

PROCESSES RELATED TO FORMATION OF ARYLCYCLOPROPYL CARBOXYLIC ACIDS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial No.
5 63/014758 filed April 24, 2020, which is expressly incorporated by reference herein.

FIELD OF THIS DISCLOSURE

This disclosure relates to processes to form arylcyclopropyl carboxylic acids useful in
forming molecules having pesticidal utility against pests in Phyla Arthropoda, Mollusca, and
10 Nematoda.

BACKGROUND OF THIS DISCLOSURE

Formation of arylcyclopropyl carboxylic acids has been disclosed in applications
WO/2016/168056; WO/2016/168058; WO/2016/168059; WO/2018/071320; and
15 WO/2018/071327.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

The official copy of the sequence listing is submitted electronically via EFS-Web as an
ASCII formatted sequence listing with a file named 81306_ST25.txt created on April 19,
20 2021 and having a size of 12 kilobytes and is filed concurrently with the specification. The
sequence listing comprised in this ASCII formatted document is part of the specification and
is herein incorporated by reference in its entirety.

DEFINITIONS USED IN THIS DISCLOSURE

25 The examples given in these definitions are not exhaustive and must not be
construed as limiting this disclosure. It is understood that a substituent should comply with
chemical bonding rules and steric compatibility constraints in relation to the particular
molecule to which it is attached. These definitions are only to be used for the purposes of
this disclosure.

30 The term "**alkoxy**" means an alkyl further consisting of a carbon-oxygen single
bond, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and *tert*-
butoxy.

The term "**alkyl**" means an acyclic, saturated, branched, or unbranched, substituent
consisting of carbon and hydrogen, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl,
35 *sec*-butyl, isobutyl, and *tert*-butyl.

The term “**aryl**” means a cyclic, aromatic substituent consisting of hydrogen and carbon, for example, phenyl, naphthyl, and biphenyl.

The term “**halo**” means fluoro, chloro, bromo, and iodo.

The term “**haloalkoxy**” means an alkoxy further consisting of, from one to the maximum possible number of identical or different, halos, for example, fluoromethoxy, trifluoromethoxy, 2,2-difluoropropoxy, chloromethoxy, trichloromethoxy, 1,1,2,2-tetrafluoroethoxy, and pentafluoroethoxy.

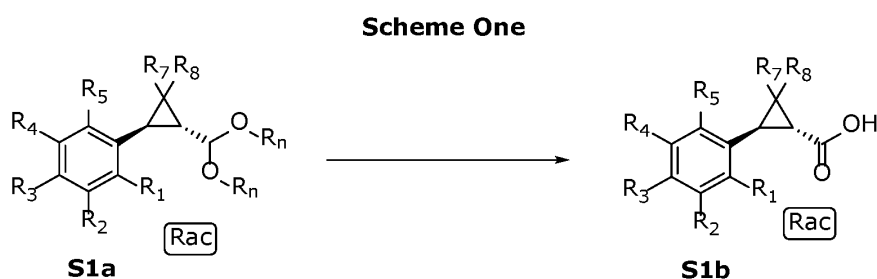
The term “**haloalkyl**” means an alkyl further consisting of, from one to the maximum possible number of, identical or different, halos, for example, fluoromethyl, trifluoromethyl, 2,2-difluoropropyl, chloromethyl, trichloromethyl, and 1,1,2,2-tetrafluoroethyl.

The term “**hydroxyalkyl**” means an alkyl containing one or more hydroxy groups, for example, hydroxymethyl, hydroxyethyl, hydroxyisobutyl, 1,3-dihydroxybutyl, and 1,3,5-trihydroxyhexyl.

DETAILED DESCRIPTION OF THIS DISCLOSURE

The following are processes related to the formation of arylcyclopropyl carboxylic acids.

In embodiment one of Scheme One



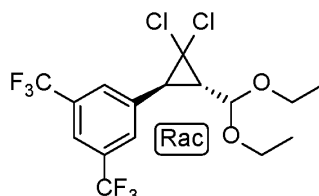
(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

(c) (1) each **R_n** is independently a (C₁-C₆)alkyl, or

(2) both **R_n** form a (C₂-C₆)alkyl link between the two oxygen atoms.

In embodiment two of Scheme One **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅**, are H; **R₇** and **R₈** are Cl; and each **R_n** is C₂H₅. This molecule ("**S1a-1**") is represented as follows.



5 ***trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene**

The reaction in Scheme One is conducted in the presence of an oxidizing agent that oxidizes **S1a** to **S1b**. In other words, functionally the oxidizing agent oxidizes -C(OR_n)₂ or -C(-O((C₂-C₆)alkyl)O-) to -C(=O)OH. Examples of oxidizing agents are oxygen (O₂), sodium hypochlorite (NaOCl), ozone (O₃), hydrogen peroxide (H₂O₂), organic peracids (-OOH), and other inorganic oxidants, such as, potassium peroxymonosulfate, potassium persulfate, potassium hydrogen peroxymonosulfate sulfate (a triple salt with the formula 2KHSO₅·KHSO₄·K₂SO₄ [CAS 70693-62-8] available from E.I. du Pont de Nemours and Company or its affiliates as OXONE®, a registered trademark of E.I. du Pont de Nemours and Company or its affiliates). In general, about 0.1 moles to about 3 moles of oxidizing agent per mole of **S1a**, more preferably, about 0.5 moles to about 1.5 moles of oxidizing agent per mole of **S1a** may be used. In general, when using hydrogen peroxide (H₂O₂) solutions a concentration of about 1% w/w to about 70% w/w may be used, however, currently, about 20% w/w to about 50% w/w is preferred. Mixtures of oxidizing agents may also be used.

The reaction in Scheme One is conducted in the presence of a polar solvent. Examples of polar solvents are polar aprotic solvents and polar protic solvents. Examples of polar aprotic solvents are ethyl acetate, tetrahydrofuran ("THF"), dichloromethane, acetone, acetonitrile ("ACN"), dimethylformamide ("DMF"), and dimethyl sulfoxide ("DMSO"). Examples of polar protic solvents are acetic acid ("AcOH"), *n*-butanol ("*n*-BuOH"), isopropanol ("*i*-PrOH"), *n*-propanol ("*n*-PrOH"), ethanol ("EtOH"), methanol ("MeOH"), formic acid ("HCOOH"), *tert*-butyl alcohol ("*t*-BuOH"), and water ("H₂O"). Optionally, mixtures of such polar solvents may be used, and examples are indicated below in **Table S1-MR**.

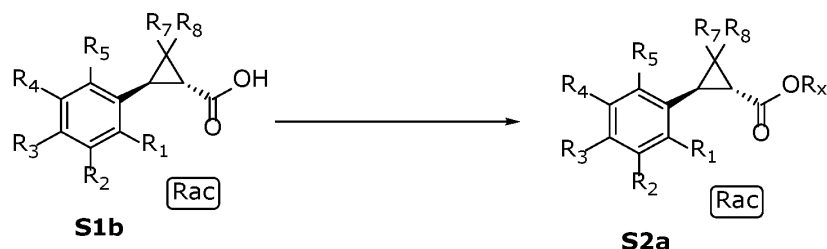
Table S1-MR	
Mixtures	Examples of Molar Ratios
H ₂ O:AcOH; H ₂ O:HCOOH; H ₂ O:ACN; H ₂ O:DMF; H ₂ O:MeOH; H ₂ O:EtOH; H ₂ O: <i>t</i> -BuOH; <i>n</i> -BuOH:AcOH; <i>i</i> -PrOH:AcOH; <i>n</i> -PrOH:AcOH; EtOH:AcOH; MeOH:AcOH; <i>t</i> -BuOH:AcOH; <i>n</i> -BuOH:HCOOH; <i>i</i> -PrOH:HCOOH; <i>n</i> -PrOH:HCOOH; EtOH:HCOOH; MeOH:HCOOH; <i>t</i> -BuOH:HCOOH; <i>n</i> -BuOH:ACN; <i>i</i> -PrOH:ACN; <i>n</i> -PrOH:ACN; EtOH:ACN; MeOH:ACN; <i>t</i> -BuOH:ACN; ACN:AcOH	1:10; 1:5; 1:3; 1:1; 10:1; 5:1; or 3:1

The reaction in Scheme One may be conducted at ambient temperatures and pressures. However, higher and lower temperatures and pressures may be used. Currently, temperatures from about 0 °C to about 80 °C may be used, preferably temperatures from about 20 °C to about 60 °C may be used. Currently, pressures from about 10 kilopascal (kPa) to about 1000 kPa may be used, preferably pressures from about 50 kPa to about 150 kPa may be used.

Optionally, an acid catalyst and water may be used to promote the conversion of an acetal to an aldehyde which can then undergo oxidation to an acid. Suitable examples of acid catalysts are organic acids (acetic acid, trifluoroacetic acid, formic acid, methanesulfonic acid, *p*-toluenesulfonic acid, citric acid), inorganic acids such as hydrogen chloride or hydrochloric acid (HCl), silico-aluminates (zeolites, alumina, silico-alumino-phosphate), sulfated zirconia (sulfated zirconium(IV) oxide), and many transition metal oxides (titanium, zirconium, and niobium). Preferably, polystyrene based ion exchange resins with strongly acidic sulfonic groups are used, an example of which is Amberlyst® (CAS Number 39389-20-3). (Amberlyst is a registered trademark of The Dow Chemical Company or an affiliated company of Dow.) Even more preferred, sulfuric acid (H₂SO₄) is used. In general, the molar ratio of acid to oxidant can range from 1:4 to 1:400, more preferably from 1:20 to 1:200. Mixture of acids can be used.

In embodiment one of Scheme Two

Scheme Two



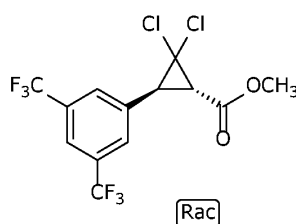
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(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

10 (c) **R_x** is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl.

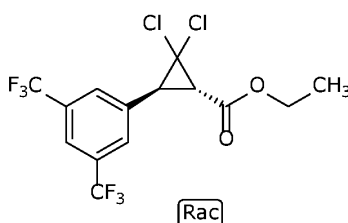
In embodiment two of Scheme Two **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** are H; **R₇** and **R₈** are Cl; and **R_x** is CH₃. This molecule ("**S2a-1**") is represented as follows.



15 **trans-rac-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate**

In embodiment three of Scheme Two **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** are H; **R₇** and **R₈** are Cl; and **R_x** is CH₂CH₃. This molecule ("**S2a-6**") is represented as follows.

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***trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate**

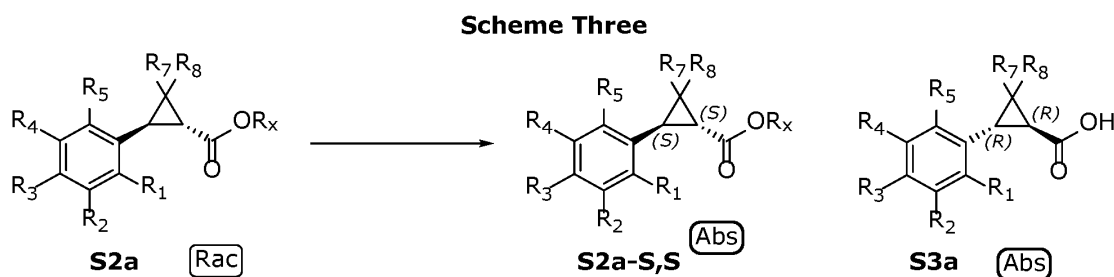
The reaction in Scheme Two is conducted in the presence of an acid that in the presence of an alcohol promotes the esterification of **S1b** to afford **S2a**. Examples of acids are sulfuric acid (H₂SO₄), *p*-toluenesulfonic acid monohydrate, methanesulfonic acid, scandium(III) triflate, and other acidic resins, such as Amberlyst® 15, Nafion™ (perfluorinated resin (CAS Number: 31175-20-9); Nafion™ is a trademark of The Chemours Company FC, LLC), as well as mixtures thereof. In general, about 0.001 moles to about 5 moles of acid per mole of **S1b**, more preferably, about 0.05 moles to about 0.5 moles of acid per mole of **S1b** may be used.

The reaction in Scheme Two is conducted in the presence of a (C₁-C₆)alcohol. Examples of (C₁-C₆)alcohols are *n*-butanol, isopropanol, *n*-propanol, ethanol, methanol, ethylene glycol, *tert*-butyl alcohol, and mixtures thereof. Optionally, mixtures of such alcohols may be used in a large variety of molar ratios, and in the presence of a solvent such as, toluene, carbon tetrachloride, benzene, diethyl ether, hexane, heptane, and dichloromethane. For example, for two component mixtures, ratios of 1:1, 1:5; 1:10, 1:50, and 1:100 may be used.

The reaction in Scheme Two may be conducted at ambient temperatures and pressures. However, higher or lower temperatures and pressures may be used. Currently, temperatures from about 0 °C to about 100 °C may be used; preferably temperatures from about 50 °C to about 70 °C may be used. Currently, pressures from about 10 kPa to about 1000 kPa may be used; preferably pressures from about 50 kPa to about 150 kPa may be used.

Any organic or inorganic drying agent may be used to remove water generated by the reaction. About 0.1 to about 5 moles of drying agent may be used per mole of **S1b**; preferably, about 0.2 to about 2 moles of drying agent may be used per mole of **S1b**. It is preferred to use an orthoester as a drying agent, especially those of formula [R_{y1}C(OR_{y2})₃] where R_{y1} is hydrogen or a (C₁-C₆)alkyl, and R_{y2} is (C₁-C₆)alkyl. Examples of such drying agents are triethyl orthoacetate, CH₃C(OCH₂CH₃)₃; trimethyl orthoacetate, CH₃C(OCH₃)₃; triethyl orthoformate, HC(OCH₂CH₃)₃; and trimethyl orthoformate, HC(OCH₃)₃. Additionally, molecular sieves, magnesium sulfate, calcium chloride, and sodium sulfate may be used. Optionally, mixtures of drying agents may be used.

In embodiment one of Scheme Three



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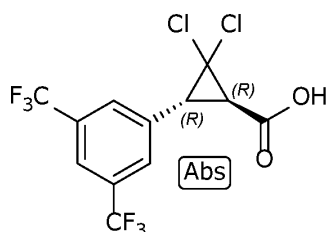
(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

10 (c) **R_x** is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl.

In embodiment two of Scheme Three, wherein **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** H; **R₇** and **R₈** are Cl; and **R_x** is CH₃, this molecule is shown above in Scheme 2 and is named as **trans-rac-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate** (also known as **S2a-1**).

15 In embodiment three of Scheme Three **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** are H; and **R₇** and **R₈** are Cl. This molecule ("**S3a-1**") is represented as follows.



(1R,3R)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid

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The transformation in Scheme Three can be a chiral *kinetic resolution*, which involves using a chiral catalyst or reagent to promote selective transformation of one enantiomer (in this case the (R,R)-enantiomer of **S2a**) over the other ((S,S)-enantiomer of **S2a**), giving a mixture of enantioenriched starting material and product, which can be separated by chemical and/or physical methods. The theoretical yield for similar kinetic resolutions is

25

about 50%, as a racemic mixture (in this case **S2a**) is comprised of equal amounts of two enantiomers. Reference: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.*

2001, 343, 5. In embodiment two of Scheme Three, two major components,

enantioenriched portion of (*S,S*)-ester and (*R,R*)-acid product, are produced from this

5 transformation; minor amounts of an (*S,S*)-acid and (*R,R*)-ester may also be present. After this transformation, the (*R,R*)-acid can be recovered using conventional separation and isolation techniques.

The transformation in Scheme Three is conducted in the presence of a hydrolase, preferably hydrolases that are classified under Enzyme Commission number EC3

10 "Hydrolases"; more preferably hydrolases that are classified under Enzyme Commission number EC3.1 – acting on ester bonds; and most preferably hydrolases that are classified under Enzyme Commission number EC3.1.1 – carboxylic ester hydrolases. Suitable hydrolyses will hydrolyze the ester in a racemic mixture of **S2a** to an enantiomerically enriched mixture of **S3a**. It is preferred if the production value (PV, as calculated in

15 Equation 1) of **S2a** is greater than 20%, more preferably more than 30%, and most preferably more than 40%. Preferably, the enantiomeric excess (ee, as calculated in Equation 2) of **S3a**, where the (*R,R*)-enantiomer is greater than 80%, preferably, greater than 90%, more preferably greater than 95%, and most preferably greater than 99%.

Suitable carboxylic ester hydrolases to use may be selected from *Pseudomonas stutzeri*

20 lipase, *Pseudomonas cepacia* lipase, *Alcaligenes* sp. Lipase E, *Alcaligenes* sp. Lipase C, *Pseudomonas fluorescens* lipase, *Burkholderia cepacia* Lipase A, and *Burkholderia cepacia* Lipase B. Other enzymes may be used but it is desired that homology of these enzymes be at least 90% homologous, preferably at least 95% homologous with at least one of the above-mentioned carboxylic ester hydrolases. The amount of hydrolase, esterase, and

25 lipase used may be from about 0.01% to about 200% by weight with respect to **S2a**, preferably about 0.1 to 1% by weight with respect to **S2a**. Commercially, hydrolases are available from a variety of suppliers, for example Almac Group Limited; Amano Enzyme USA Co., Ltd.; c-LEcta GmbH; Creative Enzymes; Codexis Inc.; Enzymaster (Ningbo) Bio-Engineering Co., Ltd.; Meito Sangyo Co., Ltd., Novozymes A/S. For further information, see

30 **Enzyme Catalysis in Organic Synthesis, 3 Volume Set** edited by Karlheinz Drauz, Harald Gröger, and Oliver May, Chapter 46 (for example, see pages 1852 – 1854), by David Rozzell; and **"Tabular Survey of Available Enzymes"** p 1849-1985, copyrighted 2012 by Wiley-VCh Verlag GmbH & Co. KGaA, and published 2012 Wiley-VCh Verlag GmbH & Co. KGaA. Optionally, a hydrolase can be immobilized or supported on a polymer, silica, or

35 other support material to allow for the recovery of the enzyme for further use. The following

sequences or those with 90% or greater amino acid sequence homology may be used for this transformation AND61386 (SEQ ID NO:1); AAA50466 (UniProt P22088) (SEQ ID NO:2); AAC60400 (UniProt P25275) (SEQ ID NO:3); EGD05490 (UniProt F0FZ41) (SEQ ID NO:4); CAA83122 (SEQ ID NO:5); BBC47796 (SEQ ID NO:6); UniProt P20261 (SEQ ID NO:7).

5 The transformation of Scheme Three is conducted in the presence of water (H₂O), preferably deionized water.

 The transformation of Scheme Three is conducted optionally in the presence of an aqueous buffer where the hydrolase is preferably soluble. Examples of suitable buffers are sodium phosphate, 2-[bis(2-hydroxyethyl)amino]-2-(hydroxymethyl)propane-1,3-diol ("Bis-tris methane"), 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid ("HEPES"),
10 potassium phosphate, 3-morpholinopropane-1-sulfonic acid ("MOPS"), piperazine-*N,N'*-bis(2-ethanesulfonic acid) ("PIPES"), sodium citrate, 3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}propane-1-sulfonic acid ("TAPS"), lysine, 2-amino-2-(hydroxymethyl)propane-1,3-diol ("TRIS"), and mixtures thereof. The buffer concentration
15 may be about 0.0001 molar (M) to about 0.5 M, preferably about 0.05 M to about 0.2 M.

 The transformation of Scheme Three may be conducted optionally in the presence of an amine base. Examples of amine bases are lysine, ethanolamine, glycine, and mixtures thereof. Consequently, lysine may be used both as a buffer. The amount of amine base is from about 0.1 wt % to about 150 wt %, preferably about 10 wt % to about 40 wt % based
20 on the weight of **S2a**.

 The transformation of Scheme Three may be conducted in the presence of a co-solvent. Examples of co-solvents are acetone, acetonitrile, methyl tetrahydrofuran, methyl *tert*-butyl ether, hexane, toluene, methyl ethyl ketone, cyclopentyl methyl ether, dimethyl sulfoxide, dimethoxyethane, and mixtures thereof. A co-solvent may be useful to increase
25 the solubility of **S2a**. The amount of co-solvent used may be from about 1% by volume to about 90% of the entire volume, preferably about 10% by volume to about 40% by volume based on the entire volume.

 The transformation in Scheme Three may be conducted at ambient temperatures and pressures. However, higher or lower temperatures and pressures may be used. Currently,
30 temperatures from about 0 °C to about 80 °C may be used; preferably temperatures from about 15 °C to about 60 °C may be used; more preferably temperatures from about 25 °C to about 50 °C may be used. Currently, pressures from about 10 kPa to about 1000 kPa may be used; preferably pressures from about 50 kPa to about 150 kPa may be used. The pH of the transformation mixture should be in the range of about pH 5 to about pH 11,
35 preferably about pH 6 to about pH 10.

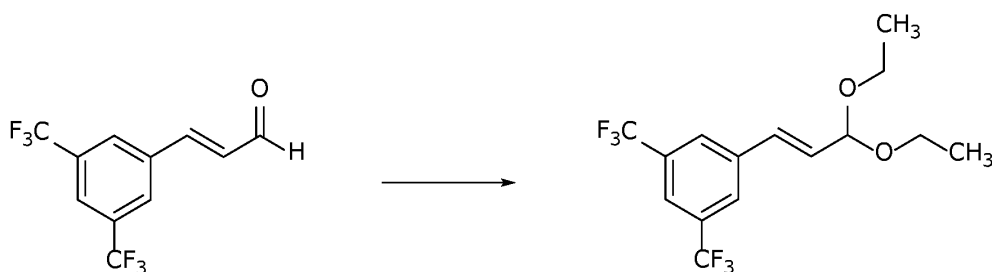
EXAMPLES

These examples are for illustration purposes and are not to be construed as limiting this disclosure to only the embodiments disclosed in these examples.

5 Starting materials, reagents, and solvents that were obtained from commercial sources were used without further purification. Anhydrous solvents were purchased as Sure/Seal™ from Aldrich and were used as received. Melting points were obtained on a Thomas Hoover Unimelt capillary melting point apparatus or an OptiMelt Automated Melting Point System from Stanford Research Systems and are uncorrected. Examples using “room
10 temperature” were conducted in climate controlled laboratories with temperatures ranging from about 20 °C to about 24 °C. Molecules are given their known names, named according to naming programs within ISIS Draw, ChemDraw, or ACD Name Pro. If such programs are unable to name a molecule, such molecule is named using conventional naming rules. ¹H NMR spectral data are in ppm (δ) and were recorded at 300, 400, 500, or 600 MHz; ¹³C
15 NMR spectral data are in ppm (δ) and were recorded at 75, 100, or 150 MHz; and ¹⁹F NMR spectral data are in ppm (δ) and were recorded at 376 MHz, unless otherwise stated.

Example 1a: Synthesis of (E)-1-(3,3-diethoxyprop-1-en-1-yl)-3,5-bis(trifluoromethyl)benzene

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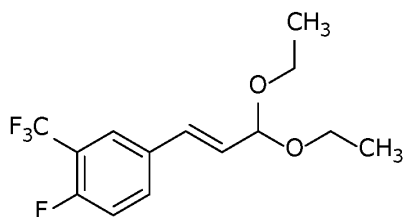


In a 3-liter (L) single-neck flask equipped with a stir bar: (E)-3-(3,5-bis(trifluoromethyl)phenyl)acrylaldehyde (290 grams (g), 1081 millimoles (mmol)) was
25 stirred in ethanol (360 milliliters (mL)). Triethyl orthoformate (187 mL, 1125 mmol) was added followed by pyridin-1-ium 4-methylbenzenesulfonate (PPTS; 0.544 g, 2.163 mmol). The suspension was stirred at 20 °C. After 4 hours, 4-methylmorpholine (2.378 mL, 21.63 mmol) was added to quench the acid. The mixture was concentrated via rotary evaporation (45 °C) to remove ethanol. The concentrate was partitioned between heptane and water
30 (pH 7). The organic portion was separated, dried over sodium sulfate, and concentrated (45

°C, <1 Torr) to provide a yellow oil (341 g, 93%): ¹H NMR (300 MHz, Chloroform-*d*) δ 7.82 (s, 2H), 7.76 (s, 1H), 6.80 (dd, *J* = 16.2, 1.2 Hz, 1H), 6.36 (dd, *J* = 16.1, 4.6 Hz, 1H), 5.12 (dd, *J* = 4.6, 1.3 Hz, 1H), 3.87 – 3.35 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 6H); ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -63.05.

- 5 In accordance with the procedure disclosed and exemplified in example 1a, the following molecule was prepared.

(*E*)-4-(3,3-diethoxyprop-1-en-1-yl)-1-fluoro-2-(trifluoromethyl)benzene

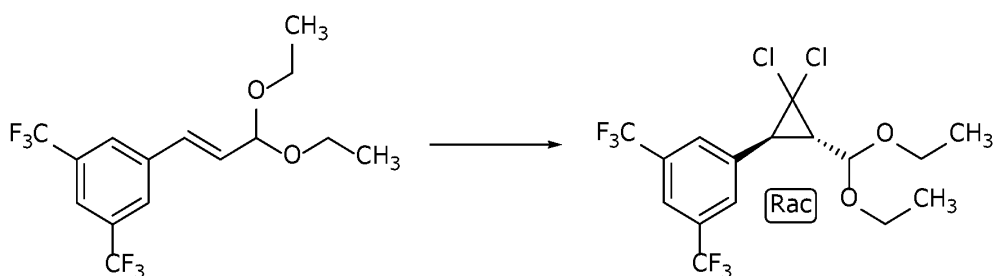


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¹H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 6.9, 2.3 Hz, 1H), 7.56 (ddd, *J* = 7.5, 4.7, 2.3 Hz, 1H), 7.15 (t, *J* = 9.3 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 6.19 (dd, *J* = 16.1, 4.9 Hz, 1H), 5.07 (dd, *J* = 4.9, 1.2 Hz, 1H), 3.71 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.56 (dq, *J* = 9.4, 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); GC-MS *m/z* 292.1.

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Example 1b: Synthesis of *trans-rac*-1,2,2-dichloro-3-(diethoxymethyl)cyclopropyl-3,5-bis(trifluoromethyl)benzene (S1a-1)



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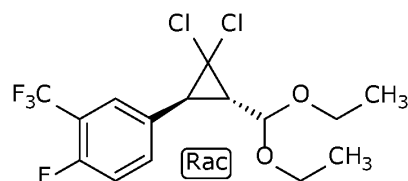
In a 5-L jacketed reactor equipped with an overhead stirrer, baffles, condenser, temperature probe, and nitrogen inlet: (*E*)-1-(3,3-diethoxyprop-1-en-1-yl)-3,5-bis(trifluoromethyl)benzene (125 g, 365 mmol) and benzyltriethylammonium chloride (0.412 g, 1.826 mmol) were stirred in a mixture of chloroform (1180 mL) and heptane (535 mL). 50% Sodium hydroxide (NaOH, aqueous; 484 mL, 9130 mmol) was added via addition

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funnel over 30 minutes. The jacket temperature was set to 45 °C. The reaction mixture was stirred vigorously at 45 °C until the reaction reached 90 to 95% conversion. After the reaction mixture was cooled to 20 °C, water (1.2 L) was charged to the reactor, and the mixture was stirred for 5 minutes. After the layers separated, the aqueous layer was removed, and the organic layer was washed with additional water (1.2 L). The organic layer was concentrated under vacuum to obtain a brown oil containing the desired product **S1a-1** (85%, in-pot): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.71 (s, 2H), 4.64 (d, *J* = 6.1 Hz, 1H), 3.82 – 3.55 (m, 4H), 2.94 (d, *J* = 8.4 Hz, 1H), 2.35 (dd, *J* = 8.5, 6.1 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ¹⁹F NMR (471 MHz, CDCl₃) δ -62.87.

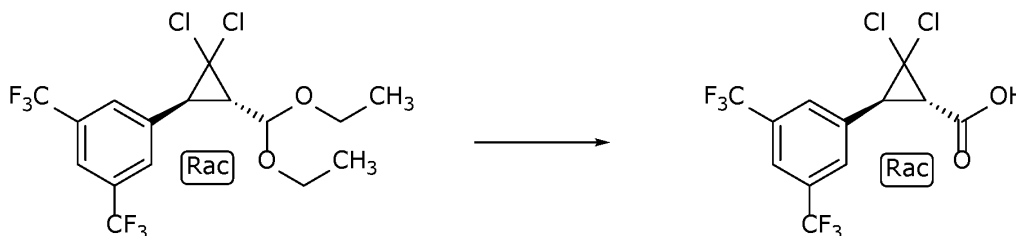
In accordance with the procedure disclosed and exemplified in example 1b, the following molecule was prepared.

***trans-rac*-4-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-1-fluoro-2-(trifluoromethyl)benzene (S1a-2)**



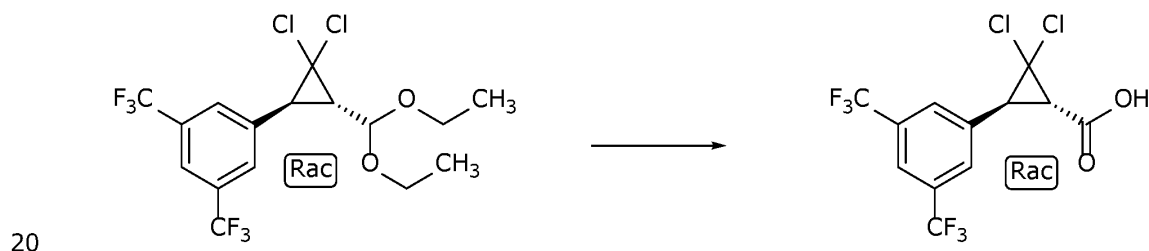
¹H NMR (400 MHz, Chloroform-*d*) δ 7.50 (dd, *J* = 6.7, 2.3 Hz, 1H), 7.43 (ddd, *J* = 7.4, 4.5, 2.4 Hz, 1H), 7.19 (t, *J* = 9.3 Hz, 1H), 4.60 (d, *J* = 6.2 Hz, 1H), 3.83 – 3.56 (m, 4H), 2.83 (d, *J* = 8.4 Hz, 1H), 2.26 (dd, *J* = 8.4, 6.2 Hz, 1H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); GC-MS *m/z* 375.1.

Example 1c: Synthesis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S1b-1)



In a 3-L four-neck flask equipped with a mechanical stirrer, temperature probe, and condenser: *trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (**S1a-1**; 96.5 g, 227 mmol) was stirred in acetic acid (779 mL). Water (82 mL) was added. OXONE® (140 g, 227 mmol) was added. The mixture was heated to 30 °C. After 30 minutes, the temperature was slowly increased to 45 °C. After 20 hours, the mixture was cooled to 25 °C. Sodium bisulfite (23.6 g, 227 mmol) was added to quench remaining peroxides. After stirring for 30 minutes, no peroxides were present when tested with potassium iodide (KI) paper. Acetonitrile (1.5 L) was added. The mixture was filtered, and the filtrate was concentrated. The concentrate was partitioned between ethyl acetate (500 mL) and brine (200 mL). The ethyl acetate portion was concentrated to provide an orange oil. The oil was partitioned between acetonitrile (500 mL) and heptane (300 mL). The heptane portion was extracted with acetonitrile (100 mL). The acetonitrile portion was concentrated to provide product **S1b-1** as an orange oil (81.8 g, 93%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.73 (s, 2H), 3.60 (d, *J* = 8.2 Hz, 1H), 2.99 (d, *J* = 8.3 Hz, 1H); ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -62.90.

Example 1d: Synthesis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S1b-1**)**

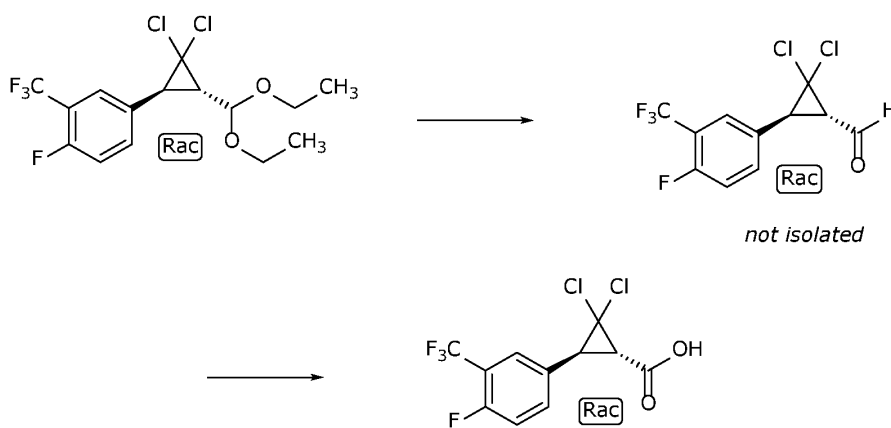


In a 1-L jacketed reactor equipped with a mechanical stirrer, temperature probe, condenser, and nitrogen inlet: *trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (**S1a-1**; 127 g, 299 mmol) was stirred in acetonitrile (478 mL). Water (118 mL) was added. OXONE® (184 g, 299 mmol) was added. The reaction mixture was heated to 35 °C. After 24 hours, analysis indicated complete conversion. The reaction mixture was cooled to 20 °C. The mixture tested positive for peroxides. Sodium bisulfite (10.88 g, 105 mmol) was added in small portions until the mixture tested negative for peroxides. Ethyl acetate (1.5 L) was added. The organic portion was separated and concentrated to provide a yellow oil. The oil was taken up in acetonitrile (600 mL) and

partitioned with *n*-heptane (2 x 200 mL). The acetonitrile layer was concentrated. The acetonitrile portion was concentrated to dryness and the residue was stirred up in *n*-heptane (800 mL) and stirred overnight. The mixture was cooled in an ice bath. After 2 hours, the slurry was vacuum filtered, and a solid was collected and vacuum-dried to give **S1b-1**

5 (102.6 g, 95%).

Example 1e: Synthesis of *trans*-rac-2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (S1b-2**)**



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In a 1-L four-neck flask equipped with a temperature probe, condenser, and nitrogen inlet: *trans*-rac-4-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-1-fluoro-2-(trifluoromethyl)benzene (**S1a-2**; 30 g, 80 mmol) was stirred in acetic acid (276 mL).

15 Water (27.6 mL) was added. The mixture was heated to 40 °C. After 16 hours, ¹H-NMR analysis showed complete formation of *trans*-rac-2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carbaldehyde (>99% conversion): ¹H NMR (400 MHz, Chloroform-*d*) δ 9.55 (d, *J* = 4.0 Hz, 1H), 7.50 (dd, *J* = 6.6, 2.3 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.24 (t, *J* = 9.1 Hz, 1H), 3.57 (d, *J* = 7.9 Hz, 1H), 2.93 (dd, *J* = 8.0, 4.0 Hz, 1H);

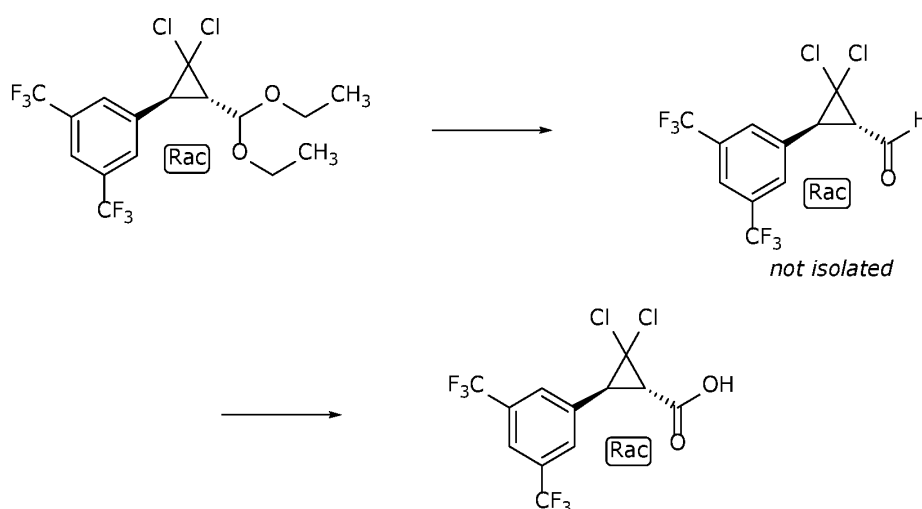
20 ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -61.51 (d, *J* = 12.9 Hz), -113.97 (q, *J* = 12.4 Hz).

As such, OXONE® (30.4 g, 49.4 mmol) was added to the reaction mixture. The mixture was heated to 50 °C and stirred for 20 hours. The mixture was allowed to cool to 23 °C. Sodium bisulfite (3.95 g, 38 mmol) was added portion-wise to quench remaining peroxides. The mixture was diluted with acetonitrile (500 mL). After stirring for 1 hour, the mixture was filtered and concentrated. The concentrate was partitioned between ethyl acetate and water. The organic portion was dried and concentrated to provide **S1b-2** as an

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orange oil (24 g, 95%): ^1H NMR (300 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 2H), 7.23 (t, J = 9.2 Hz, 1H), 3.48 (d, J = 8.3 Hz, 1H), 2.88 (d, J = 8.3 Hz, 1H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.49 (d, J = 12.9 Hz), -114.27 (q, J = 12.7 Hz).

5 **Example 1f: Synthesis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S1b-1)**



10 To a 100-mL reactor equipped with a temperature probe and nitrogen inlet were added acetic acid (280 mL) and water (28.0 mL). The reaction mixture was heated to 50 °C. *trans-rac*-1-(2,2-Dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (S1a-1; 30 g, 70.6 mmol) was added in one portion. The reaction progress was monitored by ^1H -NMR and GC-MS analysis. After 60 minutes, complete conversion of starting material

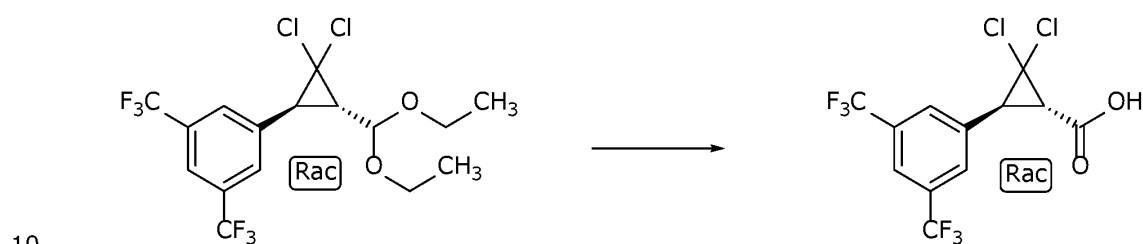
15 to *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carbaldehyde was observed (>99% conversion): ^1H NMR (300 MHz, Chloroform-*d*) δ 9.61 (d, J = 3.7 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.78 – 7.67 (m, 2H), 3.67 (d, J = 8.0 Hz, 1H), 3.05 (dd, J = 8.0, 3.7 Hz, 1H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.92; GC-MS m/z 315.

As such, OXONE® (43.4 g, 70.6 mmol) was added in one portion to the reaction

20 mixture. A mild exotherm was observed. After 3 hours, ^1H NMR analysis showed complete conversion to desired carboxylic acid product. The mixture was cooled to 20 °C and stirred overnight. The mixture was cooled to 5 °C and quenched with sodium bisulfite (9.54 g, 92 mmol) in water (30 mL). The mixture was warmed to 25 °C and diluted with water (200 mL). Methyl *tert*-butyl ether (MTBE; 300 mL) was added. The aqueous layer was extracted

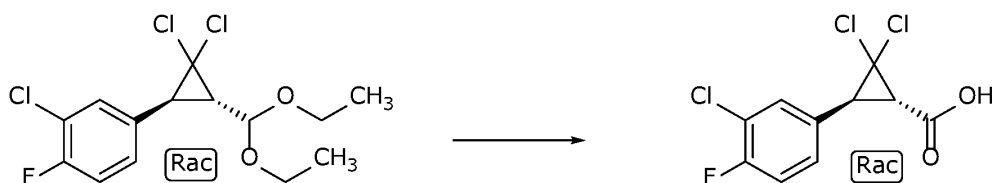
with MTBE (300 mL). The combined organic extracts were washed with water (3 x 200 mL), collected, dried (MgSO₄), filtered and concentrated. The residue was diluted with heptane (200 mL) and concentrated to dryness. A seed of solid racemic product was added. Solids began to form. The solids were triturated with *n*-heptane (200 mL), filtered and washed with *n*-heptane to afford desired product (23.5 g, 91%).

Example 1g: Synthesis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S1b-1)



In a jacketed reactor equipped with a temperature probe, nitrogen inlet, and overhead stirrer: *trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (**S1a-1**; 127 g, 78.6 wt % pure, 235 mmol) was dissolved in acetic acid (538 mL, 9391 mmol). Sulfuric acid (0.63 mL, 11.7 mmol) was added. The mixture was warmed to 50 °C. Hydrogen peroxide (30 wt %; 48 mL, 470 mmol) was added over 8 hours. After the complete addition of hydrogen peroxide, the mixture was held at 50 °C for 14 hours. Sodium bisulfite (29.3 g, 282 mmol) was added as a 10 wt % solution in water. After 30 minutes, the reaction mixture tested negative for residual peroxides with potassium iodide (KI) starch paper. The mixture was distilled (15–38 torr, 60–70 °C) until 606.8 g distillate was removed. Heptanes (743 mL) was added to the residue at 60–70 °C and the layers were separated. The heptane layer was washed twice with water (127 mL). The heptanes layer was concentrated by distillation until 255 g of distillate was collected. The concentrate was cooled to -5 °C and was held for 60 minutes. The resultant solid was collected by vacuum filtration and was vacuum dried to afford **S1b-1** (71.7 g, 82%).

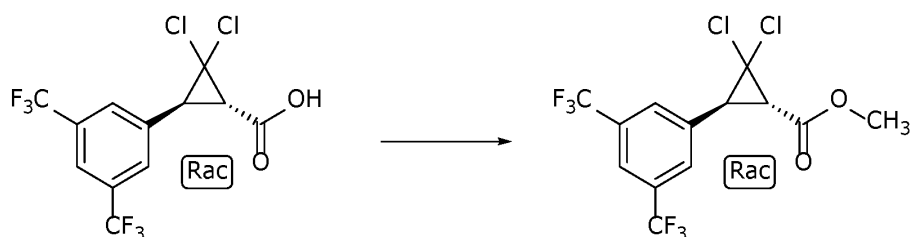
Example 1h: Synthesis of *trans-rac*-2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1-carboxylic acid (S1b-3)



In a 100 mL single-neck flask equipped with a stir bar: *trans-rac*-2-chloro-4-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-1-fluorobenzene (prepared as in Heemstra et al.,
 5 WO 2016168059 A1; 4.246 g, 12.43 mmol) was stirred in acetic acid (28.5 mL). Sulfuric acid (0.61 g, 0.621 mmol) was added. The mixture was heated to 50 °C. Hydrogen peroxide (30 wt %, 2.54 mL, 24.86 mmol) was added over 8 hours. After 22 hours, the mixture was cooled to 25 °C. Sodium bisulfite (1.552 g, 14.91 mmol) was added as a 10 wt % solution in water to quench remaining peroxides. The mixture was concentrated by approximately
 10 one-half volume under vacuum. Water (14 mL) was added. The mixture was extracted three times with dichloromethane (10 mL). The combined extracts were concentrated under vacuum to afford **S1b-3** (3.18 g, 90%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.34 (m, 1H), 7.20 – 7.15 (m, 2H), 3.43 (d, *J* = 8.2 Hz, 1H), 2.88 (d, *J* = 8.3 Hz, 1H); ¹³C NMR (126 MHz, Chloroform-*d*) δ 158.16 (d, *J* = 250.6 Hz), 129.40 (d, *J* = 4.0 Hz), 128.69 (d, *J* = 7.4 Hz), 121.57 (d, *J* = 18.2 Hz), 116.99 (d, *J* = 21.5 Hz); ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -115.20.

Example 2a: Synthesis of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1)

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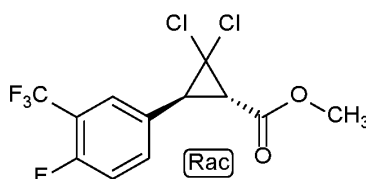
In a 3-L single-neck flask equipped with a mechanical stirrer, temperature probe, and condenser: *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S1b-1**; 123.6 g, 337 mmol) was stirred in methanol (1362 mL, 33700 mmol). Sulfuric acid (1.077 mL, 20.20 mmol) was added. The mixture was heated to a gentle reflux (about 65 °C). After 20 hours, the mixture was allowed to cool. 4-

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Methylmorpholine (3.33 mL, 30.3 mmol) was added. The mixture was concentrated. The concentrate was taken up in hexanes (1.5 L) and washed with water (500 mL). The hexanes portion was dried and concentrated to provide **S2a-1** as a solid (123.72 g, 92%): ^1H NMR (300 MHz, Chloroform-*d*) δ 7.87 (s, 1H), 7.71 (s, 2H), 3.88 (s, 3H), 3.58 (d, J = 8.3 Hz, 1H), 2.95 (d, J = 8.3 Hz, 1H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.93.

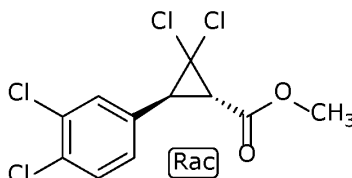
In accordance with the procedures disclosed in Scheme 2 and exemplified in example 2a, the following molecules were prepared.

***trans-rac*-methyl 2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (S2a-2)**



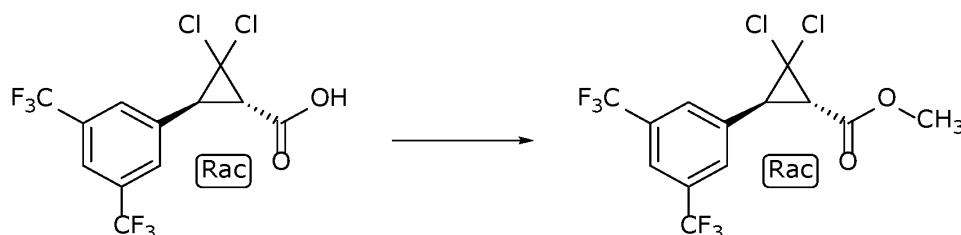
^1H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.41 (m, 2H), 7.22 (t, J = 9.2 Hz, 1H), 3.86 (s, 3H), 3.48 (d, J = 7.4 Hz, 1H), 2.85 (d, J = 8.3 Hz, 1H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.48 (d, J = 12.8 Hz), -114.60 (q, J = 12.5 Hz).

***trans-rac*-methyl 2,2-dichloro-3-(3,4-dichlorophenyl)cyclopropane-1-carboxylate (S2a-3)**



^1H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, J = 8.3 Hz, 1H), 7.35 (dd, J = 2.1, 0.7 Hz, 1H), 7.11 (ddd, J = 8.3, 2.1, 0.7 Hz, 1H), 3.85 (s, 3H), 3.42 (d, J = 8.3 Hz, 1H), 2.82 (d, J = 8.3 Hz, 1H).

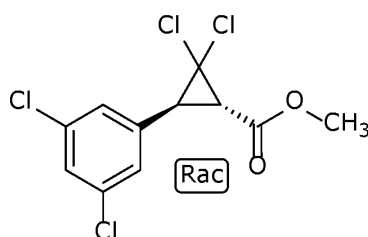
Example 2b: Synthesis of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1)



In a glass vial equipped with a magnetic stir bar: *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S1b-1**; 1.0 g, 2.72 mmol) and trimethyl orthoformate (0.343 mL, 3.13 mmol) were added. A solution of sulfuric acid (5.45 mg, 0.054 mmol) in methanol (0.441 mL, 10.90 mmol) was added in one portion. The reaction mixture was heated to 65 °C and stirred for 19 hours. The temperature was increased to 75 °C to distill off volatiles for 1 hour. The residue was cooled to 50–55 °C then heptane (4.0 mL) and potassium carbonate (0.015 g, 0.11 mmol) in water (2.0 mL) were added. The mixture was stirred for 15 minutes and then the layers were separated. The heptane layer was concentrated under vacuum to afford **S2a-1** (1.0 g, 96%).

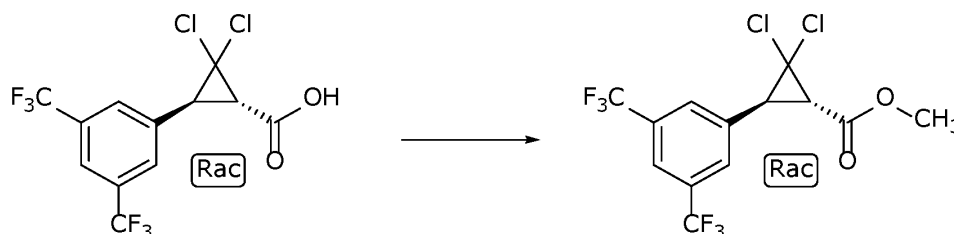
In accordance with the procedures disclosed in Scheme 2 and exemplified in example 2b, the following molecules were prepared

***trans-rac*-methyl 2,2-dichloro-3-(3,5-dichlorophenyl)cyclopropane-1-carboxylate (S2a-4)**



¹H NMR (500 MHz, Chloroform-*d*) δ 7.35 – 7.33 (m, 1H), 7.17 – 7.14 (m, 2H), 3.85 (s, 3H), 3.41 (d, *J* = 8.3 Hz, 1H), 2.84 (d, *J* = 8.3 Hz, 1H); ¹³C NMR (126 MHz, Chloroform-*d*) δ 166.62, 135.94, 135.32, 128.63, 127.47, 61.30, 53.21, 39.37, 37.46.

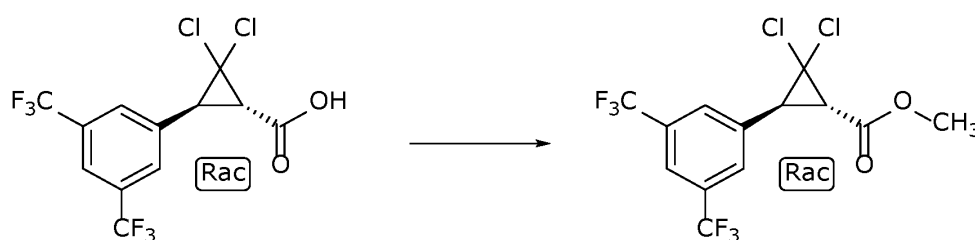
Example 2c: Synthesis of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1**)**



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In a glass vial equipped with a magnetic stir bar: *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S1b-1**; 1.0 g, 2.72 mmol) and trimethyl orthoformate (0.343 mL, 3.13 mmol) were added. A solution of sulfuric acid (5.45 mg, 0.054 mmol) in methanol (0.441 mL, 10.90 mmol) was added in one portion. The reaction mixture was heated to 65 °C and stirred for 19 hours. The temperature was increased to 75 °C to distill off volatiles for 1 hour. The residue was cooled to ambient temperature affording desired product **S2a-1** (1.0 g, 96%). The residue was cooled to 50–55 °C then heptane (4.0 mL) and potassium carbonate (0.015 g, 0.11 mmol) in water (2.0 mL) were added. The mixture was stirred for 15 minutes and then the layers were separated. The heptane layer was concentrated under vacuum to afford **S2a-1** (1.0 g, 96%). Optionally, the residue could be partitioned between heptane (4.0 mL) and potassium carbonate (0.015 g, 0.11 mmol) in water (2.0 mL) at 50–55 °C. The heptane layer can be concentrated under vacuum to afford **S2a-1**.

Example 2d: Synthesis of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1**)**

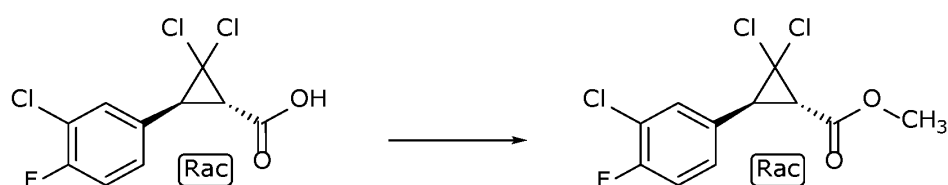


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In a glass reactor equipped with a mechanical stirrer and reflux condenser: *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S1b-1**;

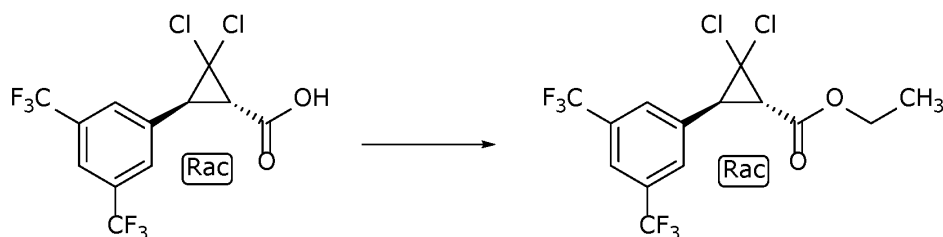
93 wt %, 260 g, 659 mmol) and trimethyl orthoformate (80.4 g, 758 mmol) were added. Methanol (84.4 g, 2638 mmol) was added. Sulfuric acid (1.3 g, 13.3 mmol) was added. The reaction mixture was heated to 65 °C and stirred for 12 hours. The temperature was increased to 75 °C and volatiles were removed by distillation. The residue was cooled to 50–55 °C. Heptanes (712.4 g) was added. A solution of potassium carbonate (3.64 g, 26.3 mmol) in water (520 g) was added. The mixture was stirred for 15–30 minutes. The layers were separated and the organic layer was concentrated by vacuum distillation affording desired product **S2a-1** (259 g, 96 wt %, 96%).

Example 2e: Synthesis of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-5**)**



In a 100 mL single-neck flask equipped with a stir bar and reflux condenser: *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S1b-3**; 5.93 g, 20.93 mmol) and trimethyl orthoformate (2.66 mL, 24.05 mmol) were added. A solution of sulfuric acid (41 mg, 0.42 mmol) in methanol (3.38 mL, 84 mmol) was added in one portion. The reaction mixture was heated to 65 °C and stirred for 19 hours. The temperature was increased to 75 °C to distill off volatiles for 1 hour. The residue was cooled to ambient temperature. The residue was partitioned between dichloromethane (20 mL) and potassium bicarbonate solution (1.16 wt %, 10 mL). The dichloromethane portion was separated and concentrated to provide desired product **S2a-5** (5.90 g, 95%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.30 (dq, *J* = 6.8, 1.3 Hz, 1H), 7.17 – 7.12 (m, 2H), 3.85 (s, 3H), 3.42 (d, *J* = 8.3, 1.0 Hz, 1H), 2.81 (d, *J* = 8.3 Hz, 1H).

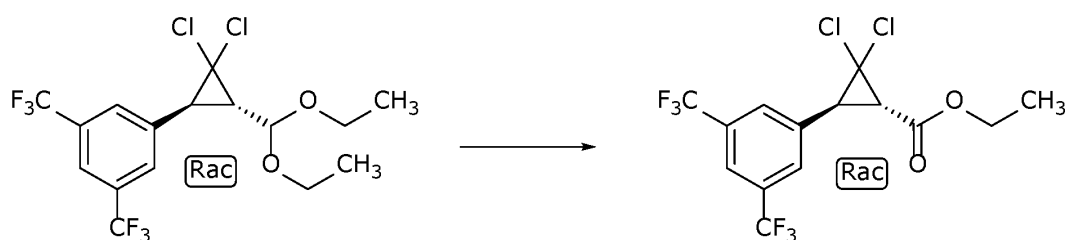
Example 2f: Synthesis of *trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-6**)**



In a 30-mL vial equipped with a magnetic stir bar, reflux condenser, and nitrogen inlet: *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S1b-1**; 3.0 g, 8.17 mmol) was mixed with triethyl orthoformate (1.56 mL, 9.40 mmol). A solution of sulfuric acid (16 mg, 0.163 mmol) in ethanol (1.91 mL) was added. The mixture was heated to 75 °C. After stirring for 1 day, ethanol (1.91 mL) was added. After stirring for 3 days, the mixture was cooled to 50 °C and concentrated to an oil. The oil was partitioned between heptane (10 mL) and 10 wt % aqueous sodium bicarbonate solution (10 mL). The heptane layer was concentrated to afford the title compound **S2a-6** as a yellow oil (2.56 g, 79%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 2H), 4.33 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.57 (d, *J* = 8.3 Hz, 1H), 2.94 (d, *J* = 8.3 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -62.91.

As an alternative to Schemes 1 and 2, the conversion of **S1a** to **S2a** can be conducted as illustrated in examples **2.5a** and **2.5b**.

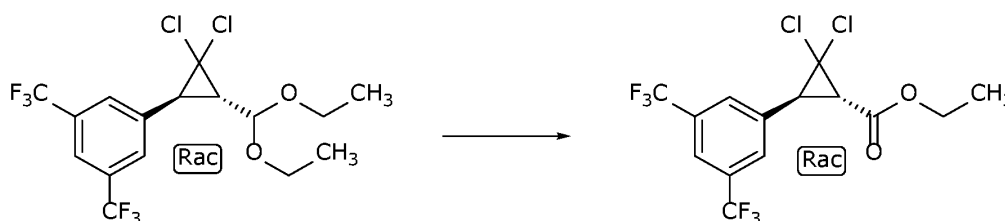
Example 2.5a: Synthesis of *trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-6**)**



In a 50-mL round bottom flask equipped with a magnetic stir bar, temperature probe, and nitrogen inlet: *trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (**S1a-1**; 2.00 g, 4.70 mmol) was stirred in ethanol (9.39 mL). Water (0.25 mL, 14.11 mmol) was added. OXONE® (2.89 g, 4.70 mmol) was added. The

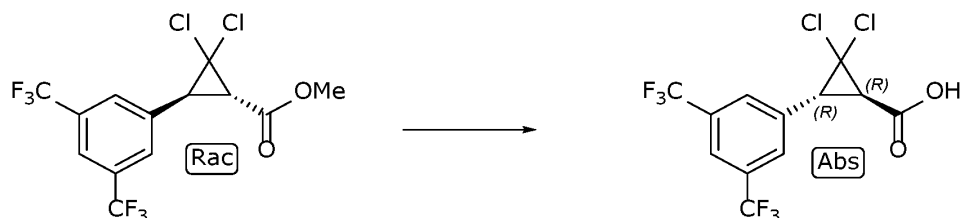
reaction mixture was heated to 55 °C. After 72 hours, analysis indicated complete conversion. The reaction mixture was cooled to 23 °C. Sodium bisulfite (0.538 g, 5.17 mmol) was added. The mixture was stirred for 30 minutes. The mixture tested negative for peroxides with potassium iodide (KI) paper. The mixture was filtered. The filtrate was concentrated to an oil. The oil was partitioned between water (10 mL) and heptane (10 mL). The heptane layer was concentrated to afford the title compound **S2a-6** as a yellow oil (1.384 g, 75%): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 2H), 4.33 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.57 (d, *J* = 8.3 Hz, 1H), 2.94 (d, *J* = 8.3 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -62.91.

Example 2.5b: Synthesis of *trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-6**)**



In an 50-mL round bottom flask equipped with a magnetic stir bar, reflux condenser, and nitrogen inlet: *trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene (**S1a-1**; 1.00 g, 2.35 mmol) was stirred in ethanol (4.70 mL). Sodium percarbonate (0.369 g, 2.35 mmol) was added. Sulfuric acid (0.28 mL, 5.17 mmol) was added. The reaction mixture was heated to 70 °C. After 20 hours, analysis indicated approximately 78% conversion. The reaction mixture was cooled to 23 °C. Sodium bisulfite (0.073 g, 0.71 mmol) was added. The mixture was stirred for 20 minutes. The mixture tested negative for peroxides (KI paper). The mixture was diluted with heptane (10 mL) and the mixture was stirred for 5 minutes. The mixture was filtered. The solid cake was washed with heptane (5 mL). The filtrate was concentrated to an oil. The oil was dissolved in heptane (10 mL). The mixture was dried over sodium sulfate. The mixture was filtered and the filtrate was concentrated to afford the title compound **S2a-6** as a yellow oil (65%, in pot) ¹H NMR (400 MHz, Chloroform-*d*) δ 7.86 (s, 1H), 7.71 (d, *J* = 1.6 Hz, 2H), 4.33 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.57 (d, *J* = 8.3 Hz, 1H), 2.94 (d, *J* = 8.3 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -62.91.

Example 3a: Synthesis of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-1**)**



5

In a 5-L jacketed reactor vessel (18.4-centimeter (cm) diameter) equipped with a mechanical stirrer with a 9-cm diameter Rushton type impeller, two 1-cm wide baffles, a temperature probe, and a condenser, a solution of L-lysine monohydrate (60 g, 365 mmol) in deionized water (1800 mL) was charged. While stirring vigorously at 280 revolutions per minute (RPM), a solution of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**); 300 g, 771 mmol) in acetone (1200 mL) was added to the reactor. The temperature of the vessel contents was increased to 30 °C and was mixed for 30 minutes. *Pseudomonas stutzeri* lipase (available from Almac Group Limited product code AH-04; 9 g) was added to the reaction as solid. The reaction mixture was stirred at 280 RPM and 30 °C for 24 hours when the reaction reached 45% production value of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) to the (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S3a-1**).

Production value was calculated using Equation 1.

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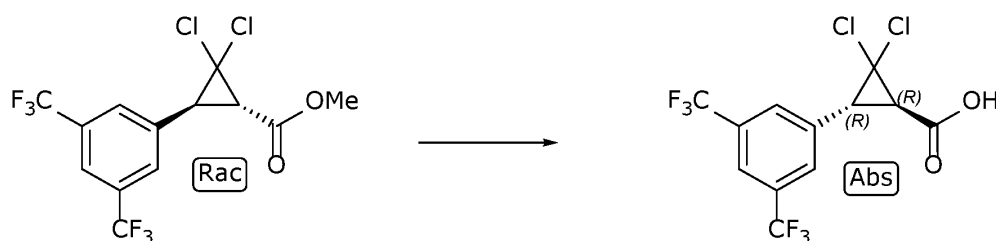
Equation 1

$$\text{production value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}} \right)$$

The HPLC analytical method was as follows: Chiral HPLC column: CHIRALCEL® OJ-3R (150 x 4.6 millimeters (mm) inside diameter, 3.0 microns (μm)); temperature: 30 °C; flow rate: 0.625 mL/minute; isocratic 50:50 0.1% formic acid in acetonitrile–0.1% formic acid in water; UV detector at 220 nanometers (nm). Expected elution time of the (S,S)-ester at 18.0 minutes and of the (R,R)-ester at 18.8 minutes.

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EXAMPLE 3b: Isolation of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-1**)**



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In a 1-L jacketed reactor vessel equipped with a mechanical stirrer with pitched blade type impeller, 0.2 M 2-amino-2-(hydroxymethyl)propane-1,3-diol buffer solution at pH 7 (131.25 mL) and 100 mg/mL lysine solution (70 mL) were added. While mixing at 200 RPM, a solution of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**; 7 g, 771 mmol) in acetone (79 mL) was added to the reactor. The temperature of the vessel contents was increased to 30 °C and was mixed for 30 minutes. *Pseudomonas stutzeri* lipase (available from Almac Group product code AH-04; 70 mg) dissolved in deionized water (35 mL) was added to the reactor. The reaction mixture was stirred at 250 RPM and 30 °C for 24 hours.

The reaction solution was harvested into a 1-L centrifuge bottle and centrifuged at 4402 Relative Centrifugal Force ("RCF") for 5 minutes in a Beckman Avanti J-26 floor centrifuge. The supernatant containing the vast majority of the **S3a-1** product was decanted away from the denser oil phase. The denser oil phase largely comprising of unreacted **S2a-1** was transferred to 50 mL polypropylene conical vials and centrifuged at 3100 RCF in a Thermo Scientific Sorvall ST8 for a sufficient duration to effect phase separation in order to recover additional **S3a-1**. The supernatant was combined with the previous supernatant. A total of 287.55 g of supernatant was recovered from 298.22 g of material harvested from the reactor, with the remainder comprising the *S,S*-methyl ester rich dense oil phase.

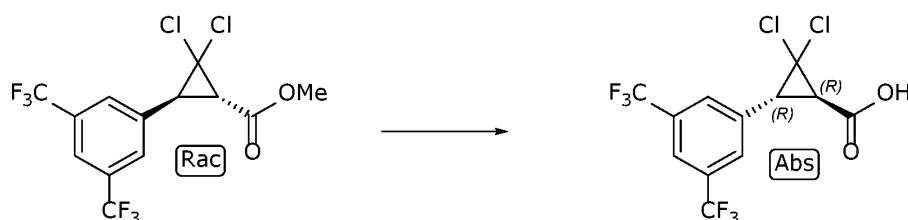
Supernatant (47.75 g) was added to a 250 mL glass beaker. 0.1 normal (N) hydrochloric acid (214.8 g) was added over 1 hour using a Watson Marlow 520SU peristaltic pump at 0.6 RPM. The hydrochloric acid reduced the pH of the solution, thereby reducing the solubility limit of **S3a-1** resulting in crystallization. The crystallization slurry was centrifuged in 50 mL conical vials at 3100 RCF in a Thermo Scientific Sorvall ST8 for a sufficient duration to sediment the crystals. The wet crystals were transferred to a glass

scintillation vial and dried overnight at 25 mm Hg vacuum pressure and ambient temperature. This yielded 0.20413 g of **S3a-1** with 92.0% purity.

Example 3c: Isolation of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-1**)**

After the synthesis of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S3a-1**) described in Example 3a, acetone was removed from the reaction mixture by evaporation under reduced pressure. The remaining mixture was made basic to pH 11.5 by addition of aqueous 2 M sodium hydroxide solution. The aqueous mixture was then extracted with methyl *tert*-butyl ether twice. The remaining aqueous layer was subjected to reactive crystallization, where aqueous 3 M hydrochloric acid solution was added slowly to adjust the pH of the mixture to pH 4.0. The resulting slurry was stirred at room temperature for 5 hours and then filtered through a fritted glass funnel to obtain **S3a-1** as off-white solid (42% isolated yield).

Example 4a: Screening of enzymes for activity and selectivity for the hydrolysis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1**) to synthesize (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S3a-1**)**



Reaction:

A solution of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) in acetone was prepared to a concentration of 200 milligrams per milliliter (mg/mL; "substrate solution"). A solution of lysine was prepared in water to a concentration of 200 mg/mL ("lysine solution"). A 15-mL conical vial was charged with lysine solution (0.25 mL), substrate solution (1.0 mL), acetone (0.5 mL), and deionized water (3.25 mL). The capped 15-mL conical vial was rotated on a tube inverter for 30 minutes at 40 RPM. Lipases selected from the list shown in Table **4a-2** were

weighed into separate 15-mL conical vials (40 mg). Water (1.0 mL) was added to each vial containing lipase. The vials were vortexed for three minutes at 3000 RPM to disperse and partially dissolve the lipase. The contents of the substrate, acetone and lysine solutions were transferred to the vials containing enzyme. The vials were inverted at 40 RPM for 24 hours at 30 °C to allow for the lipase-catalyzed hydrolysis to proceed. After 24 hours two samples were taken for analysis by HPLC to assess approximate conversion of **S2a-1** and the enantiomeric excess of the **S3a-1** product.

Analysis of approximate conversion by achiral HPLC:

Well mixed reaction solution (333 µL) was weighed into a 25 mL volumetric flask. An internal standard solution (200 µL) was added to the flask. The internal standard solution consisted of 4,4'-dihydroxydiphenylmethane (8.33 mg) dissolved into acetonitrile (0.5 mL) and water (0.5 mL). Additional 1:1 volume acetonitrile/volume water was added to bring total volume to 25 mL. The solution was vortexed for 30 seconds. An aliquot was transferred into an HPLC vial and analyzed by HPLC using the following method:

HPLC column: Agilent ZORBAX SB-Phenyl (150 mm x 4.6 mm internal diameter with 3.5 µm particle size, Agilent Part Number 863953-912); temperature: ambient (approximately 20 °C); flow rate: 1.0 mL/minute; injection volume: 5 µm; UV detection at 210 nm; solvent gradient according to table below:

Table 4a-1		
Time (min)	Water + 0.03% phosphoric acid (volume %)	Acetonitrile (volume %)
0.0	60	40
8.0	5	95

The internal standard is expected to elute at 3.9 minutes, **S3a-1** at 6.2 minutes and **S2a-1** at 7.3 minutes. The approximate conversion was calculated from the achiral HPLC results using quantification based on the internal standard and the equation:

Approximate Conversion (%)

$$= 100 * \frac{\text{Weight Percent of Acid in Solution}}{\text{Weight Percent of Acid in Solution} + \text{Weight Percent of Ester in Solution}}$$

Analysis of enantiomeric excess by chiral HPLC:

A 50-μL sample was taken from the conical reaction vial and placed into a filtering HPLC vial to which acetonitrile (400 μL) was added. The filter plunger was inserted and the filtered solution was analyzed by HPLC using the following method: Chiral HPLC column: DAICEL CHIRALCEL® OJ-3R (150 mm x 4.6 mm internal diameter, 3 μm silica gel); temperature: 30 °C; flow rate: 0.625 mL/minute; isocratic 50%:50% 0.1% formic acid in water–0.1% formic acid in acetonitrile; UV detection at 220 nm; injection volume of 5.0 μL. Expected elution time of the (S,S)-acid at 7.2 minutes, the (R,R)-acid at 7.7 minutes, the (S,S)-ester at 18.0 minutes and the (R,R)-ester at 18.8 minutes. Enantiomeric excess was calculated from chiral HPLC results using the following equation.

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$$\text{Enantiomeric Excess (ee)} = 100 * \left[\frac{(\text{R,R}) \text{ Acid Peak Area} - (\text{S,S}) \text{ Acid Peak Area}}{(\text{R,R}) \text{ Acid Peak Area} + (\text{S,S}) \text{ Acid Peak Area}} \right]$$

Table 4a-2: Summary of hydrolase activity data			
Carboxylic ester hydrolase Common Name	Almac Group Product Number	Approximate Conversion (% of total S2a-1)	Enantiomeric Excess (ee) of S3a-1 Product (%)
Lipase C from <i>Alcaligenes</i> sp.	AH-03	36.87%	97.9%
Lipase from <i>Pseudomonas stutzeri</i>	AH-04	48.99%	98.5%
Lipase from <i>Pseudomonas cepacia</i>	AH-05	23.77%	97.1%
Lipase E from <i>Alcaligenes</i> sp.	AH-08	30.04%	97.6%
Lipase A from <i>Burkholderia cepacia</i>	AH-36	24.84%	97.2%
Lipase B from <i>Burkholderia cepacia</i>	AH-37	22.85%	96.5%
Lipase B from <i>Candida antarctica</i>	AH-42	1.29%	25.3%
Lipase A from <i>Candida antarctica</i>	AH-43	3.14%	11.3%

Lipase B from <i>Candida rugosa</i> (<i>Diutina rugosa</i>)	AH-24	0.97%	6.1%
Lipase from <i>Aspergillus niger</i>	AH-27	0.77%	7.3%
Lipase from <i>Penicillium roquefort</i>	AH-28	1.61%	1.7%
Lipase from <i>Penicillium camembertii</i>	AH-32	1.27%	0.6%

Example 4b: Assessing activity and selectivity of *Pseudomonas stutzeri* lipase for the hydrolysis of *trans-rac*-methyl 2,2-dichloro-3-(3,5-dichlorophenyl)cyclopropane-1-carboxylate (S2a-4**) to synthesize (1*R*,3*R*)-2,2-dichloro-3-(3,5-dichlorophenyl)cyclopropane-1-carboxylic acid (**S3a-4**)**



Reaction:

A solution of lysine was prepared in water to a concentration of 80 mg/mL ("lysine solution"). Four 15-mL conical vials were charged with 200 mg of *trans-rac*-methyl 2,2-dichloro-3-(3,5-dichlorophenyl)cyclopropane-1-carboxylate (**S2a-4**), lysine solution (0.5 mL), and one of the following solvents: acetone (2.4 mL), dimethyl sulfoxide (0.45 mL), acetonitrile (0.6 mL) or methyl *tert*-butyl ether (3 mL). The vial fill volumes were brought to a total of 5 mL with deionized water. The capped 15-mL conical vials were rotated on a tube inverter for 30 minutes at 40 RPM. A lipase solution was prepared by dissolving *Pseudomonas stutzeri* lipase (Almac Group, AH-04) in deionized water to a concentration of 2 mg/mL ("lipase solution"). Lipase solution (1.0 mL) was added to each 15-mL conical vial. The 15-mL conical vials were inverted at 40 RPM for 24 hours at 30 °C to allow for the lipase catalyzed hydrolysis to proceed.

After 24 hours, 1 N hydrochloric acid (0.25 mL) was added to each of the 15-mL conical vials. The mixture was extracted twice with dichloromethane by adding 3 mL of

dichloromethane, vortexing, settling, and removing the dichloromethane by pipetting. The process was repeated for the second extraction. The dichloromethane extracts were combined, dried over sodium sulfate, filtered and concentrated by rotary evaporation. The resulting oil was dissolved in acetonitrile and analyzed by HPLC to assess Approximate
 5 Conversion of **S2a-4** and by chiral HPLC to access the enantiomeric excess of the **S3a-4** product. The analytical results are shown in Table **4b-1**.

Table 4b-1: Results of enzymatic hydrolysis of S2a-4 to S3a-4 using various co-solvents				
Co-solvent	40% acetone	7.5% DMSO	10% acetonitrile	50% MTBE
Approximate Conversion	29.5%	12.5%	5.9%	5.6%
Enantiomeric Excess (%ee)	95.8%	82%	67.4%	84.6%

Example 4c: Assessing activity and selectivity of *Pseudomonas stutzeri* lipase for the hydrolysis of *trans-rac*-methyl 2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1- carboxylate (S2a-5**) to synthesize (1*R*,3*R*)-2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1-carboxylic acid (**S3a-5**)**

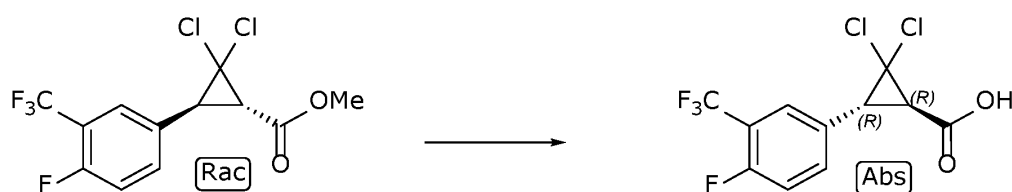


A solution of *trans-rac*-methyl 2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1- carboxylate (**S2a-5**) in acetone was prepared to a concentration of 200 mg/mL ("substrate solution"). A solution of lysine was prepared in water to a concentration of 80 mg/mL ("lysine solution"). A 15-mL conical vial was charged with lysine solution (0.5 mL), substrate solution (1.0 mL), acetone (1.4 mL), and deionized water (2.1 mL). The capped 15-mL conical vial was rotated on a tube inverter for 30 minutes at 40 RPM. A lipase solution was prepared by dissolving *Pseudomonas stutzeri* lipase (Almac Group, AH-04) in deionized water to a concentration of 2 mg/mL ("lipase solution"). Lipase solution (1.0 mL)

was added to each 15-mL conical vial. The vial was inverted at 40 RPM for 24 hours at 30 °C to allow for the lipase catalyzed hydrolysis to proceed.

To the reaction solution, 1 N hydrochloric acid (0.25 mL) was added. The mixture was extracted twice with dichloromethane by adding 3 mL of dichloromethane, vortexing, settling, and removing the dichloromethane by pipetting. The process was repeated for the second extraction. The dichloromethane extracts were combined, dried over sodium sulfate, filtered and concentrated by rotary evaporation. The resulting oil was dissolved in acetonitrile and analyzed by HPLC to assess Approximate Conversion of **S2a-5** and by chiral HPLC to assess the enantiomeric excess of the **S3a-5** product. The HPLC analysis showed 26% conversion and the chiral HPLC results showed 94.4% enantiomeric excess of the reaction product.

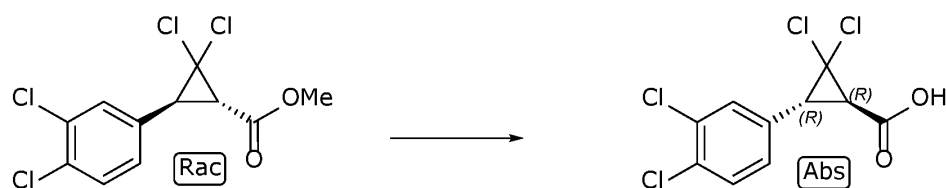
Example 5: Synthesis of (1*R*,3*R*)-2,2-dichloro-3-(3-trifluoromethyl-4-fluorophenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-2**)**



In 100 mL flask, *trans-rac*-methyl 2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate (**S2a-2**; 500 mg, 1.510 mmol) was dissolved in DMSO (10 mL) and buffer solution (0.1 M potassium phosphate dibasic and monobasic, pH 7.0; 100 mL) at room temperature. The enzyme (*Pseudomonas stutzeri* lipase, available from Almac Group product code AH-04; 250 mg) was added, and the suspension was stirred at 30 °C for 4 days. The reaction mixture was diluted with ethyl acetate and 6 N hydrochloric acid. The organic layer mostly containing ethyl acetate was separated and was washed with additional water. The organic layer was concentrated by evaporation under vacuum to afford (1*R*,3*R*)-2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylic acid (150 mg, 31.3% isolated molar yield, 96% enantiomeric excess): ¹H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.41 (m, 2H), 7.30 – 7.17 (m, 1H), 3.50 (d, *J* = 8.2 Hz, 1H), 2.89 (d, *J* = 8.3 Hz, 1H); ¹⁹F NMR (376 MHz, DMSO) δ -61.48, -114.25; LCMS *m/z* = 316 ([*M*-H]⁻). Chiral HPLC method: Column: CHIRALPAK® ZWIX(+), particle size 3 μm, dimension 3 mm x 150 mm, DAIC 511584;

Mobile phase: 49% acetonitrile–49% methanol–water with 50 millimolar (mM) formic acid and diethylamine; Flow rate: 0.5 mL/minute; Elution time: 9 minutes; Temperature: 25 °C.

Example 6: Synthesis of (1*R*,3*R*)-2,2-dichloro-3-(3,4-dichlorophenyl)cyclopropane-1-carboxylic acid (S3a-3)



trans-rac-Methyl 2,2-dichloro-3-(3,4-dichlorophenyl)cyclopropane-1-carboxylate (**S2a-3**; ~5 mg) in DMSO (50 μ L) was added to each of four 2 mL Eppendorf tubes. Solutions of *Pseudomonas stutzeri* lipase (available from Almac Group product code AH-04;) were prepared in 0.1 M potassium phosphate buffer with pH of 7.0. A sufficient volume of lipase solution and potassium phosphate buffer solution was prepared to add between 0.05 mg and 15 mg of lipase in buffer (950 μ L) to each 2 mL Eppendorf tube bringing the total volume in each tube to 1 mL. The reaction mixtures were allowed to proceed using a tube inverter to rotate the vials at 40 RPM at 30 °C for between 40 and 80 hours, according to Table 6-1. The mixture was diluted with ethyl acetate and 6 N hydrochloric acid. The organic layer containing mostly ethyl acetate was collected and analyzed by HPLC. The resulting conversion and enantiomeric excess of each reaction is shown in Table 6-1.

Chiral HPLC method: Column: CHIRALPAK® ZWIX(+), particle size 3 μ m, dimension 3 mm x 150 mm, DAIC 511584; Mobile phase: 49% acetonitrile–49% methanol–water with 50 mM formic acid and diethylamine; Flow rate: 0.5 mL/minute; Elution time: 9 minutes; Temperature: 25 °C.

Table 6-1: Summary of *Pseudomonas stutzeri* lipase (available from Almac Group product code AH-04) resolution of **S2a-3** to **S3a-3**

Reaction	Mass of S2a-3 (mg)	Mass of Lipase* (mg)	Loading of Lipase* (wt %)	Total Reaction Volume (mL)	Reaction Time (hours)	Production Value (%)**	Enantiomeric Excess (ee) of S3a-1 Product (%)
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			ratio to S2a-3)				
1	5	15	300	1	40	50	97
2	5	5	100	1	40	34	97
3	5	0.5	10	1	80	18	97
4	5	0.05	1	1	60	1	Not Determined

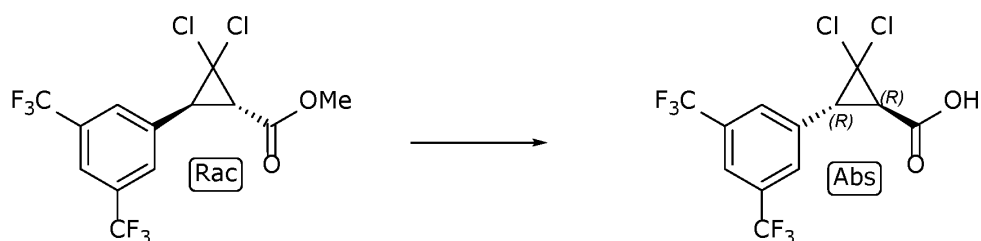
Lipase* = *Pseudomonas stutzeri* lipase (Almac AH-04)

**Production value was calculated as follows:

$$\text{production value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}}\right)$$

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Example 7: Synthesis of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-1)



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A solution of *trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) in acetone was prepared to a concentration of 200 mg/mL ("substrate solution"). A solution of lysine was prepared in water to a concentration of 100 mg/mL ("lysine solution"). A solution of *Pseudomonas stutzeri* lipase (available from Almac Group product code AH-04) in water was prepared to a concentration of 2 mg/mL ("enzyme solution"). A 15-mL conical vial was charged with lysine solution (0.25 mL), ester solution (0.5 mL), acetone (1 mL), and water (4.125 mL). The capped 15-mL conical vial was rotated on a tube inverter for 30 minutes at 40 RPM. Enzyme solution (0.125 mL) was added to the 15-mL conical vial, making the mass of *Pseudomonas stutzeri* lipase equal to 0.25% of the mass of the **S2a-1**. The tube was inverted at 40 RPM for 48 hours at 30 °C to allow for the lipase resolution to proceed. A 50-μL sample was taken from

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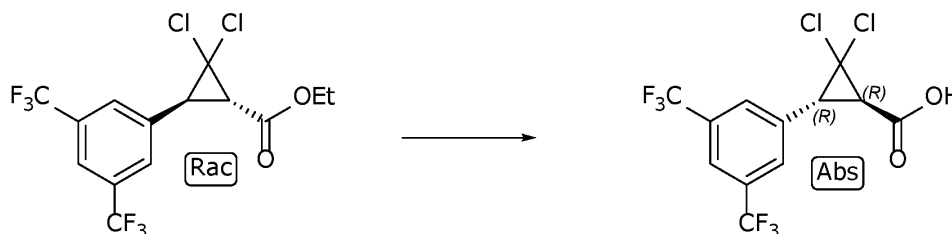
the conical vial and placed into a filtering HPLC vial to which acetonitrile (400 μ L) was added. The filter plunger was inserted, and the filtered solution was analyzed by HPLC.

The HPLC analytical method was as follows: Chiral HPLC column: DAICEL CHIRALCEL® OJ-3R (150 mm x 4.6 mm internal diameter, 3 μ m silica gel); temperature: 30 $^{\circ}$ C; flow rate: 0.625 mL/minute; isocratic 50:50 0.1% formic acid in water–0.1% formic acid in acetonitrile; UV detection at 220 nm; injection volume of 5.0 μ L. Expected elution time of the (*S,S*)-acid at 7.2 minutes, the (*R,R*)-acid at 7.7 minutes, the (*S,S*)-ester at 18.0 minutes and the (*R,R*)-ester at 18.8 minutes.

HPLC analysis showed a production value of 47.7% with an enantiomeric excess of 98.8%. Production value was calculated as follows.

$$\text{production value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}}\right)$$

Example 8: Synthesis of (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (S3a-1**) from *trans-rac*-ethyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-6**)**



A solution of *trans-rac*-ethyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-6**) in acetone was prepared to a concentration of 200 mg/mL ("substrate solution"). A solution of anhydrous lysine was prepared in water to a concentration of 80 mg/mL ("lysine solution"). A solution of *Pseudomonas stutzeri* lipase (available from Meito Sangyo Co., Ltd., product code Lipase TL) in water was prepared to a concentration of 2 mg/mL ("lipase solution"). Two 15-mL conical vials were each charged with lysine solution (0.5 mL), substrate solution (1.0 mL), acetone (0.5 mL), and water (3.0 mL). The capped 15-mL conical vials were rotated on a tube inverter for 30 minutes at 40 RPM. Lipase solution (1.0 mL) was added to one 15-mL conical vial, making the mass of

Pseudomonas stutzeri lipase equal to 1.0% of the mass of the **S2a-6**. The tubes were inverted at 40 RPM for 24 hours at 30 °C. A 50-μL sample was taken from each the conical vial and placed into a filtering HPLC vial to which acetonitrile (400 μL) was added. The filter plunger was inserted, and the filtered solution was analyzed by HPLC.

- 5 The HPLC analytical method was as follows: Chiral HPLC column: DAICEL CHIRALCEL® OJ-3R (150 mm x 4.6 mm internal diameter, 3 μm silica gel); temperature: 30 °C; flow rate: 0.625 mL/minute; isocratic 50:50 0.1% trifluoroacetic acid in water–0.1% trifluoroacetic acid in acetonitrile; UV detection at 220 nm; injection volume of 5.0 μL. Expected elution time of the (S,S)-acid at 7.2 minutes, the (R,R)-acid at 7.7 minutes, the (S,S)-ester at 18.0 minutes and the (R,R)-ester at 18.8 minutes.
- 10

Enantiomeric excess was calculated from chiral HPLC results using the equation.

$$\text{Enantiomeric Excess (ee)} = 100 * \left[\frac{(R,R) \text{ Acid Peak Area} - (S,S) \text{ Acid Peak Area}}{(R,R) \text{ Acid Peak Area} + (S,S) \text{ Acid Peak Area}} \right]$$

Production value was calculated from chiral HPLC results using the equation:

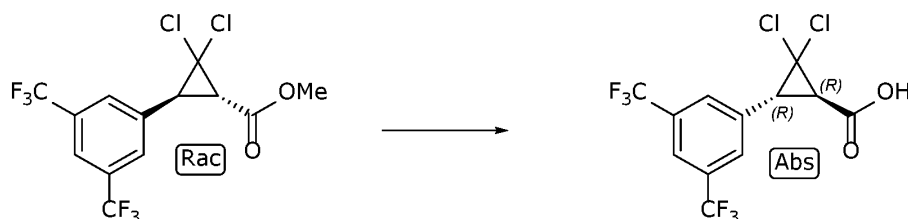
15

$$\text{Production Value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}} \right)$$

The results are presented in Table **8-1**.

Table 8-1: Production value and enantiomeric excess using <i>trans-rac</i> -ethyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-6) substrate		
Enzyme	Production Value (%)	Enantiomeric Excess (ee) of S3a-1 Product (%)
Lipase TL	47.8%	>99%

- 20 **Example 9: Use of *Pseudomonas stutzeri* lipase for the stereoselective hydrolysis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) to synthesize (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S3a-1**)**



A solution of *trans-rac*-methyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) in acetone was prepared to a concentration of 200 mg/mL ("substrate solution"). A solution of anhydrous lysine was prepared in water to a concentration of 80 mg/mL ("lysine solution"). A solution of *Pseudomonas stutzeri* lipase (available from Meito Sangyo Co., Ltd., product code Lipase TL) in water was prepared to a concentration of 2 mg/mL ("Lipase TL solution"). A solution of *Pseudomonas stutzeri* lipase (available from Almac Group, product code AH-04) in water was prepared to a concentration of 2 mg/mL ("AH-04 solution"). Two 15-mL conical vials were each charged with lysine solution (1.0 mL), substrate solution (1.0 mL), acetone (0.5 mL), and water (2.5 mL). The capped 15-mL conical vials were rotated on a tube inverter for 30 minutes at 40 RPM. Lipase solution (1.0 mL) was added to one 15-mL conical vial, making the mass of *Pseudomonas stutzeri* lipase equal to 1.0% of the mass of the **S2a-1**. Esterase solution (1.0 mL) was added to the other 15-mL conical vial, making the mass of esterase equal to 1.0% of the mass of the **S2a-1**. The tubes were inverted at 40 RPM for 24 hours at 30 °C. A 50-μL sample was taken from each of the conical vials and placed into a filtering HPLC vial to which acetonitrile (400 μL) was added. The filter plunger was inserted, and the filtered solution was analyzed by HPLC.

The HPLC analytical method was as follows: Chiral HPLC column: DAICEL CHIRALCEL® OJ-3R (150 mm x 4.6 mm internal diameter, 3 μm silica gel); temperature: 30 °C; flow rate: 0.625 mL/minute; isocratic 50:50 0.1% trifluoroacetic acid in water–0.1% trifluoroacetic acid in acetonitrile; UV detection at 220 nm; injection volume of 5.0 μL. Expected elution time of the (*S,S*)-acid at 7.2 minutes, the (*R,R*)-acid at 7.7 minutes, the (*S,S*)-ester at 18.0 minutes and the (*R,R*)-ester at 18.8 minutes. Enantiomeric excess was calculated from chiral HPLC results using the equation.

$$\text{Enantiomeric Excess (ee)} = 100 * \left[\frac{(R,R) \text{ Acid Peak Area} - (S,S) \text{ Acid Peak Area}}{(R,R) \text{ Acid Peak Area} + (S,S) \text{ Acid Peak Area}} \right]$$

Production value was calculated from chiral HPLC results using the equation:

$$\text{Production Value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}}\right)$$

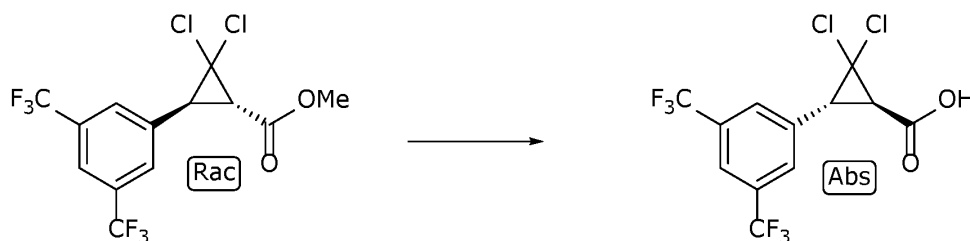
The results are presented in Table 9-1.

Table 9-1: Production value and enantiomeric excess using <i>trans-rac</i> -methyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1) substrate		
Enzyme	Production Value (%)	Enantiomeric Excess (ee) of S3a-1 Product (%)
Lipase TL	48.1	98.7%
AH-04	48.9	98.6%

5

Example 10: Use of *Pseudomonas fluorescens* lipase for the stereoselective hydrolysis of *trans-rac*-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (S2a-1**) to synthesize (1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid (**S3a-1**)**

10



Reaction:

A solution of *trans-rac*-methyl-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate (**S2a-1**) in acetone was prepared to a concentration of 100 mg/mL ("substrate solution"). A solution of lysine was prepared in water to a concentration of 100 mg/mL ("lysine solution") using anhydrous lysine as the starting material. A solution of monobasic potassium phosphate and dibasic potassium phosphate

was prepared in water to a concentration of 0.1 M ("buffer solution") in a ratio to result in a pH of 7.0. A 15 mL conical vial was charged with lysine solution (1.0 mL), substrate solution (1.0 mL), acetone (0.5 mL), and buffer solution (2.5 mL). The capped 15 mL conical vial was rotated on a tube inverter for 30 minutes at 40 RPM. A solution of *Pseudomonas fluorescens* lipase (AH-35, Almac Group) was prepared by dissolving to a concentration of 20 mg/mL ("enzyme solution") in buffer solution. To the 15 mL conical vial was added 1 mL of the enzyme solution. The vial was inverted at 40 RPM for 24 hours at 30 °C to allow for the enzyme-catalyzed hydrolysis to proceed. After 24 hours, a sample was taken for analysis by HPLC to assess the production value and the enantiomeric excess of the **S3a-1** product.

Analysis by chiral HPLC:

A 50-μL sample was taken from the conical reaction vial and placed into a filtering HPLC vial to which acetonitrile (400 μL) was added. The filter plunger was inserted and the filtered solution was analyzed by HPLC using the following method: Chiral HPLC column:

DAICEL CHIRALCEL® OJ-3R (150 mm x 4.6 mm internal diameter, 3 μm silica gel); temperature: 30 °C; flow rate: 0.625 mL/minute; isocratic 50%:50% 0.1% trifluoroacetic acid in water–0.1% trifluoroacetic acid in acetonitrile; UV detection at 220 nm; injection volume of 5.0 μL. Expected elution time of the (S,S)-acid at 7.2 minutes, the (R,R)-acid at 7.7 minutes, the (S,S)-ester at 18.0 minutes and the (R,R)-ester at 18.8 minutes.

Enantiomeric excess was calculated from chiral HPLC results using the equation.

$$\text{Enantiomeric Excess (ee)} = 100 * \left[\frac{(R,R) \text{ Acid Peak Area} - (S,S) \text{ Acid Peak Area}}{(R,R) \text{ Acid Peak Area} + (S,S) \text{ Acid Peak Area}} \right]$$

Production value was calculated from chiral HPLC results using the equation:

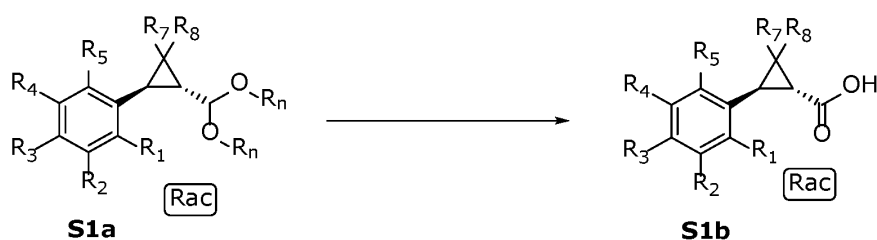
$$\text{Production Value (\%)} = 100 * 0.5 * \left(1 - \frac{\text{Area units of (R,R) ester}}{\text{Area units of (S,S) ester}} \right)$$

Analysis of the reaction vial resulted in a production value of 7.9% and an enantiomeric excess (ee) of 95%.

Consequently, in light of the above the following additional, non-exhaustive, **disclosure details (d)** are provided.

1d. A process comprising oxidizing **S1a** to **S1b** with an oxidizing agent in the presence of a polar solvent

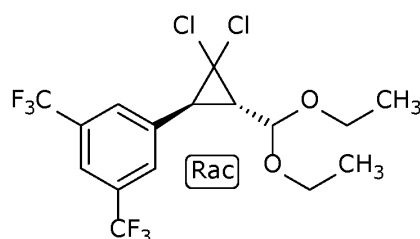
Scheme One



wherein

- (a) **R₁, R₂, R₃, R₄, and R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂, R₃, and R₄** is not H;
- (b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and
- (c) (1) each **R_n** is independently a (C₁-C₆)alkyl, or
- (2) both **R_n** form a (C₂-C₆)alkyl link between the two oxygen atoms.

2d. A process according to 1d wherein **R₂** and **R₄** are CF₃; **R₁, R₃, and R₅**, are H; **R₇** and **R₈** are Cl; and each **R_n** is C₂H₅



trans-rac-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene.

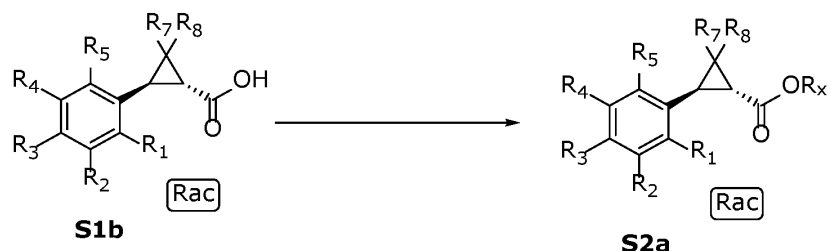
3d. A process according to **1d** or **2d** wherein said oxidizing agent is oxygen, sodium hypochlorite, ozone, hydrogen peroxide, organic peracids, potassium peroxydisulfate, potassium persulfate, potassium hydrogen peroxydisulfate sulfate, or mixtures thereof.

4d. A process according to **3d** wherein the amount of oxidizing agent used is from about 0.1 moles to about 3 moles of oxidizing agent per mole of **S1a**.

5d. A process according to **3d** wherein the amount of oxidizing agent used is from about 0.5 moles to about 1.5 moles of oxidizing agent per mole of **S1a**.

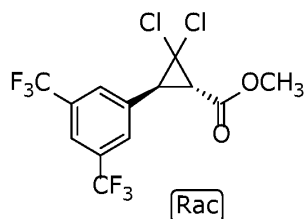
- 6d.** A process according to any of the previous details wherein said polar solvent is a polar aprotic solvent.
- 5 **7d.** A process according to any of the previous details wherein said polar solvent is a polar protic solvent.
- 8d.** A process according to any of the previous details wherein said polar solvent is ethyl acetate, tetrahydrofuran, dichloromethane, acetone, acetonitrile, dimethylformamide,
10 dimethyl sulfoxide, or mixtures thereof.
- 9d.** A process according to any of the previous details wherein said polar solvent is acetic acid, *n*-butanol, isopropanol, *n*-propanol, ethanol, methanol, formic acid, *tert*-butyl alcohol, water, or mixtures thereof.
15
- 10d.** A process according to any of the previous details wherein said solvent is a mixture of two or more polar solvents wherein said polar solvents are ethyl acetate, tetrahydrofuran, dichloromethane, acetone, acetonitrile, dimethylformamide, acetic acid, *n*-butanol, isopropanol, *n*-propanol, ethanol, methanol, formic acid, *tert*-butyl alcohol, water, mixtures thereof, or a mixture selected from **Table S1-MR**.
20
- 11d.** A process according to any of the previous details wherein said process is conducted at a temperature from about 0 °C to about 80 °C.
- 25 **12d.** A process according to any of the previous details wherein said process is conducted at a temperature from about 20 °C to about 60 °C.
- 13d.** A process according to any of the previous details wherein said process is conducted at a pressure from about 10 kPa to about 1000 kPa.
30
- 14d.** A process according to any of the previous details wherein said process is conducted at a pressure from about 50 kPa to about 150 kPa.
- 15d.** A process according to any of the previous details wherein said process is conducted
35 in the presence of an acid catalyst.

16d. A process comprising esterifying **S1b** to **S2a** in the presence of an acid and an (C₁-C₆)alcohol wherein



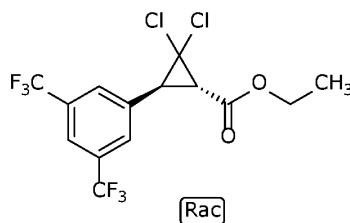
- 5 **(a)** **R₁, R₂, R₃, R₄, and R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂, R₃, and R₄** is not H;
- (b)** **R₇ and R₈** are each independently F, Cl, Br, or I;
- (c)** **R_x** is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl;
- 10 optionally wherein said **S1b** is produced according to **1d** through **15d**.

17d. A process according to **16d** wherein **R₂** and **R₄** are CF₃; **R₁, R₃, and R₅**, are H; **R₇** and **R₈** are Cl; and **R_x** is CH₃



- 15 **trans-rac-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate.**

17.5d. A process according to **16d** wherein **R₂** and **R₄** are CF₃; **R₁, R₃, and R₅**, are H; **R₇** and **R₈** are Cl; and **R_x** is CH₂CH₃



20

trans-rac-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate

5 **18d.** A process according to **16d**, **17d** or **17.5d** wherein said acid is sulfuric acid, *p*-toluenesulfonic acid monohydrate, methanesulfonic acid, scandium(III) triflate, mixtures thereof, or an acid resin.

10 **19d.** A process according to **18d** wherein about 0.001 moles to about 5 moles of an acid per mole of **S1b**.

15 **20d.** A process according to **18d** wherein about 0.05 moles to about 0.5 moles of an acid per mole of **S1b**.

20 **21d.** A process according to any of the previous details **16d** through **20d** wherein said alcohol is *n*-butanol, isopropanol, *n*-propanol, ethanol, methanol, ethylene glycol, *tert*-butyl alcohol, or mixtures thereof.

25 **22d.** A process according to any of the previous details **16d** through **21d** wherein said alcohol is in a mixture with at least one solvent selected from toluene, carbon tetrachloride, benzene, diethyl ether, hexane, heptane, or dichloromethane.

30 **23d.** A process according to any of previous details **16d** through **22d** wherein the reaction is conducted at temperatures from about 0 °C to about 100 °C.

35 **24d.** A process according to any of previous details **16d** through **23d** wherein the reaction is conducted at temperatures about 50 °C to about 70 °C.

25d. A process according to any of previous details **16d** through **24d** wherein the reaction is conducted at pressures from about 10 kPa to about 1000 kPa.

26d. A process according to any of previous details **16d** through **25d** wherein the reaction is conducted at pressures from about 50 kPa to about 150 kPa.

27d. A process according to any of previous details **16d** through **26d** wherein a drying agent is used.

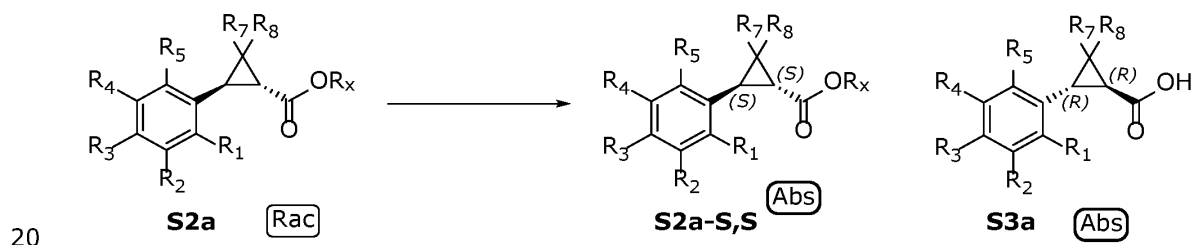
28d. A process according to any of previous details **16d** through **27d** wherein about 0.1 to about 5 moles of drying agents may be used per mole of **S1b**.

5 **29d.** A process according to any of previous details **16d** through **27d** about 0.2 to about 2 moles of drying agents may be used per mole of **S1b**.

30d. A process according to any of previous details **16d** through **29d** wherein said drying agent is an orthoester having the formula $R_{y1}C(OR_{y1})_3$ where R_{y1} is hydrogen or a (C₁-C₆)alkyl, and R_{y2} is (C₁-C₆)alkyl.

31d. A process according to any of previous details **16d** through **30d** wherein said drying agent is triethyl orthoacetate, $CH_3C(OCH_2CH_3)_3$; trimethyl orthoacetate, $CH_3C(OCH_3)_3$; triethyl orthoformate, $HC(OCH_2CH_3)_3$; trimethyl orthoformate, $HC(OCH_3)_3$, molecular sieves, magnesium sulfate, calcium chloride, and sodium sulfate or mixtures of drying agents.

32d. A process comprising hydrolyzing **S2a** to **S3a** using one or more carboxylic ester hydrolases in the presence of water and optionally an aqueous buffer

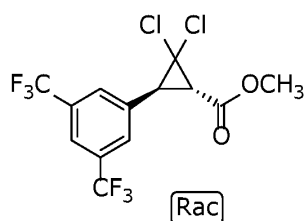


(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

25 (b) **R₇** and **R₈** are each independently F, Cl, Br, or I;

(c) **R_x** is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl; and optionally, wherein **S2a** is produced by **16d** through **31d**.

33d. A process according to **32d** wherein **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅**, are H; **R₇** and **R₈** are Cl; and **R_x** is CH₃



***trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate.**

- 5 **34d.** A process according to **32d** or **33d** wherein said one or more carboxylic ester hydrolases is, *Pseudomonas stutzeri* lipase, *Pseudomonas cepacia* lipase, *Alcaligenes* sp. Lipase E, *Alcaligenes* sp. Lipase C, *Pseudomonas fluorescens* lipase, *Burkholderia cepacia* Lipase A, *Burkholderia cepacia* Lipase B, or a mixture thereof.
- 10 **35d.** A process according to **34d** wherein the production value of **S2a** is greater than 20 percent.
- 36d.** A process according to **34d** wherein the production value of **S2a** is greater than 30 percent.
- 15 **37d.** A process according to **34d** wherein the production value of **S2a** is greater than 40 percent.
- 38d.** A process according to **34d** wherein the enantiomeric excess (ee) of S3a, where the (R,R)-enantiomer is greater than 80 percent.
- 20 **39d.** A process according to **34d** wherein the enantiomeric excess (ee) of S3a, where the (R,R)-enantiomer is greater than 90 percent.
- 40d.** A process according to **34d** wherein the enantiomeric excess (ee) of S3a, where the (R,R)-enantiomer is greater than 95 percent.
- 25 **41d.** A process according to **34d** wherein the enantiomeric excess (ee) of S3a, where the (R,R)-enantiomer is greater than 99 percent.

30

42d. A process according to any of the details **32d** through **41d** wherein said carboxylic ester hydrolase has a homology of at least 90% compared to one of the following lipases: *Pseudomonas stutzeri* lipase, *Pseudomonas cepacia* lipase, *Alcaligenes* sp. Lipase E, *Candida rugosa* Lipase B, *Pseudomonas fluorescens* lipase, *Burkholderia cepacia* Lipase A, or

5 *Burkholderia cepacia* Lipase B.

43d. A process according to any of details **32d** through **41d** wherein said carboxylic ester hydrolase has a homology of at least 95% compared to one of the following carboxylic ester hydrolases: *Pseudomonas stutzeri* lipase, *Pseudomonas cepacia* lipase, *Alcaligenes* sp. Lipase E, *Candida rugosa* Lipase B, *Pseudomonas fluorescens* lipase, *Burkholderia cepacia* Lipase A, or *Burkholderia cepacia* Lipase B.

10

44d. A process according to any of **32d** through **41d** wherein said carboxylic ester hydrolase has a homology of at least 99% compared to one of the following carboxylic ester hydrolases: *Pseudomonas stutzeri* lipase, *Pseudomonas cepacia* lipase, *Alcaligenes* sp. Lipase E, *Candida rugosa* Lipase B, *Pseudomonas fluorescens* lipase, *Burkholderia cepacia* Lipase A, or *Burkholderia cepacia* Lipase B.

15

45d. A process according to any of details **32d** through **44d** wherein the amount of carboxylic ester hydrolase used is from about 0.01% to about 200% by weight with respect to **S2a**.

20

46d. A process according to any of details **32d** through **44d** wherein the amount of carboxylic ester hydrolase used is from about 0.1% to about 5% by weight with respect the **S2a**.

25

47d. A process according to any of details **32d** through **46d** wherein the carboxylic ester hydrolase can be immobilized or supported on a polymer, silica, or other support material.

48d. A process according to any of details **32d** through **47d** wherein said aqueous buffer is sodium phosphate, 2-[bis(2-hydroxyethyl)amino]-2-(hydroxymethyl)propane-1,3-diol, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid, potassium phosphate, 3-morpholinopropane-1-sulfonic acid, piperazine-*N,N'*-bis(2-ethanesulfonic acid), sodium citrate, 3-{[1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl]amino}propane-1-sulfonic acid, lysine, 2-amino-2-(hydroxymethyl)propane-1,3-diol, or mixtures thereof.

30

35

49d. A process according to any of details **32d** through **48d** wherein the buffer concentration is from about 0.0001 molar to about 0.5 M.

5 **50d.** A process according to any of details **32d** through **48d** wherein the buffer concentration is from 0.05 M to about 0.2 M.

51d. A process according to any of details **32d** through **50d** wherein the pH of the reaction mixture is about pH 5 to about pH 11.

10

52d. A process according to any of details **32d** through **50d** wherein the pH of the reaction mixture is about pH 6 to about pH 10.

15 **53d.** A process according to any of details **32d** through **52d** wherein said process is conducted in the presence of an amine base.

54d. A process according to **53d** wherein said amine base is lysine, ethanolamine, glycine, or mixtures thereof.

20 **55d.** A process according to **53d** or **54d** wherein the amount of amine base is from about 0.1 weight percent (wt %) to about 150 weight percent based on the weight of **S2a**.

56d. A process according to **53d** or **54d** wherein the amount of amine base is from about 10 weight percent to about 40 weight percent based on the weight of **S2a**.

25

57d. A process according to any of details **32d** to **56d** wherein said reaction is conducted in the presence of a cosolvent wherein said cosolvent is acetone, acetonitrile, methyl tetrahydrofuran, methyl *tert*-butyl ether, hexane, toluene, methyl ethyl ketone, cyclopentyl methyl ether, dimethyl sulfoxide, dimethoxyethane, or mixtures thereof.

30

58d. A process according to **57d** wherein said reaction is conducted in the presence of a cosolvent and the amount of cosolvent is from about 1% by volume to about 90% of the entire volume based on the volume of the reaction.

59d. A process according to **57d** wherein said reaction is conducted in the presence of a cosolvent and the amount of cosolvent is from about 10% by volume to about 40% of the entire volume based on the volume of the reaction.

5 **60d.** A process according to any of previous **32d** through **59d** wherein the reaction is conducted at temperatures from about 0 °C to about 80 °C.

61d. A process according to any of previous **32d** through **60d** wherein the reaction is conducted at temperatures from about 15 °C to about 60 °C.

10

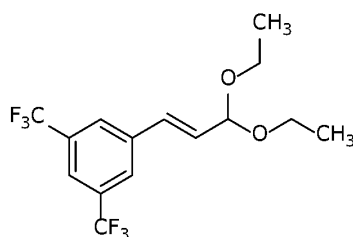
62d. A process according to any of previous **32d** through **60d** wherein the reaction is conducted at temperatures about 25 °C to about 50 °C.

15 **63d.** A process according to any of previous **32d** through **62d** wherein the reaction is conducted at pressures from about 10 kPa to about 1000 kPa.

64d. A process according to any of previous **32d** through **62d** wherein the reaction is conducted at pressures from about 50 kPa to about 150 kPa.

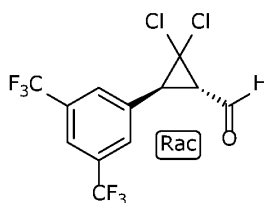
20 **65d.** A molecule useful for the production of arylcyclopropyl carboxylic acids said molecule selected from the group consisting of

(a)



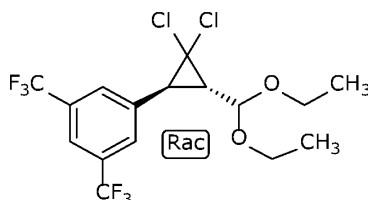
(*E*)-1-(3,3-diethoxyprop-1-en-1-yl)-3,5-bis(trifluoromethyl)benzene;

25 (b)



***trans-rac*-1-(3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carbaldehyde;**

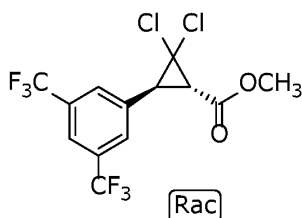
(c)



5

***trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene;**

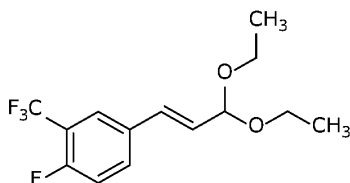
(d)



10

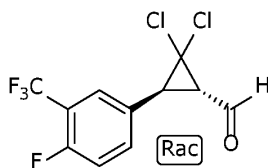
***trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate;**

(e)



(*E*)-4-(3,3-diethoxyprop-1-en-1-yl)-1-fluoro-2-(trifluoromethyl)benzene;

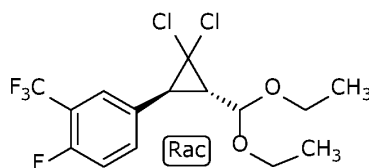
(f)



15

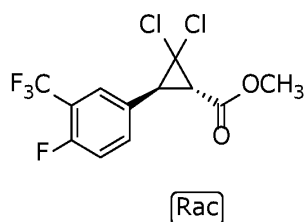
***trans-rac*-2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carbaldehyde.**

(g)



***trans-rac*-4-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-1-fluoro-2-(trifluoromethyl)benzene;**

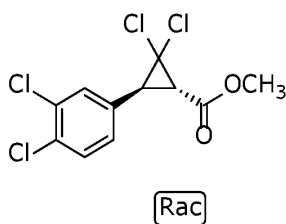
(h)



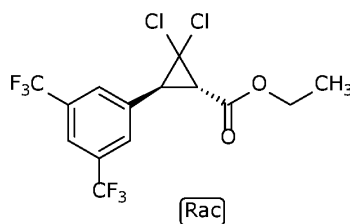
5

***trans-rac*-methyl 2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate;**

(i)

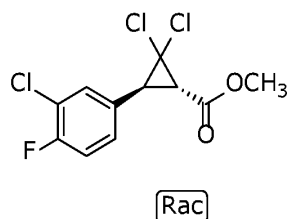


10 ***trans-rac*-methyl 2,2-dichloro-3-(3,4-dichlorophenyl)cyclopropane-1-carboxylate;**
(j)



***trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate; and**

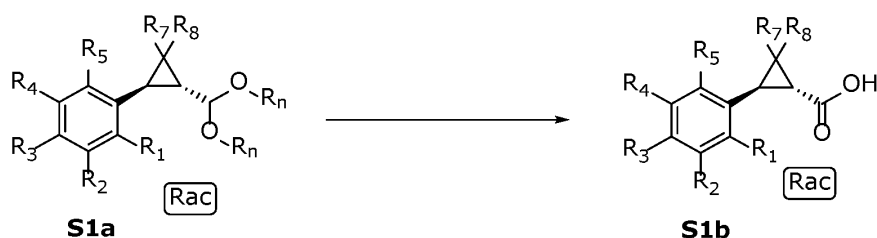
15 (k)



trans-rac-methyl 2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1-carboxylate.

5 **66d.** A process comprising the steps of

(A) oxidizing **S1a** to **S1b** with an oxidizing agent in the presence of a polar solvent



wherein

10 **(a)** **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

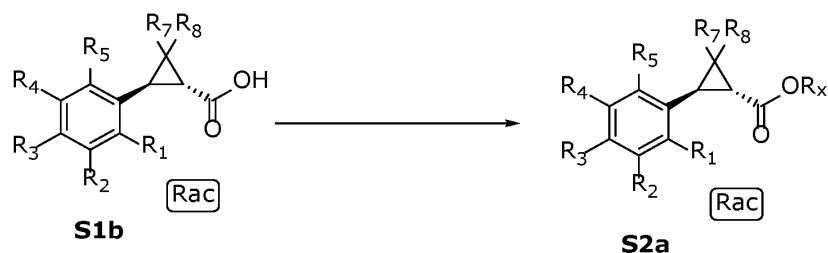
(c) **(1)** each **R_n** is independently a (C₁-C₆)alkyl, or
 15 **(2)** both **R_n** form a (C₂-C₆)alkyl link between the two oxygen atoms,

optionally wherein

any one or more of details 2d, 3d, 4d, 5d, 6d, 7d, 8d, 9d, 10d, 11d, 12d, 13d, 14d, and 15d, is also used in (A);

20 followed by

(B) esterifying **S1b** to **S2a** in the presence of an acid and an (C₁-C₆)alcohol



wherein

R₁, **R₂**, **R₃**, **R₄**, **R₅**, **R₇**, and **R₈** are as above in (A); and

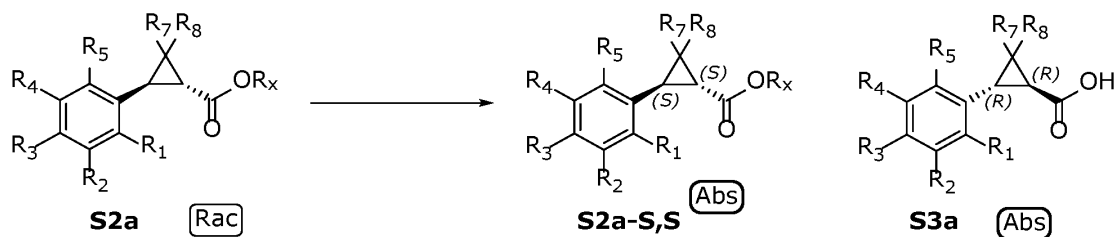
R_x is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl

5 optionally wherein

any one or more of details 17d, 17.5d, 18d, 19d, 20d, 21d, 22d, 23d, 24d, 25d, 26d, 27d, 28d, 29d, 30d, and 31d, is also used in (B);

followed by

10 (C) hydrolyzing **S2a** to **S3a** using one or more carboxylic ester hydrolases in the presence of water and optionally an aqueous buffer



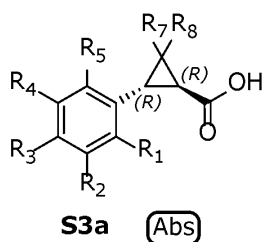
wherein

R₁, **R₂**, **R₃**, **R₄**, **R₅**, **R₇**, **R₈**, and **R_x** are as above in (B)

optionally wherein

15 **any one or more of details 33d, 34d, 35d, 36d, 37d, 38d, 39d, 40d, 41d, 42d, 43d, 44d, 45d, 46d, 47d, 48d, 49d, 50d, 51d, 52d, 53d, 54d, 55d, 56d, 57d, 58d, 59d, 60d, 61d, 62d, 63d, and 64d, is also used in (C).**

20 **67d.** An enantiomerically enriched preparation of **S3a**, wherein the enantiomeric excess of the **S3a** (*R,R*)-enantiomer is greater than 80%, greater than 90%, or greater than 95%



(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H; and

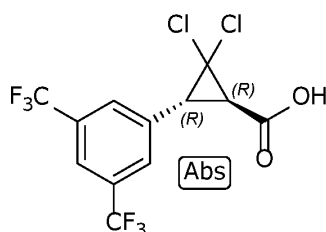
5 **(b)** **R₇** and **R₈** are each independently F, Cl, Br, or I.

68d. The preparation of detail **67d**, wherein the enantiomeric excess of the **S3a** (*R,R*)-enantiomer is greater than 96%, greater than 97%, or greater than 98%.

10 **69d.** A pesticidal formulation comprising the enantiomerically enriched preparation of details **67d** or **68d**.

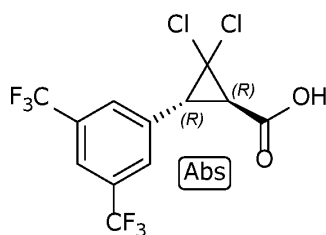
70d. A preparation according to details **67d** or **68d**, wherein **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** are H; and **R₇** and **R₈** are Cl

15



(1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid.

20 **71d.** A pesticidal formulation according to detail **69d**, wherein **R₂** and **R₄** are CF₃; **R₁**, **R₃**, and **R₅** are H; and **R₇** and **R₈** are Cl



(1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid.

15

20



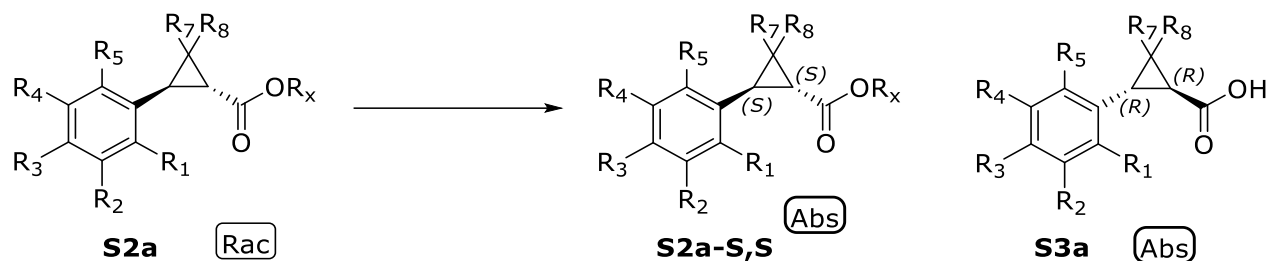
- 20

25



25

3. A process comprising hydrolyzing **S2a** to **S3a** using one or more carboxylic ester hydrolases in the presence of water and optionally an aqueous buffer



wherein

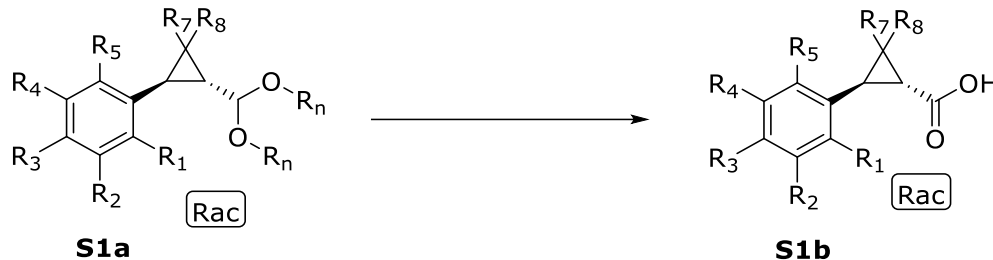
(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

(c) **R_x** is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl.

4. A process comprising the steps of

(A) oxidizing **S1a** to **S1b** with an oxidizing agent in the presence of a polar solvent



wherein

(a) **R₁**, **R₂**, **R₃**, **R₄**, and **R₅** are each independently H, F, Cl, Br, I, CN, NH₂, NO₂, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkyl, or (C₁-C₆)haloalkoxy, with the proviso that at least one of **R₂**, **R₃**, and **R₄** is not H;

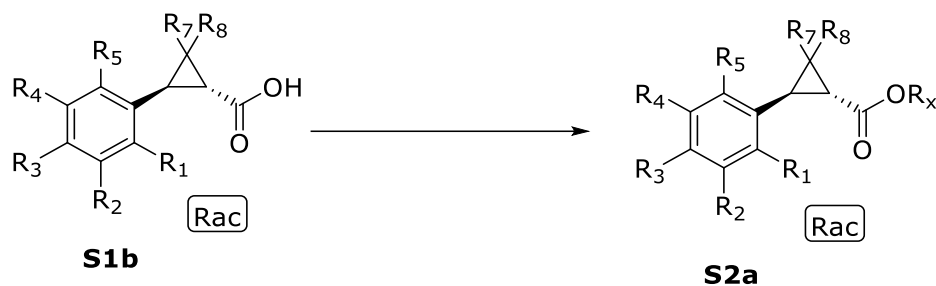
(b) **R₇** and **R₈** are each independently F, Cl, Br, or I; and

(c) (1) each **R_n** is independently a (C₁-C₆)alkyl, or

(2) both **R_n** form a (C₂-C₆)alkyl link between the two oxygen atoms

followed by

(B) esterifying **S1b** to **S2a** in the presence of an acid and an (C₁-C₆)alcohol



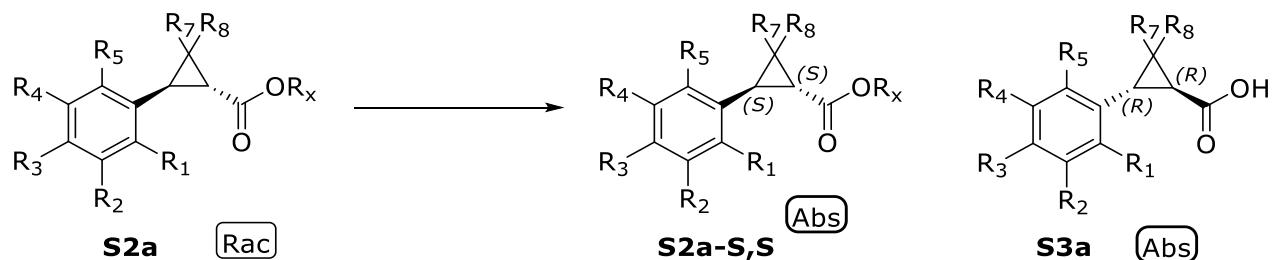
wherein

R₁, R₂, R₃, R₄, R₅, R₇, and R₈ are as above in **(A)**; and

R_x is (C₁-C₆)alkyl or (C₁-C₆)hydroxyalkyl;

5 followed by

(C) hydrolyzing **S2a** to **S3a** using one or more carboxylic ester hydrolases in the presence of water and optionally an aqueous buffer

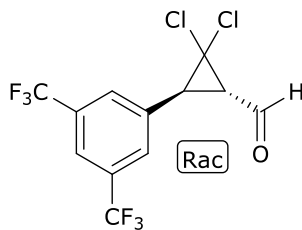


wherein

10 **R₁, R₂, R₃, R₄, R₅, R₇, R₈, and R_x** are as above in **(B)**.

5. A molecule useful for the production of arylcyclopropyl carboxylic acids said molecule selected from the group consisting of

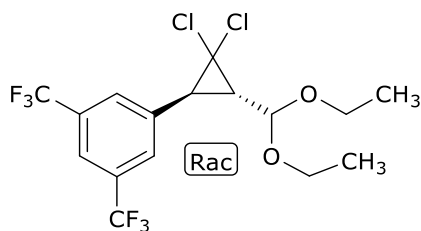
(a)



15

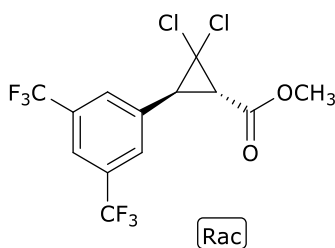
trans-rac-1-(3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carbaldehyde;

(b)



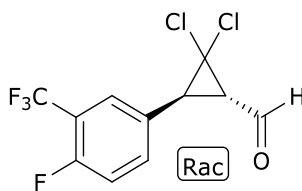
***trans-rac*-1-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-3,5-bis(trifluoromethyl)benzene;**

(c)



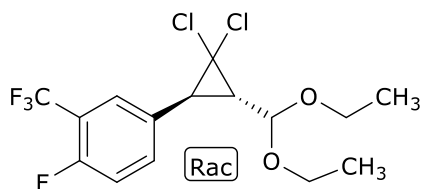
***trans-rac*-methyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate;**

(d)



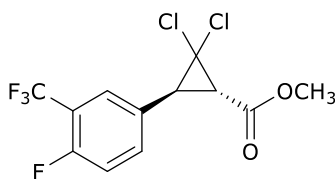
***trans-rac*-2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carbaldehyde.**

(e)



***trans-rac*-4-(2,2-dichloro-3-(diethoxymethyl)cyclopropyl)-1-fluoro-2-(trifluoromethyl)benzene;**

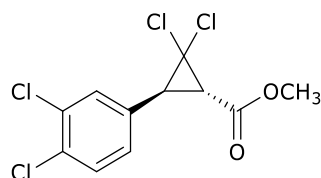
(f)



Rac

***trans-rac*-methyl 2,2-dichloro-3-(4-fluoro-3-(trifluoromethyl)phenyl)cyclopropane-1-carboxylate;**

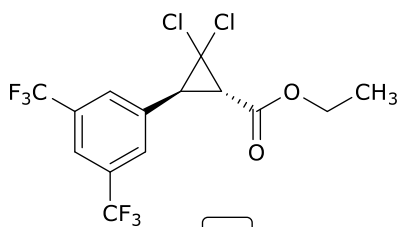
(g)



Rac

***trans-rac*-methyl 2,2-dichloro-3-(3,4-dichlorophenyl)cyclopropane-1-carboxylate;**

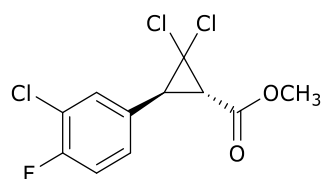
(h)



Rac

***trans-rac*-ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylate; and**

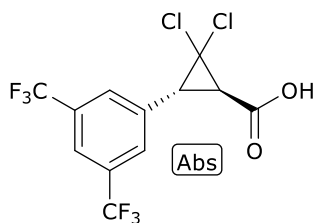
(i)



Rac

***trans-rac*-methyl 2,2-dichloro-3-(3-chloro-4-fluorophenyl)cyclopropane-1-carboxylate.**

6. An enantiomerically enriched preparation of **S3a-1**,



(1*R*,3*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dichlorocyclopropane-1-carboxylic acid.

wherein the enantiomeric excess of the **S3a-1** (*R,R*)-enantiomer is greater than 80%,
 5 greater than 90%, or greater than 95%.

7. The preparation of claim **6**, wherein the enantiomeric excess of the **S3a** (*R,R*)-enantiomer is greater than 96%, greater than 97%, or greater than 98%.

10 **8.** A pesticidal formulation comprising the enantiomerically enriched preparation of claims **6** or **7**.