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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to a method of obtaining radiopharmaceutical precursors, and in particular precursors to protected amino acid derivatives, which are used as precursors for production of radiolabelled amino acids for use in *in vivo* imaging procedures, such as positron emission tomography (PET).

BACKGROUND

[0002] In recent years, a series of radioactive halogen-labeled amino acid compounds including [¹⁸F]-1-amino-3-fluorocyclobutanecarboxylic acid ([¹⁸F]-FACBC) have been designed as novel radiopharmaceuticals. [¹⁸F]-FACBC is considered to be effective as a diagnostic agent for highly proliferative tumors, because it has a property of being taken up specifically by amino acid transporters on the tumors.

[0003] Though there are a number of published approaches for the synthesis of [¹⁸F]-FACBC and its precursors, some suffer from being lengthy (e.g., EP1978015), low yields or from problems associated with the purification of either the final product (*i.e.*, [¹⁸F]-FACBC) and/or the intermediates leading to the production of the product. For example, known methods for purification of a dihalogenated intermediate by removal of a 1,2-dihalogenated impurity involves distilling under reduced pressure (McConathy et al. 2003 Appl Radiat Isotop; 58: 657-666; US2006292073 and Avram et al. 1957 Chem Ber; 90: 1424-1431). The present inventors have observed problems with this purification method. Accordingly, there remains a need for new methods for the production of [¹⁸F]-FACBC and/or intermediates leading to the production of [¹⁸F]-FACBC.

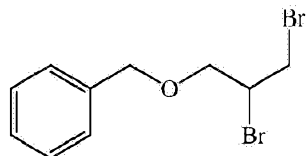
SUMMARY OF THE INVENTION

[0004] In one embodiment, the invention relates to a method for substantially removing a 1,2-dihalogen impurity from a product mixture comprising:

1. (a) reacting the product mixture with an alkoxide, thereby transforming the 1,2-dihalogen impurity into an alkene; and
2. (b) removing the alkene.

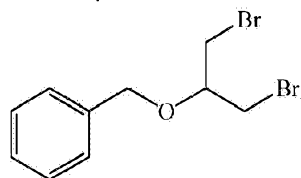
[0005] The alkoxide of the invention is a methoxide (e.g., sodium methoxide). In some embodiments, the alkene is removed by vacuum (e.g., vacuum distillation).

[0006] The invention thus relates to a method for substantially removing a 1,2-dihalogen impurity of the formula (IV)



(IV)

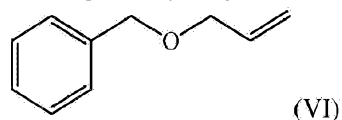
from a product mixture comprising a compound of the formula (V)



(V)

wherein the method comprises:

1. (a) reacting the product mixture with a methoxide, thereby transforming the 1,2-dihalogen impurity of the formula (IV) into an alkene of the formula (VI)



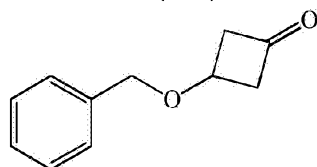
(VI)

; and

2. (b) removing the alkene of formula (VI).

[0007] In some embodiments, the methoxide is sodium methoxide. In some embodiments, the alkene of formula (VI) is removed by vacuum (e.g., vacuum distillation).

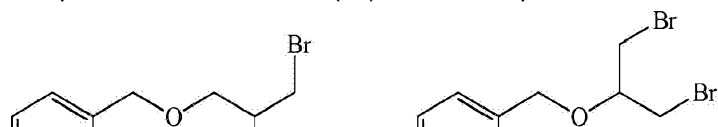
[0008] In still other embodiments, the invention relates to a method of making a compound of the formula (VIII):



(VIII)

the method comprising:

1. (a) reacting benzyl bromide with epibromohydrin to give a product mixture comprising a compound of the formula (IV) and a compound of the formula (V):



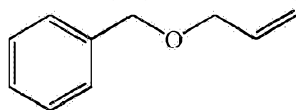


(IV)



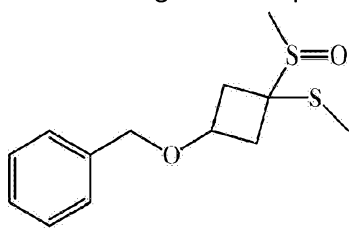
(V)

2. (b) reacting the product mixture with an alkoxide, thereby transforming the compound of formula (IV) into a compound of the formula (VI):



(VI);

3. (c) removing the compound of formula (VI) such that the compound of formula (V) remains;
4. (d) reacting the remaining compound of formula (V) with methanesulfinyl-methylsulfanyl-methane to give a compound of the formula (VII):



(VII)

and performing a work-up of the reaction with toluene;

5. (e) hydrolyzing the compound of formula (VII) in toluene to give a compound of the formula (VIII); and
6. (f) purifying the compound of formula (VIII).

[0009] In some embodiments, said purifying comprises vacuum distillation.

DETAILED DESCRIPTION

[0010] The invention relates to a method for substantially removing a 1,2-dihalogen impurity of formula (IV) from a product mixture comprising a compound of formula (V), said method comprising:

1. (a) reacting the product mixture with a methoxide, thereby transforming the 1,2-dihalogen impurity into an alkene of formula (VI); and
2. (b) removing the alkene.

[0011] As used herein, the term "halogen" or "halo," used alone or in combination, refers to fluorine, chlorine, bromine or iodine.

[0012] As used herein, the term "methoxide" means methyl-O-X⁺, wherein X⁺ is a counterion. Exemplary counterions include lithium, sodium, potassium, cesium. In some embodiments, the counterion is sodium. In some embodiments, the preferred methoxide is sodium methoxide.

[0013] As used herein, "alkyl" means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl. Preferred alkyl groups are C₁₋₁₀ alkyl groups, e.g., C₁₋₅ alkyl and C₁₋₃ alkyl.

[0014] As used herein, the term "alkene" or "alkenyl" refers to carbon chains containing at least one unsaturated carbon-carbon bond. The carbon chains may be linear, branched or combinations thereof. In some embodiments, the alkene is a C₂₋₁₀ alkene, e.g., a C₂₋₅ alkene or a C₂₋₃ alkene. In some embodiments, the alkene can comprise one or more heteroatoms. As used herein, the term "heteroatom" refers to the atoms N, O, P, B, S, and Si. In some embodiments the heteroatom is selected from N, O and S.

[0015] In some embodiments, because the alkene has a sufficiently different physical or chemical property it can be separated from the product mixture. Thus, for example, the alkene can be removed by applying a vacuum; by distillation; or by employing vacuum distillation. Alternatively, because the alkene has a sufficiently different R_f, (i.e. retardation factor) its separation and removal can be by employing chromatographic methods (e.g., HPLC, column chromatography, and the like). In still another alternative, the alkene, due to the presence of the double bond and its inherent reactivity, could be converted selectively (*i.e.*, without affecting the desired product in the product mixture) chemically into another product that can be removed by methods known in the art.

[0016] As used herein, "alkynyl" includes carbon chains containing at least one carbon-carbon triple bond.

[0017] As used herein, "alkoxy" means alkyl-O-, wherein "alkyl" is defined above.

[0018] The term "aryl" means an aromatic substituent that is a single ring or multiple rings fused together. Aryl groups encompass C₂₋₁₀ aromatic groups. Exemplary aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, pyridinyl, pyrazinyl, pyrimidinyl, triazinyl, thiophenyl, furanyl, pyrrolyl, oxazolyl, imidazolyl, triazolyl, and tetrazolyl groups. Aryl groups that contain one or more heteroatoms (e.g., pyridinyl) are often referred to as "heteroaryl groups." When formed of multiple rings, at least one of the constituent rings is aromatic. In some embodiments, at least one of the multiple rings comprise a heteroatom, thereby forming heteroatom-containing aryl groups.

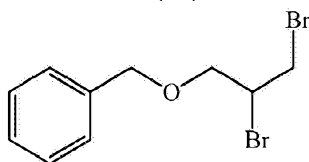
[0019] The terms "aryloxy" and "heteroaryloxy," as used herein, mean aryl-O- and heteroaryl-O-, respectively.

[0020] The terms "aralkyl" and "heteroaralkyl" as used herein, mean an aryl or heteroaryl group bonded to an alkyl group, respectively.

[0021] The term "arylalkoxy" and "heteroaryloxy," as used herein, means an aryl or heteroaryl group bonded to an alkoxy group.

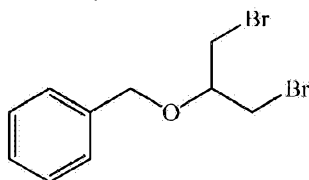
[0022] As used herein, the term "amino" means the group -NRR', wherein R and R' are, independently, hydrogen, alkyl or aryl, where the alkyl and aryl groups are optionally substituted.

[0023] The invention relates to a method for substantially removing a 1,2-dihalogen impurity of the formula (IV):



(IV)

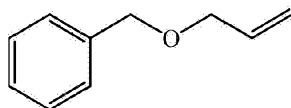
from a product mixture comprising a compound of the formula (V)



(V)

wherein the method comprises:

1. (a) reacting the product mixture with a methoxide, thereby transforming the 1,2-dihalogen impurity of the formula (IV) into an alkene of the formula (VI)



(VI); and

2. (b) removing the alkene of formula (VI).

[0024] In some embodiments, the alkene of formula (VI) is removed by vacuum (e.g., vacuum distillation).

[0025] In describing and claiming the present invention, the following terminology will be used in accordance with the additional definitions set forth below.

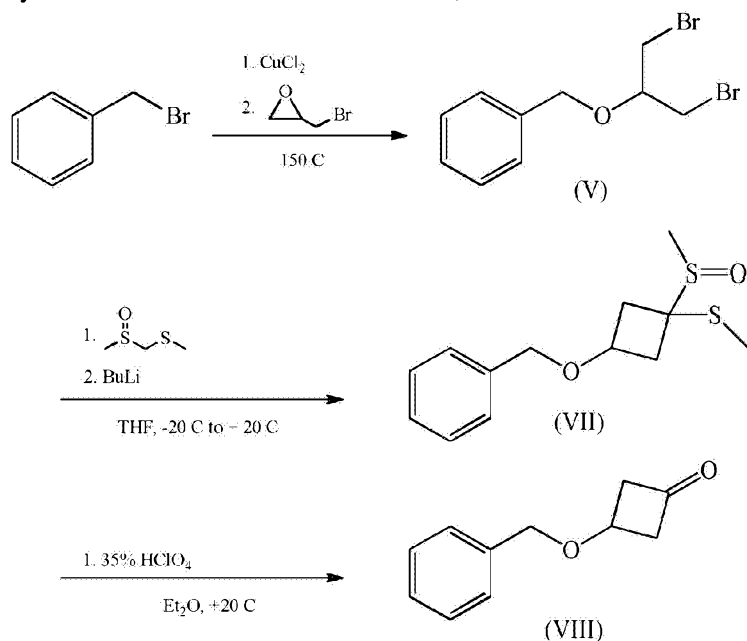
[0026] The singular forms "a," "an," and, "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an alkoxide" includes reference to

one or more alkoxides.

[0027] As used herein, the term "substantially" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is "substantially" enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation from absolute completeness may in some cases depend on the specific context. However, generally speaking the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of an action, characteristic, property, state, structure, item, or result. For example, "substantially removing a 1,2-dihalogen impurity" means either completely removing, or so nearly completely removing the 1,2-dihalogen impurity that the effect would be the same as if no 1,2-dihalogen impurity were present. In some embodiments, "substantially removing a 1,2-dihalogen impurity" means that there may still be some 1,2-dihalogen impurity, so long as there is no measurable effect thereof.

[0028] As used herein, the term "about" is used to provide flexibility to a numerical range endpoint by providing that a given value may be "a little above" or "a little below" the endpoint.

[0029] Compounds of the formula (V) are useful precursors in the preparation of [^{18}F]-FACBC. In some embodiments, compounds of the formula (V) can be converted in a number of steps into other precursors in the synthesis of [^{18}F]-FACBC. Exemplary precursors that can be synthesized are shown in Scheme I, below.



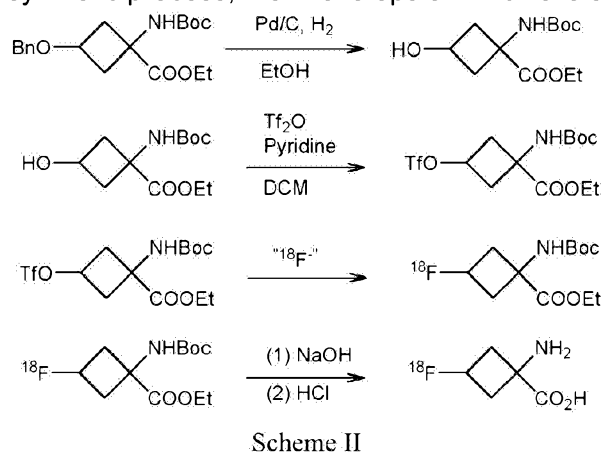
Scheme I

[0030] Although the synthetic procedure depicted in Scheme I uses specific reagents, those

skilled in the art will recognize that other solvents and reagents may be used to achieve the desired transformations. For example, the reaction step that produces the compound of the formula (IV), though it is performed with CuCl_2 , may also be performed using Hg^{2+} (e.g., HgCl_2).

[0031] Each product shown in Scheme I may be purified by methods known in the art, including crystallization, chromatographic methods (e.g., HPLC, column chromatography), or distillation.

[0032] The compound of formula (VIII) can be transformed into [^{18}F]-FACBC in a multi-step synthetic process, the final steps of which are shown below, in Scheme II.

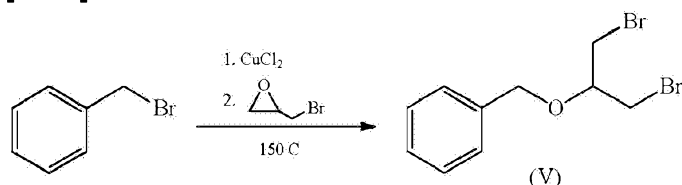


Examples

[0033] The following examples are provided to illustrate the present invention, and should not be construed as a limitation thereof.

Example 1

[0034]



[0035] Copper (II) chloride (8.37 g) and benzyl bromide (750 mL) were stirred at room temperature with a magnetic stirrer bar. Epibromohydrin (674 mL) was added to the reaction. The reaction was heated to reflux ($155\text{-}160\text{ }^\circ\text{C}$) for 11 hours before it was allowed to cool to

room temperature. The reaction mixture was distilled under reduced pressure and the main fraction collected at 155-180 °C at 0.07-0.026 mbar. The reaction produced 1.5 kg of the correct compound in ~60 % yield, with a purity of 70-75%.

[0036] Compound (V): ^1H NMR (500 MHz, CDCl_3): δ_{H} 7.42-7.28 (m, 5H), 4.66 (s, 2H), 3.80 (quin, $J=5.3$ Hz, 1H), 3.57 (d, $J=5.3$ Hz, 4H).

[0037] The main impurity in the isolated product is the compound of the formula (IV). The compound of formula (IV) and the compound of formula (V) cannot be efficiently separated due to the similarities in boiling points of the two compounds. Typically 20 mol % of the compound of formula (IV) contaminates the desired product of formula (V).

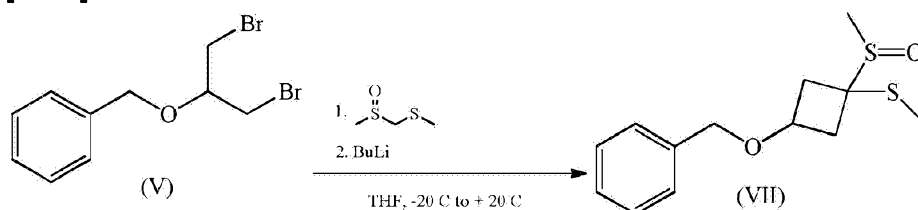
[0038] The compound of formula (IV) is efficiently removed by treating the crude reaction mixture comprising the compound of formula (IV) and (V) with sodium methoxide. The crude compound of formula (V) (100 g) was charged into a reaction vessel (1 L), fitted with a nitrogen flow. Methanol (500 mL) was added to the vessel and stirred for 10-15 min. Sodium Methoxide (170ml, 25% solution in methanol) was added to the reaction mixture. The reaction mixture was stirred for 4-6 h at room temperature. Completion of reaction monitored by HPLC.

[0039] The reaction mixture was quenched with water (300 mL). The methanol was evaporated under reduced pressure (e.g., on the rotary evaporator). The resulting residue was extracted into dichloromethane (DCM; 2 x 200 mL) and washed with water until the extract became neutral to litmus paper. The DCM was removed layer was separated and the DCM was removed under reduced pressure. The resulting residue was degassed to remove traces of DCM. The crude product was distilled under vacuum and the main fraction collected at 110-120 °C at 0.87-0.82 mbar.

[0040] Under these conditions, the compound of formula (IV) is converted into the compound of formula (VI). The resulting compound of the formula (VI) is a compound that has a sufficiently lower boiling point relative to the compound of formula (V), such that the compound of formula (VI) can be selectively removed by distillation.

Example 2

[0041]



[0042] The inventors have surprisingly and unexpectedly found that the yield of this reaction may be increased by improving the quality of the starting material by, e.g., removing the compound of formula (IV) from the reaction mixture as described above.

[0043] The equipment was dried before use, and the atmosphere kept inert (nitrogen). Tetrahydrofuran (THF; 40 L) was charged to the reactor maintaining a temperature of about -20°C. The starting material methanesulfinyl-methylsulfanyl-methane (1.5 kg) was added, followed by the addition of n-BuLi (5.33 L, 2.5M in hexane) while maintaining a temperature below -8°C. After the n-BuLi addition the reaction was stirred for 2 hours at -10°C. The compound of formula (V) (1.86 kg) was pre-diluted in THF (5 L) and added to the reactor while maintaining the temperature below -10°C. The temperature was maintained at -10°C for 1 hour before it was allowed to rise to room temperature overnight. The reaction was neutralized by adding acetic acid (~200 mL), followed by evaporation of THF. The raw product was then diluted with DCM (10 L) and washed with water (2 x 10 L). The organic phase was concentrated *in vacuo*, toluene (5 L) was added, and the crude product was azeotropically dried before separation. In some embodiments, the product is washed with cold hexanes (2 volumes) after the removal of the toluene.

[0044] Work up may be improved by replacing DCM with toluene during washing. While not being bound by theory, the toluene is believed to remove excess methanesulfinyl-methylsulfanyl-methane that may be left over from the reaction.

[0045] In some embodiments, this reaction may be conducted in toluene, thus eliminating the need to use and evaporate THF.

[0046] The raw product was diluted to 2 L with toluene and applied on to a silica gel pad. The pad was wet packed and pre-eluted with toluene. The pad used to separate a 1.5 kg batch was 40 cm in diameter and 22 cm high. After applying the raw product on to the pad it was eluted with 10 L fractions of eluents in the following order: 2 x 10 L toluene; 2 x 10 L toluene:dichloromethane (DCM) (50:50); 1 x 10 L DCM; 3 x 10 L DCM:ethylacetate (80:20); 5 x 10 L DCM:ethylacetate (70:30); 1 x 10 L DCM:ethylacetate (60:40); 5 x 10 L DCM:ethylacetate (50:50). The product fractions were collected and the solvent evaporated under vacuum. A total of 487 g of product was isolated. Side fractions containing 207 g of product were also isolated separately. The total yield of product when corrected for purity of the starting material is 56% (40% without the side fractions).

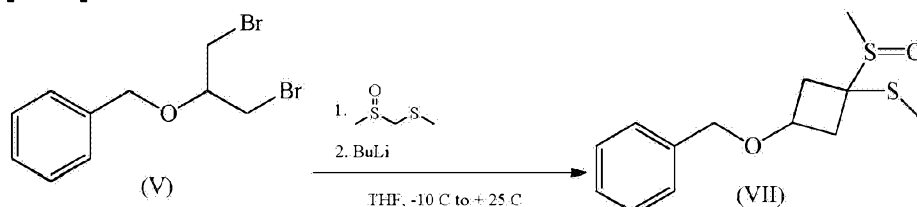
[0047] In some embodiments, the compound of formula (VII) may be distilled (e.g., high vacuum) instead of using column chromatography, as described above. In other embodiments, the compound of formula (VII) may be carried on to the next step (i.e., conversion to the compound of formula (VIII)) without purification.

[0048] Compound (VII): Diastereomer A: ¹H NMR (500 MHz, CDCl₃): δ_H 7.38-7.27 (m, 5H), 4.47 (s, 2H), 4.35 (tt, *J*=7.4,6.8 Hz, 1H), 2.79-2.73 (m, 1H), 2.71-2.66 (m, 1H), 2.47-2.40 (m,

1H), 2.18-2.13 (m, 1H), 2.45 (s, 3H), 2.12 (s, 3H). Diastereomer B: ^1H NMR (500 MHz, CDCl_3): δ_{H} 7.38-7.27 (m, 5H), 4.46 (s, 2H), 4.20 (tt, $J=7.5, 6.0$ Hz, 1H), 3.10-2.99 (m, 2H), 2.60-2.55 (m, 1H), 2.38-2.32 (m, 1H), 2.55 (s, 3H), 2.13 (s, 3H).

Example 3

[0049]

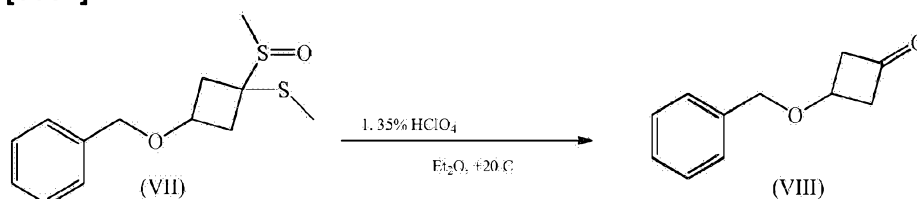


[0050] Dry THF (950 mL) was charged into a four necked reaction vessel (2 L) fitted with nitrogen flow. Methanesulfinyl-methylsulfanyl-methane (35 mL) was charged and the reaction mixture maintained at about -10°C . BuLi (140 mL) was added drop-wise to the reaction mixture, maintaining the temperature at -10°C . The reaction mixture was stirred for 1 hr. at -10°C . The compound of formula (V) (35 g), purified according to the methods described herein, was pre-diluted with THF (50 mL) was added, maintaining the temperature at -10°C . The temperature was maintained at -10°C for 1 hr. before it was allowed to reach room temperature (approximately 25°C). The reaction mixture was stirred at room temperature overnight (approximately 16 hrs).

[0051] The reaction mixture was neutralized with acetic acid and the THF was evaporated. The resulting residue was dissolved in toluene (600 mL) and washed with water (2 x 100 mL). The toluene layer containing the product can be taken as-is (*i.e.*, without further purification) to the next step. See, *e.g.*, Example 5.

Example 4

[0052]



[0053] Diethyl ether (26.5 L) was added to the reactor (30-35 L reactor), and water cooling was applied on the reactor when additions started. The compound of the formula (VII) was

added to the reactor (1.064 kg). Perchloric acid (0.932 L, 60%) was pre-diluted with water (0.664 L) and added slowly to the reactor at 10°C, over 20-30 minutes. After the addition of acid was complete, cooling was stopped, and the reaction was left to stir (vigorously) overnight at ~20°C. The reaction was quenched by the addition of NaHCO₃ (900 g) dissolved in 8 L water, until the pH was ~7. The water phase was discarded, and the reaction mixture was washed with an additional 7 L of water. The ether was removed *in vacuo*, toluene (2 L) was added, and the crude mixture was then azeotropically dried.

[0054] The raw product was diluted to ~2 L with toluene and loaded on to a silica gel pad. The pad was wet packed and pre-eluted with toluene. The pad used to separate a 1.5 kg batch was 40 cm in diameter and 22 cm high. After applying the raw product on to the pad it was eluted with 10 L fractions of eluents in the following order: 3 x 10 L toluene; 9 x 10 L toluene:ethyleacetate (95:5). The product fractions were collected and the solvent evaporated under vacuum. High vacuum was needed to remove the last 5% of toluene. A total of 533 g of product was isolated (yield = 77%). Analysis by GC showed a purity of 95%.

[0055] Compound (VIII): ¹H NMR (500 MHz, CDCl₃): δ_H 7.40-7.29 (m, 5H), 4.53 (s, 2H), 4.38 (tt, *J*=6.6,4.7 Hz, 1H), 3.3-3.1 (m, 4H)

Example 5

[0056] In some embodiments, the diethylether used in the reaction described in Example 4 can be replaced with toluene. In other embodiments, the evaporation of the organic phase during workup can advantageously lead to the azeotropic removal of all water. In still other embodiments, when adding the bicarbonate to neutralize the reaction, the reactor can be stopped, the water phase can be removed prior to conducting the neutralization and washing procedure.

[0057] Crude compound of formula (VII) in toluene (600 mL) was charged into a four necked reaction vessel (2 L). The mixture was cooled to -15°C. A cold solution of perchloric acid (24 mL, pre-diluted with 24 mL of water) was added to the reaction mixture over a period of 30 minutes, maintaining the temperature below 10 °C. The resulting mixture was allowed to reach room temperature over a period of 2 hrs. The reaction mixture was stirred overnight at 25 °C. The reaction was quenched with solid NaHCO₃ (30 g) and adjusted the pH to ~7. The water phase was discarded and the reaction mixture washed with water (2 x 100 mL). Toluene was removed under reduced pressure (e.g., on the rotary evaporator). The crude product was distilled under vacuum and the main fraction collected at 86-92°C at 0.87-0.82 mbar.

[0058] In some embodiments, the purification step (vacuum distillation) described in Example 2 can be left out. In other embodiments, toluene can be used as the solvent in Example 2 and the purification step can be eliminated, such that the compound of formula (VII) can be carried through, without purification, and transformed into the compound of formula (VIII). The

compound of formula (VIII) can then be purified by distillation or by column chromatography.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

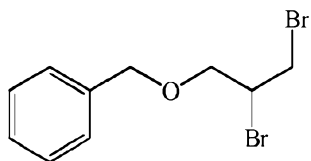
- [EP1978015A \[0003\]](#)
- [US2006292073A \[0003\]](#)

Non-patent literature cited in the description

- **MCCONATHY et al.** Appl Radiat Isotop, 2003, vol. 58, 657-666 [\[0003\]](#)
- **AVRAM et al.** Chem Ber, 1957, vol. 90, 1424-1431 [\[0003\]](#)

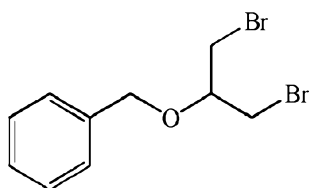
Patentkrav

1. Fremgangsmåde til i alt væsentligt at fjerne en 1,2-dihalogen-urenhed af formelen (IV)



5 (IV)

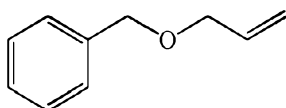
fra en produktblanding omfattende en forbindelse af formelen (V)



(V)

hvor fremgangsmåden omfatter:

10 (a) at reagere produktblandingen med et methoxid, for derved at transformere 1,2-dihalogen-urenheden af formelen (IV) til en alken af formelen (VI)



(VI)

og

(b) at fjerne alkenen af formel (VI).

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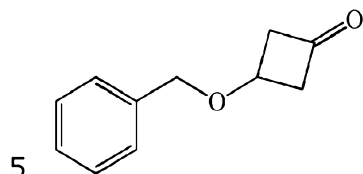
2. Fremgangsmåden ifølge krav 1, hvor nævnte methoxid er natriummethoxid.

3. Fremgangsmåden ifølge krav 1, hvor alkenen af formel (VI) fjernes ved vakuum.

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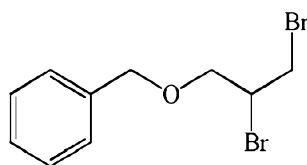
4. Fremgangsmåden ifølge krav 1, hvor alkenen af formel (VI) fjernes ved vakuum destillation.

5. Fremgangsmåde til fremstilling af en forbindelse af formelen (VIII):

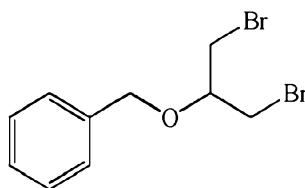


hvilken fremgangsmåde omfatter:

(a) at reagere benzylbromid med epibromhydrin for at give en produktblanding omfattende en forbindelse af formelen (IV) og en forbindelse af formelen (V):



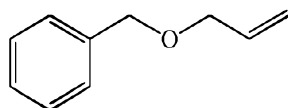
(IV)



(V)

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(b) at reagere produktblandingen med et methoxid, for derved at transformere forbindelsen af formel (IV) til en forbindelse af formelen (VI):



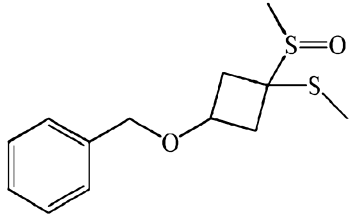
(VI);

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(c) at fjerne forbindelsen af formel (VI) således at forbindelsen af formel (V) er tilbage;

(d) at reagere den tilbageværende forbindelse af formel (V) med methansulfinyl-methylsulfanyl-methan for at give en forbindelse af formelen (VII):

3



(VII)

og at udføre en behandling af reaktionen med toluen;

(e) at hydrolysere forbindelsen af formel (VII) i toluen for at give en forbindelse af formlen (VIII); og

5 (f) at oprense forbindelsen af formel (VIII).

6. Fremgangsmåden ifølge krav 5, hvor nævnte oprensning omfatter vakuumdestillation.

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