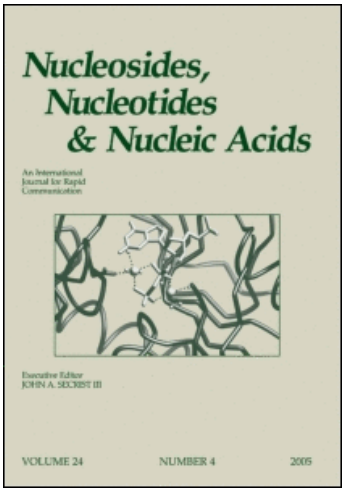


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# Synthesis of a Novel, Optically Active Uridine Analog Containing a 1,4-Dioxane Sugar Moiety. Synthesis of the Corresponding Dinucleotide

Qiang Yu[a]; Per Carlsen[a]
[a] Department of Chemistry, Norwegian University of Science and Technology, NTNU, Trondheim, Norway

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# SYNTHESIS OF A NOVEL, OPTICALLY ACTIVE URIDINE ANALOG CONTAINING A 1,4-DIOXANE SUGAR MOIETY. SYNTHESIS OF THE CORRESPONDING DINUCLEOTIDE

**Qiang Yu and Per Carlsen**

*Department of Chemistry, Norwegian University of Science and Technology, NTNU, Trondheim, Norway*

□ *A new optically active uridine nucleoside analogue in which a substituted 1,4-dioxane ring functioned as the sugar analogue was prepared from* L-*tartaric acid. The nucleoside analogue was further converted into the corresponding protected dinucleotide.*

**Keywords** Uridine analogs; 1,4-dioxane; nucleoside analogs; dinucleotide analogs; optically active; heterocycle



## INTRODUCTION

Nucleosides analogs have been a subject of considerable interest due to their potential biologic activities. In the search for new antiviral and antitumor agents, a number of nucleoside analogs have in recent years been synthesized in with the sugar moiety was modified,[1] and examples in which the sugar unit was replaced by a 1,4-dioxane group have been reported, in attempts to develop novel therapeutics.[2] Some were reported to have interesting biological activities.[2a,2b] Such an analogue may be more potent and/or selective, due to their conformational properties.[2c] Most of the reported nucleoside analogs with 1,4-dioxane groups replacing the sugar in the natural nucleosides were substitutes so that formation of polynucleotides was not possible. Few of the products described in these publications were optically active.

We here report the synthesis a new optically active nucleoside analog that consist of a 1,4-dioxane ring, substituted with uracil and a 1,2-

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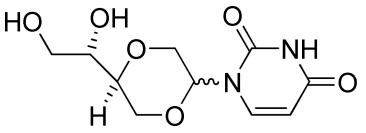
Address correspondence to Per Carlsen, Department of Chemistry, Norwegian University of Science and Technology, NTNU, N-7491, Trondheim, Norway. E-mail: per.carlsen@chem.ntnu.no




**1a**:1a-anomer, *trans*-isomer
**1b**:1a-anomer, *cis*-isomer

**FIGURE 1** Optically active 1,4-dioxane uridine analogs, **1a** and **1b**.

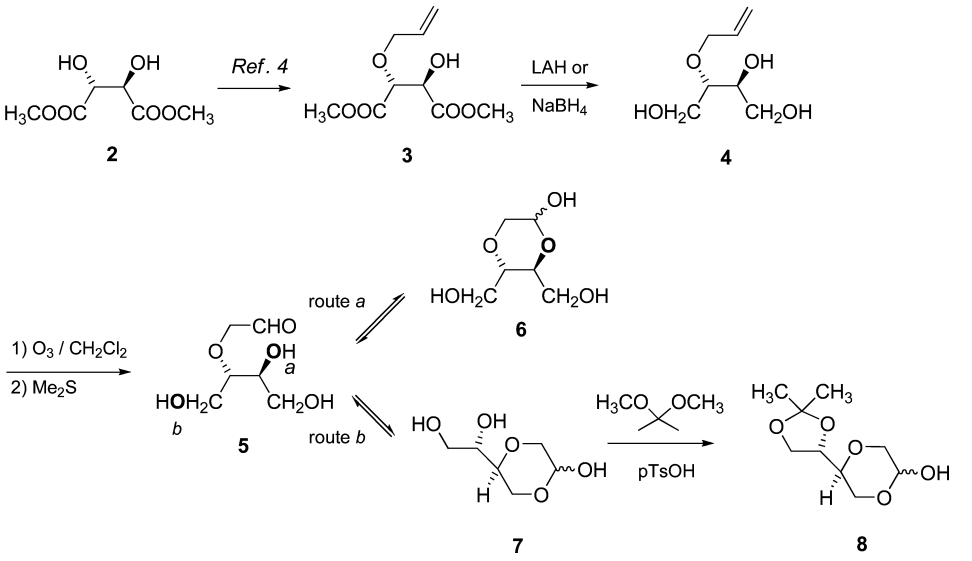
dihydroxyethyl substituent (Figure 1). With the dihydroxyethyl substituent is in the equatorial position, the uracil base is in either of the anomeric positions, thus the dihydroxyethyl substituent and the uracil ring are of either *trans*- or *cis*-configurations. This uridine analog was further elaborated into the corresponding dinucleotide using the standard phosphoraimidite procedure.[3] An additional objective was to establish if nucleoside **1** was a suitable substrate for the preparation of new oligonucleotides.



## RESULTS AND DISCUSSION

As the biologic activities of enantiomers are usually quite different, an important objective in the work was to develop a synthetic procedure that effortlessly produced either of the possible stereoisomers corresponding to structure **1**, that is, either of the four possible isomers of each anomer. The chirality of the 1,4-dioxane system was introduced through the use of tartaric acid, in this work exclusively *L*-tartaric acid, **2**, (*R,R*-tartaric acid). All the tartaric acid stereoisomers are inexpensive and readily available chiral pool materials.

Initially (2*R*,3*R*)-dimethyl tartrate was converted into the corresponding enantiomerically pure allyl ether **3** either by the reaction with allyl bromide in the presence of silver oxide[4] or in a tin assisted reaction with dibutyltin oxide.[5] Allylether **3** was next reduced to triol **4**, either using $LiAlH_4$[6] in 26% isolated yield, or as a viable alternative by reduction with $NaBH_4$[7] which gave **4** in 88% yield. The latter product contained minor borate impurities, but could be used in the subsequent steps without further purification. Ozonolysis of **4** gave the corresponding aldehyde **5**, which however spontaneously converted into the corresponding hemiacetals **6** and **7** (Scheme 1). NMR and IR measurements indicated the presence of no free aldehyde. Hemiacetal **6** was formed from **5** through ring closure with the C-3 OH group (route *a*), while hemiacetals **7** were obtained through ring closure with the C-1 OH group (route *b*). As expected separation of products **6** and **7** by chromatography was not successful. Assuming the hemiacetals being in equilibrium, it was expected that upon subjecting the mixture to acid catalyzed acetal formation with 2,2-dimethoxypropane, the more stable

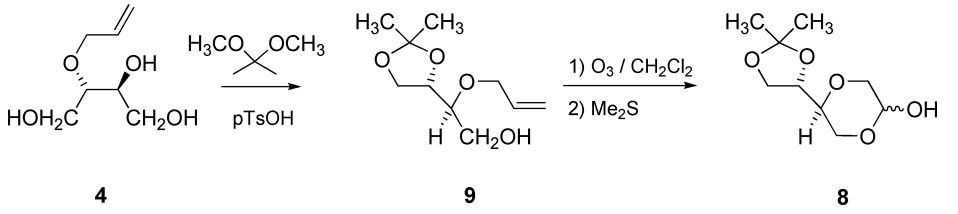



**SCHEME 1** Synthesis of chiral 1,4-dioxane sugar analogs **8** from *L*-dimethyl tartrate.

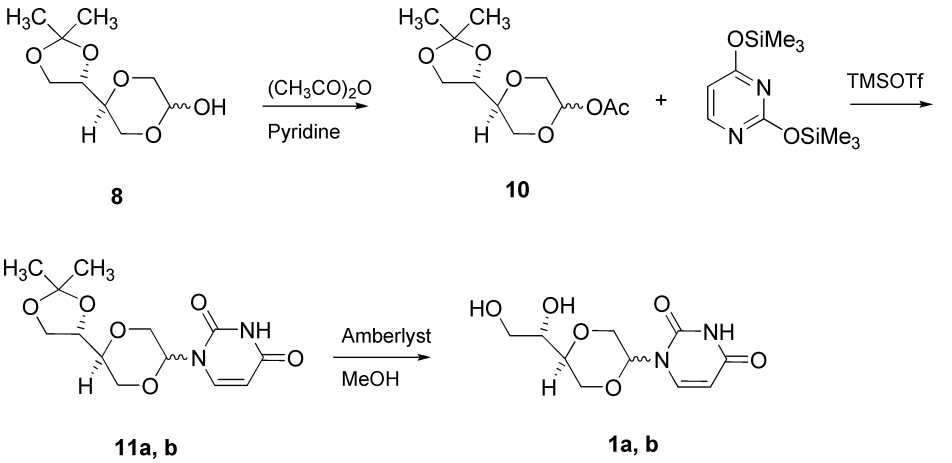


5-membered acetal **8** would be formed as the exclusive product. Diol **6** may form a less favorable 7-membered acetal. As it turned out, the desired product **8** was formed in mixture with unreacted **6**. Product **8** was isolated by flash chromatography, but obtained in merely 21% yield. That not all the components in the equilibria shown in Scheme 1 were channeled into acetal **8**, may be ascribed to the kinetic stability of hemiacetal **6** under the reaction conditions.

In order to obtain compound **8** in a better yield, the reaction sequence was altered. Thus, triol **4** was reacted with 2,2-dimethoxypropane with p-TsOH-catalysis to give the five-membered acetal **9** as the exclusive product, without any signs of the alternative seven-membered acetal. Ozonolysis of **9** gave after flash chromatography the desired 1,4-dioxane derivative **8** as the only product, isolated in 43% over-all yield from **3** (Scheme 2), as an approximately 1:1 mixture of the anomers. The stereochemistry of all stereogenic carbons were retained in all of these transformations, except for the anomeric hemiacetal carbon generated in the reaction sequence.




**SCHEME 2** Alternative synthesis of 1,4-dioxane sugar analog **8**.

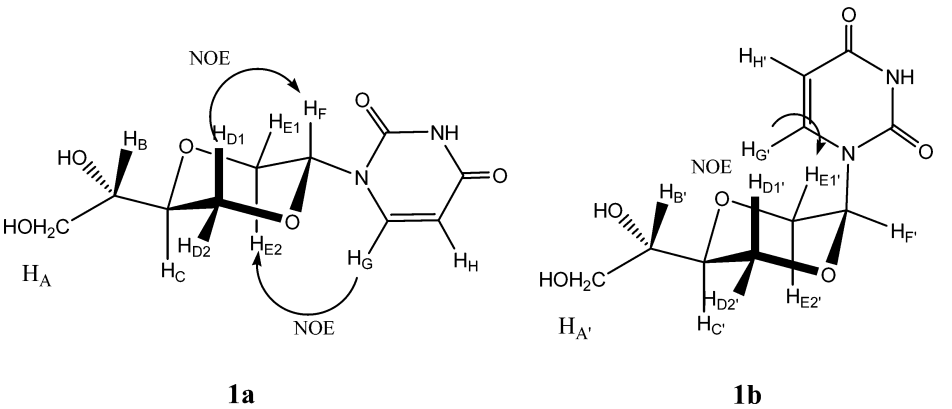



**SCHEME 3** Synthesis of 1,4-dioxane uracil analogs **1a** and **1b**.



For the introduction of the nucleic base into the pseudo-sugar, compound **8** was next acetylated with acetic anhydride in pyridine to give the mixture of anomeric acetates, **10** (Figure 3), which was then reacted in a TMSOTf-catalyzed reaction with silylated uracil[9] according to the Vorbrüggen's procedure.[8] This afforded nucleoside **11** (Figure 4), for which the acetal deprotection was removed using catalytic amount of Amberlyst 15 in methanol. This gave the desired uridine analog anomers **1a** and **1b**, as an approximately 4:1 mixture as indicated by NMR (Scheme 3) and in 59% isolated yield from compound **8**. Anomer, **1a** (Figure 5), was isolated in 42% yield from the reaction mixture by recrystallization from acetonitrile. The anomers were also readily separated by flash chromatography.

The structures of nucleoside analog **1a** and **1b** are shown in Figure 2, and were elucidated by $^{1}$H- and $^{13}$C-NMR, by DEPT and the various 2D-NMR



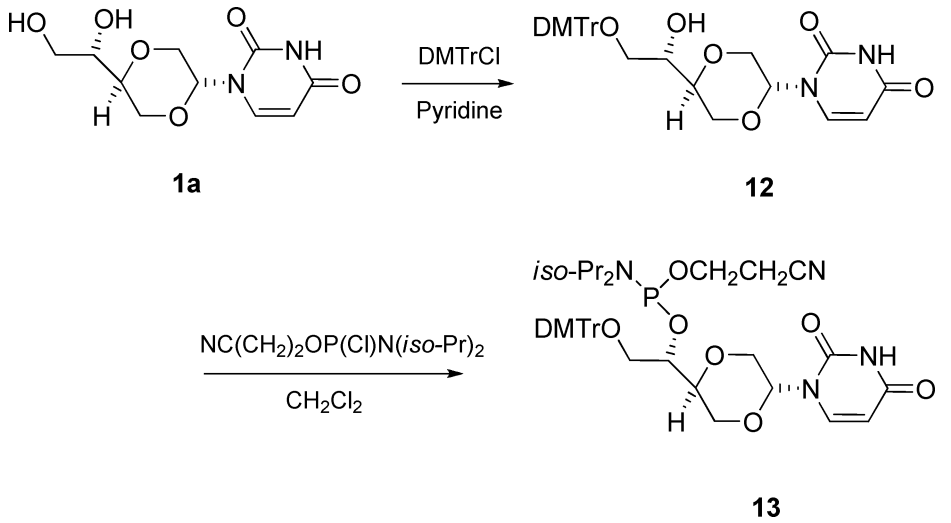

**1a** **1b**

**FIGURE 2** Structures of anomers **1a** and **1b**.

techniques, COSY, HSQC, HMBC, NOESY. In the $^1$H NMR spectrum of **1a**, a relatively large $J_{FE2}$ value (10 Hz) was observed, which indicated that $H_F$ occupied the axial position, uracil thus occupying the equatorial position. The coupling constants $J_{CD1}$ (11.2 Hz) and $J_{CD2}$ (2.8 Hz) provided evidence that $H_{D1}$ was in the axial position and $H_{D2}$ was equatorial, and $H_C$ was in an axial position. The 2D-NOESY experiment of **1a** showed a clear NOE effect between $H_F$ and $H_{D1}$. These data were in agreement with **1a** being the *trans*-compound. For diastereomer **1b**, in the $^1$H-NMR the coupling constants $J_{F'E1'}$ and $J_{F'E2'}$ were measured to 1.2 Hz and 3.7 Hz, respectively, indicating $H_{F'}$ to be in the equatorial position, hence the uracil group in the axial position. 2D-NOESY experiment with **1b** showed a clear NOE effect between $H_{G'}$ and $H_{E1'}$.

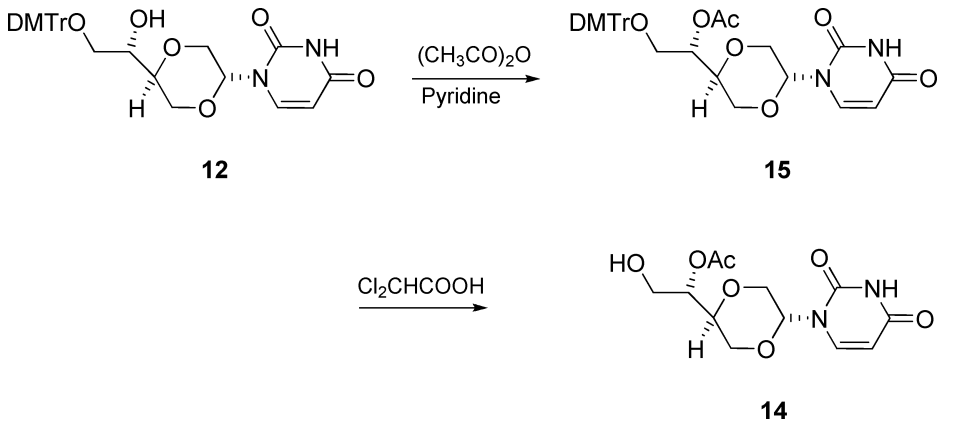
In modern polynucleotide chemistry, building oligonucleotides is usually done using solid support methods and automated synthesis machines. It was not planned here to prepare larger oligomers, but rather to elucidate if the dioxane nucleoside analogs were capable of undergoing the necessary transformations for such automated procedures. For this reason a batch procedure including the preparation of key intermediates and transformations were studied. To prepare the uridine dinucleotide analog, the phosphoramidite procedure[3] was adopted because this is extensively used in the solid phase synthesis of oligonucleotides. Uridine analog **1a** was thus reacted with 4, 4′-dimethoxyltrityl chloride in pyridine to afford primary hydroxyl group protected compound **12** (Figure 6).[10] Compound **12** was next treated with 2-cyanoethyl *N,N*-diisopropylphosphoramido chloride in the presence of *N,N*-diisopropylethylamine in anhydrous dichloromethane[11] at room temperature affording the desired intermediate **13** (Scheme 4






**1a** **12** **13**

**SCHEME 4** Synthesis of nucleoside phosphite analog **13**.




**SCHEME 5** Synthesis of uracil acetate analog **14**.



and Figure 7). Interestingly, the two diastereomers generated due to the presence of the phosphite stereogenic center, were separated by chromatography on a silica gel column.

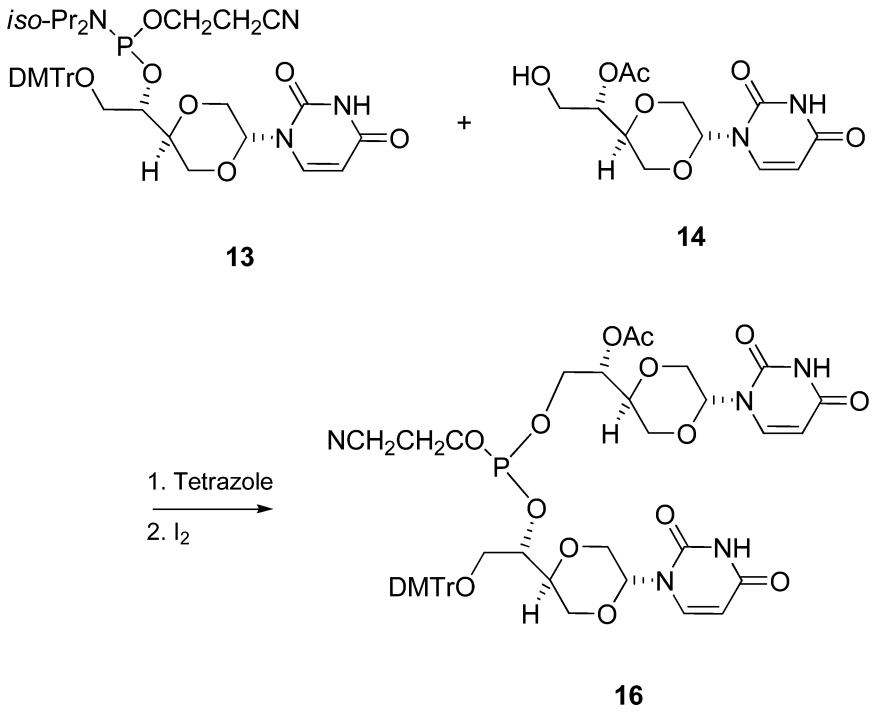
To obtain the other component required for the coupling scheme towards the protected dinucleotide **16**, intermediated **12** was first acylated with acetic anhydride in pyridine to afford compound **15** (Figure 8) and the trityl group was subsequently removed using dichloroacetic acid providing the desired primary alcohol **14** (Scheme 5 and Figure 9).

The uracil dinucleotide **16** was then prepared by coupling **13** with **14** in the presence of tetrazole in dry acetonitrile,[12] followed by iodine oxidation of the phosphite moiety to the desired protected phosphate group. The product was purification by flash chromatography on silica gel (Scheme 6). Dinucleotide **16** was formed as a diastereomeric mixture due to the phosphate stereogenic center. This resulted in rather complex $^{1}$H-NMR spectrum. The $^{31}$P NMR spectrum shows two strong signals at -1.83 and -1.90 ppm together with two very small signals at 9.0 ppm and 8.3 ppm, indicating the crude product to be of reasonable good purity. Compound **16** was further purified by column chromatography.

The synthesis was not extended beyond this point, as product **16** may now function as substrate for further oligomerization reactions, or be deprotected to give the parent uridine dinucleotide analog.

## CONCLUSIONS

In conclusion, the uridine 1,4-dioxane nucleoside analog **1** was readily prepared from tartaric acid. This compound was further converted into the corresponding partially protected dinucleotide, hence demonstrating that




**SCHEME 6** Synthesis of the protected uracil dinucleotide analog **16**.

the uridine nucleoside analog may be elaborated into larger oligomers using established standard procedure.[13]



## EXPERIMENTAL

NMR spectra were recorded on Bruker Avance DPX 300 or DPX 400 instruments (Bruker, Germany). Chemical shifts are reported in ppm using TMS (0.0) as the internal standard in $CDCl_3$ or relative to 2.50 ppm for $^1H$ and 39.99 ppm for $^{13}C$ in [$D_6$-DMSO] or 3.31 ppm for $^1H$ and 49.15 ppm for $^{13}C$ in $CD_3OD$. Structural assignments were based on $^1H$, $^{13}C$, DEPT135 and 2D spetra, COSY, HSQC, HMBC, NOESY. EI-Mass, and ESI spectra were recorded on a Finnigan MAT 95XL spectrometer (Finnegan MAT AB, Sweden). IR spectra were obtained on a FT-IR Nexus spectrometer (Thermo-Nicolet, USA) using a Smart Endurance reflection cell. For ozonolysis was used an OZ-500 Ozone Generator produced by Fischer Technology (Germany). Silica gel Kieselgel 60G (Merck) was used for Flash Chromatography. The solvents were purified by standard methods.

### (2*R*,3*R*)-Dimethyl 2-(allyloxy)-3-hydroxysuccinate, 3

This compound was prepared from dimethyl *l*-tartrate, **2**, as described earlier[14] either by reaction with allyl bromide and silver oxide,[4] resulting

in variable yields between 20 and 84% or by a reaction involving dibutyltin oxide[5] resulting in a 70% overall yield. B.p. 90°C at $10^{-3}$ torr. The spectroscopic properties were in agreement with those reported previously.[5]

### (2*S*,3*S*)-3-(Allyloxy)butane-1,2,4-triol, 4

This product was obtained by reduction of **3** with either $LiAlH_4$ or $NaBH_4$.

*$LiAlH_4$ reduction*: To a suspension of $LiAlH_4$ (3.72 g, 95%, 93 mmol) in dry diethyl ether (50 mL) was drop wise added a solution of **3** (4.36 g, 20 mmol) in 4 mL of diethyl ether at 0–5°C. The reaction mixture was refluxed for 18 hours and then cooled in an ice bath. Then 5 mL of water was added and the mixture stirred for 20 minutes, followed by addition of a 15% NaOH solution (12 mL) and then 10 mL of water. The resulting mixture was stirred and the granular salt formed, was separated by filtration, washed with hot THF (200 mL), and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3/CH_3OH$, 9:1 mixture) to give 0.83 g, 26% of the pure product **4**.

*$NaBH_4$ reduction*. Sodium borohydride (3.45 g, 93 mmol) in ethanol (50mL) was stirred for half an hour and then dropwise added a solution of **3** (4.35 g, 20 mmol) in ethanol (15 mL). The resulting solution was refluxed gently for 5 hours. The solution was cooled in an ice bath and added 10 mL of acetic acid. The mixture was stirred for 20 minutes and filtered. The solid was washed with 2 × 50 ml ethanol. The combined organic phase was concentrated under reduced pressure. The crude product was purified by flash chromatography using a 19:1 mixture of $CH_2Cl_2$/MeOH as the eluent yielding 2.88 g, 88% of the pure product, which exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.45 (q, 1H, CH-OAllyl), 3.66–3.74 (m, 3H, 1H from $CH_2$-CHOH, 2H from $CH_2$-CH-OAll), 3.80 (dd, 1H from $CH_2$-CHOH), 3.86 (q, 1H, CHOH), 4.03–4.20 (m, 2H, $OCH_2$-CH=CH2), 4.32 (s, broad, 3H, OH), 5.18–5.38 (m, 2H, $CH_2$ = CH), 5.86–5.96 (m, 1H, CH=CH2) ppm.$^{13}$C-NMR (CDCl3, 100MHz): $\delta$ = 60.6, 63.3, 71.6, 71.8, 79.1, 117.8, 134.5 ppm. MS (EI) *m/z*: 145 ($M^+$-OH), 131 ($M^+$-CH2OH), 101 (OH-$CH_2$ = $O^+CH_2$-CH=$CH_2$), 61 ($HOCH_2CH$=O+H). IR (neat): 3365, 2881, 1736, 1448 $cm^{-1}$.

### (*S*)-2-(Allyloxy)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol, 9

A solution of **4** (6.20 g, 38 mmol), 2,2-dimethoxylpropane (4.00 g, 38.5 mmol) and pTsOH (223 mg, 1.2 mmol) in 100 mL acetone was stirred overnight at room temperature. The solvent was then removed and the residue was purified by flash chromatography using a 3:2 mixture of $Et_2O$/*n*-hexane as the eluent to provide product **9** as colorless oil (5.11 g, 85%). Unreacted starting material **4** (1.05 g crude product) was recovered by

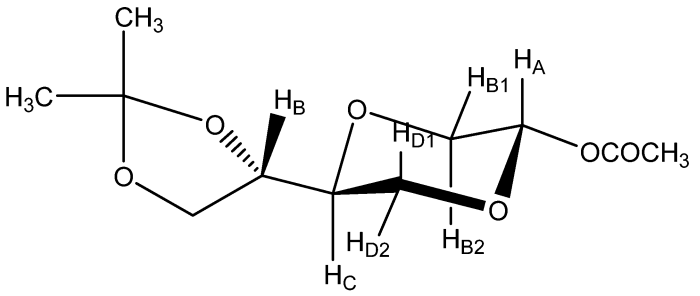
continued elusion with a 19:1 mixture of $CH_2Cl_2$/MeOH. Product **9** exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta$ = 1.37 (s, 3H, $CH_3$), 1.44 (s, 1H, $CH_3$), 2.48 (s, broad, 1H, OH), 3.49–3.53 (m, 1H, CH-OAll), 3.59 (dd, J = 10.8Hz, 12Hz, 1H, $HOCH_2$-CHOAll), 3.73 (dd, J = 4.2Hz, 12Hz, 1H, $HOCH_2$-CHOAll), 3.81 (dd, J = 7.2Hz, 8.4Hz, 1H, C-$OCH_2$CHO-C), 4.03 (dd, J = 6.4Hz, 8.4Hz, 1H, C-$OCH_2$CHO-C), 4.18–4.22 (m, 2H, $OCH_2$-CH=$CH_2$), 4.26–4.31 (m, 1H, C-$OCH_2$CHO-C), 5.24–5.33 (m, 2H, $CH_2$ = CH), 5.88–5.95 (m, 1H, CH=$CH_2$) ppm.$^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ 25.3, 26.4, 61.6, 65.4, 71.8, 76.4, 79.1, 109.4, 117.4, 134.7 ppm. MS: (EI) *m/z*: 202($M^+$), 187 ($M^+$-$CH_3$), 171($M^+$-$CH_2OH$), 101($C_5H_9O_2^+$).

### (2*R*,5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyl-1,4 -dioxane, 8a, and (2*S*,5*S*)-5-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxyl-1,4-dioxane, 8b

A solution of **9** (5.9 g, 29.2 mmol) in a mixed of methanol and dichloromethane (1:4) (200 mL) was ozonized at −78°C until a persistent blue color, 1 hour 45 minutes. The ozonolysis mixture was then purged until most of the blue color had disappeared and then added dimethyl sulfide (2.2 g, 35.5 mmol) and stirred overnight. The resulting mixture was concentrated under reduced pressure and the crude product purified by flash chromatography using a 7:3 mixture of $Et_2O$/n-hexane as the eluent, yielding the product as a colorless oil (4.62 g, 78%). The anomeric ration was approximately 1:1 as determined by NMR, however, the isomers were not separated. The product exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.36 (s, 3H, $CH_3$), 1.37(s, 3H, $CH_3$), 1.43 (s, 3H, $CH_3$), 1.44 (s, 3H, $CH_3$), 3.30 (dd, 8.4Hz, 11.2Hz, 1H, $OCH_2$CHOH-), 3.45 (dd, 11.6Hz, 2.8Hz, 1H, $CHCH_2$CHOH-), 4.84 (d, 8.4Hz, 1H, anomeric proton), 4.98 (d, 3.6Hz, 1H, anomeric proton), (3.55–3.66, m, 3H; 3.69–3.76, m, 1H; 3.78–3.84, m, 5H; 3.93–4.02, m, 3H; 4.05–4.16, m, 2H; the other protons). $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ 25.2, 26.22, 26.25, 59.3, 65.0, 65.1, 65.7, 69.2, 70.0, 74.29, 74.6, 74.9, 75.5, 88.7, 91.8, 109.8 ppm.

### (2*S*,5*S*)-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-acetyloxy-1,4 -dioxane, 10a, and (2*R*,5*S*)-5-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-acetyloxy-1,4-dioxane, 10b

To a solution of **9** (1.0 g, 4.9 mmol) in 15mL of dry pyridine was added acetic anhydride (0.62 g, 6 mmol) at 0–5°C and the reaction mixture was stirred for 6 hours. The solution was concentrated under reduced in vacuo overnight, yielding the crude product in 87% yield as a sticky oily material, which was used in the subsequent reaction step without further purification.




**10a**

**FIGURE 3** Structure **10a**.

The anomeric ration **10a**:**10b** (*trans-* *cis-* ratio) was determined to 4:1 by NMR.

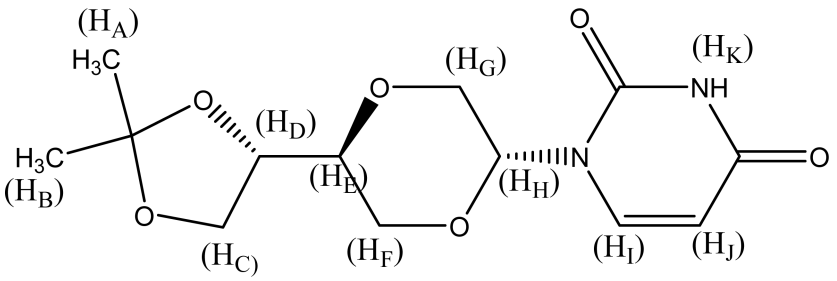
The product exhibited the following spectroscopic properties: NMR spectrum of *trans-* compound **10a** (Figure 3) was assigned the following signals: $^{1}$H-NMR ($CDCl_3$, 400MHz): $\delta$ = 1.36, 1.43 (s, 2×3H, $(CH_3)_2C$), 2.11 (s, 3H, $CH_3COO$), 3.48 (dd, J = 8.0Hz, 11.4Hz, 1H, $H_{B1}$), 3.63 (m, 1H, $H_C$), 3.69 (dd, J = 9.4Hz, 11.4Hz, 1H, $H_{D1}$), 3.81 (dd, J = 6.8Hz, 8.0Hz, 1H, $(CH_3)_2C$-O-$CH_2$), 3.89 (dd, J = 2.6Hz, 11.4Hz, 1H, $H_{D2}$), 3.93 (dd, 2.8Hz, 11.4Hz, 1H, $H_{B2}$), 4.00 (dd, 6.8Hz, 8.4Hz, 1H, $(CH_3)_2C$-O-$CH_2$), 4.15 (m, 1H, $(CH_3)_2C$-O-CH-), 5.74 (dd, 2.8Hz, 8.4Hz, 1H, $H_A$) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 20.9, 25.2, 26.3, 65.2, 65.6, 66.9, 74.2, 74.2, 89.4, 109.7, 169.0 ppm.

The protons NMR spectrum of the corresponding *cis-* compound, **10b**, could not be fully assigned due to the peaks overlap with **10a**. The carbons NMR spectrum of the *cis-* compound was assigned the following signals: $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 21.1, 25.2, 26.2, 61.0, 64.9, 67.6, 74.9, 75.1, 88.4, 109.7, 169.8 ppm.

The mixture exhibited the following mass spectrum: MS (EI) *m/z*: 247 ($M^+$+1), 231($M^+$-$CH_3$), 187($M^+$-OAc), 145 ($C_6H_9O_4$). Elem. Anal. calcd. for $C_{13}H_{18}N_2O_6$: C 53.65, H 7.37; found C, 53.84, H 7.45.

### 1-[(2*R*,5*S*)-5-[(4*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-1,4-dioxan-2-yl]uracil, 11a, and 1-[(2*S*,5*S*)-5-[(4*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)]-1,4-dioxan-2-yl]uracil, 11b

A mixture of uracil (0.92 g, 8.2 mmol) in 40 mL of hexamethyldisilazane (HMDS) was refluxed overnight. The resulting solution was concentrated and the residue was dissolved in 15 mL of dichloroethane. The solution was added **10** (0.48 g, 2 mmol) and the mixture was cooled to 0–5°C and added TMSOTf (0.37 mL, 2mmol). After 5 hours of stirring the mixture was added 60 mL dichloromethane, which was washed twice with 15 mL of




**11a**

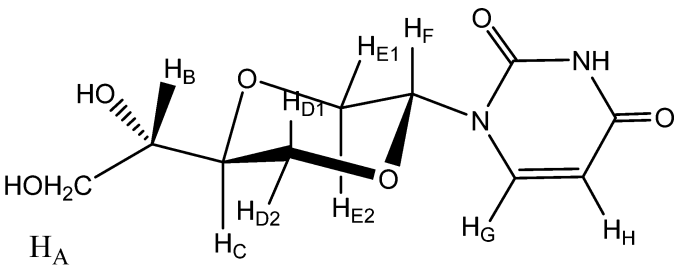
**FIGURE 4** Structure **11a**.

a saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted once with 50 mL chloroform, and the combined organic phase was washed with 20 mL saturated solution of NaCl, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give product **11** as a light yellow solid (0.37 g, 63.7%).

The *trans-cis*-ratio of the diastereomers was determined to 4:1 (NMR). The *trans*-compound **11a** (Figure 4) was assigned the following NMR signals: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta = 1.35$, 1.43 (s, 2×3H, $H_A$ and $H_B$), 3.40 (dd, 10Hz, 11.2Hz, 1H, $H_{G1}$), 3.78–3.89 (m, 2H, $H_{C1}$+$H_{F1}$), 3.94–4.06 (m, 3H, $H_{C2}$+ $H_{G2}$+$H_{F2}$), 4.10–4.17 (m, 2H, $H_D$+ $H_E$), 5.74–5.77 (m, 1H, $H_H$), 5.76 (d, J = 8.4Hz, 1H, $H_J$), 7.41 (d, J = 8.4Hz, 1H, $H_I$), 9.70 (s, 1H, $H_K$) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 25.10, 26.2, 64.9, 68.1, 68.3, 74.3, 74.5, 78.5, 102.9, 109.9, 139.4, 150.0, 163.2 ppm. It was not possible to fully assign the protons NMR spectrum of the *cis*-compound due to the overlap of the peaks with those of **11a**. The carbons NMR signals of the *cis*-compound were assigned as follow: $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 25.1, 26.1, 61.8, 64.9, 66.2, 74.37, 74.41, 75.4, 101.8, 110.0, 142.3, 151.1, 163.3 ppm. MS (EI) *m/z*: 298($M^+$), 283 ($M^+$-$CH_3$), 187 ($M^+$-uracil). IR (neat): 3197, 3098, 3065, 2986, 2937, 1688, 1452 $cm^{-1}$. Elem. anal.: Calcd. for $C_{13}H_{18}N_2O_6$: C 52.34, H 6.08, N 9.39; Found C, 52.43, H 6.41, N 9.23.

### 1-[(2*R*,5*S*)-5-[(1*S*)-1,2-dihydroxyethyl]-1,4-dioxan-2-yl]uracil, 1a, and 1-[(2*S*,5*S*)-5-[(1*S*)-1,2-dihydroxyethyl]-1,4-dioxan-2-yl] uracil, 1b

Compound **11** (0.35 g, 1.2 mmol) in 20 mL of methanol was refluxed for 2.5 hours in the presence of 50 mg of Amberlyst-15. The hot solution was filtered and the filtrate was cooled to room temperature. A white solid precipitated and was isolated by filtration. The product was dried *in vacuo* to give a pure *trans*-product **1a** (101 mg, 42%). NMR analysis of the concentrated crude product showed a 4:1 *trans-cis*-ratio (**1a**:**1b** = 4:1).




**1a**

**FIGURE 5** Structure **1a**.

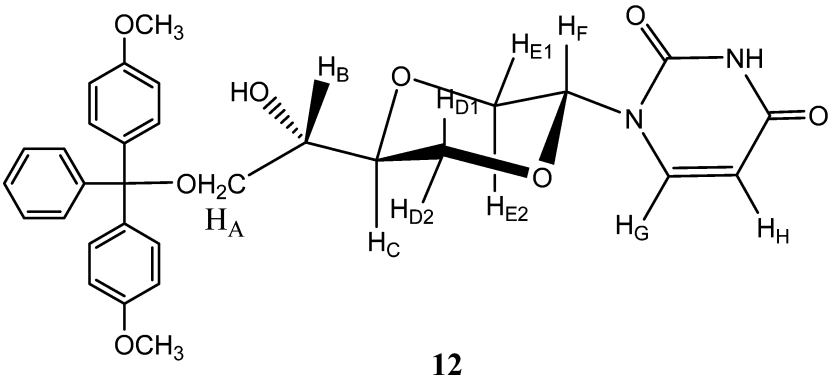
Product **1a** (Figure 5) exhibited the following spectroscopic properties: $^1$H-NMR ([$D_6$]DMSO, 400MHz): $\delta$ = 3.33 (dd, 12.8Hz, 16Hz, 1H, $H_{A1}$), 3.39–3.45 (m, 2H, $H_{A2}$ + $H_B$), 3.58 (dd, 10Hz, 11.2Hz, 1H, $H_{E2}$), 3.62 (dt, 2.8Hz, 2.8Hz, 11.2Hz, 1H, $H_C$), 3.78 (dd, 11.2Hz, 11.6Hz, 1H, $H_{D1}$), 3.83 (dd, 2.8Hz, 11.2Hz, 1H, $H_{E1}$), 3.96 (dd, 2.8Hz, 11.6Hz, 1H, $H_{D2}$), 4.61 (s, br. 2H, -OH), 5.53 (dd, 2.8Hz, 10Hz, 1H, $H_F$), 5.62 (dd, 2.4Hz, 8.0Hz, 1H, $H_H$), 7.69 (d, 8.0Hz, 1H, $H_G$), 11.41 (d, 2.4Hz, 1H, NH) ppm.$^{13}$C-NMR ([$D_6$]DMSO, 100MHz) $\delta$ 61.9, 67.0, 68.3, 70.4, 74.6, 77.9, 101.9, 140.9, 150.1, 162.9 ppm. IR (neat): 3478.9, 3430.3, 3032.2, 1704.1, 1674 $cm^{-1}$. MS (EI) *m/z*: 258($M^+$), 197($M^+$-(OHCHC$H_2$OH)), 147($M^+$-uracil). HRMS (ESI) *m/z*: for $C_{10}H_{14}N_2O_6$ $[M+Na]^+$ calcd, 281.0750; found 281.0746. Elem. anal.: Calcd, for $C_{10}H_{14}N_2O_6$: C 46.51, H 5.46, N 10.85; Found C 46.33, H 5.32, N 10.80. [$\alpha$] $^{25}_D$ +41.5 (c = 0.248, DMSO).



### 1-[(2*R*,5*S*)-5-[(1*S*)-hydroxy-2-(4,4′-dimethoxytrityl)-ethyl-1-yl]-1,4-dioxan-2-yl]uracil, 12

Compound **1a** (286 mg, 1.11 mmol) in dry pyridine (18 mL) was added 4, 4-dimethoxytrityl chloride (0.41g, 1.15mmol) at room temperature under nitrogen. The reaction mixture was stirred for 3 hours and the solution then concentrated to half volume and then added 50 mL of ethyl acetate. The resulting solution was washed with 3 × 10 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted with 50 mL ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate as the eluent to afford product **12** as a white solid (0.58 g, 93%).

The product **12** (Figure 6) exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta$ = 2.50 (d, 5.6Hz, 1H, OH), 3.17 (dd, 10Hz, 5.4Hz, 1H, $H_{A1}$), 3.27 (dd, 10Hz, 5.6Hz, 1H, $H_{A2}$), 3.37 (dd, 10.2Hz, 11.2Hz, 1H, $H_{E2}$), 3.62–3.67 (m, 1H, $H_B$), 3.71–3.75 (m, 1H, $H_C$), 3.79 (s, 2×3H, $OCH_3$), 3.78–3.84 (m, 1H, $H_{D1}$), 3.94 (dd, 2.0Hz, 11.6Hz, 1H, $H_{D2}$),




**12**

**FIGURE 6** Structure **12**.

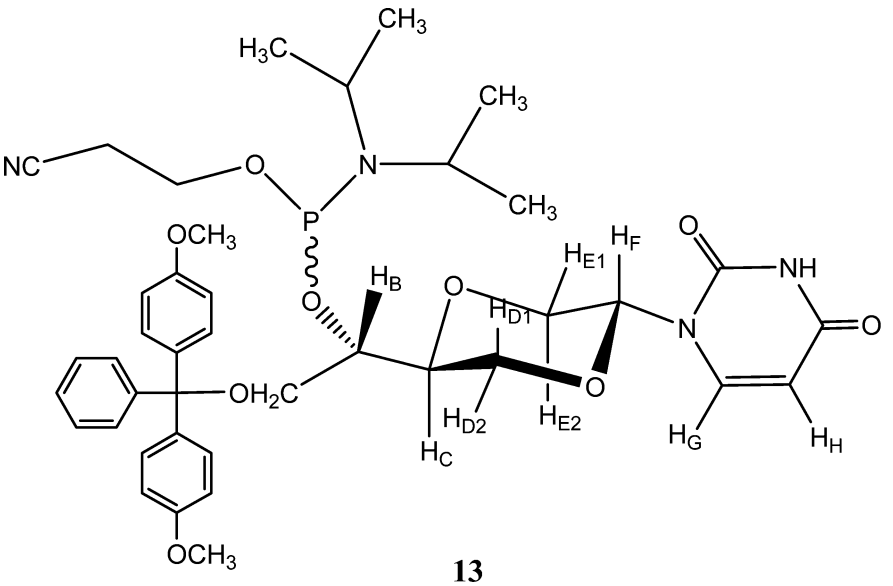
4.02 (dd, 2.8Hz, 11.2Hz, 1H, $H_{E1}$), 5.69 (dd, 2.8Hz, 9.6Hz, 1H, $H_F$), 5.74 (d, 8.4Hz, 1H, $H_H$), 6.82–6.85, 7.16–7.33 (m, aromatic hydrogen), 7.41–7.43 (m, $H_G$ and aromatic hydrogen), 9.08 (s, 1H, NH) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta = 55.4, 60.6, 63.8, 68.4, 68.9, 70.1, 75.1, 78.7, 86.6, 102.9, 113.36, 113.41, 127.1, 128.1, 128.24, 129.3, 130.2, 135.9, 136.0, 139.6, 144.8, 150.0, 158.8, 163.0$ ppm. IR (neat): 3427, 3201, 3061, 2999, 2836, 1687, 1508, 1247, 1031, 827, 756, 727, 702 $cm^{-1}$. MS (EI) *m/z*: 560.2($M^+$), 304.1(trityl), 273.1, 227.1, 197($M^+$-(OHCHCH$_2$OH)-trityl group). HRMS (ESI) *m/z*: for $C_{31}H_{32}N_2O_8$ $[M+Na]^+$ calcd, 583,2057; found 583.2050. Elem. anal.: calcd. for $C_{31}H_{32}N_2O_8$: C 66.42, H 5.75, N 5.00; found C 66.42, H 5.94, N 4.50.



### 1-[(2*R*,5*S*)-5-[(1S)-O-[2-cyanoethoxy(diisopropylamino) phosphino]-2-O-(4,4′-dimethoxy-trityl)-ethyl-1-yl]-1,4-dioxan-2-yl]uracil, 13

Compound **12** (275 mg, 0.49 mmol) in 10 mL of dry dichloromethane was added *N,N*-diisopropylethylamine (0.18 mL, 1.0 mmol) under nitrogen. To this solution was added 2-cyanoethyl *N,N*-diisopropylphosphoramido chloride (0.2 mL, 0.90 mmol). The reaction mixture was stirred for four hours. The solution was then added 20 mL of dichloromethane and washed with 2 × 5ml of a saturated $NaHCO_3$ solution and then with 10 mL of brine. The organic phase was dried over anhydrous $Na_2SO_4$, filtered and the solvent evaporated. The residue was purified by flash chromatography using a 9:1 mixture of ethyl ether and *n*-hexane as the eluent to afford three fractions of **13a** (70 mg, 17.7%) and **13b** (110 mg, 27.8%) and a mixture (60 mg, 15.2%) of **13a** and **13b**. Compounds **13a** and **13b** were the diastereomers due to the stereogenic centre of phosphorus.

Compound **13a** (Figure 7) exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta = 1.19$ (d, 4Hz, 2×3H, $H_J$), 1.21 (d, 4Hz, 2×3H, $H_J$), 2.42 (t, 6.6Hz, 2H, $H_L$), 3.09 (dd, 9.6Hz, 4.8Hz, $H_A$), 3.34

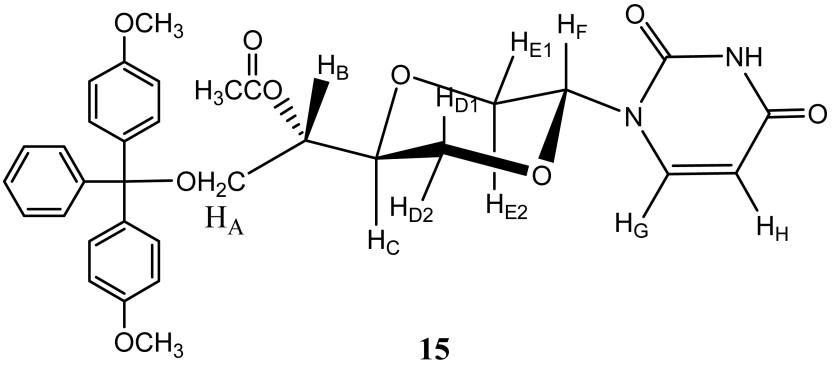



**13**

**FIGURE 7** Structure **13**.



(dd, 11.2Hz, 10Hz, $H_{E2}$), 3.41 (dd, 9.6Hz, 5.2Hz, $H_A$), 3.59–3.67 (m, 1H, $H_I$), 3.66–3.73 (m, 2H, $H_K$), 3.72–3.79 (m, 1H, $H_D$), 3.79 (s, 3H, $OCH_3$), 3.80 (s, 3H, $OCH_3$), 3.81–3.86 (m, $H_C$), 3.93–4.01 (m, 3H, $H_B$, $H_D$ and $H_{E1}$), 5.65 (dd, 9.6Hz, 2.8Hz, 1H, $H_F$), 5.74 (d, 8Hz, 1H, $H_H$), 6.80–6.86 (m, 4H, Aromatic H), 7.42–7.46 (m, Aromatic H), 7.20–7.25 (Aromatic H and $H_G$), 8.85 (broad s 1H, $H_L$) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 19.7, 19.8, 24.10, 24.16, 24.18, 24.22, 42.8, 42.9, 54.8, 57.7, 57.8, 62.1, 67.9, 68.1, 72.5, 74.7, 78.1, 85.9, 102.2, 112.2, 117.1, 126.4, 127.4, 127.7, 129.6, 135.3, 135.5, 139.1, 144.3, 149.2, 158.1, 162.2, 174.5 ppm. $^{31}$P (85% $H_3PO_4$): 151.7 ppm. Product **11b** exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta$ = 1.10 (d, 6.8Hz, 2×3H, $H_J$), 1.17 (d, 6.8Hz, 2×3H, $H_J$), 2.64 (dt, 6.4Hz, 0.4Hz, 2H, $H_L$), 3.15 (dd, 9.5Hz, 5.8Hz, $H_A$), 3.28 (dd, 9.5Hz, 5.6Hz, $H_A$), 3.40 (dd, 9.6Hz, 11.2Hz, $H_E$), 3.52–3.62 (m, 1H, $H_I$), 3.72–3.78 (m, 2H, $H_K$), 3.79 (s, 2×3H, $OCH_3$), 3.82–3.89 (m, 1H, $H_D$), 3.90–3.95 (m, 1H, $H_B$), 3.95 (dd, 11.2, 3.2Hz, $H_{E1}$), 4.00–4.07 (m, 2H, $H_D$ and $H_C$), 5.66 (dd, 9.6Hz, 2.8Hz, 1H, $H_F$), 5.73 (d, 8.2Hz, 1H, $H_H$), 6.80–6.85 (m, 4H, Aromatic H), 7.18–7.12 (m, 1H, Aromatic H) 7.25–7.30 (m, 2H, Aromatic H), 7.31–7.36 (m, 4H, Aromatic H), 7.43–7.46 (m, 2H, Aromatic H), 7.48 (d, 8.2Hz, 1H, $H_G$), 8.71 (broad s, 1H, N-H) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz): $\delta$ = 20.67, 20.74, 24.72, 24.80, 24.88, 24.94, 55.4, 58.1, 58.3, 62.7, 62.8, 68.6, 68.9, 72.6, 72.8, 75.28, 75.3, 78.7, 86.5, 102.8, 113.3, 127.0, 128.0, 128.3, 130.2, 130.3, 136.1, 136.2, 140.0, 145.0, 150.0, 158.7, 162.9 ppm. $^{31}$P (85% $H_3PO_4$): 151.3 ppm. IR (neat): 3204, 3064, 2965, 2931, 2874, 1693, 1508, 1248, 1177, 1029, 757, 726, 702




15

**FIGURE 8** Structure **15**.

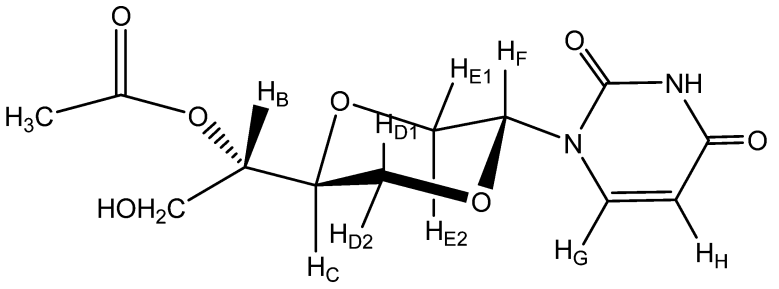
cm$^{-1}$. HRMS (ESI) *m/z*: Calcd. for $C_{40}H_{49}N_4O_9P$ $[M+H]^+$ 783.3135; found 783.3127. Elem. Anal.: Calcd. for $C_{40}H_{49}N_4O_9P$: C 63.15, H 6.49, N 7.36, P 4.07; found C, 63.03, H 6.52, N 7.25, P 3.96.



### 1-[(2*R*,5*S*)-5-[(1*S*)-acetyloxy-2-(4,4′-dimethoxytrityl)-ethyl-1-yl]-1,4-dioxan-2-yl]uracil, 15

Compound **12** (940 mg, 1.7 mmol) in 10 mL of dry pyridine was added acetic anhydride (360 ml, 3.4 mmol) at 0–5°C under an atmosphere of nitrogen. The mixture was stirred overnight. The mixture was the concentrated under reduced pressure and the residue was purified by flash chromatography using a 9:1 mixture of ethyl acetate and n-hexane as the eluent to afford product **15** (988 mg, 98%).

The product **15** (Figure 8) exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta = 2.15$ (s, 3H, $CH_3$), 3.15 (dd, 10Hz, 5.2Hz, 1H, $H_A$), 3.32 (dd, 10Hz, 5.6Hz, 1H), 3.34 (dd, 11.6Hz, 10Hz, 1H, $H_{E2}$), 3.61–3.78 (m, 1H, $H_D$), 3.79 (s, 2×3H, $OCH_3$), 3.89–3.95 (m, 2H, $H_C$ and $H_D$), 3.97 (dd, 11.4Hz, 3Hz, 1H, $H_{E1}$), 5.07 (dd, 9.6Hz, 5.2Hz, 1H, $H_B$), 5.69 (dd, 10Hz, 2.8Hz, 1H, $H_F$), 5.75 (d, 8Hz, 1H, $H_H$), 6.81–6.85 (m, 4H, aromatic H), 7.20–7.22 (m, 1H, aromatic H), 7.27–7.32 (m, 6H, aromatic H), 7.40–7.44 (m, 3H, aromatic H and $H_G$), 9.42 (broad s, 1H, N-H) ppm. $^{13}$C-NMR ($CDCl_3$, 100MHz) $\delta = 21.0$, 55.2, 61.4, 68.3, 70.9, 73.4, 78.4, 86.3, 102.8, 113.2, 126.9, 127.91, 127.98, 129.9, 130.0, 135.5, 135.6, 139.4, 144.5, 149.5, 149.8, 158.6, 163.0, 170.3 ppm. IR (neat): 3188, 3060, 2934, 2837, 1692, 1508, 1244, 1030, 827, 757, 727, 703 cm$^{-1}$. HRMS (ESI) m/z: Calcd. for $C_{33}H_{34}N_2O_9$ $[M+Na]^+$ 625.2162, Found 625.2152. Elem. Anal.: Calcd. for $C_{33}H_{34}N_2O_9$: C 65.77, H 5.69, N 4.65; found C 65.35, H 5.76, N 4.73.




**14**

**FIGURE 9** Structure **14**.

### 1-[(2*R*,5*S*)-5-[(1*S*)-acetyloxy-2-hydroxylethyl-1-yl]-1,4-dioxan-2-yl]uracil, 14

Compound **15** (849 mg, 1.4 mmol) in 25 mL of dry dichloromethane was added 40 mL solution of dichloroacetic acid (2%, v/v) in dichloromethane. The mixture was stirred for half an hour and quenched with 25 mL of a saturated aqueous $NaHCO_3$ solution. The separated aqueous phase was extracted with 3 × 40 mL dichloromethane. The combined organic phase was dried over anhydrous $Na_2SO_4$, and the solution the filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography, elution first with ethyl acetate then with methanol, to afford product **14** as a white solid (234 mg, 55%).

The product **14** (Figure 9) exhibited the following spectroscopic properties: $^1$H-NMR ($CD_3OD$, 400MHz): $\delta = 2.07$ (s, 3H, $CH_3$), 3.58 (dd, 11.4Hz, 9.8Hz, 1H, $H_{E2}$), 3.70–3.74 (m, 1H, $H_B$), 3.77–3.82 (m, 1H, $H_C$), 3.92–3.98 (m, 2H, $H_E$ and $H_{D1}$), 4.06 (dd, 11.6, 2.8Hz, 1H, $H_{D2}$), 4.13 (dd, 11.2, 6.4Hz, 1H, $H_A$), 4.16 (dd, 11.2Hz, 5.4Hz, 1H, $H_A$), 5.69 (dd, 10Hz, 2.8Hz, 1H, $H_F$), 5.70 (d, 8Hz, 1H, $H_H$), 7.71 (d, 8Hz, 1H, $H_G$) ppm. $^{13}$C-NMR ($CD_3OD$, 100MHz): $\delta$ = 20.9, 66.4, 69.2, 69.4, 69.8, 76.0, 80.0, 103.1, 142.3, 151.9, 166.0, 172.8 ppm. IR (neat): 3477, 3190, 3110, 3074, 2996, 2879, 1697, 1268, 1105 $cm^{-1}$. MS (EI): 230.3, 197($M^+$-($CH_3COCHCH_2OH$)), 189($M^+$-uracil). HRMS (ESI): Calcd. for $C_{12}H_{16}N_2O_7$ $[M+Na]^+$ 323.0856, Found 323.0862. Elem. Anal.: Calcd. for $C_{12}H_{16}N_2O_7$: C 48.00, H, 5.37, N, 9.33; found C, 47.51, H, 5.46, N, 9.85.

### Dinucleotide Analog 16

Compound **14** (8 mg, 0.027 mmol) and compound **13** (30 mg, 0.039 mmol) with a magnetic stirring bar were dried in high vacuo over night. The mixture was then added 6 mL of dry acetonitrile and 0.3 mL of 1-*H* tetrazole (0.45 M in acetonitrile). The resulting solution was stirred for 15 hours and then added a solution of iodine (1M in a mixture of THF, 2,6-lutidine and

$H_2O$ (2:2:1) until a persistent orange color. The solution was quenched with a saturated sodium thiosulfate solution, and then added 4 mL of a saturated $NaHCO_3$ solution and the phases separated. The aqueous phase was extracted with dichloromethane 4 × 8 mL. The combined organic phase was dried over anhydrous $Na_2SO_4$, filtered and then concentrated under reduced pressure. The crude product was purified by flash chromatography using gradient elution of the mixture of dichloromethane and methanol (25:1, 15:1). The product, **16**, was obtained as a white product, 16 mg, 62% yield. The product exhibited the following spectroscopic properties: $^1$H-NMR ($CDCl_3$, 400MHz): $\delta$ = 2.09, 2.11 (s, $CH_3COO$), 2.50–2.67 (m, $CH_2CN$), 2.71–2.75 (m, $CH_2CN$), 3.14–3.25, 3,38–3.52, 4.04–4.10 (m, $CH_2$-CH-Uracil), 3.79, 3.80 (s, $OCH_3$), 4.17–4.23 (m, $OCH_2CH_2CN$), 5.61–5.78 (m, CH=CH-CO in uracil and anomeric H), 6.81–6.86 (m, aromatic protons), 7.22–7.32 (aromatic protons and CH = CH-CO in uracil), 7.38–7.44 (aromatic protons and CH = CH-CO in uracil), 3.64–3.69, 3.72–3.81, 3.84–3.98, 4.21–4.33, 4.37–4.44, 4.52–4.67 (m, the other protons) ppm. $^{31}$P NMR ($CDCl_3$): -1.83, -1.90 ppm. HRMS (ESI): Calcd. for $C_{46}H_{50}N_5O_{17P}$ $[M+Na]^+$ 998.2837, Found 998.2802.



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