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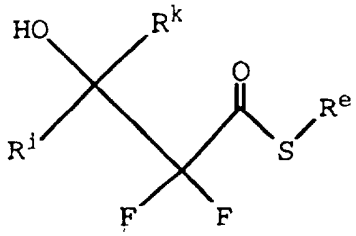
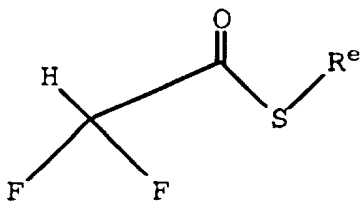
(54) Title: α, α-DIFLUORO-β-HYDROXY THIOL ESTERS AND THEIR SYNTHESIS

(57) Abstract

A process to make α, α-difluoro-β-hydroxy thiol esters of formula (IIIA), comprising reacting a difluoroethanethioate of formula (IVA), with a second reactant selected from the group consisting of aldehydes, ketones, acid halides and esters; in a solvent and in the presence of a strong base; with the proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound is described and claimed. The α, α-difluoro-β-hydroxy thiol esters can be useful in the syntheses of organic compounds including gemcitabine hydrochloride.



(IIIA)



(IVA)

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TITLE

α,α-DIFLUORO-β-HYDROXY THIOL ESTERS AND THEIR SYNTHESIS

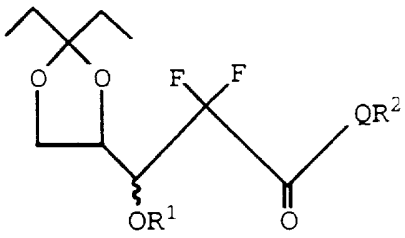
Technical Field

The invention relates to the art of organic chemistry. Specifically it relates to certain α,α-difluoro-β-hydroxy thiol esters and processes to make them.

α,α-Difluoro-β-hydroxy thiol esters are useful as intermediates in organic syntheses of valuable pharmaceutical products.

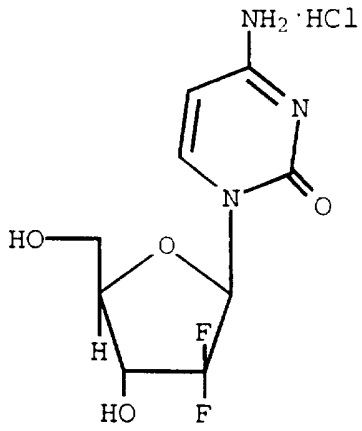
Background Art

A particularly useful α,α-difluoro-β-hydroxy ester is:



(I)

where R^1 is selected from the group consisting of H, C_1-C_4 alkyl, substituted alkyl, including silyl alkyl, trialkyl-silyl, aryl, substituted aryl, including silyl aryl, R^2 is independently selected from alkyl and aryl groups, and Q is either S (for thiol esters) or O (for esters). Compounds of formula I are known to be useful in the synthesis of



(II)

gemcitabine hydrochloride (II), a known anti-neoplastic agent.

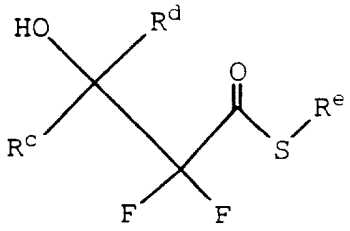
Existing methods to make compounds of formula I where R^1 is $SiR^3R^4R^5$, R^2 is R^6, Q is S, and R^3, R^4, R^5 and R^6 are independently selected from C_1-C_4 alkyl and C_5-C_6 aryl groups are known in the art. See U.S. Patent 5,428,176 . The processes to make compounds of formula (I) as described in the '176 patent require a trialkyl(or triaryl)silylhalide and the use of a catalyst.

Existing methods to make compounds of formula I where R^1 is trialkylsilyl, R^2 is alkyl and Q is O, are described and claimed in European Patent Application No. 94308806.2 (Publication No. 655454). These methods also require a trialkylsilyl halide and the use of a catalyst.

It is desirable to develop alternate processes that use fewer reagents to make certain α,α-difluoro-β-hydroxy thiol esters, because the use of fewer reagents would lower the overall cost of the synthesis. It is also desirable to synthesize additional α,α-difluoro-β-hydroxy thiol ester compounds which can be useful as intermediates in organic syntheses of valuable pharmaceutical products.

Disclosure of Invention

A first aspect of this invention is α,α-Difluoro-β-hydroxy thiol esters of formula (III)



(III)

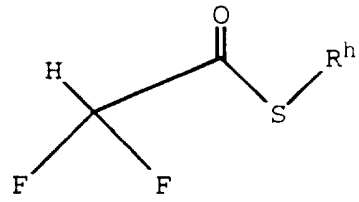
wherein:

R^c and R^d are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, *S-tert*-butyl difluorothioacet-2-yl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings; or

R^c and R^d together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl and substituted C_3-C_8 cycloalkenyl;

R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl and substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings.

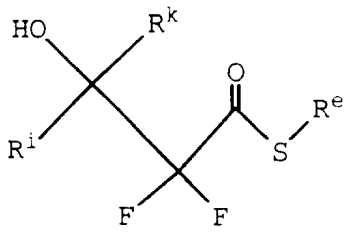
A second aspect of this invention is a difluoroethanethioate compound of formula (IV):



(IV)

wherein R^h is selected from the group consisting of C_3-C_8 cycloalkenyl and substituted C_3-C_8 cycloalkenyl.

A third aspect of this invention is a process to make α,α-difluoro-β-hydroxy thiol esters of formula (IIIA),



(IIIA)

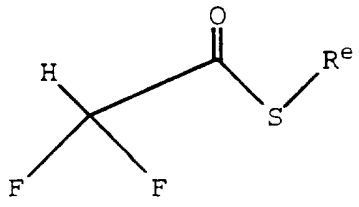
wherein:

R^i and R^k are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, *S-tert*-butyl difluorothioacet-2-yl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, 1,3-dioxolan-4-yl, substituted 1,3-dioxolan-4-yl, C_6-C_{10} fused aromatic rings, substituted C_6-C_{10} fused aromatic rings; or

R^i and R^k together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, and substituted C_3-C_8 cycloalkenyl;

R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, and substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings;

comprising reacting a difluoroethanethioate of formula (IVA)



(IVA)

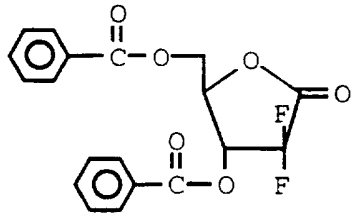
wherein

R^e is as defined previously;

with a second reactant selected from the group consisting of aldehydes, ketones, acid halides and esters; in a solvent and in the presence of a strong base; with the

proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound.

A fourth aspect of this invention is a process to make gemcitabine hydrochloride, the improvement characterized in that the lactone intermediate, 2-deoxy-2,2-difluoro-D-erythro-pentofuranose-1-ulose-3,5-dibenzoate:



is made from D-erythro-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene) pentoic acid, tert-Butyl thioester, with said D-erythro-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene) pentoic acid, tert-Butyl thioester being made by the process of the third aspect of this invention.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The term "alkyl" by itself or as part of another substituent means a monovalent compound having the stated number of carbon atoms containing only carbon and hydrogen, and which my be straight or branched chain. The term is exemplified by compounds containing from 1 to 10 carbon atoms, such as, but not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl (t-butyl), n-pentyl, iso-pentyl, n-hexyl, isohexyl, heptyl, octyl, nonyl and decyl; "C_1-C_4 alkyl" refers to alkyl compound of from 1-4 carbon atoms. "C_1-C_6 alkyl" refers to alkyl compounds of from 1-6 carbon atoms. "C_1-C_{10}" alkyl refers to alkyl compounds of from 1-10 carbon atoms.

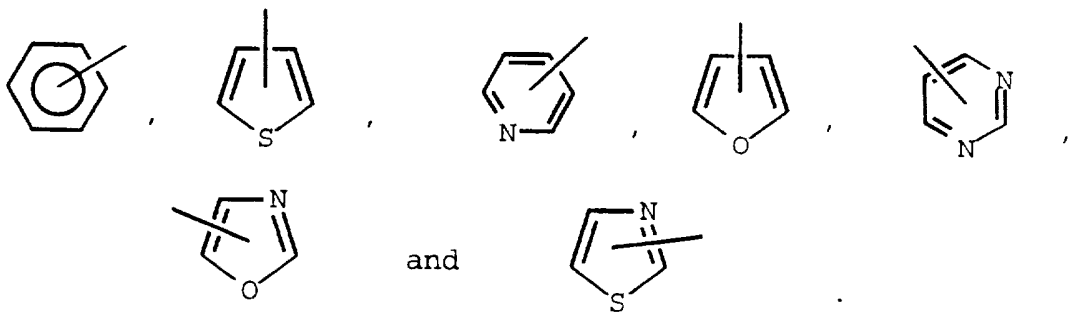
The term "substituted" means one to three hydrogens on the structure have been replaced with a like number of

moieties independently selected from the group consisting of bromo, chloro, iodo, fluoro, C_1-C_{10} alkyl, C_1-C_6 alkoxy, -COOH, amino or hydroxyl, with the proviso that any substituted structure must be so configured that it is sterically feasible, affords a stable structure and is capable of reacting as described herein.

The term "C_1-C_6 alkoxy" refers to monovalent structures of the formula -O-(C_1-C_6 alkyl). Alkoxy includes, but is not limited to, methoxy ($-OCH_3$), ethoxy ($-OCH_2CH_3$), propoxy($-OCH_2CH_2CH_3$), butoxy($-OCH_2CH_2CH_2CH_3$), pentoxy($-OCH_2CH_2CH_2CH_2CH_3$) and hexoxy($-OCH_2CH_2CH_2CH_2CH_2CH_3$).

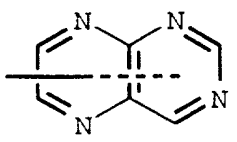
To be "aromatic" a ring must contain one or more groups of atoms in a cyclic array that contains clouds of delocalized π electrons above and below the plane of the atoms; furthermore, the π clouds must contain a total of $(4q+2)$ π electrons, where q is any positive integer.

The term "aryl" refers to:
any 5 or 6 membered aromatic ring that will afford a stable structure containing all carbon atoms; or containing carbon atoms and: one or two nitrogen atoms; one sulfur atom; one oxygen atom; one nitrogen and one sulfur atom; one oxygen atom and one sulfur atom; or one nitrogen and one oxygen atom. The 5-membered ring has one or two double bonds and the 6-membered ring has two or three double bonds. Examples of aryl structures are:



The term "C_6-C_{10} fused aromatic rings" refers to two fused aromatic rings that have at least six and at most ten carbon atoms in the rings. Fused aromatic rings are

monovalent, with the bond to the rest of the structure being attached to any available ring carbon. Fused aromatic rings are carbocyclic or contain from one to four heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. Fused aromatic rings are configured as follows: when there are six carbon atoms present in the rings, there are at least four heteroatoms in the rings and all of these heteroatoms are nitrogen; when there are seven carbon atoms present in the rings, there are at least three heteroatoms present in the rings, only one of which may be sulfur; when there are eight carbon atoms present in the rings there are at least two heteroatoms, which may be the same or different, present in the rings; when there are nine carbon atoms in the ring, there may or may not be one heteroatom in one of the rings; and when there are ten carbon atoms in the rings there are no heteroatoms in the rings. Examples of some "C_6-C_{10} fused aromatic rings" include, but are not limited to, the following structures:



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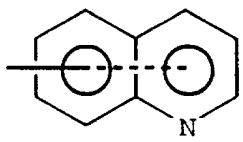

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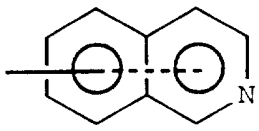

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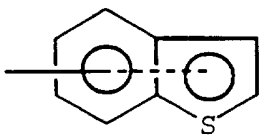

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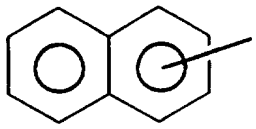
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The solid bond that becomes a dotted line bond present in the above structures indicates that the bond can be attached to any available carbon in any ring that the solid-dotted line intersects.

The term "C_3-C_8 cycloalkyl" refers to saturated carbocyclic ring structures containing from 3 to 8 carbon atoms. Examples of some "C_3-C_8 cycloalkyl" rings include, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "C_3-C_8 cycloalkenyl" refers to carbocyclic ring structures containing from 3 to 8 carbon atoms and one double bond. Examples of some "C_3-C_8 cycloalkenyl" rings include, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

The term "halo" refers to bromo, iodo, fluoro and chloro.

Preferred α,α-Difluoro-β-hydroxy thiol esters compounds of Formula (III) are selected from the group consisting of:

S-tert Butyl 2,2-Difluoro-3-hydroxy-3-phenylpropanethioate;
S-tert Butyl 2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-propanethioate;
S-tert Butyl 2,2-Difluoro-3-hydroxy-octanethioate;
S-tert Butyl 2,2-Difluoro-3-hydroxy-4,4-dimethylpentanethioate;
S-tert Butyl 2,2-Difluoro-3-hydroxy-4-methylpentanethioate;
S-tert Butyl 2,2-Difluoro-3-hydroxy-3-phenylbutanethioate;
Bis(*S-tert* Butyl) 2,2,4,4-Tetrafluoro-3-hydroxy-3-phenylpentane-1,5-dithioate;
S-tert Butyl 1-(2-(2,2-difluoroethane-thioate))cyclohex-2-en-1-ol;
D-*erythro*-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene)pentonic acid, *tert*-Butyl Thiolester; and
D-*threo*-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene)pentonic acid, *tert*-Butyl Thiolester.

Preferred difluoroethanethioate compounds of formula (IV) are selected from the group consisting of:
S-cyclobuten-3-yl difluoroethanethioate;
S-cyclopenten-1-yl difluoroethanethioate;
S-cyclopenten-3-yl difluoroethanethioate;
S-cyclopenten-4-yl difluoroethanethioate;
S-cyclohexen-1-yl difluoroethanethioate;
S-2-hydroxycyclohexen-3-yl difluoroethanethioate;
S-cyclohexen-4-yl difluoroethanethioate;

S-cyclohepten-1-yl difluoroethanethioate;
S-cyclohepten-3-yl difluoroethanethioate;
S-cyclohepten-4-yl difluoroethanethioate;
S-cyclohepten-5-yl difluoroethanethioate;
S-cycloocten-1-yl difluoroethanethioate;
S-cycloocten-3-yl difluoroethanethioate;
S-cycloocten-4-yl difluoroethanethioate and
S-cycloocten-5-yl difluoroethanethioate.

Best Mode for Carrying out the Invention

The first step in the process of the present invention to make the α,α-difluoro-β-hydroxy thiol esters of the present invention is the synthesis of a difluoroethanethioate of Formula (IVA). A preferred method to synthesize a difluoroethanethioate of Formula (IVA) is as follows:

Step 1. At a temperature of between about 20°C and about 100°C, under a suitable inert atmosphere such as nitrogen, argon or neon, add difluoroacetic acid or difluoroacetic anhydride dropwise to a solution of chloride containing compound in an aprotic solvent. The chloride containing compound may be any compound that will, under suitable conditions, release chloride to form an acid chloride. Suitable chloride containing compounds include oxaloyl chloride, thionyl chloride, phosgene, phosphorous oxychloride, phosphorous trichloride and phosphorous pentachloride. The preferred chloride containing compound is oxaloyl chloride. Any aprotic solvent may be used; for example: acetonitrile, tetrahydrofuran, dichloromethane, toluene, glyme and xylene are all useful. A preferred aprotic solvent is acetonitrile. The temperature selected depends upon the choice of chloride containing compound and solvent with about 25°C being suitable when oxaloyl chloride in acetonitrile is used. From the beginning of the reaction, and at any time thereafter, a catalytic amount of a suitable

Lewis acid catalyst may be added. One such suitable Lewis acid catalyst is cobalt (II) chloride. The use of a catalyst in this process is optional.

Step 2. Allow the reactants of step 1 to react from between one and ten hours. The overall reaction time is dependent upon temperature with the higher temperatures having the faster reaction times. Add a sufficient amount of a suitable thiol compound in a dropwise manner, with said suitable thiol compound being of the formula R^e-SH, where R^e is as defined previously, and selected such that the desired R^e component is introduced into the difluoroethanethioate product. For example when R^e is tert-butyl the suitable thiol is 2-methyl-2-propanethiol. A "sufficient amount" is at least one molar equivalent based upon the difluoro starting material.

Step 3. Stir reaction mixture for a sufficient amount of time. A sufficient amount of time could be any time up to 24 hours. Add additional suitable thiol compound, if necessary. The temperature of the reaction mixture can be anywhere between about 20°C and about 100°C with 25°C being the preferred reaction temperature.

Step 4. Perform a standard workup using standard techniques. One such workup is as follows: Pour the reaction mixture over a suitable water immiscible solvent such as diethyl ether (Et_2O) and then wash with a suitable basic aqueous solution such as saturated sodium bicarbonate ($NaHCO_3$) in water.

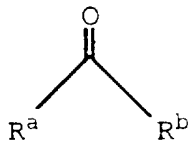
During step 4, the reaction mixture divides into two layers with the desired product contained in the organic layer. The mostly aqueous layer containing the undesired material is separated and discarded in an environmentally sound manner. The layer containing the desired product is dried over a suitable drying reagent such as sodium sulfate (Na_2SO_4).

Once the substituted difluoroethanethioate is made it may be kept either at room temperature or, more preferred, kept in a refrigerator at a temperature below 25°C until it

is needed. The substituted difluoroethanethioate (IVA) is used to begin the process to make the α,α-difluoro-β-hydroxy thiol esters (IIIA) of the instant invention. The preferred substituted difluoroethanethioate for the synthesis of gemcitabine hydrochloride is *S-tert* butyl difluoroethanethioate.

One synthetic route to α,α-difluoro-β-hydroxy thiol esters is to react a substituted difluoroethanethioate (IV) with a second reactant selected from the group consisting of aldehydes, ketones, acid halides and esters in a solvent and in the presence of a strong base; with the proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound.

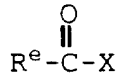
The aldehyde or ketone is of formula (V):



(V)

wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, 1,3-dioxolan-4-yl, substituted 1,3-dioxolan-4-yl, C_6-C_{10} fused aromatic rings and substituted C_6-C_{10} fused aromatic rings, or R^a and R^b together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl and substituted C_3-C_8 cycloalkenyl.

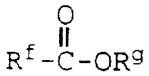
The acid halides are of formula (VI)



(VI)

where X is Cl, Fl, Br or I and R^e has the same definition as before.

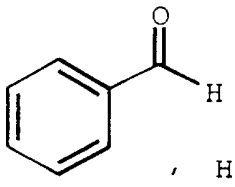
The esters are of formula (VII)



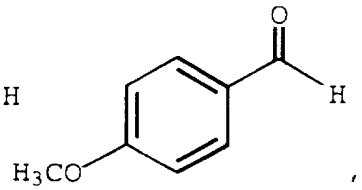
(VII)

where R^f and R^g are independently R^e, where R^e has the same definition as before.

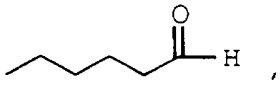
Without intending to be a limiting list, examples of suitable aldehydes, ketones, acid halides and esters are as follows.



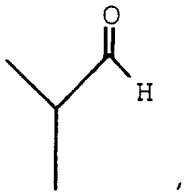
benzaldehyde (PhCHO)



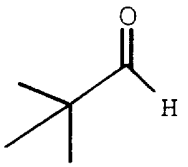
p-anisaldehyde



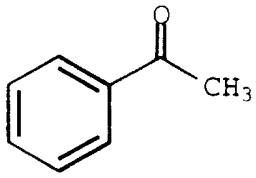
hexanal



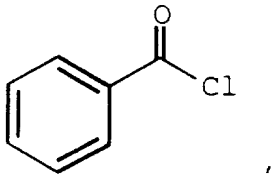
isobutyraldehyde



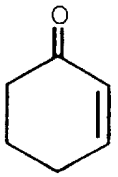
pivalaldehyde



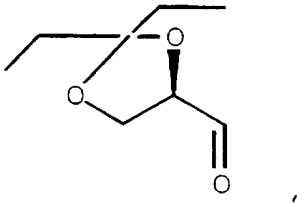
acetophenone



benzoyl chloride

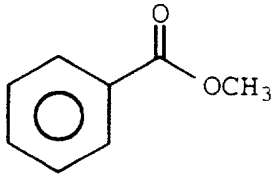


cyclohex-2-en-1-one



2,3-O-(1-ethyl-propylidene)-D-glyceraldehyde

and



methyl benzoate.

Methods to make all of these aldehydes, ketones, acid halides and esters are known in the art of organic chemistry.

The preferred second reactant, for use in the overall synthesis of gemcitabine hydrochloride, is 2,3-O-(3-pentylidene)-D-glyceraldehyde.

The synthesis involves reacting a difluoroethanethioate (IVA) with a second reactant (of formula V, VI or VII) in a solvent, in the presence of a strong base; with the proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound.

The preferred order of addition or reagents is to first add the substituted difluoroethanethioate to the solvent, then add the strong base and allow the three components to react for a sufficient length of time before adding the second reactant to the reaction mixture. Of course, this synthesis is preferably conducted under a suitable inert atmosphere such as nitrogen, argon or neon.

Suitable solvents for the synthesis include hydrocarbons, nitriles and ethers. These solvents include, but are not limited to, toluene, xylene, glyme, tetrahydrofuran, acetonitrile, hexane, heptane, diethyl ether and many other solvents of the general class. The most preferred solvent for this reaction is toluene.

The strong base is any suitable strong base such as amides, alkoxides and hydrides. Suitable strong bases include lithium diisopropylamide (LDA), lithium hexamethylsilazide, triethylamine, pyridine and n-butyl lithium. The preferred solvent is LDA.

The sufficient length of time for the substituted difluoroethanethioate, solvent and strong base to react is anywhere between about thirty seconds and about 1 hour. A preferred length of time is about 2 minutes. If desirable, the reaction mixture is capable of being stabilized at this

point, preferably by keeping it at a temperature below 25°C, and held indefinitely until needed.

The temperature of the substituted difluoro-ethanethioate/solvent mixture is lowered to between at least about -100°C and about 25°C prior to the addition of the strong base. The preferred temperature is about -78°C. After the strong base and the second reactant are added the reaction is allowed to precede at about the same temperature for between about five minutes and about 24 hours.

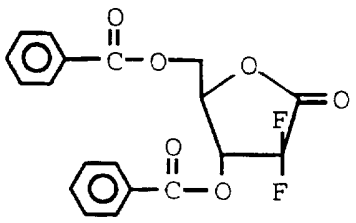
When the reaction has reached a suitable ending point the reaction mixture may be warmed to about room temperature (about 25°C). If necessary, the reaction can be quenched by addition of a suitable quenching agent, such as, phosphate buffer. Once the reaction is ended, the organic layer is separated and concentrated under reduced pressure. The crude desired product can be purified by chromatography. The undesired layer can be disposed of in an environmentally sound manner.

This procedure was followed to make the compounds of the claimed invention.

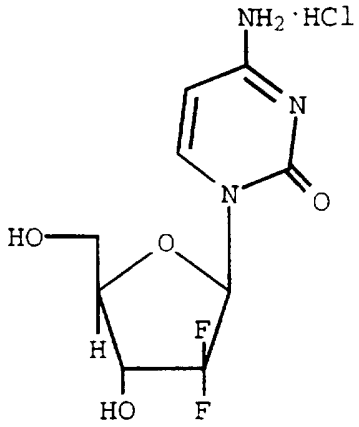
Industrial Applicability

The α,α-difluoro-β-hydroxy thiol esters of the claimed invention can be useful as intermediates in organic syntheses of valuable pharmaceutical products.

After D-erythro (a.k.a. anti-) 2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene) pentoic acid, tert-Butyl thioester is made it can be converted to a lactone of the formula:



by following the procedures described in U.S. Patent No. 4,526,988 (columns 7,8) which is incorporated by reference. The lactone is then converted to an alcohol, forming a protected 2-deoxy-2,2-difluororibose compound. This protected 2-deoxy-2,2-difluororibose compound can be reacted with a nucleobase, according to the process(es) described in European Patent Application No. 93304817.5 (Publication No. 577 303 A1), European Patent Application No. 84301463.0 (Publication No. 122 707), and in European Patent Application No. 88307750.5 (Publication No. 306 190), to form nucleosides, including pharmaceutically acceptable salts of nucleosides, with said nucleosides, and pharmaceutically acceptable salts of said nucleosides, having utility as pharmaceutical products. One such nucleoside is gemcitabine hydrochloride:



(II)

which is a commercially available (sold under the trademark, GEMZAR® by Eli Lilly and Company, Indianapolis, IN) anti-neoplastic drug.

The following examples are illustrative only and are not intended to limit the scope of the invention in any way.

Examples

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example: "°C" refers to degrees Celsius; "N" refers to normal or normality; "mol" refers to mole or moles; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mg" refers to milligrams; "ml" refers to milliliter or milliliters; "mp" refers to melting point; "M" refers to molar or molarity; "mm Hg" refers to millimeters of mercury; "Mass spec." refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy.

Unless otherwise noted, all chemicals were reagent grade materials from commercial suppliers and were used without further purification. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz and were internally referenced to residual $CHCl_3$ (7.24 ppm). ^{13}C NMR spectra were recorded at 75.5 MHz and were referenced to $CHCl_3$ (77.0 ppm). ^{19}F NMR spectra were recorded at 282.4 MHz and were referenced to internal C_6F_6 (-162.9 ppm). Assignments were derived from COSY and H/C correlation spectra and from consideration of the F/C coupling patterns observed in the carbon spectra. IR spectra were recorded as thin films.

Example 1

S-tert Butyl Difluoroethanethioate

To a solution of oxaloyl chloride (9.08 mL, 104 mmol) in acetonitrile (ACN) (50 mL) at 25 °C was added dropwise difluoroacetic acid (6.55 mL, 104 mmol). After 3 hours, 2-methyl-2-propanethiol (11.74 mL, 104 mmol) was added dropwise followed by cobalt(II) chloride (10 mg). After being stirred at room temperature for 18 hours, additional 2-methyl-2-propanethiol (4.0 mL, 35.4 mmol) was added. After

2 hours, the solution was poured onto Et_2O (500 mL) and washed with saturated $NaHCO_3$ (2 x 300 mL) and H_2O (2 x 300 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a red oil. Vacuum distillation at 30 mm Hg gave S-tert butyl difluoroethane-thioate (8.26 g, 47%) as a colorless oil: bp 59-63 °C (30 mm Hg); ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 5.67 (t, 1H, J = 54 Hz); ^{13}C NMR ($CDCl_3$) δ 29.45, 49.32, 108.94 (t, J = 255 Hz), 191.23 (t, J = 28 Hz); ^{19}F NMR ($CDCl_3$) δ -123.65 (d, J = 55 Hz); IR (film, cm^{-1}) 2969, 1684, 1154, 1093, 1064. Anal. Calcd for $C_6H_{10}F_2OS$: C, 42.84; H, 5.99. Found: C, 43.06; H, 6.15.

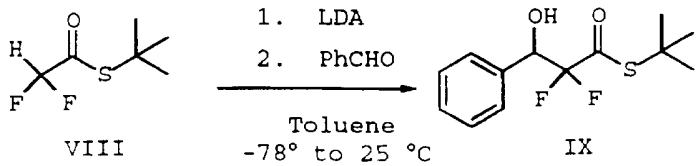
Example 2

General Process to Make α,α-difluoro-β-hydroxy thiol esters using S-tert butyl difluoroethanethioate as a starting material

To a solution of S-tert butyl difluoroethanethioate (VIII) (0.152 mL, 1.00 mmol) from Example 1 in toluene (10 mL) at -78 °C was added dropwise over 1 min LDA (0.550 mL of 2.0 M solution in heptane/THF/ethylbenzene, 1.10 mmol). After 2 min, the second reactant (aldehyde (V), ketone (V), acid chloride (VI) or ester (VII) (1.10 mmol)) was added dropwise. After 1 hour, the reaction was warmed to 25°C over 1 hour and quenched by addition of phosphate buffer (5 mL, 0.5 M, pH = 7). The resulting organic layer was concentrated under reduced pressure. The crude product was isolated and purified by chromatography.

Example 3

Synthesis of *S-tert* Butyl 2,2-Difluoro-3-hydroxy-3-phenylpropanethioate (IX)

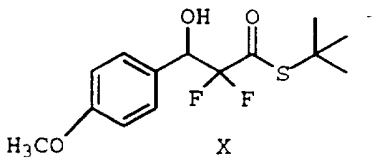


VIII IX

Following the procedure of Example 2, reaction of benzaldehyde (0.112 mL, 1.10 mmol) affords *S-tert* butyl 2,2-difluoro-3-hydroxy-3-phenylpropanethioate. (IX) (192 mg after isolation and purification, 70%) as a colorless oil, which was chromatographed using 10% EtOAc in hexane as eluent: ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.52 (br, 1H), 5.16 (dd, 1H), 7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 29.31, 49.05, 73.49 (t, J = 24 Hz), 114.78 (t, J = 260 Hz), 127.80, 128.32, 129.10, 134.56, 193.47 (t, J = 30 Hz); ^{19}F NMR ($CDCl_3$) δ -112.88 (J_{FF} = 259 Hz, J_{FH} = 9 Hz), -119.22 (J_{FF} = 259, J_{FH} = 15 Hz); IR (film, cm^{-1}) 3442, 2967, 1673, 1660, 1456, 1367, 1194, 1078, 917.

Example 4

S-tert Butyl 2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-propanethioate (X)

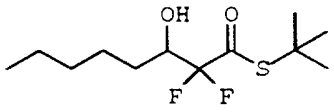


X

Following the procedure of Example 2, reaction of *p*-anisaldehyde (0.134 mL, 1.10 mmol) affords compound (X) (187 mg after isolation and purification, 62%) as a white solid, which was chromatographed using 5% EtOAc in hexane as eluent: mp 73-75 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (s 9H), 2.49 (br, 1H), 3.79 (s, 3H), 5.09 (dd, 1H), 6.87 (d, 2H), 7.31 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 29.34, 49.04, 55.26, 73.10 (t, J = 25 Hz), 113.78, 114.85 (t, J = 260 Hz), 126.58, 129.11, 160.19, 193.57 (t, J = 31 Hz); ^{19}F NMR ($CDCl_3$) δ-113.13 (J_{FF} = 258 Hz, J_{FH} = 8 Hz), -119.35 (J_{FF} = 258, J_{FH} = 15 Hz); IR (film, cm^{-1}) 3474, 2960, 1683, 1618, 1519, 1453, 1249, 1177, 1085, 1038, 920.

Example 5

Synthesis of *S-tert* Butyl 2,2-Difluoro-3-hydroxy-octanethioate (XI)

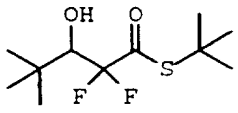


XI

Following the procedure of Example 2, reaction of hexanal (0.132 mL, 1.10 mmol) affords compound (XI) (164 mg after isolation and purification, 61%) as a colorless oil, which was chromatographed using 10% EtOAc in hexane as eluent: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.30 (m, 6H), 1.51 (s, 9H), 1.60 (m, 2H), 1.99 (br, 1H), 4.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.43, 24.88, 29.31, 29.47, 31.41, 49.10, 71.47 (t, J = 25 Hz), 115.57 (t, J = 259 Hz), 193.55 (t, J =33 Hz); ^{19}F NMR ($CDCl_3$) δ -114.11 (J_{FF} = 261 Hz, J_{FH} = 9 Hz), -119.94 (J_{FF} = 261, J_{FH} = 14 Hz); IR (film, cm^{-1}) 3450, 2965, 2935, 2859, 1683, 1461, 1367, 1121, 1075.

Example 6

Synthesis of *S-tert* Butyl 2,2-Difluoro-3-hydroxy-4,4-dimethylpentanethioate (XII)



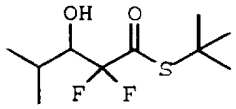
XII

Following the procedure of Example 2, reaction of pivalaldehyde (0.119 mL, 1.10 mmol) affords compound (XII) (107 mg after isolation and purification, 42%) as a colorless oil, which was chromatographed using 10% EtOAc in hexane as eluent: ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.47 (s, 9H), 2.42 (d, 1H), 3.77 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ 26.48, 29.36, 34.64, 48.78, 76.76 (t, J = 22 Hz), 117.38 (t, J = 262 Hz), 194.33 (t, J = 30 Hz); ^{19}F NMR ($CDCl_3$) δ -104.84 (J_{FF} = 264 Hz, J_{FH} =

7 Hz), -118.04 (J_{FF} = 264, J_{FH} = 20 Hz); IR (film, cm^{-1}) 3520, 2960, 1677, 1597, 1460, 1374, 1164, 1064, 854.

Example 7

Synthesis of *S-tert* Butyl 2,2-Difluoro-3-hydroxy-4-methylpentanethioate (XIII)

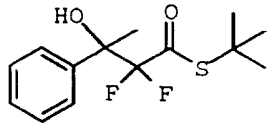


XIII

Following the procedure of Example 2, reaction of isobutyraldehyde (0.100 mL, 1.10 mmol) affords compound (XIII) (105 mg after isolation and purification, 44%) as a colorless oil, which was chromatographed using 10% EtOAc in hexane as eluent: ^1H NMR ($CDCl_3$) δ 0.99 (1, 6H), 1.49 (s, 9H), 1.95 (m, 1H), 2.42 (br, 1H), 3.81 (ddd, 1H); ^{13}C NMR ($CDCl_3$) δ 16.84, 19.93, 28.44, 29.38, 49.96, 75.01 (t, J = 23 Hz), 116.44 (t, J = 261 Hz), 193.90 (t, J = 30 Hz); ^{19}F NMR ($CDCl_3$) δ -110.50 (J_{FF} = 262 Hz, J_{FH} = 9 Hz), -117.80 (J_{FF} = 262, J_{FH} = 17 Hz); IR (film, cm^{-1}) 3474, 2967, 1677, 1479, 1466, 1367, 1163, 1064, 893.

Example 8

Synthesis of *S-tert* Butyl 2,2-Difluoro-3-hydroxy-3-phenylbutanethioate (XIV)



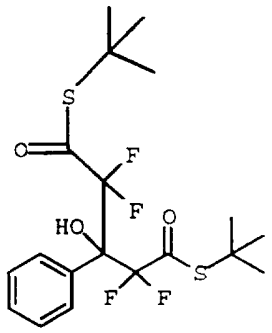
XIV

Following the procedure of Example 2, reaction of acetophenone (0.128 mL, 1.10 mmol) affords compound (XIV) (200 mg after isolation and purification, 69%) as a colorless oil, which was chromatographed using 10% EtOAc in hexane as eluent: ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.72 (t, 3H), 3.39 (br, 1H), 7.33 (m, 3H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.24

(t, J = 3 Hz), 29.10, 49.00, 76.11 (t, J = 25 Hz), 114.80 (t, J = 265 Hz), 126.33, 128.04, 128.09, 139.49, 194.66 (t, J = 32 Hz); ^{19}F NMR ($CDCl_3$) δ -114.26, -114.91 (J_{FF} = 259); IR (film, cm^{-1}) 3506, 2966, 1676, 1446, 1367, 1120, 1053, 884.

Example 9

Synthesis of Bis(*S-tert* Butyl) 2,2,4,4-Tetrafluoro-3-hydroxy-3-phenylpentane-1,5-dithioate (XV)

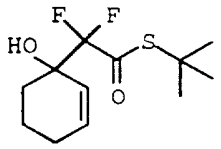


XV

Following the procedure of Example 2, reaction of benzoyl chloride (0.128 mL, 1.10 mmol) affords compound (XV) (170 mg after isolation and purification, 77%) as a white solid, which was chromatographed using 10% EtOAc in hexane as eluent: mp 80 °C; ^1H NMR ($CDCl_3$) δ 1.35 (s,18H), 4.84 (br, 1H), 7.35 (m, 3H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.14, 49.43, 78.75 (t, J = 23 Hz), 113.44 (t, J = 271 Hz), 127.84, 127.93, 129.42, 131.35, 192.48 (t, J = 31 Hz); ^{19}F NMR ($CDCl_3$) δ -109.93, -110.16 (J_{FF} = 261); IR (film, cm^{-1}) 3473, 2960, 1697, 1657, 1466, 1374, 1143, 966.

Example 10

Synthesis of *S-tert* Butyl 1-(2-(2,2-difluoroethane-thioate))cyclohex-2-en-1-ol (XVI)

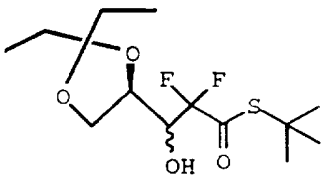


XVI

Following the procedure of Example 2, reaction of cyclohex-2-en-1-one (0.106 mL, 1.10 mmol) affords compound (XVI) (173 mg after isolation and purification, 65%) as a colorless oil, which was chromatographed using 15-20% EtOAc in hexane as eluent: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9H), 1.72 (m, 1H), 1.80 (m, 1H), 2.03 (m, 1H), 2.31 (br, 1H), 5.77 (d, 1H), 6.10 (ddd, 1H); ^{13}C NMR ($CDCl_3$) δ 17.42, 24.82, 29.48, 29.53, 49.12, 71.64 (t, J = 26 Hz), 115.98 (t, J = 263 Hz), 123.67, 135.39, 193.81 (t, J = 30 Hz); ^{19}F NMR ($CDCl_3$) δ -115.76, -116.72 (J_{FF} = 257); IR (film, cm^{-1}) 3447, 2960, 2874, 1683, 1460, 1368, 1085.

Example 11

Synthesis of D-*erythro*- and D-*threo*-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene)pentonic acid, *tert*-Butyl Thiolester (XVII, XVIII)



XVII/XVIII Anti/Syn = 85/15

2,3-*O*-(3-pentylidene)-D-glyceraldehyde was synthesized by the procedure published in "2,3-*O*-(3-Pentylidene)-D-glyceraldehyde and 2,3-*O*-(3-Pentylidene)-L-glyceraldehyde: Convenient Glyceraldehyde Surrogates Obtained via a Novel

Periodate-Based Oxidation System", Schmid, C.R.: Bradley, D.A., Synthesis, 1992, 587-590.

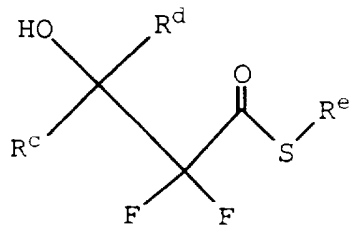
Following the procedure of Example 2, reaction of 2,3-O-(3-pentylidene)-D-glyceraldehyde (0.155 mL, 1.00 mmol) affords a mixture of compounds XVII and XVIII. Chromatography of the residue with 5% and then 20% EtOAc/hexane as eluents gave *erytho*-XVII (172 mg, 53%) and *threo*-XVIII (37 mg, 11%) as colorless oils.

Data for *erythro*-XVII: This compound was crystallized from hexane, mp 39-40 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (s, 6H), 1.50 (s, 9H), 1.60 (q, 2H), 1.62 (q, 2H), 2.47 (d, 1H), 3.96 (m, 1H), 4.06 (m, 1H), 4.23 (m, 1H), 4.32 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.90, 8.01, 28.94, 29.28, 29.40, 49.07, 65.45 (t, J = 3.8 Hz), 71.05 (t, J = 23 Hz), 73.56, 113.19, 115.21 (t, J = 260), 192.35 (t, J = 31 Hz); ^{19}F NMR ($CDCl_3$) δ -115.3 (J_{FF} = 263 Hz, J_{FH} = 10 Hz), -117.5 (J_{FF} = 263 Hz, J_{FH} = 15 Hz); IR (film, cm^{-1}) 3427, 2973, 1683, 1460, 1209, 1177, 1137, 1078.

Data for *threo*-XVIII: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 0.89 (t, 3H), 1.50 (s, 9H), 1.63 (q, 2H), 1.66 (q, 2H), 2.90 (d, 1H), 3.81 (m, 1H), 3.94 (m, 1H), 4.10 (m, 1H), 4.31 (m, 1H) ; ^{13}C NMR ($CDCl_3$) δ 7.97, 8.04, 29.02, 29.40, 29.52, 49.15, 66.53, 70.55 (J = 25 Hz), 72.36, 114.02, 114.7 (J = 263 Hz), 192.58 (J = 29 Hz); ^{19}F NMR ($CDCl_3$) δ -108.78 (J_{FF} = 267 Hz, J_{FH} = 6 Hz), -120.01 (J_{FF} = 267, J_{FH} = 16 Hz); IR (film, cm^{-1}) 3533, 3453, 2973, 1677, 1453, 1170, 1137, 1084.

What is claimed is:

1. α,α-Difluoro-β-hydroxy thiol esters of formula (III)



(III)

wherein

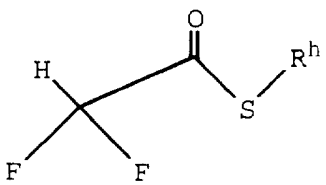
R^c and R^d are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, *S-tert*-butyl difluorothioacet-2-yl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings; or

R^c and R^d together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl and substituted C_3-C_8 cycloalkenyl;

R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl and substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings.

2. An α,α-difluoro-β-hydroxy thiol ester of Claim 1 in which R^e is tert-butyl.

3. A difluoroethanethioate compound of formula (IV);

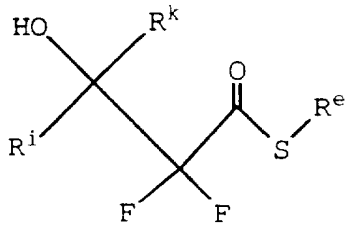


(IV)

wherein

R^h is selected from the group consisting of C_3-C_8 cycloalkenyl and substituted C_3-C_8 cycloalkenyl.

4. A process to make α,α-difluoro-β-hydroxy thiol esters of formula (IIIA),



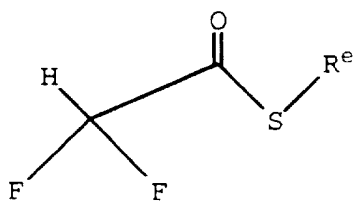
(IIIA)

wherein

R^i and R^k are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, *S-tert*-butyl difluorothio-acet-2-yl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, 1,3-dioxolan-4-yl, substituted 1,3-dioxolan-4-yl, C_6-C_{10} fused aromatic rings, substituted C_6-C_{10} fused aromatic rings; or

R^i and R^k together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, and substituted C_3-C_8 cycloalkenyl;

R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings; comprising reacting a difluoroethanethioate of formula (IVA)



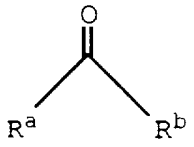
(IVA)

wherein

R^e is as defined previously;

with a second reactant selected from the group consisting of aldehydes, ketones, acid halides and esters; in a solvent and in the presence of a strong base; with the proviso that the process is conducted in the absence of a catalyst and in the absence of a silyl containing compound.

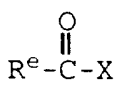
5. The process of Claim 4 in which said second reactant is an aldehyde or ketone of formula (V)



(V)

wherein R^a and R^b are independently selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, aryl, substituted aryl, 1,3-dioxolan-4-yl, substituted 1,3-dioxolan-4-yl, C_6-C_{10} fused aromatic rings and substituted C_6-C_{10} fused aromatic rings; or R^a and R^b together make up a ring selected from the group consisting of C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl and substituted C_3-C_8 cycloalkenyl.

6. The process of Claim 4 in which said second reactant is an acid halide of formula (VI)

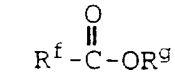


(VI)

where X is chloro, bromo, fluoro or iodo and

R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings.

7. The process of Claim 4 in which said second reactant is an ester of formula (VII)

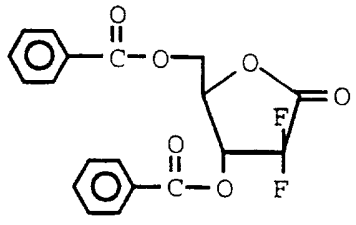


(VII)

where R^f and R^g are independently R^e, where R^e is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, aryl, substituted aryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, substituted C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkenyl, C_6-C_{10} fused aromatic rings, and substituted C_6-C_{10} fused aromatic rings.

8. The process of Claim 4 in which said α,α-difluoroethanethioate is S-tert-butyl difluoroethanethioate and said second reactant is 2,3,-O-(3-pentylidene)-D-glyceraldehyde.

9. A process to make gemcitabine hydrochloride, the improvement characterized in that the lactone intermediate, 2-deoxy-2,2-difluoro-D-erythro-pentofuranose-1-ulose-3,5-dibenzoate:



is made from D-erythro-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene) pentoic acid, tert-Butyl thioester, with said D-erythro-2-Deoxy-2,2-difluoro-4,5-O-(1-ethylpropylidene) pentoic acid, tert-Butyl thioester being made by the process of Claim 5.

10. A process to make α,α-difluoro-β-hydroxy thiol esters of formula (IIIA) substantially as hereinbefore described with reference to any one of the examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19867

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07H 19/073; C07C 327/06, 327/08
US CL : 536/28.5; 558/250, 252
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/28.5; 558/250, 252

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE: Structure-based search in File REGISTRY; additional search term: gemcitabine.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HERSHFIELD, R. et al.Hydrolysis of Acyl-activated Thiol Esters. Acid Catalysis amd Acid Inhibition. J. Am. Chem. Soc. 1973, Vol. 95, No. 12, pages 3994-4002, note especially page 4001, Experimental Section, fourth paragraph.	3
A	Chou, T.S. Stereospecific Synthesis of 2-Deoxy-22,difluororibonolactone and its Use in the Preparation of 2'-Deoxy-2',2'-difluoro-β-D-ribofuranosyl Pyrimidine Nucleosides: The Key Role of Selective Crystallization. Synthesis. Issued 1991, No. 1, pages 565-570.	

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 MARCH 1997	Date of mailing of the international search report 11 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL G. AMBROSE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/19867

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.