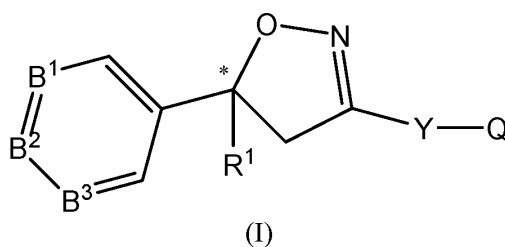


WHAT IS CLAIMED IS:

1. A process for the preparation of an isoxazoline compound of the formula (I) below, which is enriched in one enantiomer:



wherein:

B^1 , B^2 , B^3 , are each independently C-R or N;

each R is independently H, halogen, cyano, $-\text{NO}_2$, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino or alkoxy carbonyl;

R^1 is C_1 - C_3 alkyl or C_1 - C_3 haloalkyl;

Y is an optionally substituted phenylene, naphthylene, indanylene, a 5- or 6-membered heteroarylene or an 8-10-membered fused heterobicycylene, wherein the optional substituents are selected from the group consisting of halogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino, $-\text{CN}$ or $-\text{NO}_2$ and NH_2 - $\text{C}(=\text{S})$ -;

Q is $\text{T}-\text{NR}^2\text{R}^3$, the group $(-\text{CH}_2-)(-\text{CH}_2-)\text{N}-\text{R}^3$, OH, NH_2 , alkoxy, haloalkoxy, alkylamino, haloalkylamino, dialkylamino, halodialkylamino, thiol, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, or an optionally substituted 5- or 6-membered carbocyclyl, heterocyclyl or heteroaryl ring;

T is $(\text{CH}_2)_n$, $\text{CH}(\text{CH}_3)$, $\text{CH}(\text{CN})$, $\text{C}(=\text{O})$ or $\text{C}(=\text{S})$;

R^2 is H, alkyl, alkenyl, alkynyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcarbonyl or alkoxy carbonyl;

R^3 is H, OR^7 , NR^8R^9 or Q^1 ; or alkyl, haloalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcarbonyl, alkoxy carbonyl,

aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl, each optionally substituted with one or more substituents independently selected from R^4 ; or

R^2 and R^3 are taken together with the nitrogen to which they are attached to form a ring containing 2 to 6 atoms of carbon and optionally one additional atom selected from the group consisting of N, S and O, said ring optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl, halogen, $-\text{CN}$, $-\text{NO}_2$ and alkoxy;

each R^4 is independently halogen, alkyl, cycloalkyl, alkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, haloalkylamino, dialkylamino, dihaloalkylamino, cycloalkylamino, alkylcarbonyl, alkoxycarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, haloalkylaminocarbonyl, dihaloalkylaminocarbonyl, hydroxy, $-\text{NH}_2$, $-\text{CN}$ or $-\text{NO}_2$; or Q^2 ;

each R^5 is independently halogen, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino, alkoxycarbonyl, $-\text{CN}$ or $-\text{NO}_2$;

each R^6 is independently halogen, alkyl, haloalkyl, cycloalkyl, halocycloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfinyl, haloalkylsulfinyl, alkylsulfonyl, haloalkylsulfonyl, alkylamino, dialkylamino, $-\text{CN}$, $-\text{NO}_2$, phenyl or pyridinyl;

R^7 is H; or alkyl, alkenyl, alkynyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl, each optionally substituted with one or more halogen;

R^8 is H, alkyl, alkenyl, alkynyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, alkylcarbonyl or alkoxycarbonyl;

R^9 is H; Q^3 ; or alkyl, alkenyl, alkynyl, cycloalkyl, alkylcycloalkyl or cycloalkylalkyl, each optionally substituted with one or more substituents independently selected from R^4 ; or

R^8 and R^9 are taken together with the nitrogen to which they are attached to form a ring containing 2 to 6 atoms of carbon and optionally one additional atom selected from the group consisting of N, S and O, said ring optionally substituted with 1 to 4 substituents independently selected from the group consisting of alkyl, halogen, $-\text{CN}$, $-\text{NO}_2$ and alkoxy;

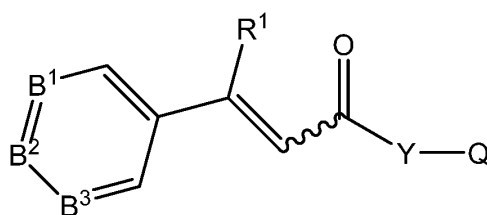
Q^1 is a phenyl ring, a 5- or 6-membered heterocyclic ring, or an 8-, 9- or 10-membered fused bicyclic ring system optionally containing one to three heteroatoms selected from up to 1 O, up to 1 S and up to 3 N, each ring or ring system optionally substituted with one or more substituents independently selected from R^5 ;

Q^2 is independently a phenyl ring or a 5- or 6-membered heterocyclic ring, each ring optionally substituted with one or more substituents independently selected from R^6 ;

Q^3 is a phenyl ring or a 5- or 6-membered heterocyclic ring, each ring optionally substituted with one or more substituents independently selected from R^6 ; and

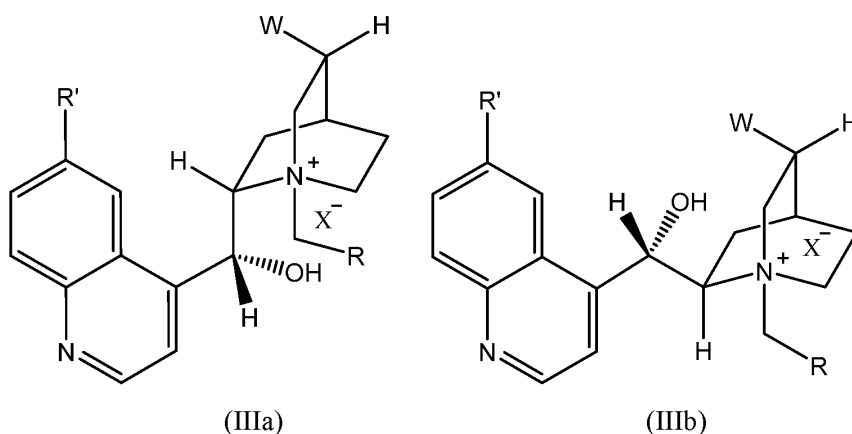
n is 0, 1 or 2;

wherein the asterisk represents that the carbon atom is a chiral quaternary carbon atom; comprising reacting a compound of formula (II):



(II)

wherein B^1 , B^2 , B^3 , R^1 , Y and Q are as defined for formula (I), with hydroxylamine in the presence of water, a base and a chiral phase transfer catalyst of formula (IIIa) or (IIIb):



(IIIa)

(IIIb)

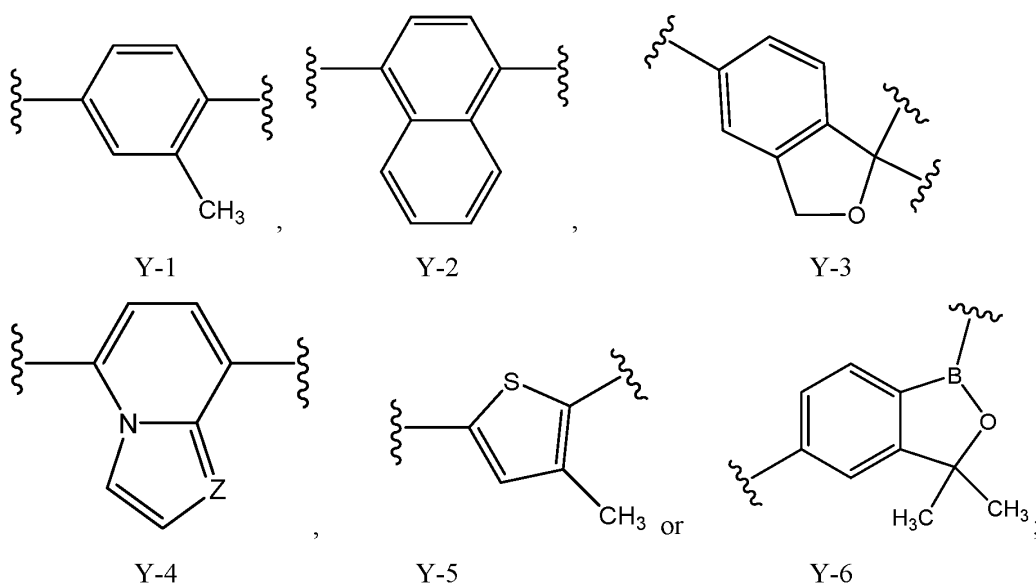
wherein R is aryl or heteroaryl substituted with one or more aralkoxy groups, amino, alkylamino or dialkylamino; R' is hydrogen or C_1 - C_3 alkoxy, W is ethyl or vinyl and X^- is an anion; and isolating the compound.

2. The process of claim 1, wherein the compound of formula (I) enriched in one enantiomer is isolated by crystallizing the compound from an aromatic solvent or a mixture of solvents comprising an aromatic solvent.

3. The process of claim 2, wherein the aromatic solvent is selected from the group

consisting of toluene, ethylbenzene, xylenes, chlorobenzene, *o*-dichlorobenzene, fluorobenzene, anisole and mesitylene, or a combination thereof.

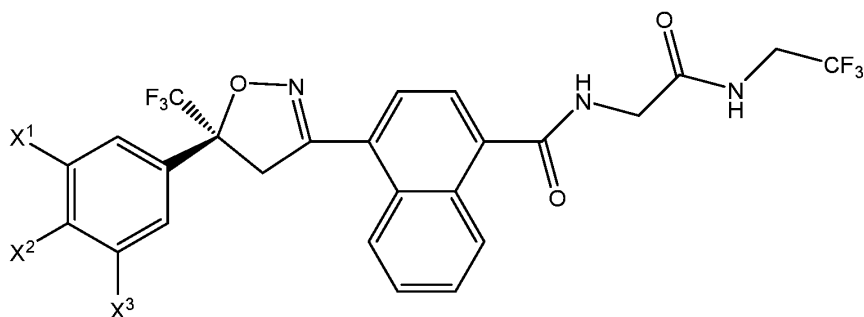
4. The process of claim 3, wherein the aromatic solvent is toluene.
5. The process of any of claims 1 to 4, wherein prior to isolating the compound of formula (I) enriched in an enantiomer, the process further comprises crystallizing racemic compound of formula (I) and removing the solid.
6. The process according to any one of claims 1 to 5, wherein Y is



wherein Z is N or CH.

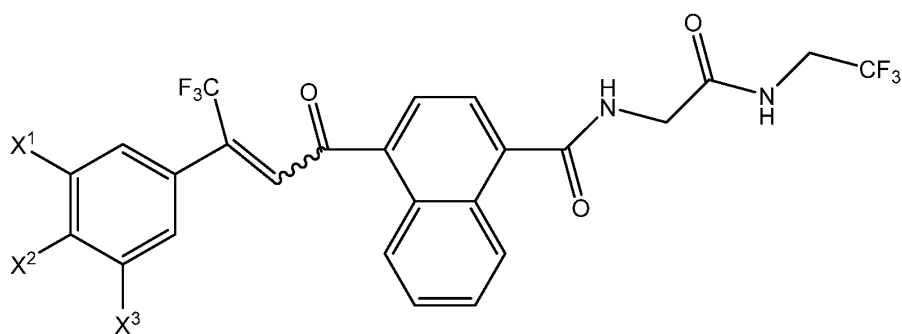
7. The process according to claim 1 or 6, wherein Q is $-\text{C}(\text{O})\text{NHCH}_2\text{C}(\text{O})\text{NHCH}_2\text{CF}_3$, $-\text{C}(\text{O})\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{SCH}_3$ or $(-\text{CH}_2-)(-\text{CH}_2-)\text{N}(\text{CO})\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$.
8. The process according to any one of claims 1 to 7, wherein X^- in the chiral phase transfer catalyst of formula (IIIa) or (IIIb) is a halogen counter ion.
9. The process according to claim 7, wherein X^- is a chloride counter ion.
10. The process according to any one of claim 1 to 9, wherein R in the chiral phase transfer catalyst of formula (IIIa) or (IIIb) is a phenyl group that is substituted by 1, 2, 3, 4 or 5 aralkoxy groups.
11. The process according to claim 10, wherein the aralkoxy group is a benzyloxy group.

12. The process according to claim 10, wherein R is substituted with 3 aralkoxy groups.
13. The process according to claim 12, wherein R is 3,4,5-tris(benzyloxy)phenyl.
14. A process for the preparation of an isoxazoline compound of Formula IA, wherein X^1 , X^2 and X^3 are each independently H, chloro, fluoro or CF_3 , which is enriched in the (*S*)-enantiomer:



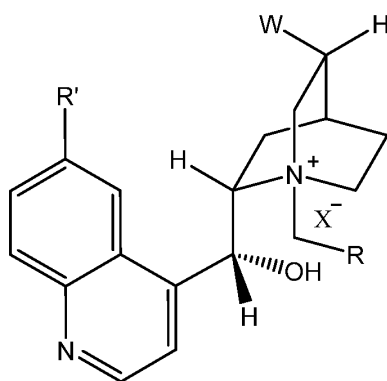
(S)-IA

comprising reacting a compound of formula (IIA):



(IIA)

wherein X^1 , X^2 and X^3 are H, chloro, fluoro or CF_3 , with hydroxylamine in the presence of water, an organic solvent that is not miscible with water, a base and a chiral phase transfer catalyst of formula (IIIa):



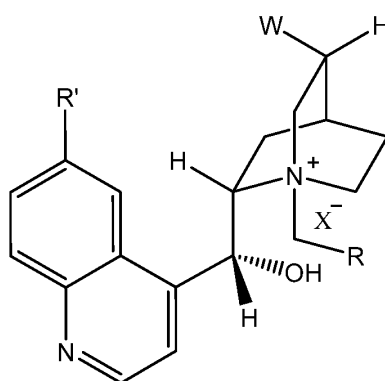
(IIIa)

wherein R is aryl or heteroaryl optionally substituted with one or more C₁-C₃alkoxy, amino, C₁-C₃alkylamino, C₁-C₃dialkylamino or aralkoxy groups, R' is hydrogen or C₁-C₃alkoxy, W is ethyl or vinyl and X⁻ is an anion; and isolating the compound of formula (S)-IA.

15. The process according to claim 14, wherein the compound of formula (S)-IA is isolated by crystallizing the compound from an aromatic solvent or a mixture of solvents comprising comprising aromatic solvent.
16. The process of claim 15, wherein the aromatic solvent is selected from the group consisting of , toluene, ethylbenzene, xylenes, chlorobenzene, *o*-dichlorobenzene, fluorobenzene, anisole and mesitylene.
17. The process of claim 16, wherein the aromatic solvent is toluene.
18. The process of any one of claims 14-17, wherein prior to isolating the compound of formula (S)-IA, the process further comprises crystallizing racemic compound of formula IA and removing the solid.
19. The process according to claim 14, wherein R in the chiral phase transfer catalyst of formula (IIIa) is phenyl substituted by 1, 2 or 3 methoxy or ethoxy groups, and R' is hydrogen or methoxy.
20. The process according to claim 14, wherein R in the chiral phase transfer catalyst of formula (IIIa) is phenyl substituted by 1, 2 or 3 benzyloxy groups, and R' is hydrogen or methoxy.
21. The process according to claim 14, wherein R in the chiral phase transfer catalyst of formula (IIIa) is 3,4,5-tris(benzyloxy)phenyl.
22. The process according to claim 14, wherein X¹ and X³ are independently chloro or CF₃

and X^2 is H or fluoro.

23. The process according to claim 14, wherein X^1 chloro; X^3 is CF_3 and X^2 is H.
24. The process according to claim 14, wherein X^1 and X^3 are chloro; and X^2 is H.
25. The process according to claim 14, wherein X^1 and X^3 are chloro and X^2 is fluoro.
26. The process according to claim 14, wherein X^1 is chloro; X^3 is CF_3 and X^2 is fluoro.
27. A chiral phase transfer catalyst of formula (IIIa):



(IIIa)

wherein R is aryl or heteroaryl substituted with one or more aralkoxy groups, R' is hydrogen or C_1 - C_3 alkoxy, W is ethyl or vinyl and X^- is an anion.

28. The chiral phase transfer catalyst of claim 27, wherein R is phenyl.
29. The chiral phase transfer catalyst of claim 27 or 28, wherein X^- is a halogen counter ion.
30. The chiral phase transfer catalyst of claim 27, wherein R is phenyl substituted by one or more benzyloxy groups.
31. The chiral phase transfer catalyst of claim 30, wherein R is 3,4,5-tris(benzyloxy)phenyl.
32. The chiral phase transfer catalyst of claim 27, wherein W is vinyl and X^- is chloride.
33. The chiral phase transfer catalyst of claim 27, wherein:
 - R is phenyl substituted by one or more benzyloxy groups;
 - R' is hydrogen or methoxy;
 - W is vinyl; and
 - X is halogen.
34. The chiral phase transfer catalyst of claim 33, wherein R' is methoxy.
35. The chiral phase transfer catalyst of claim 27, wherein:
 - R is phenyl substituted by one or more benzyloxy groups;

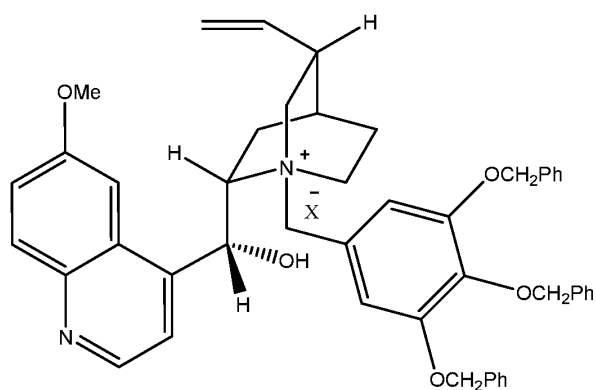
R' is hydrogen or methoxy;

W is ethyl; and

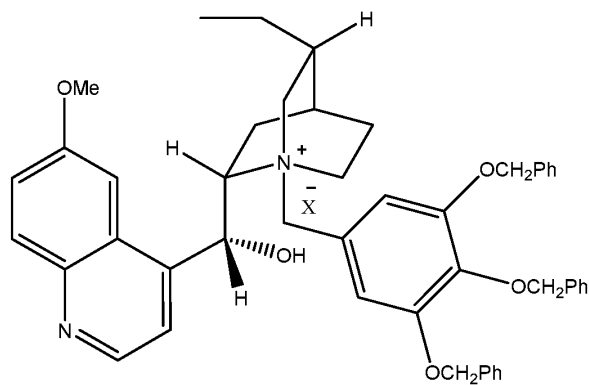
X is halogen.

36. The chiral phase transfer catalyst of claim 35, wherein R' is methoxy.

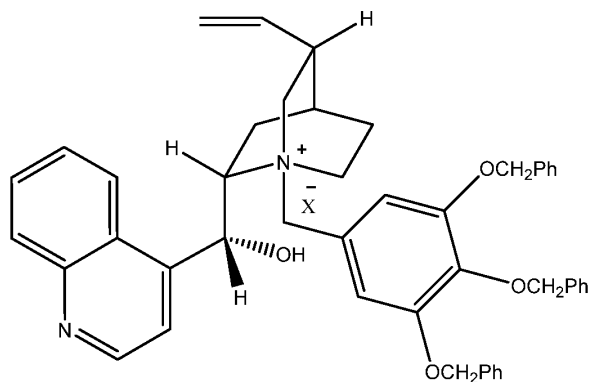
37. The chiral phase transfer catalyst of claim 27, wherein the chiral phase transfer catalyst has the formula (IIIa-13-1), (IIIa-13-2), (IIIa-13-3) or (IIIa-13-4):



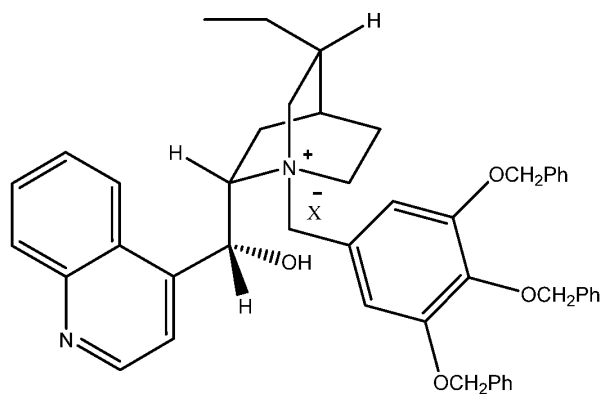
(IIIa-13-1)



(IIIa-13-2)



(IIIa-13-3)

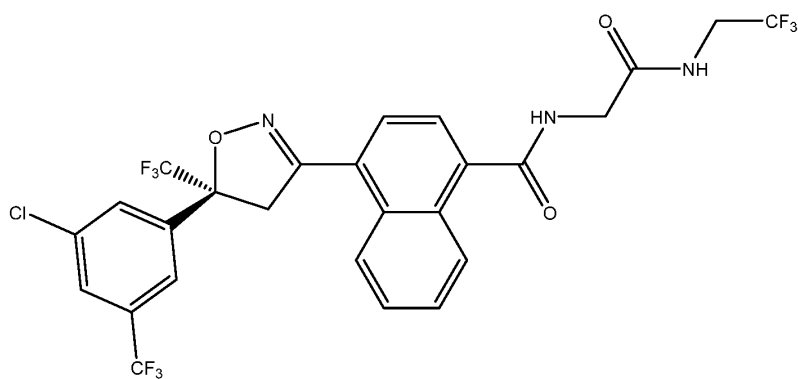


(IIIa-13-4)

wherein X^- is a halogen counter ion.

38. The chiral phase transfer catalyst of claim 37, wherein X^- is chloride.

39. A crystalline toluene solvate of (*S*)-afoxolaner having the formula:

(*S*)-afoxolaner

40. The crystalline toluene solvate of claim 39, which is characterized by an X-ray powder diffraction pattern comprising two or more of the 2-theta peaks selected from the group consisting of:

Angle 2-Theta °
4,859,
22,236,
18,838,
8,516,
25,643,
25,291,
21,859,
18,411,
19,894 and
12,746

± 0.2 2-theta, as determined on a diffractometer using Cu-K α radiation.

41. The crystalline toluene solvate of claim 39, which is characterized by an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of:

Angle 2-Theta °
4,859,
22,236,
18,838,
8,516,
25,643,
25,291,
21,859,
18,411,
19,894 and
12,746

± 0.2 2-theta.

42. The crystalline toluene solvate of claim 39 characterized by an X-ray powder diffraction pattern substantially as shown in Figure 8.
43. The crystalline toluene solvate of claim 39 which is characterized by a differential scanning calorimetry (DSC) thermogram having an endotherm at a temperature of about 83°C to about 87°C, corresponding to the toluene solvate.
44. The crystalline toluene solvate of claim 39 which is characterized by a differential scanning calorimetry (DSC) thermogram having an endotherm at a temperature of about 84.7°C, corresponding to the toluene solvate.

45. The crystalline toluene solvate of claim 39, which is characterized by a differential scanning calorimetry thermogram substantially as shown in Figure 7.
46. The crystalline toluene solvate of claim 39 characterized by a thermogravimetric analysis (TGA) thermogram characterized by weight loss of about 10.5% from about about 26°C at about 160°C.
47. The crystalline toluene solvate of claim 39 characterized by thermogravimetric analysis thermogram substantially as shown in Figure 7.
48. The crystalline toluene solvate of claim 39 characterized by unit cell parameters substantially equal to the following:

Cell Volume	1561.42 Å ³
Symmetry Cell System	Triclinic
Symmetry Space Group Name	P1
Cell Length a	8.201 Å
Cell Length b	10.7031 Å
Cell Length c	18.6462 Å
Cell Angle α	75.6862°
Cell Angle β	84.2126°
Cell Angle γ	80.592°
Density (g/cm ³)	1.497

49. The crystalline toluene solvate of claim 39 characterized by unit cell parameters substantially equal to the following cell:

Cell Volume	1561.42 Å ³
Symmetry Cell System	Triclinic
Symmetry Space Group Name	P1
Cell Length a	8.201 Å
Cell Length b	10.7031 Å
Cell Length c	18.6462 Å
Cell Angle α	75.6862°
Cell Angle β	84.2126°

Cell Angle γ	80.592°
Density (g/cm ³)	1.497
R indices	5.5%
Absolute Structure Parameter	-0.03

50. The crystalline toluene solvate of claim 39 characterized by having two or more of the following characteristics:

i) an X-ray powder diffraction pattern comprising at least three 2-theta values selected from the group consisting of

Angle 2-Theta °
4,859,
22,236,
18,838,
8,516,
25,643,
25,291,
21,859,
18,411,
19,894 and
12,746

± 0.2 2-theta;

ii) an X-ray powder diffraction pattern substantially in accordance with the X-ray powder diffraction spectrum shown in Figure 8;

iii) a differential scanning calorimetry (DSC) thermogram having an endotherm at a temperature of between about 83°C to about 87° C;

iv) a differential scanning calorimetry thermogram substantially as shown in Figure 7; and

v) a thermogravimetric analysis (TGA) diagram substantially the same as that shown in shown in Figure 7.

51. The crystalline toluene solvate of claim 39, wherein the molar ratio of (S)-afoxolaner to toluene is about 1:1.

52. The crystalline toluene solvate of claim 39, wherein the crystalline (S)-afoxolaner toluene solvate is isolated.

53. The crystalline toluene solvate of claim 39, wherein at least 90% of (S)-afoxolaner by weight is a crystalline toluene solvate form.
54. The crystalline toluene solvate of claim 39, wherein at least 80% of (S)-afoxolaner by weight is a crystalline toluene solvate form.
55. The crystalline toluene solvate of claim 39, wherein at least 70% of (S)-afoxolaner by weight is a crystalline toluene solvate form.
56. The crystalline toluene solvate of claim 39, wherein at least 60% of (S)-afoxolaner by weight is a crystalline toluene solvate form.
57. A pesticidal or parasitocidal composition comprising the crystalline toluene solvate according to claim 39, and at least one agriculturally or pharmaceutically acceptable carrier or excipient.
58. The pesticidal or parasitocidal composition of claim 57 comprising the crystalline toluene solvate according to claim 36, wherein said crystalline toluene solvate is in admixture with one or more distinct polymorphic forms and/or an amorphous compound of (S)-afoxolaner.
59. The pesticidal or parasitocidal of claim 57, wherein wherein at least 80% of (S)-afoxolaner is a crystalline toluene solvate form.
60. The pesticidal or parasitocidal composition of claim 57, wherein the composition comprises at least 95% by weight of the crystalline toluene solvate of claim 36 based on the total weight of compound of (S)-afoxolaner in the composition.
61. The pesticidal or parasitocidal composition of claim 60, wherein the composition comprises at least 98% by weight of the crystalline toluene solvate of claim 36 based on the total weight of compound of (S)-afoxolaner in the composition.
62. A process for preparing the crystalline toluene solvate of claim 39 said process comprising crystallizing (S)-afoxolaner from toluene, optionally in the presence of a second solvent.
63. The process of claim 62 comprising crystallizing (S)-afoxolaner from a mixture of toluene and cyclohexane.
64. The process of claim 63 wherein the mixture of toluene and cyclohexane comprises from a ratio of from about 50:50 to about 99:1 (v/v) toluene to cyclohexane.
65. The process of claim 62 comprising:

- a) providing a solution of (S)-afoxolaner in toluene, optionally in the presence of a second solvent;
 - b) obtaining the crystalline solvate of (S)-afoxolaner from the solution of step a); and
 - c) isolating the crystalline toluene solvate of (S)-afoxolaner.
66. The process of claim 65, wherein the solution of (S)-afoxolaner in toluene, optionally in the presence of a second solvent, is obtained by combining solid (S)-afoxolaner and toluene, optionally in the presence of a second solvent, and heating the combination.
67. The process of claim 66, wherein the combination is heated to a temperature of between about 50° C to about 80° C.
68. The process of claim 65, wherein the crystalline toluene solvate of (S)-afoxolaner is obtained by cooling the solution of step a).
69. The process of claim 68, wherein the solution of step a) is cooled to a temperature of less than about 20° C.
70. The process of claim 68, wherein the solution of step a) is cooled to a temperature of less than about 15° C.
71. The process of claim 68, wherein the solution of step a) is cooled to a temperature of about 10° C.