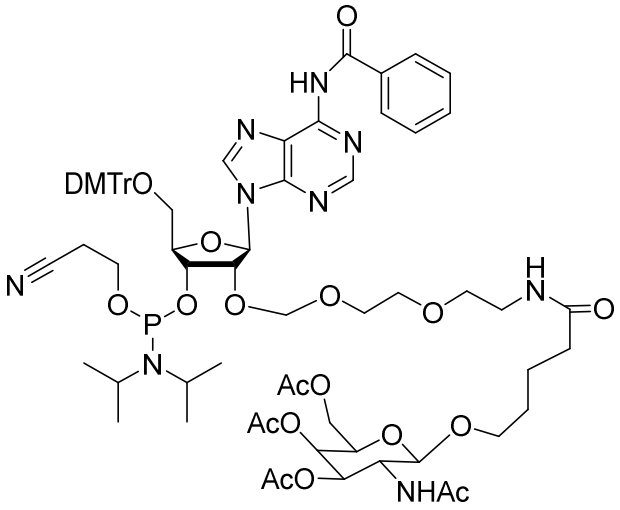
(8) deprotecting (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

(9) tritylating (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate; and

(10) phosphorylating (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2S,3S,4S,5S,6S)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate (adem-A-GalNAc phosphoramidite).

[0005a] In an aspect, there is provided a method of making a compound represented by a structure of:



(adem-A-GalNAc phosphoramidite),

the method comprising the steps of:

silylating N6-benzoyladenosine to obtain N-(9-((6aR,8R,9R,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide;

protecting N-(9-((6aR,8R,9R,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide as a methylthiomethyl ether to obtain N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide;

forming a pentaacetate on (2R,3R,4R,5R)-2-amino-3,4,5,6-tetrahydroxyhexanal hydrochloride to obtain (2R,3R,4R,5R,6R)-3-acetamido-6-(acetoxymethyl)-tetrahydro-2H-pyran-2,4,5-triyl triacetate;

forming a glycosidic bond on (2R,3R,4R,5R,6R)-3-acetamido-6-(acetoxymethyl)-tetrahydro-2H-pyran-2,4,5-triyl triacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-(hex-5-en-1-yloxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

oxidizing (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-(hex-5-en-1-yloxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)-tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid;

amidating 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-

(acetoxymethyl)tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

substituting a sulfoxide on N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide with (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

deprotecting (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

tritylating (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate; and

phosphorylating (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-

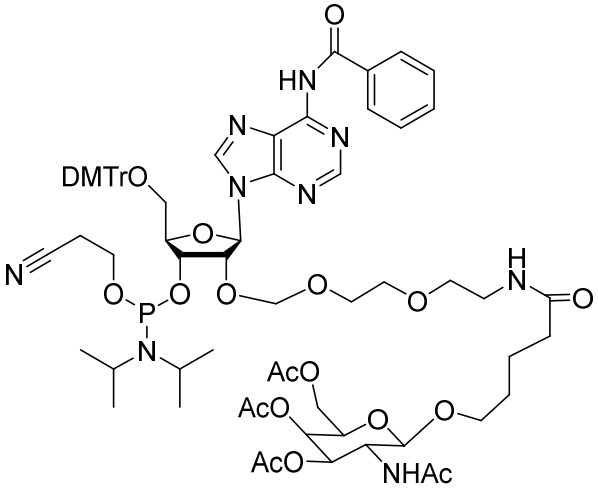
methoxyphenyl)(phenyl)methoxy)methyl)-4-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate (adem-A-GalNAc phosphoramidite).

[0006] In another instance, a method of making adem-A-GalNAc phosphoramidite is provided that includes the following steps:

(1') providing a compound comprising N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide;

methoxyphenyl)(phenyl)methoxy)methyl)-4-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate (adem-A-GalNAc phosphoramidite).

[0006a] In another aspect, there is provided a method of making a compound represented by a structure of:



(adem-A-GalNAc phosphoramidite),

the method comprising the step of:

providing a compound comprising N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide;

providing a compound comprising (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

substituting a sulfoxide on N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide with (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-

oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

deprotecting (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((6aR,8R,9R,9aR)-8-(6-benzamido-9H-purin-9-yl)-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

tritylating (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate; and

phosphorylating (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-((((2R,3R,4R,5R)-2-(6-benzamido-9H-purin-9-yl)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-(((2-cyanoethoxy)(diisopropylamino)phosphaneyl)oxy)tetrahydrofuran-3-yl)oxy)methoxy)ethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate (adem-A-GalNAc phosphoramidite).

[0007] In some instances, N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide can be prepared by a method that includes the following steps:

(1) silylating N6-benzoyladenosine to obtain N-(9-((6aR,8R,9R,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide; and

(2) protecting N-(9-((6aR,8R,9R,9aS)-9-hydroxy-2,2,4,4-tetraisopropyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide as a methylthiomethyl ether to obtain N-(9-((6aR,8R,9R,9aR)-2,2,4,4-tetraisopropyl-9-((methylthio)methoxy)tetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)-9H-purin-6-yl)benzamide.

[0008] In some instances, (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate can be prepared by a method that includes the following steps:

(1) forming a pentaacetate on (2R,3R,4R,5R)-2-amino-3,4,5,6-tetrahydroxyhexanal hydrochloride to obtain (2S,3R,4R,5R,6R)-3-acetamido-6-(acetoxymethyl)-tetrahydro-2H-pyran-2,4,5-triyl triacetate;

(2) forming a glycosidic bond on (2S,3R,4R,5R,6R)-3-acetamido-6-(acetoxymethyl)-tetrahydro-2H-pyran-2,4,5-triyl triacetate to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-(hex-5-en-1-yloxy)tetrahydro-2H-pyran-3,4-diyl diacetate;

(3) oxidizing (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-(hex-5-en-1-yloxy)tetrahydro-2H-pyran-3,4-diyl diacetate to obtain 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl)-tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid; and

(4) amidating 5-(((2R,3R,4R,5R,6R)-3-acetamido-4,5-diacetoxy-6-(acetoxymethyl) tetrahydro-2H-pyran-2-yl)oxy)pentanoic acid to obtain (2R,3R,4R,5R,6R)-5-acetamido-2-(acetoxymethyl)-6-((5-((2-(2-hydroxyethoxy)ethyl)amino)-5-oxopentyl)oxy)tetrahydro-2H-pyran-3,4-diyl diacetate.