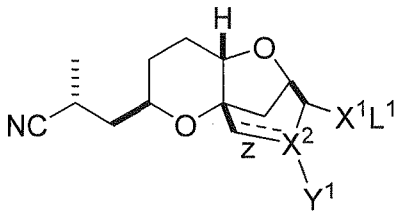
CLAIMS

1. A method of obtaining a substantially diastereomerically pure composition of a compound of formula (I), comprising:

crystallizing said compound of formula (I) from a mixture of diastereomers under appropriate crystallization conditions, wherein said compound of formula (I) is:



(I)

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is a single bond, X^2 is CH or O;

X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O;

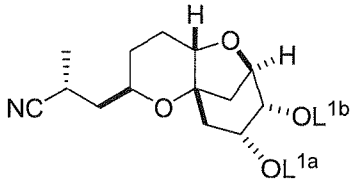
L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

2. The method of claim 1, wherein at least one of L^1 and L^2 is a protecting group, and is independently selected from the group consisting of C_1-C_6 silyl, C_1-C_6 alkyl, benzoyl, and C_1-C_8 alkyl substituted carbonyl.

3. The method of claim 1, wherein Y^1 is O-L^2; and L^1 and L^2 together form a protecting group which is a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1.

4. The method of claim 1, wherein said compound of formula (I) is of formula (Ib):



(Ib)

wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group, or L^{1a} and L^{1b} together are a divalent protecting group.

5. The method of claim 4, wherein said divalent protecting group is a cyclohexylidene protecting group.

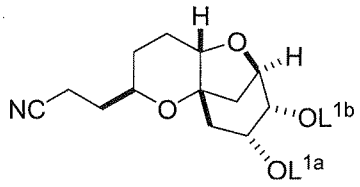
14. The method of claim 1, wherein L^1 and L^2 together are cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, or cyclic carbonate.

15. The method of claim 1, wherein at least one of L^1 and L^2 is C_1-C_6 ester.

16. The method of claim 1, wherein at least one of L^1 and L^2 is a protecting group selected from methoxymethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, methyl, t-butyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzyl, and trityl, or L^1 and L^2 together are cycloheptylidene.

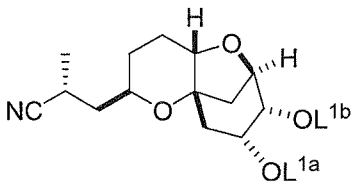
17. The method of claim 1, wherein at least one of L^1 and L^2 is C_1 alkyl carbonyl, or L^1 and L^2 together are acetonide, benzylidene, cyclohexylidene, or cyclopentylidene.

18. A method of making a substantially diastereomerically pure composition of a compound of formula (Ib) from a compound of formula (Ia), wherein the compound of formula (Ia) is:



(Ia)

and the compound of formula (Ib) is:



(Ib)

wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 alkyl ester, or L^{1a} and L^{1b} together are a divalent protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, and cyclic carbonate, provided that L^{1a} of formulae (Ia) and (Ib) are the same and L^{1b} of formulae (Ia) and (Ib) are the same, said method comprising:

reacting the compound of formula (Ia) under alkylating conditions to form a mixture comprising the compound of formula (Ib) and diastereomers thereof; and

crystallizing the compound of formula (Ib) from the mixture, under appropriate crystallization conditions.

19. The method of claim 18, wherein said alkylating conditions comprise an aprotic solvent, a base, and a C_1 alkyl halide or C_1-C_7 methyl sulfonate.

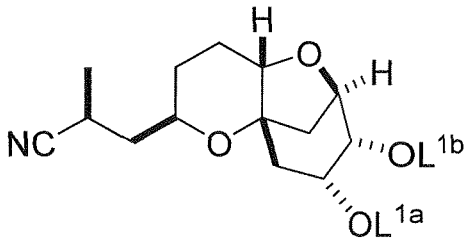
20. The method of claim 19, wherein the C_1-C_7 sulfonate is of formula R-SO_2-O-Me, in which R is C_1-C_4 alkyl or C_6 or C_7 aryl.

21. The method of claim 19, wherein said aprotic solvent is tetrahydrofuran, toluene, or t-butyl methyl ether.

22. The method of claim 18, wherein said appropriate crystallization conditions comprise the addition of a base.

23. The method of claim 22, wherein said base is lithium diisopropyl amide, potassium-hexamethyldisilazane, or potassium t-butoxide.

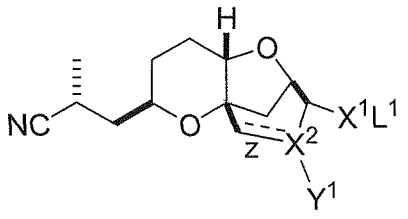
24. The method of claim 18, wherein said composition comprises a ratio of at least about 20:1 of compound of formula (Ia) to compound of formula:



25. The method of claim 18, wherein L^{1a} and L^{1b} are each protecting groups selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 alkyl ester, or L^{1a} and L^{1b} together are cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, or cyclic carbonate.

26. The method of claim 18, wherein L^{1a} and L^{1b} together are a cyclohexylidene protecting group.

27. A compound of formula (I):



(I)

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is single bond, X^2 is CH or O;

X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O; and

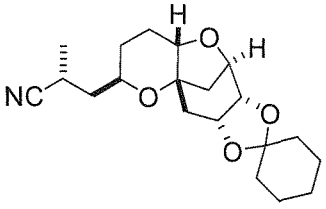
L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

28. The compound of claim 27, wherein at least one of L^1 and L^2 is a protecting group and is silyl, C_1-C_6 alkyl, or C_1-C_6 alkyl substituted carbonyl.

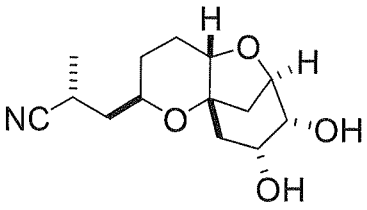
29. The compound of claim 27, wherein Y^1 is O-L^2; and L^1 and L^2 together form protecting group which is a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1.

30. The compound of claim 27, wherein said compound is:

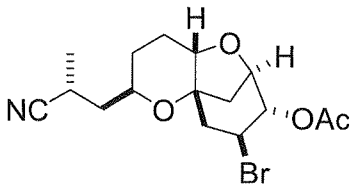


Compound AD.

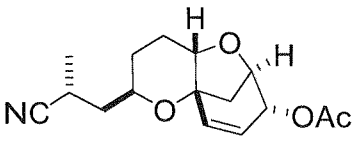
31. The compound of claim 27, wherein said compound is selected from the group consisting of:



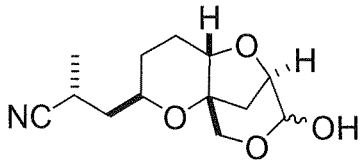
Compound AJ



Compound AK



Compound AL and

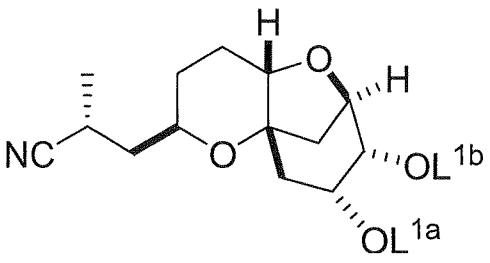


Compound AM.

32. The compound of claim 27, wherein at least one of L^1 and L^2 is a protecting group selected from methoxymethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, methyl, t-butyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzyl, and trityl, or L^1 and L^2 together are cycloheptylidne.

33. The compound of claim 27, wherien at least one of L^1 and L^2 is C_1 alkyl carbonyl, or L^1 and L^2 together are acetonide, benzylidene, cyclohexylidene, or cyclopentylidene.

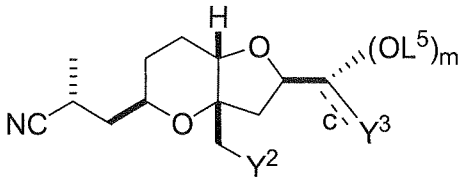
34. The compound of claim 27, wherein said compound of formula (I) is of formula (Ib):



(Ib)

wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 alkyl ester, or L^{1a} and L^{1b} together are a divalent protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, and cyclic carbonate.

35. A compound of the formula (II):



(II)

wherein:

c is a single or double bond, provided that when c is a double bond, m is 0, and Y^3 is O or $CHCO_2$-L^3, and provided that, when c is a single bond, m is 0 or 1, and Y^3 is CH_2O-L^3, CH_2CO_2-L^3 or CH_2CH_2O-L^3;

Y^2 is C_1-C_7 sulfonate, O-L^4 or a halide;

L^4 is hydrogen or a protecting group selected from C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, C_1-C_{15} alkyl silyl, t-butyldiphenylsilyl, aryl (C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, carbonate, and C_1-C_6 alkoxy-(C_1-C_6) alkyl groups; and

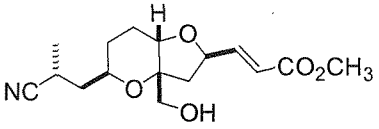
L^3 and L^5 are each independently hydrogen or a protecting group selected from C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, C_1-C_{15} alkyl silyl, t-butyldiphenylsilyl, aryl (C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, carbonate, and C_1-C_6 alkoxy-(C_1-C_6) alkyl groups, or L^3 and L^5 together are a protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, and cyclic carbonate, or, when Y^3 is CH_2CO_2-L^3, L^3 is C_1-C_{10} alkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, or C_6-C_{10} aryl;

or a salt thereof.

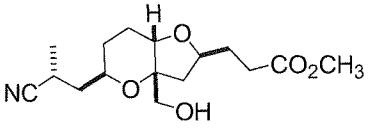
36. The compound of claim 35, wherein Y^2 is a halide.

37. The compound of claim 36, wherein said halide is iodide.

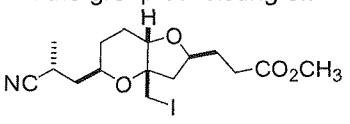
38. The compound of claim 35, wherein said compound is selected from the group consisting of:



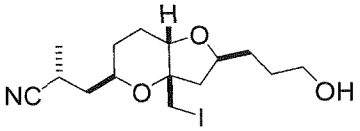
Compound AN



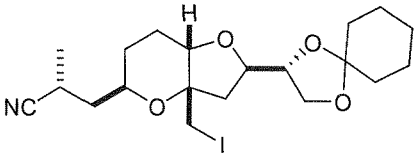
Compound AO



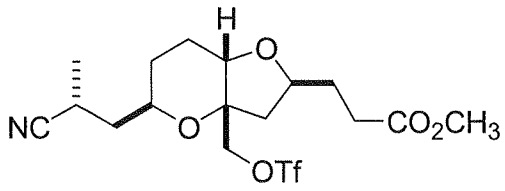
Compound AF



Compound AP,



Compound AQ, and



Compound AT

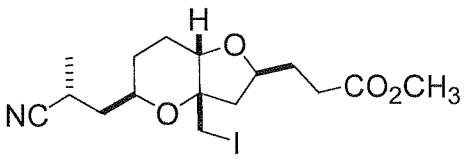
39. The compound of claim 35, wherein Y^2 is trifluoromethyl sulfonate or p-toluyl sulfonate.

40. The compound of claim 35, wherein L^3, L^4, and L^5 are each independently hydrogen or a protecting group selected from C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, C_1-C_{15} alkyl silyl, aryl (C_1-C_6) alkyl, carbonate, and C_1-C_6 alkoxy-(C_1-C_6) alkyl groups, or L^3 and L^5 together are a protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, cyclic carbonate, or, when Y^3 is CH_2CO_2-L^3, L^3 is C_1-C_{10} alkyl, C_6-C_{10} aryl-C_1-C_6 alkyl, or C_6-C_{10} aryl.

41. The compound of claim 35, wherein L^3, L^4, or L^5 is a protecting group selected from methoxymethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, methyl, t-butyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzyl, and trityl, or L^3 and L^5 together are acetonide, benzylidene, cycloheptylidene, cyclohexylidene, or cyclopentylidene.

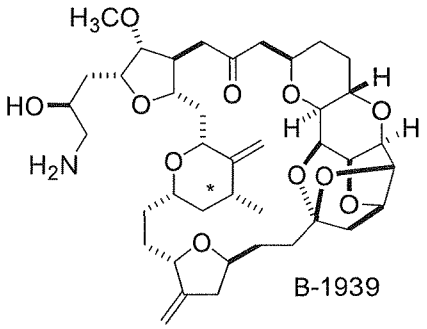
42. The compound of claim 35, wherein L^3 is present and is methyl.

43. A compound, wherein said compound is:



Compound AF.

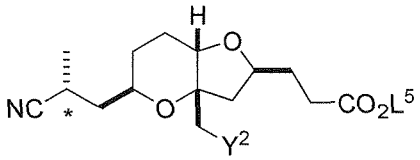
44. A method for producing compound B-1939



B-1939

which method comprises:

(i) reducing a compound of formula 8-20:



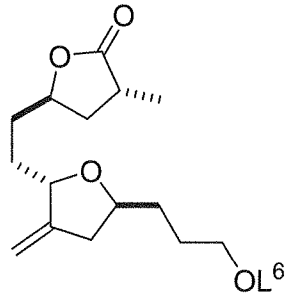
8-20

wherein:

Y^2 is a halide; and

L^5 is C_1-C_{10} alkyl, C_4-C_{10} aryl-C_1-C_6 alkyl, or C_4-C_{10} aryl

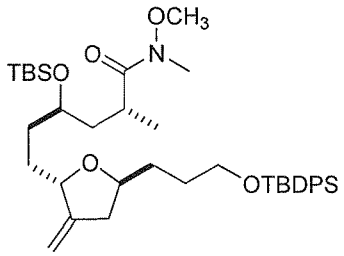
and converting the product to a compound of formula (III):



(III)

wherein: L^6 is hydrogen or silyl C_1-C_{10}; or a salt thereof;

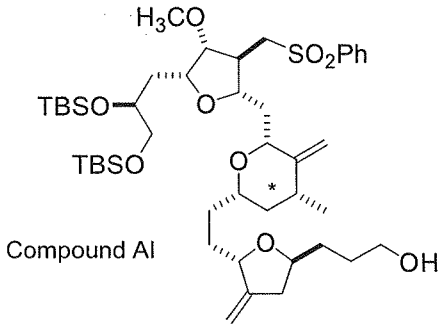
(ii) converting the compound of formula (III) or salt thereof to produce compound AV



Compound AV

and converting compound AV

into compound AI

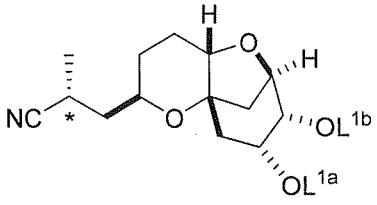


Compound AI

; and

(iii) converting compound AI into compound B-1939.

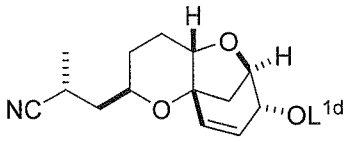
45. The method of claim 44, further comprising reacting a compound of formula (Ib):



(Ib)

wherein:

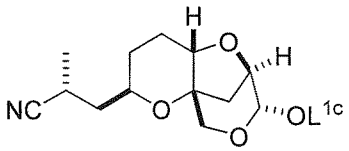
L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 alkyl ester, or L^{1a} and L^{1b} together are a protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, and cyclic carbonate under conditions suitable to produce a compound of formula 5-13:



5-13

,

wherein L^{1d} is hydrogen or a protecting group selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, C_1-C_6 ester, and a silyl (C_1-C_{10}); subjecting the compound of formula 5-13 to oxidative cleavage to form a compound of formula 6-16:



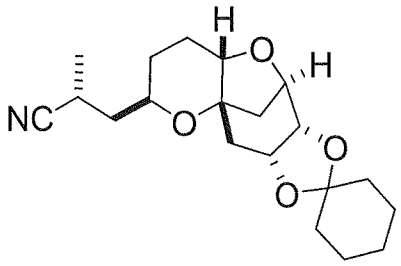
6-16

,

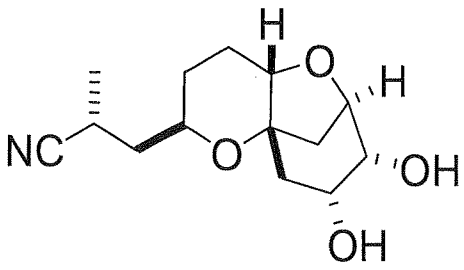
wherein L^{1c} is hydrogen or a protecting group selected from C_1-C_6 alkyl, or a C_1-C_6 ester; and subjecting the compound of formula 6-16 to Horner-Wadsworth-Emmons reaction, hydrogenation, and halide functionalization to

produce the compound of formula 8-20.

46. The method of claim 45, wherein the compound of formula (Ib) is



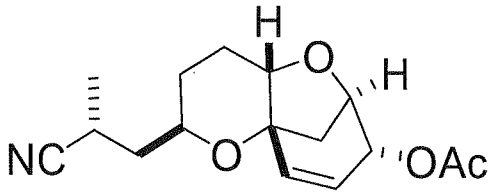
Compound AD or



Compound AJ

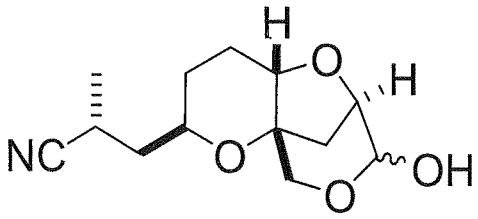
47. The method of claim 46, wherein the compound of formula (Ib) is provided at a ratio of at least 8:1 relative to the compound with the opposite stereochemistry at the chiral center marked with the asterisk.

48. The method of claim 46, wherein the compound of formula 5-13 is



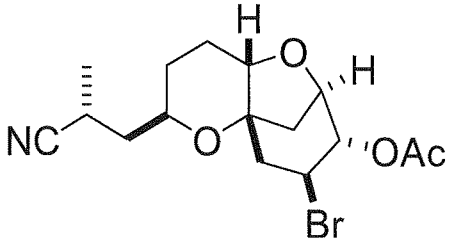
Compound AL.

49. The method of claim 46, wherein the compound of formula 6-15 is



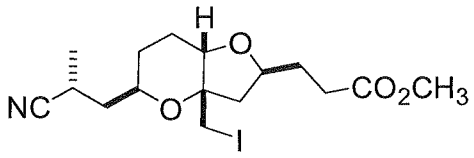
Compound AM.

50. The method of claim 46, wherein the compound of formula (Ib)



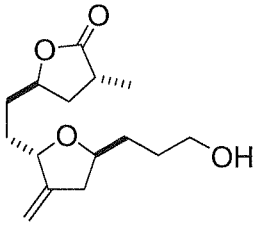
Compound AK.

51. The method of claim 45, wherein the compound of formula 8-20 is

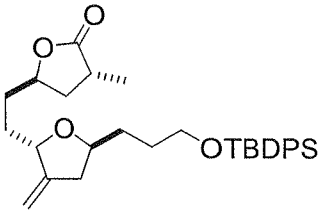


Compound AF.

52. The method of claim 45, wherein the compound of formula (III) is



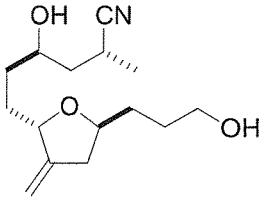
Compound AR or



Compound AH.

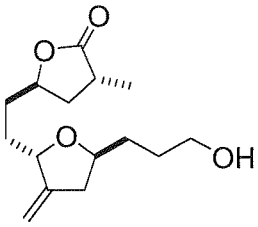
53. The method of claim 45, wherein the compound of formula 8-20 is provided at a ratio of at least 8:1 relative to the compound with the opposite stereochemistry at the chiral center marked with the asterisk.

54. A compound having the formula:



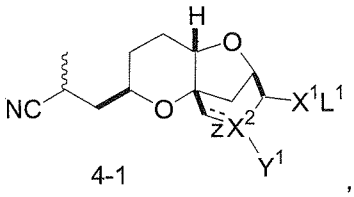
Compound AU.

55. A compound having the formula:



Compound AR.

56. A composition comprising a compound having the formula:



4-1 ,

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is a single bond, X^2 is CH or O;

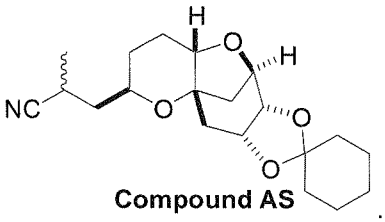
X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O;

L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

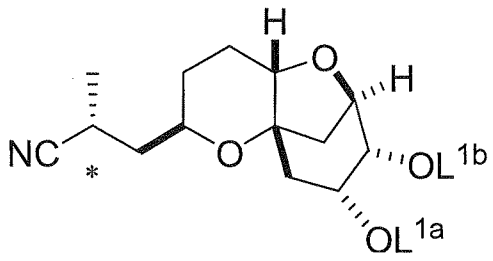
wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

57. The composition of claim 56, wherein the compound 4-1 has the formula:



Compound AS .

58. The composition of claim 56, wherein a diastereomer of the compound 4-1 has the formula:



(Ib)

wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group, or L^{1a} and L^{1b} together are a divalent protecting group.

59. The composition of claim 58, wherein L^{1a} and L^{1b} are a protecting group, which is optionally selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 ester, or L^{1a} and L^{1b} together are a divalent protecting group.

60. The composition of claim 59, wherein the divalent protecting group is cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, or cyclic carbonate.

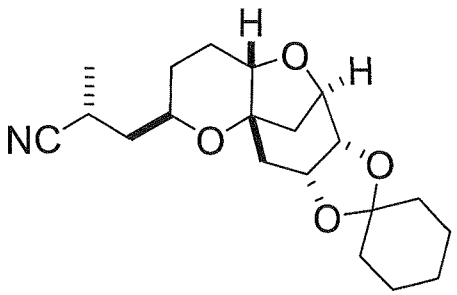
61. The composition of claim 56, wherein the protecting group of L^1 and L^2 is independently selected from silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, and C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cycloheptylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

62. The composition of claim 56, wherein at least one of L^1 and L^2 is a protecting group and is silyl, C_1-C_6 alkyl, or C_1-C_8 alkyl substituted carbonyl.

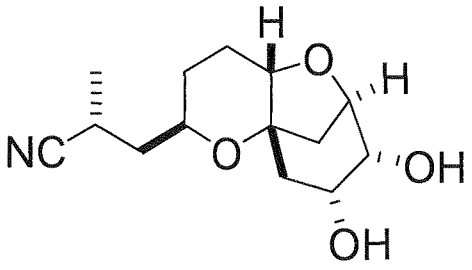
63. The composition of claim 56, wherein at least one of L^1 and L^2 is a protecting group selected from methoxymethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, methyl, t-butyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzyl, and trityl, or L^1 and L^2 together are cycloheptylidene.

64. The composition of claim 56, wherein at least one of L^1 and L^2 is C_1 alkyl carbonyl, or L^1 and L^2 together are acetonide, benzylidene, cyclohexylidene, or cyclopentylidene.

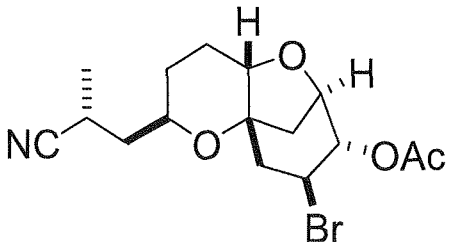
65. The composition of claim 56, wherein a diastereomer of the compound 4-1 is:



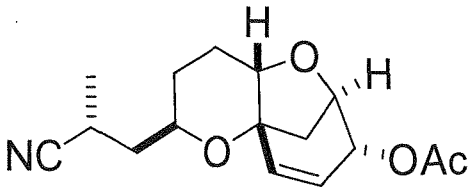
Compound AD; or a diastereomer of the compound 4-1 is selected from:



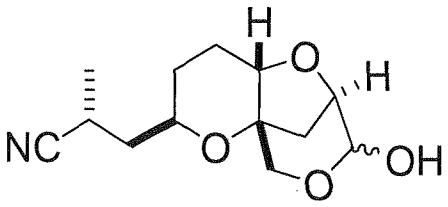
Compound AJ



Compound AK

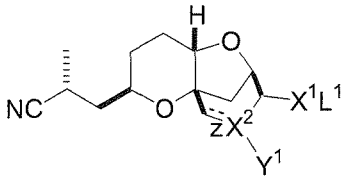


Compound AL

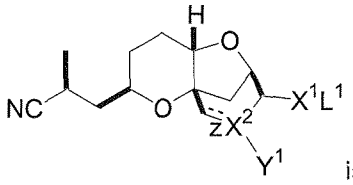


Compound AM.

66. The composition of claim 56, wherein the ratio of the diastereomer having the formula:



to the diastereomer having the formula:



is at least 8:1, 20:1, or 30:1.