A New Synthetic Route towards the Mono-*O*-protected *Anti*-conformationally Constrained Pyrimidine Acyclic Nucleoside

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Novel synthetic approach to mono-*O*-protected *anti*-conformationally constrained pyrimidine acyclic nucleoside was attained from the coupling of lithiated 2,4-dimethoxy-6-methylpyrimidine with 1-benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-one, followed by the sequential reactions of methylthiomethylation, cyclization, hydroxylation, and dealkylation.

Key words new synthetic route; pyrimidine acyclic nucleoside; oligonucleotide

Modified oligonucleotides have become an area of increased activity in the last decade due to their potential use as antiviral, antitumoral agents and effective tools for many molecular biology applications based on the hybridization technique.[1—3] However, some problems still remain, which are connected with their stability against enzymatic breakdown, solubility in biological fluids, ability to penetrate into cell membrane and affinity of binding to their duplexes. In order to overcome these problems oligonucleotides are modified either in the base, sugar or phosphate moiety. Acyclic oligonucleotides, one of these modified oligonucleotides, have been studied for these purpose.[4]

Recently, we reported[5] the synthesis and nuclease resistance of dinucleosides monophosphate containing an *anti*-conformationally constrained acyclic thymidine. These dinucleotides possess potent enzymatic stability toward nuclease S1, bovine spleen phosphodiesterase and snake venom phosphodiesterase. It therefore seemed reasonable that these nucleases stability will still remain if our *anti*-conformationally constrained acyclic nucleosides could incorporate into oligonucleotide. Thus we initiate the modification of our compounds suitable as building units for automated oligonucleotide synthesizer. To be good building units for oligonucleotide synthesizer, nucleotides require both 5′-dimethoxytrityl and 3′-phosphoamidite groups. However, modification of only one out of two primary hydroxy groups of our *anti*-conformationally constrained pyrimidine acyclic nucleotide unit to fulfill the requirement of building units for oligonucleotide synthesizer is difficult. Therefore development of a new method for the synthesis of mono-*O*-protected *anti*-conformationally constrained pyrimidine acyclic nucleoside as the key intermediate of the building unit for oligonucleotide synthesizer is an important subject. This report describes the synthesis of this compound.

In previous work,[6] 1,3-bis-*O*-benzylated-1,3-dihydroxyacetone prepared from 1,3-dihydroxyacetone served as a building block for the synthesis of *anti*-conformationally constrained pyrimidine acyclic nucleosides. However, drawback of the identical two primary hydroxy protecting groups made this compound being not suitable as building block for the preparation of title compound. Alternatively, we employ 1-benzyloxy-3-(*tert*-butyl-diphenylsilyloxy)propan-2-one (**4**) instead of 1,3-dibenzyloxy-2-propanone as intermediate for the synthesis of title compound.

1-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-one (**4**) was prepared in four steps from epichlorohydrin. Ring opening reaction of benzyl glycidyl ether (**1**), prepared following the published procedure,[7] in the presence of iodine in the acetonitrile and water solution afforded 3-benzyloxypropan-1,2-diol (**2**) in a yield of 63%. Silylation of **2** with *tert*-butylchlorodiphenylsilane in the presence of catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) furnished 64% of oily 1-benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-ol (**3**). In previous work,[6] the hydroxy group of 1,3-dibenzyloxy-2-propanol was oxidized to its corresponding ketone with *N*-chlorosuccinimide and dimethylsulfoxide. This procedure resulted in a repulsive odor. However, by using pyridinium chlorochromate (PCC) as an oxidizing agent this unpleasant odor could be circumvented. Thus, oxidation of the hydroxyl group of **3** with PCC at reflux temperature in dichloromethane provided 87% of oily **4**.

Treatment of 2,4-dimethoxy-6-methylpyrimidine with *n*-butyllithium in dry tetrahydrofuran at −70 °C gave lithio derivative, which reacted with **4** at −70 °C to afford an oily 6-{2-[1-benzyloxy-3-(*tert*-butyldiphenylsilyloxy)-2-hydroxy]-propyl}-methyl-2,4-dimethoxypyrimidine (**5**) in a yield of 92%. Conversion of the hydroxyl group of **5** to the corresponding methylthiomethyl ether of **6** was accomplished by treating **5** with a mixture of acetic anhydride and anhydrous dimethyl sulfoxide at room temperature for 33 h. Ring closure of **6** was accomplished with iodine in dry tetrahydrofuran at room temperature to give 3-benzyloxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-6-methoxy-(1*H*,3*H*,4*H*)-pyrimido[1,6-*c*][1,3]oxazin-8-one (**7**). In previous work,[6] the dealkylation of **7** was accomplished by using 2 N sodium hydroxide in dioxane under reflux overnight and the benzyl group of **7** was deprotected by hydrogenation in the presence of 20% palladium on carbon in methanol at high hydrogen pressure (50 psi). This method was not practically applicable for large scale preparation. However, by using different equivalents of trimethylsilyl iodide as dealkylating agent,[8] **7** was able to demethylate selectively (1.1 eq Me_3SiI) to 86% of 3-benzyloxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-(1*H*,3*H*,4*H*,7*H*)-pyrimido[1,6-*c*][1,3]oxazin-6,8-dione (**8**) and to debenzylate consecutively (3.0 eq Me_3SiI) to 71% of 3-hydroxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-(1*H*,3*H*,4*H*,7*H*)-pyrimido[1,6-*c*][1,3]oxazin-6,8-dione (**9**) as a white solid product.

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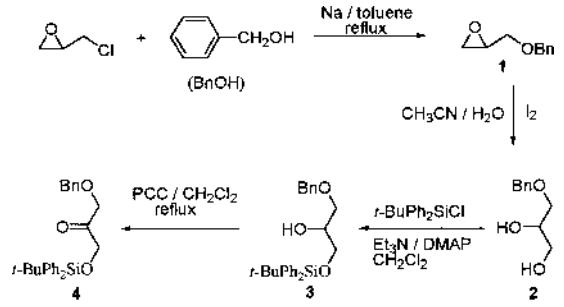

Chart 1

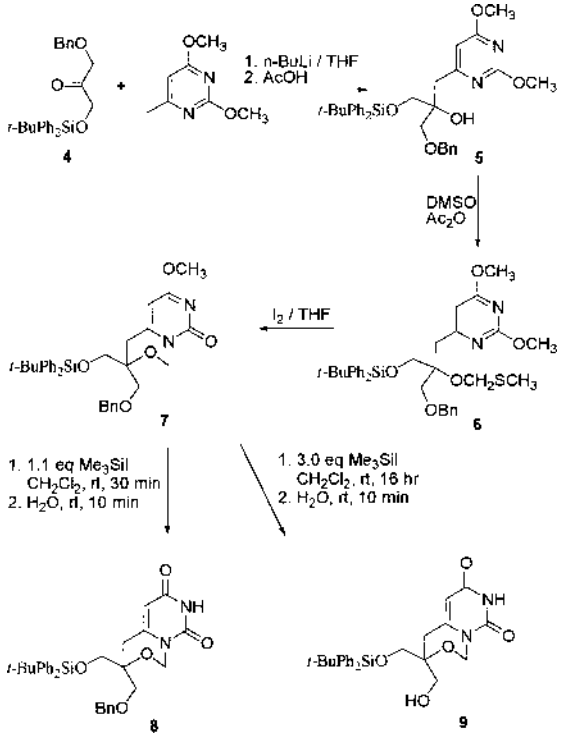

Chart 2

In conclusion, we have developed a new route for the synthesis of mono-*o*-protected *anti*-conformationally constrained pyrimidine acyclic nucleoside using 1-benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-one (**4**) as a building block in place of 1,3-dibenzyloxypropan-2-ol. This selecting provided the title compound with only one free hydroxyl group by selectively deblocking the protected hydroxyl group with certain reagents, which could be easily modified to the corresponding 5′-dimethoxytrityl and 3′-phosphoamidite acyclic nucleosides suitable for automated oligonucleotide synthesizer.

Experimental

General Melting points (mp) were taken on a BUCHI 530 apparatus and are uncorrected. Merck Art No105554 plates precoated with Silica gel 60 containing fluorescent indicator were used for thin-layer chromatography, and Silica gel 60 (Merck Art No 109385, 230—400 mesh) was employed for column chromatography. Evaporations were carried out at <50 °C using a rotary evaporator at reduced pressure (water aspirator). ^{1}H- and ^{13}C-NMR spectra were obtained at Varian 300 NMR spectrometer at 300 and 75 MHz, respectively. Where necessary, deuterium exchange experiments were used to obtained proton shift assignments. Mass spectra were recorded on a JEOL J.M.S-300 spectrophotometer. Analytical samples were dried under reduced pressure at 78 °C in the presence of P_2O_5 for at least 12 h unless otherwise specified. Elemental analyses were obtained from Perkin-Elmer 2400 Elemental Analyzer.

Benzyl Glycidyl Ether[7] (1) The solution of sodium (3.2 g, 145 mmol), benzyl alcohol (10 ml, 97 mmol) in 100 ml of toluene was heated under reflux for 1.5 h. After cooling to the r.t. (room temperature), epichlorohydrin (8 ml, 102 mmol) in 30 ml of toluene was added to the solution. The reaction mixture was heated under reflux for another 2 h. After cooling, the mixture was filtered. The filtrate was extracted with dichloromethane and water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Column chromatography on silica gel with 5 : 1 *n*-hexane/EtOAc as eluent gave **1** (7.6 g, 48%) as a light brown oil. *Rf* 0.57 (*n*-hexane/EtOAc=5/1). ^{1}H-NMR ($CDCl_3$) δ: 2.58—2.76 (2H, m, CH_2), 3.16—3.18 (1H, m, CH), 3.41 (1H , dd, J=11.4, 5.9 Hz, CHHOBn), 3.76 (1H, dd, J=11.5, 1.7 Hz, CHHOBn), 4.55 and 4.61 (1H each, d, J=11.9 Hz, OCH_2Ph), 7.29—7.36 (5H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 44.6, 51.3, 71.4, 73.8, 128.3, 128.9, 138.7. MS *m/z*: 163 (M^+-H^+). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.96; H, 7.20.

3-Benzyloxypropan-1,2-diol[7] (2) Iodine (3.1 g, 24.4 mmol) was added to a mixture of **1** (2.1 g, 12.8 mmol), 50 ml of acetonitrile and 50 ml of water. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated, ether (50 ml) was added, and the mixture was washed with 10% aqueous solution of Na_2SO_3 until disappearance of the iodine color was observed. The aqueous layer was separated and washed with ether (3×20 ml). The combined organic solution was concentrated to dryness *in vacuo*. Column chromatography on silica gel with 1 : 5 *n*-hexane/EtOAc as eluent gave **2** (1.47 g, 63%) as a colorless oil. *Rf* 0.37 (*n*-hexane/EtOAc=1/5). ^{1}H-NMR ($CDCl_3$) δ: 3.46—3.61 (2H, br, CH_2OBn), 3.88 (2H, br, CH_2OH), 4.10 (1H, m, CH), 4.51 (2H, s, OCH_2Ph), 7.32 (5H, s, ArH). ^{13}C-NMR ($CDCl_3$) δ: 64.5, 71.5, 72.1, 74.0, 128.4, 129.0, 138.4. MS *m/z*: 183 (M^++H^+). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.81; H, 8.01.

1-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-ol (3) To a chilled (0 °C) solution of **2** (1.0 g, 5.5 mmol), dimethylaminopyridine (0.2 g, 1.6 mmol), triethylamine (10 ml) in dry dichloromethane (60 ml), *tert*-butylchlorodiphenylsilane (1 M; 6 ml, 6 mmol) was added dropwisely. The resulting mixture was stirred under nitrogen at r.t. for 30 h and then poured over crushed ice and left overnight. The solution was extracted with dichloromethane. The organic extract was washed with 1 N HCl and water, dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on silica gel with 9 : 1 *n*-hexane/EtOAc as eluent to give **3** (1.48 g, 64%) as a colorless oil. *Rf* 0.24 (*n*-hexane/EtOAc=9/1). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (9H, s, $C(CH_3)_3$), 3.59—3.62 (2H, m, CH_2OBn), 3.76 (2H, d, J=5.4 Hz, CH_2OSi), 3.92—4.00 (1H, m, CH), 4.57 (2H, s, OCH_2Ph), 7.34—7.70 (15H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.9, 27.5, 65.5, 71.4, 71.7, 74.0, 128.2, 128.3, 129.0, 130.3, 133.9, 136.1, 138.7. MS *m/z*: 421 (M^++H^+). *Anal.* Calcd for $C_{26}H_{32}O_3Si$: C, 74.24; H, 7.67. Found: C, 74.06; H, 7.82.

1-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)propan-2-one (4) To a mixture of pyridinium chlorochromate (0.9 g, 4.2 mmol) in dichloromethane (30 ml) was added **3** (0.9 g, 2.1 mmol) dissolved in dichloromethane (20 ml). The resulting mixture was heated under reflux for 5 h, cooled and filtered. The filtrate was concentrated to dryness. The residue was chromatographed on silica gel with 1 : 1 *n*-hexane/CH_2Cl_2 as eluent to give **4** (0.76 g, 87%) as a colorless oil. *Rf* 0.38 (*n*-hexane/CH_2Cl_2=1 : 1). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (9H, s, $C(CH_3)_3$), 4.35 (2H, s, CH_2OBn), 4.36 (2H, s, CH_2OSi), 4.56 (2H, s, OCH_2Ph), 7.33—7.64 (15H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.8, 27.3, 69.3, 73.8, 74.0, 128.5, 128.6, 129.0, 130.6, 133.1, 136.1, 137.7, 207.1. MS *m/z*: 441 (M^++Na^+). *Anal.* Calcd for $C_{26}H_{30}O_3Si$: C, 74.60; H, 7.22. Found: C, 74.64; H, 7.38.

6-{2-[1-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)-2-hydroxy]propyl}-methyl-2,4-dimethoxypyrimidine (5) Under nitrogen atmosphere *n*-butyllithium (1.6 M; 10.0 ml, 16 mmol) was added dropwisely to a solution of 2,4-dimethoxy-6-methylpyrimidine (2.0 g, 13.0 mmol) in dry tetrahydrofuran (150 ml) at −78 °C. The mixture was raised and stirred at −50 °C for 30 min. Ketone **4** (5.4 g, 13 mmol) was added and the stirring was 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 dichloromethane and water. The organic layer was separated, dried over sodium sulfate, and concentrated to dryness. The residue was chromatographed on silica gel with 9 : 1 *n*-hexane/EtOAc as eluent to give **5** (6.8 g, 92%) as a light brown oil. *Rf* 0.15 (*n*-hexane/EtOAc=9 : 1). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s, $C(CH_3)_3$), 2.96 and 3.00 (1H each, d, J=14.9 Hz, CH_2-6), 3.49 and 3.51 (1H each, d, J=11.3 Hz, CH_2OBn), 3.60 and 3.71 (1H each, d, J=10.0 Hz, CH_2OSi), 3.91 and 3.97 (3H each, s, OCH_3), 4.54 and

4.58 (1H each, d, J=12.0 Hz, OCH_2Ph), 6.29 (1H, s, H-5), 7.30—7.64 (m, 15H, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.8, 27.4, 40.3, 54.3, 55.2, 67.2, 74.0, 74.2, 75.7, 102.8, 128.0, 128.1, 128.2, 128.8, 130.2, 130.2, 133.9, 136.1, 136.2, 138.9, 165.1, 169.5, 172.5. MS m/z: 573 (M^++H^+). *Anal.* Calcd for $C_{33}H_{40}N_2O_5Si$: C, 69.20; H, 7.04; N, 4.89. Found: C, 68.90; H, 6.85; N, 4.77.

6-{2-[1-Benzyloxy-3-(*tert*-butyldiphenylsilyloxy)-2-methylthiomethyloxy]propyl}methyl-2,4-dimethoxypyrimidine (6) Acetic anhydride (33 ml) was added to a mixture of **5** (3.3 g, 5.8 mmol) in dry dimethylsulfoxide (DMSO) (33 ml). The solution was stirred at r.t. for 33 h. The solution was extracted with CH_2Cl_2 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 *n*-hexane/EtOAc as eluent to give **6** (2.53 g, 69%) as a colorless oil. *Rf* 0.29 (*n*-hexane/EtOAc= 9 : 1). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, s, $C(CH_3)_3$), 2.00 (3H, s, SCH_3), 2.91 (2H, s, CH_2-6), 3.58, 3.60 (1H each, d, J=10.0 Hz, CH_2OBn), 3.69 and 3.77 (1H each, d, J=10.8 Hz, CH_2OSi), 3.75 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.38 and 4.42 (1H each, d, J=11.8 Hz, OCH_2Ph), 4.75 (2H, s, OCH_2S), 6.28 (1H, s, H-5), 7.18—7.55 (15H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 15.0, 19.9, 27.5, 39.9, 54.1, 55.1, 65.7, 69.2, 71.6, 74.0, 81.2, 102.9, 128.1, 128.2, 128.2, 128.4, 128.9, 130.3, 133.7, 136.1, 136.3, 138.7, 165.3, 168.7, 172.3. MS m/z: 633 (M^++H^+). *Anal.* Calcd for $C_{35}H_{44}N_2O_5SSi$: C, 66.42; H, 7.01; N, 4.43. Found: C, 66.44; H, 6.95; N, 4.17.

3-Benzyloxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-6-methoxy-(1*H*,3*H*,4*H*)-pyrimido[1,6-*c*][1,3]oxazin-8-one (7) Iodine (1.1 g, 4.3 mmol) was added to a mixture of **6** (1.7 g, 2.7 mmol) in dry tetrahydrofuran (THF) (30 ml). The mixture was stirred at r.t. for 21 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*. The residue was chromatographed on silica gel with 1 : 1 *n*-hexane/EtOAc as eluent to give **7** (1.46 g, 95%) as a colorless oil. *Rf* 0.33 (*n*-hexane/EtOAc=1 : 1). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (9H, s, $C(CH_3)_3$), 2.97 (2H, s, CH_2-4), 3.41 and 3.53 (1H each, d, J=9.9 Hz, CH_2OBn), 3.60 and 3.67 (1H each, d, J=10.7 Hz, CH_2OSi), 3.94 (3H, s, OCH_3), 4.51 (2H, s, OCH_2Ph), 5.53 (2H, s, OCH_2N), 5.68 (1H, s, H-5), 7.31—7.63 (15H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 19.8, 30.4, 54.7, 67.0, 71.1, 72.9, 74.3, 78.0, 94.8, 128.2, 128.4, 129.0, 130.5, 133.2, 136.1, 138.1, 154.7, 156.0, 172.0. MS m/z: 571 (M^++H^+). *Anal.* Calcd for $C_{33}H_{38}N_2O_5Si$: C, 69.44; H, 6.71; N, 4.91. Found: C, 69.75; H, 6.91; N, 4.69.

3-Benzyloxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-(1*H*,3*H*,4*H*,7*H*)-pyrimido[1,6-*c*][1,3]oxazin-6,8-dione (8) To a solution of **7** (1.1 g, 1.9 mmol) in dichloromethane (30 ml) was added trimethylsilyl iodide (0.3 ml, 2.1 mmol) *via* a dry syringe. The reaction mixture was stirred at r.t. for 1 h. Water (50 ml) was then poured into the mixture and the stirring was continued for 10 min. The mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane, washed with aqueous 5% sodium sulfite, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel with 1 : 1 *n*-hexane/EtOAc as eluent to give **8** (0.92 g, 86%), mp 136—137 °C. *Rf* 0.45 (*n*-hexane/EtOAc=1 : 1). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (9H, s, $C(CH_3)_3$), 2.94 and 2.98 (1H each, d, J=16.3 Hz, CH_2-4), 3.42 and 3.52 (1H each, d, J=9.9 Hz, CH_2OBn), 3.62 and 3.66 (1H each, d, J=10.8 Hz, CH_2OSi), 4.51 (2H, s, OCH_2Ph), 5.39 and 5.43 (1H each, d, J=10.0 Hz, OCH_2N), 5.55 (1H, s, H-5), 7.24—7.64 (15H, m, ArH), 10.13 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.0, 26.7, 29.4, 66.1, 69.2, 72.0, 73.5, 77.6, 100.7, 127.5, 127.7, 127.7, 128.3, 129.9, 129.9, 132.4, 132.4, 135.4, 135.4, 137.3, 149.7, 151.4, 163.3. MS m/z: 557 (M^++H^+). *Anal.* Calcd for $C_{32}H_{36}N_2O_5Si$: C, 69.04; H, 6.52; N, 5.03. Found: C, 68.89; H, 6.30; N, 4.70.

3-Hydroxymethyl-3-(*tert*-butyldiphenylsilyloxy)methyl-(1*H*,3*H*,4*H*,7*H*)-pyrimido[1,6-*c*][1,3]oxazin-6,8-dione (9) To a solution of **7** (10.5 g, 18.9 mmol) in dichloromethane (125 ml) was added trimethylsilyl iodide (8 ml, 56.0 mmol) *via* a dry syringe. The reaction mixture was stirred at r.t. for 16 h. Water (150 ml) was then poured into the mixture and the stirring was continued for 10 min. The mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane, washed with aqueous 5% sodium sulfite, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel with 1 : 4 *n*-hexane/EtOAc as eluent to give **9** (6.26 g, 71%), mp 187—188 °C. *Rf* 0.46 (*n*-hexane/EtOAc=1 : 4). ^{1}H-NMR (DMSO-d_6) δ: 0.96 (9H, s, $C(CH_3)_3$), 2.92 (2H, s, CH_2-6), 3.39—3.45 (2H, m, CH_2OH), 3.54 and 3.60 (1H each, d, J=10.6 Hz, CH_2OSi), 5.06 (1H, s, OH), 5.22 and 5.30 (1H each, d, J=9.9 Hz, OCH_2N), 5.57 (1H, s, H-5), 7.41—7.61 (10H, m, ArH), 11.20 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 18.8, 26.5, 29.4, 63.4, 66.3, 68.1, 78.5, 99.7, 127.9, 130.0, 132.6, 132.6, 135.2, 149.7, 152.2, 162.9. MS m/z: 467 (M^++H^+). *Anal.* Calcd for $C_{25}H_{30}N_2O_5Si$: C, 64.35; H, 6.48; N, 6.00. Found: C, 64.53; H, 6.53; N, 5.71.

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