(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 February 2016 (04.02.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/016446 A1

(51) International Patent Classification:
C07D 323/06 (2006.01) *C07C 47/14* (2006.01)

(21) International Application Number:
PCT/EP2015/067716

(22) International Filing Date:
31 July 2015 (31.07.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
14179387.7 31 July 2014 (31.07.2014) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2016/016446 A1

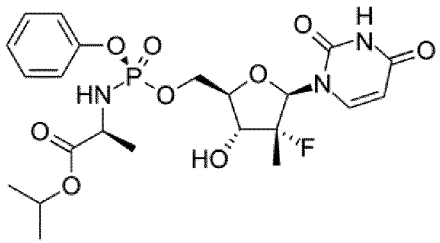
(54) Title: PROCESS FOR PREPARING 2-FLUOROPROPIONALDEHYDE

(57) Abstract: A process comprising (i) providing a 2-fluoropropionic acid halide; (ii) hydrogenating the 2-fluoropropionic acid halide by contacting it with a heterogeneous hydrogenation catalyst in an atmosphere comprising hydrogen, obtaining a mixture comprising 2-fluoropropionic aldehyde.

Process for preparing 2-fluoropropionaldehyde

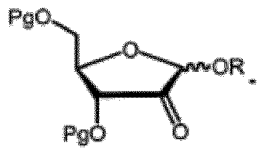
The present invention relates to a novel synthesis for preparing 2-fluoropropionaldehyde. The present invention further relates to the use of 2-fluoropropionaldehyde as a substrate for an aldol condensation reaction. The present invention further relates to the use of 2-fluoropropionaldehyde as a reagent in an aldol condensation reaction, preferably in an enzymatic aldol condensation reaction. The present invention further relates to the use of 2-fluoropropionaldehyde for preparing nucleoside phosphoramidate derivatives such as sofosbuvir and intermediates for the synthesis of nucleoside phosphoramidate derivatives such as sofosbuvir.

Sofosbuvir according to formula (I)



(A)

with IUPAC name (*S*)-isopropyl 2-(((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-amino)propanoate is a drug inhibiting the RNA polymerase used by the hepatitis C virus to replicate its RNA. 2'-deoxy-2-fluoro-2'C-methyluridine is an intermediate in the synthesis of sofosbuvir. This nucleoside is usually prepared according to a process as disclosed in patent application WO 2005/003147. 2'-deoxy-2-fluoro-2'C-methyluridine is prepared starting from a compound of formula



wherein "Pg" is a protecting group. Alternatively, 2'-deoxy-2-fluoro-2'C-methyluridine is prepared starting from a preformed nucleoside.

Ojima et al., J. Am. Chem. Soc. (JACS) 1987, 109, 7714-7720, discloses the synthesis of 2-fluoropropionaldehyde. 2-fluoropropionaldehyde is prepared by hydroformylation of vinyl fluoride. The complex compounds $Rh_4(CO)_{12}$, or $HRh(CO)(PPh3)_3$, $Ru(CO)_{12}$ or $Co(CO)_{12}$ are used as catalysts. Thus, the hydroformylation reaction includes the use of expensive and toxic metal catalysts. Moreover, the reaction makes use of the toxic carbon monoxide as a reagent and needs to be carried out at very high temperatures (80 to 100 °C) and high pres-

sures (68 to 110 atm).

Bergmann et al., Tetrahedron Letters no. 17, pages 1151-1153, 1965, discloses the preparation of 2-fluoropropionaldehyde via reduction of 2-fluoropropionic acid chloride using lithium aluminum hydride. The handling of the final product however results cumbersome due to the solubility of the product in water and the difficulty in removing the salts formed due to the presence of the lithium aluminum hydride catalyst such as aluminum salts.

Therefore, the problem underlying the present invention is the provision of a novel process for the preparation of 2-fluoropropionaldehyde which is carried out in mild and simple conditions, is economic and provides 2-fluoropropionaldehyde in good yields and leads to a product easy to be purified, which can be directly used in subsequent reactions such as in aldol reactions for example for the preparation of 2'-deoxy-2-fluoro-2'C-methyluridine and, hence, of sofosbuvir.

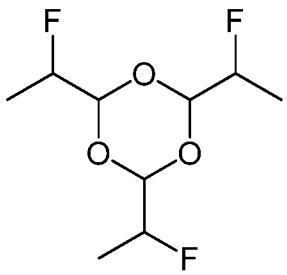
Surprisingly, it was found that this problem can be solved by a process for preparing the 2-fluoropropionaldehyde carried out by subjecting a 2-fluoropropionic acid halide to a heterogeneously catalyzed reductive hydrogenation.

Therefore, the present invention relates to a process comprising

(i) providing a 2-fluoropropionic acid halide;

(ii) hydrogenating the 2-fluoropropionic acid halide by contacting it with a heterogeneous hydrogenation catalyst in an atmosphere comprising hydrogen, obtaining a mixture comprising 2-fluoropropionic aldehyde.

Further the present invention relates to a compound of formula (II)



(II),

which is optionally at least partially dissolved in one or more solvents.

Preparation of the 2-fluoropropionic aldehyde

Step (i)

According to the present invention, the 2-fluoropropionic acid halide provided in (i) is 2-

fluoropropionic acid chloride, 2-fluoropropionic acid bromide or 2-fluoropropionic acid iodide, preferably 2-fluoropropionic acid chloride or 2-fluoropropionic acid bromide.

Generally, the 2-fluoropropionic acid halide is provided in (i) as (S)-2-fluoropropionic acid halide, as (R)-2-fluoropropionic acid halide, or as a mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide, for example comprising from 0.1 to 99.9 mol-% of the 2-fluoropropionic acid halide as (S)-2-fluoropropionic acid halide and from 99.9 to 0.01 mol-% of the 2-fluoropropionic acid halide as (R)-2-fluoropropionic acid halide, such as a racemic mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide.

Generally, there is no specific limitation how the 2-fluoropropionic acid halide is provided in (i), with the proviso that it can be subjected to the hydrogenation reaction according to (ii). Preferably, the 2-fluoropropionic acid halide is provided comprised in a mixture which subjected to (ii).

Preferably, this mixture comprises one or more suitable solvents, preferably one or more organic solvents. While there is no specific limitation with regard to the chemical nature of the organic solvents, one or more aprotic organic solvents are preferred. Apolar aprotic solvents are conceivable, including toluene, xylene, cyclohexane, hexane, heptane, diethyl ether, methyl-tert-butyl ether, diisopropyl ether. Preferred solvents are polar aprotic solvents, preferably including acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, ethyl acetate, methyl ethyl ketone, and butyl acetate, more preferably being selected from the group consisting of acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, and butyl acetate. Tetrahydrofuran and ethyl acetate are especially preferred solvents.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran as solvent.

Preferably, the mixture provided in (i) which comprises the 2-fluoropropionic acid halide further comprises one or more bases preferably one or more organic bases and/or one or more inorganic bases.

Examples of inorganic acids include carbonates, alkali metal and alkaline earth metal carbonates, such as Na_2CO_3, K_2CO_3, Ba_2CO_3, Ca_2CO_3, Cs_2CO_3 and Li_2CO_3.

Preferably, the mixture provided in (i) which comprises the 2-fluoropropionic acid halide further comprises one or more organic bases. Preferred organic bases include amines, amidines, heterocyclic compounds comprising a basic nitrogen atom in the cycle, and mixtures of two or more thereof.

Preferably, the one or more organic bases are organic tertiary nitrogen bases, wherein, more preferably, the organic tertiary nitrogen bases do not comprise primary amino groups or secondary amino groups, preferable neither primary amino groups nor secondary amino groups. Preferred organic tertiary nitrogen bases include N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, pyridine, quinoline, isoquinoline, acridine, pyrazine, and imidazole, preferably one or more of N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, and pyridine. Preferably, organic tertiary nitrogen bases include N,N'-diisopropylethylamine and triethylamine.

No specific limitations exist with regard to the amount of the one or more bases comprised in the mixture provided in (i). Preferably, the one or more bases and the 2-fluoropropionic acid halide are present in the mixture provided in (i) in a molar ratio of the one or more bases relative to the 2-fluoropropionic acid halide in the range of from 0.1 : 1 to 3 : 1, preferably in the range of from 0.75 : 1 to 1.5 : 1, more preferably in the range of from 0.95 : 1 to 1.05 : 1. If more than base is comprised in the mixture, the molar ratios relate to the total molar amount of all bases.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, and an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1.

Without wanting to be bound by any theory, it is believed that the base neutralizes the hydrogen halide which is formed during the hydrogenation reaction of the 2-fluoropropionic acid halide. Therefore, in case a base is present, a hydrogen halide-base salt may be formed during the reaction. As mentioned above, the one or more bases may serve for neutralizing the acid formed during the reaction by forming a salt. Hence, according to the present invention, the mixture obtained according to the below step (ii) may additionally contain the hydrogen halide salt of the one or more bases. Depending on the separation or purification used to purify the 2-fluoropropionaldehyde or a solution comprising the 2-fluoropropionaldehyde, the base

may be selected considering whether the salt of the base and acid formed during the reaction is insoluble under the separation conditions and optionally under the process conditions and can be easily separated, for example by filtration.

Preferably, the mixture provided in (i) which comprises the 2-fluoropropionic acid halide further comprises a solid porous adsorbent. Without wanting to be bound by any theory, it is believed that the solid porous adsorbent may adsorb the water possibly formed during the hydrogenation process, or absorb any residual water possibly present in the one or more solvent and/or the reagents that might hydrolyze the acid halide, thus possibly resulting in a lower reaction yield, and possibly prevent the formation of by-products, for example due to the condensation of the halide with the corresponding acid.

Preferred solid porous adsorbents include molecular sieves. Preferably, the solid porous adsorbent, preferably the molecular sieve, is a microporous compound having a pore size of less than 2 nm, determined according to DIN 66135-2. More preferably, the pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of tetrahydrofuran, ethyl acetate and toluene, preferably in a mixture comprising tetrahydrofuran as solvent, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2.

Step (ii)

According to (ii), the 2-fluoropropionic acid halide is hydrogenated by contacting it with a heterogeneous hydrogenation catalyst in an atmosphere comprising hydrogen, obtaining a mixture comprising 2-fluoropropionic aldehyde.

Regarding heterogeneous hydrogenation catalyst according to (ii), no specific limitations exist. Preferably, the heterogeneous hydrogenation catalyst is a solid catalyst which, more preferably, comprises one or more hydrogenation-active metals. No specific limitations exist with regard to these hydrogenation-active metals which preferably include one or more of palladium, platinum, rhodium, ruthenium, nickel and iridium, more preferably palladium and platinum. More preferably, the heterogeneous hydrogenation catalyst according to (ii) comprises palladium.

While it is conceivable that the hydrogenation-active metal is employed as such, it is preferred that the one or more the hydrogenation-active metals are employed supported in one or more suitably supports. No specific limitations exist with regard to these supports provided that they can be employed in the hydrogenation reaction according to (ii) and are substantially inert under the reaction conditions. Preferred supports are oxidic supports and preferably include one or more of silica, titania, alumina, preferably gamma-alumina, mixed oxides of two or more thereof, sulfates, preferably alkaline earth metal sulfates, carbonates, preferably alkaline earth metal carbonates. More preferably, the oxidic support comprises calcium carbonate or barium sulfate. More preferably, the oxidic support comprises, more preferably is, barium sulfate.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, and wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, and wherein the

mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate.

Surprisingly, it has been found that under the reducing hydrogenation conditions of the present invention, the acid halide is selectively dehalogenated to give the corresponding aldehyde. More surprisingly, substantially no reductive dehalogenation of the fluoro residue in alpha position to the carboxyl group has been observed.

Additionally, with respect to the prior art, J. Am. Chem. Soc. (JACS) 1987, 109, 7714-7720, the present invention provides the advantage of the use of a catalyst that does not contain toxic moieties such as carbon monoxide and that is easily separable from the solution in which the hydrogenation reaction is carried out. With respect to the prior art, Tetrahedron Letters No.17 pp 1151-1153, 1965, the present invention provides an easily separable catalyst as well. It is conceivable that the heterogeneous catalyst may optionally be suitably poisoned by any method known in the art, for example to avoid a further reduction of the aldehyde product to the corresponding alcohol.

While there is no specific limitation with regard to the amount of the heterogeneous catalyst, it is preferred that it is employed at a molar ratio of the heterogeneous catalyst relative to the 2-fluoropropionic acid halide in the range of from 0.01 : 1 to 1 : 1, more preferably in the range of from 0.05 : 1 to 0.6 : 1, more preferably in the range of from 0.06 : 1 to 0.5 : 1.

According to the present invention, it is preferred that at least 90 volume-%, more preferably at least 95 volume-%, more preferably at least 99 volume-% of the atmosphere comprising hydrogen consist of hydrogen.

Preferably, the hydrogenating according to (ii) is carried out at a hydrogen pressure in the range of from 0.5 to 2.0 bar, preferably in the range of from 0.7 to 1.7 bar, more preferably in the range of from 1.0 to 1.2 bar.

Hence, when compared with the prior art, in particular to the teaching of J. Am. Chem. Soc. (JACS) 1987, 109, 7714-7720, the present invention advantageously provides a process that can be carried out much milder pressure conditions. While the hydroformylation disclosed in JACS is carried out at a pressure of 68 to 110 atm, corresponding to 68.9 to 111.4 bar, the present process can be carried out at a far lower pressure. This allows for having a simpler and more economic reaction avoiding the problem generically associated with the carrying out of a reaction at a high pressure.

Preferably, the hydrogenating according to (ii) is carried at a temperature of the atmosphere comprising hydrogen in the range of from 10 to 40 °C, more preferably in the range of from 15 to 35 °C, more preferable in the range of from 20 to 30 °C.

Hence, when compared with the prior art, in particular the teaching of J. Am. Chem. Soc. (JACS) 1987, 109, 7714-7720, the present invention provides a hydrogenation process that can be carried out at much milder temperature condition. While the hydroformylation disclosed in JACS is carried out at a temperature of 80 to 100 °C, the present process can be carried out at a far lower temperature, resulting in a simpler and more economic process. When compared with the teaching of Tetrahedron Letters No.17 pp 1151-1153, 1965 the present invention provides a simpler and more economic process as temperature of –80 °C can be avoided.

The hydrogenation reaction according to (ii) is generally carried out by stirring the mixture as disclosed above under an atmosphere comprising hydrogen as disclosed above for a time sufficient to give the 2-fluoropropionic aldehyde. Preferably, the hydrogenating according to (ii) is carried for a period of time in the range of from 1 to 24 h, more preferably in the range of from 2 to 8 h.

Generally, the hydrogenation reaction according to (ii) can be carried out in batch mode, semi-continuous mode, or continuous mode. If it is carried in continuous mode, it can be carried out in either a fluidized bed or a fixed bed. In a fluidized bed, the heterogeneous hydrogenation catalyst is kept suspended in a portion of the mixture which is maintained in the reactor whereas in a fixed-bed reactor, the heterogeneous hydrogenation catalyst is maintained during the reaction in the form of a fixed catalyst bed, and the mixture and atmosphere comprising the hydrogen are continuously passed through the respective bed.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, and wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogenous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, and wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar.

Preferably, in case the 2-fluoropropionic acid halide is provided in (i) as (S)-2-fluoropropionic acid halide, the 2-fluoropropionic aldehyde obtained in (ii) is (S)-2-fluoropropionic aldehyde. Preferably, in case the 2-fluoropropionic acid halide is provided in (i) as (R)-2-fluoropropionic acid halide, the 2-fluoropropionic aldehyde obtained in (ii) is (R)-2-fluoropropionic aldehyde. Preferably, in case the 2-fluoropropionic acid halide is provided in (i) as as a mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide, for example comprising from 0.1 to 99.9 mol-% of the 2-fluoropropionic acid halide as (S)-2-fluoropropionic acid halide and from 99.9 to 0.01 mol-% of the 2-fluoropropionic acid halide as (R)-2-fluoropropionic acid halide, such as a racemic mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide, the 2-fluoropropionic aldehyde obtained in (ii) is a mixture of (S)- 2-fluoropropionic aldehyde and (R)- 2-fluoropropionic aldehyde, for example comprising from 0.1 to 99.9 mol-% of the 2-fluoropropionic aldehyde as (S)- 2-fluoropropionic aldehyde and from 99.9 to 0.01 mol-% of the 2-fluoropropionic aldehyde as (R)-22-fluoropropionic aldehyde, such as a racemic mixture of (S)- 2-fluoropropionic aldehyde and (R)-2-2-fluoropropionic aldehyde.

Step (iii)

According to the present invention, it is further preferred that the 2-fluoropropionic aldehyde comprised in the mixture obtained in (ii) is suitably separated. Therefore, the present invention also relates to the process as defined above, further comprising

(iii) separating the 2-fluoropropionic aldehyde from the heterogeneous hydrogenation catalyst comprised in the mixture obtained in (ii).

Preferably, the separating according to (iii) comprises subjecting the mixture obtained in (ii) to solid phase separation wherein the solids comprised in the mixture are separated from the liquid phase. As mentioned above, it is preferred that in addition to the heterogeneous hydrogenation catalyst, the mixture obtained from (ii) additionally comprises the solid porous adsorbent and optionally the possibly solid hydrogen halide salt of the one or more bases. Therefore, according to the present invention, it is preferred that during separating in (iii), the heterogeneous hydrogenation catalyst, the solid porous adsorbent and optionally the solid hydrogen halide salt of the one or more bases is separated from the liquid phase of the mixture obtained from (ii) comprising the 2-fluoropropionic aldehyde.

Preferably, the solid phase separation according to (iii) comprises centrifugation or filtration, preferably filtration.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar, and wherein the mixture obtained from (ii) is subjected to filtration, obtaining the 2-fluoropropionic aldehyde separated from the heterogeneous hydrogenation catalyst and the solid porous adsorbent.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of

from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar, and wherein the mixture obtained from (ii) is subjected to filtration, obtaining the 2-fluoropropionic aldehyde separated from the heterogeneous hydrogenation catalyst, the solid porous adsorbent, and possibly the solid hydrogen halide salt of the organic base.

Step (iv)

According to the process of the present invention, it is preferred that after the separation process according to (iii), the liquid phase obtained, comprising the one or more solvents and the 2-fluoropropionic aldehyde, is further worked-up. For example, the 2-fluoropropionic aldehyde can be separated from the solvent via distillation. More preferably, the liquid phase obtained, comprising the one or more solvents and the 2-fluoropropionic aldehyde, is subjected to extraction wherein the 2-fluoropropionic aldehyde is suitably extracted.

Therefore, the present invention also relates to the process as defined above, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised in a mixture comprising one or more organic solvents and wherein from (iii), a mixture is obtained comprising the 2-fluoropropionic aldehyde and the one or more solvents, further comprising

(iv) extracting the 2-fluoropropionic aldehyde from the mixture obtained in (iii) with one or more solvents, obtaining a mixture comprising the 2-fluoropropionic aldehyde and the one or more solvents.

Preferably, the one or more solvents according to (iv) include water and one or more organic solvents, preferably including pentane, hexane, heptane, cyclohexane, ethyl acetate, methyl isobutyl ketone, methyl tert-butyl ether, diisopropyl ether, and methyl tetrahydrofuran. More preferably, the one or more solvents according to (iv) are water or a mixture of water and one or more organic solvents. More preferably, the solvent used in (iv) is water.

Hence, when, compared with the teaching of Tetrahedron Letters No.17 pp 1151-1153, 1965 the process of the present invention provides the 2-fluoropropionaldehyde in a form that is easy to be purified and directly usable in further reactions. On the contrary, the use of $LiAl(OtBu)_3$ as a reducing agent leads at least to the formation of aluminum salts which are difficult to remove from the solution comprising the 2-fluoropropionaldehyde.

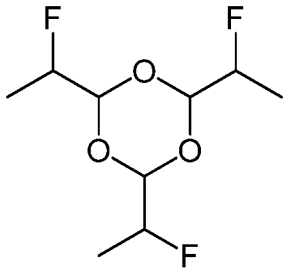
Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, and a microporous molecular

sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2., wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar, wherein the mixture obtained from (ii) is subjected to filtration, obtaining the 2-fluoropropionic aldehyde separated from the heterogeneous hydrogenation catalyst and the solid porous adsorbent, and wherein from the liquid mixture obtained from (iii), the 2-fluoropropionic aldehyde is extracted, preferably with water.

Therefore, the present invention relates to the process as defined above, wherein the 2-fluoropropionic acid halide is provided comprised in a mixture comprising a solvent selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, preferably in a mixture comprising tetrahydrofuran or ethyl acetate as solvent, an organic base selected from the group consisting of N,N'-diisopropylethylamine and triethylamine, wherein the molar ratio of the one or more bases relative to the 2-fluoro-propionic-acid halide is preferably the range of from 0.95 : 1 to 1.05 : 1, and a microporous molecular sieve, preferably having a pore size in the range of from 0.35 to 0.45 nm, determined according to DIN 66135-2, wherein the mixture is subjected in (ii) to hydrogenation reaction conditions in the presence of a heterogeneous hydrogenation catalyst, preferably palladium supported in barium sulfate or calcium carbonate, wherein the hydrogenation reaction conditions comprise a temperature in the range of from 20 to 30 °C and a hydrogen pressure in the range of from 1.0 to 1.2 bar, wherein the mixture obtained from (ii) is subjected to filtration, obtaining the 2-fluoropropionic aldehyde separated from the heterogeneous hydrogenation catalyst, the solid porous adsorbent, and possibly the solid hydrogen halide salt of the organic base, and wherein from the liquid mixture obtained from (iii), the 2-fluoropropionic aldehyde is extracted, preferably with water.

Compound of formula (II)

When being extracted according to (iv), preferably with water according to the preferred embodiment above, the 2-fluoropropionaldehyde can be present as trimeric compound. Therefore, the present invention also relates to the compound of formula (II)



(II),

which is at least partially dissolved in one or more solvents, wherein the one or more solvents are preferably selected from the group consisting of water, one or more organic solvent, and a mixture of two or more thereof, wherein the one or more solvents preferably comprise, more preferably consist of, water.

Preparation of the 2-fluoropropionic acid halide

According to the present invention, no specific limitation exist how the 2-fluoropropionic acid halide according to (i) is prepared. Preferably, it is prepared by a process comprising

a) mesylating ethyl lactate, obtaining ethyl-2-((methylsulfonyl)oxy) propanoate;
b) fluorinating the ethyl-2-((methylsulfonyl)oxy)propanoate) of step i), obtaining 2-fluoropropanoate;
c) hydrolyzing the 2-fluoropropanoate of step ii), obtaining the corresponding 2-fluoropropanoic acid;
d) converting the 2-fluoropropanoic acid of step iii) to the corresponding 2-fluoro-propionic acid halide.

Further, the present invention also relates to a process for the preparation of a 2-fluoropropionic acid halide as such, comprising

a) mesylating ethyl lactate, obtaining ethyl-2-((methylsulfonyl)oxy) propanoate;
b) fluorinating the ethyl-2-((methylsulfonyl)oxy)propanoate) of step i), obtaining 2-fluoropropanoate;
c) hydrolyzing the 2-fluoropropanoate of step ii), obtaining the corresponding 2-fluoropropanoic acid;
d) converting the 2-fluoropropanoic acid of step iii) to the corresponding 2-fluoro-propionc acid halide.

Step a)

As a general procedure, the mesylation of a) is carried out by adding ethyl lactate to a solution comprising an organic base or a combination of one or more organic bases. Preferably the one or more organic bases include N,N'-diisopropylethylamine, triethylamine, 4-dimethylaminopyridine, 1,8-diazabicycloundec-7-ene, pyridine, quinoline, isoquinoline, acridine, pyrazine, and imidazole, preferably one or more of N,N'-diisopropylethylamine, triethylamine, and 1,8-diazabicycloundec-7-ene. More preferably, the one or more bases comprise triethylamine. The reaction can be carried out in a solution comprising one or more solvents. Preferably, the one or more solvents include THF, MeTHF, dichloromethane, cyclohexane, hexane, heptane, toluene, xylene, acetonitrile, acetone, diethyl ether, methyl isobutyl

ketone, methyl-tert-butyl ether, and diisopropyl ether. Preferably, the one or more solvents comprise THF.

Preferably, the reaction according to a) is carried out at a temperature in the range of 40 to 80 °C, more preferably in the range of from 50 to 60 °C.

Preferably, the mixture comprising the lactate and the base is cooled to a suitable temperature below room temperature (RT=23 °C). Methanesulfonyl chloride is then preferably added, preferably drop-wise. The mixture is preferably allowed to warm up, preferably to room temperature. It is preferred that then, the mixture is stirred for example for 6 h at a temperature elevated with respect to room temperature, preferably in the range of from 50 to 60 °C. The mixture is then preferably filtered and optionally washed. The solvent is then preferably removed, preferably under vacuum, to yield crude 2-((methylsulfonyl)oxy)-propanoate. The crude can be used without further purification.

Step b)

The 2-fluoropropanoic ester, preferably 2-fluoropropanoic ethyl ester, can be prepared from 2-((methylsulfonyl)oxy)propanoate according to all suitable processes, such as disclosed in Tetrahedron Lett. 1993, 34(2), pages 293-296.

Preferably, the reaction is carried out in one or more solvents. Preferably, the one or more solvents include formamide, acetamide, dimethylformamide, and dimethylacetamide. More preferably the one or more solvents comprise formamide.

Preferably, the reaction according to b) is carried out at a temperature in the range of from 40 to 90 °C, more preferably in the range of from 50 to 80 °C.

According to the present invention, the 2-fluoropropanoic ester is preferably prepared by reaction of the ethyl-2-((methylsulfonyl)oxy)propanoate) of step a), preferably in the presence of potassium fluoride and formamide at the conditions and time until the ester is formed.

Step c)

According to the present invention, the 2-fluoropropanoic acid can be prepared from 2-fluoropropanoic ester, preferably the 2-fluoropropanoic ethyl ester, according to all suitable processes known in the art.

The 2-fluoropropanoic acid is preferably prepared by hydrolyzing the ester of step b) in acidic condition such as in sulphuric acid conditions.

According to the present invention, step c) is preferably carried out at a pH in the range of from 1 to 5, preferably in the range of from 2 to 4.

Step d)

According to the present invention, the 2-fluoropropionic acid halide can prepared from the 2-fluoropropanoic acid, according to all suitable processes known in the art.

The process of step d) is preferably carried in one or more solvents. The one or more solvents preferably include dimethylformamide, dichloromethane, THF, MeTHF, diethyl ether, MTBE, and dioxane. More preferably, the one or more solvents comprise DMF.

Preferably, the reaction according to d) is carried out at a temperature in the range of from 40 to 60 °C, preferably in the range of from 45 to 55 °C.

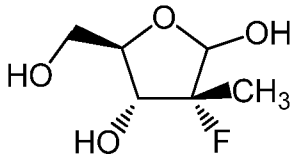
The 2-fluoropropionic acid halide is more preferably prepared by reaction of the acid of step c) in the presence of $SOCl_2$ in DMF at the conditions and time necessary for the acid halide to be formed.

Aldol Condensation

According to the present invention, the 2-fluoropropionic aldehyde can be used directly in a further reaction. Preferably, the 2-fluoropropionic aldehyde is reacted with a carbonyl compound in an aldol condensation reaction, preferably an enzymatic aldol condensation reaction.

Preferably, the aldol condensation reaction is carried out in the presence of a carbonyl compound, either an aldehyde or a ketone. According to the present invention, the carbonyl compound is preferably a glyceraldehyde derivative, preferably a (D)-glyceraldehyde derivative.

Glyceraldehyde is generally the starting molecule for the synthesis of further carbohydrates. Glyceraldehyde or derivatives thereof can be used according to the present invention to prepare a compound of formula (I) or diastereomers or stereoisomers thereof



(I).

The term "glyceraldehyde derivative" in the context of the present invention relates to a "protected glyceraldehyde" or an "activated glyceraldehyde". A protected glyceraldehyde is for example a glyceraldehyde wherein the OH groups in positions 2 and 3 are suitably protected to avoid side reactions during the aldol reaction. Any protecting group of OH groups or of diols suitable to be used in aldol reaction conditions can be used according to the present invention. For example, a suitable protecting group of the diol moiety of glyceraldehyde is an acetal. An "activated glyceraldehyde" is for example a glyceraldehyde bearing a functional group that provides the glyceraldehyde in the suitable reactive form for the subsequent reaction. For example, glyceraldehyde-3-phosphate is an activated form of glyceraldehyde in enzymatic reactions, such as an enzymatic aldol condensation reaction. An aldol condensation of (D)-glyceraldehyde-3-phosphate and 2-fluoropropionaldehyde carried out with deoxyribose-phosphate aldolase (DERA) leads, for example, to the compound of above formula (I).

The enzymatic aldol condensation reaction of the present invention is preferably carried out with a ribose phosphatase-aldolase enzyme, more preferably a deoxyribose-phosphate aldolase (DERA) enzyme.

Hence, the present invention also relates to a process comprising:

I) preparing the 2-fluoropropionaldehyde with a heterogeneous catalytic reductive hydrogenation, preferably according to a process as described above;

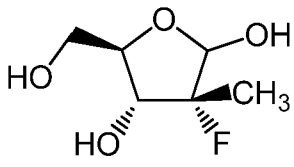
II) providing a solution, preferably an aqueous solution, comprising the 2-fluoropropionaldehyde of step I);

III) performing an aldol reaction, preferably an enzymatic aldol reaction, even more preferably enzymatic aldol reaction carried out by a DERA enzyme, with a carbonyl compound, wherein the carbonyl compound is preferably a glyceraldehyde derivative, more preferably a protected or activated glyceraldehyde, obtaining the aldol condensation product of 2-fluoropropionaldehyde and the carbonyl compound.

Preferably, I) comprises preparing the 2-fluoropropionaldehyde with a heterogeneous catalyst reductive hydrogenation according to the present invention as disclosed above. More preferably, I) comprises preparing the 2-fluoropropionaldehyde with a heterogeneous catalyst reductive hydrogenation of 2-fluoropropionic acid chloride according to the present invention as disclosed above wherein the heterogeneous catalyst is selected from the group consisting of $Pd/BaSO_4$ and $Pd/CaCO_3$.

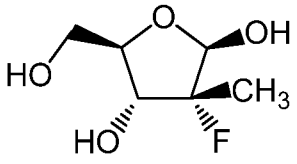
Preferably, III) comprises contacting the the 2-fluoropropionaldehyde in the solution of step II) with (D)-glyceraldehyde-3-phosphate and an enzyme, wherein the enzyme is preferably a

DERA enzyme, obtaining the compound of formula (I) or diastereomers or stereoisomers thereof

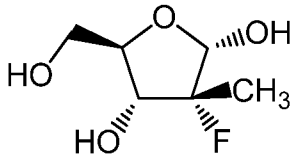


(I).

The compound of formula (I) can be obtained as a mixture of diastereoisomers



(IA) and



(IB).

Compounds (IA) and (IB) may optionally be separated before further use.

Preferably, III) is carried out in water. Hence, preferably, the 2-fluoropropionaldehyde is provided in II) in an aqueous solution.

The compound obtained in III) may be used in the preparation of phosphoramidate derivatives such as nucleoside phosphoramidate that are useful in the synthesis of biologically or pharmaceutically active compounds such as sofosbuvir.

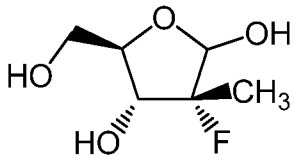
Use of the 2-fluoropropionaldehyde

The 2-fluoropropionic aldehyde or a solution thereof as disclosed above and prepared according to the process of the present invention or obtainable or obtained by the process of the present invention can be used as an intermediate for the synthesis of further compounds, for example for the preparation of biologically or pharmaceutically active compounds or intermediates of biologically or pharmaceutically active compounds.

According to the invention, valuable biologically or pharmaceutically active compounds that are prepared using the 2-fluoropropane aldehyde or a solution thereof are 2'-fluoronucleoside and pentafuranose precursors thereof for the preparation of nucleoside phosphoramidates agents that are useful for treating viral diseases. Preferably, sofosbuvir is a valuable compound that is prepared starting from the 2-fluoropropane aldehyde prepared according to the process of present invention, via intermediate of formula (I) and (I-A). Compound (I) or (I-A) is a known intermediated in the synthesis of sofosbuvir. The preparation of sofosbuvir starting from compound of formula (I) or (I-A) is disclosed for example in patent application WO 2008/121634.

Preferably, the 2-fluoropropionic aldehyde obtained or obtainable by the process of the invention is used as a reagent in aldol reaction, preferably, in an enzymatic aldol reaction. Preferably, the aldol reaction is carried out with a glyceraldehyde derivative, preferably a (D)-glyceraldehyde derivative. Without being bound to any theory it is believed that the reaction of the invention provides a highly pure 2-fluoropropionic aldehyde that can be directly used in enzymatic reaction without further purification/separation other than those disclosed above.

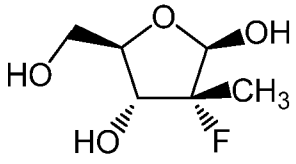
Preferably, the 2-fluoropropane aldehyde or a solution thereof obtained or obtainable by the process of the invention is used in an enzymatic aldol reaction to prepare the compound of formula (I) or diastereomers or stereoisomers thereof



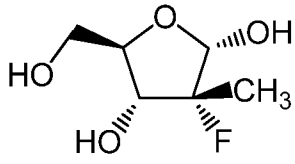
(I).

In general, according to the present invention, the compound of formula (I) is prepared by contacting a solution, preferably an aqueous solution, comprising 2-fluoropropionaldehyde and a glyceraldehyde derivative, preferably a D-glyceraldehyde-3-phosphate with an enzyme, preferably a deoxyribose-phosphate aldolase enzyme.

The compound of formula (I) can be obtained as a mixture of diastereoisomers.



(IA) and



(IB)

Compounds (IA) and (IB) may optionally be separated before further use.

The present invention is further illustrated by the following embodiments and combinations of embodiments as indicated by the respective dependencies and references.

1. A process comprising
   (i) providing a 2-fluoropropionic acid halide;
   (ii) hydrogenating the 2-fluoropropionic acid halide by contacting it with a heterogeneous hydrogenation catalyst in an atmosphere comprising hydrogen, obtaining a mixture comprising 2-fluoropropionic aldehyde.

2. The process of embodiment 1, wherein the 2-fluoropropionic acid halide provided in (i) is 2-fluoropropionic acid chloride or 2-fluoropropionic acid bromide.

3. The process of embodiment 1 or 2, wherein the 2-fluoropropionic acid halide provided in (i) is 2-fluoropropionic acid chloride.

4. The process of any of embodiments 1 to 3, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised a mixture comprising one or more organic solvents.

5. The process of embodiment 4, wherein the one or more organic solvents are one or more aprotic organic solvents.

6. The process of embodiment 4, wherein the one or more organic solvents are one or more polar aprotic organic solvents.

7. The process of any of embodiments 4 to 6, wherein the one or more organic solvents are selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate.

8. The process of any of embodiments 4 to 7, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised a mixture comprising tetrahydrofuran.

9. The process of any of embodiments 4 to 7, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised a mixture comprising ethyl acetate.

10. The process of any of embodiments 4 to 7, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised a mixture comprising toluene.

11. The process of any of embodiments 4 to 10, wherein the mixture provided in (i) further comprises one or more bases, wherein the one or more bases are preferably one or more organic bases or inorganic bases.

12. The process of embodiment 11, wherein the mixture provided in (i) further comprises one or more inorganic bases, preferably comprising a carbonate, more preferably an alkaline metal carbonate, more preferably sodium carbonate.

13. The process of embodiment 12, wherein the mixture provided in (i) further comprises one or more organic bases, preferably one or more organic tertiary nitrogen bases.

14. The process of embodiment 13, wherein the one or more tertiary nitrogen bases do not comprise a primary amine group.

15. The process of embodiment 13 or 14, wherein the one or more tertiary nitrogen bases do not comprise a secondary amine group.

16. The process of any of embodiments 13 to 15, wherein the one or more bases are one or more of N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, pyridine, quinoline, isoquinoline, acridine, pyrazine, and imidazole, preferably one or more of N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, and pyridine.

17. The process of embodiment 16, wherein the one or more bases are one or more of N,N'-diisopropylethylamine and triethylamine.

18. The process of any of embodiments 11 to 17, wherein in the mixture provided in (i), the one or more bases and the 2-fluoropropionic acid halide are present in a molar ratio of the one or more bases relative to the 2-fluoropropionic acid halide in the range of from 0.1 : 1 to 3 : 1, preferably in the range of from 0.75 : 1 to 1.5 : 1, more preferably in the range of from 0.95 : 1 to 1.05 : 1, wherein, if more than base is comprised in the mixture, the molar ratios relate to the total molar amount of all bases.

19. The process of any of embodiments 11 to 18, wherein the mixture obtained according to (ii) additionally contains a hydrogen halide salt of the one or more bases.

20. The process of any of embodiments 4 to 19, wherein the mixture provided in (i) further comprises a solid porous adsorbent.

21. The process of embodiment 20, wherein the solid porous adsorbent is a molecular sieve.

22. The process of embodiment 20 or 21, wherein the solid porous adsorbent is a microporous adsorbent having a pore size of less than 2 nm, determined according to DIN 66135-2.

23. The process of any of embodiments 20 to 22, wherein the solid porous adsorbent is a microporous adsorbent having a pore size of from 0.35 to 0.45 nm, determined according to DIN 66135-2.

24. The process of any of embodiments 1 to 23, wherein the heterogeneous hydrogenation catalyst according to (ii) comprises one or more hydrogenation-active metals.

25. The process of embodiment 24, wherein the one or more hydrogenation-active metals are one or more of palladium, platinum, rhodium, ruthenium, nickel and iridium.

26. The process of embodiment 24 or 25, wherein the one or more hydrogenation-active metals are one or more of palladium and platinum.

27. The process of any of embodiments 24 to 26, wherein the heterogeneous hydrogenation catalyst comprises palladium.

28. The process of any of embodiments 1 to 27, wherein the heterogeneous hydrogenation catalyst according to (ii) comprises a support, preferably an oxidic support.

29. The process of embodiment 28, wherein the oxidic support is one or more of silica, titania, alumina, preferably gamma-alumina, mixed oxides of two or more thereof, sulfates, preferably alkaline earth metal sulfates, carbonates, preferably alkaline earth metal carbonates.

30. The process of embodiment 29, wherein the oxidic support is calcium carbonate or barium sulfate, preferably barium sulfate.

31. The process of any of embodiments 1 to 30, wherein the heterogeneous hydrogenation catalyst according to (ii) comprises, for example consists of, palladium supported on $BaSO_4$.

32. The process of any of embodiments 1 to 30, wherein according to (ii), the molar ratio of the heterogeneous catalyst relative to the 2-fluoropropionic acid halide in the range of from 0.01 : 1 to 1 : 1, preferably in the range of from 0.05 : 1 to 0.6 : 1, more preferably in the range of from 0.06 : 1 to 0.5 : 1.

33. The process of any of embodiments 1 to 32, wherein according to (ii), at least 90 volume-%, preferably at least 95 volume-%, more preferably at least 99 volume-% of the atmosphere comprising hydrogen consist of hydrogen.

34. The process of any of embodiments 1 to 33, wherein the hydrogenating according to (ii) is carried out at a temperature of the atmosphere comprising hydrogen in the range of from 10 to 40 °C.

35. The process of embodiment 34, wherein the temperature is in the range of from 15 to 35 °C.

36. The process of embodiment 34 or 35, wherein the temperature is in the range of from 20 to 30 °C.

37. The process of any of embodiments 1 to 36, wherein the hydrogenating according to (ii) is carried out at a hydrogen pressure in the range of from 0.5 to 2.0 bar, preferably in the range of from 0.7 to 1.7 bar, more preferably in the range of from 1.0 to 1.2 bar.

38. The process of any of embodiments 1 to 37, wherein the hydrogenation according to (ii) is carried out in batch mode.

39. The process of embodiment 38, wherein the hydrogenating according to (ii) is carried for a period of time in the range of from 1 to 24 h, preferably in the range of from 2 to 8 h.

40. The process of any of embodiments 1 to 37, wherein the hydrogenation according to (ii) is carried out in continuous mode.

41. The process of any of embodiments 1 to 40, further comprising
(iii) separating the 2-fluoropropionic aldehyde from the heterogeneous hydrogenation catalyst comprised in the mixture obtained in (ii).

42. The process of embodiment 41, wherein the separating according to (iii) comprises subjecting the mixture obtained in (ii) to solid phase separation.

43. The process of embodiment 42, wherein the solid phase separation comprises centrifugation or filtration, preferably filtration.

44. The process of any of embodiments 41 to 43, wherein the mixture provided in (i) further comprises one or more bases, the mixture obtained according to (ii) contains a hydrogen halide salt of the one or more bases and a solid porous adsorbent, and wherein during solid phase separation, the hydrogen halide salt of the one or more bases and the solid porous adsorbent are separated from the 2-fluoropropionic aldehyde.

45. The process of any of embodiments 41 to 44, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised in a mixture comprising one or more

organic solvents and wherein from (iii), a mixture is obtained comprising the 2-fluoropropionic aldehyde and the one or more solvents, the process further comprising

(iv) extracting the 2-fluoropropionic aldehyde from the mixture obtained in (iii) with one or more solvents, obtaining a mixture comprising the 2-fluoropropionic aldehyde and the one or more solvents.

46. The process of embodiment 45, wherein the one ore more solvents according to (iv) are water or a mixture of water and one or more organic solvents.

47. The process of embodiment 46, wherein the one or more organic solvents include pentane, hexane, heptane, cyclohexane, ethyl acetate, methyl isobutyl ketone, methyl tert-butyl ether, diisopropyl ether, and methyl tetrahydrofuran.

48. The process of embodiment 45 or 46, wherein the one or more solvents according to (iv) are water.

49. The process of any of embodiments 1 to 48 wherein the 2-fluoropropionic acid halide provided according to (i) is prepared by a method comprising

a) mesylating ethyl lactate, obtaining ethyl-2-((methylsulfonyl)oxy) propanoate;

b) fluorinating the ethyl-2-((methylsulfonyl)oxy)propanoate) of step a), obtaining 2-fluoropropanoate;

c) hydrolyzing the 2-fluoropropanoate of step b), obtaining the corresponding 2-fluropropanoic acid;

d) converting the 2-fluoropropanoic acid of step c) to the corresponding 2-fluoropropionc acid halide.

50. The process of embodiment 49, wherein mesylating according to a) is carried in one or more solvents, preferably comprising tetrahydrofuran.

51. The process of embodiment 49 or 50, wherein mesylating according to a) is carried out at a temperature in the range of from 40 to 80 °C, preferably in the range of from 50 to 60 °C.

52. The process of any of embodiments 49 to 51, wherein fluorinating according to b) is carried out in one or more solvents, preferably comprising formamide.

53. The process of any of embodiments 49 to 52 wherein fluorinating according to b) is carried out at temperature in the range of from 40 to 90 °C, preferably in the range of from 50 to 80 °C.

54. The process of any embodiments 49 to 53 wherein hydrolyzing according to c) is carried out at a pH in the range of from 1 to 5, preferably in the range of from 2 to 4, as determined with a pH sensitive glass electrode.

55. The process of any of embodiments 49 to 54 wherein converting according to d) is carried in one or more solvents, preferably comprising dimethylformamide.

56. The process of any of embodiments 49 to 55 wherein converting according to d) is carried out at a temperature in the range of from 40 to 60 °C, preferably in the range of from 45 to 55 °C.

57. The process of any of embodiments 1 to 56, further comprising reacting the 2-fluoropropionic aldehyde with a carbonyl compound in an aldol condensation reaction, obtaining an aldol condensation product.

58. The process of embodiment 57, wherein the aldol condensation reaction is an enzymatic aldol condensation reaction.

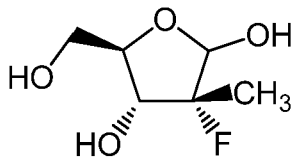
59. The process of embodiment 57 or 58, wherein the carbonyl compound is a glyceraldehyde derivative such as a phosphorylated glyceraldehyde or glyceraldehyde acetonide.

60. The process of embodiment 59, wherein the glyceraldehyde derivative is a (D)-glyceraldehyde derivative.

61. The process of any of embodiments 57 to 60, wherein the aldol condensation reaction is an enzymatic aldol condensation reaction and wherein the enzymatic aldol reaction is carried out using a ribose phosphatase-aldolase enzyme.

62. The process of any of embodiments 57 to 61, wherein the aldol condensation reaction is an enzymatic aldol condensation reaction and wherein the enzymatic aldol reaction is carried out in an aqueous solution.

63. The process of any of embodiments 57 to 62, wherein the aldol condensation product is the compound of formula (I) or diastereomers or stereoisomers thereof.



(I).

64. The process of any of embodiments 1 to 63, wherein in (i), the 2-fluoropropionic acid halide is provided as (S)-2-fluoropropionic acid halide.

65. The process of any of embodiments 1 to 63, wherein in (i), the 2-fluoropropionic acid halide is provided as (R)-2-fluoropropionic acid halide.

66. The process of any of embodiments 1 to 63, wherein in (i), the 2-fluoropropionic acid halide is provided as a mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide, preferably comprising from 0.1 to 99.9 mol-% of the 2-fluoropropionic acid halide as (S)-2-fluoropropionic acid halide and from 99.9 to 0.01 mol-% of the 2-fluoropropionic acid halide as (R)-2-fluoropropionic acid halide.

67. The process of embodiment 66, wherein in (i), the 2-fluoropropionic acid halide is provided as a mixture of (S)-2-fluoropropionic acid halide and (R)-2-fluoropropionic acid halide.

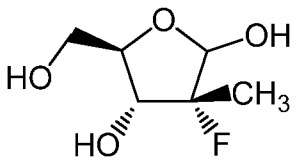
68. Use of 2-fluoropropionaldehyde as a reagent in an aldol condensation reaction, preferably in an enzymatic aldol reaction.

69. The use of embodiment 68, wherein the 2-fluoropropionaldehyde is comprised in a mixture obtainable or obtained according to a process of any of embodiments 45 to 48.

70. The use of embodiment 68 or 69, wherein the aldol reaction is carried out with a glyceraldehyde derivative, preferably a (D)-glyceraldehyde derivative.

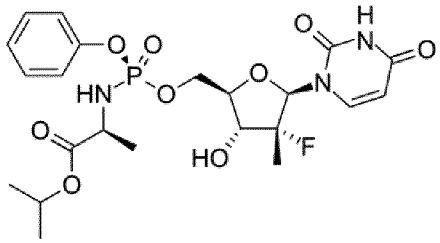
71. The use of any of embodiments 68 to 70, comprising preparing the 2-fluoropropionaldehyde by a process according to any of embodiments 1 to 56.

72. The use of any of embodiments 68 to 71, wherein the product of the aldol condensation reaction is the compound of formula (I) or diastereomers or stereoisomers thereof.



(I).

73. The use of embodiment 72, wherein the compound of formula (I) is used for the preparation of a compound of formula (S)



(S).

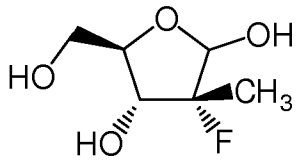
74. An aldol condensation process, preferably an enzymatic aldol condensation process, comprising reaction 2-fluoropropionaldehyde with a carbonyl compound.

75. The process of embodiment 74, wherein the 2-fluoropropionaldehyde is comprised in a mixture obtainable or obtained according to a process of any of embodiments 45 to 48.

76. The process of embodiment 74 or 75, wherein the carbonyl compound is a glyceraldehyde derivative, preferably a (D)-glyceraldehyde derivative.

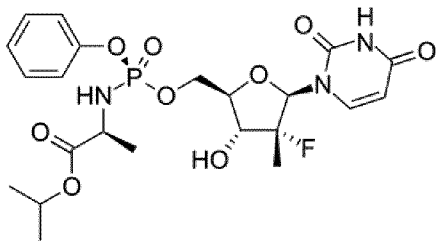
77. The process of any of embodiments 74 to 76, comprising preparing the 2-fluoropropionaldehyde by a process according to any of embodiments 1 to 56.

78. The process of any of embodiments 74 to 77, wherein the product of the aldol condensation reaction is the compound of formula (I) or diastereomers or stereoisomers thereof



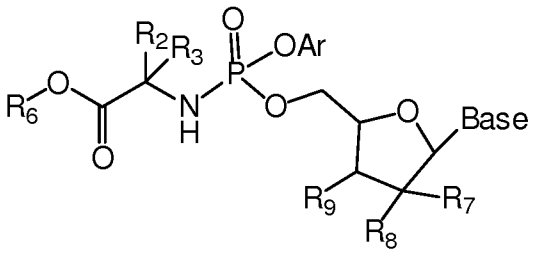
(I).

79. The process of embodiment 78, wherein the compound of formula (I) is used for the preparation of a compound of formula (S)



(S).

80. Use of 2-fluoropropionaldehyde for the preparation of a compound of formula (P)



(P).

81. The use of claim 80, wherein

Ar is phenyl, naphthyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, each optionally substituted with at least one of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 cycloalkyl, aryl, halogen, COOH, CHO, C(O)(C_1-C_6 alkyl), C(O)(aryl), COO(C_1-C_6 alkyl), $COONH_2$, COONH(C_1-C_6 alkyl), and CN;

R_2 and R_3 are independently H or C_1-C_6 alkyl optionally substituted with at least one of OH, C_1-C_6 alkoxy, aryl, heteroaryl, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, F, Cl, Br, I, NO_2, or carbonyl;

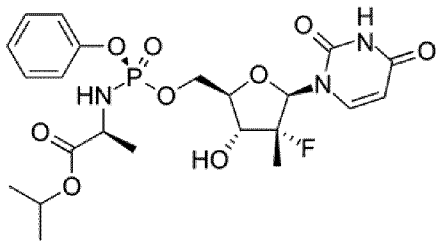
R_6 is C_1-C_6 alkyl or C_3-C_{10} cycloalkyl optionally substituted with at least one of C_1-C_6 alkyl and aryl;

Base is a purinyl residue or a pyrimidinyl residue linked to the furanose ring according to formula (III) through a carbon or nitrogen atom;

R_7 and R_8 are independently H, OH, F, Cl, Br, I, azide, nitrile, NH_2, NHR_{23}, $NR_{23}R_{24}$, (CO)-NH_2, (CO)-NHR_{23}, (CO)-$NR_{23}R_{24}$, C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl, or C_3-C_{10} cycloalkyl optionally substituted with C_1-C_6 alkyl, wherein R_{23} and R_{24} are independently C_1-C_6 alkyl;

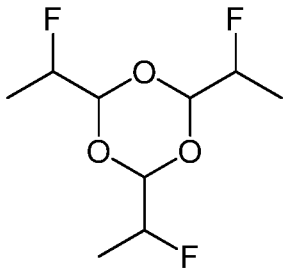
R_9 is H, OH, C_1-C_6 alkoxy, $SiR_aR_bR_c$, $OC(O)R_{25}$, or C_1-C_6 alkyl optionally substituted with C_1-C_6 alkyl or aryl, wherein R_{25} is C_1-C_6 alkyl or aryl, and wherein R_a, R_b, R_c are independently C_1-C_6 alkyl or aryl.

82. The use of embodiment 80 or 81, wherein the compound of formula (P) is the compound of formula (S)



(S).

83. A compound of formula (II)



(II).

84. The compound of embodiment 83, at least partially dissolved in one or more solvents, wherein the one or more solvents are preferably selected from the group consisting of water, one or more organic solvent, and a mixture of two or more thereof, wherein the one or more solvents preferably comprise, more preferably consist of, water.

85. A process for the preparation of 2-fluoropropionic acid halide, comprising
a) mesylating ethyl lactate, obtaining ethyl-2-((methylsulfonyl)oxy) propanoate;
b) fluorinating the ethyl-2-((methylsulfonyl)oxy)propanoate) of step a), obtaining 2-fluoropropanoate;
c) hydrolyzing the 2-fluoropropanoate of step b), obtaining the corresponding 2-fluropropanoic acid;
d) converting the 2-fluoropropanoic acid of step c) to the corresponding 2-fluoro-propionc acid halide.

86. The process of embodiment 85 wherein mesylating according to a) is carried in one or more solvents, preferably comprising tetrahydrofuran.

87. The process of embodiment 85 or 86, wherein mesylating according to a) is carried out at a temperature in the range of from 40 to 80 °C, preferably in the range of from 50 to 60 °C.

88. The process of any of embodiments 85 to 87, wherein fluorinating according to b) is carried out in one or more solvents, preferably comprising formamide.

89. The process of any of embodiments 85 to 88 wherein fluorinating according to b) is carried out at temperature in the range of from 40 to 90 °C, preferably in the range of from 50 to 80 °C.

90. The process of any embodiments 85 to 89 wherein hydrolyzing according to c) is carried out at a pH in the range of from 1 to 5, preferably in the range of from 2 to 4, as determined with a pH sensitive glass electrode.

91. The process of any of embodiments 85 to 90 wherein converting according to d) is carried in one or more solvents, preferably comprising dimethylformamide.

92. The process of any of embodiments 85 to 91 wherein converting according to d) is carried out at a temperature in the range of from 40 to 60 °C, preferably in the range of from 45 to 55 °C.

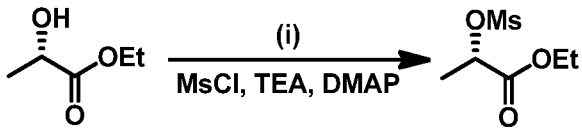
93. A mixture, obtainable or obtained by a process according to any of embodiments 1 to 56.

94. A mixture, obtainable or obtained by a process according to any of embodiments 85 to 89.

The present invention is further illustrated by the following examples.

Examples

Reference Example 1: Synthesis of (S)-2-((methylsulphonyl)oxy) propanoate



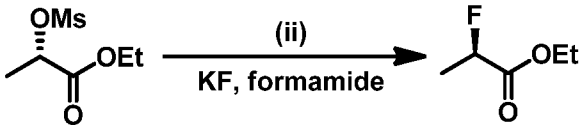
(S)-Ethyl lactate (10 mL, 87 mmol, purchased from Aldrich) was added to a solution of triethylamine (TEA, 15 ml, 108 mmol) and 4-dimethylaminopyridine (DMAP, 220 mg, 1.74 mmol) in 160 mL THF and the mixture was cooled to -15 °C. Methanesulfonyl chloride (MsCl, 8.0 mL, 104 mmol) was added dropwise and the mixture was allowed to warm up to room temperature and stirred for 6 hours at 60 °C.

The mixture was filtered over Celite® and washed with 20 mL diethyl ether. The solvent was removed under vacuum to yield 18.95 g of crude (S)-2-((methylsulfonyl)oxy)propanoate, which was used without further purification. Characterization of the product:

^{1}H NMR ($CDCl_3$, 300 MHz, d): 5.06 (q, J = 7.0 Hz, 1H, CH), 4.21 (q, J = 7.1 Hz, CH_2), 3.10 (s, 3H, OMs), 1.56 (d, J = 7.0 Hz, 3H, CH_3), 1.26 (t, J = 7.1 Hz, 3H, CH_2CH_3).

^{13}C NMR (CDCI3, 75MHz, d): 169.4, 74.3, 62.0, 39.0, 18.3, 14.0.

Reference Example 2: Synthesis of (R)-2-fluoropropanoic acid ethyl ester

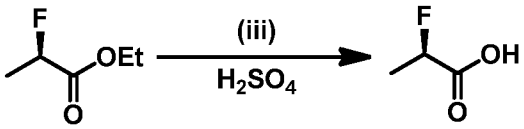


(S)-2-((methylsulfonyl)oxy) propanoate (15.0 g, 76 mmol) according to Reference Example 1 and potassium fluoride (KF , 17.8 g, 310 mmol) were suspended in 60 mL formamide and heated to 75 °C. (R)-Ethyl-2-fluoropropanoate was distilled off during the reaction (20-25 °C, 15 mbar). Yield: 6.9 g (75 %). Characterization of the product:

^{1}H NMR ($CDCl_3$, 300 MHz, d): 4.96 (dq, JHH = 6.8 Hz, JHF = 48.6 Hz, 1H, CH), 4.23 (q, J =7.1 Hz, CH_2 (1.56 *d, JHH = 6.8 Hz, JHF = 23.5 Hz, 3H, CH_3), 1.26 (t , J=7.1 Hz, 3H, CH_2CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, d): 170.4 (d, JCF=23.4 Hz) 85.6 (d, JCF=181.3 Hz) 61.4, 18.2 (d, JCF = 22.5 Hz), 14.0.

Reference Example 3: Synthesis of (R)-2-fluoropropionic acid

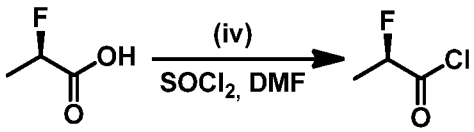


(R)-ethyl-2-fluoropropanoate (99.6 g, 0.83 mol) according to Reference Example 2 was suspended in 1000 mL 10 % H_2SO_4 and the reaction mixture was refluxed for 2.5 hours. The aqueous phase was saturated with sodium chloride and extracted repeatedly with methyl tert-butyl ether (MTBE). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under vacuum to yield (R)-2-fluoropropionic acid as a pale yellow oil (Yield; 52.1 g, 70 %). Characterization of the product:

^{1}H NMR ($CDCl_3$, 300 MHz, d): 11.94 (s, 1H, COOH), 5.07 (dq, JHH = 7.0 Hz, JHF = 48.4 Hz, 1H, CH), 1.63 (d, JHH = 7.0 Hz, JHF = 23.5 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, d): 175.0 (d, JCF = 23.9 Hz), 85.2 (d, JCF = 181.7 Hz), 18.1 (d, JCF = 22.5 Hz).

Reference Example 4: Synthesis of (R)-2-fluoropropionic acid chloride

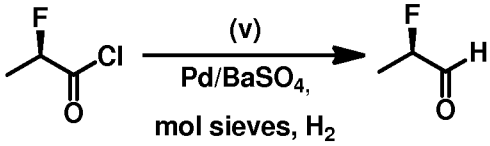


Dimethylformamide (DMF, 3.8 mL) and thionyl chloride (81.3 mL, 1.12 mol) were added to (R)-2-fluoropropionic acid (90.0 g, 0.98 mol) according to Reference Example 3 and the mixture was stirred at 50 °C for 18 hours. The product was distilled from the mixture under vacuum to give 63.10 g of crude (R)-2-fluoropropionic acid chloride, which was purified by re-distillation. Characterization of the product:

^{1}H NMR ($CDCl_3$, 300 MHz, d): 5.07 (dq, JHH = 6.9 Hz, JHF = 48.6 Hz, 1H, CH) 1.63 (d, JHH = 6.9 Hz, JHF = 22.8 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz, d): 172.6 (d, JCF = 27.7 Hz), 90.3 (d, JFC = 193.8 Hz), 17.7 (d, JFC = 22.0 Hz)

Example 1: Synthesis of (R)-2-fluoropropionaldehyde according to the present invention



5.1 0.17 mol Scale

(R)-2-fluoropropionic acid chloride (19.37 g, 0.17 mol) according to Reference Example 4 was dissolved in 310 mL THF and 51.1g molecular sieve (powdered, 4 Angstrom pore size), N,N'-diisopropylethylamine (20.1 mL, 0.11 mol) and the heterogeneous hydrogenation catalyst $Pd/BaSO_4$ (21.7 g, 5 weight-% Pd, 10 mmol, 6 mol-%) were added.

The mixture was stirred at a temperature of 23 to 25 °C under a hydrogen atmosphere at a hydrogen pressure of about 1 atm for 24 hours, after which the solids were filtered off, yielding (R)-2-fluoropropionaldehyde as a solution in THF in 47 % yield. The yield was determined via HPLC by derivatizing the aldehyde sample to the 2,4-dinitrophenyl hydrazone.

5.2 4.5 mmol Scale

2-Fluoropropionic acid chloride (500 mg, 4.5 mmol) according to Reference Example 4 was dissolved in 8 mL THF and 1.32 g molecular sieve (powdered, 4 Angstrom pore size) and the heterogeneous hydrogenation catalyst $Pd/BaSO_4$ (560 mg, 5 weight-% Pd, 10 mmol, 6 mol-%) were added.

The mixture was stirred at a temperature of 23 to 25 °C under a hydrogen atmosphere at a hydrogen pressure of about 1 atm for 3 hours, providing 2- fluoropropionaldehyde in 47 % yield. The yield was determined via HPLC by derivatizing the aldehyde sample to the 2,4-dinitrophenyl hydrazone. Characterization of the product:

^{1}H NMR (THF-d8, 300 MHz, d): 9.69 (d, JHH = 6.4 Hz, 1H, CHO), 4.94 (dq, JHH = 7.0 Hz, JHF = 48.5 Hz, 1H, CH), 1.41 (d, JHH = 7.0 Hz, JHF = 28.1 Hz, 3H, CH_3).

Cited Prior Art

- WO 2005/003147
- Ojima et al. J. Am. Chem. Soc., no. 109, pages 7714-7720 (1987)
- Bergmann et al. Tetrahedron Letter, no. 17, pages 1151-1153 (1965)
- WO 2008/121634
- Tetrahedron Lett. 1993, 34(2), pages 293-296

Claims

1. A process comprising
   (i) providing a 2-fluoropropionic acid halide;
   (ii) hydrogenating the 2-fluoropropionic acid halide by contacting it with a heterogeneous hydrogenation catalyst in an atmosphere comprising hydrogen, obtaining a mixture comprising 2-fluoropropionic aldehyde.

2. The process of claim 1, wherein the 2-fluoropropionic acid halide provided in (i) is 2-fluoropropionic acid chloride or 2-fluoropropionic acid bromide.

3. The process of claim 1 or 2, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised in a mixture comprising one or more organic solvents, preferably one or more aprotic organic solvents, more preferably one or more polar aprotic organic solvents, preferably selected from the group consisting of toluene, acetone, acetonitrile, dioxane, tetrahydrofuran (THF), methyl tetrahydrofuran, methyl ethyl ketone, ethyl acetate and butyl acetate, wherein more preferably, the 2-fluoropropionic acid halide is provided comprised in a mixture comprising tetrahydrofuran.

4. The process of claim 3, wherein the mixture provided in (i) further comprises one or more bases, wherein the one or more bases are preferably one or more organic bases or inorganic bases, more preferably one or more organic bases, more preferably one or more organic tertiary nitrogen bases, the tertiary nitrogen bases preferably not comprising a primary or secondary amino group.

5. The process of claim 4, wherein the one or more bases are one or more of N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, pyridine, quinoline, isoquinoline, acridine, pyrazine, and imidazole, preferably one or more of N,N'-diisopropylethylamine, triethylamine, 1,8-diazabicycloundec-7-ene, and pyridine.

6. The process of any of claims 3 to 5, wherein the mixture provided in (i) further comprises a solid porous adsorbent, preferably a molecular sieve.

7. The process of any of claims 1 to 6, wherein the heterogeneous hydrogenation catalyst according to (ii) comprises one or more hydrogenation-active metals, preferably one or more of palladium, platinum, rhodium, ruthenium, nickel and iridium, more preferably one or more of palladium and platinum, wherein more preferably, the heterogeneous hydrogenation catalyst comprises palladium, said heterogeneous hydrogenation catalyst according to (ii) preferably comprising a support, preferably an oxidic support, more

preferably a one or more of silica, titania, alumina, preferably gamma-alumina, mixed oxides of two or more thereof, sulfates, preferably alkaline earth metal sulfates, more preferably barium sulfate, carbonates, preferably alkaline earth metal carbonates, more preferably calcium carbonate.

8. The process of any of claims 1 to 7, wherein the heterogeneous hydrogenation catalyst according to (ii) comprises palladium supported on $BaSO_4$.

9. The process of any of claims 1 to 8, wherein the hydrogenating according to (ii) is carried out at a temperature of the atmosphere comprising hydrogen in the range of from 10 to 40 °C, preferably in the range of from 15 to 35 °C, more preferably in the range of from 20 to 30 °C, and at a hydrogen pressure in the range of from 0.5 to 2.0 bar, preferably in the range of from 0.7 to 1.7 bar, more preferably in the range of from 1.0 to 1.2 bar.

10. The process of any of claims 1 to 9, further comprising:
(iii) separating the 2-fluoropropionic aldehyde from the hydrogenation heterogeneous catalyst comprised in the mixture obtained in (ii), wherein the separating according to (iii) preferably comprises subjecting the mixture obtained in (ii) to solid phase separation, preferably filtration.

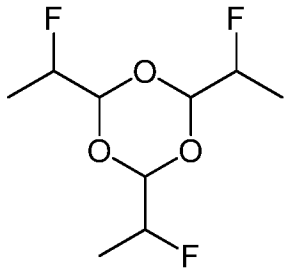
11. The process of claim 10, wherein the mixture provided in (i) further comprises one or more bases, the mixture obtained according to (ii) contains a hydrogen halide salt of the one or more bases and a solid porous adsorbent, and wherein during solid phase separation, the hydrogen halide salt of the one or more bases and the solid porous adsorbent are separated from the 2-fluoropropanaldehyde.

12. The process of claim 10 or 11, wherein according to (i), the 2-fluoropropionic acid halide is provided comprised in a mixture comprising one or more organic solvents and wherein from (iii), a mixture is obtained comprising the 2-fluoropropionic aldehyde and the one or more solvents, the process further comprising
(iv) extracting the 2-fluoropropionic aldehyde from the mixture obtained in (iii) with one or more solvents, wherein the one or more solvent are preferably water or a mixture of water and one or more organic solvents, said one or more organic solvents preferably including pentane, hexane, heptane, cyclohexane, ethyl acetate, methyl isobutyl ketone, methyl tert-butyl ether, diisopropyl ether, and methyl tetrahydrofuran, the one or more solvents more preferably being water, obtaining a mixture comprising the 2-fluoropropionic aldehyde and the one or more solvents.

13. The process of any claims 1 to 12, wherein the 2-fluoropropionic acid halide provided according to (i) is prepared by a method comprising
    a) mesylating ethyl lactate, obtaining ethyl-2-((methylsulfonyl)oxy) propanoate;
    b) fluorinating the ethyl-2-((methylsulfonyl)oxy)propanoate) of step a), obtaining 2-fluoropropanoate;
    c) hydrolyzing the 2-fluoropropanoate of step b), obtaining the corresponding 2-fluropropanoic acid;
    d) converting the 2-fluoropropanoic acid of step c) to the corresponding 2-fluoro-propionc acid halide.

14. The process of any of claims 1 to 13, wherein in (i), the 2-fluoropropionic acid halide is provided as (R)-2-fluoropropionic acid halide, obtaining in (ii) a mixture comprising the 2-fluoropropionic aldehyde as (R)-2-fluoropropionic aldehyde.

15. A compound of formula (II)



(II),

optionally at least partially dissolved in one or more solvents, wherein the one or more solvents are preferably one or more of water and one or more organic solvent, wherein the one or more solvents preferably comprise, more preferably consist of, water.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067716

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D323/06 C07C47/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 61 007228 A (SAGAMI CHEM. RES. CENTER) 13 January 1986 (1986-01-13)	1-14
A	E. ELKIK: "Aldéhydes .alpha.-fluorés. I. Aldéhydes aliphatiques saturés", BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, no. 9, 1964, pages 2254-2257, XP002730373, ISSN: 0037-8968 page 2255	1-14
Y	BERGMANN ET AL.: TETRAHEDRON LETTERS, vol. 6, no. 17, 1965, pages 1151-1153, XP009179846, cited in the application the whole document	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2015	25/11/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Samsam Bakhtiary, M

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067716

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	C. BOTTEGHI ET AL.: "A new preparative route to .alpha.-fluoroacrylic acid", JOURNAL OF FLUORINE CHEMISTRY, vol. 107, no. 1, 2001, pages 113-116, XP002730374, ISSN: 0022-1139 Scheme 1 -----	1-14
Y	CAVALLERI B ET AL: "Composti Organici Fluorurati A Potenziale Attitiva Biolgica. Nota III. Derivati dell'acido [alpha-]fluorofenilacetico", FARMACO, EDIZIONE SCIENTIFICA, SOCIETA CHIMICA ITALIANA, PAVIA, IT, vol. 23, 1 January 1968 (1968-01-01), pages 1127-1140, XP009185811, ISSN: 0430-0920 page 1129 - page 1130; compounds VI,VII page 1138, paragraphs 3,4; compound VII -----	1-14

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/067716

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

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

see additional sheet

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

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

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

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

1-14

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14

   Process for the production of 2-fluoropropionaldehyde

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2. claim: 15

   Compound of formula II

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/067716

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 61007228 A	13-01-1986	----------	