CYANO / DIALLYLAMINE ADDITIONS TO GLYCOSIDE AND NUCLEOSIDE ALDEHYDES AND ITS APPLICATION TO THE SYNTHESIS OF POLYOXIN L AND URACIL POLYOXIN C

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Abstract - Three efficient, high yielding syntheses of precursors (**1**) of carbamoylpolyoxamic acid from *L*-arabinose, based on the simultaneous addition of the acid and amine functionalities, are described. Utilizing the same methodology and uridine as the starting material, an expedient 3 step (61% overall yield) synthesis of protected uracil polyoxin C (or the nucleoside moiety of polyoxin L, **2**), is also described.

INTRODUCTION

Polyoxins C and L are part of a class of closely related peptidyl-nucleoside antibiotics from the culture broths of *Streptomyces cacaoi* var. *asoesis*, isolated by Suzuki *et al* in 1964.[2] All members of the polyoxin family possess 1-(5'-amino-5'-deoxy-β-D-allofuranuronosyl)pyrimidines such as uracil polyoxin C (Scheme 1). Polyoxins are potent competitive inhibitors of the chitin synthetase enzyme in a variety of phytopathogenic fungi (e.g. the human fungal pathogen, *Candida albicans*)[3] and have been extensively used as agricultural fungicides in Japan since 1967.[4] The chitin synthetase enzyme is the polymerizing enzyme responsible for the synthesis of chitin; a polysaccharide constituted of β-(1→4)-2-acetamido-2-deoxy-*D*-glucose units. Chitin is an essential structural component for growth in most fungi, where it is responsible for the shape and rigidity of the cell walls, and invertebrates, where it forms the exoskeleton, but is not synthesized by plants or vertebrates.[5] It is thought that the structural analogy of the nucleoside moiety of polyoxins and UDP-GlcNAc, the natural enzyme substrate, provides the basis for the binding ability of polyoxins, which are strengthened through extra contributing interactions of the polyoxamic acid moiety.[6] The interest in these compounds dictates the need for expedient and high yielding syntheses of intermediates that are generally applicable to the synthesis of polyoxins and derivatives.

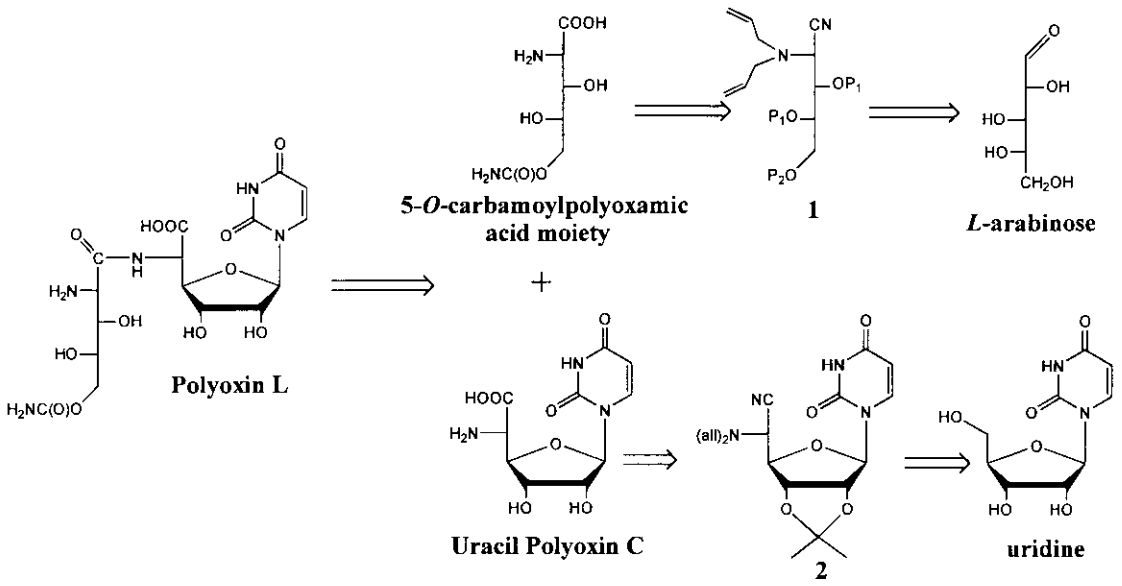
Interest in the synthesis of the polyoxins and related compounds began in the early 1970's with the first published synthesis of the sugar component of the nucleoside portion of the polyoxins.[7] Since then the synthesis of polyoxin C,[8] polyoxin L,[9] polyoxin J,[10] and/or fragments of the polyoxins[11] have been undertaken by various groups. We were interested in designing a synthesis of polyoxin L intermediates, which would be short, efficient and commence with relatively inexpensive starting materials.

The first detachment in a retrosynthesis of polyoxin L is commonly viewed in all reported syntheses as the breakage of the peptide bond to form the nucleoside and carbamoylpolyoxamic acid moieties (shown below).

In our design, polyoxamic acid derivatives (**1**) are procured starting from commercially available and inexpensive *L*-arabinose. *It is actually the L-threose sugar that is desired, for it has the correct* stereochemistry at the two hydroxyl positions, has a free terminal hydroxyl group, which can be functionalized as the carbamoyl functionality, and has an electrophilic formyl group, to which can be added a one carbon nucleophile to generate the amino acid portion of the polyoxamic acid. The problem with the use of *L*-threose as a starting material is cost and availability; therefore we decided to form, through oxidative cleavage of the terminal carbon, the desired 4-carbon threose from the 5-

carbon arabinose. In our design for the synthesis of polyoxamic acid derivatives, we chose to look at the simultaneous addition of the amine functionality and a one carbon fragment that would represent a protected acid functionality.

Scheme 1. Retrosynthetic Analysis.



A similar approach was planned for the synthesis of protected uracil polyoxin C (**2**). Most of the literature syntheses involve the stereocontrolled formation of the amino acid / sugar portion, followed by pyrimidine base addition utilizing Vorbruggen's methodology.[12] We chose to work with the nucleoside uridine directly since it is readily available and would decrease the number of steps in the synthesis.

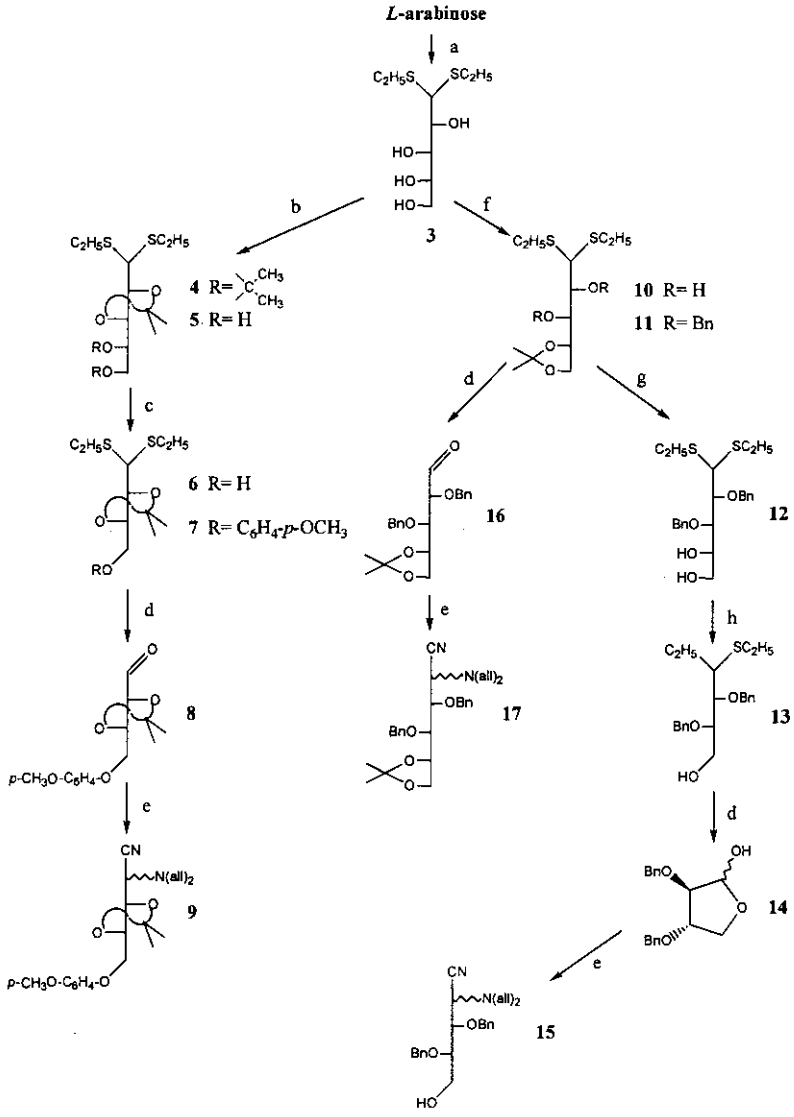
RESULTS AND DISCUSSION

(i) Synthesis of polyoxamic acid intermediates (**1**).

With the goal of developing protected polyoxamic acid derivatives we embarked on the synthesis of suitably protected sugars, onto which we could perform the simultaneous masked acid / protected amine addition reaction. This was accomplished in the following manner; first, protection of the formyl group of *L*-arabinose as a dithioacetal (**3**) and protection of all four hydroxy groups as isopropylidenes (**4**). To obtain the essential stereochemical centers in the target sugar moiety, the *L*-arabinose sugar must be shortened by one carbon. This was achieved by selective deprotection of the position 4,5-hydroxy groups to obtain a diol (**5**), which was subjected to sodium periodate modulated with a pH 6.4 buffer, to prevent isopropylidene cleavage, followed by reduction with sodium borohydride to form alcohol (**6**) in 77% yield from diol (**5**) (Scheme 2). Next, the terminal hydroxy group was protected by affixing the *p*-methoxyphenyl protecting group,[13] under Mitsonobu conditions, to afford the fully protected *L*-threose (**7**) in quantitative yield. The final step in the preparation of the suitably protected *L*-threose comprised of the deprotection of the aldehyde. This was accomplished with mercury oxide and mercury chloride in 10% aqueous acetone to produce (**8**) (Scheme 2).

Transformation of *L*-threose to our desired polyoxamic acid requires the addition of a one carbon nucleophile. The masked acid nucleophile that we were interested in using was a cyanide as literature precedence[14] existed for the simultaneous addition of a cyanide nucleophile and the amine functionality. In this procedure diallylamine was used as the amine source and diethyl

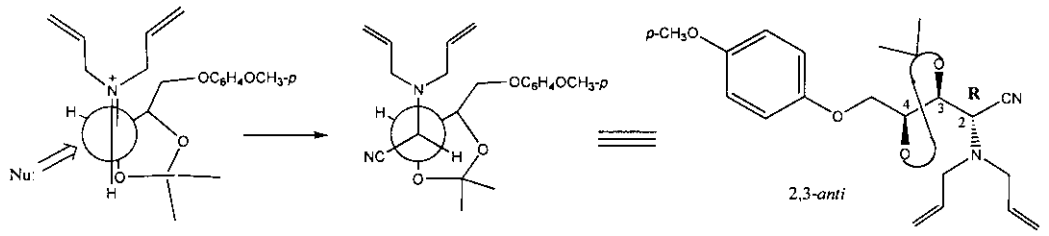
cyanophosphonate (DEPC) was used as the cyanide source. This Schiff's base / nucleophilic addition reaction, to produce α-amino nitrile (**9**), proceeded in 72% yield and gave a 4.5:1 mixture of epimers.



Scheme 2. **a.** C_2H_5SH, HCl (80%); **b.** *(i)* $(CH_3)_2C(OCH_3)_2$, TsOH, $(CH_3)_2CO$ (quant.); *(ii)* 80% HOAc, heat (87%); **c.** *(i)* $NaIO_4$, $NaBH_4$, CH_3OH, pH 6.4 (77%); *(ii)* *p*-$CH_3OC_6H_4OH$, PPh_3, DEAD, THF, heat (99%); **d.** Hg(II)O, $Hg(II)Cl_2$, 10% aq. $(CH_3)_2CO$ (**8**, 95%; **14**, 92%; **16**, quant.); **e.** DEPC, $HN(all)_2$, THF (**9**, 72%; **15**, 71%; **17**, 64%); **f.** *(i)* $(CH_3)_2C(OCH_3)_2$, $pyH^+OS(O)_2C_6H_4CH_3$, $(CH_3)_2CO$ (81%); *(ii)* NaH, BnBr, $(C_4H_9)_4NI$, THF (quant.); **g.** TFA / THF / H_2O, 1:2:1 (88%); **h.** $NaIO_4$, $NaBH_4$, CH_3OH, pH 6.4 (71%).

In the case of compound (**9**), the major epimer produced possesses the *R* configuration about the C-2 center. This was postulated on the basis that the schiff's base intermediate adopts an *anti* conformation due to heteroatom repulsion of the nitrogen with the oxygen on the adjacent carbon. The nucleophile (CN) would then preferentially approach from the less hindered face producing the 2,3-*anti* conformation or *R* configuration about the C-2 center (see diagram below). Molecular modeling

calculations[15] of the epimeric products also indicate that the *R* configuration is of lower energy and therefore favored.



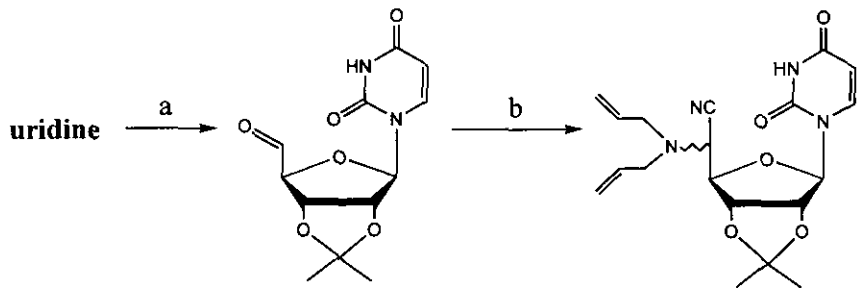
To start the synthesis of the dibenzylated derivatives (**15**) and (**17**), the hydroxy groups on the 4 and 5 positions were selectively protected so that the 2 and 3 positions would be free for benzylation. This was accomplished by the formation of an acetonide (**10**), with the catalytic aid of pyridinium *p*-toluenesulfonate, on the terminal hydroxyl groups.[16] The next step was protection of the remaining hydroxyl groups as benzyl ethers (compound (**11**), Scheme 2), which was accomplished in quantitative yield applying standard conditions of sodium hydride, benzyl bromide and tetrabutylammonium iodide. The acetonide protecting group was then removed using TFA, providing arabinose (**12**) in 88% yield. Truncation of the sugar was achieved in the same manner as described previously, utilizing sodium periodate and sodium borohydride, to procure the threose sugar (**13**) in 71% yield. Deprotection of threose sugar (**13**) using HgO and $HgCl_2$ gave threose furanose (**14**) in 92% yield (Scheme 2). From the ^{1}H-NMR spectrum we know that the deprotected sugar (**14**) exists in the ring form and we were able to assign the individual stereochemistry of the diasteriomers (shown in the experimental section). Once again, the cyano and diallylamine functionalities were added yielding 71% of an epimeric mixture of the *L*-xylononitrile(lyxononitrile) sugars (**15**).

In another approach, *L*-arabinose (**11**) was used as our starting material because we felt that it would be interesting to have some derivatives which were one carbon longer. Deprotection of dithioacetal (**11**) was performed under standard conditions (HgO, $HgCl_2$), and the desired aldehyde (**16**) was obtained in quantitative yield (Scheme 2). Addition of the cyano and amine functionalities by reaction of (**16**) with diallylamine and DEPC, to furnish *L*-glucononitrile(mannonitrile) (**17**), proceeded in 64% yield.

Compounds (**9**, **15**, and **17**) represent 3 orthogonally protected polyoxamic acids, which are ideally suited for the synthesis of polyoxins or of polyoxamic acid modified derivatives of polyoxins. Methods exist that allow for the deprotection of any one of the protecting groups utilized in the presence of the other protecting groups. Non stereo-selective conversion of (**9**, **15**, or **17**) into their corresponding α-amino acids can be achieved by the method of Boehm and Kingsbury.[11c] In this method, an analog of amino nitrile (**2**) is first hydrolyzed to the amide with alkaline hydrogen peroxide, followed by treatment with nitrosyl sulfuric acid to obtain the α-amino acid. Separation of the amino nitrile or α-amino acid diastereomers can be achieved via silica gel preparative HPLC.[11c]

(ii) Synthesis of protected uracil polyoxin C (2).

To achieve the synthesis, the 2' and 3'-positions of uridine were first protected by forming a 2',3'-isopropylidene derivative. This is a well known literature reaction[17] which proceeds in quantitative yield. For the oxidation, the conditions employed were obtained by following the protocol of Pfitzner and Moffatt[18] for the formation of compound (**18**). Using the same methodology of simultaneous introduction of the amino and carboxyl functionalities as already demonstrated, we achieved the synthesis of the fully protected chitin synthetase inhibitor uracil polyoxin C (**2**). This reaction was performed using diethyl cyanophosphonate (DEPC) and diallylamine to produce compound (**2**) in 67% yield as an approximately 1:1 mixture of diastereomers (Scheme 3).



Scheme 3. **a.** *(i)* $(CH_3)_2CO$, $CuSO_4$, H_2SO_4; *(ii)* DMSO, DCC, H_3PO_4 (91%); **b.** DEPC, $HN(all)_2$, THF (67%).

This route provides an expeditious synthesis of uracil polyoxin C based on a new approach to the key intermediate (**2**), similar cyano nucleosides have been shown to be intermediates in the synthesis of uracil polyoxin C.[11c,e] Deprotection of the amine functionality can be achieved through rhodium-catalyzed isomerization of the allyl protecting groups.[19]

CONCLUSION

The syntheses described herein demonstrate the utility of the simultaneous bifunctional (CN / $N(allyl)_2$) addition reaction for the short path synthesis of protected polyoxamic acids and protected uracil polyoxin C from their corresponding aldehydes, which contribute to the total synthesis of uracil polyoxin C and polyoxin L. The syntheses developed here have great potential since they are relatively short, commence from inexpensive, commercially available, starting material, and proceed in good overall yield (protected polyoxamic acids: **9** - 36.3%, **15** - 41.5%, and **17** - 26.4%; protected uracil polyoxin C: **2** - 61%). This method also proceeds with reasonable stereocontrol in the synthesis of polyoxamic acid derivative **9**.

EXPERIMENTAL

General Methods

Melting points were determined on a Gallenkamp block and are uncorrected. Solution IR were recorded on an Analect AQS-18 FT-IR spectrophotometer in the indicated solvent. Low and high resolution chemical ionization MS were obtained on a DuPont 21-492B mass spectrometer or a HP-5980A quadrapole mass spectrometer in the direct inlet mode. ^{1}H-NMR spectra were obtained on either a Varian XL-200 or XL-300 spectrometer at 200 MHz and 300 MHz, respectively, and the peak assignments were made with the aid of homonuclear decoupling experiments. Chemical shifts are given in the scale of parts per million (ppm). The residual proton signal of chloroform (assigned value of δ 7.24) was used as reference. The multiplicities are recorded using the following abbreviations: **s**, singlet; **d**, doublet; **dd**, doublet of doublet; **ddd**, doublet of doublet of doublet; **t**, triplet; **q**, quartet; **m**, multiplet; **br**, broad; **ex**, exchangeable. ^{13}C-NMR spectra were obtained on a Varian XL-300 spectrometer at 75.4 MHz and the peak assignments were made with the aid of APT and/or HETCOR experiments. The ^{13}C signals of $CDCl_3$ (assigned value of δ 77.00) was used as reference.

Methanol was distilled from magnesium. DMSO was distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. TLC was performed on silica gel (Kieselgel 60 F_{254}) aluminum-backed plates (0.2 mm thickness) and visualized by UV and/or dipping into a solution of 2.5 g ammonium molybdate and 1 g ceric sulfate in 10 mL sulfuric acid / 90 mL water, followed by heating. Kieselgel 60 (Merck 230-400 mesh) silica gel was used for flash chromatography.[20]

2,3-*O*-Isopropylidene-*L*-arabinose diethyl mercaptal (5).
A solution of 2,3:4,5-di-*O*-isopropylidene-*L*-arabinose diethyl dithioacetal (**4**) (11.04 g, 32.8 mmol) in 80% aqueous acetic acid (100 mL) was heated at 55°C for 2 h with stirring, after which it was evaporated to near dryness *in vacuo*. The residue was diluted with ethyl acetate (100 mL), washed with saturated aqueous $NaHCO_3$ (2 X 80 mL) and water (80 mL) and the washings re-extracted with ethyl acetate (2 X 100 mL). The combined ethyl acetate layers were dried over $MgSO_4$ and evaporated *in vacuo* yielding 9.14 g of the crude product. Since the crude product contains a small amount of starting material as well as some tetra-ol, further purification was effected by flash chromatography over silica gel (eluent: hexanes / ethyl acetate, 2:1, v/v) to yield diol (**5**) (8.46 g, 87%) as a white solid, mp 72-74°C. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.30 (dd, J = 3.9 and 6.9 Hz, 1H, H2), 4.10 (t, J = 6.9 Hz, 1H, H3), 4.00 (d, J = 3.9 Hz, 1H, H1), 3.84 - 3.68 (m, 3H, H4 and H5), 2.82 (br s ex, 1H, OH at position 4), 2.72 (q, J = 7.4 Hz, 4H, $SC\mathbf{H}_2CH_3$), 2.21 (br s ex, 1H, OH at position 5), 1.43 & 1.37 (2s, 6H, $C\mathbf{H}_3$ of isopropylidene), 1.25 & 1.24 (2t, J = 7.4 Hz, 6H, $SCH_2C\mathbf{H}_3$); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 110.10 [$\mathbf{C}(CH_3)_2$], 83.15 [**C**2], 79.40 [**C**3], 72.88 [**C**4], 63.95 [**C**5], 53.12 [**C**1], 27.31, 2703 [$C(\mathbf{C}H_3)_2$], 25.44, 25.15 [$S\mathbf{C}H_2CH_3$], 14.34 [$SCH_2\mathbf{C}H_3$]}.

2,3-*O*-Isopropylidene-*L*-threose diethyl mercaptal (6).
To a stirred solution of diol (**5**) (8.20 g, 27.7 mmol) in 100 mL of methanol was added 100 mL of a pH 6.4 buffer (Hydrion) and then $NaIO_4$ (5.92 g, 27.7 mmol). Almost immediately following the addition of $NaIO_4$, a flocculent white precipitate ($NaIO_3$) was seen to form. To ensure completion of the cleavage reaction, it was left to stir for approximately 45 min. The $NaIO_3$ precipitate was filtered off, washed with methanol (20 mL) and to the filtrate was added $NaBH_4$ (1.05 g, 27.7 mmol), to reduce the aldehyde formed in the periodate cleavage reaction. The reduction was left to proceed for 1 h after which the reaction mixture was extracted with CH_2Cl_2 (2 X 500 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated *in vacuo* yielding 8.24 g of the crude product. Further purification was effected by flash chromatography over silica gel (eluent: ethyl acetate / hexanes, 1:1, v/v) to yield 5.00 g of **6** (67%, 77% based on recovered diol) and 1.05 g of diol. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.13 (br d, 2H, H2 and H3), 3.96 - 3.86 (doublet of A of ABX, J = 2.4, -11.9 and 5.3 Hz, 1H, H4a), 3.87 (d, J = 2.0 Hz, 1H, H1), 3.80 - 3.69 (doublet of B of ABX, J = 4.6, -11.9, and 7.8 Hz, 1H, H4b), 2.78 - 2.61 (m, 4H, $SC\mathbf{H}_2CH_3$), 1.97 (dd ex, J = 5.3 and 7.8 Hz 1H, OH at position 4), 1.44, 1.40 (2s, 6H, $C\mathbf{H}_3$ of isopropylidene), 1.27, 1.25 (2t, J = 7.4 Hz 6H, $SCH_2C\mathbf{H}_3$); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 109.50 [$\mathbf{C}(CH_3)_2$], 80.19 [**C**2], 79.45 [**C**3], 62.86 [**C**4], 53 .01 [**C**1], 27.22, 26.96 [$C(\mathbf{C}H_3)_2$], 25.33, 24.91 [$S\mathbf{C}H_2CH_3$], 14.33, 14.22 [$SCH_2\mathbf{C}H_3$]}.

2,3-*O*-Isopropylidene-4-*O*-*p*-methoxyphenyl-*L*-threose diethyl mercaptal (7).
To a stirred solution of the *L*-threose (**6**) (4.69 g, 17.5 mmol) in 62 mL of dry THF was added *p*-methoxyphenol (6.52 g, 52.5 mmol), triphenylphosphine (5.97 g, 22.8 mmol), and diethyl azodicarboxylate (3.6 mL, 22.8 mmol). The mixture was refluxed under a nitrogen atmosphere for 30 min. It was then evaporated to dryness *in vacuo* and purified by flash chromatography over silica gel (eluent: hexanes / ethyl acetate, 4:1, v/v) to yield the fully protected *L*-threose (**7**) as a clear oil (6.51 g, 99%). {^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.83 (AB q, J = 9.3 Hz, 4H, aromatic of *p*-methoxyphenyl), 4.44 - 4.38 (m, 1H, H3), 4.28 (dd, J = 5.3 and 7.4 Hz, 1H, H2) 4.14 (d, J = 5.1 Hz, 2H, H4), 3.96 (d, J = 5.3 Hz, 1H, H1), 3.74 (s, 3H, OCH_3), 2.73, 2.72 (2q, J = 7.4 Hz, 4H, $SC\mathbf{H}_2CH_3$), 1.48, 1.44 (2s, 6H, $C\mathbf{H}_3$ of isopropylidene), 1.27, 1.24 (2t, J = 7.4 Hz, 6H, $SCH_2C\mathbf{H}_3$); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 154.06, 152.75 [quaternary aromatics], 115.53, 114.59 [aromatics], 110.19 [$\mathbf{C}(CH_3)_2$], 81.00 [**C**2], 78.03 [**C**3], 69.63 [**C**4], 55.68 [$O\mathbf{C}H_3$], 53.01 [**C**1], 27.11 [$C(\mathbf{C}H_3)_2$], 25.51, 25.14 [$S\mathbf{C}H_2CH_3$], 14.41,

14.32 [SCH_2CH_3]; LRMS (CI-NH_3): m/e 315 ([MH^+ - $(CH_3)_2CO$], 0.52%), 253 ([$C_{15}H_{23}O_3S_2^+$(315) - CH_3CH_2SH], 100%); HRMS (CI-NH_3): m/z calcd for $C_{18}H_{29}O_4S_2$ [MH^+], 373.1507; found, 373.1507}.

2,3-*O*-Isopropylidene-4-*O*-*p*-methoxyphenyl-*L*-threose (8).
To a stirred solution of fully protected *L*-threose (**7**) (1.22 g, 3.3 mmol) in 30 mL of 9:1 acetone / water were added Hg(II)O (1.96 g, 8.2 mmol) and $Hg(II)Cl_2$ (2.45 g, 8.2 mmol) and the mixture was stirred at rt for 3 h. The initial medium orange colored reaction mixture became lighter orange in color over the course of the reaction. After the 3 h period, the reaction mixture was filtered through a bed of celite, washed with CH_2Cl_2 (50 mL) and the filtrate washed with 10% aqueous KI (50 mL) and then water (50 mL). The organic phase was then dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* at rt. For characterization purposes, the purification could be effected by flash chromatography over silica gel (eluent: initially 3:1, hexanes / ethyl acetate, v/v, followed by 2:1, hexanes / ethyl acetate, v/v to elute the aldehyde) to yield 835 mg (95%) of **8** as a clear oil. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.81 (d, J = 1.5 Hz, 1H, H1), 6.83 (AB q, J = 9.2 Hz, 4H, aromatic of *p*-methoxyphenyl), 4.42 - 4.37 (m, 1H, H3), 4.33 (dd, J = 1.5 and 7.2 Hz, 1H, H2), 4.09 (d, J = 4.1 Hz, 2H, H4), 3.74 (s, 3H, OCH_3), 1.51, 1.44 (2s, 6H, CH_3 of isopropylidene); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 204.62 [**C**1], 154.26, 152.44 [quaternary aromatics], 115.66, 114.62 [aromatics], 111.99 [$C(CH_3)_2$], 81.92 [**C**2], 75.59 [**C**3], 68.57 [**C**4], 55.64 [OCH_3], 26.79, 26.28 [$C(CH_3)_2$]}.

1-Cyano-1-*N*-diallyl-2,3-*O*-isopropylidene-4-*O*-*p*-methoxyphenyl-*L*-threose (9).
Crude aldehyde (**8**) (~3.3 mmol) was dissolved in 33 mL dry THF and to this solution were added diethyl cyanophosphonate, DEPC (0.7 mL, 3.9 mmol), and diallylamine (1.0 mL, 7.2 mmol). After stirring at rt under a nitrogen atmosphere for 3 h, the reaction mixture was then evaporated to dryness. Further purification was effected by flash chromatography over silica gel (eluent: hexanes / ethyl acetate, 20:1, v/v) to yield one spot of an approximately 4.5:1 diastereomeric mixture of **9** (874 mg, 72%), as a colorless oil with a very slight yellow tinge. {IR (CH_2Cl_2): 2359 cm^{-1}, -C≡N; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.81 (AB q, J = 9.2 Hz, 4H, aromatic), 5.90 - 5.70 (m, 2H, -N-CH_2-**CH**=CH_2), 5.31 - 5.15 (m, 4H, -N-CH_2-CH=**CH**$_2$), 4.48 - 4.39 (m, 1H, H3), 4.26 (dd, J = 5.0 and 7.6 Hz, 1H, H2), 4.11 (A of ABX, J = 4.7 and -10.1 Hz, 1H, H4a), 4.01 (B of ABX, J = 5.3 and -10.1 Hz, 1H, H4b), 3.98 (d, J = 5.0 Hz, 1H, H1), 3.75 (s, 3H, OCH_3), 3.64 - 3.55 (m, 2H, N-**CH**$_2$-CH=CH_2), 2.98 - 2.92 (m, 2H, N-**CH**$_2$-CH=CH_2), 1.44, 1.43 (2s, 6H, CH_3 of isopropylidene); **R** (major): ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 154.20, 152.44 [quaternary aromatics], 134.51 [N-CH_2-**C**H=CH_2], 118.97 [N-CH_2-CH=**C**H_2], 115.44, 114.60 [aromatics of *p*-methoxyphenol], 115.36 [C1-**C**N], 110.54 [**C**$(CH_3)_2$], 78.17 [**C**2], 75.64 [**C**3], 68.69 [**C**4], 55.70 [-N-**C**H_2-CH=CH_2], 55.68 [OCH_3 of *p*-methoxyphenol], 53.97 [**C**1], 26.95, 26.78 [$C(CH_3)_2$]; **S** (minor): ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 154.20, 152.44 [quaternary aromatics], 134.26 [-N-CH_2-**C**H=CH_2], 119.28 [-N-CH_2-CH=**C**H_2], 115.44, 114.60 [aromatics of *p*-methoxyphenol], 115.36 [C1-**C**N], 111.02 [**C**$(CH_3)_2$], 77.88 [**C**2], 77.67 [**C**3], 68.69 [**C**4], 54.98 [-N-**C**H_2-CH=CH_2], 55.68 [OCH_3 of *p*-methoxyphenol], 54.95 [**C**1], 27.17, 27.09 [$C(CH_3)_2$]; Anal. Calcd for $C_{21}H_{28}N_2O_4$ (372.4664): C, 67.72; H, 7.58; N, 7.52. Found: C, 67.36; H, 7.86; N, 7.77}.

4,5-*O*-isopropylidene-*L*-arabinose diethyl mercaptal (10).
To a stirred solution of *L*-arabinose diethyl dithioacetal (**3**) (2.2 g, 9 mmol) in 90 mL of acetone were added 2,2-dimethoxypropane (2.2 mL, 18 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate (112 mg, 0.45 mmol). After stirring for 90 min at rt, the reaction mixture was evaporated to near dryness *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), washed with

water (2 X 30 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Further purification was effected by recrystallisation from hot toluene (~5 mL) to yield 2.07 g (81%) of pure diol (**10**), mp 63-65°C. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.12 - 3.90 (m, 2H, H5), 4.10 (d, J = 2.6 and 4.9 Hz, 1H, H4), 4.06 (s, 1H, H1), 3.99 (dd, J = 9.4, 9.1 and 2.6 Hz, 1H, H3), 3.71 (dd, J = 9.4 and 2.4 Hz, 1H, H2), 3.23 (d ex, J = 2.4 Hz, 1H, OH at position 2), 2.77 - 2.61 (m, 4H, SCH_2CH_3), 2.31 (d ex, J = 9.1 Hz, 1H, OH at position 3), 1.40, 1.33 (2s, 6H, CH_3 of isopropylidene), 1.26 (t, J = 7.4 Hz, 6H, SCH_2CH_3)}.

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-*L*-arabinose diethyl mercaptal (11).
To a stirred solution of diol (**10**) (1.75 g, 5.9 mmol) in 12 mL of dry THF at 0°C was added a 60% mineral oil dispersion of NaH (571 mg, 14.3 mmol). When the mixture became homogeneous, benzyl bromide (1.7 mL, 14.3 mmol) and tetrabutylammonium iodide (109 mg, 0.3 mmol) were added. Subsequently, the reaction mixture was allowed to warm to rt and then stirred for a further 3 h, after which ~600 mg of Florisil was added and the mixture evaporated to dryness *in vacuo*. The residue was repeatedly triturated with petroleum ether to extract the product and the extracts evaporated *in vacuo* to furnish the clean desired product (**11**) in quantitative yield. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40 - 7.27 (m, 10H, aromatic benzyl), 4.80 (q, J = -11.1 Hz, 2H, CH_2Ph), 4.75 (q, J = -11.3 Hz, 2H, CH_2Ph), 4.22 (q, J = 5.7, 6.6 and 6.1 Hz, 1H, H4), 4.13 (d, J = 6.0 Hz, 1H, H1), 4.12 (dd, J = 5.4 and 5.7 Hz, 1H, H3), 4.01 (A of ABX, J = 6.6 and -8.2 Hz 1H, H5a), 3.86 (B of ABX, J = 6.1 and -8.2 Hz, 1H, H5b), 3.78 (dd, J = 6.0 and 5.4 Hz, 1H, H2), 2.66, 2.64 (2q, J = 7.4 Hz, 4H, SCH_2CH_3), 1.40, 1.31 (2s, 6H, CH_3 of isopropylidene), 1.23, 1.21 (2t, J = 7.4 Hz, 6H, SCH_2CH_3)}.

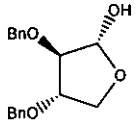
2,3-Di-*O*-benzyl-*L*-arabinose diethyl mercaptal (12).
A solution of the *L*-arabinose (**11**) (2.81 g, 5.9 mmol) in 30 mL of trifluoroacetic acid / THF / water (1:2:1, v/v/v) was stirred at rt for 90 min and then neutralized at 0°C with 1N NaOH (~1-2 mL). After warming to rt, the mixture was diluted with water (20 mL) and extracted with ether (3 X 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness *in vacuo* to afford 3.51 g of a whitish oil. Further purification was effected by flash chromatography over silica gel (eluent: 2:1, hexanes / ethyl acetate, v/v) to yield 2.27 g (88%) of diol (**12**) as a clear oil. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40 - 7.26 (m, 10H, aromatic benzyl), 4.81 (q, J = -11.3 Hz, 2H, CH_2Ph), 4.64 (q, J = -11.5 Hz, 2H, CH_2Ph), 4.15 (d, J = 4.2 Hz, 1H, H1), 4.00 (t, J = 4.2 and 3.8 Hz, 1H, H2), 3.92 - 3.86 (m, 2H, H3 and H4), 3.79 - 3.73 (m, 1H, H5a), 3.71 - 3.64 (m, 1H, H5b), 2.72 (br s ex, 1H, OH at position 4), 2.72, 2.60 (2q, J = 7.4 and 7.3 Hz, 4H, SCH_2CH_3), 2.32 (br s ex, 1H, OH at position 5), 1.24, 1.22 (2t, J = 7.4 and 7.3 Hz, 6H, SCH_2CH_3)}.

2,3-Di-*O*-benzyl-*L*-threose diethyl mercaptal (13).
To a stirred solution of arabinose sugar (**12**) (2.27 g, 5.2 mmol) in 50 mL of methanol were added 50 mL of a pH 6.4 buffer (Hydrion) and then $NaIO_4$ (1.23 g, 5.7 mmol) and the mixture stirred for approximately 45 min. The $NaIO_3$ precipitate was filtered off, to the filtrate was added $NaBH_4$ (197 mg, 5.2 mmol) and the reduction was left to proceed for 1 h. Subsequently, the mixture was extracted with CH_2Cl_2 (2 X 500 mL), the combined CH_2Cl_2 layers were dried over $MgSO_4$ and evaporated, yielding 2.09 g of the crude product. Further purification was effected by flash chromatography over silica gel (eluent: ethyl acetate / hexanes, 10:1, v/v) to yield 1.52 g (71%) of the title compound as an oil. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.40 - 7.24 (m, 10H, aromatic benzyl), 4.86 (q, J = -11.2 Hz, 2H, CH_2Ph), 4.66 (q, J = -11.5 Hz, 2H, CH_2Ph), 4.05 (d, J = 3.8 Hz, 1H, H1), 3.96 (dd, J = 3.8 and 6.0 Hz, 1H, H2), 3.89 (ddd, J = 6.0, 4.1 and 4.3 Hz, 1H, H3), 3.82 (A of ABX, J = 4.1 and -11.8 Hz, 1H, H4a), 3.68 (B of ABX, J = 4.3 and -11.8 Hz, 1H, H4b), 2.71, 2.66 (2q, J = 7.4 Hz, 4H, SCH_2CH_3), 2.12 (br s ex, 1H, OH at position 4), 1.25, 1.23 (2t, J = 7.4 Hz, 6H, SCH_2CH_3); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ

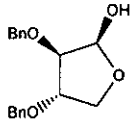
138.28 [quaternary aromatic of benzyl], 128.43, 128.30, 127.95, 127.79, 127.66 [aromatic CH of benzyl], 82.83 [**C**2], 80.82 [**C**3], 75.14, 73.30 [CH_2Ph], 61.68 [**C**4], 52.82 [**C**1], 25.81, 25.47 [SCH_2CH_3], 14.46, 14.39 [SCH_2CH_3]}.

2,3-Di-*O*-benzyl-*L*-threose (14).

To a stirred solution of *L*-threose (**13**) (100 mg, 0.25 mmol) in 3 mL of 10% aqueous acetone were added Hg(II)O (135 mg, 0.63 mmol) and $Hg(II)Cl_2$ (170 mg, 0.63 mmol) and the mixture stirred at rt for 2 h. The reaction mixture was then filtered through a bed of celite, washed with CH_2Cl_2 (20 mL) and the filtrate washed with 10% aqueous KI (20 mL) and then water (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure to yield 68 mg (92%) of an oily mixture of diastereomers (~2:1 ratio) of deprotected threose in the furanose form (**14**) (see structural assignment below). **major:** {^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 - 7.26 (m, 10H, aromatic benzyl), 5.32 (s, 1H, H1), 4.58 (q, J = -11.8 Hz, 2H, CH_2Ph), 4.53 (s, 2H, CH_2Ph), 4.17 (A of ABX, J = 1.9 and -9.7 Hz, 1H, H4a), 4.11 (B of ABX, J = 4.6 and -9.7 Hz, 1H, H4b), 4.09 - 4.04 (m, 1H, H3), 3.99 (d, J = 1.1 Hz, 1H, H2), 3.32 (br s ex, 1H, OH at position 4); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 137.40, 137.04 [quaternary aromatic of benzyl], 128.62, 128.58, 128.50, 128.10, 128.02 [aromatic CH of benzyl], 101.03 [**C**1], 85.14 [**C**2], 81.08 [**C**3], 73.01, 69.12 [CH_2Ph], 71.60 [**C**4]}. **minor:** {^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38 - 7.26 (m, 10H, aromatic benzyl), 5.43 (d, J = 4.2 Hz, 1H, H1), 4.61 (s, 2H, CH_2Ph), 4.48 (s, 2H, CH_2Ph), 4.17 (A of ABX, J = 1.9 and -9.7 Hz, 1H, H4a), 4.11 (B of ABX, J = 4.6 and -9.7 Hz, 1H, H4b), 4.09 - 4.04 (m, 1H, H3), 3.95 (dd, J = 4.2 and 2.0 Hz, 1H, H2), 3.32 (br s ex, 1H, OH at position 4); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 137.58, 136.89 [quaternary aromatic of benzyl], 127.98, 127.90, 127.81, 127.72, 127.69 [aromatic CH of benzyl], 96.57 [**C**1], 82.29 [**C**2], 81.30 [**C**3], 73.01, 69.12 [CH_2Ph], 71.91 [**C**4]}. {LRMS (CI-NH_3): m/e 300 ([M + NH_4^+ - H_2O], 0.5%), 282 ([300 - H_2O], 72.1%), 192 ([300 - $C_6H_5CH_2OH$], 38.5%), 174 ([192 - H_2O], 55.0%)}.



14 (major)



14 (minor)

1-Cyano-1-*N*-diallyl-2,3-di-*O*-benzyl-*L*-threose (15).

The threose furanose (**14**) (~30 mg, 0.1 mmol) was dissolved in 1 mL of dry THF and to this solution were added diethyl cyanophosphonate (18 μL, 0.12 mmol), and diallylamine (27 μL, 0.22 mmol). After stirring at rt under a nitrogen atmosphere overnight, the reaction mixture was evaporated to dryness *in vacuo*. Further purification was effected by flash chromatography over silica gel (eluent: hexanes / ethyl acetate, 10:1, v/v) to yield a diastereomeric mixture of **15** (29 mg, 71%) as a clear oil. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.32, 7.30 (2s, 10H, aromatic benzyl), 5.90 - 5.74 (m, 2H, -N-CH_2-CH=CH_2), 5.23 - 5.07 (m, 2H, -N-CH_2-CH=CH_2), 4.59 (AB q, 2H, -CH_2Ph), 4.48 (s, 2H, -CH_2Ph), 4.54 - 4.46 (m, 1H, H1), 4.20 -4.01 (m, 1H, H3), 3.96 - 3.92 (m, 2H, H2, H4a), 3.83 (B of ABX, J = 5.9 and -10.3 Hz, 1H, H4b), 3.45 (dd, J = 2.9, 6.7 and -15.0 Hz, 2H, -N-CH_2-CH=CH_2), 3.21 (dd, J = 2.9, 6.7 and -15.0 Hz, 2H, -N-CH_2-CH=CH_2), 1.55 (br s ex, 1H, OH at position 4); LRMS (CI-NH_3): m/e 380 ([MH^+ - HCN], 16.47%), 300 ([380 + NH_3 - HN(all)$_2$], 39.16%), 272 ([380 - $C_6H_5CH_2OH$], 100%); Anal. Calcd for $C_{25}H_{30}N_2O_3$ (406.5261): C, 73.86; H, 7.44; N, 6.89. Found: C, 73.53; H, 7.71; N, 7.04}.

2,3-Di-*O*-benzyl-4,5-*O*-isopropylidene-*L*-arabinose (16).

To a stirred solution of *L*-arabinose (**11**) (140 mg, 0.3 mmol) in 3 mL of 10% aqueous acetone were added Hg(II)O (162 mg, 0.75 mmol) and $Hg(II)Cl_2$ (204 mg, 0.75 mmol) and the mixture stirred at rt for 2 h. The reaction mixture was then filtered through a bed of celite, washed with CH_2Cl_2 (20 mL) and

the filtrate washed with 10% aqueous KI (2 X 20 mL)) and then water (20 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure to yield 108 mg of oily product (**16**), which was used as such for the next reaction. {^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.70 (s, 1H, H1), 7.38 - 7.24 (m, 10H, aromatic benzyl), 4.70 (q, J = -11.7 Hz, 2H, -C**H**$_2$Ph), 4.56 (s, 2H, -C**H**$_2$Ph), 4.25 (q, J = 6.0, 6.4 and 6.0 Hz, 1H, H4), 4.06 (A of ABX, J = 6.4 and -8.5 Hz, 1H, H5a), 4.02 - 3.94 (m, 2H, H2 and H3), 3.92 (B of ABX, J = 6.0 and -8.5 Hz, 1H, H5b), 1.41, 1.34 (2s, 6H, C**H**$_3$ of isopropylidene)}.

1-Cyano-1-*N*-diallyl-2,3-di-*O*-benzyl-4,5-*O*-isopropylidene-*L*-arabinose (17).
Aldehyde (**16**) (0.3 mmol) was dissolved in 3 mL of dry THF and to this solution were added diethyl cyanophosphonate (55 μL, 0.36 mmol) and diallylamine (82 μL, 0.66 mmol). After stirring at rt under a nitrogen atmosphere for 7 h, the reaction mixture was evaporated to dryness *in vacuo*. Further purification was effected by flash chromatography over silica gel (eluent: hexanes / ethyl acetate, 20:1, v/v) to yield a diastereomeric mixture of a clear oil (**17**) (92 mg, 64%). {^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.31, 7.30 (2s, 10H, aromatic benzyl), 5.87 - 5.71 (m, 2H, -N-CH_2-C**H**=CH_2), 5.33 - 5.15 (m, 4H, -N-CH_2-CH=C**H**$_2$), 4.76 (AB q, J = -11.1 Hz, 2H, -C**H**$_2$Ph), 4.71 (AB q, J = -10.7 Hz 2H, -C**H**$_2$Ph), 4.69 (d, J = 8.3 Hz, 1H, H1), 4.26 (d, J = 8.3 Hz, 1H, H2), 4.07 - 3.82 (m, 4H, H3, H4, H5ab), 3.54 (dd, J = 5.2, 8.1 and -14.4 Hz, 2H, -N-C**H**$_2$-CH=CH_2), 2.97 (dd, J = 5.2, 8.1 and -14.4 Hz, 2H, -N-C**H**$_2$-CH=CH_2), 1.43, 1.31 (2s, 6H, C**H**$_3$ of isopropylidene); Anal. Calcd for $C_{29}H_{36}N_2O_4$ (476.6173): C, 73.08; H, 7.61; N, 5.88. Found: C, 72.81; H, 7.75; N, 6.02}.

2',3'-*O*-Isopropylidene-5'-cyano-5'-*N*-diallyl-5'-deoxyuridine (2).
To a stirred solution of crude aldehyde (**18**) (564 mg, ~2 mmol) in 20 mL of dry THF were added diethyl cyanophosphonate (364 μL, 2.4 mmol) and diallylamine (543 μL, 4.4 mmol), and the mixture stirred for 3 h at rt under a nitrogen atmosphere. The reaction mixture was then evaporated to dryness *in vacuo* and purified by flash chromatography over silica gel (eluent: ethyl acetate / hexanes, 1:1, v/v) to yield 528 mg (67%) of epimeric (**2**) as a light yellow oil. **S (55%):** {^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.91 (br s ex, 1H, NH of uracil), 7.22 (d, J = 7.9 Hz, 1H, H6), 5.87 - 5.63 (m, 2H, H2" of diallyl), 5.73 (d, J = 7.9 Hz, 1H, H5), 5.48 (s, 1H, H1'), 5.28 - 5.12 (m, 4H, H3" of diallyl), 5.06 (dd, J = 1.3 and 6.4 Hz, 1H, H2'), 4.90 (dd, J = 6.4 and 3.6 Hz, 1H, H3'), 4.26 (t, J = 3.6 and 3.5 Hz, 1H, H4'), 4.11 (d, J = 3.5 Hz, 1H, H5'), 3.61 - 3.33 & 3.04 - 2.89 (m, 4H, H1" of diallyl), 1.50, 1.32 (2s, 6H, C**H**$_3$ of isopropylidene); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 163.80 [**C**4], 149.96 [**C**2], 143.75 [**C**6], 134.15 [**C**2" of diallyl], 119.13 [**C**3" of diallyl], 116.13 [**C**N], 114.22 [quaternary **C** of isopropylidene], 102.58 [**C**5], 96.98 [**C**1'], 86.35 [**C**4'], 83.91 [**C**2'], 82.88 [**C**3'], 55.84 [**C**5'], 55.13 [**C**1" of diallyl], 26.86, 25.07 [CH_3's of isopropylidene]}.
R (45%): {^{1}H-NMR (200 MHz, $CDCl_3$): δ 10.08 (br s ex, 1H, NH of uracil), 7.21 (d, J = 8.1 Hz, 1H, H6), 5.87 - 5.63 (m, 2H, H2" of diallyl), 5.72 (d, J = 8.1 Hz, 1H, H5), 5.53 (s, 1H, H1'), 5.28 - 5.12 (m, 4H, H3" of diallyl), 5.04 (m, 1H, H2'), 4.99 (dd, , J = 6.4 and 3.6 Hz, 1H, H3'), 4.30 (dd, J = 3.6 and 1.3 Hz, 1H, H4'), 4.07 (d, J = 1.3 Hz, 1H, H5'), 3.61 - 3.33 & 3.04 - 2.89 (m, 4H, H1" of diallyl), 1.53, 1.32 (2s, 6H, C**H**$_3$ of isopropylidene); ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 163.80 [**C**4], 150.11 [**C**2], 143.43 [**C**6], 134.06 [**C**2" of diallyl], 118.84 [**C**3" of diallyl], 117.66 [**C**N], 114.62 [quaternary **C** of isopropylidene], 102.58 [**C**5], 96.02 [**C**1'], 86.01 [**C**4'], 84.12 [**C**2'], 82.00 [**C**3'], 55.77 [**C**2'], 54.62 [**C**1" of diallyl], 26.80, 24.92 [CH_3's of isopropylidene]}. {IR (CH_2Cl_2): 2360 cm^{-1}, -C≡N; LRMS (CI-NH_3): m/e 389 ([MH^+], 100%), 362 ([MH^+ - HCN], 58.5%); HRMS (CI-NH_3): m/z calcd for $C_{19}H_{25}N_4O_5$ [MH^+], 389.1826; found, 389.1825; Anal. Calcd for $C_{19}H_{24}N_4O_5 \cdot H_2O$(406.4265): C, 56.15; H, 6.45; N, 13.79 Found: C, 55.88; H, 6.51; N, 13.64}.

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