

An Efficient Synthesis of β -L-5-[(*E*)-2-bromovinyl]-1-((2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolane-4-yl) uracil] (L-BH DU) *via* Chiral Pure L-Dioxolane

[001] Field of the Invention

[002] The present invention relates to novel methods for synthesizing L-BDHU and related starting materials and intermediate compounds from (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**7**) in as few as 7 steps. The present invention eliminates expensive chiral purification of L-dioxolane (**11**), resulting in an enantiomerically enriched (ee > 99%) compound. The optically pure compound **11** was utilized to construct L-BH DU (**15**) and its monophosphate prodrug (POM-L-BH DU, **22**). Novel methods of synthesis and novel intermediate compounds represent additional embodiments of the present invention.

[003] Related Applications

[004] This application claims the benefit of priority of United States provisional application serial numbers us63/621,722, filed 17 January 2024 and us63/716,343, filed 5 November 2024, the entire contents of each application in their entirety being incorporated by reference in this application.

[005] Background and Overview of the Invention

[006] Varicella zoster virus (VZV) is a highly contagious alpha herpesvirus that causes chickenpox (varicella) on primary infection and shingles (herpes zoster) on reactivation from latency.¹ The Centers for Disease Control and Prevention (CDC) has estimated that in the U.S., there are annually approximately one million cases of zoster.² People over the age of 50, immunocompromised persons, HIV-infected people, and organ transplant patients are at a higher risk of VZV infections.³ The VZV infection induces significant complications, it causes painful skin vesicular rash that contains abundant infectious virus. A significant problem of shingles is postherpetic neuralgia, which is long-lasting pain that persists for months or years even after the rashes healed.⁴ Accordingly, there is a need for effective and safe new antivirals for the treatment and management of VZV infection. However, vaccination is available for both stages of VZV infections, and adjuvant subunit vaccine is approved to prevent shingles, but these only apply for use in healthy persons.⁵

[007] Acyclovir (ACV), valacyclovir (VACV), and famciclovir (FCV, **FIGURE 1**) are approved drugs and are being used to treat VZV infections.⁶ However, these approved drugs are not highly effective against VZV, and large doses and long-term use are required, which usually promotes drug resistance.⁷ Cidofovir (CDV), a broad-spectrum antiviral, is active against VZV, but it is associated with nephrotoxicity and lacks oral administration.⁶ Another antiviral drug, brivudine (BVDU), is approved to treat VZV infection in Europe.^{8,9} A major drawback associated with BVDU is that it metabolizes in the liver into bromovinyl-uracil (BVU).⁸ BVU impedes the activity of dihydropyridine dehydrogenase (DPD), which catabolizes thymidine and uracil. Thus, cancer treating patients with 5-fluorouracil (5-FU) creates a life threatening concern with the co-treatment of brivudine.¹⁰ Due to the significant adverse effects of currently approved drugs, there is an urgent need for new antivirals to treat VZV and its resistant strains.

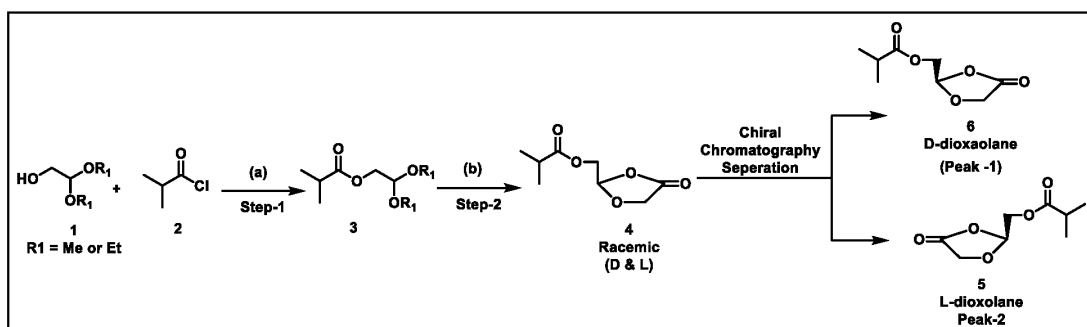
[008] For the last two decades, in search of better antiviral compounds against VZV, herpes simplex viruses 1 & 2, and Epstein Barr virus (EBV), the research group of the present inventors have been involved in the discovery of modified D and L-dioxolane-nucleos(t)ides. In these efforts, the inventors have invented, 2-(hydroxymethyl)-1,3-dioxolan-4-yl]5-vinyl uracil (L-HDVD, **Figure 2**)¹¹ 2-bromovinyl-2-(hydroxymethyl)-1,3 dioxolan uracil (L-BHDU)^{12, 13} with potent antiviral activity against EBV and VZV & HSV1. L-HDVD is highly active against EBV (EC₅₀ value of 0.01 μ M) and Kaposi's sarcoma-associated herpesvirus (KSHV) (EC₅₀ = 0.09 μ M).¹¹ L-BHDU has demonstrated an EC₅₀ value of 0.25 μ M without any cytotoxic in human foreskin fibroblasts (HFFs) up to 200 μ M, with a selectivity index (SI) of >909.¹² In *in vivo* studies, L-BHDU significantly reduces the viral load in comparison to the ACV and VACV. It is noteworthy to mention that in the metabolic studies, it was found that L-BHDU does not inhibit DPD and would have a better safety and antiviral profile than brivudine.¹²

[009] Recently, to increase cellular bioavailability and uptake of L-BHDU with enhanced pharmacokinetic properties, inventors has developed L-BHDU monophosphate pivaloyloxymethyl ester prodrug (POM-L-BHDU-MP, **FIGURE 2**).^{14, 15} POM-L-BHDU-MP has expressed similar antiviral activity to L-BHDU in infected cells. In contrast, POM-L-BHDU-MP was superior to L-BHDU in a VZV mouse model.¹⁶ The pharmacokinetic (PK) studies revealed that POM-L-BHDU-MP had better oral absorption compared to L-BHDU.¹⁴

Recent conducted PK studies also revealed that POM-L-BHDU-MP releases almost equal concentration of L-BHDU in blood either *via* IV route or oral administration. This proves that the POM-L-BHDU-MP is orally demonstrate equally effect in compared to IV administration. Repeated assay in humanized mice showed that POM-L-BHDU-MP was effective orally given once per day at 11.3 mg/kg and higher, which indicates its potency and bioavailability *in vivo*.¹⁶ POM-L-BHDU-MP was evaluated as a topical treatment for VZV and HSV infections in a human skin explant model, and it was highly effective against both viruses at 0.2% formulated in cocoa butter.¹⁶ Based on these findings, POM-L-BHDU-MP was selected for the preclinical development against the VZV & HSV-1 infections.

[010] To develop POM-L-BHDU-MP as a preclinical candidate, further extended biological, pharmacokinetic, and toxicological studies are required, which demands a significant amount of POM-L-BHDU-MP. Consequently, the development of a robust, practical, and cost-effective synthetic procedure of POM-L-BHDU-MP was needed. Earlier synthesis of L-BHDU was carried out by the L-dioxolane key intermediate (**5**, **FIGURE 3**, **Scheme 1**). The procedure reported by Sznajdman et al.^{17, 18} was used for the synthesis of L-dioxane **5**, which is a critical intermediate for the synthesis of L-modified nucleoside analogs.

[011] **Scheme 1**. Synthesis of chiral pure D & L dioxolane *via* chiral separation of racemic dioxolane (**4**).¹⁷



Reagents and Conditions: (a) DMAP, Et₃N, *tert*-butylmethyl ether, rt; (b) BF₃·Et₂O, acetonitrile 0°C-rt.

[012] However, this reported process has involved the chiral chromatographic separation of racemic dioxolane (**4**), which limits the scalable and commercial utility of Scheme 1.

Furthermore, during the large-scale synthesis, in the presence of excess boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{Et}_2\text{O}$), the decomposition of intermediate **4** was observed. Chiral pure D & L-dioxolane (**5** & **6**) also revealed stability issues in courses of chiral separation, and undesired impurities were formed during the concentration or lyophilization of collected chiral pure fractions. These downsides of **Scheme 1** limit the process for a large-scale synthesis of both L & D dioxolane (**5** & **6**). To overcome the challenges of Scheme 1, herein inventors report a scalable, practical synthesis of L-BH DU in 7 steps from the methyl (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, **7**. However, the reported process in this communication is a revised procedure, especially for the synthesis of L-Dioxolane, which was previously reported by Bera S. et al.¹⁹ Earlier reported procedure and patent encountered many unclear information and challenges medicinal chemists for the specific synthesis of chiral pure L-dioxolane (enantiomeric excess $\geq 99\%$).²⁰ Nevertheless, the present application is directed to a straightforward synthesis and purification of chiral pure L-dioxolane *via* diastereomeric chiral amine salt formation. This novel procedure also eliminates chiral separation and certain step column chromatography, which makes the process feasible for the scalable synthesis of POM-L-BH DU-MP for clinical and commercial applications.

[013] **Brief Description of the FIGURES**

[014] **FIGURE 1** shows the chemical structures of a number of antiviral drugs for the treatment of VZV infection.

[015] **FIGURE 2** shows the chemical structures of L-HDVD, L-BH DU and POM-L-BH DU-MP

[016] **FIGURE 3, SCHEME 1**, shows the chemical synthesis of chiral pure D & L dioxolane *via* chiral separation of racemic dioxolane (**4**).¹⁷ *Reagents and Conditions*: (a) DMAP, Et_3N , *tert*-butylmethylether, rt; (b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, acetonitrile 0° C-rt.

[017] **FIGURE 4, SCHEME 2**, shows the synthesis of L-BH DU *via* chiral pure critical intermediate L-dioxolane (**11**). *Reagents and Conditions*: (a) *p*-TSA, or Dowex 50W X8 toluene 80 °C; (b) 1 M aqueous LiOH, THF, 0 °C- rt; (c) i) (*S*)-phenylethylamine, acetonitrile 75 °C- rt; $\text{BF}_3 \cdot \text{Et}_2\text{O}$, acetonitrile 0 °C-rt; (ii) EtOAc:IPA (3:1), rt; (d) 1 N aqueous

HCl, rt; (e) manganese diacetate (Mn(II)(OAc)_2), diacetoxy iodobenzene, acetic acid, 2-Me-THF 65 °C, or alternatively Pb(OAc)_4 , pyridine, acetonitrile, 0 °C-rt; (f) Bromo vinyl uracil, TBDMSOTf, TMSI, DCM, rt; (g) BCl_3 , DCM, -78 °C.

[018] **FIGURE 5** shows (a) ORTEP diagram of compound **10** confirms the relative stereochemistry of L-dioxolane. (b) Shows the stereo structure of D and L-dioxolane; in the case of D-dioxolane C-2 and C-4 hydrogen are cis, whereas in L-dioxolane C-2 and C-4 hydrogen atoms are trans to each other.

[019] **FIGURE 6, SCHEME 3** shows a revised synthesis of L-BH DU *via* intermediate **18** from L-dioxolane **11**. *Reagents and Conditions*: (a) 5% Pd/C, H_2 gas, MeOH, r.t.; (b) Isobutyric anhydride, pyridine, DMAP, DCM, 0 °C - rt; (c) Mn(OAc)_2 , diacetoxy iodobenzene, acetic acid, 2-Me-THF, 65°C, or alternatively Pb(OAc)_4 , pyridine, acetonitrile, 0°C-rt ; (d) Bromovinyl-uracil, TBDMSOTf, TMSI, DCM, rt.; (e) Solution of 7 N NH_3 in methanol rt.

[020] **FIGURE 7, SCHEME 4** shows the synthesis of POM-L-BH DU-MP prodrug *via* L-BH DU (**15**). *Reagents and conditions*: (a) NMI, THF, 0 °C to rt, 3 h.

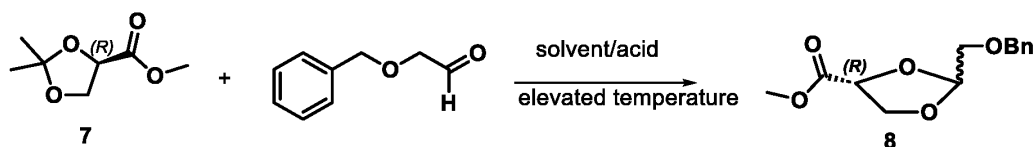
[021] **Brief Description of the Invention**

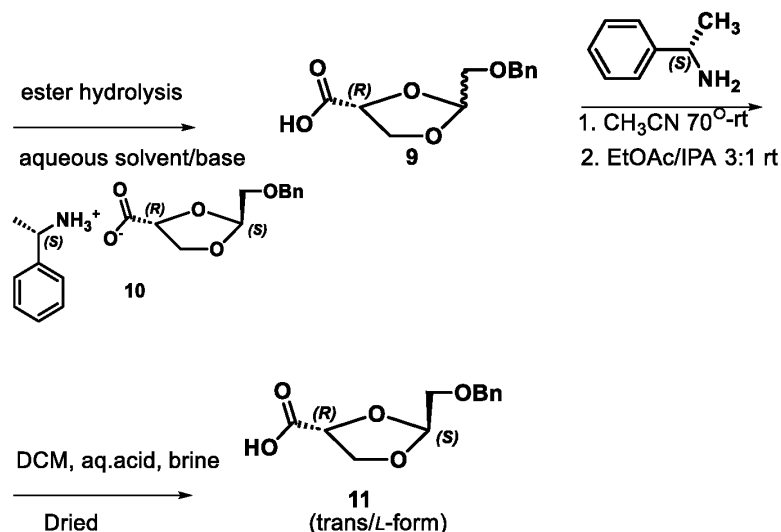
[022] In embodiments, the present invention is directed to methods of synthesizing L-BH DU (**15**) through chemical precursors and chemical intermediates resulting in efficient syntheses of

L-BH DU (**15**), POM-L-BH DU-MP (**22**) and a number of precursors and/or chemical intermediates which are used in the syntheses of these compounds.

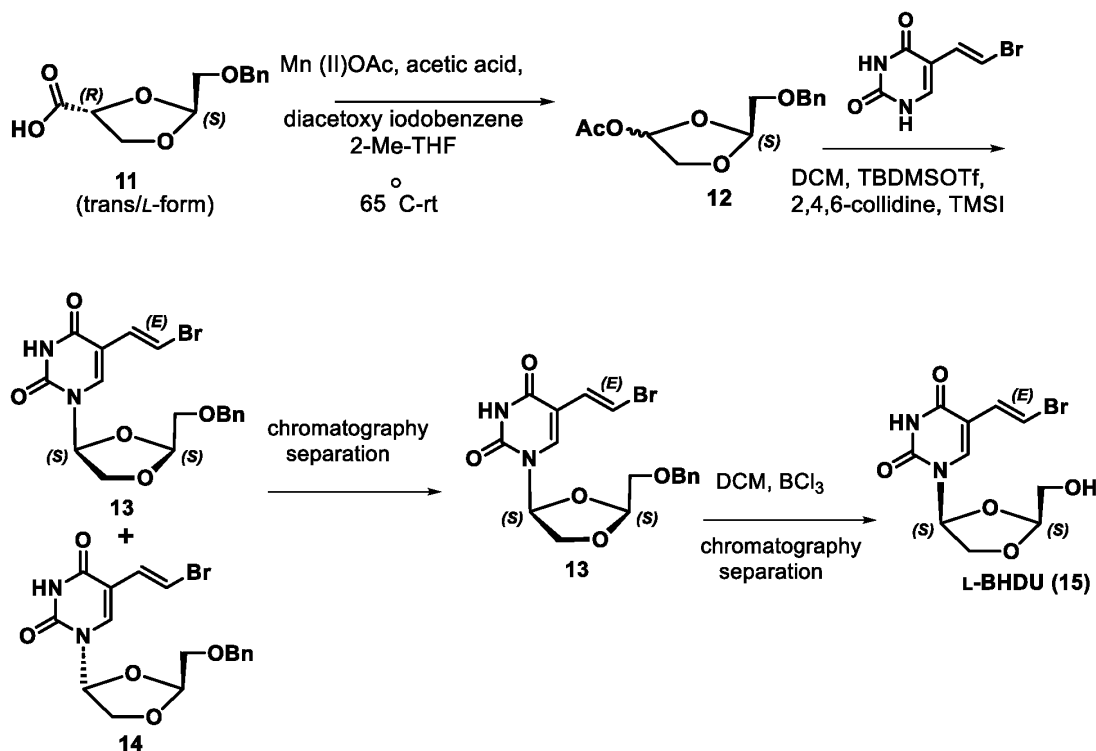
[023] In an embodiment, the present invention is directed to a method for synthesizing L-BH DU (**15**) from compound (7) pursuant to the synthetic steps which are described in enclosed FIGURE 4, Scheme 2. Compound 7 is first converted to pure key intermediate L-dioxolane acid (**11**) in four steps and L-dioxolane acid **11** is thereafter converted to L-BH DU (**15**) by one of two synthetic routes as disclosed herein below. Pursuant to a first embodiment

method, methyl-(*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (compound **7**) is used to produce L-dioxolane compound **11** by first being reacted with 2-(benzyloxy)acetaldehyde in solvent (preferably toluene) with a catalytic amount of acid (preferably, toluene/*p*-toluene sulfonic acid or Dowex 50W X8)) at elevated temperature (above room temperature, e.g. 60-100 °C for several hours) to provide a diastereomeric mixture (often 1:1) of benzyl-protected dioxolane ester compound **8** in high yield (often >70%) as depicted herein below. Compound **8** is thereafter subjected to ester hydrolysis in aqueous solvent/base (e.g. 1 M LiOH/THF) to remove the ester group and provide the corresponding benzyl protected carboxylate compound **9**, often in greater than 90% yield. Compound **9** is complexed with (*S*)-phenylethylamine *via* formation of acid base salt to provide substantially pure (i.e., *de* ≥ 90%, often *de* ≥ 99%) compound **10** by first complexing the benzyl protected racemic carboxylate compound **9** with (*S*)-phenylethylamine in solvent (e.g. acetonitrile, preferably conducted for about 2 hours at an elevated temperature of 70 °C followed by cooling to room temperature for another 2 hours) to provide a salt of compound **10** which contains a mixture of both D and L isomers (15% D, 85% L, *de* ≥ 70%, referenced as compound mixture **10M**) which was precipitated and/or crystallized to provide a salt mixture of D and L isomers of acid amine **10** (referred to as compound **10M**), which mixture was taken up (preferably, several times) in a 3:1 volume ratio of ethyl acetate:isopropyl alcohol, stirred at room temperature for several hours (e.g., 3, 4 or 5, often 4 hours) and precipitated. The mixture was taken up from 2-5 times, often 3-5 times, often 3 times in preferred embodiments) to provide substantially pure (*de* ≥ 90%, often ≥ 99%) (*S*)-phenylethylaminium salt (acid amine salt) **10**. The (*S*)-phenylethylaminium acid amine salt **10** is then taken up in methylene chloride (DCM) and exposed/sequentially washed with cold aqueous acid (e.g., 1 N aq. Solution of HCl), brine and dried (e.g. sodium sulfate) to provide compound **11** (**L-dioxolane**) as a diastereomerically pure or substantially diastereomerically pure compound (*de* ≥ 90%, *de* > 95%, often ≥ 99%, most often 99+%-100%). Compound **11** (as the *trans/L* form) is thus obtained from compound **9** by precipitation in the absence of chromatographic separation in high purity. It is noted that one or more of the aforementioned steps is conducted in separate steps or in a single pot reaction vessel.



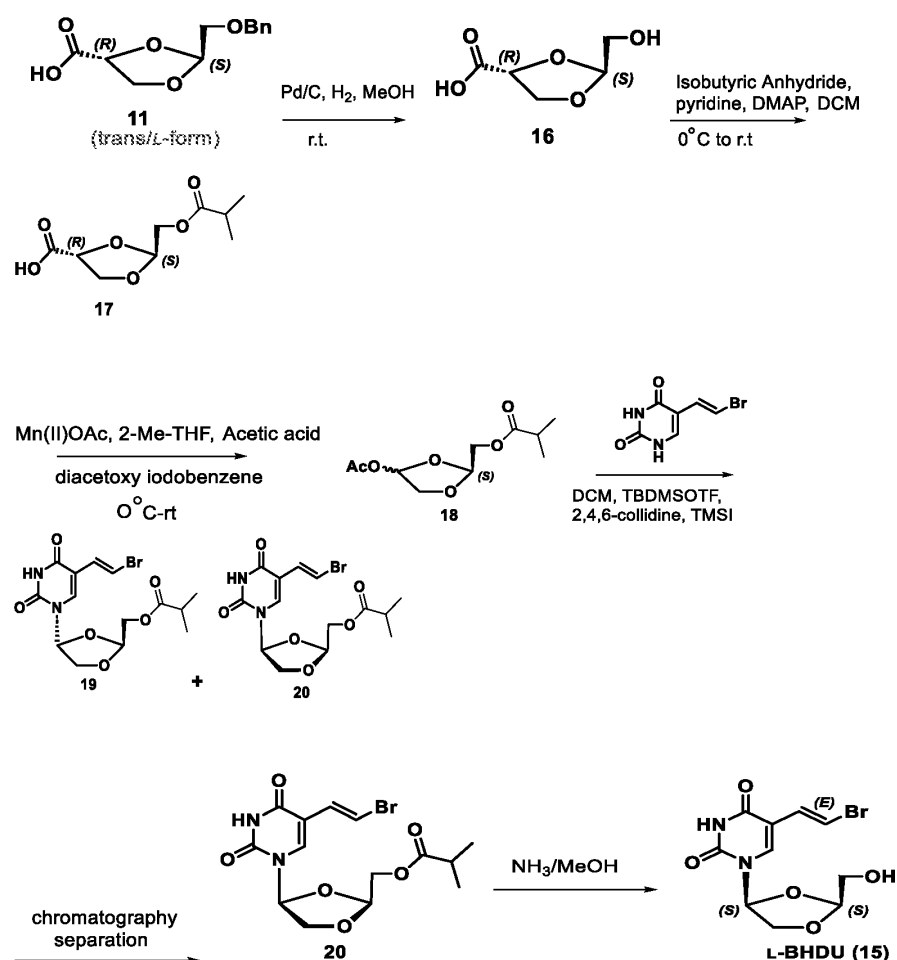


[024] In an embodiment, compound **11** is converted to compound **15** through compounds **12** and **13** as described herein below and in enclosed FIGURE 4, SCHEME 2. In this embodiment, compound **11** is first reacted with Mn(II)OAc , diacetoxy iodobenzene, acetic acid in 2-Me-THF at 65 $^\circ\text{C}$ (or alternatively, lead tetraacetate Pb(OAc)_4 in acetonitrile/base, often pyridine or trimethylamine, more often pyridine with the components combined at 0 $^\circ\text{C}$, followed by rt for 16 hours, step not shown in Scheme, below) and chromatographic separation (preferably using column chromatography, elution with ethyl acetate/hexanes) to provide a mixture of α and β anomers (α/β ratio often of about 2:1) of benzyl protected dioxolane acetate compound **12**. Compound **12** (as a mixture of α and β anomers) is coupled to bromovinyl uracil in dry solvent (e.g. dichloromethane (DCM)) using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), iodotrimethylsilane (TMSI) and 2,4,6-collidine and thereafter subjected to chromatography (e.g. silica gel column, 1:4 EtOAc/hexane as eluent) to provide a minor component of α -isomer compound **14** (about 10-20% yield, undesired) and desired β -isomer compound **13** in $\geq 50\%$ yield (often 55% or more). Compound **13** is then subjected to deprotection of the benzyl group (e.g. in DCM using BCl_3 at low temperature, e.g. -78 $^\circ\text{C}$) to provide compound **15** in $\geq 50\%$ yield. Each of the aforementioned synthetic steps may be conducted in separate steps or together in a single reaction vessel.



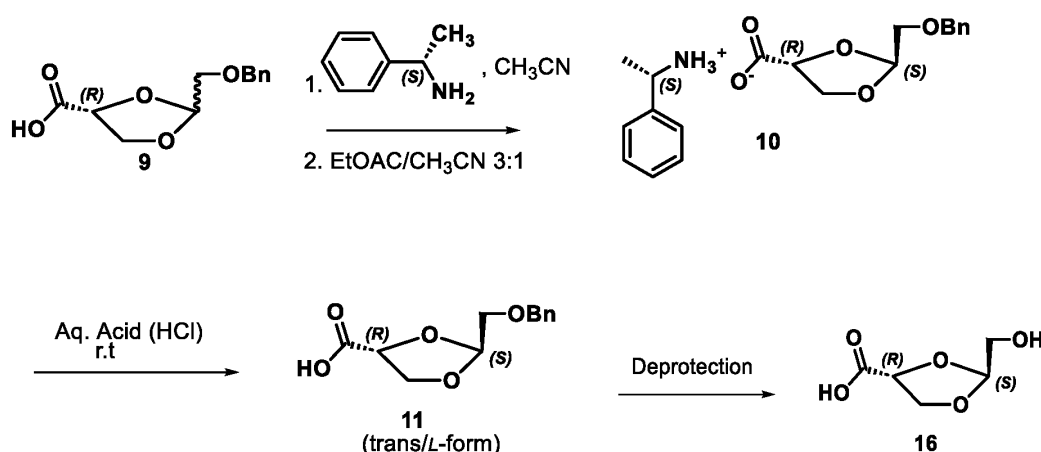
[025] In an embodiment, the present invention is directed to a method for synthesizing compound **15** from L-dioxolane acid **11** through compounds **16-20** as depicted herein below and in enclosed FIGURE 6, SCHEME 3. In this embodiment of the present invention, compound **11** is subjected to benzyl deprotection (preferably utilizing reductive cleavage, often with Pd/C, hydrogen gas, in MeOH at r.t) to provide unprotected dioxolane acid compound **16** in high yield which is subsequently protected on the free hydroxyl group with an isobutyrate group. This step is performed, for example, by reacting compound **16** with isobutyric anhydride in base (e.g. pyridine and dimethylamino pyridine (DMAP)) in dichloromethane solvent, initially at 0 °C followed by reaction at RT (e.g. overnight, from 12-20 hours, often 16 hours) to provide isobutyrate protected compound **17**, often in greater than 80-85% yield. Compound **17** was acylated to form compound **18** as a mixture of diastereomers using Mn(II)OAc, diacetoxyl iodobenzene, acetic acid in 2-Me-THF (e.g. initially at 0 °C, followed by RT overnight or from 12-20 hours, often 16 hours, then at 65 °C for 4h). Alternatively, lead tetraacetate Pb(OAc)₄ in acetonitrile/base, often pyridine or trimethylamine, more often pyridine with the components combined at 0°C, followed by rt for 16 hours can be used (alternative step not shown in Scheme, below). Compound **18** was

thereafter coupled to bromovinyluracil in dichloromethane (DCM) using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), iodotrimethylsilane (TMSI) and 2,4,6-collidine which provided a diastomeric mixture of compound **19** and **20**, which mixture was thereafter subjected to chromatography (e.g. silica gel using 15-18% EtOAc/hexanes) to provide compound **20**, often in greater than about 45-50% yield, which could be readily converted to L-BH DU (**15**) by exposure to base in solvent (e.g. NH₃/MeOH). Each of the aforementioned synthetic steps may be conducted in separate steps or together in a single reaction vessel.



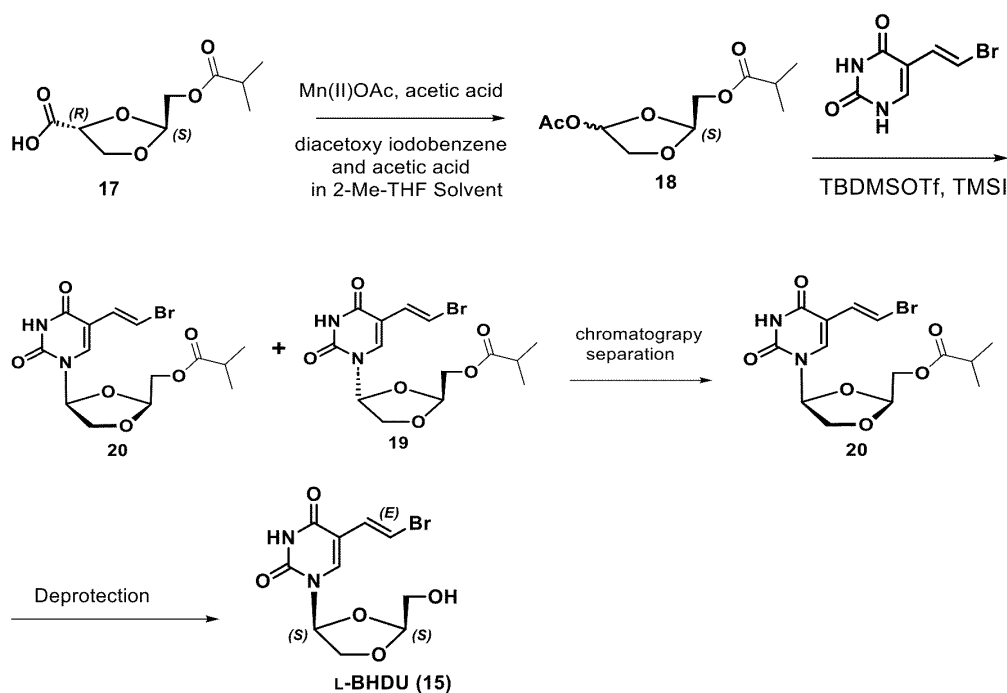
[026] In an embodiment, the present invention is directed to the synthesis of benzyl protected dioxolane acid **11** from benzyl protected dioxolane acid **9** by reacting (*S*)-phenylethamine with compound **9** in acetonitrile at room temperature for several hours (e.g.

often about 4 hours) to form a mixture of D and L isomeric benzyl protected phenylethylaminium salts **10** (the mixture of isomeric compounds is also referred to as **10M**) which solid mixture is resuspended in a 3:1 ratio (volume) of ethylacetate/isopropanyl for 4 hours and filtered. This resuspension process is optionally and preferably repeated several times until the undesired D isomer is removed from the salt mixture) to provide the substantially pure L-isomer compound **10** (*de* of at least 90%, often at least 95%, at least 99%, 99+%, 99.3+%). The L-isomer (compound **10**) is exposed to aqueous acid (e.g. 1N aqueous HCl) at room temperature for a time sufficient to provide the benzyl protected L-dioxolane acid **11**. Compound **11** is readily converted to the deprotected L-dioxolane acid **16** by removing the benzyl protecting group under reduction conditions (e.g. Pd/C, H₂).



[027] In an embodiment, the present invention is directed to a method for synthesizing isobutyrate protected nucleoside compound **20** from isobutyrate protected L-dioxolane acid **17** by acylating compound **17** using Mn (II) OAc, diacetoxyl iodobenzene, acetic acid in 2-Me-THF (or alternatively, lead tetraacetate Pb(OAc)₄ in acetonitrile/base, often pyridine or trimethylamine, more often pyridine with the components combined at 0°C, followed by rt for 16 hours, not shown in the Scheme below) to form a diastereomeric mixture of the acylated protected L-dioxolane compound **18**. Compound **18** is then coupled with bromovinyl-uracil in dichloromethane (DCM) using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), followed by iodotrimethylsilane (TMSI) to provide a diastereomeric mixture of compounds **19** and **20**. The diastereomeric mixture of compounds **19** and **20** is subjected to column chromatography to afford compound **20**. Compound **20** is

then exposed to ammonia/methanol (or other appropriate base) to remove the isobutyrate protecting group to afford final compound L-BH DU **15**. Each of the aforementioned synthetic steps may be conducted in separate steps or together in a single reaction vessel.



[028] In an embodiment, as presented in FIGURE 7, SCHEME 4, L-BH DU (**15**) is converted to POM-L-BH DU-MP (**22**) by reacting compound **15** with bis(POM)phosphorochloridate (**21**) in THF solvent in the presence of weak base (e.g. *N*-methylimidazole, NMI) and purified (e.g. chromatography) and crystallized to afford compound **22** in greater than 40% yield.

[029] In embodiments, the present invention is also directed to any one or more of the compounds, including intermediate compounds identified above, or a salt, including a pharmaceutically acceptable salt, thereof.

[030] These and/or other embodiments of the present invention may be readily gleaned from a review of the presentation of the specification and the identified discussion and examples which follow.

[031] **DETAILED DESCRIPTION OF THE INVENTION**

[032] The following terms are used to describe the present invention. In instances where a term is left undefined, the term is given its art recognized meaning. In accordance with the present invention there may be employed conventional chemical synthetic methods and other biological and pharmaceutical techniques within the skill of the art. Such techniques are well-known and are otherwise explained fully in the literature.

[033] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[034] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described.

[035] It is to be noted that as used herein and in the appended claims, the singular forms "a," "and" and "the" include plural references unless the context clearly dictates otherwise. The term "about" when used, signifies an amount within $\pm 5\%$ of the amount or number specifically set forth.

[036] The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound or intermediate disclosed herein, and often refers to β -L nucleoside analogs or D & L dioxolane intermediates used to produce these nucleoside compounds using the synthetic steps described herein, but may include, within context, tautomers, regioisomers, geometric isomers, anomers, and where applicable, optical isomers (enantiomers) or often diastereomers (two chiral centers or more) thereof of these compounds, as well as pharmaceutically acceptable salts thereof, solvates and/or polymorphs thereof. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures and/or diastereomers as described herein) as well as specific enantiomers, enantiomerically enriched or individual diastereomers or mixtures of these disclosed compounds. It is noted that if a carbon range is provided for a compound, that range signifies that each and every carbon individually is considered part of the range. For example, a C₁-C₂₀ group describes a group with a single carbon, two carbon atoms, three carbon atoms, four carbon atoms, etc. up to twenty carbons.

[037] The term “salt” or “pharmaceutically acceptable salt” is used throughout the specification to describe, where applicable, a salt form of one or more of the compounds described herein which are presented to increase the outcome of a synthetic reaction, or alternatively, the solubility of a compound, in certain embodiments where administration has been effected, in the gastric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids well known in the pharmaceutical art. Sodium and potassium salts are particularly preferred as neutralization salts of the phosphates according to the present invention, where relevant.

[038] The term "pharmaceutically acceptable derivative" is used throughout the specification to describe any pharmaceutically acceptable prodrug form (such as an ester, ether or amide, phosphoramidate, phosphate ester, phosphonate or other prodrug group) which, upon administration to a patient, provides directly or indirectly the present compound or an active metabolite of the present compound.

[039] The term "D-configuration" as used in the context of the present invention refers to the configuration of the nucleoside compounds as well as other intermediates according to the present invention which mimics the natural configuration of sugar moieties as opposed to the unnatural occurring nucleosides or "L" configuration, which describes most of the compounds used in the chemical syntheses or as final products as set forth herein. The term " β " or " β anomer" is used to describe intermediates or nucleoside analogs according to the present invention in which the nucleoside base is configured (disposed) above the plane of the dioxolane moiety in the compound.

[040] The term "diastereomeric excess", "*de*" or "enantiomeric excess", "*ee*" is used throughout the specification to describe an intermediate compound or a nucleoside compound which has a diastereomeric or enantiomeric excess of at least about 90%, often at least about 95%, preferably at least about 96%, more preferably at least about 97%, even more preferably, at least about 98%, and even more preferably at least about 100% or more of a single diastereomer or a single enantiomer of that compound. Dioxolane nucleoside compounds such as L-BH DU or its derivatives according to the present invention are generally β -L-nucleoside compound analogs. When the present compounds according to the present invention are referred to in this specification, it is presumed that the intermediates or final nucleoside compounds have the L-nucleoside configuration and are diastereomerically and/or enantiomerically enriched (preferably, about 100% of the L-nucleoside), unless otherwise stated. The term "diastereomerically pure", "diastereomerically enriched", or "diastereomeric excess" or *de*" is used to describe a single diastereomer of a compound according to the present invention which contains an excess of at least 90%, 95%, 96%, 97%, 98%, 99%, 99+%, 99.5% or 100% by weight of that diastereomer to the exclusion of other possible diastereomers.

[041] The term “stereoselective” is used to describe a synthetic step or series of steps in which a single reactant produces a particular isomer, enantiomer or diastereomer (of at least two possible isomers or diastereomers) in greater quantities than one or more possible isomer(s) or diastereomer(s) from that reactant. In some instances, the stereoselectivity of a reaction may be close to 100%.

[042] The term “protecting group” or “blocking group” is used to describe a chemical group or moiety which is introduced into a molecule by chemical modification of a functional group to obtain chemo selectivity and/or stereoselectivity in a subsequent chemical reaction. The protecting group/blocking group plays an important role in providing precursors to chemical components which provide compounds according to the present invention. Blocking groups are often used to protect hydroxyl groups on the intermediate based in order to form compounds according to the present invention. Typical blocking groups are typically used on alcohol groups or phosphate groups in the present invention and include principally benzyl groups (removed by hydrogenolysis), isobutyrate groups (removed by base), methyl ester groups (removed by base), acetyl groups (removed in coupling reactions) and pivaloylmethyl ester (POM) groups on phosphate group intermediates. Pivaloyloxymethyl ester (POM) groups are also used on phosphate groups in final compound POM-L-BH DU-MP to instill prodrug characteristics to nucleoside compounds to enhance bioavailability. These and other/or groups are described herein.

[043] **CHEMICAL SYNTHESIS OVERVIEW AND RESULTS**

[044] Numerous efforts by various groups to construct chiral pure L-dioxolane often lead to a racemic mixture of D & L dioxolane and demand expensive chiral SFC purification to obtain chiral pure D and L dioxolane. To remove the chiral SFC separation, Bera S. et al.¹⁹ reported the synthesis of chiral dioxolane *via* methyl-(*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate. However, the reported procedure was ambiguous and required a close analytical technique to confirm the D & L stereoisomers, which may sometimes occur to the end of the final undesired conformational product. In the present instance, the inventors obtained an L-BH DU authentic sample that was matched with synthesized L-BH DU *via* the reported protocol of Bera S. al. After that, the inventors found that this procedure without an authentic sample and chiral HPLC proved to be very challenging to furnish the desired isomers of the

targeted compound. To accomplish the scalable synthesis of L-BH DU, a new protocol for the synthesis of exclusively chiral pure L-dioxolane was urgently needed, thus precipitating studies which led to the present invention. The present invention is principally focused on the synthesis of chiral L-dioxolane with an excellent enantiomeric excess (e.e. $\geq 99\%$). Notably, this procedure may be suitable for the large-scale synthesis of L-derived dioxolane nucleosides such as troxacitabine.²¹ It may also expedite the extended structure-activity relationship (SAR) studies of both D & L-dioxane-derived molecules of therapeutic interest.

[045] The synthesis of chiral pure L-dioxolane (**11**) key intermediate was initiated by condensation of commercially available methyl (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**7**) with 2-benzyloxyacetaldehyde *via* trans ketalization in the presence of *p*-TSA to give the racemic 1,3-dioxolane derivative in 1:1 diastereomeric mixture dioxolane esters, **8** (FIGURE 4, SCHEME 2) in 72% yield. Next, hydrolysis of methyl ester (**8**) was carried out by the 1 M aqueous solution of LiOH in THF to afford a diastereomeric mixture of acids (**9**) in 92% yield.

[046] Thereafter the goal was to obtain pure L-dioxolane acid (**11**) in high enantiomeric purity (e.e. $> 99\%$) by avoiding the chromatographic separation of racemic acid (**9**). However, the selective separation of L-dioxolane was also challenging. One approach was to insert chiral auxiliary *via* esterification of carboxy acid **9**, followed by a fractional crystallization to render enantiomeric pure L-dioxolane. However, this strategy unnecessarily increases the additional two-step process of esterification and hydrolysis, which is not efficient for the large-scale synthesis of L-dioxolane. To reduce the additional steps, it was thought to perform resolution of racemic **9** *via* a diastereomeric salt formation with a chiral amine. Noteworthy to mention is that compound **9** is oily in nature, and other fractional crystallization techniques may not be appropriate for the resolution of chiral pure L-dioxolane (**11**). Singh et al. reported chiral resolution of racemic amines *via* chiral pure L-(+)-tartaric acid.²² Taking the lead from the reported procedure by Singh et al. it was thought to adopt a reverse strategy, chiral resolution of racemic acid (**9**) *via* salt formation with a chiral pure amine.

[047] To achieve diastereomerically pure salt formation of racemic **9**, several (*R*) or (*S*) chiral amines were utilized (see **Table 1**, below) in various solvent systems. In the investigational resolution of racemic acid **9**, diastereomeric salt formation of **9** with (*S*)-phenylethylamine produced pure chiral dioxolane salt **10** with a diastereomeric excess (*de*) of 99.37% (entry 4 **Table 1**). Racemic acid **9** was taken in acetonitrile and treated with 0.8 eq. of (*S*)-phenylethylamine which gives a precipitate of white salt of acid amine. The next goal was to determine the chiral purity of the precipitated salt as well as the stereo conformation of diastereomeric salt. The precipitated diastereomeric salt was treated with 1 N aq. HCl to afford free diastereomeric dioxolane. The chiral purity of obtained free dioxolane was determined by chiral HPLC, which indicates the optical purity of precipitated isomers is 85% and 15% presence of another isomer. The obtained results of diastereomeric salt formation *via* resolution of racemic **9** were not encouraging because, for the construction of optically pure L-BH DU, there was a need for L-dioxolane with the optical purity of more than 99% (*ee* $\geq$ 99%).

[048] Hence, the process of the diastereomeric salt formation of racemic **9** was revisited. To enrich the diastereomeric excess (*de*) of precipitated salt (*via* acetonitrile), the obtained salt was re-suspended in EtOAc-IPA (3:1) and stirred for 4 h at room temperature, then filtered and neutralized by 1 N aqueous HCL aqueous solution. The afforded, dioxolane was reexamined for the chiral purity *via* chiral HPLC, which demonstrated *ee* of more than 99% (*ee* $\geq$ 99.3%) in 38% yield. Therefore, it was concluded that treatment of a double solvent system, first in acetonitrile followed by EtOAc: isopropanol (3:1), enhances the diastereomeric excess (*de*) of precipitate salt (*de* $\geq$ 99.3%), an unexpected result. The subsequent objective was the stereo conformation determination of precipitated salt, either D or L-form of dioxolane. The X-ray crystal of precipitated salt was developed, and it confirmed the formed diastereomeric salt matches with the stereo conformation of L-dioxolane (**10**). The X-ray structure revealed that hydrogen atoms present at carbon-2 (C-2) and C-3 are trans (see **FIGURE 5b**) to each other, which confirms L-dioxolane salt precipitation.

[049] However, a single solvent salt formation approach was tried with various chiral amines mentioned in **Table 1**, below, but in each case, the results of *de* were unsatisfactory.

To improve the yield of intermediate **11**, an altered ratio of EtOAc & IPA was tried, but in all efforts, either less yield or less chiral purity of intermediate **11** was achieved.

Table 1: Diastereomeric salt formation results of racemic compounds **10** with various chiral amines

Entry	Chiral mine	Solvent	Temp.	Time	Result	Yield
1	(<i>R</i>)-phenylethylamine	EtOAc:IPA (2:0.5)	rt	4h	Salt contains both D & L isomers in 1:1 (de ~50%)	>10%
2	(<i>R</i>)-phenylethylamine	EtOAc:IPA (2:1)	45 °C to rt	4h	Salt contains both D & L isomers in 1:1 (de ~50%)	>10%
3	(<i>R</i>)-phenylethylamine	Acetonitrile	70 °C to rt	4h	Salt contains both D & L isomers in 1:1 (de ~50%)	15%
		Acetonitrile (Step-1)	70 °C to rt	4h	Salt contains both D (15%) & L isomer (85%) (de ≥70%)	
4	(<i>S</i>)-phenylethylamine	Obtained salt from step-1 was resuspended in with EtOAc:IPA (3:1) (Step-2)	rt	4h	Yielded salt contain L-isomers (de ≥ 99.3%)	38% after both step 1& 2
5	(<i>S</i>)-phenylethylamine	EtOAc:IPA (1:1)	60 °C -rt	4h	Salt formation was but moister sensitive during filtration	NA
6	(<i>S</i>)-phenylethylamine	EtOAc:IPA (1:2)	60°C - rt	4h	Salt formation was but moister sensitive during filtration	NA
7	(<i>S</i>)-phenylethylamine	EtOA:IPA 3:1	rt	6h	Yielded salt contain L-isomers (de ≥ 90.0%)	23%

8	(S)-(+)-1-(1-Naphthyl) ethylamine	Acetonitrile	70 °C to rt	78h	No salt formation	NA
9	(R)-(+)-1-(1-Naphthyl) ethylamine	Acetonitrile	70 °C to rt	16h	No salt formation	NA
10	(S)-(-)-N-benzyl-1-phenylethylamine	Acetonitrile	70 °C to rt	32h	No salt formation	NA

[050] L-dioxolane compound **11** served as the key intermediate for the synthesis of L-BHDU. Treatment of **11** with Mn(II)OAc, acetic acid, diacetoxy iodobenzene in 2-methyl THF, or alternatively lead (IV) acetate Pb(OAc)₄, in the presence of pyridine in acetonitrile, converts the 2-carboxyl group of **11** to the 2-acetoxy intermediate **12** in an α/β ratio of 2:1 (racemic) in 74% yield. Furthermore, glycosylation coupling of **12** with bromovinyl-uracil was carried out under Vorbrüggen coupling condition.²³ Bromouracil base treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) followed by (iodotrimethylsilane) TMSI, which *in situ* generates silylated bromo vinyl uracil and condenses with acetate intermediate **12** (α/β ratio 2:1) to render coupled β and α isomer of **13** (in 55% yield) and **14** (in 18% yield) in ratio of 3:1. Separation of isomers by column chromatography afforded desired β -isomer in 55% yield and α -isomer in 18% yield. Finally, deprotection of the 5'-benzyl group of coupled product **13** was performed by 1 M solution of boron trichloride (BCl₃) in DCM to furnish targeted compound L-BHDU in 60% yield. This series of reactions is presented in accompanying FIGURE 4, SCHEME 2.

[051] It was determined that the exothermic final deprotection of benzyl group of compound **13** using BCl₃ was not suitable for large-scale synthesis. To avoid the use of BCl₃, a protection group replacement strategy was adopted, and the 5-O-benzyl of intermediate **11** was replaced with isobutyric ester as a hydroxyl protecting group. The debenzylation of **11** was carried out with 5% Pd/C under hydrogenation conditions to afford intermediate **16** in 91% yield. Intermediate **16** was treated with isobutyric anhydride in the presence of pyridine to produce compound **17** in 88% yield. Acylation of compound **17** followed by the coupling with bromovinyl-uracil afforded coupled desired (β) nucleoside **20** (54% yield) and undesired (α) nucleoside **19** (yield 22%) in approximately 2:1 ratio (see FIGURE 6, SCHEME 3).

[052] Deprotection of the isobutyl ester group of **20** was performed in base (7 N NH₃ solution in MeOH) to give L-BH DU in 92% yield. Optical rotation and other analytical data of **15** were consistent with previously synthesized authentic L-BH DU.²⁴

[053] To synthesize POM-L-BH DU-MP prodrug, first synthesis of bis(POM)phosphorochloridate (**21**) was carried out according to the reported protocol by Hawang Y. et al.²⁵ Next, coupling of L-BH DU (**15**) was performed with POM chloride (**21**), in the presence of *N*-methyl imidazole (NMI) in THF to furnish POM-L-BH DU-MP (**22**) in 47% yield (FIGURE 7, SCHEME 4).

[054] **CONCLUSIONS DRAWN**

[055] To determine the full biological evaluation of POM-L-BH DU-MP, an efficient and scalable synthetic method of L-BH DU has been developed *via* commercially available methyl (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate, **7**. The selective diastereomeric salt formation of racemic **9** *via* a chiral (*S*)-phenylethylamine followed by neutralization of **10** gave optically pure L-dioxolane, **11** (ee ≥ 99%). Compound **11** was converted to acetate intermediate **12**, which was utilized for Vorbrüggen coupling with bromovinyl-uracil followed by the benzyl deprotection of coupled nucleoside afforded the target compound **15** (L-BH DU) in 7 steps with approximately 4.9 % overall yield. This process removes the expensive chiral separation of racemic D & L dioxolane and is more efficient than the previously reported method for the synthesis of L-BH DU. Further coupling of bis(POM)phosphorochloridate, **21** with L-BH DU produced L-BH DU-monophosphate ester prodrug **22** (POM-L-BH DU-MP). The removal of chiral separation and reduction of column chromatography in synthetic steps in comparison to the previously reported methods and the use of economical reagents make the current methodology amenable for large scale preparation of POM-L-BH DU-MP and selective synthesis of chiral pure L-dioxolane (**11**).

[056] It was noted during chemical synthesis that the use of Mn(OAc)₂ was found unexpectedly to be a particularly effective substitute for Pb(OAc)₄ for forming compounds **12** and **18** (conversion of precursor carboxylic acid to acetate group at the 4-position of the dioxolanyl moiety) and has become the preferred reagent for conducting these steps in scale-up reactions of the present invention. The reactivity of Mn(OAc)₂ turned out to be at least

equal to and in some instances somewhat greater than $\text{Pb}(\text{OAc})_4$ and has other attributes which make this reagent substantially more favorable than $\text{Pb}(\text{OAc})_4$ for use in the present invention despite the overwhelming prevalence of $\text{Pb}(\text{OAc})_4$ in conventional chemistry, particularly of this nature. Moreover, $\text{Mn}(\text{OAc})_2$ is about 25% of the cost of $\text{Pb}(\text{OAc})_4$ and offers substantial cost savings, especially in commercial applications. This reagent is also more readily available from commercial suppliers due to its far lower reagent toxicity compared to $\text{Pb}(\text{OAc})_4$. Reaction time for the conversion of the carboxylic acid group to the acetate in compounds **12** and **18**, respectively turns out to be substantially faster for $\text{Mn}(\text{OAc})_2$ (4h) compared to $\text{Pb}(\text{OAc})_4$ (>14h), which will support the expedited synthesis of POM-L-BHDU-MP. Additionally, the handling of $\text{Mn}(\text{OAc})_2$ is far less challenging than is the handling of $\text{Pb}(\text{OAc})_4$ in commercial applications, inasmuch as $\text{Pb}(\text{OAc})_4$ is very hygroscopic (moisture sensitive) and in large settings (>25g) makes its use difficult often requiring special handling, whereas $\text{Mn}(\text{OAc})_2$ is very stable (not moisture sensitive) and easy to handle.

[057] $\text{Pb}(\text{OAc})_4$ is highly exothermic in >50g scale reactions and in the present invention it was required to add reagent in portion wise to control the reaction temperature and to run the reaction under cooling conditions. This took considerably longer than with the use of $\text{Mn}(\text{OAc})_2$, because the reaction steps with $\text{Mn}(\text{OAc})_2$ is not exothermic and does not require external cooling. In the reactions utilizing $\text{Pb}(\text{OAc})_4$, pyridine is required in equimolar quantity and in the completion of the reaction and final work product removing pyridine is difficult and produces a particularly pungent smell in large scale reactions. The $\text{Mn}(\text{OAc})_2$ reactions do not require pyridine (or any amine), thus substantially reducing clean up and final processing of compound. Additional considerations include the fact that the product obtained from $\text{Pb}(\text{OAc})_4$ reaction must be purified by column chromatography to obtain pure enough to take to the next step, whereas $\text{Mn}(\text{OAc})_2$ results in an almost clean conversion and crude product may be readily used for the next step reaction, thus avoiding column chromatographic purifications. This is particularly important in commercial applications of the present invention.

[058] In the present invention, in $\text{Pb}(\text{OAc})_4$ reaction conditions at large scale, colloidal solutions in the reaction mixture and during work up generate challenges to process the reaction mixture and break up the reaction mixture colloidal state. This colloidal solution formation can often compromise the yield of reaction. The $\text{Pb}(\text{OAc})_4$ reaction conditions are

not ecofriendly, whereas those utilizing $\text{Mn}(\text{OAc})_2$ are eco friendly and substantially safe for the environment. Accordingly, $\text{Mn}(\text{OAc})_2$ represents a substantially better reagent for the scalable synthesis for use in the present invention.

[059] **EXAMPLES**

[060] **EXPERIMENTAL SECTION**

[061] **General Analytical Methods**

[062] Reagents and anhydrous solvents were purchased from commercial sources and used without further purification. Moisture-sensitive reactions were performed using oven-dried glassware under a nitrogen or argon atmosphere. Reactions were monitored by thin-layer chromatography plates (TLC silica gel GF 250 microns) that were visualized using a Spectroline UV lamp (254 nm) and developed with 15% solution of sulfuric acid in methanol. Column chromatography was performed on silica gel 60 Å, 40-63 μm (230 X 400 mesh, Sorbent Technologies). Preparative normal phase chromatography was performed on a CombiFlash Rf 150 (Teledyne Isco) with pre-packed RediSep Rf silica gel cartridges or on RediSep® gold C18 reverse phase columns. Melting points were recorded on a Mel-temp II laboratory device and are uncorrected. Nuclear magnetic spectra were recorded on Varian Inova 500 spectrometer at 500 MHz for ^1H NMR, 202 MHz for ^{31}P NMR, and 125 MHz for ^{13}C NMR with tetramethylsilane as an internal standard. Chemical shifts (δ) are quoted as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet) and dt (double triplet). Optical rotations were measured on a JASCO DIP-370 digital polarimeter. High-resolution mass spectroscopy (HRMS) spectra were measured on Bruker Ultra-high resolution QTOF MS Impact II spectrometer. Samples were infused at 3 μL/min, and spectra were obtained in the positive or negative ionization mode with a typical resolution of 20,000 or greater. Purity of all tested compounds are $\geq 95\%$, as determined by their elemental analysis or by HPLC/UV. Elemental analysis were performed by the Atlantic Microlab Inc. Norcross, GA. HPLC/UV were determined with a Waters HPLC coupled to a photodiode array. 5 μL of sample 0.5 mg/mL in methanol, or in acetonitrile or in mixture of DMSO/MeOH (0.5:10) were injected, using an XBrigde C18, 3.5 μm, (4.6 X 150) mm column at 25 °C with flow rate 0.8 mL/min or with UPLC BEH C18, 1.7 μm (100 X 2.1) mm at 50 °C with a flow rate 0.55 mL/min. The mobile phases were a mixture of A = 10 mM ammonium acetate in water and B = acetonitrile (ACN), and A = 0.05% formic acid (FA) in water and B = 0.05% in acetonitrile (ACN). Purity is given as % of absorbance at Max plot.

Optical purity of chiral intermediates and final compound were determined by the chiral HPLC. Chiral HPLC/UV were determined with a Waters HPLC coupled to a photodiode array. 10 μ L of samples 0.5 mg/mL in methanol, were injected, using an CHIRALCEL OX-H, 5 μ m (4.6 X 250mm) column at 30 °C with flow rate 3.0 mL/min.

[063] **Methyl (4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate (8):** To a solution of 2-(benzyloxy)acetaldehyde (100 g, 665.91 mmol) and methyl (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**7**, 106.65 g, 665.91 mmol) in toluene (700 mL), *p*-toluene sulfonic acid or Dowex 50W X8 was added (5.06 g, 26.63 mmol) and the mixture was stirred at 80 °C for 2 h. (Reaction mixture turned to dark black color). The reaction mixture was cooled to room temperature and the volatiles were evaporated and the crude mixture was purified by the flash silica gel column chromatography (12-18% EtOAc/hexane) as eluent to obtain an inseparable mixture of methyl (4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate **8** as light-yellow oil. Yield (122.5 g, 72%); ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.32 (m, 11H), 7.30-7.27 (m, 2H), 5.33 (t, *J* = 4.0 Hz, 1H), 5.22 (t, *J* = 4.5 Hz, 1H), 4.68-4.58 (m, 7H), 4.31 (dd, *J* = 8.2, 7.3 Hz, 1H), 4.24 (dd, *J* = 8.6 & 3.9 Hz, 1H), 4.13-4.09 (m, 1H), 3.99 (dd, *J* = 8.3 & 5.4 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.71 (d, *J* = 3.8 Hz, 1H), 3.67-3.61 (m, 2H), 3.59 (d, *J* = 4.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 171.35, 171.1, 128.49, 128.46, 127.91, 127.83, 127.81, 127.79, 104.87, 104.33, 74.10, 73.90, 73.80, 73.74, 70.87, 70.30, 68.71, 68.31, 52.49; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd for C₁₃H₁₆O₅Na 275.0895; Found 275.0883.

[064] **(4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylic acid (9):** To a solution of methyl (4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate **8** (60 g, 237.84 mmol) in THF (250 mL) at 0 °C 1 M aqueous LiOH was added (198 mL) dropwise and the mixture was slowly brought to room temperature and stirred for 36 h. THF was removed under reduced pressure and mixture was washed with EtOAc (3 X 75 mL). The separated aqueous layer was cooled to 0 °C and acidified with 28% aq. HCl to pH ~3, and extracted with DCM (3 X 125 mL). The combined organic layer was washed with brine and dried over Na₂SO₄, filtered, and concentrated to obtain racemic acid (4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylic acid **9** as a light brown thick liquid. Yield (52.5 g, 92%); ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.32 (m, 10H), 7.31-7.27 (m, 1H), 5.34 (t, *J* = 3.6 Hz, 1H), 5.20 (s, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.70-4.64 (m, 3H), 4.61 (s, 2H), 4.42-4.34 (m, 2H), 4.15-4.09 (m, 2H), 4.04 (dd, *J* = 8.4 & 5.4 Hz, 1H), 3.80 (dd, *J* = 11.4 & 1.7 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 1H),

3.61 (dd, $J = 5.9$ & 3.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.76, 173.56, 137.68, 136.02, 128.77, 128.53, 128.28, 127.91, 127.85, 104.44, 104.25, 74.28, 73.83, 73.65, 70.48, 70.19, 68.27, 67.50; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{Na}$ 261.0739; Found 261.0739.

[065] **(2*S*,4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate-(*S*)-1-phenylethan-1-aminium (10)**: A solution of methyl (4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate **9** (25 g, 105.0 mmol) in ACN (50 mL) was heated to 70 °C for 20 minutes. After that, (*S*)-(-)-1-phenylethylamine (10.80 g, 89.25 mmol) was dropwise. The mixture was heated at same temperature at 70 °C for 2 h then slowly cool to room temperature and stirred for 3 h to give white solid precipitate. The precipitate was filtered. To remove the undesired D-dioxolane salt (15%) from the precipitate, filtered solid was resuspended in a mixture of EtOAc: isopropanol (50 mL, 3:1) and stirred for 4 h at rt and filtered. The diastereomeric purity of **10** was monitored by TLC and NMR, and the process was repeated 3 times until the undesired isomer (D dioxolane salt) was completely removed from the solid precipitate. Compound **10** was obtained as a white amorphous solid. Yield (11.5 g, 32%); ^1H NMR (500 MHz, CDCl_3) δ 8.37 (bs, 3H), 7.35-7.25 (m, 10H), 5.03 (t, $J = 3.9$ Hz, 1H), 4.57-4.50 (m, 2H), 4.27-4.21 (m, 2H), 4.04 (t, $J = 7.7$ Hz, 1H), 3.63 (t, $J = 7.1$ Hz, 1H), 3.46-3.43 (m, 2H), 1.49 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.74, 139.31, 137.81, 128.91, 128.50, 128.47, 127.89, 127.86, 126.63, 103.01, 75.66, 73.373, 70.84, 68.69, 50.93, 21.13.

[066] **(2*S*,4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylic acid (11)**: (2*S*,4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylate-(*S*)-1-phenylethan-1-aminium, **10** (11.2 g, 31.18 mmol) was dissolved in DCM (200 mL), and sequentially washed with cold 1 N aqueous HCl (20 mL), water (100 mL), and finally with brine (100 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give (2*S*,4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylic acid **11** as a thick colorless liquid. Yield (7.1 g, 95%); $[\alpha]_D^{25} = +20.82$ (c 0.5, CHCl_3) ^1H NMR (500 MHz, CDCl_3) δ 7.61 (bs, 1H), 7.36-7.31 (m, 4H), 7.30-7.25 (m, 1H), 5.32 (t, $J = 3.5$ Hz, 1H), 4.69-4.66 (m, 1H), 4.60 (s, 2H), 4.34 (t, $J = 7.9$ Hz, 1H), 4.02 (dd, $J = 8.4$ & 5.4 Hz, 1H), 3.60 (dd, $J = 5.9$ & 3.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.74, 139.31, 137.81, 128.91, 128.50, 128.47, 127.89, 127.86, 126.63, 103.01, 75.66, 73.373, 70.84, 68.69, 50.93, 21.13; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5\text{Na}$ 261.0739; Found 261.0729.

[067] **(2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (12)**: To a stirred solution of (2*S*,4*R*)-2-((benzyloxy)methyl)-1,3-dioxolane-4-carboxylic acid (**11**, 0.5 g, 2.09 mmol) in 2-Me-THF (12 mL) was degassed with argon then added acetic acid (0.25 mL, 42.18 mmol), Mn(II)OAc (994 mg, 5.74 mmol), diacetoxyl iodobenzene (2g, 6.27 mmol) and again degassed for 3 mins. The reaction mixture under argon was heated to 65 °C for 4.5h. The reaction mixture cooled to rt and filtered through a celite bed. The obtained filtrate was diluted with EtOAc (60 mL); washed sequentially with saturated Na₂S₂O₃ (15 mL), cold 2M NaHCO₃ (15 mL) water (25 mL), and finally with saturated brine (30 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography using 16-19% EtOAc/Hexane as eluent to obtain a diastereomeric mixture of (2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate as a colorless liquid (**12**). Yield (385 mg, 72%); ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.27 (m, 8H), 6.39 (dd, *J* = 4.4 & 2.1 Hz, 1H), 6.33 (d, *J* = 3.7 Hz, 0.6H), 5.38-5.36 (m, 1H), 5.30-5.27 (m, 0.7H), 4.64-4.59 (m, 3H), 4.23 (dd, *J* = 9.5 & 4.7 Hz, 1H), 4.18 (d, *J* = 9.6 Hz, 0.6H), 3.99-3.93 (m, 2H), 3.67-3.57 (m, 4H), 2.09 (s, 3H), 2.03 (s, 2H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 170.4, 137.8, 128.5, 127.8, 105.3, 103.8, 94.6, 94.1, 73.8, 73.8, 73.7, 71.4, 71.1, 70.9, 70.2, 21.2; HRMS-ESI (*m/z*): [M + Na]⁺ calculated for [C₁₃H₁₆O₅]⁺ 275.0895; found 275.0885.

[068] **(2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (12) (Alternative Synthesis)**: To a stirred solution of (2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate, **11** (2.0 g, 8.39 mmol) and anhydrous pyridine (0.95 mL, 12.08 mmol) in acetonitrile (15 mL), Pb(OAc)₄ (4.46 g, 1.48 mmol) was added portion wise at 0 °C and continue stirred for 16 h at rt. The reaction mixture was filtered through a celite bed. The obtained filtrate was diluted with water (100 mL) and extracted with EtOAc (2 X 50 mL), the combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography using 15-18% EtOAc/hexanes as eluent to obtain (2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate **12** as a colorless liquid. Yield (1.35 g, 74%); ¹H NMR (500 MHz, CDCl₃) δ 7.37-7.27 (m, 8H), 6.39 (dd, *J* = 4.4 & 2.1 Hz, 1H), 6.33 (d, *J* = 3.7 Hz, 0.6H), 5.38-5.36 (m, 1H), 5.30-5.27 (m, 0.7H), 4.64-4.59 (m, 3H), 4.23 (dd, *J* = 9.5 & 4.7 Hz, 1H), 4.18 (d, *J* = 9.6 Hz, 0.6H), 3.99-3.93 (m, 2H), 3.67-3.57 (m, 4H), 2.09 (s, 3H), 2.03 (s, 1.6H); ¹³C NMR (125 MHz, CDCl₃) δ 170.04, 137.75, 128.51, 127.84, 105.29, 103.81, 94.58, 94.10, 73.82, 73.82, 73.71, 71.38,

71.10, 70.87, 70.16; HRMS-ESI (m/z): $[M + H]^+$ Calcd for $C_{13}H_{16}O_5Na$ 275.0895; Found 275.0884.

[069] **1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione (13):** To a suspension of (*E*)-5-bromovinyluracil (500 mg, 2.30 mmol) in dry DCM (15 mL), TBDMSOTf (1.37 mL, 5.99 mmol) and 2,4,6-collidine (0.97 mL, 5.99 mmol) were added at rt and stirred for 30 min. To the resulting solution, a solution of **12** (580 mg, 2.30 mmol) in DCM (20 mL) was slowly added dropwise, followed by addition of TMSI (0.36 mL, 2.53 mmol). The mixture was stirred at room temperature for 3 h and quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (1:4 EtOAc/Hexane as eluent) to give undesired α -isomer **14** (185 mg, 18%) as a white solid and desired β -isomer **13** (525 mg, 55%) as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ 8.27 (brs, 1H), 7.91 (s, 1H), 7.40-7.29 (m, 6H), 6.37-6.31 (m, 2H), 5.12 (s, 1H), 4.69-4.61 (m, 2H), 4.23 (d, $J = 10.1$ Hz, 1H), 4.15 (dd, $J = 10.2$ & 5.3 Hz, 1H), 3.84 (dd, $J = 5.6$ & 1.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.83, 149.26, 138.0, 136.93, 128.82, 128.52, 128.13, 127.94, 111.62, 110.01, 104.91, 81.44, 74.36, 71.99, 67.99; HRMS-ESI (m/z): $[M + H]^+$ Calcd for $C_{17}H_{17}BrN_2O_5Na$ 431.0219; Found 431.0209.

[070] **5-((*E*)-2-bromovinyl)-1-((2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (15):** To a solution of 1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione, **13** (500 mg, 1.22 mmol) in DCM (2 mL) at $-78^\circ C$, 1 M BCl_3 in DCM (1.34 mL, 1.34 mmol) was added dropwise and stirred at same temperature for 30 min. After that, the reaction mixture was quenched with MeOH (1 mL) and warmed to room temperature and the inorganic salts were filtered. The organic layer was concentrated under reduced pressure and crude was purified by silica gel column chromatography (DCM/MeOH, 9:1) to give 1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione, **15** (235 mg, 60%) as a white solid. $[\alpha]_D^{23} = -6.2$ (c 0.2.7, MeOH); 1H NMR (500 MHz, $CDCl_3$) δ 11.61 (brs, 1H), 8.16 (s, 1H), 7.22 (d, $J = 13.6$ Hz, 1H), 6.82 (d, $J = 13.6$ Hz, 1H), 6.21 (d, $J = 5$ Hz, 1H), 5.31 (t, $J = 6.0$ Hz, 1H), 4.97-4.94 (m, 1H), 4.31 (d, $J = 9.9$ Hz, 1H),

4.09 (dd, $J = 9.9, 5.6$ Hz, 1H), 3.74-3.67 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.25, 150.10, 140.10, 130.35, 110.18, 107.01, 105.83, 81.15, 71.07, 60.36; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{11}\text{BrN}_2\text{O}_5\text{Na}$ 340.9749; Found 340.9738.

[071] **(2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (16):** A suspension of (2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (**11**, 3.0 g, 12.60 mmol) and 5% Pd/C (150 mg) in MeOH (20 mL) at ambient temperature was treated with hydrogen at 8 psi in a Parr hydrogenator for 3 h. The mixture was diluted with methanol (20 mL) and passed through a celite bed. The filtrate was concentrated under reduced pressure to obtain (2*S*,4*R*)-2-(hydroxymethyl)-1,3-dioxolane-4-carboxylic acid **16** as a colorless thick liquid. Yield (1.72 g, 92%); ^1H NMR (500 MHz, CDCl_3) δ 5.26 (dt, $J = 2.9, 11.0$ Hz, 1H), 4.71 (ddd, $J = 5.8, 7.3$ & 17.4 Hz, 1H), 4.43-4.32 (m, 1H), 4.04 (ddd, $J = 5.7, 8.4$ & 29.7 Hz, 1H), 3.78-3.74 (m, 2H); HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_5\text{H}_8\text{O}_5$ 148.0372; Found 148.0364.

[072] **(2*S*,4*R*)-2-((isobutyryloxy)methyl)-1,3-dioxolane-4-carboxylic acid (17):** To a solution of (2*S*,4*R*)-2-(hydroxymethyl)-1,3-dioxolane-4-carboxylic acid **16** (2.0 g, 13.50 mmol) in dry pyridine (15 mL) at 0 °C, isobutyric anhydride (3.2 mL, 20.26 mmol) was added followed by addition of DMAP (8 mg) and mixture was stirred at rt for 16 h. The reaction mixture was diluted with DCM (60 mL), washed with water (2 X 25 mL) and finally with brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography using 60-65% EtOAc/Hexane as eluent to give (2*S*,4*R*)-2-[(isobutyryloxy)methyl]-1,3-dioxolane-4-carboxylic acid **17** as a colorless liquid. Yield (2.60 g, 88%); ^1H NMR (500 MHz, CDCl_3) δ 5.38 (t, $J = 3.7$ Hz, 1H), 4.67 (dd, $J = 5.1, 7.1$ Hz, 1H), 4.30-4.25 (m, 1H), 4.18 (t, $J = 3.6$ Hz, 2H), 4.02 (dd, $J = 5.1$ & 8.4 Hz, 1H), 2.60 (p, $J = 7.0$ Hz, 1H), 1.18 (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.04, 135.94, 128.88, 128.61, 128.30, 104.21, 74.34, 70.60, 67.30; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_9\text{H}_{14}\text{O}_6\text{Na}$ 241.0688; Found 241.0673.

[073] **(2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (18):** To stirred solution of (2*S*,4*R*)-2-((isobutyryloxy)methyl)-1,3-dioxolane-4-carboxylic acid (5.0 g, 2.09 mmol) in 2-Me-THF (150 mL) was degassed with argon then added acetic acid (2.7 mL, 4.58 mmol), $\text{Mn}(\text{II})\text{OAc}$ (10.7 g, 6.19 mmol), diacetoxyl iodobenzene (22.15 g, 6.88 mmol) and again degassed for 3 mins. The reaction mixture under argon was heated to 65 °C for 4.5 h. The reaction mixture cooled to rt and filtered through a celite bed. The obtained filtrate was diluted with EtOAc (160 mL); washed sequentially with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (150 mL), cold 2M NaHCO_3 (150 mL) water (200 mL), and finally with saturated brine (150 mL). The

organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography using 16-19% EtOAc/hexane as eluent to obtain a diastereomeric mixture of (2*S*)-4-acetoxy-1,3-dioxolan-2-yl)methyl isobutyrate (**18**). Yield (4.5 mg, 84%); ¹H NMR (500 MHz, CDCl₃) (mix of diastereomers) δ 6.34-6.28 (m, 1H), 5.35, 5.25 (t, *J* = 4.0 Hz, 1H), 4.33-3.90 (m, 4H), 2.58-2.51 (m, 1H), 2.04-2.02 (m, 3H), 1.13-1.11 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 176.5, 176.5, 170.2, 170.1, 103.6, 102.6, 102.3, 94.5, 94.0, 71.3, 70.8, 64.1, 63.5, 63.4, 63.2, 33.8, 21.1, 21.0, 18.9, 18.8; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₀H₁₆O₆Na 255.0839; found 255.0834.

[074] **(2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate (**18**) (Alternative Synthesis):**

To a solution of (2*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl acetate **17** (1.5 g, 6.87 mmol) and dry pyridine (0.78 mL, 9.90 mmol) in acetonitrile, Pb(OAc)₄ (3.80 g, 8.58 mmol) was added portion wise at 0 °C and stirred for 16 h at rt. After that, the reaction mixture was passed through a celite bed. The filtrate was diluted with EtOAc (100 mL), washed with water (50 mL) finally with brine (50 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by flash silica gel column chromatography (12-16% EtOAc/Hexane) to obtain (2*S*)-4-acetoxy-1,3-dioxolan-2-yl)methylisobutyrate **18** as a colorless liquid. Yield (1.23 g, 78%); ¹H NMR (500 MHz, CDCl₃) (mix of diastereomers) δ 6.34-6.28 (m, 1H), 5.35, 5.25 (t, *J* = 4.0 Hz, 1H), 4.33-3.90 (m, 4H), 2.58-2.51 (m, 1H), 2.04-2.02 (m, 3H), 1.13-1.11 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 176.5, 176.5, 170.2, 170.1, 103.6, 102.6, 102.3, 94.5, 94.0, 71.3, 70.8, 64.1, 63.5, 63.4, 63.2, 33.8, 21.1, 21.0, 18.9, 18.8; HRMS (ESI-TOF) *m/z*: [M + Na]⁺ Calcd for C₁₀H₁₆O₆Na 255.0839; found 255.0834.

[075] **1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-**

bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione (20**):** To a suspension of (*E*)-5-bromovinyluracil (350 mg, 1.62 mmol) in dry DCM (12 mL), TBDMSOTf (0.96 mL, 4.21 mmol) and 2,4,6-collidine (0.55 mL, 4.21 mmol) were added at room temperature. The reaction mixture was stirred for 30 min. After that, in the resulting solution, a solution of **18** (375 mg, 1.78 mmol) in DCM (10 mL), was added dropwise followed by addition of TMSI (0.25 mL, 1.78 mmol). The mixture was stirred at room temperature for 3 h and quenched with a saturated aqueous solution of Na₂S₂O₃. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column

chromatography (15-18% EtOAc/Hexane) to give undesired α -isomer **19** (140 mg, 22%) as a white solid and desired β -isomer **20** (340 mg, 54%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.27 (brs, 1H), 7.91 (s, 1H), 7.40-7.29 (m, 6H), 6.37-6.31 (m, 2H), 5.12 (s, 1H), 4.69-4.61 (m, 2H), 4.23 (d, $J = 10.1$ Hz, 1H), 4.15 (dd, $J = 10.2$ & 5.3 Hz, 1H), 3.84 (dd, $J = 5.6$ & 1.8 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.83, 149.26, 138.0, 136.93, 128.82, 128.52, 128.13, 127.94, 111.62, 110.01, 104.91, 81.44, 74.36, 71.99, 67.99; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{17}\text{BrN}_2\text{O}_5\text{Na}$ 431.0219; Found 431.0210.

[076] **5-((*E*)-2-bromovinyl)-1-((2*S*,4*S*)-2-(hydroxymethyl)-1,3-dioxolan-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (15):** To a stirred solution of 1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione (250 mg, 0.64 mmol) in MeOH (5 mL) in a sealed tube at 0 °C, a 7 N solution of NH_3 in MeOH was added and mixture was stirred at room temperature for 16 h. The volatiles were removed under reduced pressure and the obtained residue was triturated with diethyl ether (2 X 5 mL) to give 1-((2*S*,4*S*)-2-((benzyloxy)methyl)-1,3-dioxolan-4-yl)-5-((*E*)-2-bromovinyl)pyrimidine-2,4(1*H*,3*H*)-dione (L-BH DU, **15**) (180 mg, 88%) as an off-white solid. $[\alpha]_{\text{D}}^{23} = -6.1$ (c 0.2.7, MeOH); ^1H NMR (500 MHz, CDCl_3) δ 11.61 (brs, 1H), 8.16 (s, 1H), 7.22 (d, $J = 13.6$ Hz, 1H), 6.82 (d, $J = 13.6$ Hz, 1H), 6.21 (d, $J = 5$ Hz, 1H), 5.31 (t, $J = 6.0$ Hz, 1H), 4.97-4.94 (m, 1H), 4.31 (d, $J = 9.9$ Hz, 1H), 4.09 (dd, $J = 9.9, 5.6$ Hz, 1H), 3.74-3.67 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 162.25, 150.10, 140.10, 130.35, 110.18, 107.01, 105.83, 81.15, 71.07, 60.36; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{11}\text{BrN}_2\text{O}_5\text{Na}$ 340.9749; Found 340.9741.

[077] **Bis(POM) prodrug of L-BH DU-MP (POM-L-BH DU-MP, 22):** To a stirred solution of L-BH DU (**15**, 80 mg, 0.25 mmol) and *N*-methylimidazole (0.16 mL, 2.0 mmol) in dry THF (3 mL), bis(POM) phosphorochloridate²⁵ **21** (500 mg, 1.23 mmol) at 0 °C was added by dissolving in dry THF (3 mL) and stirred for 15 min. After that, reaction was warmed to rt and stirred for 3 h. Mixture was quenched with methanol and solvent were removed under reduced pressure. The crude was purified by silica gel column chromatography (0.5% MeOH/DCM) to give **22** as a colorless sticky oil which was crystallized in DCM-pentane to render as off-white solid. Yield: (75 mg, 47%). Mp: 80-85 °C; ^1H NMR (500 MHz, CDCl_3) δ 8.97 (bs, 1H), 7.71 (s, 1H), 7.45 (d, $J = 13.6$ Hz, 1H), 6.79 (d, $J = 13.6$ Hz, 1H), 6.35 (d, $J = 4.5$ Hz, 1H), 5.72-5.65 (m, 4H), 5.15 (s, 1H), 4.43-4.39 (m, 1H), 4.35-4.31 (m, 1H), 4.26-4.21

(m, 1H), 4.20-4.17 (m, 1H), 1.23 (s, 18H); ^{31}P NMR (202 MHz, CDCl_3) δ -3.02; ^{13}C NMR (125 MHz, CDCl_3) δ 176.9, 161.1, 149.5, 137.3, 128.4, 112.2, 110.6, 102.9, 83.2, 81.4, 71.6, 65.1, 38.9, 26.9; Anal. Calcd for $\text{C}_{22}\text{H}_{32}\text{BrN}_2\text{O}_{12}\text{P}$: C, 42.12; H, 5.14; N, 4.47. Found: C, 42.34, H, 5.23; N, 4.26; HRMS (EI) Calcd For $(\text{C}_{22}\text{H}_{32}\text{BrN}_2\text{O}_{12}\text{P}+\text{H})^+$ 627.0954, found m/z 627.0953.

[078] **Supporting Information**

[079] The supporting information may be found free of charge at the website pubs.acs.org.

[080] Includes, X-ray crystallographic data and copies of ^1H , ^{13}C , & ^{19}F NMR spectra of all intermediates and final compounds **3-28** (PDF).

[081] **Accession Codes**

[082] CCDC contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at the website ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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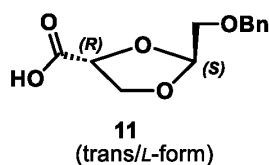
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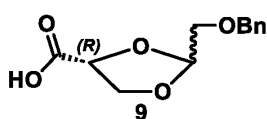
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Claims:

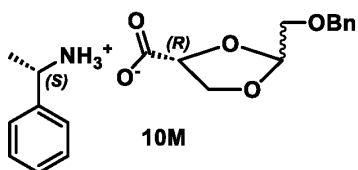
1. A method of synthesizing a compound according to the chemical structure **11**,



from compound **9** (a mixture of α and β isomers)

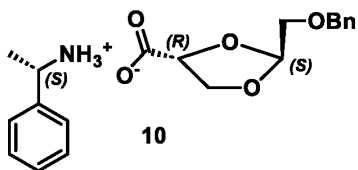


comprising complexing compound **9** with (S)-phenylethylamine in acetonitrile as solvent to form a phenylethylaminium salt and precipitating and/or crystallizing the phenylethylaminium salt (acid amine salt) as a mixture of D and L isomers **10M**,



, and

said salt mixture of D and L isomers **10M** is taken up in 3:1 ethyl acetate:isopropanol and precipitated at least two additional times to provide compound **10** with a diastereomeric excess of at least 95%,



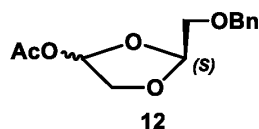
, which compound **10** is subsequently washed with aqueous acid to provide compound **11** with a diastereomeric excess of at least 95%.

2. The method according to claim 1 wherein said mixture of D and L isomers of said acid amine salt **10M** is taken up in 3:1 ethyl acetate:isopropanol and precipitated at least three times and the resulting compound **10** has a diastereomeric excess of at least 95%.

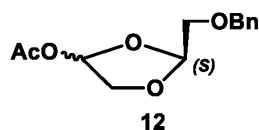
3. The method according to claim 2 wherein resulting compound **10** has a diastereomeric excess of at least 99%.

4. The method according to claim 1 wherein said aqueous acid is 1.0 N HCl.

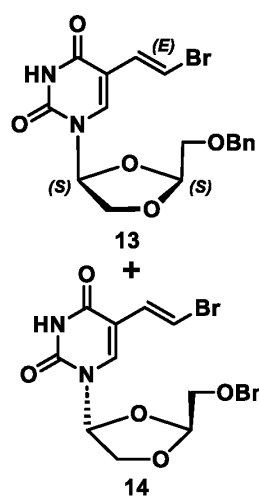
5. The method according to any one of claims 1-4 wherein said compound **11** is reacted with $\text{Mn}(\text{OAc})_2$, diacetoxymethyl iodobenzene and weak acid in solvent to form compound **12**



6. The method according to any one of claims 1-4 wherein said compound **11** is reacted with lead tetraacetate ($\text{Pb}(\text{OAc})_4$) and weak base to form compound **12**



7. The method according to claim 5 or 6 wherein compound **12** is coupled to bromovinyl uracil using tert-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) followed by iodotrimethylsilane (TMSI) to provide a mixture of compound **13** and compound **14**

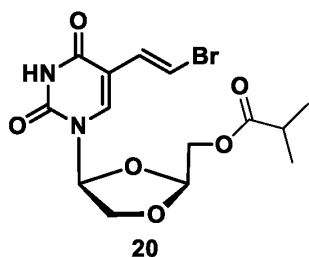


8. The method according to claim 7 wherein said mixture of compounds **13** and **14** is separated utilizing column chromatography to provide compound **13**.

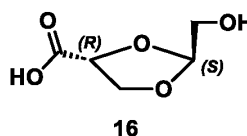
9. The method according to claim 8 wherein said compound **13** is exposed to boron trichloride (BCl_3) in solvent at low temperature followed by chromatographic separation to provide compound LBH DU (**15**).

10. The method according to claim 9 wherein said LBH DU (15) is reacted with bis(POM)phosphorochloridate in weak base in solvent to provide POM-L-BH DU-MP (22).

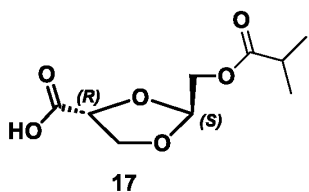
11. A method of synthesizing a compound according to the chemical formula 20



from compound 16

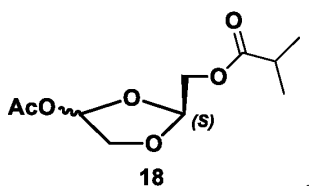


Comprising protecting the free hydroxyl group in compound 16 with an isobutyrate group to provide compound 17



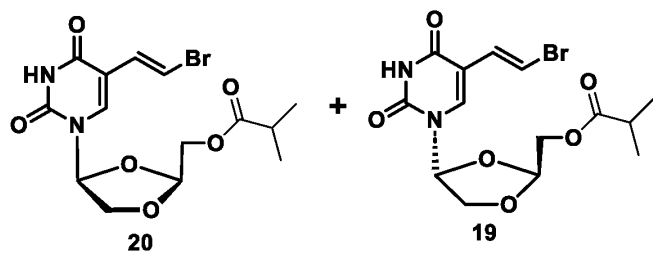
;

Reacting compound 17 with $\text{Mn}(\text{OAc})_2$, diacetoxyl iodobenzene in weak acid in solvent to provide compound 18, or reacting compound 17 with lead tetraacetate ($\text{Pb}(\text{OAc})_4$) and weak base to provide compound 18



;

Coupling compound 18 to bromovinyl uracil using tert-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) followed by iodotrimethylsilane (TMSI) to provide a mixture of compound 19 and compound 20



Which mixture of compounds 19 and 20 are separated using chromatography to provide compound 20.

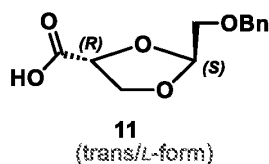
12. The method according to claim 11 wherein compound 17 is reacted with $\text{Mn}(\text{OAc})_2$, diacetoxyl iodobenzene in weak acid in solvent order to provide compound 18.

13. The method according to claim 11 wherein compounds 19 and 20 are separated using silica gel column chromatography.

14. The method according to claim 11 wherein compound 20 is deprotected to remove the isobutyrate protecting group to provide L-BH DU (15).

15. The method according to claim 14 wherein said isobutyrate group is removed in ammonia/methanol.

16. The method according to claim 11 wherein compound 16 is prepared from compound 11

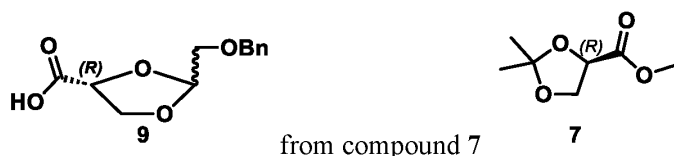


by reacting compound 11 with hydrogen gas using Pd/C as catalyst in methanol to remove the benzyl protecting group of compound 11.

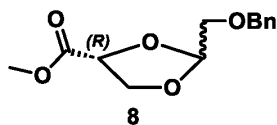
17. The method according to claim 14 or 15 wherein L-BH DU (15) is reacted with bis(POM)phosphorochloridate in the presence of weak base in solvent to provide POM-L-BH DU-MP.

18. The method according to claim 17 wherein said weak base is N-methylimidazole (NMI), and said solvent is tetrahydrofuran (THF).

19. A method of preparing compound 9



comprising reacting compound 7 with 2-(benzyloxy)acetaldehyde in solvent in the



presence of acid to form compound **8** ; and hydrolyzing the methyl ester group in compound **8** to provide compound **9** as a racemic mixture.

20. The method according to claim 19 wherein said compound **8** is purified using chromatography.

21. The method according to any one of claims 1-20 wherein said reaction steps are performed separately or in a single pot.

22. A compound which is selected from the group consisting of compound **8**, compound **9**, compound **10M**, compound **10**, compound **11**, compound **12**, compound **13** or a mixture thereof.

23. A compound which is selected from the group consisting of compound **16**, compound **17**, compound **18**, compound **20**, or a mixture thereof.