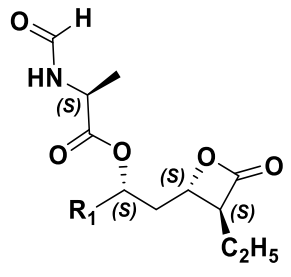


Compound I-A

[0006] Current methods of synthesizing **Compound I-A** include the synthetic procedure shown in **Figure 1**. While **Compound I-A** may be produced by such methods, the methods may not be suitable for large scale and/or cGMP manufacturing. In addition, such methods may have chemical processing issues, including strong sulfur/thiol odors that are difficult to contain on scale-up and significant health hazards due to the use of corrosive aqueous hydrofluoric acid. In addition, the overall synthesis may produce low to moderate yields and may require seven chromatography purification steps. A such, new methods for synthesizing **Compound I-A** may be desirable.

Summary

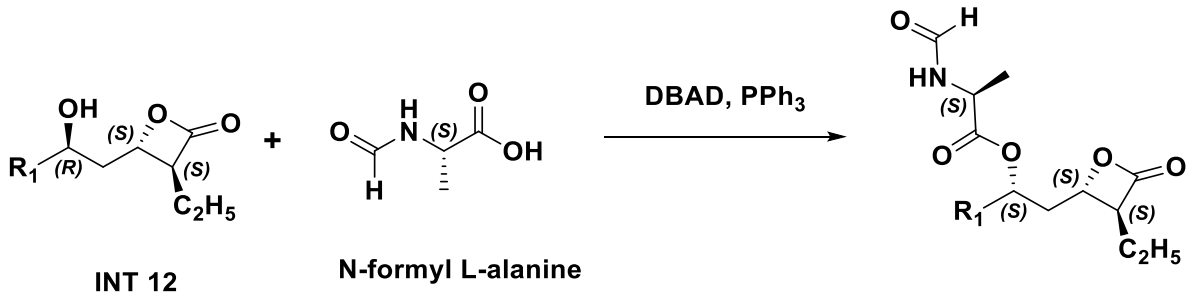
[0006a] In one aspect, the present disclosure refers to a method for synthesizing a compound of **Formula I**,



(I)

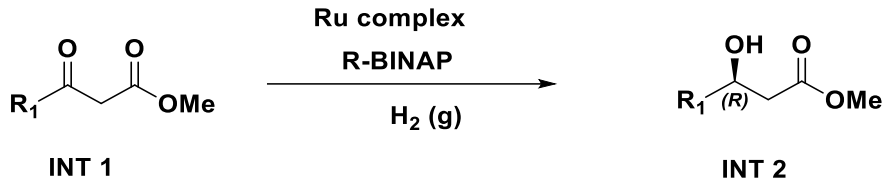
wherein R_1 is a C_5-C_{15} alkyl (e.g., C_5-C_{15} straight chain alkyl), the method comprising:

contacting a compound of **INT 12** with N-formyl L-alanine, in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form the compound of **Formula I**:

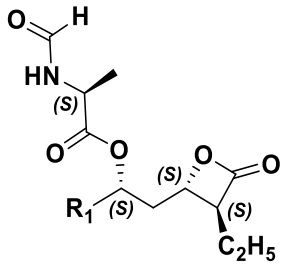


[0006b] In another aspect, the present disclosure refers to a method for synthesizing a compound of **INT 2**, comprising

contacting a compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas in a reaction mixture in a pressure vessel to form a compound of **INT 2**:



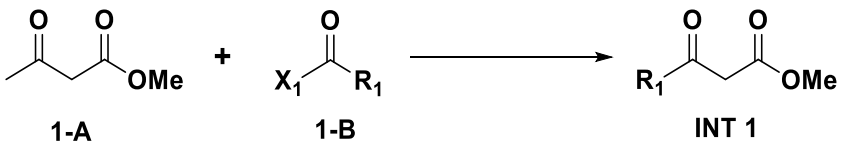
[0006c] In another aspect, the present disclosure refers to a method for synthesizing a compound of **Formula I**,



(**I**)

wherein R_1 is a C_5-C_{15} alkyl (e.g., C_5-C_{15} straight chain alkyl), the method comprising:

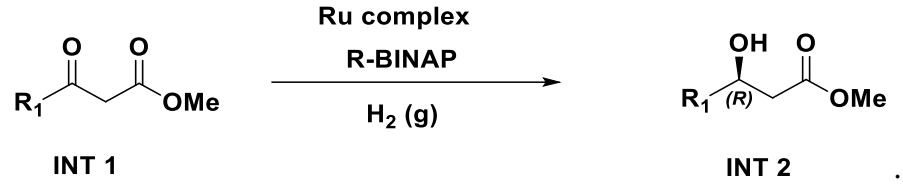
(a) contacting a compound of **1-A** with a compound of **1-B**, optionally in the presence of an alkali metal (e.g., magnesium), to form a compound of **INT 1**:



,

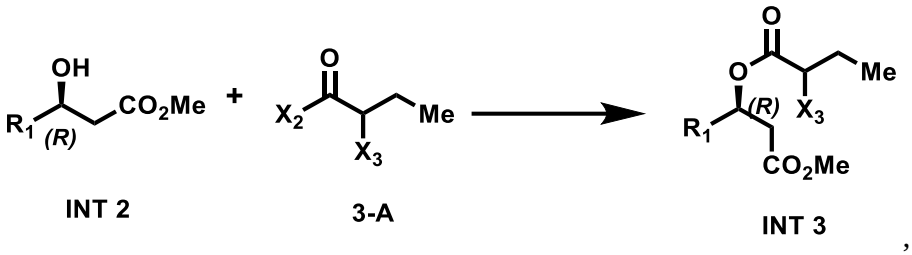
wherein X_1 is a halo (e.g., Cl or Br);

(b) contacting the compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas to form the compound of **INT 2**:



;

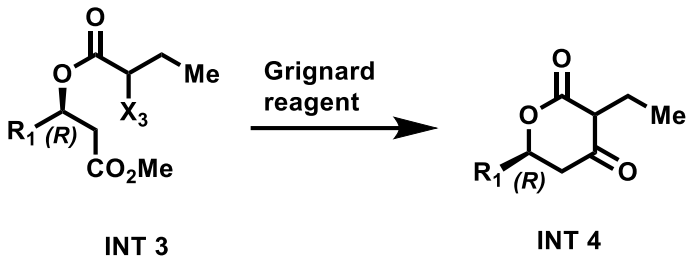
(c) contacting the compound of **INT 2** with a compound of **3-A** to form a compound of **INT 3**:



,

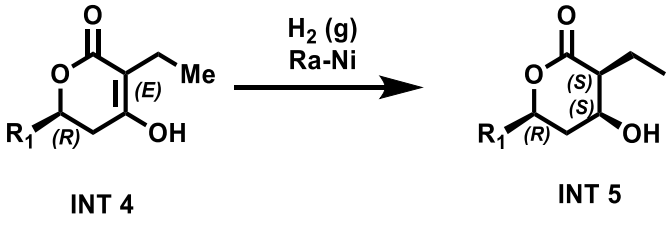
wherein X_2 and X_3 are each independently halo (e.g., Br);

(d) contacting the compound of **INT 3** with a Grignard reagent to form a compound of **INT 4**:



;

(e) contacting the compound of **INT 4** with hydrogen gas in the presence of a Raney Ni catalyst to form a compound of **INT 5**:



;

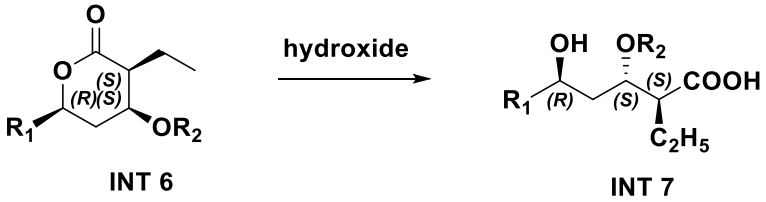
(f) contacting the compound of **INT 5** with a first protecting agent to form a compound of **INT 6**:



,

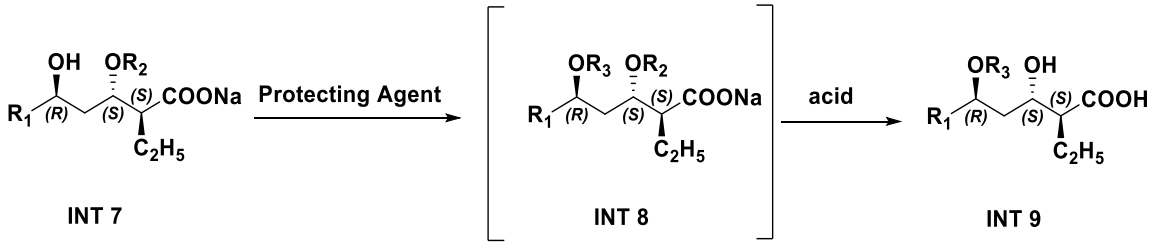
wherein R_2 is a protecting group (e.g., THP);

(g) contacting the compound of **INT 6** with a hydroxide (e.g., from a hydroxide salt such as NaOH) to form a compound of **INT 7**:



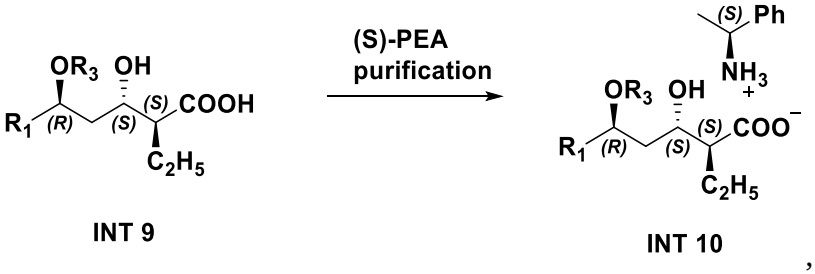
;

(h) protecting a free hydroxy group on a compound of **INT 7** by reacting **INT 7** with a second protecting agent to form a compound of **INT 8**, and then deprotecting a protected hydroxy group on the compound of **INT 8** by contacting **INT 8** with acid to form the compound of **INT 9**:



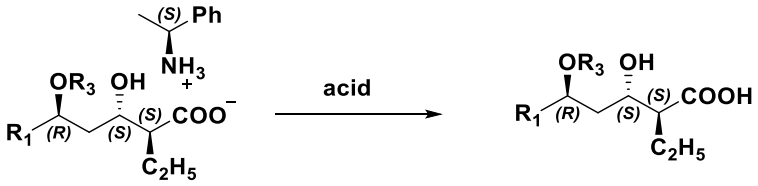
wherein R_3 is a protecting group (e.g., benzyl);

(i) optionally, purifying the compound of **INT 9** by contacting the compound of **INT 9** with (S)-(-)-1-phenyethylamine to form a compound of **INT 10**:



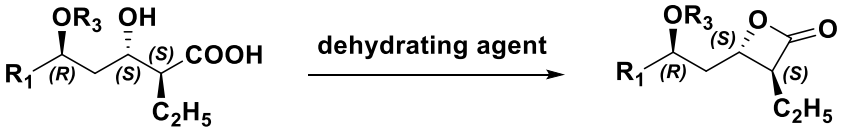
,

crystallizing and isolating **INT 10A**, and then contacting **INT 10** with an acid (e.g., HCl) to form **INT 9 (purified)**:



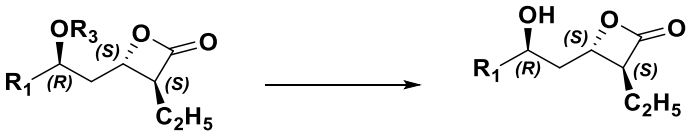
INT 10 INT 9 (purified) ;

(j) dehydrating the compound of **INT 9** or the compound of **INT 9 (purified)** with a dehydrating agent to form a compound of **INT 11**:



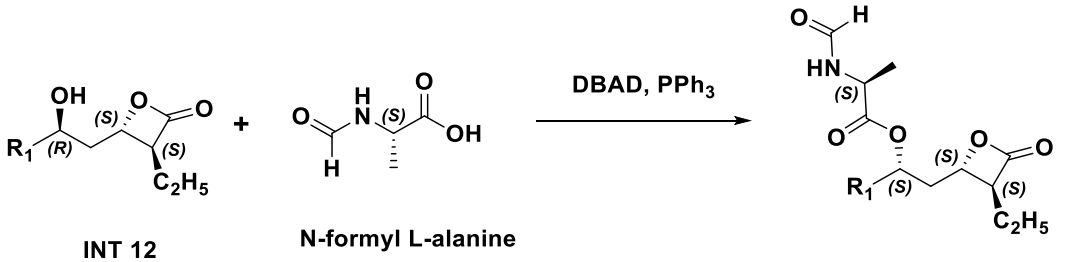
INT 9 INT 11 ;

(k) deprotecting the compound of **INT 11** to form a compound of **INT 12**:



INT 11 INT 12 ; and

(l) contacting the compound of **INT 12** with N-formyl L-alanine, in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form a compound of **Formula I**:



INT 12 N-formyl L-alanine Formula I .

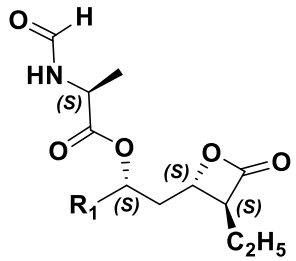
[0006d] In another aspect, the present disclosure refers to a compound of Formula I formed by a method as defined above or a pharmaceutically acceptable salt thereof.

[0006e] In another aspect, the present disclosure refers to a composition as defined above and a pharmaceutically acceptable carrier.

[0006f] In another aspect, there is provided the use of the compound as defined above or a pharmaceutically acceptable salt thereof and/or the composition as defined above in the manufacture of a medicament for inhibiting lipase activity.

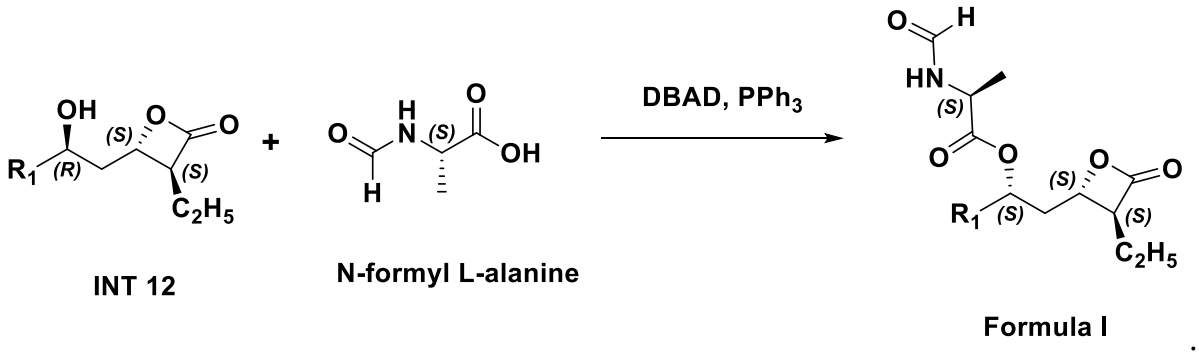
[0006g] In another aspect, there is provided the use of the compound as defined above or a pharmaceutically acceptable salt thereof and/or the composition as defined above in the manufacture of a medicament for treating pancreatitis.

[0007] Provided according to examples of the disclosure are methods for synthesizing a compound of **Formula I**:

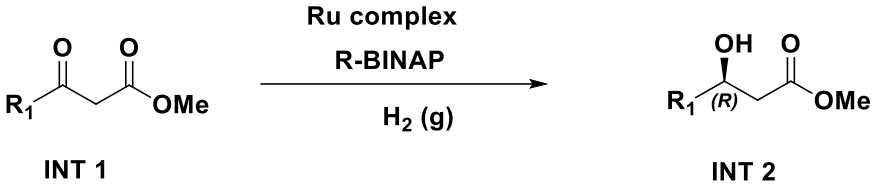


(**I**)

wherein R_1 is a C_5-C_{15} alkyl (e.g., C_{11} alkyl). In some examples, the methods include contacting a compound of **INT 12** with N-formyl L-alanine, in the presence of di-*t*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form the compound of **Formula I**:



[0008] In some examples of the disclosure, provided are methods for synthesizing a compound of **INT 2**. In some examples, such methods include contacting a compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas in a reaction mixture in a pressure vessel to form a compound of **INT 2**:

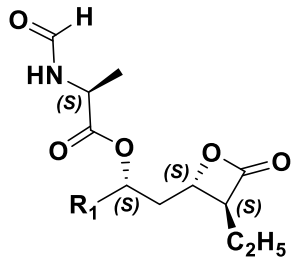


INT 1 INT 2

.

[0009] In some examples, the pressure of the hydrogen gas in the pressure vessel is less than or equal to 200 psi (e.g., in a range of 100 to 200 psi). Further, in some examples, a volume ratio of dead space to the reaction mixture in the pressure vessel is 3:1 or more.

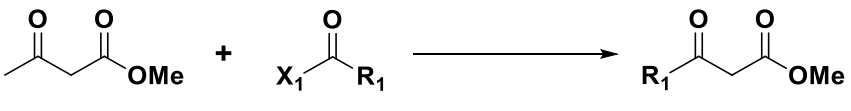
[0010] Also provided according to examples of the disclosure are methods for synthesizing the compound of **Formula I**:



(**I**)

wherein R_1 is a C_5-C_{15} alkyl (e.g., C_{11} alkyl), that include:

(a) contacting a compound of **1-A** with a compound of **1-B**, optionally in the presence of magnesium, to form a compound of **INT 1**:

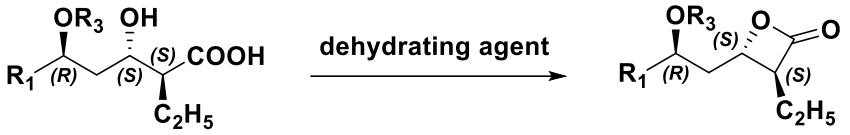


1-A 1-B INT 1

,

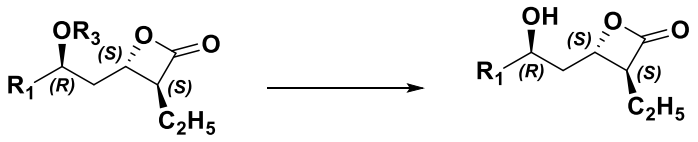
wherein X_1 is a halo (e.g., Cl or Br);

(b) contacting the compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas to form the compound of **INT 2**:



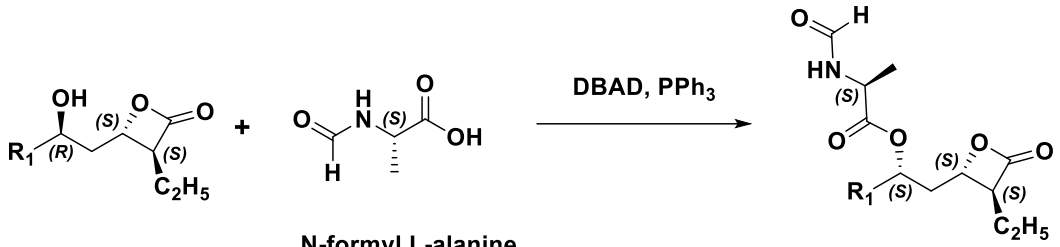
INT 9 INT 11 ;

(k) deprotecting the compound of **INT 11** to form a compound of **INT 12**:



INT 11 INT 12 ; and

(l) contacting the compound of **INT 12** with N-formyl L-alanine, in the presence of di-*t*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form the compound of **Formula I**:



INT 12 N-formyl L-alanine Formula I .

[0011] Further provided according to examples of the disclosure are compounds of **Formula I** formed by a method of the disclosure or a pharmaceutically acceptable salt thereof. Also provided are compositions that include a compound of the disclosure and a pharmaceutically acceptable carrier.

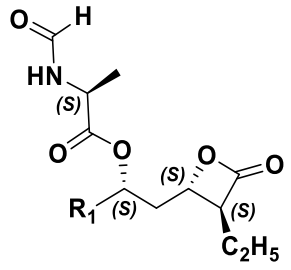
[0012] Additionally, provided according to examples of the disclosure are methods of inhibiting lipase activity in a subject in need thereof that include administering a therapeutically effective amount of a compound of the disclosure or a pharmaceutically acceptable salt thereof and/or a composition of the disclosure to the subject, thereby inhibiting lipase activity in the subject.

[0013] Also provided according to examples of the disclosure are methods of treating pancreatitis in a subject in need thereof that include administering a therapeutically effective amount of a compound of the disclosure or a pharmaceutically acceptable salt thereof and/or a composition of of the disclosure to the subject, thereby treating pancreatitis in the subject.

[0014] These and other examples of the disclosure are set forth in more detail in the description of the disclosure below.

THAT WHICH IS CLAIMED IS:

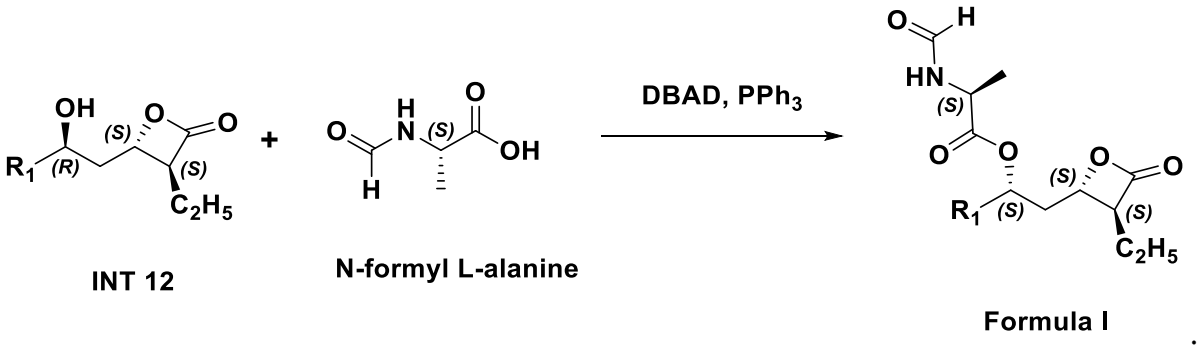
1. A method for synthesizing a compound of **Formula I**,



(**I**)

wherein R_1 is a C_5-C_{15} alkyl (e.g., C_5-C_{15} straight chain alkyl), the method comprising:

contacting a compound of **INT 12** with N-formyl L-alanine, in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form the compound of **Formula I**:



2. The method of claim 1, wherein R_1 is C_{11} alkyl (e.g., $C_{11}H_{23}$).

3. The method of any of claims 1 and 2, wherein the contacting occurs in a tetrahydrofuran (THF) solvent, or wherein the contacting comprises the steps of:

(a) combining **INT 12**, N-formyl L-alanine, triphenylphosphine, and a solvent (e.g., THF) to form a reaction mixture;

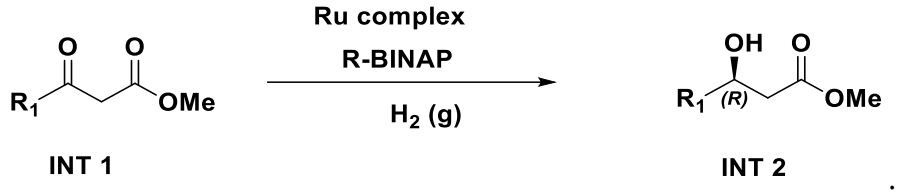
(b) cooling the reaction mixture to a temperature in a specified temperature range below room temperature (e.g., 5-10 °C);

(c) dissolving DBAD in a solvent (e.g., THF);

(d) adding DBAD to the reaction mixture at a rate sufficient to maintain the temperature within the specified temperature range until the compound of **Formula I** is formed.

4. A method for synthesizing a compound of **INT 2**, comprising

contacting a compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas in a reaction mixture in a pressure vessel to form a compound of **INT 2**:



5. The method of claim 4, wherein the pressure of the hydrogen gas in the pressure vessel is less than or equal to 200 psi (e.g., in a range of 100 to 200 psi).

6. The method of claim 4 or 5, wherein a volume ratio of dead space to the reaction mixture in the pressure vessel is 3:1 or more.

7. The method of any of claims 4-6, wherein contacting comprises

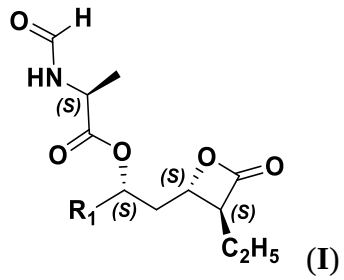
(a) combining a ruthenium precatalyst (e.g., $[RuCl_2benzene]_2$) and R-BINAP to form the ruthenium (R)-BINAP catalyst;

(b) combining the **INT 1** with a solvent (e.g., methanol) to form the reaction mixture;

(c) adding the ruthenium (R)-BINAP catalyst to the reaction mixture; and

(d) heating the reaction mixture (e.g., to 100 °C), to form **INT 2**.

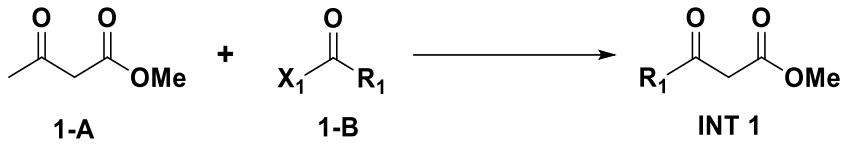
8. A method for synthesizing a compound of **Formula I**,



(**I**)

wherein R_1 is a C_5-C_{15} alkyl (e.g., C_5-C_{15} straight chain alkyl), the method comprising:

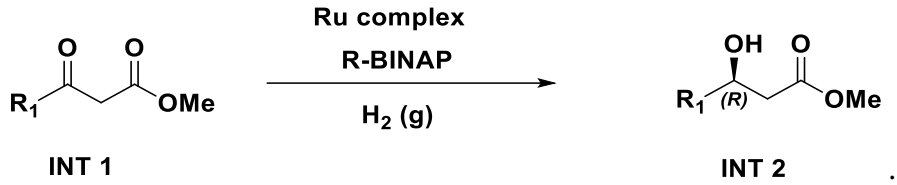
(a) contacting a compound of **1-A** with a compound of **1-B**, optionally in the presence of an alkali metal (e.g., magnesium), to form a compound of **INT 1**:



,

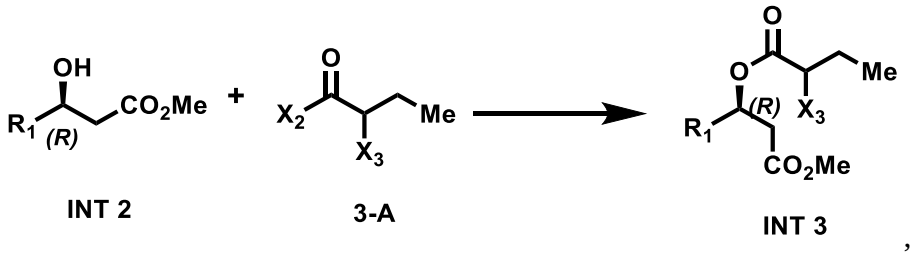
wherein X_1 is a halo (e.g., Cl or Br);

(b) contacting the compound of **INT1** with a ruthenium (R)-BINAP catalyst and hydrogen gas to form the compound of **INT 2**:



;

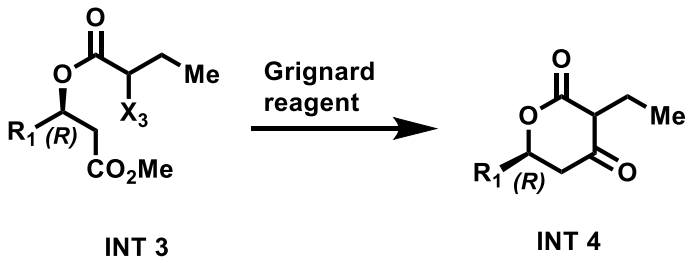
(c) contacting the compound of **INT 2** with a compound of **3-A** to form a compound of **INT 3**:



,

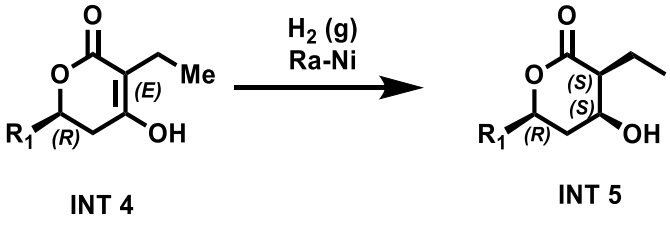
wherein X_2 and X_3 are each independently halo (e.g., Br);

(d) contacting the compound of **INT 3** with a Grignard reagent to form a compound of **INT 4**:



;

(e) contacting the compound of **INT 4** with hydrogen gas in the presence of a Raney Ni catalyst to form a compound of **INT 5**:



;

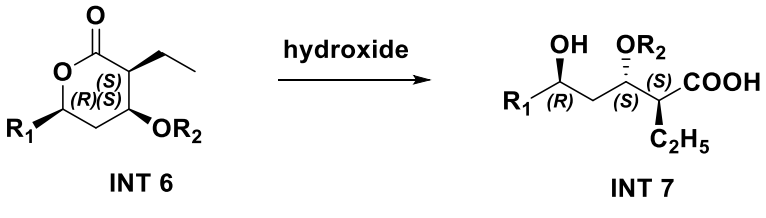
(f) contacting the compound of **INT 5** with a first protecting agent to form a compound of **INT 6**:



,

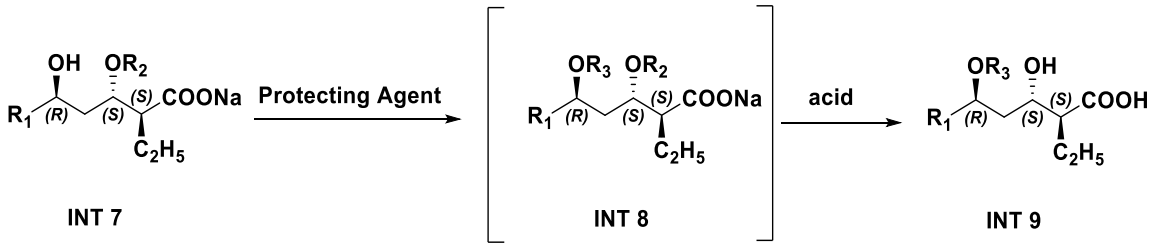
wherein R_2 is a protecting group (e.g., THP);

(g) contacting the compound of **INT 6** with a hydroxide (e.g., from a hydroxide salt such as NaOH) to form a compound of **INT 7**:



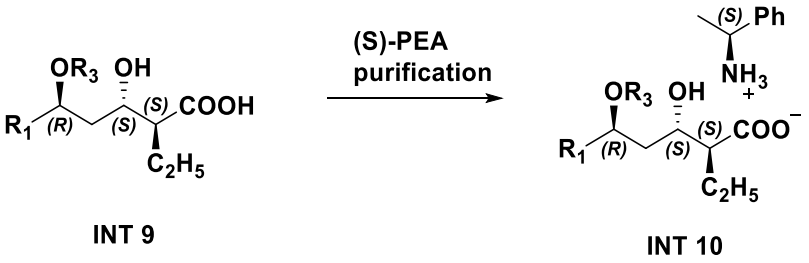
;

(h) protecting a free hydroxy group on a compound of **INT 7** by reacting **INT 7** with a second protecting agent to form a compound of **INT 8**, and then deprotecting a protected hydroxy group on the compound of **INT 8** by contacting **INT 8** with acid to form the compound of **INT 9**:



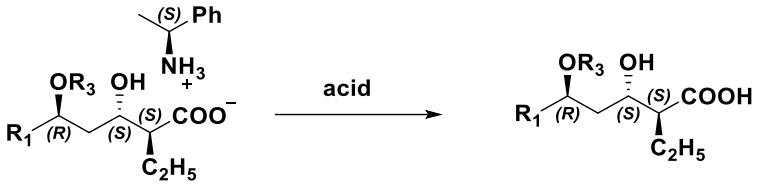
wherein R_3 is a protecting group (e.g., benzyl);

(i) optionally, purifying the compound of **INT 9** by contacting the compound of **INT 9** with (S)-(-)-1-phenyethylamine to form a compound of **INT 10**:



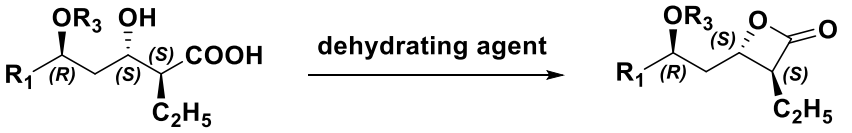
,

crystallizing and isolating **INT 10A**, and then contacting **INT 10** with an acid (e.g., HCl) to form **INT 9 (purified)**:



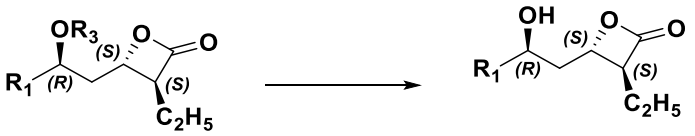
INT 10 INT 9 (purified) ;

(j) dehydrating the compound of **INT 9** or the compound of **INT 9 (purified)** with a dehydrating agent to form a compound of **INT 11**:



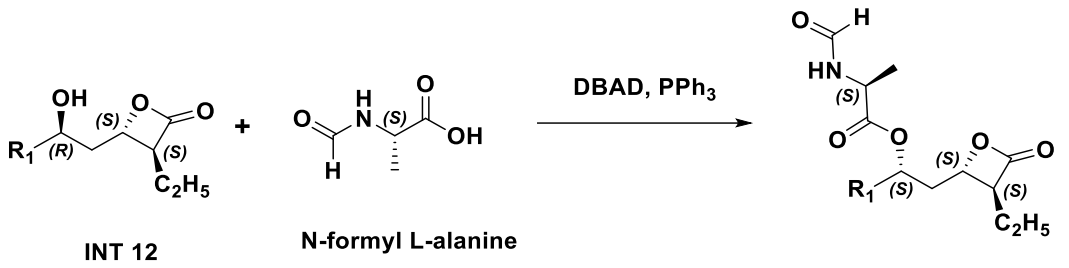
INT 9 INT 11 ;

(k) deprotecting the compound of **INT 11** to form a compound of **INT 12**:



INT 11 INT 12 ; and

(l) contacting the compound of **INT 12** with N-formyl L-alanine, in the presence of di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine, to form a compound of **Formula I**:



INT 12 N-formyl L-alanine Formula I .

9. The method of claim 8, wherein in step (b), contacting the compound of **INT 1** with the ruthenium (R)-BINAP catalyst and hydrogen gas occurs in a reaction mixture in a pressure vessel, and wherein a ratio of the volume of dead space to the volume of the reaction mixture in the pressure vessel is 3:1 or more, or wherein the pressure of the hydrogen gas is less than 200 psi (e.g., in a range of 100 to 200 psi).

10. The method of claim 8, wherein in step (c), the contacting occurs in the presence of a dimethylaminopyridine (DMAP) and aqueous potassium bicarbonate ($KHCO_3$) in a two-phase reaction.

11. The method of claim 8, wherein in step (d), the Grignard reagent comprises *tert*-butylMgBr.

12. The method of claim 8, wherein in step (e) the Raney Ni catalyst is freshly prepared, and the pressure of the hydrogen gas is in a range of 0.5 to 2 atm.

13. The method of claim 8, wherein in step (f), the protecting agent is 3,4-dihydro-2H-pyran (DHP) and R_2 is a tetrahydropyran (THP) group.

14. The method of claim 8, wherein in step (i), after crystallization and isolation of the compound of **INT 10**, the compound of **INT 10** is contacted with an acid to form purified **INT 9**.

15. The method of claim 8, wherein the dehydrating agent in step (j) comprises benzene sulfonyl chloride.

16. The method of claim 8, wherein in step (k), the deprotecting comprises a debenzylation reaction, optionally using Pd/C and hydrogen gas.

17. A compound of Formula I formed by a method of any of claims 1-16 or a pharmaceutically acceptable salt thereof.

18. A composition comprising the compound of claim 17 and a pharmaceutically acceptable carrier.

19. Use of the compound of claim 17 or a pharmaceutically acceptable salt thereof and/or the composition of claim 18 in the manufacture of a medicament for inhibiting lipase activity.

20. Use of the compound of claim 17 or a pharmaceutically acceptable salt thereof and/or the composition of claim 18 in the manufacture of a medicament for treating pancreatitis.