# A process for the preparation of tert-butyl (R)-3-vinylpyrrolidine-1-carboxylate and intermediates therefor

## Description

### Field of the Invention

**[0001]** The present invention relates to compounds that bind to and modulate the activity of neuronal nicotinic acetylcholine receptors, to novel salts thereof, to processes for preparing these compounds, to pharmaceutical compositions containing these compounds, and to methods of using these compounds for treating a wide variety of conditions and disorders, including those associated with dysfunction of the central nervous system (CNS).

### Background of the Invention

**[0002]** The therapeutic potential of compounds that target neuronal nicotinic receptors (NNRs), also known as nicotinic acetylcholine receptors (nAChRs), has been the subject of several reviews. See, for example, Breining et al., Ann. Rep. Med. Chem. 40: 3 (2005), Hogg and Bertrand, Curr. Drug Targets: CNS Neurol. Disord. 3: 123 (2004). Among the kinds of indications for which NNR ligands have been proposed as therapies are CNS disorders mentioned below. There exists a heterogeneous distribution of nAChR subtypes in both the central and peripheral nervous systems. For instance, the nAChR subtypes which are predominant in vertebrate brain are $\alpha 4\beta 2$, $\alpha 7$, and $\alpha 3\beta 2$, whereas those which predominate at the autonomic ganglia are $\alpha 3\beta 4$ and those of neuromuscular junction are $\alpha 1\beta 1\gamma\delta$ and $\alpha 1\beta 1\gamma\varepsilon$.

**[0003]** A limitation of some nicotinic compounds is that they are associated with various undesirable side effects due to non-specific binding to multiple nAChR subtypes. For example, binding to and stimulation of muscle and ganglionic nAChR subtypes can lead to side effects which can limit the utility of a particular nicotinic binding compound as a therapeutic agent.

**[0004]** The commercial development of a drug candidate involves many steps, including the development of a cost effective synthetic method that is adaptable to a large scale manufacturing process. Commercial development also involves research regarding salt forms of the drug substance that exhibit suitable purity, chemical stability, pharmaceutical properties, and characteristics that facilitate convenient handling and processing. Furthermore, compositions containing the drug substance should have adequate shelf life. That is, they should not exhibit significant changes in physicochemical characteristics such as, but not limited to, chemical composition, water content, density, hygroscopicity, stability, and solubility upon storage over an appreciable period of time. Additionally, reproducible and constant plasma concentration profiles of drug upon administration to a patient are also important factors.

**[0005]** Solid salt forms are generally preferred for oral formulations due to their tendency to exhibit these properties in a preferential way; and in the case of basic drugs, acid addition salts are often preferred salt. However, different salt forms vary greatly in their ability to impart these properties and such properties cannot be predicted with reasonable accuracy. For example, some salts are solids at ambient temperatures, while other salts are liquids, viscous oils, or gums at ambient temperatures. Furthermore, some salt forms are stable to heat and light under extreme conditions and others readily decompose under much milder conditions. Salts also vary greatly in their hygroscopicity, the less hygroscopic being more advantageous. Thus, the development of a suitable acid addition salt form of a basic drug for use in a pharmaceutical composition is a highly unpredictable process.

**[0006]** Because of the advantageous pharmacological properties of a single enantiomer over its racemate, there is a need for a stereospecific synthesis, preferably a process suitable for large-scale production. Furthermore, there is a need for salt forms that display improved properties, such as for example purity, stability, solubility, and bioavailability. Preferential characteristics of these novel salt forms include those that would increase the ease or efficiency of manufacture of the active ingredient and its pharmaceutical composition into a commercial drug product and improved stability of the drug over a prolonged period of time.

### Summary of the Invention

**[0007]** One aspect of the invention is diethyl (R)-2-(1-(tert-butoxycarbonyl) pyrrolidin-3-yl-)malonate. Another aspect at the invention is (R)-2-(1-(tert-butoxycarbonyl) pyrrolidin-3-yl) malonic acid. Another aspect of the invention is tert-butyl (R)-3-(2-hydroxy-ethyl)pyrrolidine-1-carboxylate. Another aspect or the invention is tert-butyl (R)-3-(2-iodoethyl) pyrrolidine-1-carboxylate.

**[0008]** Another aspect includes a method of making *tert*-butyl (R)-3-vinylpyrrolidine-1-carboxylate through the intermediacy of one or more of diethyl (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonate, (R)-2-(1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl)malonic acid, *tert*-butyl (R)-3-(2-hydroxyethyl)pyrrofidine-1-carboxylate, and *tert*-butyl (R)-3-(2-iodoethyl) pyrrolidine-1-carboxylate.

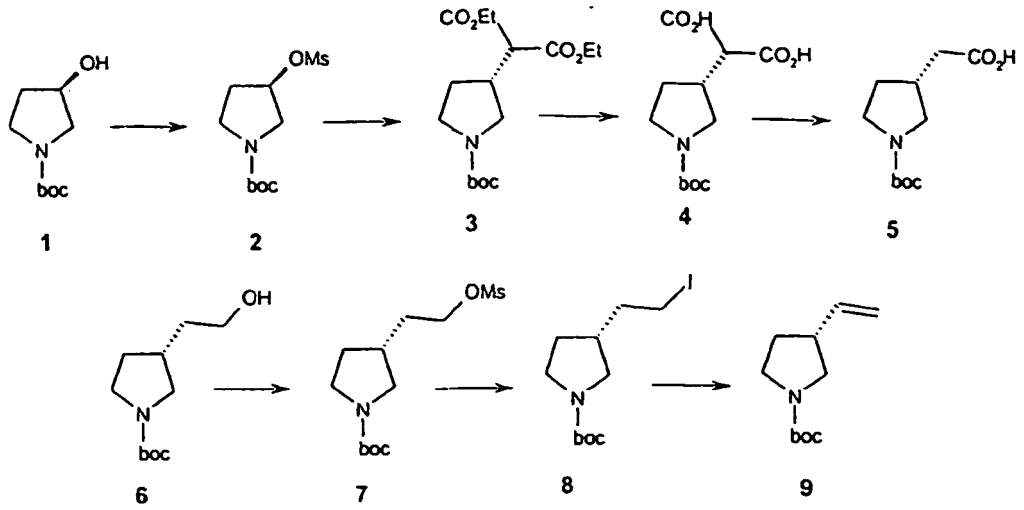
Detailed Description

**Compounds**

**[0009]** One embodiment of the present invention relates to diethyl (R)-2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl) malonate. Another embodiment of the present invention relates to (R)-2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl) malonic acid. Another embodiment relates to tert-butyl (R)-3-(2-hydroxy-ethyl)pyrrolidine-1-carboxylate. Another embodiment relates to tert-butyl(R)-3-(2-iodoethyl)pyrrolidine-1-carboxylate.

Process

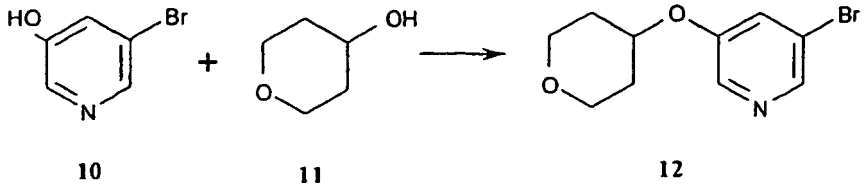
**[0010]** One embodiment of the present invention relates to a method for the preparation of tert-butyl(R)-3-vinylpyrrolidine-1-carboxylate (compound 9) as outlined in Scheme 1. Commercially available tert-butyl (R)-3-hydroxypyrrolidine-1-carboxylate (compound 1) is treated with methanesulfonyl chloride to give *tert*-butyl (R)-3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (compound 2), which then is reacted with diethylmalonate and a suitable base (e.g., potassium *tert*-butoxide or sodium ethoxide) to give diethyl (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonate (compound 3) with inverted stereochemistry around the chiral carbon.
Suitable solvents for these reactions may be selected from the group of toluene, xylenes, 1-methyl-2-pyrrolidinone, dimethylformamide, dimethylacetamide, ethanol, *tert*-butanol, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, and mixtures thereof. In one embodiment the solvent for the methanesulfonic ester formation toluene, and the solvent for the malonate displacement is 1-methyl-2-pyrrolidinone. In another embodiment the solvent for the malonate displacement is ethanol. Suitable bases for these reactions may be selected from the group of triethylamine, diethylisopropylamine, diisopropylethylamine, potassium *tert*-butoxide, sodium metal, sodium hydride, sodium ethoxide, potassium hydride and lithium hydride. In one embodiment the base for the methanesulfonic ester formation is triethylamine, and the base for the malonate displacement is potassium *tert*-butoxide. In another embodiment the base for the malonate displacement is sodium ethoxide.
**[0011]** Hydrolysis of diester 3 with aqueous potassium hydroxide yields (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl) malonic acid (compound 4), which is decarboxylated to afford (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)acetic acid (compound 5). Suitable solvents for these reactions may be selected from the group of water, ethanol, tetrahydrofuran, dimethylformamide, dimethylacetamide, 1,2-dimethoxyethane, dioxane, 1-methyl-2-pyrrolidinone, toluene, dimethylsulfoxide, and mixtures thereof. In one embodiment the solvent for the ester hydrolysis is aqueous tetrahydrofuran, and the solvent for the decarboxylation is 1-methyl-2-pyrrolidinone. In another embodiment the solvent for the ester hydrolysis is ethanol, and the solvent for the decarboxylation is a mixture of dimethylsufloxide and toluene. Suitable bases for the hydrolysis reaction may be selected from the group of potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, barium hydroxide and cesium carbonate. In one embodiment the base is potassium hydroxide.
**[0012]** Reduction of compound 5 gives *tert*-butyl (R)-3-(2-hydroxyethyl)pyrrolidine-1-carboxylate (compound 6), which may be reacted with methanesulfonyl chloride and then sodium iodide to give *tert*-butyl (R)-3-(2-(methylsulfonyloxy) ethyl)pyrrolidine-1-carboxylate (compound 7) and *tert*-butyl (R)-3-(2-iodoethyl)pyrrolidine-1-carboxylate (compound 8), respectively. Suitable solvents for the reduction reaction may be selected from the group of tetrahydrofuran, ether, dioxane, 1,2-dimethoxyethane, and mixtures thereof. In one embodiment the solvent is tetrahydrofuran. Suitable reducing agents may be selected from the group of borane, diborane, boranetetrahydrofuran complex, borane-dimethyl ether complex and borane-dimethylsulfide complex. Suitable solvents for the methanesulfonic ester formation may be selected from the group of toluene, xylenes, ether, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, and mixtures thereof. In one embodiment the solvent for the methanesulfonic ester formation is toluene. Suitable bases for the methanesulfonic ester formation may be selected from the group of triethylamine, diethylisopropylamine and diisopropylethylamine. In one embodiment the base for the methanesulfonic ester formation is triethylamine. Suitable solvents for the iodide displacement may be selected from the group of 1-methyl-2-pyrrolidinone, dimethylformamide, dimethylacetamide, ethanol, *tert*-butanol, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, dimethylsulfoxide, and mixtures thereof. In one embodiment the solvent for the iodide displacement is 1,2-dimethoxyethane.
**[0013]** Finally, treatment of compound **8** with potassium *tert*-butoxide gives of compound **9.** Suitable solvents for this reaction may be selected from the group of 1,2-dimethoxyethane, 1-methyl-2-pyrrolidinone, dimethylformamide, dimethylacetamide, ethanol, tetrahydrofuran, dioxane and mixtures thereof. In one embodiment the solvent is 1,2-dimethoxyethane. Suitable bases for this reaction may be selected from the group of potassium *tert*-butoxide, sodium ethoxide and diazabicycloundecane. In another embodiment the base is potassium *tert*-butoxide.




**Scheme 1**

**[0014]** Also described herein is the preparation of 3-bromo-5-(tetrahydro-2H-pyran-4-yloxy)-pyridine (compound 12) as outlined in Scheme 2. Coupling of 3-bromo-5-hydroxypyridine (compound **10**) with 4-hydroxytetrahydro-2H-pyran (compound **11**) gives compound **12**. Suitable conditions for the coupling include those in which a phosphine (e.g., triphenylphosphine) and an azo compound (e.g., diethyl azodicarboxylate, also known as DEAD) are used, in an inert solvent, to effect the coupling (e.g., toluene). Alternately, other conditions, in which the oxo anion of 3-bromo-5-hydroxypyridine displaces a leaving group from the 4-position of tetrahydropyran, may be employed.

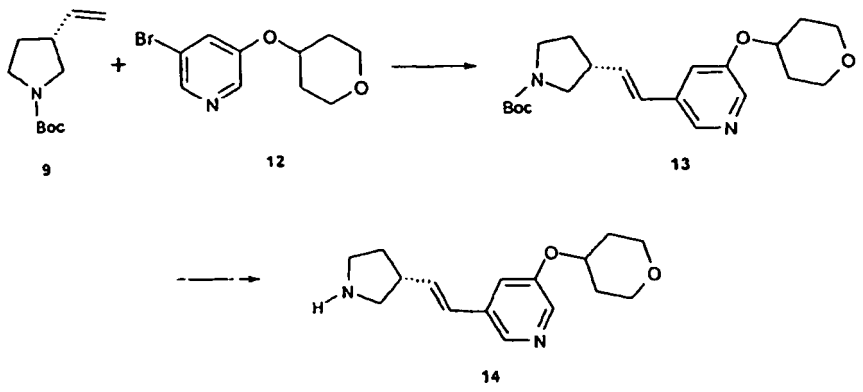
**[0015]** Also described herein is a process for the preparation of compound 12 using the reaction steps as outlined in Scheme 2 and above.




**Scheme 2**

**[0016]** Also described herein are the final-steps in the preparation of (R)-3-((E)-2-(pyrrolidin-3-yl)vinyl)-5-(tetrahydropyran-4-yloxy)pyridine (free base form) is illustrated in Scheme 3. Compounds 9 and 12 are coupled via a palladium acetate mediated coupling reaction to afford tert-butyl (R)-(E)-3-(2-(5-(tetrahydro-2H-pyran-4-yloxy)pyridin-3-yl)vinyl) pyrrolidine-1-carboxylate (also known as (R)-5-(1-(tert-butoxycarbonyl)-(E)-2-(pyrrolidin-3-yl)vinyl)-5-(tetrahydropyran-4-yloxy)pyridine , compound **13**), which is de-protected to give (R)-3-((E)-2-(pyrrolidin-3-yl)vinyl)-5-(tetrahydropyran-4-yloxy)pyridine (compound **14**). Suitable solvents for the palladium-catalyzed coupling reaction may be selected from the group of 1-methyh-2-pyrrolidinone, dimethylformamide, dimethylacetamide and acetonitrile. In one embodiment the solvent is 1-methyl-2-pyrrolidinone. Suitable bases for the palladium catalyzed coupling reaction may be selected from the group of triethylamine, diethylisopropylamine, diisopropylethylamine. In one embodiment the base is diisopropylethylamine. Suitable phosphine ligands for the palladium catalyzed coupling reaction may be selected from the group of tri-n-butylphosphine, tri-tert-butylphosphine, tricyclohexylphosphine, triphenylphosphine and tri-o-tolylphosphine. In one embodiment the phosphine ligand is tricyclohexylphosphine. Suitable palladium catalysts for the palladium catalyzed coupling reaction may be selected from the group of palladium acetate, palladium chloride and dipalladium tris(dibenzylacetone). In one embodiment the palladium catalyst is palladium acetate. Suitable solvents for the de-protection reaction may be selected from the group of water, dichloromethane, chloroform and dichloroethane. In one embodiment the solvent is dichloromethane. In another embodiment the solvent for the de-protection reaction is water.

Suitable acids for the de-protection reaction may be selected from the group of trifluoroacetic acid, hydrochloric acid and sulfuric acid. In one embodiment the acid is trifluoroacetic acid.




**Scheme 3**

Examples

**[0017]** The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted.

**Example Synthesis of diethyl (R)-2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)malonate (3)**

**[0018]** Preparation A: To a solution of potassium *tert*-butoxide (187 g, 1.62 mol) in 1-methyl-2-pyrrolidinone (1.19 L) was added diethyl malonate (268 g. 1.67 mol) while maintaining the temperature below 35°C. The solution was heated to 40 °C and stirred for 20-30 min. *tert*-Butyl (R)-3-(methylsulfonyloxyl)pyrrolidine-1-carboxylate (112 g, 420 mmol) was added and the solution was heated to 65 °C and stirred for 6 h. The reaction solution was sampled every 2 h and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction (10-12 h), the mixture was cooled to around 25 °C. De-ionized water (250 mL) was added to the solution, and the pH was adjusted to 3-4 by addition of 2N hydrochloric acid (650 mL). The resulting suspension was filtered, and water (1.2 L) and chloroform (1.4 L) were added. The solution was mixed thoroughly, and the chloroform layer was collected and evaporated under reduced pressure to give a yellow oil. The oil was dissolved in hexanes (2.00 L) and washed with deionized water (2 x 1.00 L). The organic layer was concentrated under reduced pressure at 50-55 °C to give a pale yellow oil (252 g) which $^1$H NMR analysis indicates to be 49.1% of 3 (123.8 g) along with 48.5% diethyl malonate (122g), and 2% of 1-methyl-2-pyrrolidinone (5 g). The material was carried forward into the next step without further purification. $^1$H NMR ($CDCl_3$, 400 MHz) 6 4.20 (q, 4H), 3.63 (m, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 3.27 (d, J = 10 Hz, 1H), 3.03 (m, 1H), 2.80 (m, 1H), 2.08 (m, 1H), 1.61 (m, 1H), 1.45 (s, 9H), 1.27 (t, 6H).

**[0019]** Preparation B: A reactor, maintained under a nitrogen atmosphere, was charged with 200 proof ethanol (5.50 kg) and 21% (by weight) sodium ethoxide in ethanol (7.00 kg, 21.6 mol) The mixture was stirred and warmed to 30 °C. Diethyl malonate (3.50 kg, 21.9 mol) was added over a 20 min period. The reaction mixture was then warmed at 40°C for 1.5 h. A solution of *tert*-butyl (R)-3-(methylsulfonyloxyl)pyrrolidine-1-carboxylate (3.00 kg of the product from Example 2, Procedure B, 10.7 mol) in 200 proof ethanol (5.50 kg) was added, and the resulting mixture was heated at reflux (78 °C) for 2 h. Both GC and TLC analysis (ninhydrin stain) indicated that no starting material remained. The stirred mixture was then cooled to 25 °C, diluted with water (2.25 kg), and treated slowly with a solution of concentrated hydrochloric acid (1.27 kg, 12.9 mol) in water (5.44 kg). This mixture was washed twice with methyl *tert*-butyl ether (MTBE) (14.1 kg and 11.4 kg), using 15 min of stirring and 15 min of settling time for each wash. The combined MTBE washes were dried over anhydrous sodium sulfate (1 kg), filtered and concentrated under vacuum at 50 °C for 6 h. The residue (red oil) weighed 4.45 kg and was 49% desired product by GC analysis (62% overall yield from *tert*-butyl (R)-3-hydroxypyrrolidine-1-carboxylate).

**Example 2. Synthesis of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonic acid (4)**

**[0020]** Procedure A: To a solution of the product of Example 1, Procedure A (232 g), containing 123.8 g (380 mmol) of **3** and 121.8 g (760 mmol) of diethyl malonate, in tetrahydrofuran (1.2 L) was added a 21% potassium hydroxide solution (450 g in 0.50 L of deionized water) while maintaining the temperature below 25 °C. The reaction mixture was heated to 45 °C and stirred for 1 h. The reaction solution was sampled every hour and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction (2-3 h), the mixture was cooled to around 25 °C. The aqueous layer was collected and cooled to 5 °C. The pH was adjusted to 2 by addition of 4N hydrochloric acid (750 mL), and the

resulting suspension was held at 5 -10°C for 30 min. The mixture was filtered, and the filter cake was washed with hexanes (1 L). The aqueous filtrate was extracted with chloroform (1 L) and the chloroform layer was put aside. The solids collected in the filtration step were re-dissolved in chloroform (1 L) by heating to 40 °C. The solution was filtered to remove un-dissolved inorganic solids. The chloroform layers were combined and concentrated under reduced pressure at 50 - 55 °C to give an off-white solid (15 g). The solids were combined and dissolved in ethyl acetate (350 mL) to give a suspension that was warmed to 55 - 60 °C for 2h. The suspension was filtered while hot and the resulting cake washed with ethyl acetate (2 x 150 mL) and hexanes (2 x 250 mL) to give 83.0 g (80.1%) of **4** as a white solid which was used in the next step without further purification. $^1$H NMR ($d_4$-$CH_3OH$, 400 MHz) $\delta$ 3.60 (m, 1H), 3.46 (m, 1H), 3.29-3.32 (m, 2H), 2.72 (m, 1H), 2.09 (m, 1H), 1.70 (m, 1H), 1.45 (s, 9H).

**[0021]** Procedure B: A solution of the product of Example 1, Procedure B (4.35 kg), containing 2.13 kg (6.47 mol) of **3**, in tetrahydrofuran (13.9 kg) was added to a stirred, cooled solution of potassium hydroxide (1.60 kg, 40.0 mol) in deionized water (2.00 kg) under a nitrogen atmosphere, while maintaining the temperature below 35°C. The reaction mixture was heated and maintained at 40 - 45 °C for 24 h, by which time GC and TLC analysis indicated that the reaction was complete. The mixture was cooled to 25 °C and washed with MTBE (34 kg), using 15 min of stirring and 15 min of settling time. The aqueous layer was collected and cooled to 1 °C. A mixture of concentrated hydrochloric acid (2.61 kg, 26.5 mol) in deionized water (2.18 kg) was then added slowly, keeping the temperature of the mixture at <15 °C during and for 15 min after the addition. The pH of the solution was adjusted to 3.7 by further addition of hydrochloric acid. The white solid was collected by filtration, washed with water (16 kg), and vacuum dried at ambient temperature for 6 d. The dry solid weighed 1.04 kg. The filtrate was cooled to <10°C and kept at that temperature as the pH was lowered by addition of more hydrochloric acid (1.6 L of 6 N was used; 9.6 mol; final pH = 2). The white solid was collected by filtration, washed with water (8 L), and vacuum dried at 40 °C for 3 d. The dry solid weighed 0.25 kg. The combined solids (1.29 kg, 73% yield) were chromatographically identical to previously prepared samples.

**Example 3. Synthesis of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidine-3-yl)acetic acid (5)**

**[0022]** Procedure A: A solution of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonic acid (83 g) in 1-methyl-2-pyrrolidinone (0.42 L) was stirred under nitrogen at 110-112 °C for 2 h . The reaction solution was sampled every hour and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction the reaction solution was cooled to 20-25 °C. The solution was mixed with de-ionized water (1.00 L), and MTBE (1.00 L) was added. The phases were separated, and the organic layer was collected. The aqueous phase was extracted with MTBE (1.00 L), then chloroform (1.00 L). The organic layers were combined and concentrated under reduced pressure at 50-55 °C to give an oil. This oil was dissolved in MTBE (2.00 L) and washed twice with 0.6N hydrochloric acid (2 x 1.00 L). The organic layer was collected and concentrated under reduced pressure at 50-55 °C to give a semi-solid. The semi-solid was suspended in 1:4 ethyl acetate/hexanes (100 mL), heated to 50 °C, held for 30 min, cooled to - 10 °C, and filtered. The filtrate was concentrated under reduced pressure to give an oil, which was dissolved in MTBE (250 mL) and washed twice with 0.6N hydrochloric acid (2 x 100 mL). The organic layer was concentrated under reduced pressure at 50-55 °C to give a semi-solid which was suspended in 1:4 ethyl acetate/hexanes (50 mL), heated to 50 °C, held for 30 min, cooled to -10 °C, and filtered. The solids were collected, suspended in hexanes (200 mL), and collected by filtration to give 54.0 g (77.6%) of **5**. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 11.00 (br s, 1H), 3.63 (m, 1H), 3.45 (M, 1H), 3.30 (M, 1H), 2.97 (m, 1H), 2.58 (m, 1H), 2.44 (m, 2H), 2.09 (m, 1H), 1.59 (M, 1H), 1.46 (s, 9H).

**[0023]** Procedure B: A solution of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonic acid (1.04 kg, 3.81 mol) in 1-methyl-2-pyrrolidinone (6.49 kg) was stirred under nitrogen at 110 °C for 5 h , by which time TLC and HPLC analysis indicated that the reaction was complete. The reaction mixture was cooled to 25 °C (4 h) and combined with water (12.8 kg) and MTBE (9.44 kg). The mixture was stirred vigorously for 20 min, and the phases were allowed to separate (10 h). The organic phase was collected, and the aqueous phase was combined with MTBE (9.44 kg), stirred for 15 min, and allowed to settle (45 min). The organic phase was collected, and the aqueous phase was combined with MTBE (9.44 kg), stirred for 15 min, and allowed to settle (15 min). The three organic phases were combined and washed three times with 1 N hydrochloric acid (8.44 kg portions) and once with water (6.39 kg), using 15 min of stirring and 15 min of settling time for each wash. The resulting solution was dried over anhydrous sodium sulfate (2.0 kg) and filtered. The filtrate was concentrated under reduced pressure at 31 °C (2 h) to give an solid. This solid was heated under vacuum for 4 h at 39 °C for 4 h and for 16 h at 25 °C, leaving 704 g (81%) of 5 (99.7% purity by GC).

**[0024]** Procedure C (streamlined synthesis of **5**, using **2** as starting material): A stirred mixture of sodium ethoxide in ethanol (21 weight percent, 343 g, 1.05 mol), ethanol (anhydrous, 300 mL) and diethyl malonate (168 g, 1.05 mol) was heated to 40 °C for 1.5 h. To this mixture was added a solution of (R)-*tert*-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate (138 g, 0.592 mol) in ethanol (100 mL) and the reaction mixture was heated to 78 °C for 8 h. The cooled reaction mixture was diluted with water (2.0 L) and acidified to pH = 3 with 6M HCl (100 mL). The aqueous ethanol mixture was extracted with toluene (1.0 L), and the organic phase concentrated under vacuum to afford 230 g of a red oil. The red oil was added at 85 °C to a 22.5 weight percent aqueous potassium hydroxide (748 g, 3.01 mol). After the

addition was complete, the reaction temperature was allowed to slowly rise to 102 °C while a distillation of ethanol ensued. When the reaction temperature had reached 102 °C, and distillation had subsided, heating was continued for an additional 90 min. The reaction mixture was cooled to ambient temperature and washed with toluene (2 × 400 mL). To the aqueous layer was added 600 mL 6M hydrochloric acid, while keeping the internal temperature below 20 °C. This resulted in the formation of a precipitate, starting at pH of about 4-5. The suspension was filtered, and the filter cake was washed with 300 mL water. The solid was dried under vacuum to afford 77 g of (R)-2-(1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl)malonic acid as an off-white solid (54% yield with respect to (*R*)-*tert*-butyl 3-(methylsulfonyloxy)pyrrolidine-1-carboxylate). $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.47 (m, 1H); 3.32 (m, 1H); 3.24 (m, 1H); 3.16 (m, 1H); 3.92 (m, 1H); 2.86 (m, 1H); 1.95 (m, 1H); 1.59 (m, 1H); 1.39 (s, 9H).
A suspension of (R)-2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)malonic acid (15 g, 55 mmol) in toluene (150 mL) and dimethylsulfoxide (2 mL) was heated to reflux for a period of 2 h. The mixture was allowed to reach ambient and diluted with MTBE (150 mL). The organic solution was washed with 10% aqueous citric acid (2 × 200 mL), and the solvent was removed under vacuum to afford 11.6 g of (*R*)-2-(1-(tert-butoxycarbonyl)-pyrrolidin-3-yl)acetic acid as an off-white solid (92% yield). $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 12.1 (s, 1H); 3.36-3.48 (m. 1H); 3.20-3.34 (m, 1H); 3.05-3. 19 (m, 1H; 2.72-2.84 (m, 1H); 2.30-2.42 (m, 1H), 2.22-2.30 (m, 2H); 1.85-2.00 (m, 1H); 1.38-1.54 (m, , 1H), 1.35 (2, 9H).

**Example 4. Synthesis of *tert*-butyl (R)-3-(2-hydroxyethyl)pyrrolidine-1-carboxylate (6)**

**[0025]** Procedure A: A solution of (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidine-3-yl)acetic acid (49.0 g, 214 mmol) in tetrahydrofuran (THF) (200 mL) was cooled to -10 °C. 250 mL (250 mmol) of a 1 M borane in THF solution was added slowly to the flask while maintaining the temperature lower than 0 °C. The solution was warmed to ambient temperature and stirred for 1 h. The solution was sampled hourly and analyzed by HPLC to establish completion of the reaction. Upon completion of the reaction, the solution was cooled to 0 °C, and a 10% sodium hydroxide solution (80 mL) was added drop-wise over a 30 minute period to control gas evolution. The solution was extracted with 500 mL of a 1:1 hexanes/ethyl acetate solution. The organic layer was washed with saturated sodium chloride solution and dried with 10 g of silica gel. The silica gel was removed by filtration and washed with 100 mL of 1:1 hexanes/ethyl acetate. The organic layers were combined and concentrated under vacuum to give 6 (42 g, 91.3 %) as a light-orange oil that solidified upon sitting. $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.67 (m, 2H), 3.38-3.62 (m, 2H), 3.25 (m, 1H), 2.90 (m, 1H), 2.25 (m, 1H), 1.98-2.05 (m, 1H), 1.61-1.69 (m, 2H), 1.48-1.59 (m, 2H), 1.46 (s, 9H).
**[0026]** Procedure B: Borane-THF complex (3.90 kg or L of 1M in THF, mol) was added slowly to a stirred solution of (*R*)-2-(1-(*tert*-butoxycarbonyl)pyrrolidine-3-yl)acetic acid (683 g, 3.03 mol) in THF (2.5 kg), kept under nitrogen gas, and using a water bath to keep the temperature between 23 and 28 °C. The addition took 1.75 h. Stirring at 25 °C was continued for 1 h, after which time GC analysis indicated complete reaction. The reaction mixture was cooled to <10 °C and maintained below 25 °C as 10% aqueous sodium hydroxide (1.22 kg) was slowly added. The addition took 40 min. The mixture was stirred 1 h at 25 °C, and then combined with 1:1 (v/v) heptane/ethyl acetate (7 L). The mixture was stirred for 15 min and allowed to separate into phases (1h). The organic phase was withdrawn, and the aqueous phase was combined with a second 7 L portion of 1:1 heptane/ethyl acetate. This was stirred for 15 min and allowed to separate into phases (20 min). The organic phase was again withdrawn, and the combined organic phases were washed with saturate aqueous sodium chloride (4.16 kg), using 15 min of mixing and 1 h of settling time. The organic phase was combined with silica gel (140 g) and stirred 1h. The anhydrous sodium sulfate (700 g) was added, and the mixture was stirred for 1.5 h. The mixture was filtered, and the filter cake was washed with 1:1 heptanelethyl acetate (2 L). The filtrate was concentrated under vacuum at <40 °C for 6 h. The resulting oil weighed 670 g (103% yield) and contains traces of heptane, but is otherwise identical to previously prepared samples of 6, by NMR analysis.

**Example5: *tert*-butyl (R)-3-(2-(methylsulfonyloxy)ethyl)pyrrotidine-1-carboxytate (7)**

**[0027]** Procedure A: To a solution of *tert*-butyl (R)-3-(2-hydroxymethyl)pyrrolidine-1-carboxylate (41.0 g, 190 mmol)) was added triethylamine (40 mL) in toluene (380 mL) and cooled to -10 °C. Methanesulfonyl chloride (20.0 mL, 256 mmol) was added slowly so as to maintain the temperature around -5 to 0 °C. The solution was warmed to ambient temperature and stirred for 1 h. The solution was sampled hourly and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction, the solution was filtered, and the filtrate was washed with a 5% sodium bicarbonate solution (250 mL). The organic layer was collected and washed with a saturated aqueous sodium chloride solution (250 mL). The organic layer was collected, dried over silica gel (10 g), and concentrated under vacuum to give 7 (53.0 g, 92.8 %) as a light-yellow viscous oil. $^1$H NMR ($CDCl_3$, 400 MHz) δ 4.26 (t, J = 6.8 Hz, 2H), 3.41-3.63 (m, 2H),3.27 (m, 1H), 3.02 (s, 3H), 2.92 (m, 1H), 2.28 (m, 1H), 2.05 (m, 1H), 1.83 (m, 2H), 1.50-1.63 (m, 1H), 1.46 (s, 9H).
**[0028]** Procedure B: Under a nitrogen atmosphere, a solution of triethylamine (460 g, 4.55 mol) and *tert*-butyl (R)-3-(2-hydroxymethyl)pyrrolidine-1-carboxylate (the entire sample from Example 7, Procedure B, 3.03 mol) in toluene (5.20 kg) was stirred and cooled to 5 °C. Methanesulfonyl chloride (470 g, 4.10 mol) was added slowly, over a 1.25 h, keeping

the temperature below 15 °C using ice bath cooling. The mixture was gradually warmed (over 1.5 h) to 35 °C, and this temperature was maintained for 1.25 h, at which point GC analysis indicated that the reaction was complete. The mixture was cooled to 25 °C, and solids were filtered off and the filter cake washed with toluene (1.28 kg). The filtrate was stirred with 10% aqueous sodium bicarbonate (4.0 kg) for 15 min, and the phases were allowed to separate for 30 min. The organic phase was then stirred with saturated aqueous sodium chloride (3.9 kg) for 30 min, and the phases were allowed to separate for 20 min. The organic phase was combined with silica gel (160 g) and stirred for 1 h. Anhydrous sodium sulfate (540 g) was added, and the mixture was stirred an additional 40 min. The mixture was then filtered, and the filter cake was washed with toluene (460 g). The filtrate was concentrated under vacuum at 50 °C for 5 h, and the resulting oil was kept under vacuum at 23 °C for an additional 8h. This left 798 g of 7, 93% pure by GC analysis.

**Example 6: Synthesis of *tert*-butyl (R)-3-vinylpyrrolidine-1-carboxylate (9)**

**[0029]** Procedure A: A solution of *tert*-butyl (R)-3-((methylsulfonyloxy)ethyl)pyrrolidine-1-carboxylate (49.0 g, 167 mmol), sodium iodide (30.0 g, 200 mmol) and 1,2-dimethoxyethane (450 mL) was stirred at 50-60 °C for 4h. The solution was sampled hourly and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction, the solution was cooled to -10 °C, and solid potassium *tert*-butoxide (32.0 g, 288 mmol) was added while maintaining temperature below 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 1 h. The mixture was sampled hourly and analyzed by HPLC to establish completion of the reaction. Upon completion of reaction, the mixture was filtered through a pad of diatomaceous earth (25 g dry basis). The cake was washed with 1,2-dimethoxyethane (100 mL). The combined filtrates were concentrated under vacuum, to yield an orange oil with suspended solids. The oil was dissolved in hexanes (400 mL), stirred for 30 min, and filtered to remove the solids. The organic layer was dried over silica gel (10 g), and concentrated under vacuum to give 9 (26.4 g, 82.9 %) as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.77 (m, 1H), 5.10 (dd, J = 1.2 Hz, J = 16 Hz, 1H), 5.03 (dd, J = 1.2 Hz, J = 8.8 Hz, 1H), 3.41-3.59 (m, 2H), 3.29 (m, 1H), 3.05 (m, 1H), 2.78 (m, 1H), 2.01 (m, 1H), 1.62-1.73 (m, 1H), 1.46 (m, 9H).

**[0030]** Procedure B: A solution of *tert*-butyl (R)-3-(2-(methylsulfonyloxy)ethyl)pyrrolidine-1-carboxylate (792 g of the product of Example 5, Procedure B, ~2.5 mol), sodium iodide (484 g, 3.27 mol) and 1,2-dimethoxyethane (7.2 L) was stirred at 55 °C for 4.5 h under nitrogen, at which time GC analysis indicated that the reaction was complete. The solution was cooled to <10 °C, and solid potassium *tert*-butoxide (484 g, 4.32 mol) was added in portions (1.25 h addition time) while maintaining temperature below 15 °C. The reaction mixture was stirred 1 h at 5 °C, warmed slowly (6 h) to 20 °C, and stirred at 20 °C for 1 h. The solution was filtered through a pad of diatomaceous earth (400 g dry basis). The filter cake was washed with 1,2-dimethoxyethane (1.6 kg). The combined filtrates were concentrated under vacuum, and the semisolid residue was stirred with heptane (6.0 L) for 2h. The solids were removed by filtration (the filter cake was washed with 440 mL of heptane), and the filtrate was concentrated under vacuum at 20 °C to give 455 g of 9 (90.7% pure). A sample of this material (350 g) was fractionally distilled at 20-23 torr to give 296 g of purified 9 (bp 130-133 °C) (>99% pure by GC analysis).

## Claims

**1.** A compound diethyl (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonate.

**2.** A compound (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonic acid.

**3.** A compound *tert*-butyl (R)-3-(2-hydroxyethyl)pyrrolidine-1-carboxylate.

**4.** A compound *tert*-butyl (R)-3-(2-iodoethyl)pyrrolidine-1-carboxylate.

**5.** A method of making *tert*-butyt (R)-3-vinylpyrrolidine-1-carboxylate through the intermediacy of one or more of diethyl (R)-2-(1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonate, (R)-2-(l-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)malonic acid, *tert*-butyl (R)-3-(2-hydroxyethyl)pyrrotidine-1-carboxylate, and *tert*-butyl (R)-3-(2-iodoethyl)pyrrolidine-1-carboxylate.