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A new protecting group and linker for uridine ureido nitrogen

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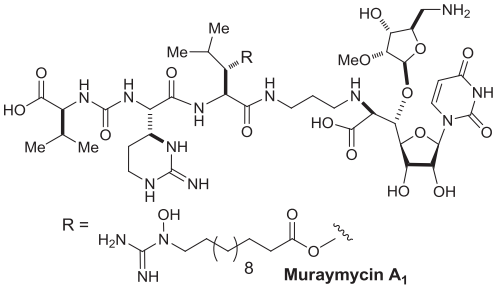
ABSTRACT

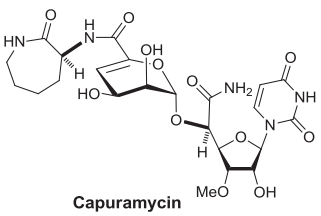
(2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methoxymethyl chloride [**1**, monomethoxydiphenylmethoxylmethyl chloroide (MDPM-Cl)] shows a significant relative stability and **1** reacts with uridine ureido nitrogen in the presence of DBU to form the corresponding protected uridine **8** in 95% yield. The MDPM-protected uridines are stable to a wide variety of conditions utilized for the synthesis of analogs of capuramycin and muraymycins. Significantly, the MDPM protecting group can conveniently be deprotected by using 30% TFA in CH_2Cl_2. In addition, polymer-bound MDPM-Cl **23** is useful for immobilization of uridine derivatives.

1. Introduction

Uridine is an essential biological compound for multiple biosynthetic processes and found in all cells.[1] To date, a large number of uridine-containing natural products that show significant biological activities have been isolated.[2] Uridine-containing antibiotics, such as liposidomycin, caprazamycin, muraymycins, and capuramycin have been of increasing interest to the development of new antibacterial agents for MDR-bacterial infections.[3]

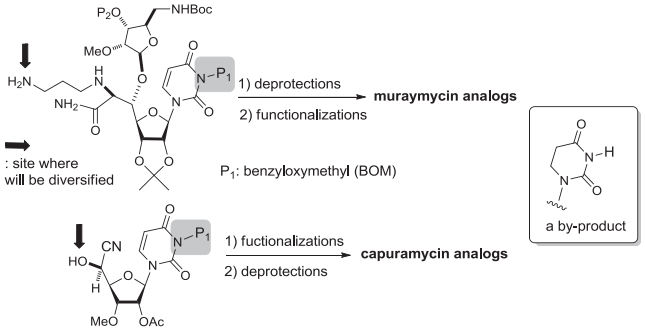


Muraymycin A_1



Capuramycin

In our ongoing program of development of drug leads for MDR *Mycobacterium tuberculosis*, we have synthesized analogs of muraymycins A_1 and capuramycin.[4] Protection of the uridine ureido nitrogen was indispensable to achieve the synthesis of a wide range of uridine-containing molecules. Benzyloxymethyl (BOM) group has been utilized as a convenient protecting group for the uridine ureido nitrogen (P_1).[5] However, we and other groups observed that BOM deprotection of uridine derivatives under hydrogenation conditions often resulted in poor yield with over-reduction product(s).[6] In general, hydrogenolytic deprotection is the only method to remove the BOM group of the uridine ureido nitrogen.



We have sought an alternative methoxymethyl-type protecting group for the uridine ureido nitrogen that (1) is stable to reaction conditions for the syntheses of a wide range of muraymycin and capuramycin analogs, but (2) can be cleaved with mild and volatile acids. In this paper we report our studies of (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methoxymethyl chloride

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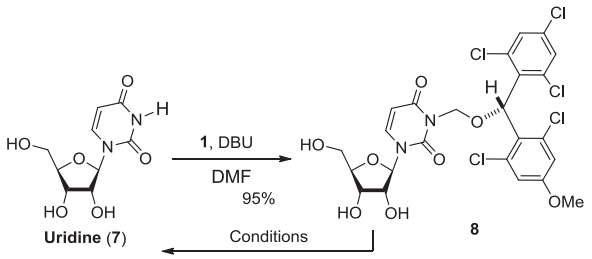
[**1**, monomethoxydiphenylmethoxylmethyl chloroide (MDPM-Cl) for the protection of the uridine ureido nitrogen and application of **1** to the polymer-bound MDPM-Cl for synthesis of analogs on polymer-support.

2. Results and discussion

We have previously reported utilities of *rac*-**5a** and optically pure **5a** for protections of alcohols, amines, and carboxylic acids, and as a chiral derivatizing agent.[7] (2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol (**5a**) could efficiently be synthesized via a Friedel–Crafts reaction followed by $LiBH_4$ reduction. Similarly, a large quantity of (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methanol (**5b**) could be synthesized efficiently. Stability tests of **5a** and **5b** against a wide variety of Lewis and Brønsted acids revealed that **5b** exhibited longer half-life in the acidic conditions summarized in Table 1; **5a** was converted to the corresponding TFA ester in 30 min when exposed to 30% TFA in CH_2Cl_2 at rt, on the other hand, **5b** required more than 1 h to form its TFA ester under the same reaction conditions. In addition, we have recognized that *rac*-**5a** forms diastereomers in NMR spectra when reacted with chiral substrates. However, **5b** has not formed noticeable diastereomers in NMR spectra. In addition, generated diastereomers have not been separated via HPLC.[8] Because of the reasons stated above, we decided to utilize **5b** for further investigation. As illustrated in Scheme 1 (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methanol (**5b**) could be converted to the corresponding MDPM-Cl **1**. The alcohol **5b** was first transformed to the (alkoxymethyl)methyl sulfide **6** in 98% yield, which was then subjected to a Cl-displacement reaction with SO_2Cl_2 to yield **1** in greater than 95% yield.[9] MDPM-Cl **1** was stable at rt and

Table 1
Protection of the uridine ureido nitrogen with **1** and its relativities against representative reagents



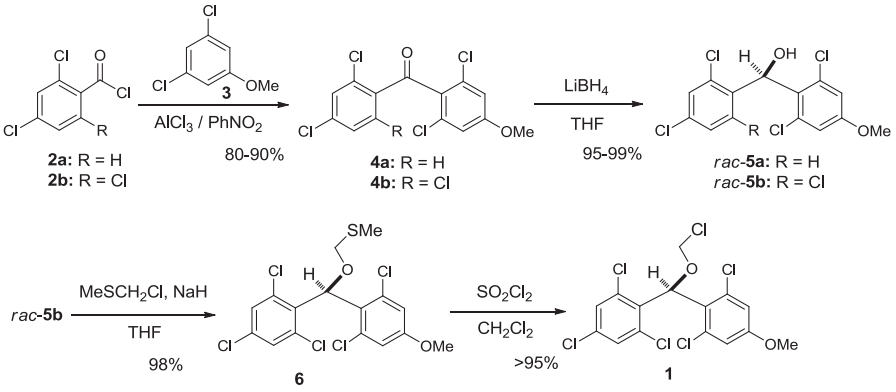
Conditions[a]	**8** ($t_{1/2}$)	Conditions[a]	**8** ($t_{1/2}$)
20% TFA CH_2Cl_2	>6 h	DBU Toluene	>24 h
10% TMSOTf CH_2Cl_2	>2 h	Al(Hg) 1,4-Dioxane	>12 h
10% HCl McCN	>6 h	Raney Ni 1,4-Dioxane	>12 h
10% HCl 1,4-Dixoane	>6 h	^{n}Bu$_3$SnH, AIBN Toluene, reflux	>6 h
30% HF MeCN	>12 h	NBS THF	>6 h
80% AcOH	>12 h	*hν* MeCN	
30% TsOH 1,4-Dioxane	>12 h	H_2/Pd–C, 1 atom MeOH	>6 h
La(OTf)$_3$ THF	>12 h	H_2/Pd–C, 100 psi MeOH	>12 h[b]
10% BF_3–OEt_2 CH_2Cl_2	>12 h	H_2/Pd–C, 50 psi MeOH	>12 h[b]
10% $TiCL_4$ CH_2Cl_2	>4 h	H_2/Pd–C, 100 psi MeOH	>12 h[b]
DDQ CH_2Cl_2–water	>12 h	H_2/Pd black MeOH	>12 h[b]

[a] Reaction was carried out at rt.
[b] The uracil double bond of **8** was reduced.

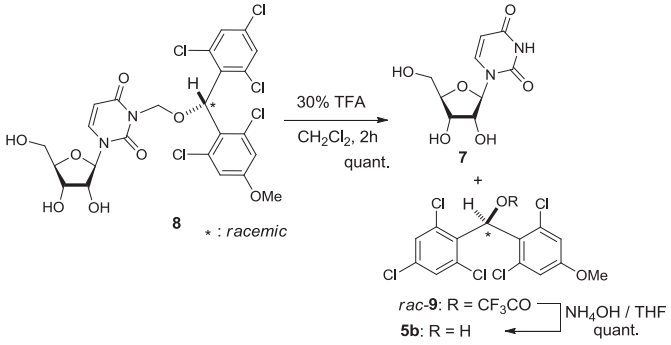
can be stored for several months without loss of purity. The uridine ureido nitrogen was efficiently protected with **1** in the presence of DBU in DMF to afford **8** in 95% yield (Table 1). The MDPM group of **8** exhibited excellent stability against a variety of Brønsted and Lewis acids such as 20% TFA, 10% TMSOTf, 10% HCl, 30% HF, 80% AcOH, 30% TsOH, La(OTf)$_3$, $BF_3\cdot OEt_2$, and $TiCl_4$ at rt. The MDPM-protected uridine **8** also showed stability under basic conditions; **8** was intact under NH_4OH (40% in aq MeOH), LiOH (10% in aq THF/MeOH), and DBU (10% in toluene) at rt for over 24 h. Selected examples are summarized in Table 1. Moreover, the MDPM protecting group of **8** was stable to the reduction conditions, such as Al(Hg), ^{n}Bu$_3$SnH/AIBN, and Raney Ni. The MDPM-protected uridine **8** was stable to NBS, and was photolytically stable (200–350 nm for over 6 h). The MDPM protecting group of **8** was not cleaved by hydrogenation conditions using Pd–C or Pd black even at 100 psi. The MDPM group could not be cleaved by using the standard conditions for the deprotection of PMB (*p*-methoxybenzyl) ether groups, however, could be deprotected with 30% TFA in CH_2Cl_2 to afford uridine (**7**). The (2,4-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methyl cation generated by the treatment of **8** with 30% TFA is a sterically hindered species and stabilized by the electron-withdrawing Cl atoms, being efficiently reacted with the trifluoroacetate ion to afford (2,4-trichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methyl 2,2,2-trifluoroacetate (**9**) in quantitative yield. The treatment of **9** with NH_3/MeOH of **7** gave rise to the parent alcohol **5b** in quantitative yield (Scheme 2). Thus, the MDPM-Cl **1** can be regenerated through the chemical steps illustrated in Scheme 1.

In order to demonstrate robustness of MDPM group as a protecting group for the uridine ureido nitrogen, the MDPM-protected uridine **8** was transformed to a wide range of uridine derivatives that can be utilized for the syntheses of analogs of muraymycins and capuramycin.[4d] Selected examples are summarized in Table 2. Ketal formations of **10** or **8** under acidic conditions provided the corresponding 2,3-protected derivatives in good to high yields (entries 1 and 5). The primary TBS and TIPS group of **11a** or **13** could be deprotected selectively with 50% HF in CH_3CN to furnish **12** and **8**, respectively, without cleavage of the MDPM group (entries 2 and 4). The trityl group of **11b** was selectively removed by using $BF_3\cdot OEt_2$ in the presence of TolSH without affecting the MDPM group (entry 3). Selective hydrogenolytic deprotection of the benzyl group of **15** was carried out via 10% Pd–C in ^{i}PrOH-water to furnish **13** without over-reduction of the uracil double bond (entry 6). Olefination of the carbonodithioate **16** was achieved by using ^{n}Bu$_3$SnH and AIBN in toluene at refluxing temperature to provide 2′,3′-didehydro-2′,3′-dideoxy derivative **17** in a reasonable yield (entry 7). Hydrogenation of the double bond of **17** was also achieved under a standard hydrogenation condition with 10% Pd–C within 1 h to provide the MDPM-protected uridine-2′,3′-dideoxy derivative **18** in high yield (entry 8). Thus, it was experimentally proved that MDPM group is a robust protecting group for the uridine ureido nitrogen to synthesize a wide range of uridine derivatives.

We have previously developed a novel ester linker **27**, whose esters are stable against Brønsted and Lewis acids, Brønsted bases and a wide variety of nucleophiles.[7c] If the uridine ureido nitrogen can be immobilized onto polymer-resin, systematic syntheses of capuramycin and muraymycin analogs would be dramatically enhanced. As summarized in Scheme 3, the (2,6-dichloro-4-hydroxyphenyl) (2,4,6-trichlorophenyl) methanone (**20**)[10] could efficiently be linked with hydroxymethylpolystyrene (PS) (~2 mmol/g) via a Mitsunobu reaction.[11] The carbonyl group of **21** was reduced by $LiBH_4$ in THF to afford the PS-alcohol **22**. Available alcohol-linkers on the polymer surface were determined to be 1.8–2.0 mmol/g by coupling of the linkers with Fmoc-β-Ala-OH and subsequent release of Fmoc chromophore and elemental analyses of the Cl atoms for **22**. According to the procedure summarized in Scheme 1, the PS-alcohol was transformed to the PS-MDPM-Cl **23**, whose available chloromethoxy group

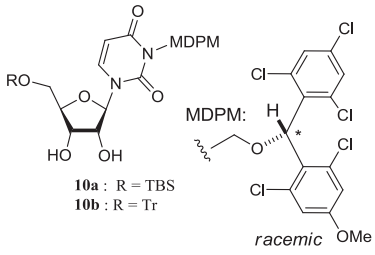
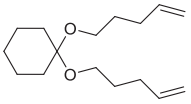
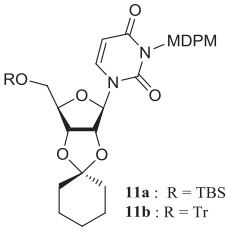
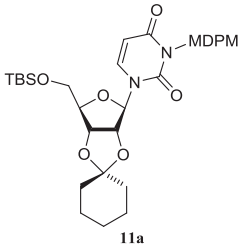
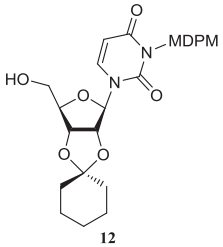
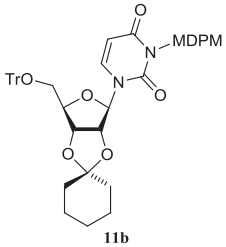
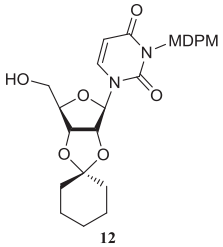


Scheme 1. Syntheses of monomethoxydiphenylmethoxylmethyl chloroides **1**.



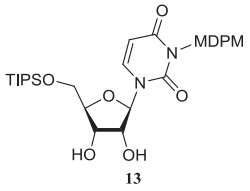
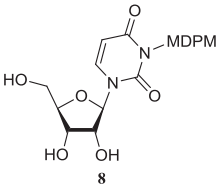
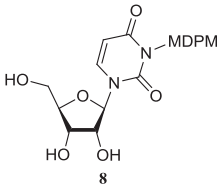
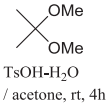
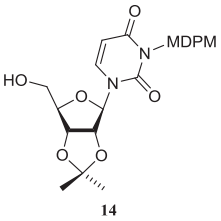
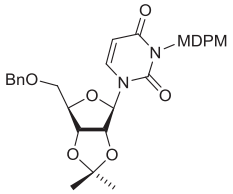
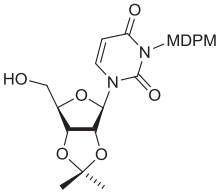
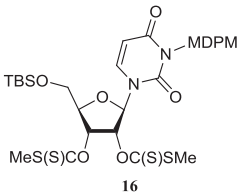
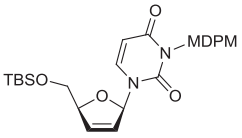
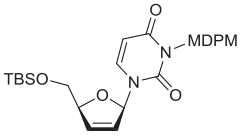
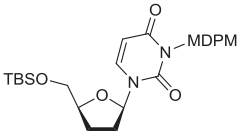
Scheme 2. Deprotection of MDPM group.

Table 2
Functionalizations of MDPM-protected uridines

Entry	Starting material	Conditions	Product	Yield[a] (%)
1	 **10a** : R = TBS **10b** : R = Tr; MDPM: racemic	 NBS, TMSOTf / CH_3CN, rt, 1h	 **11a** : R = TBS **11b** : R = Tr	75 (95)[b] for **10a** 90 (98)[b] for **10b**
2	 **11a**	50% HF/CH_3CN, rt, 1 h	 **12**	80
3	 **11b**	BF_3—OEt_2 (3 equiv), TolSH/CH_2Cl_2, rt, 1 h	 **12**	90

(*continued on next page*)

Table 2 (*continued*)

Entry	Starting material	Conditions	Product	Yield[a] (%)
4	 **13**	50% HF/CH_3CN, rt, 12 h	 **8**	88
5	 **8**	 TsOH-H_2O / acetone, rt, 4h	 **14**	90
6	 **15**	H_2 (1 atom)/10% Pd–C ^{i}PrOH-water, 2 h	 **14**	95[c]
7	 **16**	^{n}BuSnH, AIBN/toluene, reflux, 2 h	 **17**	75
8	 **17**	H_2 (1 atom)/10% Pd–C MeOH, 2 h	 **18**	95[c]

[a] Product was isolated by SiO_2 chromatography or PTLC.
[b] Yield based on recovering starting material.
[c] No over-reduction was observed.

was determined to be 1.5–1.8 mmol/g by its elemental analysis. Uridine (**7**) and 2,3-isopropylidene uridine **24** could be loaded onto the linker resin in 6 h via a twofold excess of **7** or **24** and DBU in DMF. The loaded uridine or 2,3-isopropyliden uridine were cleaved with 30% TFA in CH_2Cl_2 in 3 h to afford uridine (**7**) in greater than 85% yields.

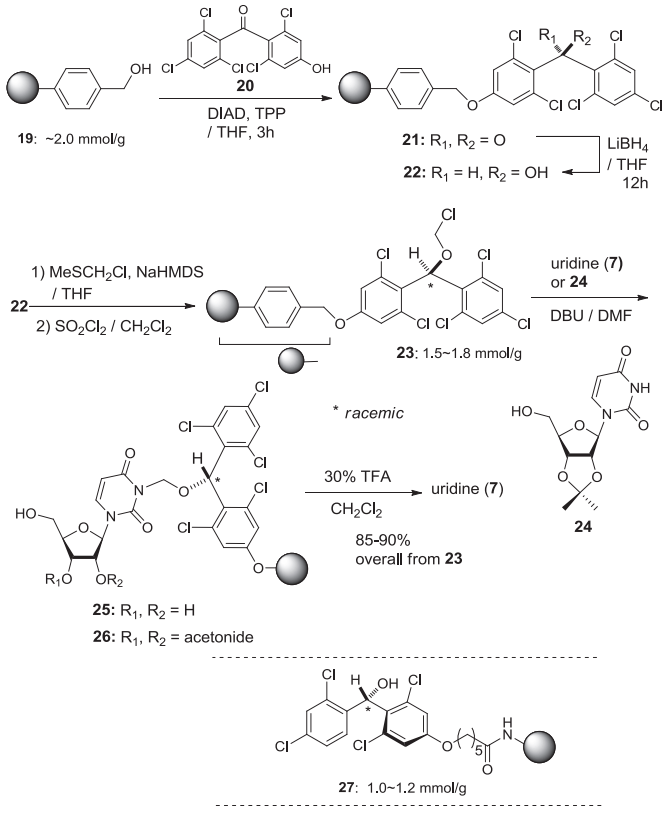
3. Conclusion

In conclusion, we have developed a new protecting group, (2,6-dichloro-4-methoxyphenyl)(2,4,6-dichlorophenyl) methoxymethyl chloride (**1**) for the uridine ureido nitrogen. MDMP protecting group has significant advantages over BOM protecting group for the syntheses of muraymycin and capuramycin analogs systematically in that MDMP group (1) is stable to a wide variety of acids, (2) is also stable to hydrogenation conditions, and (3) can efficiently be deprotected by solvolytic cleavage with TFA (at 30% concentrations) at rt within 2 h without the addition of a cation scavenger.[11] Similarly, the MDMP resin **23** has been developed to immobilize uridine and a uridine derivative. In this article we have demonstrated robustness of the MDMP group in uridine derivatives and utility of the linker resin **23** with a limited number of molecules. Moreover, as BOM group has been widely utilized in organic syntheses, a new protecting group **1** and linker resin **23** described here will be valuable assets to protect not only for ureido nitrogens, but also for *primary*, *secondary*, and phenolic alcohols, and carboxylic acids.[12] It is worth mentioning that immobilization of the uridine ureido nitrogen on polymer-support is not possible with previously reported linker resins. Utility of **1** and **23** in generation of optimized libraries of uridine-containing antibiotics in solution or on polymer-support will be reported elsewhere.

4. Experimental section

4.1. General

All glasswares were oven dried, assembled hot, and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques. Commercially available reagents were used as received without further purification. Thin layer chromatography was performed using 0.25 mm silica gel 60 plates visualizing at 254 nm, or stained with anisaldehyde solution by heating with a hot-air gun. Specified



Scheme 3. The linker **23** for immobilizations of uridine derivatives.

products were purified by flash column chromatography using silica gel 60. IR absorptions were performed on NaCl plates. ^{1}H NMR spectral data were recorded on 500 or 400 MHz NMR spectrometer. The residual solvent signal was utilized as an internal reference $CDCl_3$ (7.26). ^{13}C NMR spectral data were recorded at 125, 100 MHz instruments. The residual solvent signal was utilized as an internal reference $CDCl_3$ (77.23). For all NMR spectra, δ values are given in parts per million and J values in hertz.

4.2. (2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methanone (4b)

Anhydrous $AlCl_3$ (450 mg, 3.4 mmol) was added to $PhNO_2$ (10 mL). The reaction mixture was cooled to 0 °C, and 2,4,6-trichlorobenzoyl chloride (0.53 mL, 3.4 mmol) and 3,5-dichloroanisole (500 mg, 2.82 mmol) were added. The reaction mixture was stirred at rt for 24 h, then it was diluted with Et_2O (10 mL) at 0 °C and quenched by 1 N NaOH (~3 mL). The mixture was stirred vigorously until precipitate was formed. Filter and wash the precipitate with DCM. The organic layer was dried over Na_2SO_4 and concentrated to give the crude product. Purification by silica gel chromatography (hexanes/EtOAc=20/1) provided **4b** (867 mg, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz) 7.36 (s, 2H), 6.88 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.25, 163.33, 141.89, 138.12, 136.31, 129.29, 127.78, 117.65, 57.03; IR (film): 1633, 1557, 1388, 1341 cm^{-1}; HRMS (EI) m/z=382.8967 calcd for $C_{14}H_8Cl_5O_2$ (MH^+); found: 382.8975.

4.3. (2,6-Dichloro-4-methoxyphenyl)-(2,4,6-trichloro-phenyl) methanol (*rac*-5b)

A stirred solution of **4b** (385 mg, 1 mmol) in THF (2 mL) was added $LiBH_4$ (2 mL, 2.0 M in THF) dropwise at 0 °C. After 12 h at rt, the reaction mixture was quenched by satd aq NH_4Cl (4 mL) at 0 °C. The water phase was extracted with Et_2O. The combined extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=5/1) gave *rac*-**5b** (368 mg, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31 (s, 2H), 6.85 (s, 2H), 6.69 (d, J=10 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.23, 135.91, 135.04, 133.92, 129.57, 127.85, 115.55, 72.82, 55.88; IR (film): 3476, 1457, 1431, 1309 cm^{-1}; HRMS (EI) m/z=384.9123 calcd for $C_{14}H_{12}Cl_5O_2$ [M+H]; found: 384.9116.

4.4. (2,6-Dichloro-4-methoxyphenyl)-(2,4,6-trichlorophenyl) methoxymethyl methyl sulfide (6)

To a stirred suspension of NaH (31 mg, 60% in oil, 0.47 mmol) in THF (0.4 mL) *rac*-**5b** (100 mg, 0.26 mmol) in THF (0.3 mL) was added at 0 °C. After 30 min, chloromethyl methyl sulfide (0.044 mL, 0.52 mmol) was added. Reaction mixture was stirred at 0 °C for 3 h, and quenched by satd aq NH_4Cl. The aqueous layer was extracted with Et_2O, and the combined extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=10/1) gave **6** (114 mg, 98%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31 (s, 2H), 6.86 (s, 2H), 6.68 (s, 1H), 4.72 (q, J=11.6 Hz, 2H), 3.79 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.26, 136.77, 133.95, 132.79, 129.57, 125.47, 115.53, 75.67, 74.29, 55.70, 14.88; IR (film): 3469, 1544, 1368, 1351 cm^{-1}; HRMS (EI) m/z=446.8977 calcd for $C_{16}H_{13}Cl_5O_2SNa$ ([M+Na]$^+$); found: 446.8985.

4.5. (2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)-methoxy methyl chloride (1)

To a stirred solution of **6** (447 mg, 1.0 mmol) in CH_2Cl_2 (2.5 mL) was added sulfuryl chloride (0.08 mL, 1.0 mmol) at rt. The reaction mixture was stirred for 1 h and all volatiles were evaporated to provide the cure product, which was solidified by addition of hexanes (2 mL). The white solid was washed with hexanes twice to afford **1** (418 mg, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33 (s, 2H), 6.88 (s, 2H), 6.77 (s, 1H), 5.57 (q, J=6.4 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.56, 136.83, 136.63, 134.40, 131.73, 129.68, 124.31, 115.62, 80.11, 55.75; IR (film): 3473, 1445, 1309 cm^{-1}; Anal. Calcd $C_{15}H_{10}Cl_6O_2$: C, 41.42; H, 2.32; Cl, 48.91. Found: C, 41.81; H, 2.41; Cl, 48.97.

4.6. 3-[(2,6-Dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl) methoxymethyl]-1-(3,4-dihydroxy-5-hydroxymethyl tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (8)

To a stirred solution of uridine (**7**, 1.83 g, 7.5 mmol) in DMF (15 mL) at 0 °C DBU (1.5 mL, 10.0 mmol) and **1** (2.18 g, 5.0 mmol) were added. After 1 h, MeOH (2 mL) was added, and the reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined extract was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (DCM/MeOH=15/1) afforded **8** (2.70 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.67 (d, J=6.8 Hz, 1H), 7.30 (d, J=3.6 Hz, 2H), 6.83 (d, J=4.8 Hz, 2H), 6.57 (s, 1H), 5.77 (d, J=8.4 Hz, 1H), 5.59 (m, 3H), 4.32 (m, 2H), 4.24 (s, 1H), 3.97 (d, J=12.0 Hz, 1H), 3.90 (s, 1H), 3.83 (m, 1H), 3.78 (s, 3H), 3.05 (s, 1H), 2.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.94, 159.36, 151.86, 140.07, 136.64, 134.06, 132.46, 129.49, 125.15, 115.49, 101.61, 93.18, 85.71, 77.85, 74.79, 70.39, 69.14, 61.69, 55.73, 36.61, 31.51; IR (film): 3435, 1719, 1665, 1440, 1081 cm^{-1}; HRMS (EI) m/z=640.9819 calcd for $C_{24}H_{22}Cl_5N_2O_8$ [M+H]; found: 640.9825.

4.7. 1-[5-(*tert*-Butyldimethylsilanyloxymethyl)-3,4-dihydroxy-tetrahydrofuran-2-yl]-3-[(2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxymethyl]-1*H*-pyrimidine-2,4-dione (10a)

To a stirred solution of **8** (64 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) were added imidazole (14 mg, 0.2 mmol) and TBSCl (18 mg,

0.12 mmol). After 4 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined extract was dried over Na_2SO_4, evaporated in vacuo. Purified by silica gel chromatography (hexanes/EtOAc=5/1) provide **10a** (62 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J=8.4 Hz, 1H), 7.28 (s, 2H), 6.81 (s, 2H), 6.56 (s, 1H), 5.76 (t, J=4.0 Hz, 1H), 5.72 (d, J=8.4 Hz, 1H), 5.55 (s, 1H), 4.18 (br s, 3H), 4.12 (m, 1H), 3.96 (d, J=11.6 Hz, 1H), 3.79 (d, J=11.6 Hz, 1H), 3.75 (s, 3H), 3.13 (br s, 1H), 0.90 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.80, 159.33, 152.24, 138.47, 136.65, 134.03, 132.48, 129.47, 125.22, 115.47, 101.46, 91.72, 85.99, 77.93, 76.44, 70.51, 69.17, 62.29, 55.69, 36.57, 31.6, −5.48, −5.56; $[\alpha]_D^{20}$ +28 (c 2.5 in $CHCl_3$); IR (film): 3420, 1701, 1659, 1439, 1255, 1088 cm^{-1}; HRMS (EI) m/z=755.0684 calcd for $C_{30}H_{36}Cl_5N_2O_8Si$ [M+H]; found: 755.0681.

4.8. 3-[(2,6-Dichloro-4-methoxy-phenyl)(2,4,6-trichlorophenyl) methoxymethyl]-1-(3,4-dihydroxy-5-trityloxymethyl tetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (10b)

To a stirred solution of **8** (128 mg, 0.2 mmol) in pyridine (0.7 mL) were added trityl chloride (67 mg, 0.24 mmol) and DMAP (2 mg). The reaction mixture was stirred at 60 °C for 4 h and cooled to rt. All volatiles were removed. The partition between EtOAc and water was conducted. EtOAc phase was washed with 1 N HCl and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=6/1) gave the **10b** (155 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (t, J=8.5 Hz, 1H), 7.31 (d, J=7.5 Hz, 6H), 7.25 (m, 6H), 7.22 (m, 5H), 6.74 (s, 2H), 6.47 (s, 1H), 5.64 (s, 1H), 5.51 (m, 2H), 5.39 (d, J=7.0 Hz, 1H), 4.27 (br s, 1H), 4.14 (br s, 2H), 4.10 (br s, 1H), 3.65 (d, J=4.5 Hz, 3H), 3.42 (d, J=11.0 Hz, 1H), 3.33 (m, 1H), 2.94 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.70, 159.35, 152.09, 143.18, 138.42, 136.68, 134.05, 132.56, 129.51, 128.64, 128.09, 127.48, 125.25, 115.50, 101.65, 91.90, 87.56, 84.51, 77.86, 76.19, 70.61, 69.17, 62.40, 55.71, 25.64; $[\alpha]_D^{20}$ +23 (c 1.5 in $CHCl_3$); IR (film): 3425, 1718, 1669, 1446, 1096 cm^{-1}; HRMS (EI) m/z=883.0914 calcd for $C_{43}H_{36}Cl_5N_2O_8$ [M+H]; found: 883.0916.

4.9. 3-[(2,6-Dichloro-4-methoxy-phenyl)(2,4,6-trichloro-phenyl)methoxymethyl]-1-(3,4-dihydroxy-5-triisopropylsilanyloxymethyltetrahydrofuran-2-yl)-1*H*-pyrimidine-2,4-dione (13)

The same procedure for the synthesis of **10a** was applied, but TIPSCl was used. Yield: 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (q, J=8.0 Hz, 1H) 7.30 (s, 2H), 6.83 (d, J=1.5 Hz, 2H), 6.57 (s, 1H), 5.74 (m, 2H), 5.57 (m, 2H), 4.32 (br s, 1H), 4.19 (m, 2H), 4.06 (d, J=12.5 Hz, 1H), 3.77 (s, 3H), 2.92 (br s, 1H), 1.16 (m, 3H), 1.08 (d, J=6.5 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.68, 159.35, 152.37, 138.26, 136.69, 134.05, 132.58, 129.50, 125.25, 115.50, 101.48, 92.01, 86.31, 77.95, 76.64, 70.59, 69.17, 62.55, 55.72, 25.65, 18.02, 11.85, −3.58; $[\alpha]_D^{20}$ +27 (c 5.5 in $CHCl_3$); IR (film): 3422, 1700, 1657, 1441,1243, 1093 cm^{-1}; HRMS (EI) m/z=797.1153 calcd for $C_{33}H_{42}Cl_5N_2O_8Si$ [M+H]; found: 797.1159.

4.10. General procedure of desilylations

To a stirred solution of **13** (26 mg, 0.03 mmol) in MeCN (0.5 mL) at rt was added 50% HF (100 μL). After 5 h, the reaction mixture was quenched by aq $NaHCO_3$. The organic layer was washed with brine, and then dried over Na_2SO_4. Purification by silica gel chromatography (hexanes/EtOAc=4/1) gave the product **8** (19 mg, 88%).

4.11. Cyclohexylidenation of 10a

To a stirred solution of **10a** (75.6 mg, 0.1 mmol) in MeCN (0.5 mL) were added dipent-4-enyl acetal (30 mg, 0.12 mmol), NBS (47 mg, 0.26 mmol), and BF_3−OEt_2 (0.01 mmol). The reaction mixture was stirred at rt and protected from light with an aluminum foil for 15 min. The reaction mixture was quenched with Et_3N (50 μL), and extracted with CH_2Cl_2. The organic extract was washed with 10% $Na_2S_2O_3$, and satd aq $NaHCO_3$, and dried over Na_2SO_4. Purified by silica gel chromatography (hexanes/EtOAc=10/1) afforded **11a** (63 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=8.5 Hz, 1H), 7.29 (d, J=3.5 Hz, 2H), 6.82 (d, J=3.5 Hz, 2H), 6.59 (d, J=8.5 Hz, 1H), 5.94 (d, J=4.0 Hz, 1H), 5.72 (d, J=8.0 Hz, 1H), 5.59 (m, 2H), 4.73 (m, 1H), 4.65 (m, 1H), 4.29 (d, J=2.5 Hz, 1H), 3.93 (d, J=11.5 Hz, 1H), 3.79 (d, J=11.5 Hz, 1H), 3.77 (s, 3H), 1.77 (m, 2H), 1.67 (m, 2H), 1.57 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.53, 159.24, 151.44, 141.79, 136.70, 133.94, 132.58, 129.47, 125.18, 115.50, 114.94, 102.13, 97.64, 87.33, 83.16, 79.85, 78.03, 69.25, 63.28, 55.68, 37.17, 34.89, 25.89, 24.91, 23.95, 23.63, 18.33, −5.40, −5.45; Yield:75%. $[\alpha]_D^{20}$ +19 (c 2.0 in $CHCl_3$); IR (film): 1726, 1703, 1656, 1442, 1261, 1088 cm^{-1};. HRMS (EI) m/z=835.1310 calcd for $C_{36}H_{44}Cl_5N_2O_8Si$ [M+H]; found: 835.1316.

4.12. 3-[(2,6-Dichloro-4-methoxyphenyl)-(2,4,6-trichloro phenyl)methoxymethyl]-1-(2-cyclohexyl-6-trityloxymethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-pyrimidine-2,4-dione (11b)

Procedure, see Section 4.11. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J=4.0 Hz, 1H), 7.39 (d, J=7.6 Hz, 7H), 7.29 (m, 9H), 6.82 (d, J=3.2 Hz, 2H), 6.54 (d, J=8.4 Hz, 1H), 5.85 (d, J=3.2 Hz, 1H), 5.55 (t, J=11.6 Hz, 1H), 5.46 (t, J=10.0 Hz, 1H), 5.36 (br s, 1H), 4.78 (d, J=6.4, 2H), 4.35 (s, 1H), 3.75 (s, 3H), 3.40 (br s, 2H), 1.74 (m, 2H), 1.59 (m, 2H), 1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.60, 159.33, 152.07, 143.19, 138.02, 136.48, 134.15, 132.76, 129.50, 128.69, 128.09, 127.48, 125.28, 115.51, 101.66, 97.63, 91.91, 87.56, 84.51, 77.80, 76.19, 70.51, 69.19, 62.42, 55.71, 37.15, 34.60, 25.04, 23.55; $[\alpha]_D^{20}$ +17 (c 2.3 in $CHCl_3$); IR (film): 1736, 1719, 1674, 1444, 1231, 1075 cm^{-1}; HRMS (EI) m/z=963.1540 calcd for $C_{49}H_{44}Cl_5N_2O_8$ [M+H]; found: 963.1544.

4.13. 3-[(2,6-Dichloro-4-methoxy-phenyl)-(2,4,6-trichloro-phenyl)-methoxymethyl]-1-(2-cyclohexyl-6-hydroxymethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-pyrimidine-2,4-dione (12)

To a stirred solution of **11b** (35 mg, 0.04 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C were added TolSH (14 mg, 0.12 mmol) and $BF_3 \cdot Et_2O$ (100 μL). After 1 h at rt, the reaction was quenched with satd aq $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic extract was dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexanes/EtOAc=4/1) to provide **12** (26 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.30 (d, J=5.2 Hz, 2H), 6.83 (d, J=6.4 Hz, 2H), 6.58 (s, 1H), 5.77 (dd, J=8.0 Hz, 1H), 5.57 (s, 2H), 5.47 (dd, J=5.6 Hz, 1H), 5.00 (d, J=2.8 Hz, 1H), 4.93(dd, J=3.6 Hz, 1H), 4.28 (d, J=2.8 Hz, 1H), 3.88 (d, J=8.0 Hz, 1H), 3.79 (d, J=8.0 Hz, 1H), 3.77 (s, 3H), 2.50 (br s, 1H), 1.67 (m, 2H), 1.64 (m, 2H), 1.59 (m, 4H), 1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.56, 159.27, 151.34, 141.88, 136.70, 133.96, 132.55, 129.46, 125.17, 115.52, 115.04, 102.16, 97.66, 87.43, 83.15, 79.88, 78.00, 69.26, 62.86, 55.70, 37.12, 34.66, 24.92, 23.98, 23.54; $[\alpha]_D^{20}$ +17 (c 1.0 in $CHCl_3$); IR (film): 3464, 1743, 1710, 1665, 1456, 1222 cm^{-1}; HRMS (EI) m/z=721.0445 calcd for $C_{30}H_{30}Cl_5N_2O_8$ [M+H]; found: 721.0450.

4.14. Acetonization of 8

To a stirred solution of **8** (64 mg, 0.1 mmol) in acetone (0.6 mL) at 0 °C were added PTSA (2 mg) and 2,2-dimethoxypropane (15 μL, 0.12 mmol). The mixture was stirred for 4 h at the same temperature and concentrated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=4/1) afford **14** (59 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.30 (d, J=5.6 Hz, 2H), 6.83 (d,

J=6.0 Hz, 2H), 6.58 (s, 1H), 5.76 (d, J=8.0 Hz, 1H), 5.55 (br s, 2H), 5.47 (dd, J=5.6 Hz, 1H), 5.02 (d, J=2.0 Hz, 1H), 4.94 (d, J=5.6 Hz, 1H), 4.28 (d, J=2.8 Hz, 1H), 3.90 (dd, J=4.8 Hz, 1H), 3.89 (s, 1H), 3.88 (s, 3H), 2.52 (br s, 1H), 1.57 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.55, 159.28, 151.35, 141.74, 136.69, 133.97, 132.53, 129.46, 125.18, 115.46, 114.24, 102.13, 97.58, 87.30, 83.67, 80.34, 78.03, 69.24, 62.84, 55.70, 27.25, 25.25; $[\alpha]_D^{20}$ +17 (c 1.5 in $CHCl_3$); IR (film): 3462, 1740, 1713, 1666, 1448, 1221 cm^{-1}; HRMS (EI) m/z=681.0132 calcd for $C_{27}H_{26}Cl_5N_2O_8$ [M+H]; found: 681.0138.

4.15. 1-(6-Benzyloxymethyl-2,2-dimethyl-tetrahydro-furo [3,4-*d*][1,3]dioxol-4-yl)-3-[(2,6-dichloro-4-methoxy-phenyl)-(2,4,6-trichloro-phenyl)methoxymethyl]-1*H*-pyrimidine-2,4-dione (15)

To a stirred suspension of NaH (5 mg, 60% in oil, 0.125 mmol) in DMF (0.5 mL) at 0 °C was added **14** (78 mg, 0.1 mmol) in DMF (0.5 mL). After 5 min BnBr (36 μL, 0.3 mmol) was added. After 3 h, the reaction mixture was quenched with H_2O, and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give the crude product. This was used for the study of debenzylation.

4.16. General procedure of hydrogenation

To a solution of **15** (76 mg, 0.1 mmol) in ^{i}PrOH/H_2O (2/1, 3 mL) was added 10% Pd/C (10 mg) under N_2. H_2 was introduced by using a balloon. After 2 h, Pd/C was filtered with a Celite pad. The filtrate was concentrated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=4/1) afforded **14** (65 mg, 95%). Physical data for **14**, see Section 4.14.

4.17. *O*,*O*′-((2*R*,3*S*,4*S*,5*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(3-(((2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methoxy)methyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl) *S*,*S*′-dimethyl dicarbonodithioate (16)

To a stirred solution of **10a** (160 mg, 0.21 mmol) in DMSO (0.3 mL) was added 5 N NaOH (0.2 mL). After 20 min, CS_2 (0.2 mL) was added. After an additional 30 min, MeI (0.3 mL) was added. Then the reaction mixture was stirred for 2 h, and quenched by satd aq NH_4Cl, and extracted with EtOAc. The combined organic extract was washed with brine, dried over Na_2SO_4, concentrated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=10/1) gave **15** (135 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J=8.0 Hz, 1H), 7.28 (d, J=11.6 Hz, 2H), 6.82 (d, J=9.2 Hz, 2H), 6.60 (t, J=7.6 Hz, 1H), 6.55 (d, J=9.2 Hz, 1H), 6.25 (t, J=5.2 Hz, 1H), 6.05 (m, 1H), 5.77 (t, J=6.8 Hz, 1H), 5.60 (m, 2H), 4.45 (s, 1H), 4.03 (dd, J=27.2 Hz, 2H), 3.76 (s, 3H), 2.59 (s, 3H), 2.52 (d, J=15.2 Hz, 3H); 0.95 (s, 9H), 0.19 (d, J=12.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.70, 162.61, 159.23, 151.29, 138.36, 136.69, 134.58, 133.93, 132.88, 129.38, 125.23, 115.53, 102.83, 85.97, 84.37, 80.01, 78.77, 77.81, 69.47, 63.35, 55.69, 26.01, 19.11, 18.40, −5.25, −5.59; $[\alpha]_D^{20}$ +23 (c 2.5 in $CHCl_3$); IR (film): 1711, 1648, 1446, 1259, 1079 cm^{-1}; HRMS (EI) m/z=956.9699 calcd for $C_{34}H_{39}Cl_5N_2O_8S_4SiNa$ ([M+Na]$^+$); found: 956.9702.

4.18. 1-[5-(*tert*-Butyl-dimethylsilanyloxymethyl)-2,5-dihydrofuran-2-yl]-3-[(2,6-dichloro-4-methoxyphenyl)(2,4,6-trichloro-phenyl)methoxymethyl]-1*H*-pyrimidine-2,4-dione (17)

To a stirred solution of **15** (47 mg, 0.05 mmol) in toluene (0.5 mL) were added AIBN (4 mg) and ^{n}Bu$_3$SnH (0.07 mL, 0.25 mmol) at 100 °C. After 30 min, the reaction mixture was cooled to rt and all volatiles were evaporated in vacuo. Purification by silica gel chromatography (hexanes/EtOAc=10/1) gave **16** (26 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.31 (d, J=2.0 Hz, 2H), 6.88 (br s, 1H), 6.75 (d, J=4.8 Hz, 2H), 6.23 (d, J=9.2 Hz, 1H), 5.81 (m, 1H), 5.69 (m, 1H), 5.61 (m, 2H), 4.88 (br s, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 3.69 (s, 1H), 3.68 (s, 3H), 0.90 (s, 9H), 0.17 (d, J=12.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.10, 159.26, 139.28, 136.78, 133.94, 132.83, 129.42, 126.83, 125.24, 115.43, 101.80, 90.59, 87.41, 77.80, 69.21, 64.14, 55.68, 25.92, 18.52, −5.36, −5.50; $[\alpha]_D^{20}$ +20 (c 1.5 in $CHCl_3$); IR (film): 1705, 1658, 1443, 1255, 1079 cm^{-1}; HRMS (EI) m/z=721.0629 calcd for $C_{30}H_{34}Cl_5N_2O_6Si$ [M+H]; found: 721.0623.

4.19. 1-[5-(*tert*-Butyl-dimethylsilanyloxymethyl)-tetrahydrofuran-2-yl]-3-[(2,6-dichloro-4-methoxyphenyl)(2,4,6-trichloro-phenyl)methoxymethyl]-1*H*-pyrimidine-2,4-dione (18)

The procedure described for **15** was applied. Yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.29 (d, J=2.0 Hz, 2H), 6.77 (d, J=4.8 Hz, 2H), 6.21 (d, J=9.2 Hz, 1H), 5.85 (m, 1H), 5.78 (m, 1H), 5.63 (m, 1H), 4.80 (br s, 1H), 3.82 (m, 1H), 3.71 (m, 1H), 3.68 (s, 1H), 3.66 (s, 3H), 2.15 (m, 2H), 1.85 (m, 2H), 0.90 (s, 9H), 0.17 (d, J=12.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.11, 159.22, 139.25, 136.79, 133.96, 132.85, 125.21, 115.40, 101.87, 90.64, 87.39, 77.82, 69.19, 64.11, 55.66, 28.01, 25.95, 21.33, 18.55, −5.35, −5.51; $[\alpha]_D^{20}$ +21 (c 1.3 in $CHCl_3$); IR (film): 1707, 1650, 1440, 1245, 1083 cm^{-1}; HRMS (EI) m/z=723.0785 calcd for $C_{30}H_{36}Cl_5N_2O_6Si$ [M+H]; found: 723.0789.

4.20. Polymer-supported (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methanone 21

Hydromethylstyrene resin **19** (purchased from Aldrich, 1.0 g, ~2 mmol) was washed with THF. Compound **19** was suspended in THF (20 mL) and TPP (5.24 g, 20 mmol), DIAD (3.93 mL, 20 mmol), and **20** (1.11 g, 3 mmol) were added. The reaction mixture was gently stirred for 12 h. The polymer-resins were filtered, and thoroughly washed with THF/H_2O (4/1), THF, EtOAc, and hexanes, and dried dried under high vacuum to give **21** (1.75 g).

4.21. Polymer-supported (2,6-dichloro-4-methoxyphenyl)(2,4,6-trichlorophenyl)methanol 22

To a gently stirred polymer-resin **21** (1.75 g) in THF (8 mL) was added $LiBH_4$ (10 mL, 2.0 M in THF) at 0 °C. After 12 h at rt, the reaction mixture was quenched with H_2O (5 mL). The polymer-resins were thoroughly washed with THF/1% HCl (4/1), THF, EtOAc, and hexanes, and dried under high vacuum to afford the polymer-resin **22** (1.66 g).

4.22. Polymer-supported MDPM-Cl 23

To a suspension of **22** (0.44 g) in THF (10 mL) was added NaHMDS (0.6 mL, 1.0 M in THF, 0.6 mmol). After 30 min, chloromethyl methyl sulfide (0.09 mL, 1.3 mmol) was added. After 8 h, the polymer was thoroughly washed with THF/H_2O (4/1), THF, EtOAc, and hexanes, and dried in vacuo to give the polymer-supported methyl sulfide (464 mg). This was suspended in CH_2Cl_2 (2 mL) and sulfuryl chloride (0.17 mL, 4.1 mmol) was added. After 5 h, the polymer-resins were washed thoroughly with CH_2Cl_2, and dried under high vacuum to afford **23**. Anal. Found Cl 232 mg/g.

4.23. Loading uridine on PS-MDPM-Cl resin 23

To a suspension of PS-MDPM-Cl **23** (800 mg) in DMF (1 mL) were added DBU (30 μL, 0.2 mmol) and uridine (49 mg, 0.2 mmol). After 3 h, the polymer-resins were thoroughly washed with THF/H_2O (4/1), THF, EtOAc, and hexanes, and then dried under high vacuum to afford **25** (55 mg).

4.24. Loading 24 on PS-MDPM-Cl resin 23

The procedure was same as described in Section 4.23.

4.25. Cleavage of linker

The resin **25** was washed with CH_2Cl_2, and added 30% TFA in CH_2Cl_2 (2 mL). After 4 h at rt, the polymer-resins were washed thoroughly with CH_2Cl_2. The filtrate was concentrated in vacuo. Purification by silica gel chromatography ($CHCl_3$/MeOH=10/1) furnished uridine (**7**) (19 mg, 90%). The resin **26** was cleaved via the same procedure to afford **7** (21 mg, 85%).

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