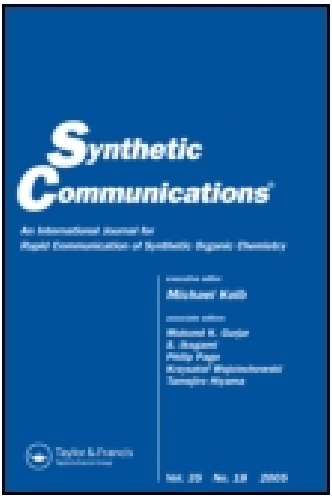


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# AN IMPROVED SYNTHETIC PREPARATION OF ANTI CONFORMATIONALLY CONSTRAINED ACYCLIC NUCLEOSIDES

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# AN IMPROVED SYNTHETIC PREPARATION OF ANTI CONFORMATIONALLY CONSTRAINED ACYCLIC NUCLEOSIDES

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## ABSTRACT

Practical large-scale synthesis of anti conformationally constrained acyclic nucleosides has been attained from the coupling of lithiated 2,4-dimethoxy-5,6-dimethylpyrimidine with 1,3-bis(*tert*-butyldiphenylsilyloxy)-propan-2-one, followed by the sequential reactions of methylthiomethylation, ring cyclization, hydrolysis, and desilylation.

Modified nucleosides and oligonucleotides have attracted much interest due to their potential use as antineoplastic and antiviral agents. Over the years, a major part of our research efforts has been directed towards the synthesis of a new class of modified anti conformationally constrained acyclic nucleoside.[1–9]

Some of them showed moderate activity against HIV[2] or certain cancer cell lines.[5,6] More recently, this modified nucleoside was also used as building units for oligonucleoside[8,9] synthesis. In connection with our

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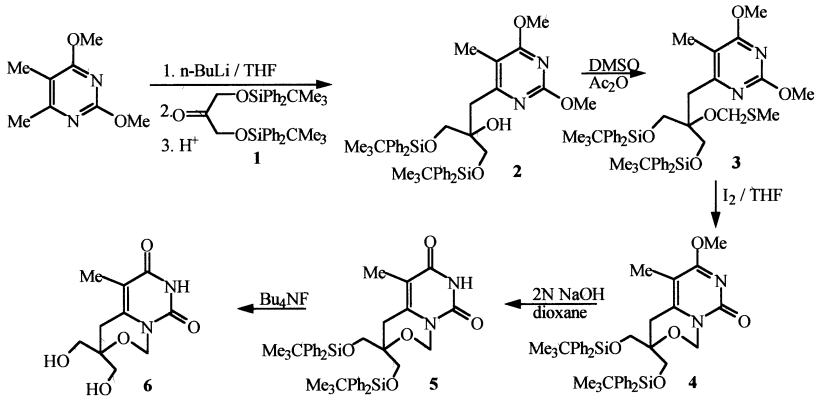
ongoing research program on exploring potent antineoplastic and antiviral agents, we required gram quantities of 3,3-Bis(hydroxymethyl)-5-methyl-1*H*,3*H*,4*H*,7*H*-pyrimido-[1,6-*c*][1,3] oxazine-6,8-dione (**6**),[2] a key intermediate in the synthesis of modified anti conformationally constrained acyclic nucleoside.




In the synthesis of title compound 1,3-bis-*O*-protected-1,3-dihydroxyacetone can serve as a building block of two geminal or vicinal hydroxymethyl group at the conformationally constrained nucleoside skeleton. In previous work, synthesis of 1,3-bis-*O*-protected-1,3-dihydroxyacetone was started from 1,3-dibenzyloxy-2-propanol[2] that was oxidized to the corresponding ketone with the *N*-chlorosuccinimide/dimethylsulfoxide. The obtained oily ketone was purified by distillation in a kugelrohr apparatus under high vacuum or column chromatography. Although the synthesis was straightforward, these two procedures resulted in a repulsive, garlic-like odor, time-consuming purification, and low yield, and were not practically applicable for large-scale preparation. Alternatively, 1,3-bis (*tert*-butyldiphenylsilyloxy)propan-2-one (**1**) was selected in the present work. Protection of the hydroxy group of easily accessible 1,3-dihydroxyacetone with *tert*-butylchlorodiphenylsilane gave **1** as a white solid, which was easily purified from crystallization (Hexane/AcOEt) in high yield (83%). This procedure circumvented the unpleasant odor and time-consuming purification steps, and obtained high-yield product. We thought **1** should be superior to 1,3-dibenzyloxy-2-propanone in the synthesis of title compound. Treatment of 2,4-dimethoxy-5,6-dimethylpyrimidine with *n*-butyllithium in dry tetrahydrofuran at $-70^{\circ}C$ gave lithio derivative, which was reacted with **1** at $-70^{\circ}C$ to afford **2**. Compound (**2**), a solid

product, was easily purified from crystallization (MeOH) and obtained in high yield (75%). By contrast, the similar 1,3-dibenzyloxy product in previous synthesis was an oily product that required time-consuming column chromatography purification and yield was low (60%). Conversion of the hydroxy group of **2** to the corresponding methylthiomethyl ether of **3** was accomplished by treating **2** with a mixture of acetic anhydride and anhydrous dimethyl sulfoxide at room temperature for 36 h. Ring closure of **3** was accomplished with iodine in dry tetrahydrofuran at room temperature to give **4**. Treatment of **4** with 2 N sodium hydroxide in dioxane at reflux overnight to give **5**. Desilylation of **5** with tetrabutylammonium fluoride in tetrahydrofuran at room temperature afforded **6**. By contrast, **6** in previous synthesis[2] was obtained from the intermediate containing the protected 1,3-dibenzyloxy groups by hydrogenation in the presence of 20% palladium on carbon in methanol at high hydrogen pressure (50 psi), but this method was not practically applicable for large-scale preparation.

In conclusion, we have developed an improved and practical procedure for the synthesis of anti conformationally constrained acyclic nucleosides using 1,3-bis(*tert*-butyldiphenylsilyloxy)propan-2-one (**1**) as a building block of two geminal hydroxymethyl groups in place of 1,3-dibenzyloxy-2-propanol. This selecting circumvented several limitations of unpleasant odor, time-consuming purification, and high-pressure hydrogenation, and provided an easily purified way and high yield of the target compound.

## EXPERIMENTAL

Melting points were taken on a BUCHI 530 apparatus and are uncorrected. The silica gel used for chromatography was silica gel 60 70-230 mesh (E. Merck, Darmstadt, Germany). TLC was performed on prescored DC-Alufolien Kieselgel $60F_{254}$ (E. Merck, Darmstadt, Germany). Compounds were visualized by illuminating under UV light (254 nm). Evaporations were carried out at $< 50^{\circ}C$ using a rotary evaporator at reduced pressure (water aspirator). Solvent ratios are reported as v/v. $^{1}H$ and $^{13}C$ NMR spectra were obtained at Varian 300 NMR spectrometer. Where necessary, deuterium exchange experiments were used to obtain proton shift assignments. Analytical samples were dried under reduced pressure at $78^{\circ}C$ in the presence of $P_2O_5$ for at least 12 h unless otherwise specified. Elemental analyses were obtained from a Perkin-Elmer 2400 elemental analyzer.

### 1,3-Bis-[(tert-butyldiphenylsilyloxy)]propan-2-one (1)

To a chilled (0°C) solution of 1,3-dihydroxyacetone (8.1 g, 90 mmol) and dimethylaminopyridine (2.57 g, 21 mmol) in dry pyridine (100 mL), *tert*-butylchlorodiphenylsilane (50 g, 182 mmol) was added over a period of 1 h. The resulting mixture was stirred under nitrogen at room temperature for four days. The reaction mixture was poured over crushed ice and left overnight. The precipitate was taken out and dissolved in AcOEt. The filtrate was extracted with AcOEt (3 × 150 mL). The combined organic extract was washed with 1 N HCl (3 × 150 mL) and water (3 × 150 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a white solid. Recrystallization (AcOEt/Hexane) afforded **1** (42.4 g, 83%): m.p. 99°–100°C (lit. 100°–101°C).[10]

### 6-[2-[(1,3-Bis-(tert-butyldiphenylsilyloxy)-2-hydroxy)propyl]methyl]-2,4-dimethoxy-5-methylpyrimidine (2)

Under nitrogen atmosphere *n*-butyllithium (1.6 M, 35 mL, 56 mmol) was added dropwise to a solution of 2,4-dimethoxy-5,6-dimethylpyrimidine (8.43 g, 50 mmol) in dry tetrahydrofuran (100 mL) at −70°C. The mixture was raised to −55°C and stirred for 30 m. Compound (**1**) (29 g, 51 mmol) was added and the stirring continued for 2 h. The solution was neutralized with acetic acid to pH 7, and the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separeted, dried over sodium sulfate, and concentrated to give the product. Crystallization (MeOH) afforded **2** (27.5 g, 75%): $R_f$ 0.35 (Hexane/AcOEt = 4/1); m.p. 77°–79°C; $^1$H NMR (300 MHz, $CDCl_3$)$\delta$ 7.6–7.3(m, 20H, Ph), 5.75(s, 1H, OH), 4.01(s, 4H, $OCH_2$), 3.79, 3.78(s, 3H each, $OCH_3$), 2.99(s, 2H, $CH_2$-6), 2.00(s, 3H, $CH_3$), 1.30–1.01(s, 18H, *t*-butyl); MS (m/z): 735 ($M^+$); Anal. calcd. for $C_{43}H_{54}N_2O_5Si_2$(735.08): C, 70.26%; H,7.40%; N, 3.81%. Found: C, 69.94%; H, 7.36%; N, 3.68%.

### 6-[2-[(1,3-Bis(tert-butyldiphenylsilyloxy)-2-methylthiomethyloxy)propyl]methyl]-2,4-dimethoxy-5-methylpyrimidine (3)

Acetic anhydride (25 mL) was added to a mixture of **2** (40.1 g, 54 mmol) in dry DMSO (250 mL). The solution was stirred at room temperature for 36 h. The solution was extracted with $CHCl_3$ and washed with brine and water. The organic layer was dried over $MgSO_4$ and concentrated

to an oily residue. This residue was purified by flash chromatography on silica gel with 9:1 hexane-AcOEt as eluant to give 30.2 g of **3** (70%). $R_f$ 0.25 (Hexane/AcOEt = 9/1); $^1$H NMR(300 MHz, $CDCl_3$)$\delta$ 7.6–7.3(m, 20H, Ph), 4.80(s, 2H, $CH_2OS$), 4.08, 4.02(s, 3H each, $OCH_3$), 3.98, 3.58(s, 2H each, $CH_2O$), 3.14(s, 2H, $CH_2$-6), 2.12(s, 3H, $SCH_3$), 2.08(s, 3H, $CH_3$), 1.02–1.3(s, 18H, *t*-butyl). Anal. calcd. for $C_{45}H_{58}N_2O_5SSi_2$ (795.21): C, 67.97%; H,7.35%; N, 3.52%. Found: C, 67.64%; H, 7.61%; N, 3.87%.



### 3,3-Bis(tert-butyldiphenylsilyloxymethyl)-6-methoxy-5-methyl-1H, 3H,4H-pyrimido[1,6-c][1,3]oxazine-8-one (4)

Iodine (12 g, 94 mmol) was added to a mixture of **3** (26 g, 32 mmol) in dry THF (150 mL). The mixture was stirred at room temperature for 64 h. A 5% aq. sodium sulfite solution was added until the brown color of the mixture disappeared and the resulting solution was extracted with $CH_2Cl_2$. The combined extracts were washed with brine and water, dried over $MgSO_4$, and concentrated in vacuo. Crystallization (MeOH) afforded **4** (22 g, 94%): $R_f$ 0.2 ($CHCl_3$/AcOEt/n-hexane = 10:10:1); m.p. 121°–122°C; $^1$H NMR(300 MHz, $CDCl_3$)$\delta$ 7.60–7.26(m, 20H, Ph), 5.56(s, 2H, $NCH_2O$), 3.99(s, 3H, $OCH_3$), 3.59(s, 2H, $CH_2O$), 3.54(s, 2H, $CH_2O$), 3.06(s, 2H, $CH_2$-4), 1.93(s, 3H, $CH_3$), 1.07, 1.01, 0.95(s, 6H each, *t*-butyl); Anal. calcd. for $C_{43}H_{53}O_5N_2Si_2$(733.07): C, 70.45%; H, 7.15%; N, 3.82%. Found: C, 70.54%; H, 7.48%; N, 3.63%.

### 3,3-Bis(tert-butyldiphenylsilyloxymethyl)-5-methyl-1H,3H,4H,7H-pyrimido-[1,6-c][1,3]-oxazine-6,8-dione (5)

A solution of **4** (26 g, 32 mmol) in 2 N NaOH/dioxane (1/1, 300 mL) was stirred under reflux overnight. The solvent was removed in vacuo. The residue was taken up in EtOAc. The solution was neutralized by Dowex-X2 ($H^+$ form) to pH 7, and then filtered. The filtrate was concentrated to give a white powder. Crystallization (MeOH) afforded **5** (10.2 g, 72%): $R_f$0.32 ($CHCl_3$/AcOEt = 4:1); m.p. 82°–84°C; $^1$H NMR(300 MHz, $CDCl_3$) $\delta$ 9.17(s, 1H, NH), 7.60–7.26(m, 20H, Ph), 5.43(s, 2H, $NCH_2O$), 3.58(s, 2H, $CH_2O$), 3.55(s, 2H, $CH_2O$), 3.11(s, 2H, $H_2$-4), 1.94(s, 3H, $CH_3$), 1.07–0.95 (m, 18H, *t*-butyl); MS (*m*/*z*): 720 ($M^+$); Anal. calcd. for $C_{42}H_{51}O_5N_2Si_2$(719.05): C, 70.16%; H, 7.01%; N, 3.90%. Found: C, 69.74%; H, 6.98%; N, 3.98%.

### 3,3-Bis-(hydroxymethyl)-5-methyl-1H,3H,4H,7H-pyrimido [1,6-c][1,3]oxazine-6,8-dione (6)

Tetrabutylammonium fluoride (12.12 g, 46.4 mmol) was added into a solution of **5** (16 g, 23.2 mmol) in THF (250 mL). The mixture was stirred at room temperature for 2 h and then concentrated to give a white product. Crystallization (MeOH) afforded **6** (5.0 g, 88%): m.p. 197°–198°C (lit. 197°–198°C).[2]



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