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Synthesis of dendritic oligodeoxyribonucleotide analogs with nonionic diisopropylsilyl linkage

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ABSTRACT

Series of new dendritic oligodeoxyribonucleotide analogs with diisopropylsilyl linkage were prepared via liquid-phase synthesis. Dendron was employed as soluble support, which facilitated purification of the products by simple solvent precipitation. Sequences leading to the dendritic octamer 5′-$T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}$***D*$_2$**-3′ (**T8*D*$_2$**) were prepared and each isolated intermediate was characterized by NMR and mass spectrometry. The recognition properties of two complementary dendritic dinucleotide analogs of $T_{Si}T_{Si}$***D*$_2$** (**T2*D*$_2$**) and $A_{Si}A_{Si}$***D*$_2$** (**A2*D*$_2$**) were also studied by NMR and FT-MS spectra in a nonaqueous aprotic environment.

1. Introduction

Backbone-modified nucleic acids are of interest in antisense technology as potential antiviral, antibacterial, and anticancer agents,[1] as well as in DNA-based nanotechnology.[2] It is reported that various oligonucleotide analogs with nonphosphodiester scaffold,[3-8] including phosphorothioate,[4] amide backbones,[5] and bis(methylene) sulfones,[6] have been prepared. More recently, efforts have been devoted toward recognition and assembly properties of the nonionic oligonucleotide analogs in organic solvents,[6,7] and a series of complex conformation for the nonionic analogs was observed, providing valuable information on the factors that govern the formation of Watson-Crick structures.[6a]

Among many backbone-modified nucleic acids, nonionic oligonucleotide analogs with diisopropylsilyl linkage are attractive candidates owing to several unique characters of the system,[8] (i) diisopropylsilyl linkage is neutral, achiral and lipophilic; (ii) silicon atom on the backbone is similar with phosphorus in size, bond angles and bond lengths; (iii) nonionic oligonucleotide analogs are more suitable for studying recognition properties in apolar organic solvent due to their low polarity as comparison with the sulfone-linked analogs.[7] Although the first example of silyl-linked dinucleotides was reported in 1985 by Ogilvie and Cormier,[8a] diisopropylsilyl-linked oligonucleotide analogs have received less attention over the past several decades. In 1993, a hindered base procedure was developed in the preparation of intermediate 3′-*O*-diisopropylsilyl triflate by Saha and co-workers.[8d] This improved method was successfully employed in the synthesis of tetrathymidine analogs in a good yield, but synthesis of longer chain (>5 nucleobases) was found to be tedious and complex. Then, they transferred their solution synthesis to solid-phase synthesis, and prepared a thymidylate decanucleotide analog. However, mixtures were obtained, which required further purification with preparative HPLC. Therefore, more efficient and practical synthesis strategy of long chain of oligodeoxyribonucleotide analogs with diisopropylsilyl linkage is desirable.

In comparison with solid-phase synthesis, liquid-phase synthesis uses soluble polymer, particularly the well-defined dendrimers as support,[9a,b] allowing the reaction to be carried out homogeneously under precisely controlling manner.[9,10a] In addition, the resulting product can be purified through simple solvent precipitation utilizing the different solubilities of macromolecular/dendrimer supports and small molecular byproducts. Over the past several decades, this methodology has achieved great success in oligonucleotide synthesis.[10] To our knowledge, however, synthesis of nonionic oligonucleotide analogs via liquid-phase synthesis by using dendron as support has not been reported. As a part of our efforts on the synthesis of DNA/dendron hybrids and on the liquid-phase synthesis with dendrimer supports,[11,12] herein, we report the

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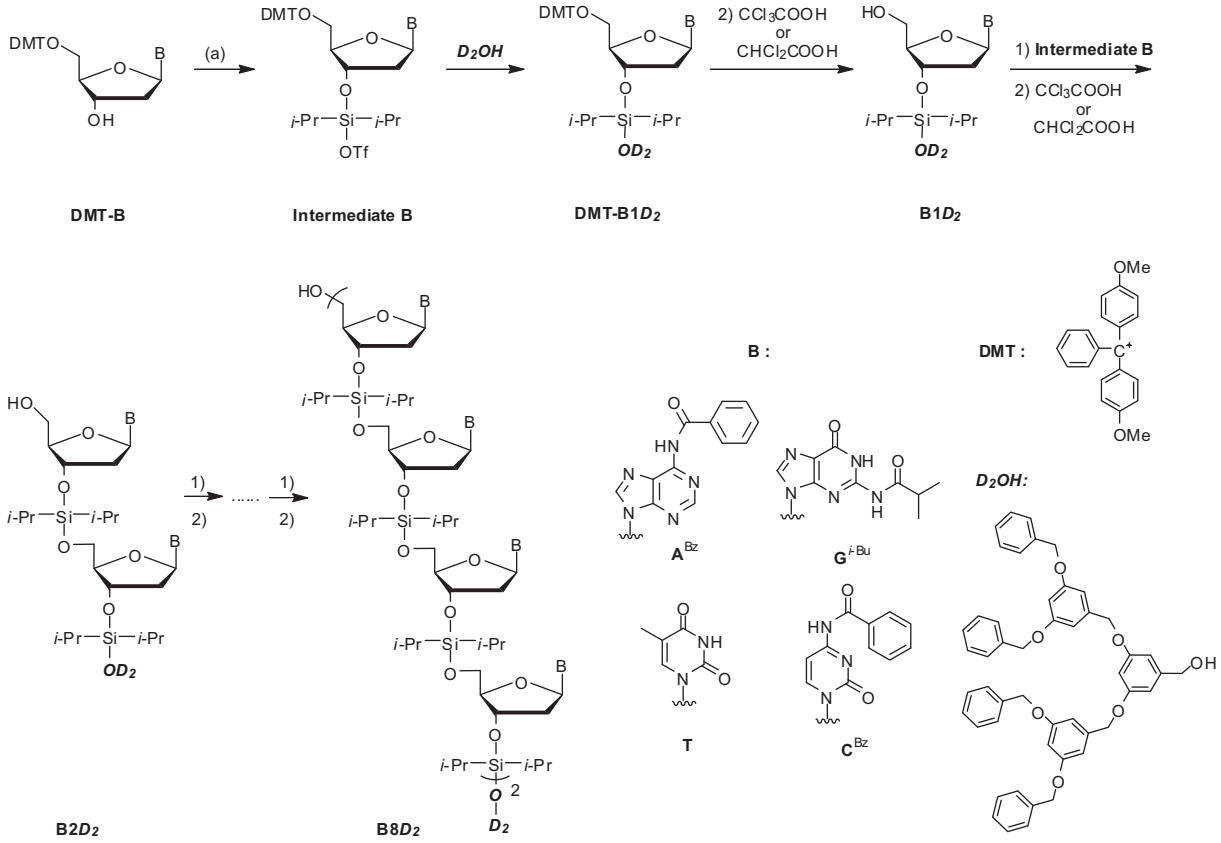
synthesis of diisopropylsilyl-linked oligodeoxyribonucleotide analogs bearing a second-generation Fréchet-type poly(aryl ether) dendron (***D*₂**) at the 3′-end of the analogs,[13] and the dendron facilitated purification of the reaction intermediates and the products. With this method, a dendritic thymidylate octanucleotide analog 5′-$T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}T_{Si}$***D*₂**-3′ (**T8*D*₂**) was synthesized in a good yield.[14] The recognition properties of two complementary dendritic dinucleotide analogs of $T_{Si}T_{Si}$***D*₂** (**T2*D*₂**) and $A_{Si}A_{Si}$***D*₂** (**A2*D*₂**) were also studied by NMR and FT-MS spectra in a non-aqueous aprotic environment.

2. Result and discussion

The readily available second-generation Fréchet's dendron was chosen for our study due to its high inertness toward organic reagents.[13] Similar to the traditional solid-phase synthesis, as shown in Scheme 1, chain extension of our method was from 3′- to 5′-end involving the formation of Si–O bond together with protection and deprotection strategy.

to give the crude product **T1*D*₂**.[15] Further purification of **T1*D*₂** was achieved by precipitation in ether and *n*-hexane to give the pure product in 62% yield. Following this procedure, **T1*D*₂** was used for the next round of coupling with the freshly prepared intermediate **T** to give **DMT-T2*D*₂**. After detritylation, **T2*D*₂** was obtained in 69% yield by solvent precipitation for two steps. Repetitive coupling and detritylation reaction sequence led to the formation of a series of diisopropylsilyl-linked oligonucleotide **T3*D*₂**, **T4*D*₂**, **T5*D*₂**, **T6*D*₂**, **T7*D*₂**, and **T8*D*₂** in 45–63% yields for every two-step. In order to maintain the high coupling efficiency, the equivalent amount of substrates were reduced gradually from 0.80 (**T2*D*₂**) to 0.50 (**T7*D*₂**) while the equivalent amount of intermediate **T** was kept at 0.92. All these analogs were well soluble in apolar solvent, such as CH_2Cl_2 and $CHCl_3$.

Unlike solid-phase synthesis, the reaction progress in liquid-phase synthesis could be easily monitored by thin layer chromatography (TLC). The purity and structure of all reaction intermediates and final products could be confirmed by using ^1H and ^{13}C NMR and TOF mass spectrometry. In addition, the resulting



Scheme 1. Reagents and conditions: (a) *i*-$Pr_2Si(OTf)_2$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_3CN, DMF, −40 °C, 1 h; (1) Intermediate B, −40 °C, 1 h; (2) 3% CCl_3COOH, CH_2Cl_2, 15 min or 3% $CHCl_2COOH$, CH_2Cl_2, 5 min.

5′-*O*-(4,4′-dimethoxytrityl)thymidine (**DMT-T**) and the second-generation Fréchet's dendron bearing hydroxyl group at the focal point (***D*₂OH**) were used as starting materials. **DMT-T** was first silylated in the presence of 2,6-di-*tert*-butyl-4-methyl-pyridine as the hindered base and bis(trifluoromethanesulfony1)-diisopropylsilane as the silylating reagent, giving the intermediate **T** in almost quantitative yield.[8d] In order to avoid the formation of 3′,3′-coupling byproducts, **DMT-T** should be added dropwise to the mixed solution of silylating reagent and hindered base at −40 °C under nitrogen atmosphere. The intermediate **T** was then reacted in situ with ***D*₂OH**, which was dissolved in dried DMF and added to the solution at one moment. **DMT-T1*D*₂** was obtained after precipitated from water, and detritylated with 3% trichloroacetic acid in dried methylene chloride

analogs were easily purified by a simple solvent precipitation at the end of the reaction. For example, according to the ^1H NMR shown in Fig. 1, precipitation of the crude product **T2*D*₂** in ether and *n*-hexane removed all the byproducts 4,4′-dimethoxytrityl alcohol (DMTOH) and the base catalyst. In the cases of synthesizing long chain analogs, additional purification by flash chromatography was required to ensure the coupling efficiency.

Next, we sought to test whether this method can be used for the synthesis of diisopropylsilyl-linked oligonucleotide analogs with four different bases. A sequence of $G^{i\text{-}Bu}C^{Bz}A^{Bz}$**T*D*₂** was designed and the synthetic route was the same as Scheme 1. **T1*D*₂** was coupled and detritylated with intermediate **A**, **C**, and **G** in succession to give A^{Bz}**T*D*₂**, $C^{Bz}A^{Bz}$**T*D*₂**, and $G^{i\text{-}Bu}C^{Bz}A^{Bz}$**T*D*₂**, respectively, in

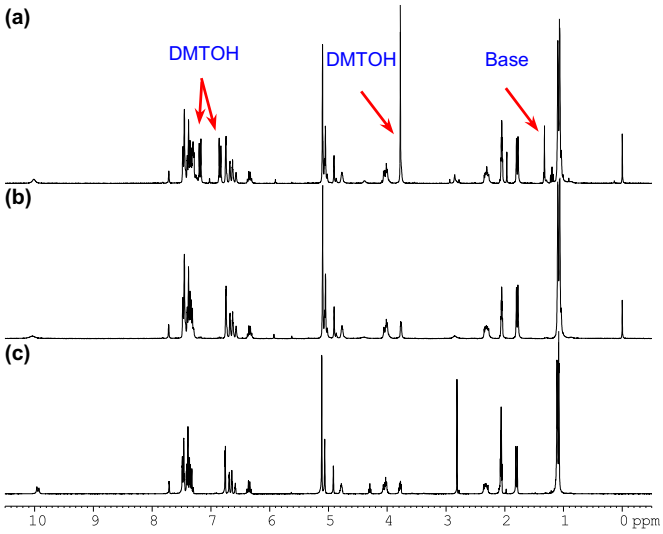


Fig. 1. ^{1}H NMR (acetone-d_6) of **T2*D*$_2$**: (a) crude product **T2*D*$_2$**; (b) after purification by precipitation in ether and *n*-hexane; and (c) after purification by silica gel column chromatography.

52–79% yields, indicating that any sequence could be synthesized following this synthetic method. The protecting groups of benzoyl and isobutyryl were quantitatively removed by treatment with mixture ethane-1,2-diamine/ethanol (1:1) as solvent at 55 °C for 50 min,[16] providing the deprotected product **GCAT*D*$_2$**, which was confirmed by MALDI-TOF mass spectrometry. The purine nucleosides exhibited higher sensitivity to acid than pyrimidine nucleosides, it was necessary to use the mild deprotection method.[17] The less acidic dichloroacetic acid was found to give better results compared to trichloroacetic acid due to its minimal extent of depurination. Also, the reaction time of deprotection should be kept within 5 min to reduce depurination byproducts.

The above resulting diisopropylsilyl-linked oligonucleotide analogs were well characterized by ^{1}H, ^{13}C, and ^{29}Si NMR as well as MALDI-TOF or FT-HRMS. For example, as shown in Table 1, the molecular weight was confirmed by MALDI-TOF spectroscopy, and the obtained results have a good agreement with the calculated values.

Table 1
MALDI-TOF results of a series of diisopropylsilyl-linked oligonucleotide analogs

Sample	Calculated		Found	
	$[M+Na]^+$	$[M+K]^+$		
T1*D*$_2$	1121.5	1137.4	1121.3	1137.3
T2*D*$_2$	1475.6	1491.6	1476.3	1492.4
T3*D*$_2$	1829.8	1845.8	1829.3	1845.3
T4*D*$_2$	2183.9	2199.9	2183.4	2200.4
T5*D*$_2$	2538.1	2554.1	2538.5	2554.6
T6*D*$_2$	2892.3		2894.2	
T7*D*$_2$	3246.4		3250.7	
T8*D*$_2$	3600.6		3603.7	
A^{Bz}T*D*$_2$	1588.7		1590.1	
C^{Bz}A^{Bz}T*D*$_2$	2031.8		2032.8	
G$^{i\text{-}Bu}$C^{Bz}A^{Bz}T*D*$_2$	2481.1		2481.1	
GCAT*D*$_2$	2203.0		2204.3	

To further investigate the recognition properties of diisopropylsilyl-linked oligonucleotide analogs, the complementary dendritic dinucleotide analog of **T2*D*$_2$** was also synthesized by using the same strategy. As shown in Scheme 1, N^6-benzoyl-5′-*O*-(4,4′-dimethoxytrityl)-2′-deoxyadenosine (**DMT-A^{Bz}**) was silylated to give the intermediate **A**, which directly coupled with ***D*$_2$*OH*** and detritylated with 3% dichloroacetic acid to give **A^{Bz}1*D*$_2$**. Then **A^{Bz}1*D*$_2$** was coupled with the freshly prepared intermediate **A** again. Finally, **A^{Bz}2*D*$_2$** was obtained after detritylation, the benzoyl groups were removed by treatment with mixture ethane-1,2-diamine/ethanol (1:1) as solvent at 55 °C for 50 min to give **A2*D*$_2$**.

It is well-known that complementary natural oligonucleotides can form a double helix. However, relatively little is known about the impact on the base-base recognition induced by modifications of the backbone.[6,7,18] With two complementary components **T2*D*$_2$** and **A2*D*$_2$** in hand, we further investigated their recognition properties. Their assemblies by hydrogen bonding in an apolar environment were prepared by mixing 1 equiv of **T2*D*$_2$** with 1 equiv of **A2*D*$_2$** in anhydrous $CDCl_3$. The formed complex was studied by ^{1}H NMR and FT-MS spectra.

To our delight, the base-base interaction between **T2*D*$_2$** and **A2*D*$_2$** could be monitored by ^{1}H NMR spectra (Fig. 2). For example, the proton NMR spectrum of a 1:1 (molar ratio) mixture of **T2*D*$_2$** (3 mM) and **A2*D*$_2$** (3 mM) showed a large downfield shift for the thymine NH of **T2*D*$_2$** and the adenine NH_2 of **A2*D*$_2$**. After complexation, the imide protons of **T2*D*$_2$** shifted greatly downfield from 8.01 and 8.10 ppm to 10.21 and 10.47 ppm, respectively, and the amino protons of **A2*D*$_2$** also shifted downfield from 5.81 and 5.90 ppm to 6.28 and 6.40 ppm, respectively. The NMR data indicated that the association of **T2*D*$_2$** and **A2*D*$_2$** by intermolecular hydrogen bonds involving NH and NH_2 protons.

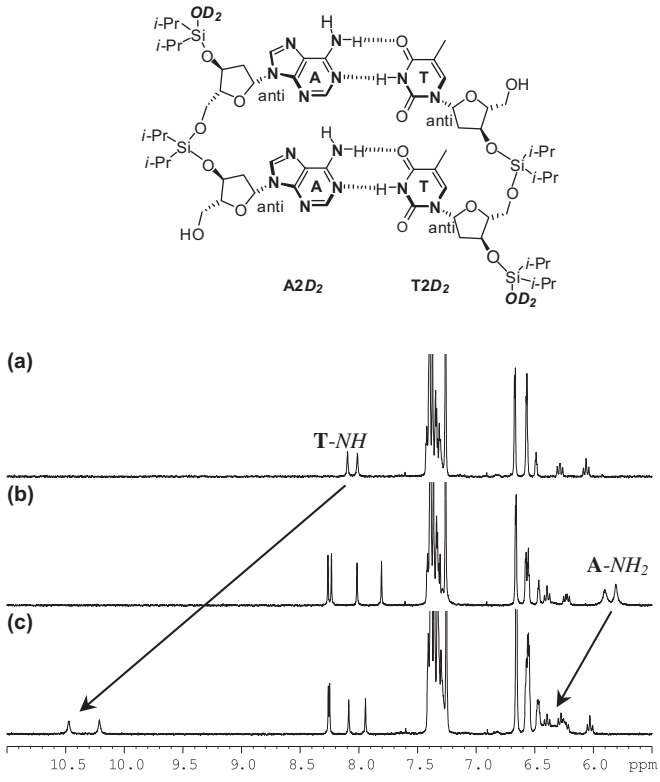


Fig. 2. Schematic model for base-base interaction between **T2*D*$_2$** and **A2*D*$_2$**; and partial ^{1}H NMR spectra (300 MHz) of (a) **T2*D*$_2$** (3 mM), (b) **A2*D*$_2$** (3 mM) and (c) **T2*D*$_2$** (3 mM)+**A2*D*$_2$** (3 mM) 25 °C in $CDCl_3$.

In addition, we also employed the FT-MS to further investigate the formation of **T2*D*$_2$**·**A2*D*$_2$** complex. Due to the base-base interaction of **T2*D*$_2$** and **A2*D*$_2$**, the FT-MS spectra showed molecular ion peak at *m*/*z*: 1462.6497 $[$**T2*D*$_2$**·**A2*D*$_2$**+2H$]^{2+}$, in good agreement with the calculated value (1462.6503) and thus indicative of the formation of **T2*D*$_2$**·**A2*D*$_2$** complex.

Furthermore, the **T2*D*$_2$**·**A2*D*$_2$** complex was characterized by its equilibrium constant K_a determined by a nonlinear regression

analysis of the thymine imide proton chemical shift measured as a function of complex concentration in $CDCl_3$. Thus, an association constant of 219 M^{-1} is obtained at 298 K, which is similar to that of the corresponding complex without the dendron (92 M^{-1}; for details, see the Supplementary data) and that reported in the reference.[7,19] This result suggest that the attached dendron has no significant influence on the base-base recognition.[20]

3. Conclusions

A new kind of dendritic diisopropylsilyl-linked oligodeoxyribonucleotide analog was successfully prepared via liquid-phase synthesis. The Fréchet-type dendron, serving as soluble support, could faciliate purification of the products by simple solvent precipitation. Series of analogs including a thymidylate octanucleotide and a sequence with four different bases were successfully prepared. Base-base recognition between two complementary dendritic dinucleotide analogs **T2*D*$_2$** and **A2*D*$_2$** was observed. The results imply that this type of analogs were valuable candidates for studying the recognition effect of nonionic oligonucleotides. Current work is aiming at the synthesis of diisopropylsilyl-linked oligodeoxyribonucleotide analogs by using cleavable linkage and the detailed investigation of recognition and assembly properties of this type of nonionic analogs.

4. Experimental section

4.1. General

Unless otherwise noted, all experiments were carried out under an inert atmosphere of dry nitrogen by using standard Schlenk-type techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 300 Spectrometer (^{1}H: 300 MHz; ^{13}C: 75 MHz and ^{29}Si NMR 53.5 MHz, respectively) at 298 K. Chemical shifts are reported in parts per million (ppm) relative to the internal standards, partially deuterated solvents or tetramethylsilane (TMS). Coupling constants (J) are denoted in hertz and chemical shifts (δ) in ppm. Multiplicities are denoted as follows: s=singlet, d=doublet, m=multiplet, br=broad. Matrix-assisted laser desorption-ionization (time of flight) mass spectrometry (MALDI-TOF) was performed on a Bruker Biflex III MALDI-TOF spectrometer with α-cyano-4-hydroxylcinnamic acid (CCA) as the matrix. Fourier transform ion cyclotron resonance mass spectrometer (FT-MS) was performed on Bruker 7.0 T Apex IV.

4.2. General procedure for preparation of intermediates (taking intermediate T as an example)

Bis(trifluoromethanesulfony1)diisopropylsilane (2.47 g, 5.99 mmol, 1 equiv) was added via syringe to a solution of 2,6-di-*tert*-butyl-4-methylpyridine (1.23 g, 5.99 mmol, 1 equiv) in CH_3CN (15 mL) in a 200-mL round-bottom flask under N_2 atmosphere. The resulted clear solution was cooled to −40 °C, followed by addition of a solution of 5′-*O*-(4,4′-dimethoxytrityl)thymidine (**DMT-T**) (3.00 g, 5.51 mmol, 0.92 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (295 mg, 1.44 mmol, 0.24 equiv) in DMF (25 mL) dropwise via syringe over 10 min. The reaction mixture was stirred at −40 °C for further 1 h, and the intermediate **T** was obtained, which was directly used for the next step without purification.[8d]

4.3. General procedure for synthesis of Tn*D*$_2$ (*n*=1–8)

T1*D*$_2$. ***D*$_2$*OH*** (4.10 g, 5.51 mmol, 0.92 equiv) in DMF (25 mL) was added to a solution of intermediate **T** (0.92 equiv) prepared as above. The reaction was stirred for 1 h and then poured into a vigorously-stirred ice-water mixture (500 mL). The mixture was filtered to give a white solid, which was dissolved in EtOAc and dried over anhydrous Na_2SO_4. All solvents were filtered and removed by evaporation under reduced pressure to give crude product **DMT-T1*D*$_2$**.

A solution of the above obtained crude **DMT-T1*D*$_2$** (5.51 mmol, 0.92 equiv) in CH_2Cl_2 (50 mL) was added to 3% trichloroacetic acid in CH_2Cl_2 (200 mL). The bright orange solution was stirred at room temperature for 15 min, and 5% aqueous $NaHCO_3$ (200 mL) was poured into the mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a residue (7.36 g crude product of **T1*D*$_2$**).

The residue was dissolved in 24 mL CH_2Cl_2 and added dropwise to 450 mL ether. After it was suspended in the ether, 450 mL of *n*-hexane was poured into the stirring solution, white particles precipitated from the solution all at once, then it adhered to the flask as oily sample gradually. The solution was stirred for 15 min and the solvent was poured out, giving **T1*D*$_2$** (3.78 g, 62% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.86 (br s, 1H), 7.73 (s, 1H), 7.48–7.30 (m, 20H), 6.76–6.37 (m, 9H), 6.35–6.32 (m, 1H), 5.11–5.06 (m, 12H), 4.91 (s, 2H), 4.80–4.78 (m, 1H), 4.25 (s, 1H), 4.01 (s, 1H), 3.78–3.77 (m, 2H), 2.32–2.29 (m, 2H), 1.78 (d, J=3.3 Hz, 3H), 1.11–1.09 (m, 14H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 161.2, 161.0, 151.4, 144.5, 140.9, 138.3, 136.9, 129.3, 128.6, 128.5, 110.7, 107.2, 105.8, 102.0, 101.7, 88.9, 85.8, 73.7, 70.6, 70.4, 65.3, 62.8, 41.3, 17.7, 17.7, 12.9, 12.9, 12.6. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −8.23. MALDI-TOF (m/z): $[M+Na]^+$ and $[M+K]^+$ calcd for $C_{65}H_{70}NaN_2O_{12}Si$ and $C_{65}H_{70}KN_2O_{12}Si$: 1121.5, 1137.4, found 1121.3, 1137.3. FT-MS (m/z): $[M+H]^+$ calcd for $C_{65}H_{71}N_2O_{12}Si$: 1099.47763, found 1099.47708.

4.3.1. ***T2D*$_2$***. Following the procedure for preparing **T1*D*$_2$**, 0.85 equiv (3.13 g) of **T1*D*$_2$** was coupled with intermediate **T** (0.92 equiv), giving **T2*D*$_2$** (2.85 g, 69% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.96–9.93 (m, 2H), 7.71 (d, J=1.2 Hz, 1H), 7.49–7.32 (m, 21H), 6.76–6.58 (m, 9H), 6.36–6.34 (m, 2H), 5.11–5.06 (m, 12H), 4.92 (s, 2H), 4.79–4.77 (m, 2H), 4.30 (t, J=4.3 Hz, 1H), 4.07–4.01 (m, 4H), 3.79–3.76 (m, 2H), 2.36–2.29 (m, 4H), 1.80 (dd, J=7.2, 0.9, 6H), 1.11–1.08 (m, 28H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.1, 164.1, 161.2, 161.0, 151.4, 151.3, 144.4, 140.8, 138.3, 136.8, 136.2, 129.3, 128.6, 128.5, 111.0, 110.8, 107.3, 105.9, 102.0, 101.6, 88.8, 88.1, 85.8, 85.4, 73.9, 73.3, 70.6, 70.4, 65.4, 63.9, 62.8, 41.4, 40.9, 17.8, 17.7, 12.9, 12.9, 12.8, 12.7, 12.6, 12.6. MALDI-TOF (m/z): $[M+Na]^+$ and $[M+K]^+$ calcd for $C_{81}H_{96}NaN_4O_{17}Si_2$ and $C_{81}H_{96}KN_4O_{17}Si_2$: 1475.6, 1491.6, found 1476.3, 1492.4. FT-MS (m/z): $[M+H]^+$ calcd for $C_{81}H_{97}N_4O_{17}Si_2$: 1453.63873, found 1453.63818.

4.3.2. ***T3D*$_2$***. Following the procedure for preparing **T1*D*$_2$**, 0.80 equiv (2.54 g) of **T2*D*$_2$** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using CH_2Cl_2/EtOAc=1:1 as eluent to give **T3*D*$_2$** (1.96 g, 62% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.97–9.94 (m, 2H), 7.74 (s, 1H), 7.48–7.30 (m, 22H), 6.75–6.59 (m, 9H), 6.35–6.31 (m, 3H), 5.11–5.06 (m, 12H), 4.91 (s, 2H), 4.76 (s, 3H), 4.31–4.29 (m, 1H), 4.04 (s, 7H), 3.79–3.78 (m, 2H), 2.35–2.33 (m, 6H), 1.81 (s, 9H), 1.10–1.09 (m, 42H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 164.1, 164.1, 161.1, 161.0, 151.4, 151.3, 144.4, 140.8, 138.3, 136.9, 136.4, 136.2, 129.3, 128.6, 128.5, 111.1, 111.0, 110.8, 107.2, 105.8, 102.0, 101.6, 88.8, 88.1, 85.9, 85.5, 74.0, 73.6, 73.3, 70.6, 70.4, 65.3, 63.9, 62.8, 41.4, 40.9, 40.7, 17.8, 17.8, 17.7, 17.7, 12.9, 12.9, 12.8, 12.8, 12.7, 12.7, 12.6, 12.6. MALDI-TOF (m/z): $[M+Na]^+$ and $[M+K]^+$ calcd for $C_{97}H_{122}NaN_6O_{22}Si_3$ and $C_{97}H_{122}KN_6O_{22}Si_3$: 1829.8, 1845.8, found 1829.3, 1845.3. FT-MS

(*m*/*z*): $[M+H]^+$ calcd for $C_{97}H_{123}N_6O_{22}Si_3$: 1807.79982, found 1807.79928.

4.3.3. ***T4D₂***. Following the procedure for preparing **T1*D*₂**, 0.70 equiv (1.96 g) of **T3*D*₂** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using CH_2Cl_2/EtOAc=2:3 as eluent to give **T4*D*₂** (1.27 g, 56% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.99–9.95 (m, 3H), 7.74 (s, 1H), 7.47–7.31 (m, 23H), 6.74–6.57 (m, 9H), 6.34–6.31 (m, 4H), 5.10–5.05 (m, 12H), 4.90 (s, 2H), 4.75 (s, 4H), 4.31–4.29 (m, 1H), 4.02 (s, 10H), 3.79 (s, 2H), 2.33 (s, 8H), 1.80 (s, 12H), 1.08 (s, 56H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 164.1, 161.2, 161.0, 151.5, 151.3, 144.4, 140.8, 138.3, 136.9, 136.5, 136.3, 136.2, 129.3, 128.6, 128.5, 111.1, 111.0, 110.9, 107.3, 105.8, 102.0, 101.6, 88.9, 88.1, 85.9, 85.6, 74.0, 73.7, 73.6, 73.2, 70.6, 70.4, 65.3, 64.1, 62.8, 41.4, 40.9, 40.7, 17.8, 17.7, 12.9, 12.8, 12.7, 12.6. MALDI-TOF (*m*/*z*): $[M+Na]^+$ and $[M+K]^+$ calcd for $C_{113}H_{148}NaN_8O_{27}Si_4$ and $C_{113}H_{148}KN_8O_{27}Si_4$: 2183.9, 2199.9, found 2183.4, 2200.4. FT-MS (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{113}H_{152}N_9O_{27}Si_4$: 2178.98747, found 2178.98692.

4.3.4. ***T5D₂***. Following the procedure for preparing **T1*D*₂**, 0.70 equiv (1.27 g) of **T4*D*₂** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using CH_2Cl_2/EtOAc=1:4 as eluent to give **T5*D*₂** (0.83 g, 56% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.00 (br s, 3H), 7.75 (s, 1H), 7.48–7.30 (m, 24H), 6.76–6.58 (m, 9H), 6.37–6.29 (m, 5H), 5.11–5.06 (m, 12H), 4.91 (s, 2H), 4.79–4.74 (m, 5H), 4.06–4.03 (m, 13H), 3.81 (s, 2H), 2.38–2.35 (m, 10H), 1.84–1.82 (m, 15H), 1.11–1.09 (m, 70H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 164.1, 161.2, 161.0, 151.3, 144.4, 140.8, 138.3, 136.9, 136.5, 136.4, 136.2, 129.3, 128.6, 128.5, 111.1, 111.1, 111.0, 110.9, 107.3, 105.8, 102.0, 101.6, 88.9, 88.2, 88.1, 85.9, 85.7, 85.5, 74.0, 73.7, 73.7, 73.6, 73.2, 70.6, 70.4, 65.3, 64.0, 62.8, 41.4, 40.9, 40.7, 17.8, 17.7, 12.9, 12.9, 12.8, 12.7, 12.7, 12.6, 12.6. MALDI-TOF (*m*/*z*): $[M+Na]^+$ and $[M+K]^+$ calcd for $C_{129}H_{174}NaN_{10}O_{32}Si_5$ and $C_{129}H_{174}KN_{10}O_{32}Si_5$: 2538.1, 2554.1, found 2538.5, 2554.6. FT-MS (*m*/*z*): $[M+NH_4]^+$ calcd for $C_{129}H_{178}N_{11}O_{32}Si_5$: 2533.14857, found 2533.14802.

4.3.5. ***T6D₂***. Following the procedure for preparing **T1*D*₂**, 0.60 equiv (766 mg) of **T5*D*₂** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using CH_2Cl_2/EtOAc=1:4 as eluent to give **T6*D*₂** (553 mg, 63% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.03 (br s, 5H), 7.76 (s, 1H), 7.48–7.30 (m, 25H), 6.76–6.58 (m, 9H), 6.37–6.29 (m, 6H), 5.11–5.06 (m, 12H), 4.91 (s, 2H), 4.81–4.74 (m, 6H), 4.32–4.31 (m, 1H), 4.07–4.03 (m, 16H), 3.83–3.80 (m, 2H), 2.37 (s, 12H), 1.84–1.82 (m, 18H), 1.12–1.08 (m, 84H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 164.2, 164.1, 161.2, 161.0, 151.5, 151.4, 151.3, 144.4, 140.8, 138.3, 136.5, 129.3, 128.6, 128.5, 111.2, 111.1, 111.0, 110.9, 107.3, 105.8, 102.0, 88.9, 88.2, 85.9, 85.7, 74.0, 73.7, 73.5, 70.6, 70.4, 64.0, 40.7, 17.8, 17.7, 177, 12.9, 12.9, 12.8, 12.8, 12.7, 12.7, 12.6. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −4.03. MALDI-TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{145}H_{200}NaN_{12}O_{37}Si_6$: 2892.3, found 2894.2. FT-MS (*m*/*z*): $[M+2NH_4]^{2+}$ calcd for $C_{145}H_{208}N_{14}O_{37}Si_6$: 1452.67202, found 1452.67147.

4.3.6. ***T7D₂***. Following the procedure for preparing **T1*D*₂**, 0.50 equiv (300 mg) of **T6*D*₂** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using EtOAc as eluent to give **T7*D*₂** (277 mg, 45% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.09 (br s, 3H), 7.76 (d, *J*=1.2 Hz, 1H), 7.47–7.29 (m, 26H), 6.74–6.57 (m, 9H), 6.36–6.28 (m, 7H), 5.10–5.05 (m, 12H), 4.90 (s, 2H), 4.77–4.72 (m, 7H), 4.05–4.02 (m, 19H), 3.80–3.79 (m, 2H), 2.35 (s, 14H), 1.82–1.80 (m, 21H), 1.10–1.06 (m, 98H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.2, 161.1, 161.0, 151.4, 144.4, 140.8, 138.3, 136.9, 136.5, 136.3, 129.3, 128.5, 111.2, 111.1, 111.1, 110.9, 107.2, 105.7, 101.9, 101.5, 88.9, 88.1, 88.0, 85.8, 85.6, 74.0, 73.7, 73.6, 73.5, 73.1, 70.6, 70.3, 65.3, 64.0, 62.7, 41.4, 40.9, 40.7, 17.8, 17.8, 12.7, 12.7. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −5.81. MALDI-TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{161}H_{226}NaN_{14}O_{42}Si_7$: 3246.4, found 3250.7. FT-MS (*m*/*z*): $[M+2NH_4]^{2+}$ calcd for $C_{161}H_{234}N_{16}O_{42}Si_7$: 1629.75257, found 1629.75202.

4.3.7. ***T8D₂***. Following the procedure for preparing **T1*D*₂**, 0.50 equiv (252 mg) of **T7*D*₂** was coupled with intermediate **T** (0.92 equiv). In addition to precipitation method, the detritylated residue was further purified by flash column chromatography using EtOAc as eluent to give **T8*D*₂** (130 mg, 46% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.21 (br s, 6H), 7.77 (s, 1H), 7.48–7.29 (m, 27H), 6.74–6.57 (m, 9H), 6.35–6.33 (m, 8H), 5.10–5.05 (m, 12H), 4.90 (s, 2H), 4.73 (s, 8H), 4.04 (s, 22H), 3.80 (s, 2H), 2.87 (s, 16H), 1.83–1.81 (m, 24H), 1.09 (s, 112H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.3, 161.1, 160.9, 151.4, 151.4, 144.4, 140.8, 138.2, 137.0, 136.5, 136.3, 129.3, 128.7, 128.5, 111.1, 111.1, 110.9, 107.2, 105.7, 101.9, 101.5, 88.9, 88.1, 88.0, 85.8, 85.6, 85.4, 74.0, 73.7, 73.1, 70.6, 70.3, 65.3, 64.0, 62.8, 41.4, 40.9, 40.7, 17.9, 17.8, 12.9, 12.8, 12.7, 12.7. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −5.41. MALDI-TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{177}H_{252}NaN_{16}O_{47}Si_8$: 3600.6, found 3603.7. FT-MS (*m*/*z*): $[M+2NH_4]^{2+}$ calcd for $C_{177}H_{260}N_{18}O_{47}Si_8$: 1806.83312, found 1806.83257.

4.4. General procedure for preparation of $A^{Bz}TD_2$, $C^{Bz}A^{Bz}TD_2$, $G^{i\text{-}Bu}C^{Bz}A^{Bz}TD_2$ and $A^{Bz}1D_2$, $A2D_2$

$A^{Bz}TD_2$: **T1*D*₂** (2.10 g, 1.91 mmol, 0.90 equiv) in DMF (12 mL) was added to a solution of intermediate **A** (0.92 equiv) prepared as intermediate **T**. The reaction mixture was stirred for 1 h and then poured into a vigorously-stirred ice-water mixture (150 mL). The suspension was filtered to give a white solid, which was dissolved in EtOAc and dried over anhydrous Na_2SO_4. The solvent was filtered and removed by evaporation under reduced pressure to give crude product **DMT-$A^{Bz}TD_2$**.

A solution of the obtained crude **DMT-$A^{Bz}TD_2$** (1.91 mmol, 0.90 equiv) in CH_2Cl_2 (30 mL) was added to 3% dichloroacetic acid in CH_2Cl_2 (100 mL). The bright orange solution was stirred at room temperature for 5 min, and the mixture was poured into 5% aqueous $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc as eluent to give **$A^{Bz}TD_2$** (2.36 g, 79% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.38 (s, 1H), 8.61 (s, 1H), 8.49 (s, 1H), 8.11 (d, *J*=7.2 Hz, 2H), 7.60–7.27 (m, 24H), 6.73–6.55 (m, 10H), 6.33 (t, *J*=7.1 Hz, 1H), 5.07–5.03 (m, 12H), 4.94–4.93 (m, 1H), 4.89 (s, 2H), 4.79 (s, 1H), 4.14–4.05 (m, 4H), 3.82–3.76 (m, 2H), 3.00–2.93 (m, 1H), 2.54–2.48 (m, 1H), 2.35–2.31 (m, 2H), 1.77 (s, 3H), 1.09 (s, 28H). ^{13}C NMR (75 MHz, acetone-d_6) δ 166.0, 164.3, 164.2, 161.0, 160.9, 152.3, 152.1, 151.3, 151.2, 144.3, 143.7, 140.7, 138.2, 136.2, 134.9, 133.2, 129.5, 129.3, 129.2, 128.6, 128.4, 126.0, 111.0, 107.1, 105.6, 101.8, 101.4, 89.9, 87.9, 86.6, 85.2, 74.2, 72.9, 70.5, 70.3, 65.2, 63.7, 63.0, 41.5, 40.8, 17.8, 17.8, 17.7, 12.8, 12.8, 12.6, 12.6. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −3.18, −3.79.MALDI-TOF (*m*/*z*): $[M+Na]^+$ calcd for $C_{88}H_{99}NaN_7O_{16}Si_2$: 1588.7, found 1590.1.

4.4.1. ***$C^{Bz}A^{Bz}TD_2$***. Following the procedure for preparing **$A^{Bz}TD_2$**, 0.80 equiv (1.50 g) of **$A^{Bz}TD_2$** was coupled with intermediate **C**

(0.92 equiv), and the detritylated residue was purified by silica gel column chromatography using EtOAc as eluent to give $\mathbf{C^{Bz}A^{Bz}TD_2}$ (1.51 g, 78% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 10.09 (br s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 8.37 (d, J=7.5 Hz, 1H), 8.14–8.11 (m, 4H), 7.63–7.29 (m, 28H), 6.73–6.48 (m, 10H), 6.34–6.22 (m, 2H), 5.08–5.03 (m, 13H), 4.88 (s, 2H), 4.77 (s, 1H), 4.62–4.60 (m, 1H), 4.10–4.02 (m, 7H), 3.71 (s, 2H), 3.22–3.13 (m, 1H), 2.64–2.45 (m, 2H), 2.35–2.31 (m, 2H), 2.21–2.13 (m, 1H), 1.76 (s, 3H), 1.13–0.99 (m, 42H). ^{13}C NMR (75 MHz, acetone-d_6) δ 164.4, 163.6, 161.0, 160.8, 152.8, 152.5, 151.3, 151.1, 145.7, 144.2, 143.8, 140.7, 138.1, 136.4, 134.8, 134.5, 133.5, 133.1, 129.3, 129.2, 129.1, 128.6, 128.4, 125.9, 111.0, 107.1, 105.6, 101.8, 101.3, 89.4, 88.2, 88.0, 88.0, 85.4, 85.1, 73.3, 73.0, 70.5, 70.3, 65.2, 63.8, 63.2, 62.3, 42.6, 40.9, 40.1, 17.9, 17.8, 17.7, 17.7, 17.7, 17.6, 12.8, 12.8, 12.7, 12.6, 12.5. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −7.07. MALDI-TOF (m/z): $[M+Na]^+$ calcd for $C_{110}H_{128}NaN_{10}O_{21}Si_3$: 2031.8, found 2032.8.

4.4.2. $\mathbf{G^{i\text{-}Bu}C^{Bz}A^{Bz}TD_2}$. Following the procedure for preparing $\mathbf{A^{Bz}TD_2}$, 0.80 equiv (201 mg) of $\mathbf{C^{Bz}A^{Bz}TD_2}$ was coupled with intermediate **G** (0.92 equiv), and the detritylated residue was purified by silica gel column chromatography using EtOAc/MeOH=20:1 as eluent to give $\mathbf{G^{i\text{-}Bu}C^{Bz}A^{Bz}TD_2}$ (130 mg, 52% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 12.06 (br s, 1H), 10.80 (br s, 1H), 10.19 (br s, 1H), 10.09 (br s, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 8.23 (d, J=7.5 Hz, 1H), 8.11–8.05 (m, 5H), 7.59–7.30 (m, 28H), 6.73–6.55 (m, 10H), 6.34–6.23 (m, 2H), 6.17–6.12 (m, 1H), 5.08–5.03 (m, 13H), 4.88 (s, 2H), 4.77–4.70 (m, 3H), 4.51 (s, 1H), 4.13–4.00 (m, 10H), 3.70 (s, 2H), 3.20–3.14 (m, 1H), 3.01–2.92 (m, 1H), 2.81–2.73 (m, 1H), 2.63–2.59 (m, 2H), 2.36–2.33 (m, 3H), 2.29–2.22 (m, 1H), 1.77 (s, 3H), 1.22–1.19 (m, 6H), 1.13–1.03 (m, 56H). ^{13}C NMR (75 MHz, acetone-d_6) δ 180.9, 164.5, 163.9, 161.1, 160.9, 156.0, 152.8, 151.4, 151.1, 149.3, 149.1, 145.2, 144.3, 143.9, 140.8, 138.6, 138.2, 136.5, 134.5, 133.6, 133.3, 129.4, 129.3, 129.2, 128.7, 128.5, 125.9, 121.9, 111.1, 107.2, 105.7, 101.9, 101.4, 89.5, 88.8, 88.6, 88.1, 85.4, 84.9, 74.1, 73.5, 73.1, 70.5, 70.3, 65.3, 63.8, 63.4, 62.8, 42.4, 41.4, 40.9, 40.1, 36.4, 19.5, 18.0, 17.9, 17.8, 12.9, 12.9, 12.8, 12.7, 12.6. ^{29}Si NMR (53.5 MHz, acetone-d_6) δ −6.22, −6.83. MALDI-TOF (m/z): $[M+Na]^+$ calcd for $C_{130}H_{159}NaN_{15}O_{26}Si_4$: 2481.1, found 2481.1.

4.4.3. $\mathbf{GCATD_2}$. $\mathbf{G^{i\text{-}Bu}C^{Bz}A^{Bz}TD_2}$ (10 mg) was added into 3 mL mixture solvent of ethane-1,2-diamine/ethanol (1:1) and stirred at 55 °C for 50 min. The solvent was removed to give $\mathbf{GCATD_2}$. MALDI-TOF (m/z): $[M+Na]^+$ calcd for $C_{112}H_{145}NaN_{15}O_{23}Si_4$: 2203.0, found 2204.3.

4.4.4. $\mathbf{A^{Bz}1D_2}$. Following the procedure for preparing $\mathbf{T1D_2}$, 0.92 equiv (2.10 g, 3.04 mmol) of $\mathbf{D_2OH}$ was coupled with intermediate **A** (0.92 equiv). After detritylation in 3% dichloroacetic acid in CH_2Cl_2 (50 mL) for 5 min, crude product was purified by silica gel column chromatography using CH_2Cl_2/EtOAc=2:1 as eluent to give $\mathbf{A^{Bz}1D_2}$ (2.31 g, 63% yield for two steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.89 (br s, 1H), 8.59 (s, 1H), 8.45 (s, 1H), 8.10 (d, J=7.2 Hz, 2H), 7.66–7.61 (m, 1H), 7.57–7.52 (m, 2H), 7.47–7.28 (m, 20H), 6.75–6.54 (m, 10H), 5.09–4.91 (m, 15H), 4.16–4.14 (m, 1H), 3.85–3.68 (m, 2H), 3.03–2.94 (m, 1H), 2.53–2.46 (m, 1H), 1.13–1.12 (m, 14H). ^{13}C NMR (75 MHz, acetone-d_6) δ 166.0, 161.1, 161.0, 152.5, 151.4, 144.5, 143.9, 140.8, 138.2, 135.0, 133.3, 129.4, 129.3, 129.2, 128.9, 128.7, 128.5, 126.2, 107.2, 105.8, 102.1, 101.7, 90.2, 86.7, 74.3, 70.6, 70.5, 65.4, 63.3, 41.7, 18.0, 13.0, 12.9. MALDI-TOF (m/z): $[M+Na]^+$ calcd for $C_{72}H_{73}NaN_5O_{11}Si$: 1234.5, found 1234.9.

4.4.5. $\mathbf{A2D_2}$. Following the procedure for preparing $\mathbf{T1D_2}$, 0.92 equiv (2.10 g) of $\mathbf{A^{Bz}1D_2}$ was coupled with intermediate **A** (0.92 equiv). Detritylation in 3% dichloroacetic acid in CH_2Cl_2 (50 mL), gave crude $\mathbf{A^{Bz}2D_2}$, which was directly used for the next step without further purification. $\mathbf{A^{Bz}2D_2}$ was added into 20 mL mixture solvent of ethane-1,2-diamine/ethanol (1:1) and stirred at 55 °C for 50 min. After the solvent was removed, the residue was purified by silica gel column chromatography using EtOAc as eluent to give $\mathbf{A2D_2}$ (0.74 g, 29% yield for three steps) as white foam. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.17–8.16 (m, 4H), 7.45–7.27 (m, 20H), 7.05 (br s, 2H), 6.89 (br s, 2H), 6.72–6.49 (m, 9H), 6.49–6.42 (m, 2H), 5.87–5.85 (m, 1H), 5.07–5.02 (m, 13H), 4.94 (s, 2H), 4.84 (d, 1H), 4.19–4.10 (m, 3H), 3.99 (t, 1H), 3.78–3.63 (m, 2H), 3.18–3.09 (m, 1H), 2.99–2.90 (m, 1H), 2.54–2.47 (m, 1H), 2.40–2.34 (m, 1H), 1.11–1.03 (m, 28H). ^{13}C NMR (75 MHz, acetone-d_6) δ 161.1, 160.9, 157.6, 157.5, 157.2, 157.1, 153.6, 153.1, 150.5, 149.7, 144.5, 141.3, 140.8, 140.6, 138.2, 129.3, 128.7, 128.5, 121.5, 120.9, 107.2, 105.7, 101.9, 101.5, 90.5, 88.4, 87.5, 85.2, 74.8, 73.5, 70.5, 70.3, 65.3, 63.9, 63.6, 41.6, 40.1, 17.9, 17.8, 17.7, 17.7, 12.9, 12.9, 12.7, 12.6. MALDI-TOF (m/z): $[M+Na]^+$ calcd for $C_{81}H_{94}NaN_{10}O_{13}Si_2$: 1493.6, found 1494.5.

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Supplementary data

^{1}H NMR of $\mathbf{T1D_2}$ and $\mathbf{T2D_2}$ by precipitation and chromatography; ^{1}H NMR chemical shifts of $\mathbf{T2D_2}\cdot\mathbf{A2D_2}$ (i) in DMSO, (ii) titration with DMSO, (iii) variable temperature studies, (iv) determination of association constant K_a for $\mathbf{T2D_2}\cdot\mathbf{A2D_2}$ and $\mathbf{T2}\cdot\mathbf{A2}$; FT-MS spectrum of $\mathbf{T2D_2}\cdot\mathbf{A2D_2}$; and characterization data for new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.108. These data include MOL files and InChIKeys of the most important compounds described in this article.

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