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3,3′-Oxybis(dimethoxytrityl chloride) (O-DMTCl): synthesis and applications of a novel bifunctional protecting group

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Abstract—3,3′- Oxybis(dimethoxytrityl chloride) (O-DMTCl) was synthesized as a novel, acid-labile bifunctional protecting reagent. The reactions of O-DMTCl with base-protected ribonucleosides afforded unexpectedly 2′,5′-cyclic protected ribonucleosides in addition to the expected 3′,5′-cyclic protected ribonucleosides in good yields.

Regioselective protection of nucleosides is an important reaction in the nucleic acid chemistry.[1] Compared to DNA, the presence of an additional 2′-OH group in RNA makes the regioselective protection of the secondary hydroxyl groups chemically challenging. Moreover, the recent advances in RNA interference[2] have increased the need for synthetic approaches toward modified RNA which, in turn, requires substantial developments in protecting group chemistry.

Bifunctional silyl protecting groups have often been used in nucleic acid chemistry.[3] Among them, the Markiewicz reagent[3a] ($TIPDSCl_2$, **1**, Fig. 1) has been widely used in the synthesis of 2′-*O*-Me[3f,4] and 2′-*O*-methoxyethoxy (MOE)[3e,5] ribonucleosides that are key building blocks for the assembly of therapeutic oligonucleotides.[6] However, despite its advantages this reagent suffers from drawbacks that become particularly serious during large-scale applications. Specifically, its high cost of synthesis, its fragility during basic treatment, the noncrystalline nature of protected nucleosides and the inability to reuse such a protecting group after cleavage, render **1** unattractive for commercial scale manufacturing of modified nucleosides.

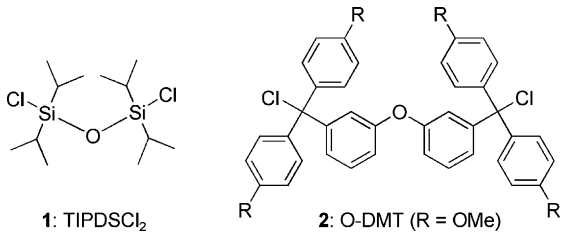

Figure 1. Chemical structures of $TIPDSCl_2$ **1** and O-DMTCl **2**.

Recognizing the limitations of **1**, we sought to develop a novel class of bifunctional protecting groups with the following attributes: (i) they should be readily available and from inexpensive starting materials, (ii) they should provide regioselectivity during the protection of nucleosides, (iii) they should be stable under basic conditions, and (iv) they should be hydrophobic enough to make the protected nucleosides soluble in organic solvents for easy extraction.

The above criteria led us to consider bifunctional protecting groups based on the trityl motif. In addition to their good hydrophobicity and extended stability under neutral or basic conditions, trityl groups possess two important qualities: (a) the trityl ethers can be cleaved under acidic conditions and their rate of cleavage can be modulated by the presence of substituents at the *o*-and *p*-positions of the aromatic ring;[7] and (b) due to its size, the trityl group can protect the 5′-hydroxyl groups in nucleosides with very high regioselectivity.[8] With this in mind, we envisioned that a dimeric trityl chloride, in which two trityl units are connected through a flexible

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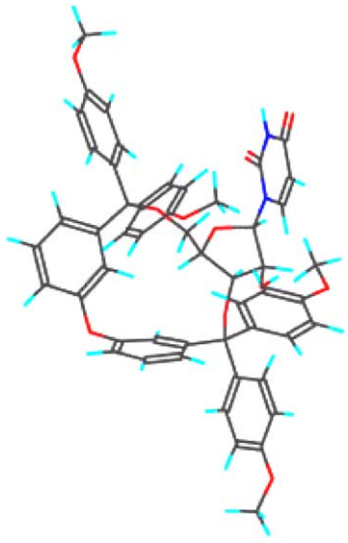
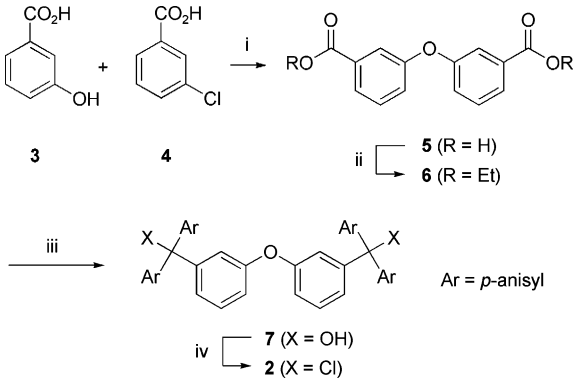


Figure 2. PM3 optimized geometry of the 3′,5′-protected uridine with **2**.

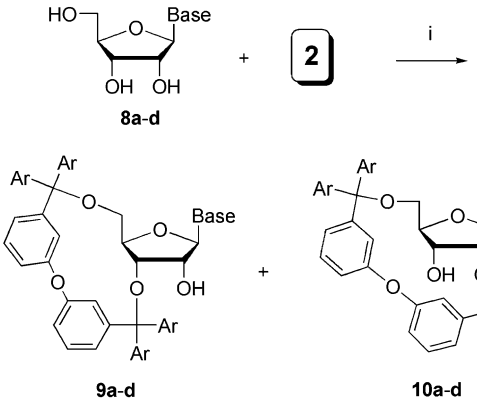
linker,[9] would react initially with the less-hindered 5′-hydroxyl group and then, in an intramolecular fashion, with one of the secondary hydroxyl groups of the ribose moiety.

To increase the possibility for such a bifunctional group to protect regioselectively the 5′,3′-hydroxyl groups of the ribose, we carried out *semi-empirical* molecular orbital calculations (PM3) of various 3′,5′-protected uridine analogs (Fig. 2). These studies suggested attachment of the two-trityl groups via an oxygen bridge at the *m*-positions of the aromatic rings. Being at the *m*-position the effect of the bridge on the stability of the trityl groups was expected to be minimal. To further mimic the stability properties of the well established 4,4′-dimethoxytrityl (DMT) group,[8] we considered to introduce methoxy groups at the *p*-positions of the aromatic rings. These thoughts led us to synthesize 3,3′-oxybis(dimethoxytrityl chloride) (O-DMTCl, **2**, Fig. 1) and evaluate it for the protection of ribonucleosides.



Scheme 1. Reagents and conditions: (i) K_2CO_3 (1.5 equiv), CuCl (0.4 equiv), 8-quinolinol (0.4 equiv), tris[2-(2-methoxyethoxy)ethyl]-amine (0.03 equiv), tetramethylene sulfone, 170 °C, 12 h, 49%; (ii) conc H_2SO_4 (0.6 equiv), EtOH, reflux, 36 h, 73%; (iii) *p*-anisylmagnesium bromide (5 equiv), THF, rt, 18 h, 99%; (iv) $(COCl)_2$ (18 equiv), CH_2Cl_2–toluene, rt, 2 h, 100%.

Table 1. Reaction of O-DMTCl **2** with base protected ribonucleosides **8a–d**[a]



Entry	Base[b]	Yield/% (**9**:**10**)[c]
1	Ur (**8a**)	70 (38:62)
2	N^4–Bz–Cy (**8b**)	75 (44:56)
3	N^6–Bz–Ad (**8c**)	78 (32:68)
4	N^2–Pac–Gu (**8d**)	70 (70:30)

[a] Reagents and conditions: (i) 2,4,6-Collidine (5 equiv), $AgClO_4$ (2.2 equiv), pyridine, 65 °C, 1 h.
[b] Ar = *p*-anisyl; Bz = benzoyl; Pac = phenylacetyl.
[c] In the parentheses, the ratio of **9** and **10** are given (determined by ^1H NMR).[13]

The route for synthesis of O-DMTCl **2** is shown in Scheme 1. Key compound **5** was synthesized from commercially available starting materials, *m*-hydroxybenzoic acid (**3**) and *m*-chlorobenzoic acid (**4**), following a published protocol.[10] Esterification of **5** furnished the diethyl ester **6** in 73% yield. Grignard reaction of **6** with *p*-anisylmagnesium bromide gave the bis(trityl carbinol) **7** in quantitative yield.[11] Treatment of **7** with excess of $(COCl)_2$ resulted in visual bubbling and a change of color (pale yellow to red) indicating that the conversion from the trityl carbinol to the corresponding trityl chloride was complete. Since O-DMTCl is susceptible to hydrolysis, we found that it was more convenient to store the carbinol precursor (**7**), itself a stable compound, and prepare **2** immediately before use via $(COCl)_2$ chlorination.

Next, the protection of four ribonucleosides **8a–d** (Table 1) was studied with O-DMTCl under a variety of conditions. Among these, best results were obtained when a pyridine solution of **8a–d** was added dropwise to a solution of **2**, 2,4,6-collidine and $AgClO_4$ in pyridine at 65 °C.[12,13] The role of silver salt was crucial for this reaction, in order to transform the starting trityl chloride into the more reactive trityl perchlorate,[14] thereby facilitating the intramolecular protection of the secondary hydroxyl group. In fact, when this reaction was carried out in absence of $AgClO_4$ with uridine at room temperature or at 65 °C, the 5′-tritylated uridine was isolated as the major product.

Under the optimized conditions, the reaction of **2** with uridine **8a** produced two products with very similar R_f values. Separation by preparative TLC (CH_2Cl_2–MeOH; 95:5 v/v) of these two products furnished pure

Table 2. ^{1}H NMR chemical shifts of **9a–d**, **10a–d**

Entry	Compound	1′	4′	3′	5′	2′
1[a]	**9a**	5.79	4.31	4.18	3.56, 3.12	2.63
2[a]	**9b**	5.90	4.20	4.20	3.53, 2.91	2.87
3[a]	**9c**	6.00	4.37	4.56	3.61, 3.22	3.20
4[b]	**9d**	5.84	3.98	4.28	3.37, 2.93	3.24
		1′	2′	4′	3′	5′
5[a]	**10a**	6.44	4.51	4.09	3.30	3.14, 2.93
6[a]	**10b**	6.69	4.54	4.12	3.30	3.17, 2.97
7[a]	**10c**	6.29	5.66	4.25	3.42	3.51, 2.83
8[b]	**10d**	6.21	4.61	3.91	3.06	3.37, 2.45

[a] $CDCl_3$.
[b] DMSO-d_6.

compounds. The molecular mass of both products was identical and corresponded to the mass of the expected diprotected uridine.[13] The less polar purified product was analyzed by ^{1}H, ^{13}C, HH-COSY NMR spectroscopy first. The HH-COSY spectrum showed a crosspeak between the 2′-H and 2′-OH that are in agreement with the desired structure of the 3′,5′-protected uridine (**9a**). Similar analysis of the more polar product of the reaction showed a crosspeak between the 3′-H and 3′-OH suggesting that the structure is that of a 2′,5′-protected uridine (**10a**).

Similar observations were made during the reaction of **2** with other nucleosides, such as the cytidine (**8b**), adenosine (**8c**) and guanosine (**8d**) derivatives. In all cases the combined yield of the diprotected nucleosides was 70–78% (Table 1). Moreover, in the case of uridine, cytidine and adenosine the 2′,5′-protected nucleosides were the major products. Detailed analysis of the ^{1}H NMR data of two products **9** and **10** indicated striking resemblance between the spectral data of **9a–d** or **10a–d** (^{1}H chemical shift values of the ribose moiety are given in Table 2) confirming the structure and their close relationship.[13] Further structural analysis of **9** and **10** is currently in progress.

Next, the deprotection of the O-DMTCl group was evaluated by treatment of **9a** and **10a** with 1% of trifluoroacetic acid–CH_2Cl_2 or 3% dichloroacetic acid–CH_2Cl_2, conventional detritylation conditions for dimethoxytrityl group.[15] In both cases, the cleavage was complete within 3 min to furnish uridine in quantitative yield indicating that O-DMTCl can be removed quickly under mild acidic conditions as the parent DMT group.

In summary, 3,3′-oxybis(dimethoxytrityl chloride) (O-DMTCl, **2**) was synthesized in four steps from readily available materials (36% combined yield). Diprotection of ribonucleosides with **2** required further activation of the trityl group and proceeded smoothly in the presence of $AgClO_4$. The observed regioselectivity of the cyclic protection in four natural ribonucleosides was 32:68 to 70:30 (3′,5′:2′,5′). Interestingly, the 2′,5′-protected **10** was generated as a major product in case of uridine, cytidine, and adenosine. To the best of our knowledge, this is the first report on the formation of a 2′,5′-cyclic protected ribonucleoside with an acid labile protecting group. Our ability to synthesize this unique class of compound is expected to open new possibilities of manipulations in the DNA[16] and RNA chemistry that was not possible with conventional protecting groups. The commercial availability of **7**, a precursor for O-DMTCl,[17] should encourage applications in other discipline.

Acknowledgements

We gratefully acknowledge ISIS Pharmaceuticals, Inc. for partially supporting this research.

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11. Characterization data of **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, $J = 8.2$ Hz, 2H), 7.14 (dt, $J = 9.0$, 2.6 Hz, 8H), 6.98–6.95 (m, 4H), 6.85–6.81 (m, 2H), 6.81 (dt, $J = 9.0$, 4.2 Hz, 8H), 3.79 (s, 12H), 2.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.5, 149.2, 138.9, 128.9, 128.9, 122.6, 118.3, 117.0, 113.1, 81.2, 55.3. ESI-MASS m/z for $C_{42}H_{38}NaO_7$ ($M+Na^+$) 677.
12. Genaral procedure for the reaction of **2** with **8a**–**d**: 0.1 M solution of **7** in dry CH_2Cl_2–toluene (1:1, v/v) (11.0 mL, 1.1 mmol) was treated with $(COCl)_2$ (1.74 mL, 20 mmol) for 2 h at rt, then the mixture was concentrated under reduced pressure in an argon atmosphere. Dry pyridine (10.0 mL), 2,4,6-collidine (0.66 mL, 5.0 mmol), and a 1 M solution of $AgClO_4$ in pyridine (2.2 mL, 2.2 mmol), which was dried over MS 4A for 12 h prior to use, were added to the residue. A solution of **8** in dry pyridine (0.1 M for **8a**, **c**, **d**; 0.033 M for **8b**) was added dropwise to the mixture over 2 h at 65 °C and the mixture was stirred for 1 h at the same temperature. The mixture was cooled to rt and pored into an ice-cold saturated $NaHCO_3$ aqueous solution (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography [treated with CH_2Cl_2–Et_3N (100:1, v/v) prior to use; eluent: CH_2Cl_2–MeOH–Et_3N (100:0:1 to 100:2:1, v/v)]. The fractions containing **9** and **10** were collected and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 0.2 M phosphate buffer (pH 7.0, 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a mixture of **9** and **10** (70–78% yield, see, Table 1). One-fifth of the mixture of **9a** and **10a** was purified by preparative TLC [treated with CH_2Cl_2–Et_3N (100:1, v/v) prior to use; eluent: AcOEt–hexane–MeOH–Et_3N (60:40:1:1, v/v)] to give **9a** (44.0 mg, 51 μmol, 25%) and **10a** (71.6 mg, 83 μmol, 41%); the mixture of **9c** and **10c** was purified by column chromatography [treated with CH_2Cl_2–Et_3N (100:1, v/v) prior to use; eluent: CH_2Cl_2–MeOH–Et_3N (100:0:1 to 97:3:1, v/v)] to give **9c** (0.25 g, 0.25 mmol, 25%) and **10c** (0.52 g, 0.53 mol, 53%).
13. Characterization data for **9a**, **9c**, **10a**, and **10c**: **9a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.37–6.75 (m, 24 H), 5.79 (d, $J = 1.6$ Hz, 1H), 5.58 (d, $J = 8.0$ Hz, 1H), 4.32–4.30 (m, 1H), 4.18 (dd, $J = 6.6$, 4.6 Hz, 1H), 3.79 (s, 6H), 3.76 (s, 6H), 3.56 (dd, 11.2, 1.2 Hz, 1H), 3.12 (dd, $J = 11.2$, 3.6 Hz, 1H), 2.63 (m, 1H), 2.40 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 159.6, 158.2, 158.2, 158.1, 156.9, 156.5, 149.7, 144.9, 142.7, 140.0, 137.8, 137.5, 133.7, 133.5, 131.6, 129.9, 129.4, 129.3, 128.3, 127.7, 125.0, 124.2, 119.6, 118.8, 118.1, 117.8, 113.3, 113.2, 90.7, 87.6, 86.9, 81.4, 74.3, 72.7, 62.4, 55.4, 55.2. HRMS: calcd for $C_{51}H_{47}N_2O_{11}$ ($M+H^+$) 863.3174, found 863.3169; **10a** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (br s, 1H), 7.64 (s, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.48–6.53 (m, 23H), 6.44 (m, 1H), 5.28 (d, $J = 8.0$ Hz, 1H), 4.51 (m, 1H), 4.09 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.30 (m, 1H), 3.14 (dd, $J = 10.2$, 4.4 Hz, 1H), 2.93 (d, $J = 10.2$ Hz, 1H), 2.63 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 158.7, 158.4, 158.2, 158.1, 157.3, 153.7, 150.4, 146.4, 142.7, 140.1, 137.6, 134.5, 134.4, 131.4, 130.7, 129.8, 129.7, 128.2, 127.6, 127.3, 122.6, 122.4, 122.1, 115.8, 113.7, 113.4, 113.1, 113.1, 110.3, 102.9, 87.6, 86.7, 85.8, 76.1, 64.0, 55.2, 55.2, 55.2. HRMS: calcd for $C_{51}H_{47}N_2O_{11}$ ($M+H^+$) 863.3174, found 863.3144; **9c** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (br s, 1H), 8.76 (s, 1H), 8.12 (s, 1H), 8.01 (d, $J = 7.6$ Hz, 2H), 7.61 (m, 1H), 7.53 (t, $J = 7.6$ Hz, 2H), 7.35–7.28 (m, 8H), 7.11–7.00 (m, 8H), 6.80–6.70 (m, 8H), 6.00 (d, $J = 2.4$ Hz, 1H), 4.56 (dd, $J = 6.8$, 4.8 Hz, 1H), 4.37 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.61 (dd, $J = 10.8$, 1.6 Hz, 1H), 3.24–3.20 (m, 2H), 2.57 (d, $J = 2.8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 159.6, 158.1, 158.0, 158.0, 157.3, 156.1, 152.3, 150.9, 149.2, 145.1, 143.1, 141.5, 138.0, 136.8, 134.9, 133.5, 132.9, 132.6, 132.0, 129.7, 129.5, 128.8, 128.7, 128.5, 127.6, 127.5, 124.9, 124.4, 123.2, 119.6, 119.3, 119.0, 116.5, 113.3, 113.3, 113.3, 113.1, 90.0, 87.5, 86.5, 82.0, 73.5, 73.4, 62.7, 55.3, 55.2, 55.2. HRMS: calcd for $C_{59}H_{52}N_5O_{10}$ ($M+H^+$) 990.3709, found 990.3679; **10c** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.29 (br s, 1H), 8.03 (m, 3H), 7.62–7.52 (m, 4H), 7.34–6.63 (m, 21H), 6.31–6.25 (m, 3H), 5.66 (m, 1H), 4.25 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.55 (s, 3H), 3.53–3.49 (m, 1H), 3.42 (m, 1H), 2.83 (dd, $J = 9.4$, 3.0 Hz, 1H), 2.70 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 158.6, 158.6, 158.3, 158.1, 158.0, 157.8, 154.2, 151.9, 151.2, 149.1, 146.3, 142.8, 142.6, 138.1, 136.7, 134.1, 133.5, 132.6, 131.2, 130.9, 129.7, 129.2, 129.0, 128.8, 127.9, 127.6, 127.3, 123.4, 123.3, 122.8, 122.7, 116.2, 113.3, 113.0, 112.9, 112.8, 112.6, 112.5, 87.5, 87.3, 84.6, 74.9, 71.7, 62.8, 55.2, 55.2, 55.2, 55.1. HRMS: calcd for $C_{59}H_{52}N_5O_{10}$ ($M+H^+$) 990.3709, found 990.3669.
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