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(54) Title: SYNTHESIS OF NOVEL INTERMEDIATES FOR SUBSTITUTED 3,4-DIHYDROISOQUINOLINONES

(57) Abstract: This invention relates novel intermediates used for the synthesis of substituted 3,4-dihydroisoquinolinone compounds which are EZH2 inhibitors and the synthesis of said intermediates.

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SYNTHESIS OF NOVEL INTERMEDIATES FOR SUBSTITUTED 3,4-DIHYDROISOQUINOLINONES

FIELD OF INVENTION

This invention relates to the synthesis of novel substituted 3,4-dihydroisoquinolinone compounds which are EZH2 inhibitors and the intermediates used for such synthesis.

BACKGROUND OF THE INVENTION

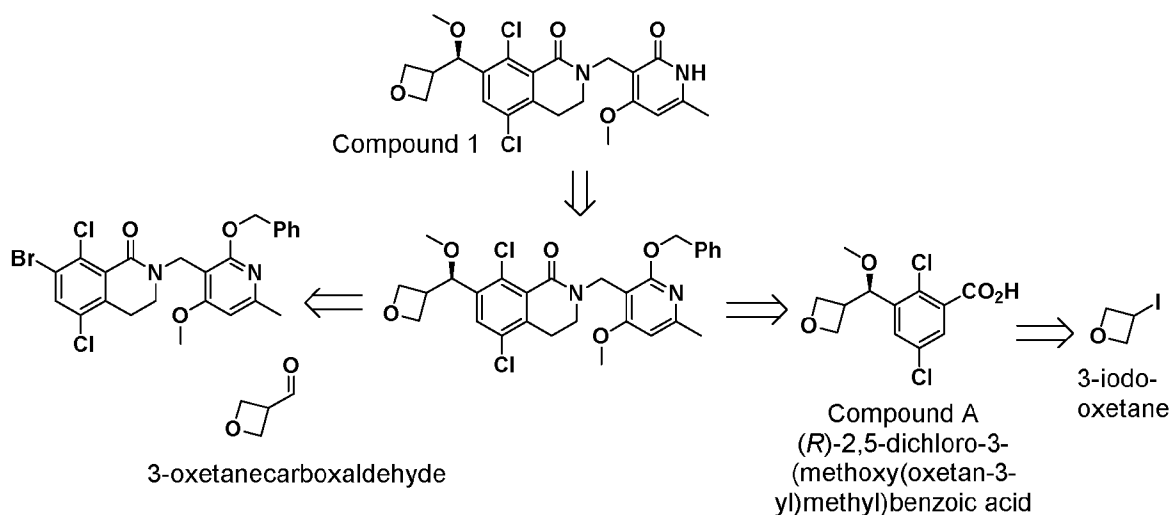
This invention relates to (*R*)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl)benzoic acid (Compound A), an intermediate used in a synthesis of compounds like that of Compound 1 and other compounds as disclosed in WO 2015/193765, incorporated herein by reference, which are EZH2 inhibitors.

Compound A offers several advantages as a synthetic precursor to these compounds. Earlier routes of synthesis disclosed in WO 2015/193765 and described in Kung, P.-P. et al., *J. Med. Chem.* **2018**, 61, 650-665, utilized 3-oxetanecarboxaldehyde as the source of the oxetane moiety. This oxetane intermediate is expensive and difficult to purify. Therefore, alternative intermediates and processes are desired for making compounds like that of Compound 1.

SUMMARY OF THE INVENTION

Because of the issues around the 3-oxetanecarboxaldehyde intermediate, Compound A provides beneficial routes to the preparation of compounds, like Compound 1 and others as disclosed in WO 2015/193765 and provided in Scheme 1.

Scheme 1



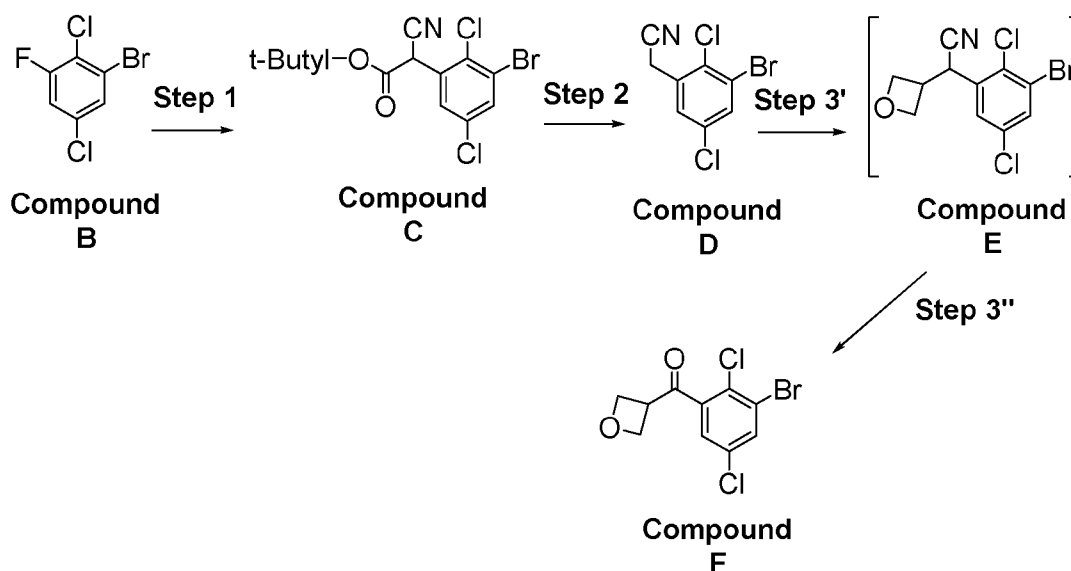
DETAILED DESCRIPTION OF THE INVENTION

Epigenetic alterations play an important role in the regulation of cellular processes, including cell proliferation, cell differentiation and cell survival. The epigenetic silencing of tumor suppressor genes and activation of oncogenes may occur through alteration of CpG island methylation patterns, histone modification, and dysregulation of DNA binding protein.

Polycomb genes are a set of epigenetic effectors. EZH2 (enhancer of zeste homolog 2) is the catalytic component of the Polycomb Repressor Complex 2 (PRC2), a conserved multi-subunit complex that represses gene transcription by methylating lysine 27 on Histone H3 (H3K27). EZH2 plays a key role in regulating gene expression patterns that regulate cell fate decisions, such as differentiation and self-renewal. EZH2 is overexpressed in certain cancer cells, where it has been linked to cell proliferation, cell invasion, chemoresistance and metastasis. High EZH2 expression has been correlated with poor prognosis, high grade, and high stage in several cancer types, including breast, colorectal, endometrial, gastric, liver, kidney, lung, melanoma, ovarian, pancreatic, prostate, and bladder cancers. Recurring somatic mutations in EZH2 have been identified in diffuse large B-cell lymphoma (DLBCL) and follicular lymphomas (FL). Mutations altering EZH2 tyrosine 641 (e.g., Y641C, Y641F, Y641N, Y641S, and Y641H) were reportedly observed in up to 22% of germinal center B-cell DLBCL and 7% of FL. EZH2 activating mutations have been suggested to alter substrate specificity resulting in elevated levels of trimethylated H3K27 (H3K27me3). Accordingly, compounds that inhibit the activity of wild type and/or mutant forms of EZH2 may be of interest for the treatment of cancer.

An aspect of this invention is illustrated by Schemes 2, 3 and 4. In Scheme 2, Compound F is prepared by a three-step-sequence consisting of a nucleophilic substitution of Compound B with tert-butyl-cyanoacetate to form Compound C (Step 1), hydrolysis/decarboxylation to give Compound D (Step 2), and a telescoped alkylation/oxidative decyanation (Step 3') provides Compound F by way of the nitrile intermediate of Compound E.

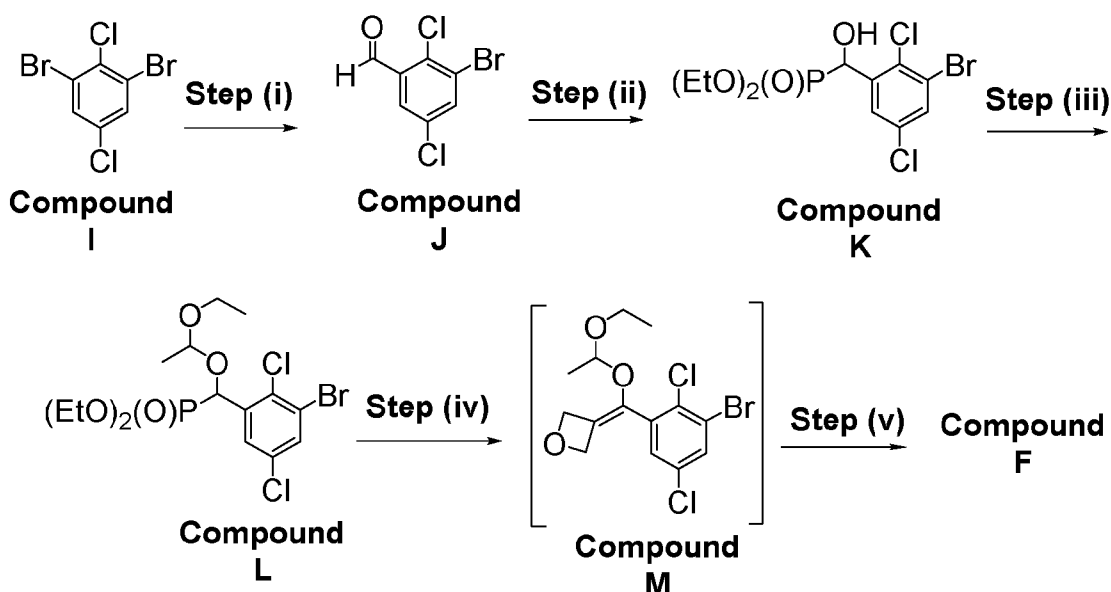
Scheme 2:



Alternatively, Compound F can be prepared as presented in Scheme 3, via a 4-step telescoped sequence. Compound I is mono-formylated with dimethylformamide via the aryl

magnesium intermediate. This is converted to Compound K with diethyl phosphite and protection of the hydroxyl with ethoxyvinyl ether provides Compound L. Compound F is prepared in a telescoped process by reacting compound L with 3-oxetanone, followed by deprotection.

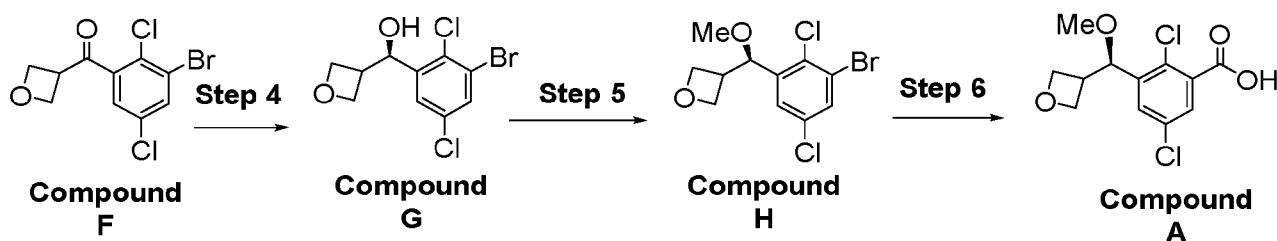
5 **Scheme 3**



Compound A is then obtained from Compound F as shown in Scheme 4. The chiral center is prepared with high enantioselectivity by a keto-reductase conversion of a ketone, Compound F, to an alcohol, Compound G. Compound G is converted in two steps to

10

Scheme 4



The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described herein.

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Definitions:

¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

20

The mass spectra (m/z) were recorded using either electrospray ionisation (ESI), atmospheric pressure chemical ionisation (APCI), or flame ionization detector (FID).

Ambient temperature is generally between 20 and 25 °C.

Aq means aqueous.

CDCl₃ is deuteriochloroform.

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

DMSO-d₆ is fully deuterated dimethyl sulfoxide.

As used herein, the terms "enantiomerically pure" or "optically pure" mean a composition that comprises one enantiomer of a compound and is substantially free of the opposite enantiomer of the compound. This is measured by enantiomeric excess (ee), providing the percentage of one enantiomer over the other.

Me is methyl (-CH₃).

MeOH is methanol.

THF is tetrahydrofuran.

UPLC is ultra high performance liquid chromatography

Examples

All reactions were performed under a nitrogen atmosphere. All reagents purchased from vendors were used as received unless specified otherwise. All reactions were performed in glass-lined reaction vessels equipped with either overhead or magnetic stirrers, unless noted otherwise. Reaction progress was monitored by pulling a 10 microliter aliquot, diluting with acetonitrile, and injecting on a reverse phase UPLC system equipped with a Waters Acquity HSS T3 column using a gradient elution with acetonitrile/water buffered with 0.1% trifluoroacetic acid.

Example 1

Preparation of Compound F: ((3-bromo-2,5-dichlorophenyl)-oxetan-3-yl) methyl ketone

Compound F was prepared according to Scheme 2.

Step 1 - Compound C: *tert*-Butyl 2-(3-bromo-2,5-dichlorophenyl)-2-cyanoacetate

Compound B (1-bromo-2,5-dichloro-3-fluorobenzene, CAS [202865-57-4], 30.0 g, 123 mmol) was reacted with triethylbenzyl ammonium chloride (2.8 g, 12 mmol), *tert*-butyl 2-cyanoacetate (23.4 g, 166 mmol) and DBU (56.2 g, 369 mmol) in anhydrous sulfolane (150 mL) at 80-92 °C for 1-2 h. The reaction mixture was cooled to ambient temperature, and water (200 mL) and iso-propyl acetate (200 mL) were added. The layers were separated, and the organic phase was washed with 200 mL of 10 wt% aq NH₄Cl and then with 200 mL of 10 wt% aq NaCl. The iso-propyl acetate was replaced with MeOH by distillation and distilled down to 2 mL/g of MeOH (60 mL). While stirring, water (150 mL) was added over 30 minutes, leading

to Compound C forming a solid that was isolated by filtration, rinsing the filter cake with water (150 mL), and air-dried to provide Compound C as a solid (47.6 g, 85% yield from Compound B, solid comprising about 80% of desired product). ¹H NMR (400 MHz, DMSO-d₆) δ 8.07 (d, 2.4 Hz, 1H); 7.67 (d, 2.4 Hz, 1H); 6.03 (s, 1H); 1.43 (s, 9H). MS-ESI (m/z) [M+H]⁺: 368.0 (62.2).

Step 2 - Compound D: 2-(3-bromo-2,5-dichlorophenyl)acetonitrile

Compound C (55 g, 80% Compound C by quantitative ¹H NMR, 120 mmol, combined batches made by following Step 1 procedure), 1,4-dioxane (387 mL), and water (100 mL) were combined and heated to 85-90 °C for 8-12 hours. The mixture was cooled to ambient temperature, and concentrated by distillation, during which the product solidified. The slurry was cooled back to ambient temperature, and MeOH (55 mL) was added. The product was isolated by filtration, rinsing with 9:1 water-MeOH (100 mL), and then heptane (100 mL). The product was dried in a vacuum oven to provide Compound D as a solid (30 g, 91% yield from Compound C, solid comprising about 97% of desired product). ¹H NMR (400 MHz, DMSO-d₆) δ 7.98 (d, 2.4 Hz, 1H); 7.67 (d, 2.4 Hz, 1H); 4.18 (s, 2H). MS-ESI (m/z) [M+H]⁺: 367.8 (62.2).

Step 3' – Compound E: 2-(3-bromo-2,5-dichlorophenyl)-2-(oxetan-3-yl)acetonitrile

Compound D (8.0 g, 30 mmol) was combined with potassium carbonate (12.6 g, 90 mmol) and dimethyl sulfoxide (80 mL) in a reaction vessel equipped with a magnetic stirrer, nitrogen inlet, and outlet line. The outlet line is attached to a scrubber system exiting sequentially through aq NaOCl (bleach) and sodium hydroxide-water scrubbers (for consumption of cyanide waste streams). 3-Iodo-oxetane (8.0 mL, 91 mmol) was added, and the mixture was heated to 43-47 °C. The reaction mixture was stirred for 12-16 h. Compound E was carried through to the next step directly.

In this specific preparation, Compound E was not isolated. However, Compound E was isolated from a batch prepared under similar conditions, making non-critical modifications, by precipitating Compound E with addition of water. The solid was removed, purified by slurrying in methanol, and removed by filtration and dried. ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, 2.4 Hz, 1H); 7.58 (d, 2.4 Hz, 1H); 5.04 (d, 7.8 Hz, 1H); 4.73 (dd, 7.8 Hz, 6.4 Hz, 1H); 4.65 – 4.61 (m, 2H); 4.35 (t, 6.4 Hz, 1H); 3.79 – 3.70 (m, 1H). MS-FID (m/z): 320.9 (97.3).

Step 3'' – Compound F: ((3-bromo-2,5-dichlorophenyl)-oxetan-3-yl) methyl ketone:

An additional portion of potassium carbonate (6.3 g, 45 mmol) was added to the reaction mixture of Step 3' containing Compound E, without isolating Compound E, and the nitrogen inlet was replaced with an air inlet for the next stage of the reaction (oxidative decyanation). Air was bubbled through the reaction mixture at 45 °C for 16h. The reaction was cooled to ambient temperature and the air bubbler was removed. The mixture was diluted with ethyl

acetate (30 mL), and water (30 mL) was added slowly, to keep the exotherm at <10 °C. The mixture was then transferred to a separatory funnel, rinsing with additional small portions of ethyl acetate and water. The phases were separated, and the organic phase was washed with water and brine. The organic phase was concentrated, then diluted with isopropanol (40 mL). The resulting brown solution was seeded with a small amount Compound F, seeds prepared previously with the same procedure as described here without seeding, and stirred for 60 minutes, during which time Compound F began forming a solid from solution. This slurry was diluted with water (80 mL), added over 90 minutes, and stirred overnight. The resulting solids were settled, and the supernatant mother liquor was decanted. The solids were dissolved in isopropanol (40 mL) by heating to 60 °C. The solution was then cooled to 40 °C, and water (80 mL) was added over 60 minutes. The resulting slurry was cooled to ambient temperature, and the solids were collected by filtration, rinsing with 1:2 isopropanol-water, and dried in a vacuum oven. Compound F was obtained as a brown solid (5.8 g, 62% yield from Compound D, solid comprising about 87% of desired product). ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (d, 2.4 Hz, 1H); 7.74 (d, 2.4 Hz, 1H); 4.78 – 4.71 (m, 2H); 4.70 – 4.62 (m, 3H). MS-FID (m/z): 320.9 (100.0).

Example 2

Preparation of Compound F: ((3-bromo-2,5-dichlorophenyl)-oxetan-3-yl) methyl ketone

Compound F was prepared according to alternative Scheme 3.

Step (i) - Compound J: 3-Bromo-2,5-dichlorobenzaldehyde

Compound I (1,3-dibromo-2,5-dichlorobenzene, CAS [81067-41-6], 10.0 g, 32.8 mmol) and THF (100 mL) were cooled to -35 to -40 °C. Isopropylmagnesium chloride-lithium chloride complex (1.3 mol/L) in THF (30 mL, 39.0 mmol) was added, followed by dimethylformamide (3.6 g, 49.3 mmol). The mixture was warmed to ambient temperature and hydrochloric acid (0.5 Mol/L, aq) (100 mL, 50 mmol) was added. Water (1000 mL) was added, followed by ethyl acetate (150 mL). The phases were separated, and the solvent removed by distillation to provide Compound J as a solid (8.0 g, 96% yield from Compound I). ¹H NMR (400 MHz, CDCl₃) δ 10.40 (s, 1H); 7.87 (d, 2.4 Hz, 1H); 7.86 (d, 2.4 Hz, 1H).

Step (ii) - Compound K: Diethyl ((3-bromo-2,5-dichlorophenyl)(hydroxy)methyl) phosphonate

Compound J (3-bromo-2,5-dichlorobenzaldehyde, 8.0 g, 31.5 mmol), THF (80 mL), diethylphosphite (4.44 g, 32.2 mmol), and triethylamine (3.19 g, 3.15 mmol) were combined at ambient temperature. After 2 to 3 hours, the mixture was concentrated then partitioned with hydrochloric acid (0.5 Mol/L, aq) (100 mL, 50 mmol) and ethyl acetate (100 mL). The organic phase was concentrated *in vacuo* to give a residue. A solid was obtained from adding a

mixture of cyclohexane (192 mL) and methyl tert-butyl ether (64 mL) to the residue. Compound K was dried *in vacuo* (8.80 g, 72% yield from Compound J). ¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, 2.4 Hz, 1H); 7.61 (d, 2.4 Hz, 1H); 5.55 (dd, 1H), 4.32 (m, 1H), 4.21-4.04 (m, 2H+2H), 1.32-1.26 (m, 3H+3H).

5 **Step (iii) - Compound L: Diethyl ((3-bromo-2,5-dichlorophenyl)(1-ethoxyethoxy)methyl) phosphonate**

Compound K (diethyl ((3-bromo-2,5-dichlorophenyl)(hydroxy)methyl) phosphonate (9.0 g, 23.0 mmol), dichloromethane (63 mL), pyridinium p-toluenesulfonate (0.18 g, 0.72 mmol) and ethyl vinyl ether (5.0 g, 69 mmol) were combined at ambient temperature for 4 to
10 5 hours. The mixture was washed three times with saturated sodium bicarbonate (aq) (3 x 108 mL). The organic phase was concentrated *in vacuo* to provide Compound L as an oil (10.0 g, 94% from Compound K). ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.56 (m, 2H); 5.52 (dd, 1H), 4.94 (q, 0.5H), 4.58 (q, 0.5H), 4.21-3.99 (m, 4H), 3.70 (d-quint., 0.5H), 3.49 (dq, 1H), 3.31 (d-quint., 0.5H), 1.32-1.20 (m, 9H), 1.19 (t, 1.5 H), 1.04 (t, 1.5H).

15 **Steps (iv) and (v) - Compound F:**

Compound L (diethyl ((3-bromo-2,5-dichlorophenyl)(1-ethoxyethoxy)methyl) phosphonate, 5.0 g, 10.8 mmol) and THF (50 mL) were combined at ambient temperature. Lithium bis(trimethylsilyl)amide (1 Mol/L) in THF (32.4 mL, 32.4 mmol) was added and then warmed to 40 to 45 °C. The mixture was then cooled to -5 to -10 °C. 3-Oxetanone (1.60 g,
20 22.2 mmol) was added, then warmed to ambient temperature. Ammonium Chloride (23% w/w, aq) (60 mL) was added, followed by methyl tert-butyl ether (60 mL). The layers were separated and the organic phase was concentrated *in vacuo* to provide Compound M (not purified or characterized). The residue was dissolved in MeOH (45 mL) and acetic acid (5 mL, 87.4 mmol) was added. The mixture was heated to 60 to 65 °C for 70 to 75 hours. Sodium bicarbonate
25 (1.14 Mol/L, aq) (50 mL) was added and extracted with methyl tert-butyl ether (50 mL). The phases were separated and the aqueous layer was extracted twice with methyl tert-butyl ether (2 x 50 mL). The combined extracts were concentrated *in vacuo* to a residue. A solid was obtain using n-heptane (100 mL). Compound F was isolated as a solid (1.4 g, 42% from Compound L). ¹H NMR (400 MHz, DMSO-d₆) δ 8.12 (d, 2.4 Hz, 1H); 7.74 (d, 2.4 Hz, 1H); 4.78
30 - 4.71 (m, 2H); 4.70 - 4.62 (m, 3H). MS-FID (m/z): 320.9 (100.0).

Example 3

Preparation of Compound A: (R)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl) benzoic acid

35 Compound A was prepared according to Scheme 4.

Step 4 – Compound G: (*R*)-(3-bromo-2,5-dichlorophenyl)(oxetan-3-yl)methanol

A mixture was prepared containing 0.1 M potassium phosphate buffer (pH 7.6, 576 mL, 8 mL/g), nicotinamide adenine dinucleotide phosphate (NADP⁺, 288 mg, 4 mg/g), a dehydrogenase enzyme (either Catalog #-ADH101, purchased from Johnson Matthey; or
5 Catalog #-GDH CDX901, purchased from Codex) (72-720 mg, 1-10 mg/g), and KR51-754 (1.44 g, 20 mg/g).

KR51-754 was generated starting with nucleic acid encoding the wildtype aldehyde reductase 2 sequence (UniProt accession number Q9UUN9) and employing site-directed mutagenesis to generate two substitutions in the protein sequence, W226L and Q245C. When
10 using ADH101, isopropanol (72 mL, 1 mL/g) was included. When using GDH CDX901, glucose (41.8 g, 0.58 g/g) was used, and pH titration was required to adjust the reaction pH from creation of gluconic acid. The amino acid sequence of KR51-754 is shown below:

MAKIDNAVLPEGSLVLTGANGFVASHVVEQLLEHGKYKVRGTARSASKLANLQKRWDKAY
PGRFETAVVEDMLKQGAYDEVIKGAAGVAHIASVVSFSN KYDEVVTPAIGGTLNALRAAA
15 ATPSVKRFVLTSSSTVSALIPKPNVEGIYLDEKSWNLESIDKAKTLPESDPQKSLWVYAAS
KTEAELAAWKFM DENKPHFTLNAVLPNYTIGTIFDPETQSGSTSGLMMSLFNGEVSPALA
LMPPCYVVS AVDIGLLHLGCLVLPQIERRRVYGTAGTFDWNTVLATFRKLYPSKTFPADF
PDQGQDLSKFDTAPSLEILKSLGRPGWRSIEESIKDLVGSETA (SEQ ID NO: 1).

Compound F (72 g, 232 mmol, Compound F prepared in multiple batches, prepared
20 as described in Step 3") in dimethyl sulfoxide (72 mL, 1 mL/g) was added to the stirred mixture described immediately above. The resulting mixture was stirred at 35 °C for 18 h, at which point UPLC analysis indicated complete conversion. The reaction mixture was diluted with ethyl acetate (720 mL, 10 mL/g) and stirred for 10 minutes, then filtered through Celite® (36 g, 0.5 g/g) on a sintered glass funnel. The resulting solution was transferred to a separatory
25 funnel and the phases were separated. A second extraction of the aqueous phase with ethyl acetate (324 mL, 4.5 mL/g) was performed and passed through the same Celite® filtration bed, and the resulting solution was transferred to a separatory funnel and the phases were separated. The combined organic phases were rinsed with brine (144 mL, 2 mL/g), and the organic phase was concentrated on a rotary evaporator to provide Compound G as an oil
30 (72.2 g, 99% ee for the R enantiomer, 99% yield from compound G, oil comprising about 99% of desired solid). ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, 2.0 Hz, 1H); 7.49 (d, 2.0 Hz, 1H); 5.36 (t, 4.4 Hz, 1H); 4.76 – 4.72 (m, 2H); 4.67 – 4.61 (m, 2H); 3.46 – 3.37 (m, 1H); 2.62 (d, 3.6 Hz, 1H). MS-ESI (m/z) [M-H]⁺: 308.9 (100.0).

Step 5 – Compound H: (*R*)-3-((3-bromo-2,5-dichlorophenyl)(methoxy)methyl)oxetane

35 Compound G (3.0 g, 8.7 mmol, 90% purity determined by ¹H quantitative NMR) was combined with THF (30 mL), potassium *tert*-butoxide (1 M solution in THF, 11.3 mL, 11.3

mmol) and cooled to 0 to 5 °C. Dimethyl sulfate (1.42 g, 11.3 mmol) was added over 10 to 15 minutes to moderate the exotherm (temperature increase of 7 °C was observed). The reaction was stirred for an additional 15 minutes, then warmed to ambient temperature. Methyl *tert*-butyl ether (30 mL) and water (30 mL) were added, and the phases separated. The organic phase was combined with heptane (30 mL) and concentrated by distillation to a volume of 30 mL. The organic solution of Compound H was filtered through Celite® to remove solids, then concentrated to the minimal volume that allowed stirring, and used directly in the next reaction. (2.90 g, 98% yield from Compound G, solid comprising about 97% of desired product). Compound H prepared in similar manner was isolated for characterization. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, 2.0 Hz, 1H); 7.38 (d, 2.0 Hz, 1H); 4.90 (d, 6.3 Hz, 1H); 4.72 (t, 6.3 Hz, 1H); 3.36 – 3.27 (m, 3H, overlapping); 3.31 (s, 4H). MS-ESI (m/z) [M+H]⁺: 325.0 (100.0)

Step 6 – Compound A: (*R*)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl) benzoic acid

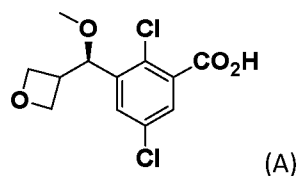
Compound H (1.5 g, 4.6 mmol, 97% purity determined by quantitative ¹H NMR) was combined with THF (23 mL) and cooled to -15 to -20 °C. A solution of isopropylmagnesium chloride-LiCl complex (4.5 mL of a 1.3 M solution in THF, 5.9 mmol) was added over 10 to 15 minutes, at which addition rate, the reaction temperature remained below -10 °C. The resulting mixture was stirred at -15 to -20 °C. Carbon dioxide gas was then bubbled through the mixture for 2 to 5 minutes, during which time the temperature rose from -5 to 0 °C. The mixture was then warmed to ambient temperature and then held for 30 minutes. The reaction mixture was then sparged with nitrogen for 10 to 15 minutes, followed by addition of 0.4 N aq NaOH (10 mL). The pH of the mixture was adjusted from an initial value of 8 by addition of 1N aq NaOH, to a pH of 10. The mixture was washed with toluene (7.5 mL). The organic layer was discarded and the aqueous layer was acidified to a pH=2 by addition of conc. HCl and extracted with ethyl acetate (7.5 mL). The organic phase was solvent swapped to methanol by distillation, to a final volume of 4.5 mL. While maintaining this solution at 50 °C, water (4.5 mL) was slowly added, and the mixture was seeded (seeds prepared previously using the same procedure as described here without seeding). The resulting slurry was cooled to ambient temperature over 60 minutes. An additional portion of water (3 mL) was added, and the solids were collected by filtration, rinsing the filter cake with water (4.5 mL). Compound A was obtained as a white solid (1.19 g, 99% ee for R enantiomer, 89% yield from Compound H, solid comprising >95% of desired product). ¹H NMR (400 MHz, DMSO-d₆) δ 13.80 (br s, 1H); 7.72 (d, 1.4 Hz, 1H); 7.55 (d, 1.4 Hz, 1H); 4.95 (d, 6.7 Hz, 1H); 4.59 (t, 6.1 Hz, 1H); 3.36 – 3.27 (m, 2H); 4.41 (t, 6.1 Hz, 1H); 3.42 – 3.33 (m, 1H); 3.22 (s, 3H). MS-ESI (m/z) [M-H]⁻: 289.0 (100.0).

This invention also concerns an optically pure Compound A that comprises greater than about 80% by weight of the (*R*) enantiomer of Compound A and less than about 20% by weight of the (*S*) enantiomer of Compound A, more preferably greater than about 90% by weight of the (*R*) enantiomer of Compound A and less than about 10% by weight of the (*S*) enantiomer of Compound A, even more preferably greater than about 95% by weight of the (*R*) enantiomer of Compound A and less than about 5% by weight of the (*S*) enantiomer of Compound A, and most preferably greater than about 99% by weight of the (*R*) enantiomer of Compound A and less than about 1% by weight of the (*S*) enantiomer of Compound A. For example, when Compound A is 99% optically pure, such purity could be represented as a compound that is (*R*)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl)benzoic acid that is 99% ee.

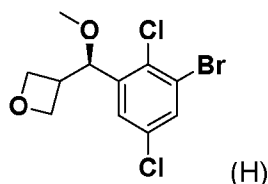
Compound A can be isolated as the carboxylic acid or a salt thereof. Salts that may be used to prepare salts of Compound A include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

The present invention also includes the preparation of Compound A. Non-limiting examples of the preparation of Compound A include the following.

Embodiment 1: A process for preparing Compound A



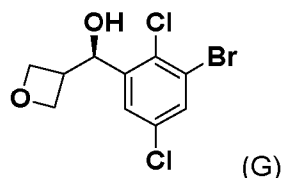
which comprises treating Compound H



with a bromine-magnesium exchange reagent and reacting the resulting arylmagnesium species with carbon dioxide.

Embodiment 2. The process according to Embodiment 1, wherein the bromine-magnesium exchange reagent is an isopropyl magnesium chloride-lithium chloride complex.

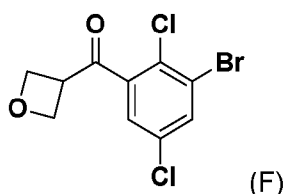
Embodiment 3. The process according to Embodiment 1, further comprising the preparation of Compound H by treating Compound G



with a base and a methylating agent.

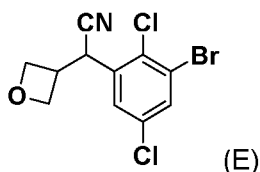
Embodiment 4. The process of Embodiment 3, wherein the base is potassium *tert*-butoxide and the methylating agent is dimethyl sulfate.

- 5 Embodiment 5. The process according to Embodiment 4, further comprising the preparation of Compound G by treating Compound F



with an enantioselective ketoreductase enzyme.

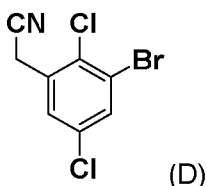
- 10 Embodiment 6. The process according to Embodiment 5, further comprising the preparation of Compound F by treating Compound E



with oxygen gas in the presence of a base in a polar, aprotic solvent.

Embodiment 7. The process of Embodiment 6, wherein the base is potassium carbonate and the solvent is dimethyl sulfoxide.

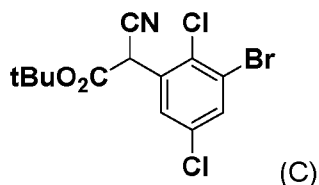
- 15 Embodiment 8. The process according to Embodiment 6, further comprising the preparation of Compound E by treating Compound D



with an alkylating agent and a base in a polar, aprotic solvent.

- 20 Embodiment 9. The process of Embodiment 8, wherein the alkylating agent is 3-iodooxetane, the base is potassium carbonate, and the solvent is dimethyl sulfoxide

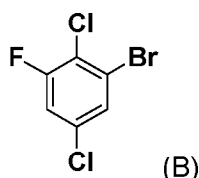
Embodiment 10. The process according to claim 9, further comprising the preparation of Compound D by treating Compound C



with water and a polar, aprotic solvent at a temperature above 50 °C such that decarboxylation occurs.

Embodiment 11. The process of Embodiment 10, wherein the solvent is selected from dioxane, dimethyl sulfoxide and sulfolane and the temperature is between 85-90 °C.

Embodiment 12. The process according to Embodiment 10, further comprising the preparation of Compound C by treating Compound B

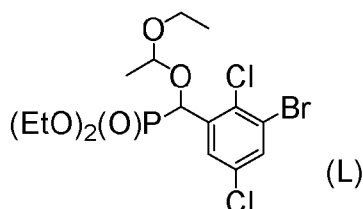


with a malononitrile reagent and a base in a polar, aprotic solvent.

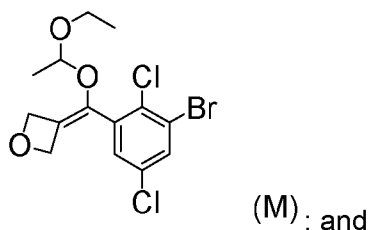
Embodiment 13. The process of Embodiment 12, wherein the malononitrile reagent *tert*-butyl malononitrile, the base is selected from DBU, cesium carbonate, and potassium carbonate, and the solvent is dimethyl sulfoxide or sulfolane.

Embodiment 14. The process according to Embodiment 5, further comprising the preparation of Compound F by:

a. treating Compound L



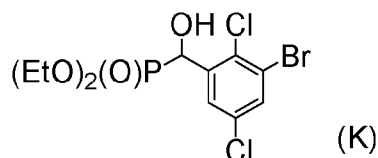
with a base and then 3-oxetanone to provide a Compound M



b. treating Compound M with an acid.

Embodiment 15. The process of Embodiment 14, wherein the base is lithium hexamethyldisilazide, lithium diisopropylamide or potassium *tert*-butoxide; and the acid is acetic acid.

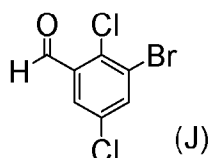
Embodiment 16. The process according to Embodiment 14, further comprising the preparation of Compound L by treating Compound K



with ethoxy vinyl ether and an acid

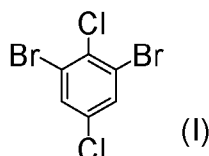
- 5 Embodiment 17. The process according to Embodiment 16, wherein the acid is pyridinium 4-toluenesulfonate.

Embodiment 18. The process according to Embodiment 17, further comprising the preparation of Compound K by treating Compound J



- 10 with diethyl phosphite.

Embodiment 19. The process according to Embodiment 18, further comprising the preparation of Compound J by treating Compound I



- 15 with a bromine-magnesium exchange reagent and reacting the resulting arylmagnesium species with dimethylformamide.

Embodiment 20. A SEQ of SEQ ID No. 1:

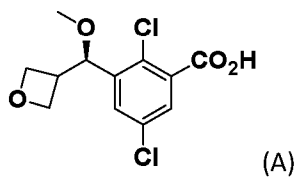
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 RAAAATPSVKRFVLTSSSTVSALIPKPNVEGIYLDEKSWNLESIDKAKTLPESDPQKSLW
 VYAASKTEAELAAWKFMDENKPHFTLNAVLPNYTIGTIFDPETQSGSTSGLMMSLFNG
 EVSPALALMPPCYYVSAVDIGLLHLGCLVLPQIERRRVYGTAGTFDWNTVLATFRKLYP
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Embodiment 21. A use of SEQ ID No. 1 for the reduction of a ketone to an alcohol.

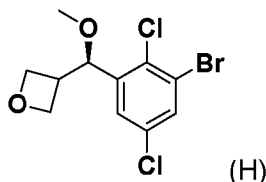
CLAIMS

What is claimed:

1. A process for preparing Compound A



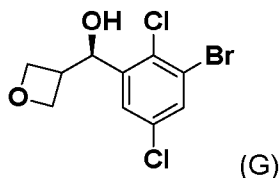
which comprises treating Compound H



with a bromine-magnesium exchange reagent and reacting the resulting arylmagnesium species with carbon dioxide.

2. The process according to claim 1, wherein the bromine-magnesium exchange reagent is an isopropyl magnesium chloride-lithium chloride complex.

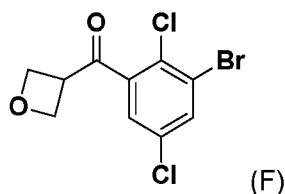
3. The process according to claim 1, further comprising the preparation of Compound H by treating Compound G



with a base and a methylating agent.

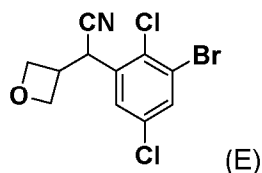
4. The process of claim 3, wherein the base is potassium *tert*-butoxide and the methylating agent is dimethyl sulfate.

5. The process according to claim 4, further comprising the preparation of Compound G by treating Compound F



with an enantioselective ketoreductase enzyme.

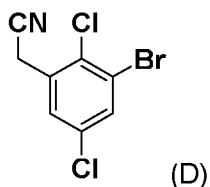
6. The process according to claim 5, further comprising the preparation of Compound F by treating Compound E



with oxygen gas in the presence of a base in a polar, aprotic solvent.

7. The process of claim 6, wherein the base is potassium carbonate and the solvent is dimethyl sulfoxide.

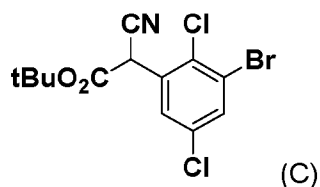
8. The process according to claim 6, further comprising the preparation of Compound E by treating Compound D



with an alkylating agent and a base in a polar, aprotic solvent.

9. The process of claim 8, wherein the alkylating agent is 3-iodooxetane, the base is potassium carbonate, and the solvent is dimethyl sulfoxide.

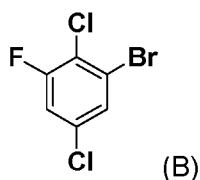
10. The process according to claim 9, further comprising the preparation of Compound D by treating Compound C



with water and a polar, aprotic solvent at a temperature above 50 °C such that decarboxylation occurs.

11. The process of claim 10, wherein the solvent is selected from dioxane, dimethyl sulfoxide and sulfolane and the temperature is between 85-90 °C.

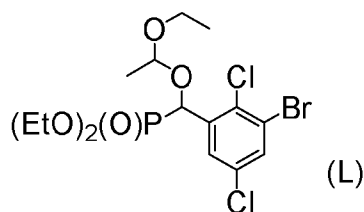
12. The process according to claim 10, further comprising the preparation of Compound C by treating Compound B



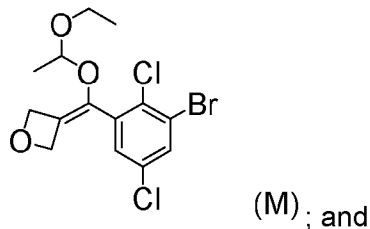
with a malononitrile reagent and a base in a polar, aprotic solvent.

13. The process of claim 12, wherein the malononitrile reagent is *tert*-butyl malononitrile, the base is selected from DBU, cesium carbonate, and potassium carbonate, and the solvent is dimethyl sulfoxide or sulfolane.

14. The process according to claim 5, further comprising the preparation of Compound F by:
a. treating Compound L



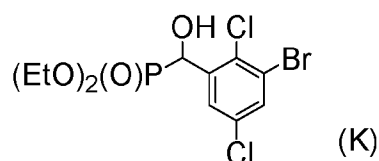
with a base and then 3-oxetanone to provide Compound M



b. treating Compound M with an acid.

15. The process of claim 14, wherein the base is lithium hexamethyldisilazide, lithium diisopropylamide or potassium *tert*-butoxide; and the acid is acetic acid.

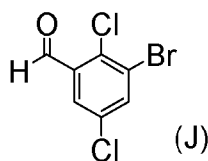
16. The process according to claim 14, further comprising the preparation of Compound L by treating Compound K



with ethoxy vinyl ether and an acid.

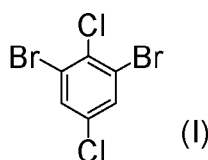
17. The process according to claim 16, wherein the acid is pyridinium 4-toluenesulfonate.

18. The process according to claim 17, further comprising the preparation of Compound K by treating Compound J



with diethyl phosphite.

19. The process according to claim 18, further comprising the preparation of Compound J by treating Compound I



with a bromine-magnesium exchange reagent and reacting the resulting arylmagnesium species with dimethylformamide.

20. A compound selected from the group consisting of ((3-bromo-2,5-dichlorophenyl)-oxetan-3-yl) methyl ketone, (*R*)-(3-bromo-2,5-dichlorophenyl)(oxetan-3-yl)methanol, (*R*)-3-((3-bromo-2,5-dichlorophenyl)(methoxy)methyl)oxetane, and (*R*)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl) benzoic acid or a salt thereof.

21. The compound of claim 20 that is (*R*)-2,5-dichloro-3-(methoxy(oxetan-3-yl)methyl) benzoic acid having a 99% enantiomeric excess (ee).

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2021/056451

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D305/06
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

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/193765 A1 (PFIZER [US]) 23 December 2015 (2015-12-23) cited in the application	1,2
A	page 173 - page 174; example 81 -----	3-21
Y	PAUL KNOCH ET AL: "Highly Functionalized Organomagnesium Reagents Prepared through Halogen-Metal Exchange", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 42, no. 36, 22 September 2003 (2003-09-22), pages 4302-4320, XP55039357, ISSN: 1433-7851, DOI: 10.1002/anie.200300579 column 4307 ----- -/--	1,2



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

20 September 2021

Date of mailing of the international search report

30/09/2021

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Seelmann, Marielle

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2021/056451

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOPP FELIX ET AL: "Halogen-magnesium exchange on unprotected aromatic and heteroaromatic carboxylic acids", CHEMICAL COMMUNICATIONS, no. 20, 1 January 2007 (2007-01-01), pages 2075-2077, XP55779521, UK ISSN: 1359-7345, DOI: 10.1039/B618923G the whole document -----	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2021/056451

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		WO 2015193765 A1	23-12-2015