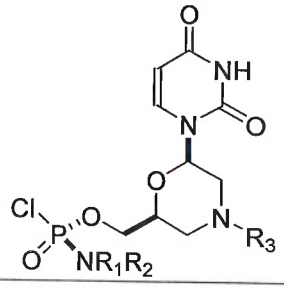
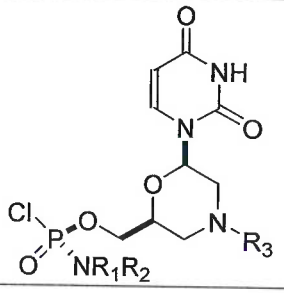
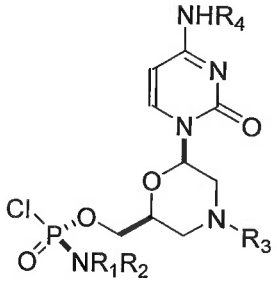
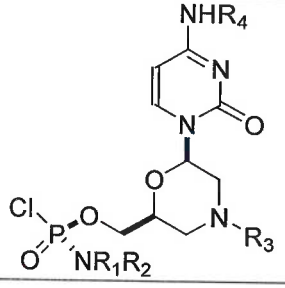
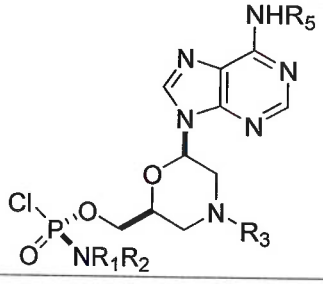
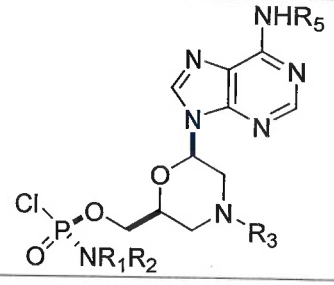
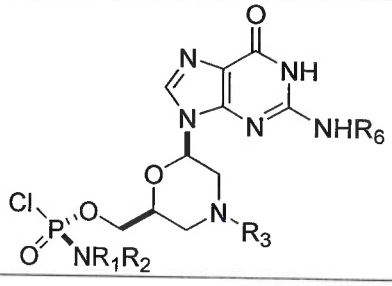
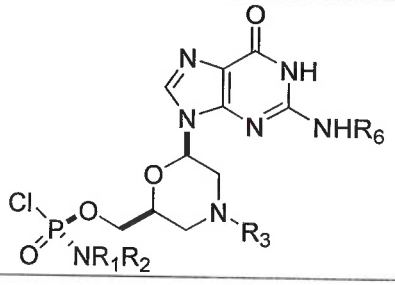
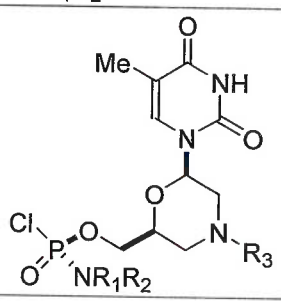
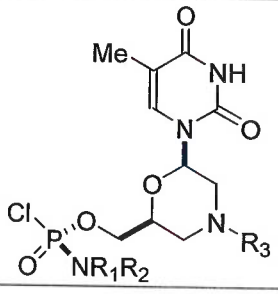
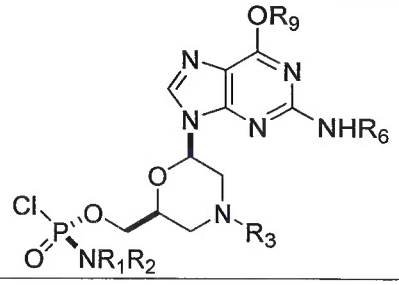
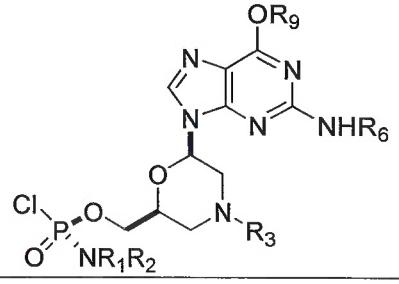
BRIEF SUMMARY

[0010] In one aspect, the present disclosure refers to a substantially diastereomerically pure compound selected from the group consisting of the compound of Formula 20, the compound of Formula 21, the compound of Formula 22, the compound of Formula 23, the compound of Formula 24, the compound of Formula 25, the compound of Formula 26, the compound of Formula 27, the compound of Formula 28, the compound of Formula 29, the compound of Formula 30, and the compound of Formula 31 as shown in Table 1, wherein R1 and R2 may be the same or different, and are selected from the group consisting of -H, optionally substituted C1-C3 alkyl, optionally substituted phenyl, optionally substituted naphthyl, or, with the nitrogen to which they are attached, form an optionally substituted heterocycle, which may be, for example, pyrrolidine, piperazine, and morpholine; wherein R3 is selected from the group consisting of trityl (Tr), which may be substituted trityl, including but not limited to such as MMTr (p-methoxyphenyldiphenylmethyl); optionally substituted benzyl, 4-methoxybenzyl (PMB, MPM), 3,4-dimethoxybenzyl, diphenylmethyl (Dpm), 4-methoxybenzyl, and sulfonyl; R4, R5, and R6 are selected from the group consisting of -H, –C(O)R7, and –C(O)OR7, where R7 is C1-C6 alkyl, benzyl, 2,2,2-trichloroethyl, and aryl; R9 is selected from the group consisting of optionally substituted alkyl, cyanoethyl, acyl, carbonate, carbamate, optionally substituted benzyl, 4-pivaloyloxy benzyl, and silyl, and enantiomers thereof. Also disclosed herein are one or more stereochemically pure or substantially stereochemically pure compounds of Table 1. Further examples may also provide enantiomers of the compounds of Table 1. Typically the stereochemistry of those enantiomers varies from that of the compounds of Table 1 by the alteration of the stereochemistry of the morpholino ring.

[0011] TABLE 1

Compound	Formula #
	20
	21
	22
	23
	24

	25
	26
	27
	28
	29

	30
	31

[0012] R_1 and R_2 may be the same or different, and may be -H, optionally substituted C1-C3 alkyl, optionally substituted phenyl, optionally substituted naphthyl, or, with the nitrogen to which they are attached, form an optionally substituted heterocycle, which may be, for example, pyrrolidine, piperazine, or morpholine.

[0013] Optionally substituted moieties may be substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano.

[0014] R_3 may be trityl (Tr), which may be substituted trityl, including but not limited to such as MMTr (p-methoxyphenyldiphenylmethyl), optionally substituted benzyl, 4-methoxybenzyl (PMB, MPM), 3,4-dimethoxybenzyl, diphenylmethyl (Dpm), , or sulfonyl, which may be a cleavable sulfonyl. In some embodiments, sulfonyl is 2-nitrobenzenesulfonyl, 4-nitrobenzenesulfonyl, or 2,4-dinitrobenzenesulfonyl.

[0015] R_4, R_5, R_6 may be -H, $-C(O)R_7$, or $-C(O)OR_7$, where R_7 is alkyl (methyl, ethyl, isopropyl, or other C1-C6 alkyl), benzyl, 2,2,2-trichloroethyl, or aryl (including but not limited to phenyl, 4-methoxy phenyl, 4—bromophenyl, and 4-nitrophenyl). R_9 may be optionally substituted alkyl, cyanoethyl, acyl, carbonate, carbamate, optionally substituted benzyl, 4-pivaloyloxy benzyl, and silyl.

[0016] In further examples, morpholino nucleosides in addition to those shown in Table 1 may be prepared in diastereomerically pure or substantially diastereomerically pure form.

[0017] In another aspect, the present disclosure refers to a method for preparing a stereochemically pure oligonucleotide, comprising reacting substantially diastereomerically pure compounds of the present invention. In another aspect, the present disclosure refers to a method for preparing a substantially diastereomerically pure phosphorodiamidate oligomer, comprising: selecting a substantially stereochemically pure phosphoramidochloridate monomers; and synthesizing a substantially diastereomerically pure phosphorodiamidate oligomer from the selected substantially stereochemically pure phosphoramidochloridate monomer. Examples may also provide methods for separation of diastereomeric mixtures of the above-disclosed compounds into stereochemically pure or substantially stereochemically pure compounds. In another aspect, the present invention refers to a substantially diastereomerically pure composition comprising a substantially diastereomerically pure compound of the present

invention or a substantially diastereomerically pure oligomer made by the method of the present invention. In another aspect, the present invention refers to a pharmaceutical composition comprising a substantially diastereomerically pure oligomer of the present invention, or a pharmaceutically acceptable salt thereof. Further examples may provide pharmaceutical compositions comprising stereochemically pure or substantially stereochemically pure compounds as reported herein. Further examples may provide pharmaceutical compositions comprising pharmaceutically acceptable salts of stereochemically pure or substantially stereochemically pure compounds as reported herein. Pharmaceutical compositions may be administered in effective amounts to patients in need of treatment. Pharmaceutical compositions may further include pharmaceutically acceptable carriers.

[0018] In some examples the following moiety in each of the compounds of Table 1 may be substituted at positions a, b, and e with one or two methyl groups, and may be substituted at positions c and d with one methyl group. In each case the methyl group may be oriented on either side of the plan of the morpholino ring. In further examples, an additional methylene, optionally substituted with one or more methyl groups, may be inserted adjacent to the nitrogen in the morpholino group to allow for expansion to a seven-membered ring.

[0019] Examples further provide for preparation of stereochemically pure oligonucleotides through stereospecific coupling of activated monomers. Further examples provide substantially diastereomerically pure oligomer made by stereospecific coupling of activated monomers. Still further examples provide substantially diastereomerically pure compositions comprising substantially diastereomerically pure compounds as reported herein.

DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0020] FIG. 1 shows phosphodiester, phosphorothioate, and phosphorodiamidate oligonucleotide linkages.

[0021] FIG. 2 shows the R- and S- phosphorous linkages in a phosphorodiamidate morpholino oligomer (PMO). FIG. 2 also shows the proliferation of diastereomers that typically results when diastereomeric mixtures of phosphorodiamidate oligomer precursors are used to synthesize dinucleotides (2-mers), trinucleotides (3-mers), tetranucleotides (4-mers), and N-mers.

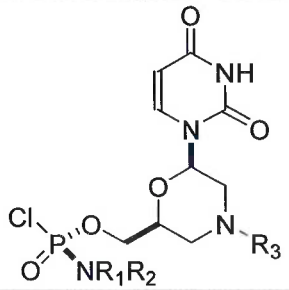
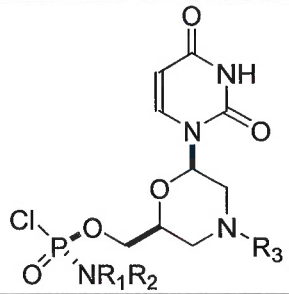
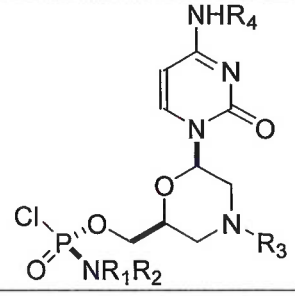
[0022] FIG. 3 shows preparation of diastereomerically pure dinucleotides both by using diastereomerically pure phosphoramidochloridates and by using diastereomeric mixture of phosphoramidochloridates.

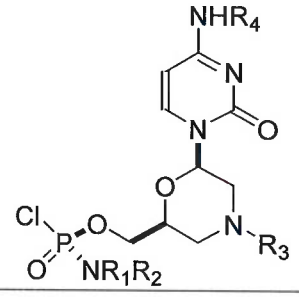
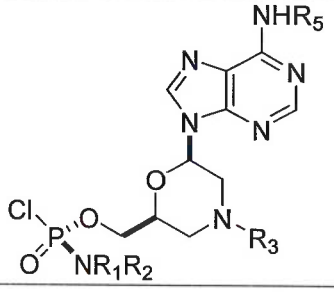
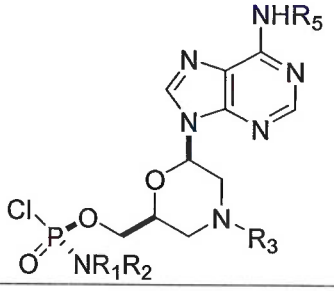
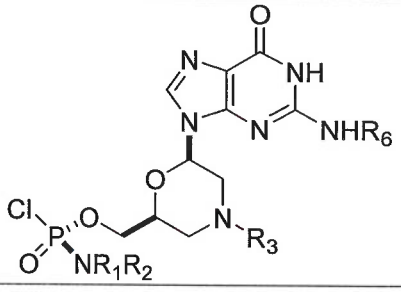
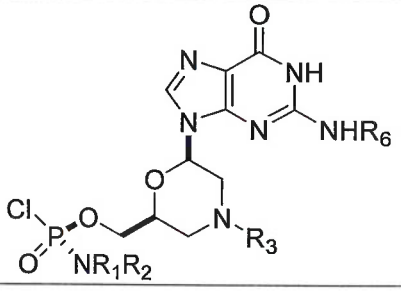
[0023] FIG. 4A and FIG. 4B show generalized diastereomeric mixtures of phosphoramidochloridates that may be useful for preparation of diastereomerically pure or substantially diastereomerically pure diastereomeric subunits.

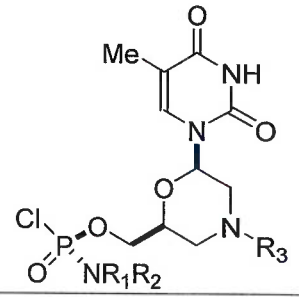
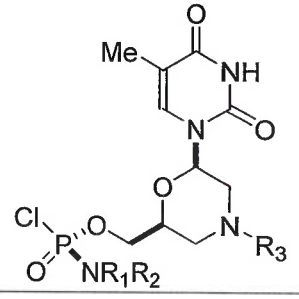
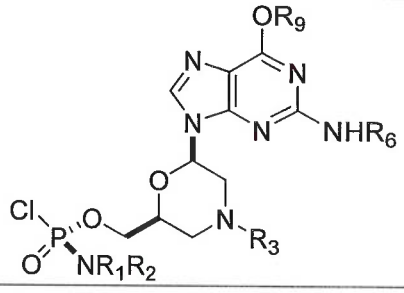
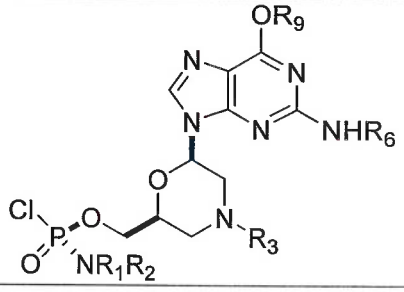
[0024] FIG. 5 shows preparation of diastereomerically pure (homogeneous) oligonucleotides using diastereomerically pure phosphoramidochloridates as reported herein.

We claim:

1. A substantially diastereomerically pure compound selected from the group consisting of the compound of Formula 20, the compound of Formula 21, the compound of Formula 22, the compound of Formula 23, the compound of Formula 24, the compound of Formula 25, the compound of Formula 26, the compound of Formula 27, the compound of Formula 28, the compound of Formula 29, the compound of Formula 30, and the compound of Formula 31,

Compound	Formula #
	20
	21
	22

	23
	24
	25
	26
	27

	28
	29
	30
	31

wherein R_1 and R_2 may be the same or different, and are selected from the group consisting of -H, optionally substituted C_1-C_3 alkyl, optionally substituted phenyl, optionally substituted naphthyl, or, with the nitrogen to which they are attached, form an optionally substituted heterocycle, which may be, for example, pyrrolidine, piperazine, and morpholine;

wherein R_3 is selected from the group consisting of trityl (Tr), which may be

substituted trityl, including but not limited to such as MMTr (p-methoxyphenyldiphenylmethyl); optionally substituted benzyl, 4-methoxybenzyl (PMB, MPM), 3,4-dimethoxybenzyl, diphenylmethyl (Dpm), 4-methoxybenzyl, and sulfonyl;

R_4, R_5, and R_6 are selected from the group consisting of -H, $-C(O)R_7$, and $-C(O)OR_7$, where R_7 is C1-C6 alkyl, benzyl, 2,2,2-trichloroethyl, and aryl;

R_9 is selected from the group consisting of optionally substituted alkyl, cyanoethyl, acyl, carbonate, carbamate, optionally substituted benzyl, 4-pivaloyloxy benzyl, and silyl,

and enantiomers thereof.

2. The compound of claim 1, wherein the sulfonyl is a cleavable sulfonyl selected from the group consisting of 2-nitrobenzenesulfonyl, 4-nitrobenzenesulfonyl, and 2,4-dinitrobenzenesulfonyl.

3. The compound of claim 1, wherein R_7 is selected from the group consisting of phenyl, 4-methoxy phenyl, 4—bromophenyl, and 4-nitrophenyl.

4. A method for preparing a stereochemically pure oligonucleotide, comprising reacting substantially diastereomerically pure compounds of claim 1.

5. A method for preparing a substantially diastereomerically pure phosphorodiamidate oligomer, comprising:

selecting a substantially stereochemically pure phosphoramidochloridate monomers; and

synthesizing a substantially diastereomerically pure phosphorodiamidate oligomer from the selected substantially stereochemically pure phosphoramidochloridate monomer.

6. The method of claim 5, further comprising separating a diastereomeric mixture of

phosphoramidochloridates into two substantially stereochemically pure phosphoramidochloridate monomers prior to the step of selecting a substantially stereochemically pure phosphoramidochloridate monomer.

7. The method of claim 6, wherein the separation of the diastereomeric mixture occurs by at least one member of the group consisting of chromatography and crystallization.

8. The method of claim 5, wherein the phorphorodiamidate oligomer is a phosphorodiamidate morpholino oligomer.

9. A substantially diastereomerically pure composition comprising a substantially diastereomerically pure compound of claim 1.

10. A substantially diastereomerically pure composition comprising a substantially diastereomerically pure compound of claim 2.

11. A substantially diastereomerically pure composition comprising a substantially diastereomerically pure compound of claim 3.

12. A substantially diastereomerically pure oligomer made by the method of claim 4.

13. A pharmaceutical composition comprising a substantially diastereomerically pure oligomer of claim 12, or a pharmaceutically acceptable salt thereof.