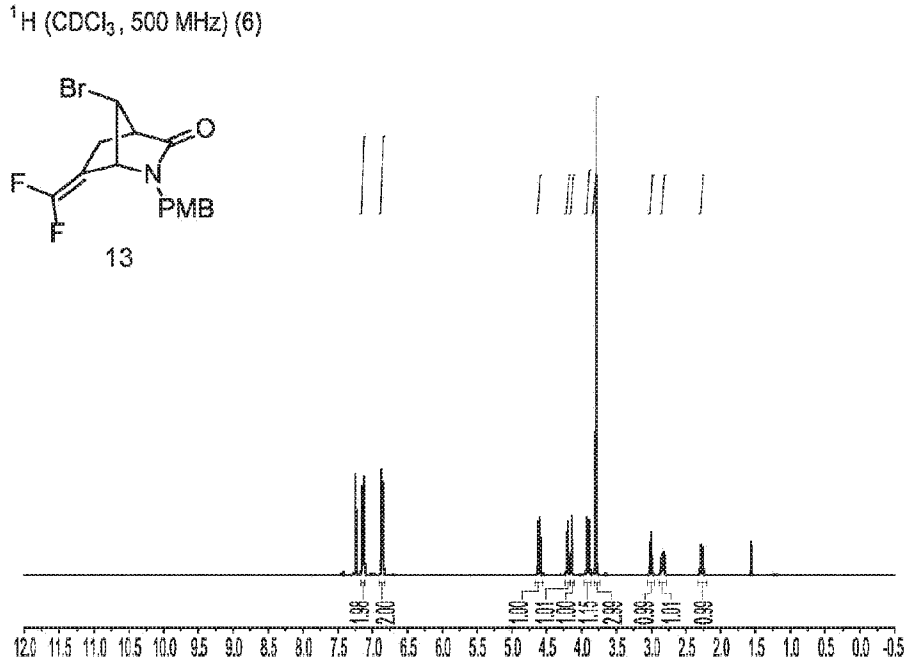


FIG. 1

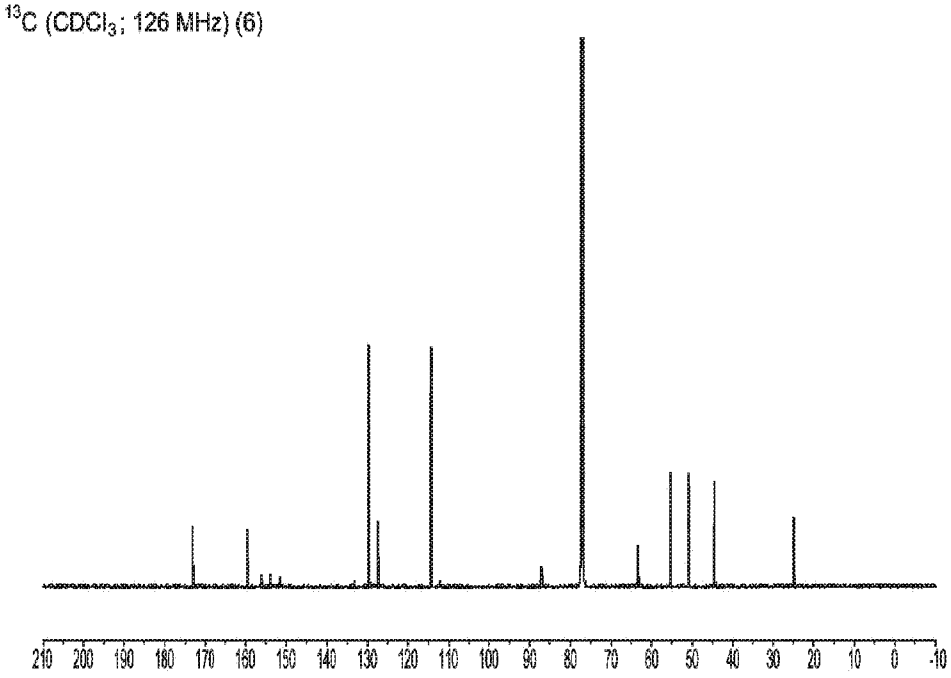


FIG. 2

^{19}F ($CDCl_3$; 127.5 MHz) (6)

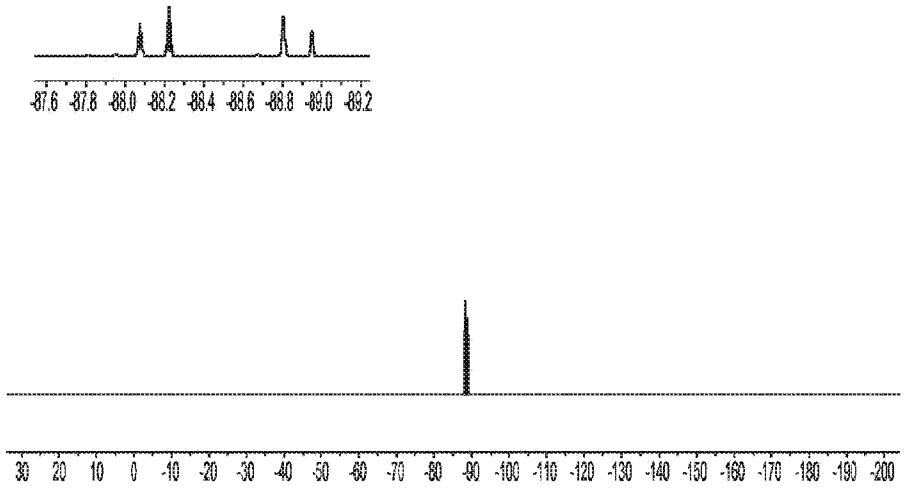


FIG. 3

^{1}H ($CDCl_3$, 500 MHz) (7)

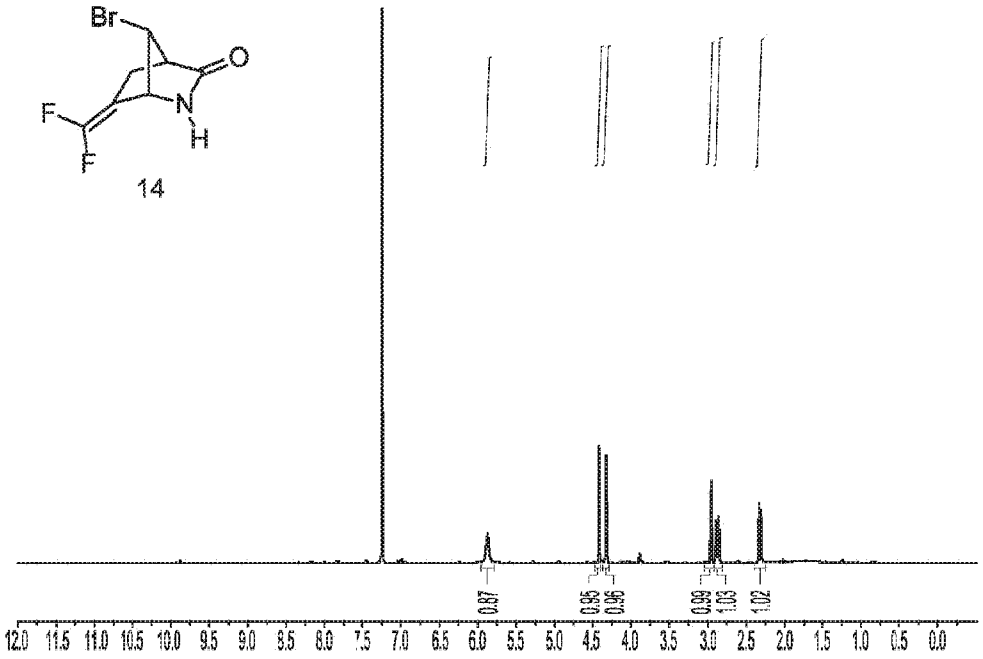


FIG. 4

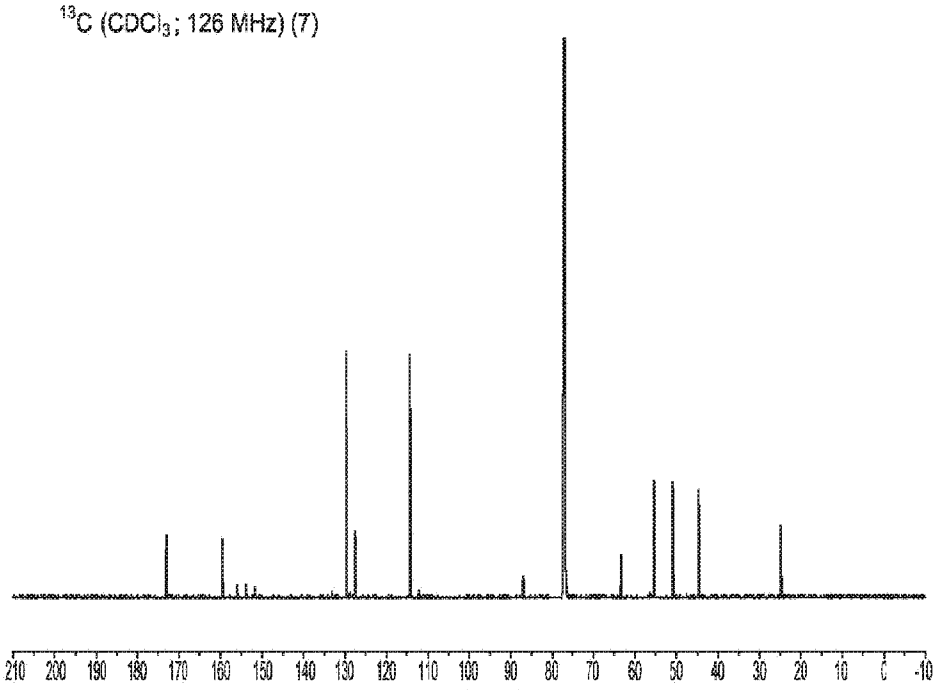

^{13}C ($CDCl_3$; 126 MHz) (7)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

FIG. 5

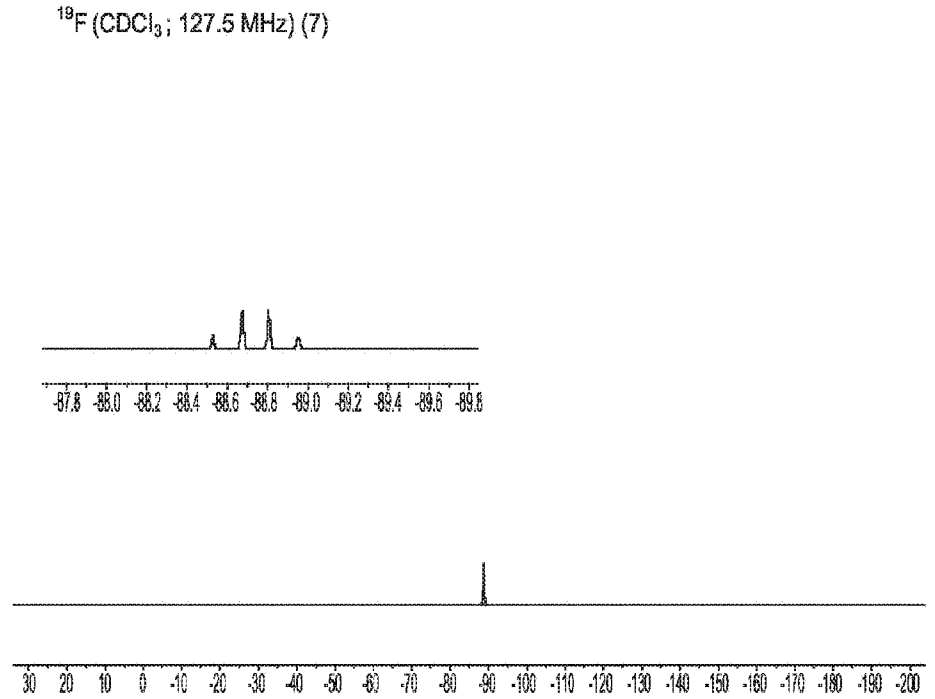

^{19}F ($CDCl_3$; 127.5 MHz) (7)
-87.8 -88.0 -88.2 -88.4 -88.6 -88.8 -89.0 -89.2 -89.4 -89.6 -89.8
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

FIG. 6

^{1}H ($CDCl_3$, 500 MHz) (9)

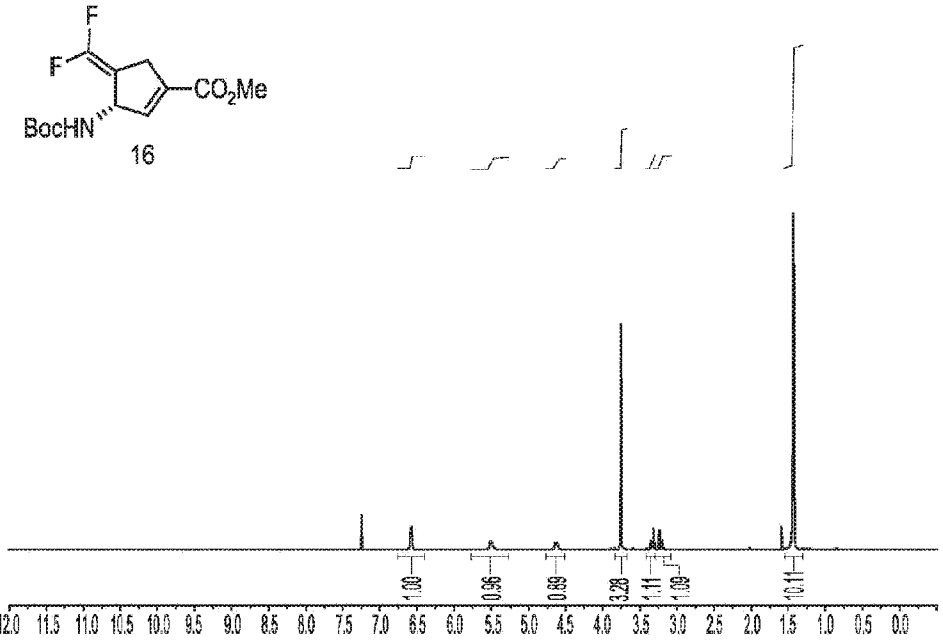


FIG. 7

^{13}C ($CDCl_3$; 126 MHz) (9)

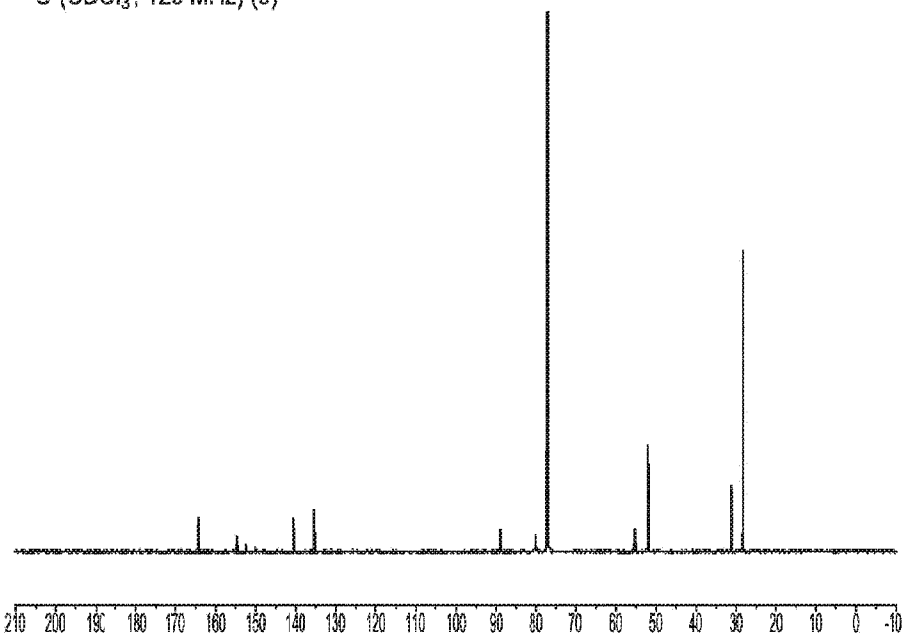


FIG. 8

^{19}F ($CDCl_3$; 127.5 MHz) (9)

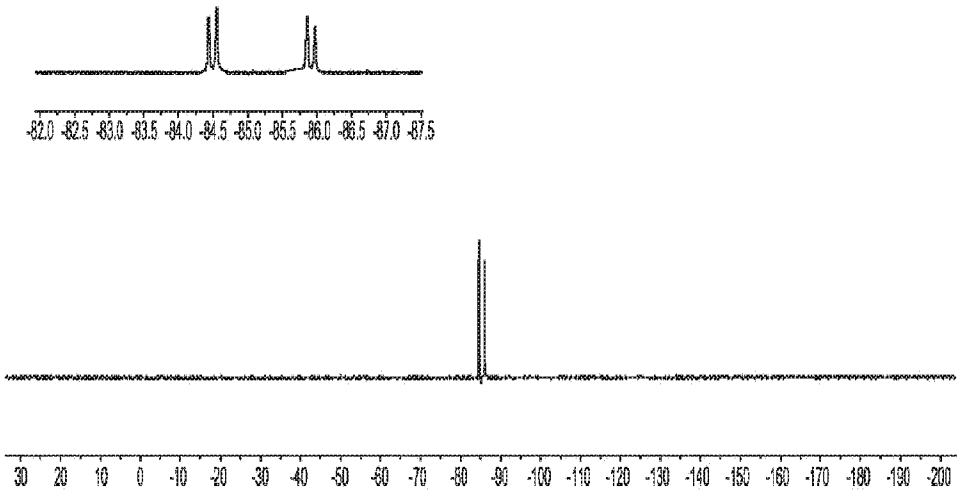
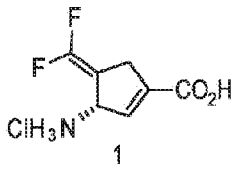


FIG. 9

^{1}H ($CDCl_3$, 500 MHz) (1)



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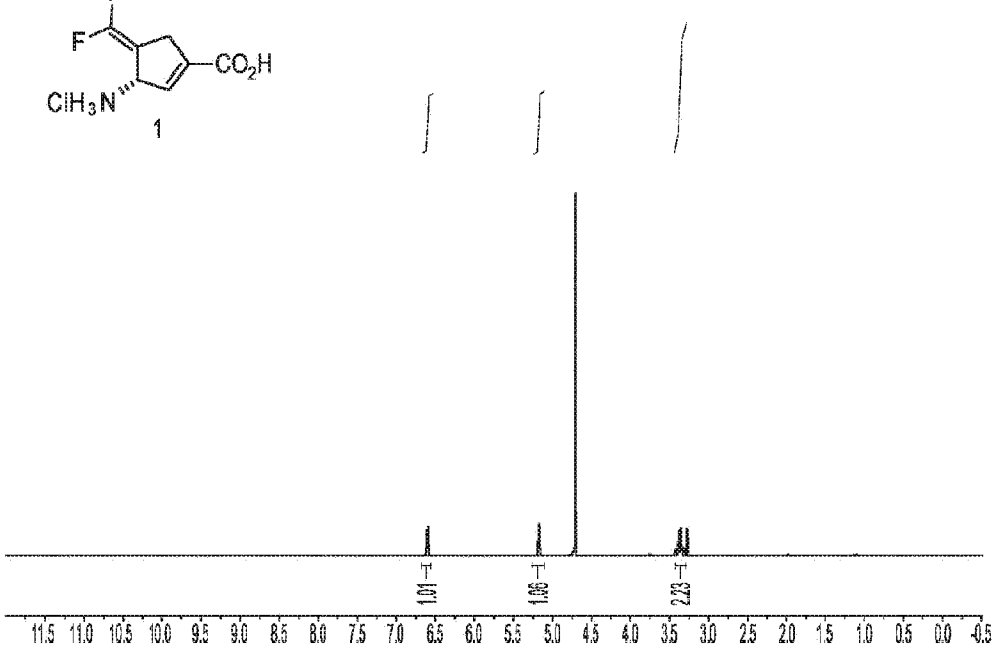

FIG. 10

^{13}C ($CDCl_3$; 126 MHz) 1

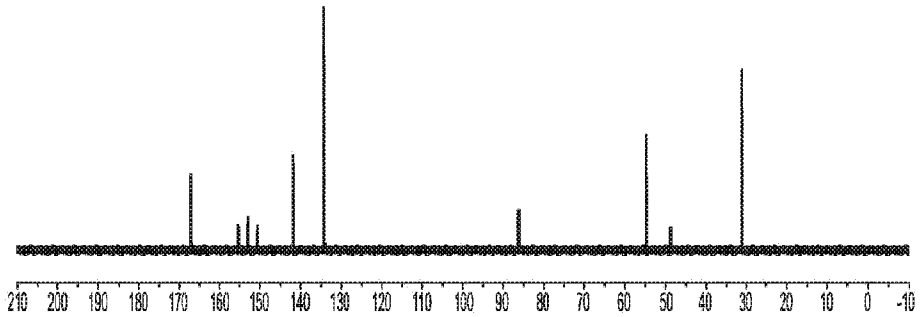

FIG. 11

^{19}F ($CDCl_3$; 127.5 MHz) 1

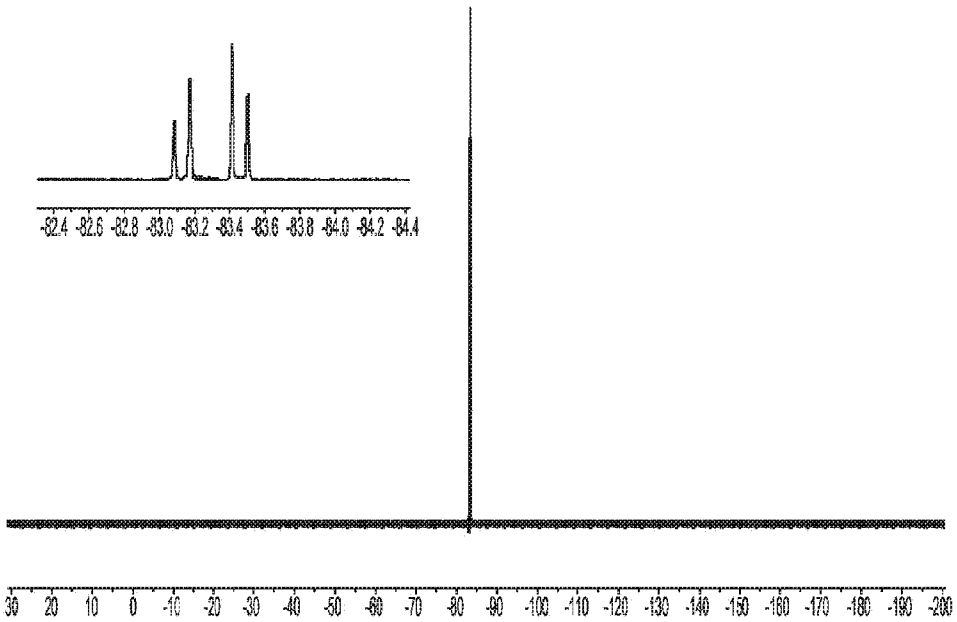

FIG. 12