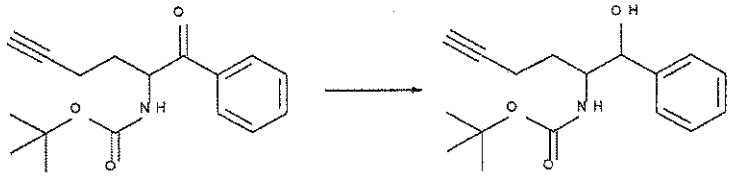
What is claimed is:

1. An engineered ketoreductase polypeptide capable of converting substrate compound (2), tert-butyl(1-oxo-1-phenylhex-5-yn-2-yl)carbamate, to product compound (1), tert-butyl(1-hydroxy-1-phenylhex-5-yn-2-yl)carbamate,



(2) (1)

the ketoreductase polypeptide comprising an amino acid sequence having at least 80% sequence identity to SEQ ID NO:4 and the following residue differences as compared to SEQ ID NO:4: ~~features~~ X40R; ~~and~~ X206~~L or F~~; ~~with the proviso that when X206 is F, the sequence further comprises one or more residue differences as compared to SEQ ID NO:4 selected from: X7S; X17M;~~ X17Q; ~~X17R; X23V; X27L; X29G; X60I;~~ X64V; X71P; ~~X87L; X94A;~~ X94P; ~~X94S; X95M; X96L; X96Y; X105G; X113I; X122A; X127R; X131S;~~ X144V; ~~X145L;~~ X147I; ~~X147L; X147Q; X150Y; X152G; X153G;~~ X157C; ~~X173L; X195A; X195G;~~ X196M; and ~~X198S; X199H; X208R; X216R; X221S; X243S; X245I;~~ X249F~~; X249G; and X249~~Y.

2. The engineered ketoreductase polypeptide of **claim** 1 in which the amino acid sequence further comprises ~~X40R and X206F, and~~ one or more residue differences as compared to SEQ ID NO:4 selected from: X7S; ~~X17M; X17Q; X17R;~~ X23V; X27L; X29G; X60I; ~~X64V; X71P;~~ X87L; ~~X94A; X94P; X94S;~~ X95M; X96L; X96Y; X105G; X113I; X122A; X127R; X131S; ~~X144V;~~ X145L; ~~X147I; X147L; X147Q;~~ X150Y; X152G; X153G; ~~X157C;~~ X173L; X195A; X195G; ~~X196M;~~ X198S; X199H; X208R; X216R; X221S; X243S; and X245I; ~~X249F; X249G; and X249Y.~~

~~3. The engineered ketoreductase polypeptide of **claim** 1 in which the amino acid sequence comprises X40R and X206F or L, and at least one or more residue differences as compared to SEQ ID NO:4 selected from: X17Q/R/M; X64V; X94P; X144V; X147Q/I/L; X157C; and X196M.~~

~~4. The engineered ketoreductase polypeptide of **claim** 1 in which the amino acid sequence comprises at least a combination of residue differences as compared to SEQ ID NO:4 selected from:~~

~~(a) X40R, X196M, and X206F/L;~~

~~(b) X40R, X144V, and X206F/L;~~

~~(c) X40R, X17H/R/Q, and X206F/L;~~

~~(d) X40R, X94P, and X206F/L;~~

~~(e) X40R, X196M, and X206F/L;~~

~~(f) X40R, X198S, and X206F/L;~~

~~(g) X40R, X17H/R/Q, X94P and X206F/L;~~

~~(h) X40R, X71P, X157C and X206F/L;~~

~~(i) X40R, X94P, X144V, X196M and X206F/L;~~

~~(j) X17H/R/Q, X40R, X64V, X147I/Q/L, and X206F/L;~~

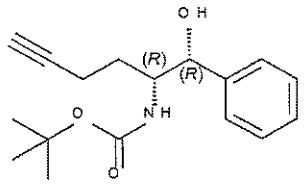
~~(k) X17H/R/Q, X40R, X64V, X94P, X144V, X147I/Q/L, X157C, X196M and X206F/L; and~~

~~(l) X17Q, X40R, X64V, X71P, X94P, X144V, X147I, X157C, X196M, X206F, and X249F.~~

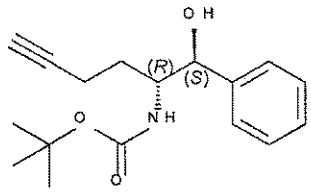
~~5.~~3. The engineered ketoreductase polypeptide of **claim** 1 which is capable of converting the substrate compound (**2**) to the product compound (**1**) with at least 10 fold the activity of the reference polypeptide of SEQ ID NO:4, wherein the amino acid sequence further ~~comprises the features X40R and X206L or F, and~~ one or more residue differences as compared to SEQ ID NO:4 selected from: X60I~~; X71P; X94P; X94A;~~ X95M; X96L; X96Y; X127R;~~ X144V;~~ X145I; X150Y; X152G; X153G; ~~X157C;~~ X195A; X195G; ~~X196M;~~ X198S; X199H; ~~X206F;~~ X216R, X245I, and X245F~~; X249Y; and X249F~~.

~~6.~~4. The engineered ketoreductase polypeptide of **claim** 1 which has increased thermal stability as compared to the reference polypeptide of SEQ ID NO:4 or 32, wherein the amino acid sequence further comprises ~~the features X40R and X206L or F, and~~ one or more residue differences as compared to SEQ ID NO:4 selected from: ~~X17Q; X17R; X17W; X64V; X71P;~~ X87L; ~~X94S; X94P; X147Q; X147I; X147L; X157C;~~ and X198S~~; X249Y; and X249F~~.

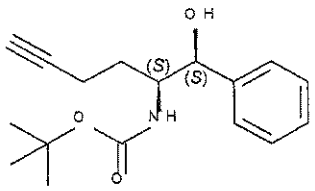
~~7.~~5. The engineered ketoreductase polypeptide of **claim** 1 which is capable of forming product *syn*-tert-butyl(1-hydroxy-1-phenylhex-5-yn-2-yl)carbamate compounds (**1a**) and (**1c**)



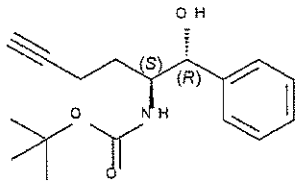
(1a)



(1b)



(1c)



(1d)

in diastereomeric excess of *anti*-tert-butyl(1-hydroxy-1-phenylhex-5-yn-2-yl)carbamate compounds (**1b**) and (**1d**).

~~8.~~6. The engineered ketoreductase polypeptide of **claim** ~~7~~ 5 in which the amino acid sequence further comprises ~~one or more residue differences~~X87L as compared to SEQ ID NO:4 ~~selected from: X17Q; X64V; X71P; X87L; X147I; X157C; X196M; and X249F~~.

~~9.~~7. The engineered ketoreductase polypeptide of **claim** ~~7~~5 which is capable of forming product compounds (**1a**) and (**1c**) in a diastereomeric ratio of at least 50 over compounds (**1b**) and (**1d**).

~~10.~~8. The engineered ketoreductase polypeptide of **claim** 1 in which the amino acid sequence comprises a sequence selected from the group consisting of SEQ ID NO: ~~18, 20, 22, 24, 26, 28, 30, 32,~~ 34, 36, ~~38, 40,~~ and 42, ~~44, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170 and 172~~.

~~11.~~9. The engineered ketoreductase polypeptide of any one of **claims** 1 to ~~10~~8 in which the polypeptide is immobilized on a solid support

~~12.~~10. A polynucleotide encoding an engineered ketoreductase polypeptide of any of **claims** 1 to ~~10~~8.

~~13.~~11. The polynucleotide of **claim** ~~12~~10 which comprises a nucleotide sequence selected from the group consisting of SEQ ID NO: ~~17, 19, 21, 23, 25, 27, 29, 31,~~ 33, 35 and, ~~37, 39,~~ 41, ~~43, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169 and 171~~.

~~14.~~12. An expression vector comprising the polynucleotide of **claim** ~~12~~10.

~~15.~~13. The expression vector of **claim** ~~14~~12 comprising a control sequence.

~~16.~~14. The expression vector of **claim** ~~15~~13 in which the control sequence is a promoter.

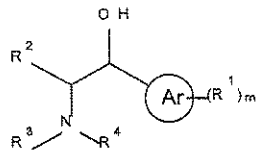
~~17.~~15. A host cell comprising the polynucleotide of **claim** ~~12~~ 10.

~~18.~~16. The host cell of **claim** ~~17~~15 which is *E. coli*.

~~19.~~17. A method for preparing an engineered ketoreductase polypeptide of any one of **claims** 1 to ~~10~~8, comprising culturing the host cell of **claim** ~~17~~15 under culture conditions suitable for expression of the engineered polypeptide.

~~20.~~18. The method of **claim** ~~19~~17, further comprising isolating the expressed polypeptide.

~~21.~~19. A process for preparing the product compound of formula (I)



(I)

wherein

Ar is a 5 to 7-membered carbocyclic or heterocyclic ring;

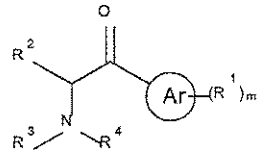
each occurrence of R^1 is independently selected from halo, $-COOR^a$, $-C(O)R^b$, $-OR^c$, $-SO_2$,$-SR^d$, $-S(O)R^e$, $-NR^fR^g$, $-C(O)NR^hR^i$,$-NO_2$, -CN, alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and R^i are independently selected from H and an optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

R^2 is selected from an optionally substituted alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkenyl, heterocycloalkylalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, alkylthio, alkylsulfinyl, and arylsulfinyl;

R^3 and R^4 are, independently of the other, selected from H, an optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkyloxycarbonyl, arylalkyloxycarbonyl, heteroarylalkyloxycarbonyl, and a protecting group, or one of R^3 and R^4 forms an optionally substituted 5 to 7-membered heterocyclic ring with R^2, and

m is 0 to 10;

comprising contacting the substrate compound of formula **(II)**,



(II)

wherein

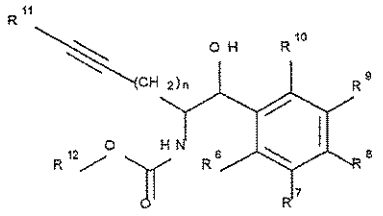
R^1, R^2, R^3, R^4, and *m* are as defined above,

with an engineered ketoreductase polypeptide of any one of **claims** 1 to ~~10~~8 in presence of cofactor NADPH or NADH under suitable reaction conditions.

~~22.~~20. The process of **claim** ~~21~~-19 in which Ar is a 5 to 7-membered aryl or heteroaryl group.

~~23.~~21. The process of **claim** ~~22~~19 in which Ar is selected from thienyl, phenyl, and pyridyl.

~~24.~~22. The process of **claim** ~~21~~19 in which the product compound of formula (**II**) comprises the compound of formula (**Ib**),



(Ib)

wherein

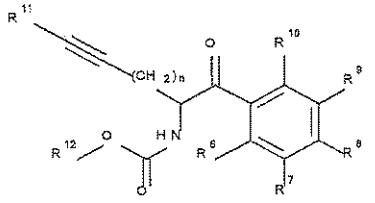
R^6, R^7, R^8, R^9, and R^{10} are each independently selected from H, halo, -$COOR^a$, -$C(O)R^b$, -OR^c, -SO_2,-SR^d, -$S(O)R^e$, -NR^fR^g, -$C(O)NR^hR^i$,-NO_2, -CN, alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and R^i are independently selected from H and an optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

n is 1 to 4,

R^{11} is selected from H and an optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl; and

R^{12} is selected from H, an optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl and a protecting group;

the process comprising contacting the substrate compound of formula (**IIb**)



(IIb)

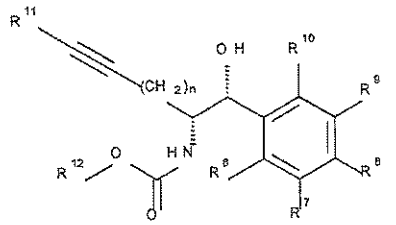
wherein

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and *n* are as defined above,

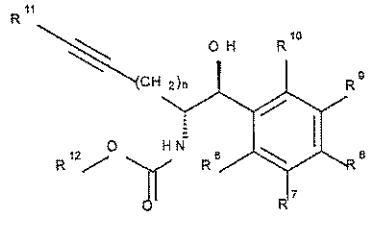
with an engineered ketoreductase polypeptide of any one of **claims** 1 to ~~8~~10 in presence of cofactor NADPH or NADH under suitable reaction conditions.

~~25.~~23. The process of **claim** 22~~3~~422 in which R^{11} is an optionally substituted phenyl.

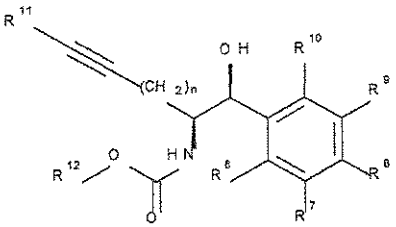
~~26.~~24. The process of **claim** ~~2~~422 in which the product compound of formula (**Ib**) comprises compounds of formula (**Ib1**) and (**Ib3**) and the process forms product compounds of formula (**Ib1**) and (**Ib3**) in diastereomeric excess of compounds of formula (**Ib2**) and (**Ib4**),



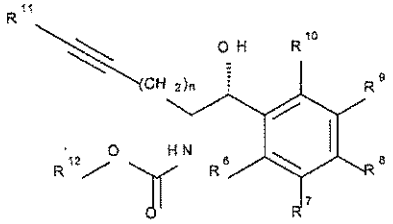
(Ib1)



(Ib2)



(Ib3)

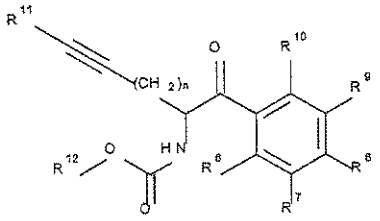


(Ib4)

wherein

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and *n* are as in defined **claim** ~~24~~22;

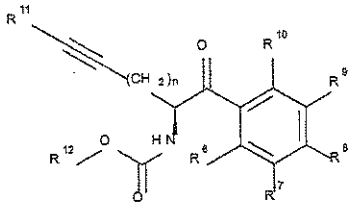
the process comprising contacting the substrate compound of formula **(IIb)**



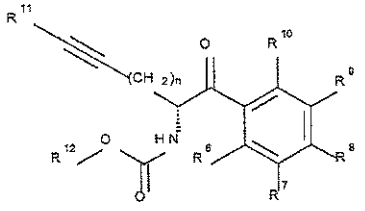
(IIb)

with an engineered ketoreductase polypeptide of any one of **claims** ~~7~~5 to ~~9~~7 in presence of cofactor NADPH or NADH under suitable reaction conditions.

~~27.~~25. The process of any one of **claims** ~~24~~22 to ~~26~~24 in which the substrate compound of formula **(IIb)** comprises a mixture of compounds of formula **(IIb1)** and **(IIb2)**



(IIb1)

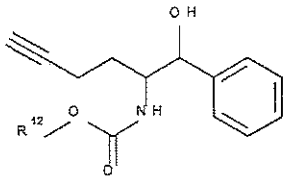


(IIb2)

~~28.~~26. The process of **claim** ~~27~~25 in which the mixture comprises a racemic mixture of compounds of formula **(IIb1)** and **(IIb2)**.

~~29.~~27. The process of any one of claims ~~24~~22 to ~~28~~26 in which n is 2.

~~30.~~28. The process of **claim** ~~24~~22 in which the product compound of formula (**Ib**) comprises compound of formula (**Id**)

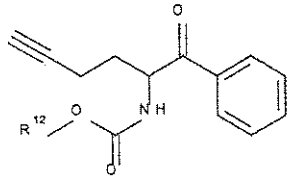


(Id)

wherein

R^{12} is as defined **claim** ~~24~~22;

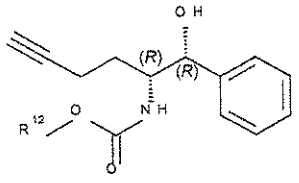
the process comprising contacting the substrate compound of formula (**IId**)



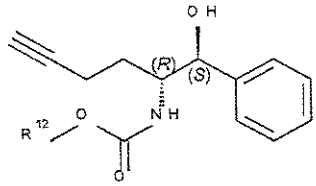
(IId)

with an engineered ketoreductase polypeptide of any one of **claims** 1 to ~~10~~8 in presence of cofactor NADPH or NADH under suitable reaction conditions.

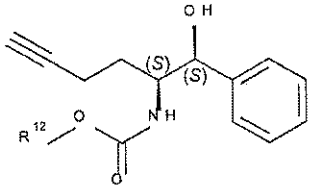
~~31.~~29. The process of **claim** ~~24~~22 in which the product compound of formula (**Ib**) comprises compounds of formula (**Id1**) and (**Id3**) and the process forms product compounds of formula (**Id1**) and (**Id3**) in diastereomeric excess of compounds of formula (**Id2**) and (**Id4**),



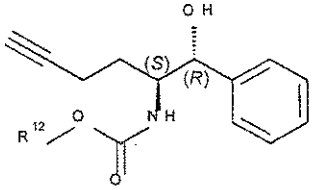
(Id1)



(Id2)



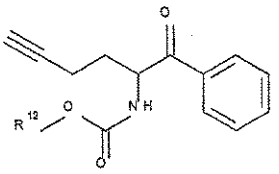
(Id3)



(Id4)

wherein R^{12} is as defined in **claim ~~24~~ 22**;

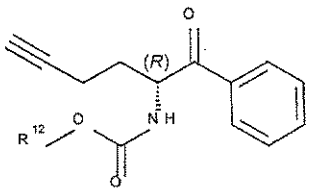
the process comprising contacting the substrate compound of formula (**IId**)



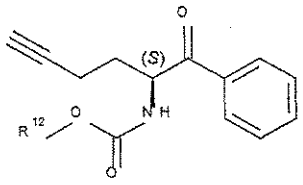
(IId)

with an engineered ketoreductase polypeptide of any one of **claims ~~7~~5** to ~~9~~7 in presence of cofactor NADPH or NADH under suitable reaction conditions.

~~32.~~30. The process of **claim ~~30~~28** or ~~31~~29 in which the substrate compound of formula (**IId**) comprises a mixture of compounds of formula (**IId1**) and (**IId2**)



(IId1)



(IId2)

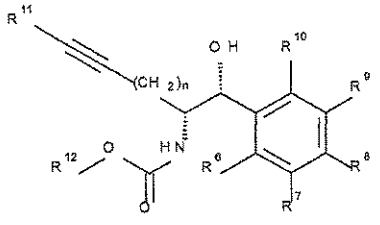
~~33.~~31. The process of **claim ~~32~~30** in which the mixture is a racemic mixture of compounds of formula (**IId1**) and (**IId2**).

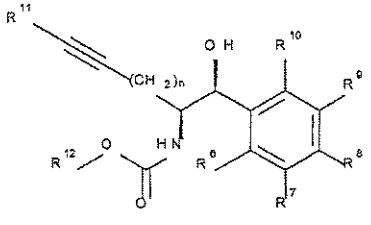
~~34.~~32. The process of any one of **claims ~~24~~22** to ~~33~~31 in which R^{12} is selected from methyl, ethyl, n-propyl, isopropyl, -butyl, iso-butyl, sec-butyl, and tert-butyl.

~~35.~~33. The process of **claim ~~34~~32** in which R^{12} is tert-butyl.

~~36.~~34. The process of **claim ~~31~~29** in which the product compounds of formula (**Id1**) and (**Id3**) are formed in a diastereomeric ratio of at least 50 over compounds of formula (**Id2**) and (**Id4**), the process comprising contacting the substrate compound of formula (**IId**) with an engineered ketoreductase polypeptide of **claim** ~~7~~9 in presence of cofactor NADPH or NADH under suitable reaction conditions.

~~37.~~35. A process for preparing product compound of formula (**Ib1**) in diastereomeric excess of compound of formula (**Ib3**),





(Ib1) **(Ib3)**

wherein,

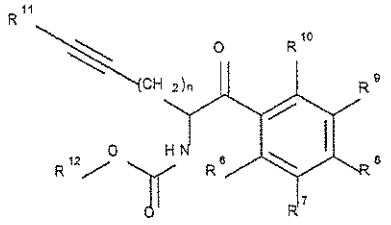
R^6, R^7, R^8, R^9, and R^{10} are each independently selected from H, halo, -$COOR^a$, -$C(O)R^b$, -OR^c, -SO_2,-SR^d, -$S(O)R^e$, -NR^fR^g, -$C(O)NR^hR^i$,-NO_2, -CN, alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, wherein R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and R^i are independently selected from H and an optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

n is 1 to 4;

R^{11} is selected from H or an optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl; and

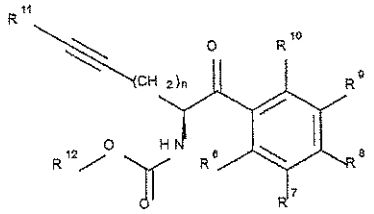
R^{12} is selected from H, an optionally substituted alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and a protecting group;

the process comprising contacting the substrate compound of formula (**IIb**)

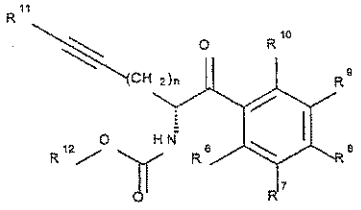


(IIb)

wherein R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} and *n* are as defined above, with an engineered ketoreductase of any one of **claims** ~~75~~ to ~~97~~ in presence of NADPH or NADH under suitable reaction conditions for equilibration of substrate compounds of formula (**IIb1**) and (**IIb2**)



(IIb1)



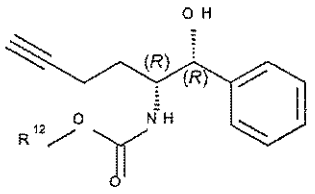
(IIb2)

~~38.~~36. The process of **claim** ~~37~~35 in which the substrate compound (**IIb**) comprises a mixture of compounds of formula (**IIb1**) and (**IIb2**).

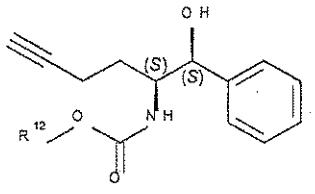
~~39.~~37. The process of **claim** ~~38~~36 in which the mixture comprises a racemic mixture of compounds of formula (**IIb1**) and (**IIb2**).

~~40.~~38. The process of any one of **claims** ~~37~~35 to ~~39~~37 in which *n* is 2.

41.39. The process of **claim** ~~37~~35 in which the product compound of formula (**Ib1**) comprises a compound of formula (**Id1**), and compound of formula (**Id1**) is formed in diastereomeric excess of compound of formula (**Id3**),

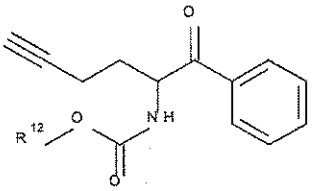


(Id1)



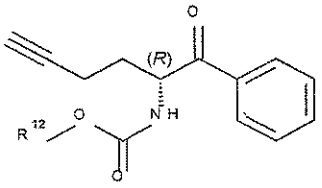
(Id3)

the process comprising contacting the substrate compound of formula (**IId**)

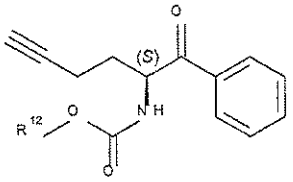


(IId)

with an engineered ketoreductase of any one of **claims** ~~7~~5 to ~~9~~7 in presence of NADPH or NADH under suitable reaction conditions for equilibration of substrate compounds of formula (**IId1**) and (**IId2**)



(IId1)



(IId2)

42.40. The process of **claim** ~~41~~39 in which the compound of formula (**IId**) comprises a mixture of substrate compounds of formula (**IId1**) and (**IId2**).

43.41. The process of **claim** ~~42~~40 in which the mixture comprises a racemic mixture of substrate compounds of formula (**IId1**) and (**IId2**).

44.42. The process of any one of **claims** ~~37~~35 to ~~43~~41 in which the reaction conditions for equilibration of substrate compounds comprise a pH of about 9 to about 12 and a temperature of about 45°C to about 60°C.

45.43. The process of **claim** ~~41~~39 in which the suitable reaction conditions comprise a substrate compound loading concentration of about 1 g/L, about 10 g/L, about 20 g/L, about 40 g/L, about 50 g/L, about 75 g/L, about 100 g/L, about 125 g/L, about 150 g/L, about 175 g/L, or about 200 g/L.

~~46.~~44. The process of **claim** ~~41~~39 in which the suitable reaction conditions comprise an engineered ketoreductase polypeptide concentration of about 20 g/L, about 10 g/L, about 5 g/L, about 4 g/L, about 2 g/L, about 1 g/L, about 0.5 g/L, about 0.2 g/L or about 0.1 g/L.

~~47.~~45. The process of any one of **claims** ~~21~~19 to ~~46~~44 further comprising converting NAD+ or NADP+ to NADH or NADPH with a cofactor regeneration system.

~~48.~~46. The process of **claim** ~~47~~45 in which the cofactor regeneration system comprises a ketoreductase and a secondary alcohol.

~~49.~~47. The process of **claim** ~~48~~46 in which the secondary alcohol is isopropyl alcohol (IPA).

~~50.~~48. The process of **claim** ~~49~~47 further comprising the step of removing acetone formed from ketoreductase-mediated conversion of the IPA to acetone.

~~51.~~49. The process of **claim** ~~48~~46 in which the ketoreductase of the cofactor regeneration system is the ketoreductase of any one of **claims** 1 to ~~10~~8.

~~52.~~50. The process of **claim** ~~48~~46 in which the ketoreductase of the cofactor regeneration system is a different ketoreductase than the ketoreductase of any one of **claims** 1 to ~~10~~8.

~~53.~~51. The process of **claim** ~~41~~39 in which the reaction conditions comprise a co-solvent system comprising an aqueous buffer solution and IPA, wherein the IPA concentration is about 5% (v/v), about 10% (v/v), about 20% (v/v), about 30% (v/v), about 40% (v/v), about 45% (v/v), about 50% (v/v), about 55% (v/v), about 60%, (v/v), about 65% (v/v), about 70% (v/v), about 75% (v/v), about 80% (v/v), about 85% (v/v), or about 90% (v/v).

~~54.~~52. The process of **claim** ~~21~~19 in which the reaction conditions comprise:

(a) engineered ketoreductase polypeptide concentration of about 1 g/L to about 10 g/L;

(b) substrate compound at a loading concentration of about 50g/L to about 200/g/L;

(c) NADP(H) concentration of about 0.1 g/L to about 0.5 g/L;

(d) a co-solvent solution of an aqueous buffer, and IPA of about 30% to about 70% (v/v); and

(e) a temperature of 35°C to about 60°C.

~~55.~~53. The process of any one of **claims** ~~21~~19 to ~~54~~52 further comprising one or more steps selected from: extraction of the product compound; isolation of the product compound; purification of the product compound; and crystallization of the product compound.

~~56.~~54. The process of any one of **claims** ~~21~~19 to ~~55~~53 wherein the substrate compound of formula (II) is a deuterated version of the compound.