Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Syntheses of Novel 3-Substituted-2′-deoxy-3-deazauridine Nucleosides

Balekudru Devadas [a], Thomas E. Rogers [a] & Steven H. Gray [a]
[a] G. D. Searle , 700 Chesterfield Parkway North, St. Louis, MO, 63198
Published online: 23 Sep 2006.

To cite this article: Balekudru Devadas , Thomas E. Rogers & Steven H. Gray (1995) Syntheses of Novel 3-Substituted-2′-deoxy-3-deazauridine Nucleosides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:20, 3199-3210, DOI: 10.1080/00397919508015471

To link to this article: http://dx.doi.org/10.1080/00397919508015471

SYNTHETIC COMMUNICATIONS, 25(20), 3199-3210 (1995)

SYNTHESES OF NOVEL 3-SUBSTITUTED-2′-DEOXY-3-DEAZAURIDINE NUCLEOSIDES

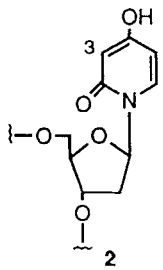
Balekudru Devadas,* Thomas E. Rogers and Steven H. Gray
G. D. Searle, 700 Chesterfield Parkway North, St. Louis, MO 63198.

Abstract : Syntheses of novel 3-ethynyl (**8**), 3-vinyl (**10**) and 3-acetoxy (**13**)-2′-deoxy-3-deazauridine analogs starting from the protected 2′-deoxy-3-deazauridine derivative **4** are described.

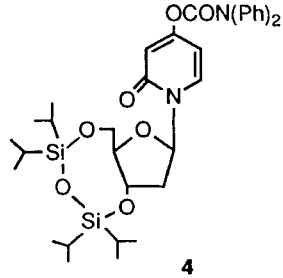
Oligonucleotides containing modified bases and phosphodiester linkages are useful tools in diagnostics and in the regulation of gene expression.[1,2] In recent years, several sequence specific antisense oligonucleotides which modulate translation processes by base pairing have found a niche in therapeutics as a novel class of antiviral agents.[3,4] For the past several years we have been interested in developing oligos with modified bases which may form stable duplexes ($T_m > 90$ °C) with a target sequence of interest. Towards this goal, we were pleased to discover that a 20 mer 3′-ACCTGGTACACXTTCGACGG (**1**) where X = 2′-deoxy-3-deazauridine (**2**), hybridized with a complementary sequence 5′-TGGACCATGTGYAAGCTGCC (**3**) where Y = guanosine and the resulting duplex exhibited significantly higher stability ($T_m > 90$ °C) than the corresponding duplex where X = cytosine ($T_m = 63$ °C).[5] This increase in T_m may be attributed to

* To whom correspondence should be addressed.

the tight binding between **1** and **3** due to the presence of 2′-deoxy-3-deazauridine. However, no increase in T_m was observed when Y was cytosine. Furthermore, the increase in T_m was noted only when 3-deazauridine was flanked by at least ten nucleotides.



2



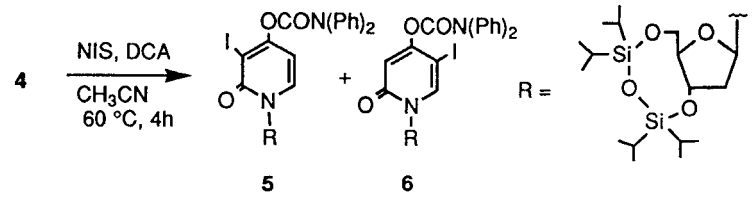
4

Based on these observations we reasoned that, introduction of an electron withdrawing or unsaturated group in position 3 in 3-deazauridine might generate a reactive base, which when incorporated into an oligonucleotide sequence, may have the potential to cross-link with guanosine in a complementary target sequence. In this communication we wish to disclose the facile syntheses of the hitherto unknown 3-ethynyl (**8**) 3-vinyl (**10**) and 3-acetoxy-2′-deoxy-3-deazauridine (**13**), starting from the readily available precursor **4**. The key starting material **4** was obtained in four steps[5] starting from 3-deazauridine, using the deoxygenation methodology described by Robins *et al*.[6]

Iodination of **4** with the aid of N-iodosuccinimide in THF at 55 °C in the presence of catalytic amounts of dichloroacetic acid gave a mixture of **5** (80%) & **6** (4%) iodo derivatives which were easily separated by flash chromatography (Scheme I).

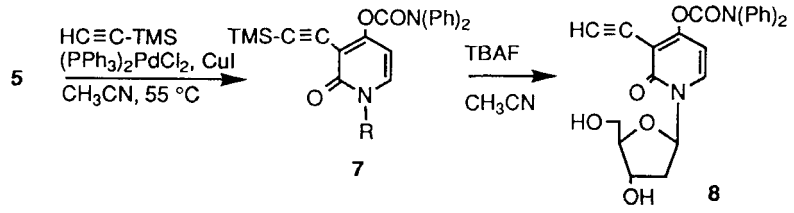
Ethynylation of **5** under optimum conditions involving heating a mixture of **5**, trimethylsilylacetylene and triethylamine in acetonitrile at 60 °C in the presence of

SCHEME I



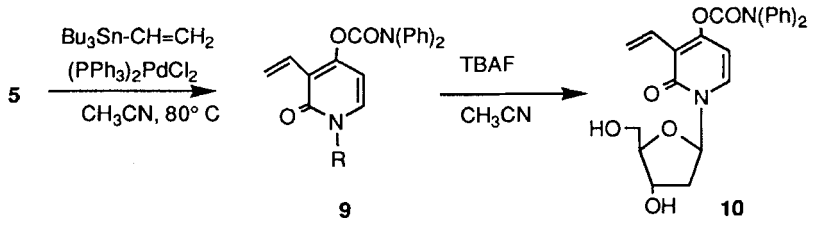
$(PPh_3)_2PdCl_2$ and CuI afforded **7** in high yield (83%). Subsequent desilylation of **7** with tetrabutylammonium fluoride gave the title compound **8** (Scheme II).

SCHEME II



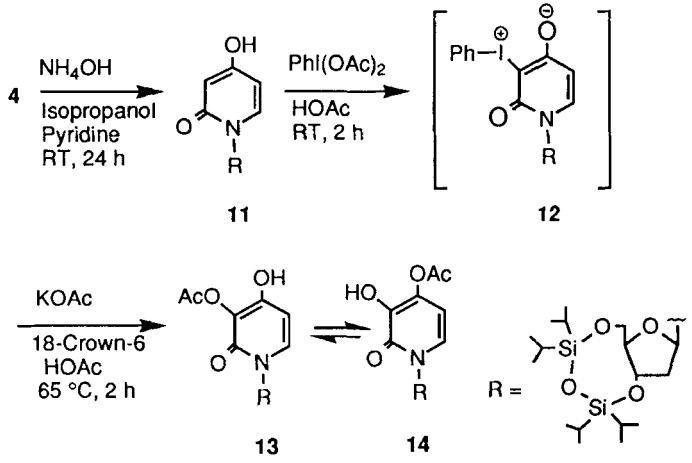
Likewise, the 3-vinyl analog **9** was synthesized in high yield (85%) by the reaction of vinyltributylstannane with **5** in the presence of catalytic amounts of $(PPh_3)_2PdCl_2$ in refluxing acetonitrile. Cleavage of the silyl groups with tetrabutylammonium fluoride treatment provided the title compound **10** (Scheme III). Analogs **8** & **10** are useful nucleoside precursors for derivatization for solid phase synthesis of biologically important modified oligonucleotides.[7]

SCHEME III



The synthesis of 3-acetoxy derivative **13** began with the conversion of **4** to **11** using ammonium hydroxide in a solvent mixture of isopropanol and pyridine

SCHEME IV



(Scheme IV). The reaction of **11** with iodobenzenediacetate[8] in acetic acid furnished the unexpected iodonium betaine intermediate[9] **12** in 83% yield, which on heating in acetic acid in the presence of potassium acetate gave approximately a 1: 2 equilibrium mixture of 3-acetoxy (**13**) and 4-acetoxy (**14**) compounds in 62% yield. Thus, this methodology provides a novel route to the synthesis of 3-hydroxy-3-deazauridine. To the best of our knowledge, this is the first reported synthesis of 3-hydroxy substituted 2′-deoxy-3-deazauridine derivative. The intermediate **12** may also serve as a convenient precursor to the synthesis of novel 3-azido or 3-fluoro substituted deazauridine analogs.

In conclusion, 3-iodo-3-deazauridine derivative **5** is a versatile precursor, for the preparations of novel 3-ethynyl and 3-vinyl analogs. In a similar manner, the 5-iodo compound **6** can be elaborated to the corresponding 5-ethynyl and 5-

vinyl derivatives which may serve as useful intermediates for the synthesis of potential antiviral analogs of uridine.[11] The new synthetic methodology developed for the 3-acetoxy-2′-deoxy-3-deazauridine analog **13** should be applicable to the synthesis of 3-hydroxy substituted 3-deazauridine.[10]

Experimental

3-Deazauridine was purchased from Sigma Company. All reactions were performed under anhydrous conditions in an atmosphere of argon. Flash chromatography was performed using Merck silicagel (230-400 mesh, 60Å). Melting points were determined on a MEL-TEMP apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Varian XL-300 spectrometer and chemical shifts (δ) *are reported in ppm relative to tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. Low-resolution mass spectra were recorded on a VG40-250T instrument and high-resolution mass spectra were recorded on a Finnigan MAT 90 mass spectrometer operating in the FAB mode. Elemental analyses were obtained from Galbraith Laboratories, Knoxville, Tennessee.*

4-O-Diphenylcarbamoyl-1-[2′-deoxy-3′,5′-O-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]-ß-ribofuranosyl-2-(1H)-pyridone (4): R_f = 0.52 (EtOAc/Hexane 1:1 v/v); ^{1}H NMR δ ($CDCl_3$): 7.84 (d, 1H, *J*= 7.8 Hz, H-6), 7.4-7.24 (m, 10H, aromatic), 6.31 (d, 1H, *J* = 2.1 Hz, H-3), 6.22 (m, 2H, H-5 & H-1′), 4.4 (m, 1H, H-3′), 4.14 (m, 1H, H-4′), 4.05 (m, 1H, H-5′), 3.81 (m, 1H, H-5″), 2.60 (m, 1H, H-2′). 2.25 (m, 1H, H-2″), 1.09-0.98 (m, 28H, 2 x Si(i-propyl)$_2$); FAB-MS *m/z* 672 (M+Li), 482, 313; high-

resolution FAB-MS: calculated for $C_{35}H_{48}N_3O_7Si_3Li$ (M+Li) 671.3160, found 671.3171.

4-O-Diphenylcarbamoyl-3-iodo-1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis (1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (5) and **4-O-Diphenylcarbamoyl-5-iodo-1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (6)**: A mixture of **4** (3.9 g, 5.9 mmol), N-iodosuccinimide (1.4 g, 6.2 mmol) in acetonitrile (40 mL) containing dichloroacetic acid (0.18g, 1.4 mmol) was heated at 60 °C for 4 hours. TLC of the reaction mixture (EtOAc/Hexane, 1:1 v/v) revealed the formation of two products. The dark brown reaction mixture was concentrated under reduced pressure, the residue dissolved in CH_2Cl_2 (125 mL), washed with saturated $NaHCO_3$ (3 x 25 mL) followed by water (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The dark brown residue thus obtained was purified by flash chromatography using EtOAc/Hexane (1:4 v/v) as the eluent. The fractions containing the faster moving product were combined, concentrated and the residue crystallized from MeOH to give **5** as shiny white flakes (3.7 g, 80%): m.p. 132-33 °C; R_f = 0.57 (EtOAc/Hexane 1:1), ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 1H, *J*= 7.8 Hz , H-6), 7.44-7.2 (m, 10H, aromatic), 6.32 (d, 1H, *J* = 7.8 Hz, H-5), 6.17 (d, 1H, *J* = 6.73 Hz, H-1′), 4.39 (m, 1H, H-3′), 4.18 (m, 1H, H-5′), 4.04 (m, 1H, H-5″), 3.8 (m, 1H, H-4′), 2.59 (m, 1H, H-2′), 2.26 (m, 1H, H-2″), 1.1-0.9 (m, 28H); FAB-MS *m/z* 797 (M+Li), 439. Analysis calculated for $C_{35}H_{47}IN_2O_7Si_2$: C, 53.16; H, 5.95; N, 3.54. Found: C, 52.82, H, 5.95; N, 3.47. The fractions containing the slower moving compound were combined and concentrated to give

(**6**) : R_f = 0.48 (EtOAc/Hexane 1:1), ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H, H-6), 7.4-7.2 (m, 10H, aromatic), 6.52 (s, 1H, H-3), 6.13 (dd, 1H, H-1′) , 4.36 (m, 1H, H-5′), 4.04 (m, 1H, H-5″), 3.8 (m,1H, H-4′), 2.55 (m, 1H, H-2″), 1.2-0.95 (m, 28H); FAB-MS *m/z* 797 (M+Li), 439; high-resolution FAB-MS: calculated for $C_{35}H_{47}IN_2O_7Si_2Li$ (M+Li) 797.2127. Found: 797.2134.

4-O-Diphenylcarbamoyl-3-[(2-trimethylsilylethynyl)]-1-[2′-deoxy-3′, 5′-O-1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (7): A mixture of **5** (1.0 g, 1.26 mmol), trimethylsilylacetylene (1.0 mL), and triethylamine (0.58 g, 5.7 mmol) in acetonitrile, containing bistriphenylphosphine-palladium chloride (0.09 g, 0.128 mmol) and cuprous iodide (0.05 g), was heated at 60 °C under an atmosphere of argon for 16 h. The reaction mixture was concentrated under reduced pressure, CH_2Cl_2 (25 mL) was added and filtered through a bed of celite. The filtrate was washed with 5% EDTA (2 x 10 mL), water (2 x 10 mL), dried (Na_2SO_4) and concentrated to give a dark syrupy residue which was purified by flash chromatography using 20% EtOAc in hexane. The appropriate fractions were pooled, concentrated and the resulting residue was crystallized from ethanol to give **7** (0.8 g, 83%) as pale yellow needles; m. p. 175-176 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.25 (s, 9H), 1.03-1.57 (m, 28H), 2.3 (m, 1H), 2.60 (m, 1H), 3.78 (m, 1H) 4.15, (m, 1H), 4.20 (m, 1H), 4.35(m, 1H), 6.18 (d, 1H, *J* = 6.0 Hz), 6.19 (d, 1H, *J* = 7.5 Hz), 7.4-7.26 (m, 10H), 7.88 (d, 1H, *J* = 7.5 Hz); UV (MeOH), λ_{max}: 206, 234, 332 nm; mass spectrum (FAB) 767 (M + Li), 409 and 196. Anal. Calcd. for $C_{40}H_{56}N_2O_7Si_3$: C, 63.15; H, 7.37; N, 3.68. Found: C, 63.01, H, 7.47; N, 3.58.

4-O-Diphenylcarbamoyl-3-ethynyl-1-(2′-deoxy-β-D-ribofuranosyl)-2(1H)-pyridone (8): To a solution of **7** (1.3 g, 1.7 mmol) in CH_3CN (25 mL) at 0 °C, tetrabutylammonium fluoride (0.27g, 1 mmol) was added and stirred for 15 min. After stirring at room temperature for 45 min, the reaction mixture was concentrated to dryness under reduced pressure, and resulting material was purified by flash chromatography using 6% MeOH in CH_2Cl_2 to give **8** (0.69 g, 90%) as an amorphous substance: ^1H NMR (DMSO-d_6) δ 8.1 (d, 1H, J = 7.69 Hz, H-6), 7.44-7.29 (m, 10H, aromatic), 6.46 (d, 1H, J = 7.69 Hz , H-5), 6.26 (dd, 1H, J = 6.44 Hz, H-1′), 5.27 (d, 1H, 4.31 Hz, 3′-OH), 5.07 (t, 1H, 5.2 Hz, 5′-OH), 4.6 (s, 1H, C CH), 4.22 (m, 1H, 3′H), 3.86 (m, 1H, H-4′), 3.61 (m, 2H, H-5′, H-5″), 2.3 (m, 1H, H-2′), 1.95 (m, 1H, H-2″); FAB-MS *m/z* 453 (M+Li); high-resolution FAB-MS : calcd for $C_{25}H_{22}N_2O_6Li$ (M+Li) 453.1638, found 453. 1635.

4-O-Diphenylcarbamoyl-3-ethenyl-1-[2′-deoxy-3,5-O-1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (9): A mixture of **5** (1.2 g, 1.5 mmol), vinyl-tri-n-butyltin, (0.8 mL, 2.7 mmol) and $PdCl_2(PPh_3)_2$ (0.1 g, 0.14 mmol) in acetonitrile (20 mL) was heated at 60 °C for 16 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure, and excess vinylbutyltin was removed by repeated distillation with DMF. The resulting viscous oil was dissolved in EtOAc (15 mL), filtered through a celite pad and the filtrate was concentrated to give a syrup which was purified by flash chromatography using EtOAc/Hexane (1:4, v/v) as the eluent. The fractions containing the desired product (visualized under UV lamp) were combined, concentrated under reduced pressure and the resulting

residue was dried *in vacuo* to give **9** (0.85 g, 82%) as a pale yellow amorphous substance: R_f = 0.63 (EtOAc/ Hexane 1:1 v/v); ^{1}H-NMR ($CDCl_3$) δ:7.8 (d, 1H, *J* = 7.69Hz, 1H, H-6), 7.42-7.2 (m, 10H aromatic), 6.45 (dd, 1H, *J* = 11.88 & 17.7 Hz), 6.35 (d, 1H, *J* = 7.69 Hz), 6.23 (m, 2H, H-1′), 5.35 (dd, 1H, J_1= 2.42Hz, J_2= 11.88 Hz), 4.39 (m, 1H, H-3′), 4.2 (m, 2H, H-5′, 5″), 3.8 (m, 1H, H-4′), 2.6 (m, 1H, H-2′), 2.26 (m, 1H, H-2″), 1.15-0.85 (m, 28H); UV (MeOH) λ_{max}: 208, 238, 324 nm; mass spectrum (FAB): 697 (M + Li), 502, 339; high-resolution FAB-MS *m/z* calculated for $C_{37}H_{50}N_2O_7Si_2$ (M+Li) 697.3317, found: 697.3321.

4-O-Diphenylcarbamoyl-3-ethenyl-1-(2′-deoxy-β-D-ribofuranosyl)-2(1H)-pyridone (10): Obtained in 94% yield as described for **8** : R_f = 0.26 (5% MeOH in CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 7.98 (d, 1H, *J* = 7.7 Hz), 7.55-7.2 (m, 10H, aromatic), 6.5 (m, 2H), 6.49 (d, 1H, *J* = 7.7 Hz, H-5), 6.39 (dd, 1H, *J* = 6.4 Hz, H-1′), 5.35 (dd, 1H, *J* = 3.01 & 11.9 Hz), 5.24 (d, 1H, *J* = 4.25Hz, 2′-OH), 5.04 (t, 1H, *J* = 5.14 Hz, 5′-OH), 4.23 (m, 1H, H-3′), 3.86 (m, 1H, H-4′), 3.62 (m, 2H, H-5′ & 5″), 2.35 (m,1H, H-2′), 2.00 (m,1H, H-2″); FAB-MS : *m/z* 499 (M+Li); high-resolution FAB-MS: calcd for $C_{25}H_{24}N_2O_6Li$ (M+Li) 455.1794, found 455.1795.

1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (11): To a solution of **4** (1.5 g, 2.26 mmol) in EtOH (20 mL) & isopropanol (30 mL) containing pyridine (10 mL), ammonium hydroxide (35 mL) was added, the flask was sealed with a rubber septum and stirred for 24 h at room temperature. The solvents were

removed under reduced pressure, and residue was purified by flash chromatography using 30% EtOAc in hexane and the product was crystallized from EtOAc: m. p. 210-212 °C; ^{1}H NMR ($CDCl_3$) δ 11.2 (br s, 1H), 7.78 (d, 1H, J = 7.5 Hz, H-6), 6.22 (d, 1H, J = 6.3 Hz, H-1′) 6.02 (m, 2H, H-3 & H-5), 4.45 (m, 1H, H-4′), 4.15 (m, 1H, H-5′), 4.05 (m, 1H, H-5″), 3.78 (d, 1H, J = 8.4 Hz, H-3′), 2.55 (m, 1H, H-2′), 2.25 (m, 1H, H-2″), 1.2-0.8 (m, 28H); mass spectrum FAB-MS *m/z* 476 (M+Li). Analysis calcd for $C_{22}H_{39}NO_6Si_2$: C, 56.29; H, 8.31; N, 2.98. Found: C, 56.13; H, 8.37; N, 2.93.

3-Phenyliodo-1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (12):

A solution of **11** (0.2 g, 0.43 mmol) in acetic acid (4 mL) was treated with iodobezenediacetate (0.165, 0.51 mmol) and stirred at room temperature for 2 h. Acetic acid was removed by distillation with toluene *in vacuo* and the residue was purified by flash chromatography using 3% MeOH in CH_2Cl_2 to give **12** (0.24 g, 81%) as a white amorphous substance: ^{1}H-NMR ($CDCl_3$) δ: 7.9 (d over d, 2H), 7.4-7.52 (m, 4H), 6.3 (m, 1H), 5.92 (d, 1H, J = 8.1 Hz), 4.48 (m, 1H), 4.06 (m, 2H), 3.74 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 0.94-1.08 (m, 28H); mass spectrum FAB-MS: 678 (M + Li); high-resolution FAB-MS *calculated for:* $C_{28}H_{42}NIO_6Si_2$ (M+Li) 678.1756, found: 678.1710.

3-Acetoxy-4-hydroxy-1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone (13) and **4-Acetoxy-3-hydroxy-1-[2′-deoxy-3′,5′-[1,1,3,3,-tetrakis(1-methylethyl)-1,3-disiloxanediyl)]-β-D-ribofuranosyl-2(1H)-pyridone**

(**14**) : A mixture of **12** (0.21 g, 0.3 mmol), KOAc (0.02 g, 0.2 mmol), 18-crown-6 (0.01 g, 0.04 mmol) in acetic acid (3 mL) was heated at 65 °C under argon atmosphere. After 4 h, the reaction mixture was concentrated *in vacuo* in the presence of toluene. The residue was dissolved in EtOAc (25 mL), washed successively with 5% sodium sulphite (3 x10 mL), water (3 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography using 3% MeOH in CH_2Cl_2 to give a 1: 2 mixture of **13** and **14** (0.1 g, 61%) as an amorphous substance: ^{1}H-NMR ($CDCl_3$) δ: 7.45 & 7.7 (2d, 1H, J = 7.8 Hz, H-6), 6.3 & 6.25 (2d, 1H, H-5, J = 7.8 Hz), 6.13 (m, 1H, H-1′), 4.45 (m, 1H, H–4′), 4.1 (m, 2H, H–5′ & H–5″), 3.8 (m, 1H, H–3′), 2.55 (m, 1H, H-2′), 2.25 (2s over m, 4H, OAc & H–2″), 1.09– 0.93 (m, 28H); mass spectrum FAB-MS: *m/z* 534 (M +Li); high-resolution FAB-MS calculated for $C_{24}H_{41}NO_8Si_2$ (M+Li): 534.2531, found 534.2504.

Acknowledgment We thank Deborah Connors and Dudley McMackins for their technical assistance.

References

1. Cohen, J. S. Ed., " Oligonucleotides, Antisense Inhibitors of Gene Expression," **1989**, CRC Press Boca Raton, FL.

2. Englisch, U. and Gauss, D. H., *Angew. Chem., Int. Ed. Engl*, **1991**, *30*, 613-629.

3. Zamecnik, P. C. and Stephenson, M. L., *Proc. Natl. Acad. Sci. USA*, **1978**, *75*, (1), 280-284.

4. Smith, C. C., Aurelian, L., Reddy, M. R., Miller, P. S.,Ts'o, P. O. P., *Proc. Natl. Acad. Sci. USA*, **1986**, *83*, 2787-2791.

5. Rogers, T. E., Gray, S. H., Devadas, B., Adams, S. P., US Patent, **1992**, 5134066.

6. Robins, M. J., Wilson, J. S., and Hansske, F., *J. Amer. Chem. Soc.* **1983**, *105* (12), 4059-4065.

7. Rogers, T. E., Gray, S. H., Devadas, B., Adams, S. P., US Patent, **1994**, 5359053.

8. Moriarty, R. M. and Om Prakash, *Acc. Chem. Res.*, **1986**, *19*, 244-250.

9. Similar iodonium derivatives of β-diketones obtained by the reaction of $PhI(OAc)_2$ with $CH_2(COOEt)_2$, have been isolated and characterized, see *Zh. Organ. Khim.* **1965**, *1* (10), 1854.

10. For example 2′-deoxy-5-vinyluridine is an antiviral agent, active against HSV-1 and HSV-2 viruses, Chang, Y. C., Domin, B. A., Sharma, R. A. and Bobek, M. *Antimicrob. Agents and Chemotherapy*, **1976**, *10*, 119.

11. 3-Deazauridine is a synthetic analog of uridine with antitumor activity, Creaven, P. J., Priore, R. L., Mittlelman, A., Bruno, S., Henderson, E. S., Rustom, Y. M.,and Solomon, J. K. *Cancer Treat. Rep*; **1982**, *66*, 81.

(Received in the USA 16 March 1995)