Stereoselective Functionalization of 1'-Position of 4'-Thionucleosides

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Supporting Information

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Experimental

Ultra violet (UV) spectra were recorded on a Beckman DU-68 spectrometer and ^{1}H and ^{13}C spectra were recorded on Varian-400 (400MHz) using $CDCl_3$ or CD_3OD and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as internal standard. FAB mass spectra were recorded on Jeol HX 110 spectrometer. Elemental analyses were performed at the general instruments laboratory of Ewha Womans University, Korea. TLC was performed on Merck pre-coated $60F_{254}$ plates. Column chromatography was performed using silica gel 60 (230-400 mesh, Merck). All the anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to the reaction.

(*2S,3R*)- Acetic acid 2,2-dimethyl-tetrahydro-thieno[3,4-d][1,3]dioxol-4-yl ester (9). Diol **4** (9.8 g, 44.5 mmol) was dissolved in ethyl acetate (300 mL) and cooled to 0 ^{o}C with ice salt mixture. To this mixture was added lead (IV) aceate (39.5 g, 88.97 mmol) portionwise and the mixture was stirred for 1 h at 0 ^{o}C and then stirred for 5 h at room temperature. The mixture was filtered through a Celite pad and the filtrate was washed with saturated $NaHCO_3$ solution three times and with brine twice, dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting syrup was purified by silica gel column chromatography (hexane/ethylacetate = 6/1) to give **2** (6.6 g. 68%): MS (FAB) *m/z* 241.0 ($M+Na^+$); IR 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 3.01 (d, 1 H, *J* = 13.2 Hz , 4-H_a), 3.23 (dd, 1 H, *J* = 4.0, 12.8 Hz, 4-H_b), 4.79 (d, 1 H, *J* = 4.8 Hz, 2-H), 5.04 (t, 1 H, *J* = 4.8 Hz, 3-H), 6.01 (s, 1 H, 1-H); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.6, 26.1, 38.0, 82.6, 86.7, 88.2, 111.4, 169.0; Anal. Calcd for $C_9H_{14}O_4S$: C, 49.52; H, 6.46; S, 14.69. Found C, 49.88; H, 6.87; S, 14.29.

(*1S,2S,3R*)-2,6-Dichloro-9-(2,2-dimethyl-tetrahydro-thieno[3,4-d][1,3]dioxol-4-yl)-9*H*-purine (**10**).

2,6-Dichloropurine (5.52 g, 29.2 mmol), ammonium sulfate (655 mg, 4.6 mmol), and HMDS (20 mL) were refluxed under inert and dry conditions for 12 h. The clear solution was evaporated under high vacuum. The resulting solid was redissolved in 1,2-dichloroethane (25 mL) and cooled in ice. To this solution was added dropwise a solution of **9** (5.1 g, 23.4 mmol) in 1,2- dichloroethane (100 mL) followed by addition of TMSOTf (4.96 mL, 30.38 mmol) and the mixture was stirred for 30 minutes at 0 ^{o}C and then heated at 70 ^{o}C for 4 h. The mixture was cooled, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The resulting syrup was purified by silica gel

column chromatography (hexane/ethylacetate = 2/1) to give **10** (7.63 g, 94%): UV (MeOH) λ_{max} 276.0 nm (pH 7); $[\alpha]_D^{25}$ +88.42 (*c* 0.328); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 3.26 (d, 1 H, *J* = 12.6 Hz, 4'-H_a,), 3.75 (dd, 1 H, *J* = 4.4, 12.8 Hz, 4'-H_b), 5.22 (d, 1 H, *J* = 5.6 Hz, 2'-H), 5.33 (t, 1 H, *J* = 4.4 Hz, 3'-H), 5.88 (s, 1 H,1'-H), 8.19 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) 24.8, 26.5, 41.2, 70.6, 84.6, 89.8, 112.1, 131.7, 145.0, 152.3, 152.4, 153.2; Anal. Calcd for $C_{12}H_{12}Cl_2N_4O_2S$: C, 41.51; H, 3.48; N, 16.14; S, 9.24. Found C, 41.82; H, 3.85; N, 16.25; S, 9.21.

(*1R,2S,3R*)-4-(2,6-Dichloro-purin-9-yl)-2,2-dimethyl-tetrahydro-thieno[3,4-d][1,3]dioxole-4-carboxylic acid methyl ester (11) and (*1R,2S,3R*)-4-(2,6-Dichloro-purin-9-yl)-2,2-dimethyl-tetrahydro-thieno[3,4-d][1,3]dioxole-4-carboxylic acid ethyl ester (**12**).

Compound **10** (2.5 g, 7.2 mmol) was dissolved in dry THF (150 mL) and cooled to -78 ^{o}C. To the stirring mixture was added dropwise LiHMDS (7.92 mL, 1 M solution in THF, 7.92 mmol) and the mixture was allowed to stir at -78 ^{o}C for 90 min. To this mixture was added dropwise methyl chloroformate (1.67 mL, 21.6 mmol) and the solution was stirred at the same temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The resulting syrup was purified by silica gel column chromatography (hexane/ethylacetate = 2/1) to give **11** (2.56 g, 88%): ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 3.21 (d, 1 H, *J* = 12.4 Hz, 4'-H_a), 3.87 (dd, 1 H, *J* = 4.4, 12.8 Hz, 4'-H_b), 4.09 (s, 3 H, OCH_3), 5.44 (d, 1 H, *J* = 5.6 Hz, 2'-H), 5.48 (t, 1 H, *J* = 4.4 Hz, 3'-H), 6.95 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) 24.6, 26.6, 41.8, 54.2, 72.0, 86.1, 89.7, 111.8, 129.8, 142.8, 152.9, 154.8, 155.2 and 159.2 Anal. Calcd for $C_{14}H_{14}Cl_2N_4O_4S$: C, 41.49; H, 3.48; N, 13.83; S, 7.91. Found C, 41.88; H, 3.86; N, 13.75; S, 7.81.

Similarly, **12** (144 mg, 48%) was also obtained using **10** (250 mg, 0.72 mmol), LiHMDS (1 M solution in THF) (0.80 mL, 0.80 mmol) and ethyl chloroformate (0.185 mL, 2.16 mmol): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.50 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.61 (s, 3 H, CH_3), 3.21 (d, 1 H, J = 12.4 Hz, 4'-H_a), 3.87 (dd, 1 H, J = 4.0, 12.4 Hz, 4'-H_b), 4.57 (m, 2 H, CH_2), 5.43 (d, 1 H, *J* = 5.2 Hz, 2'-H,), 5.49 (t, 1 H, *J* = 4.0 Hz, 3'-H), 6.94 (s, 1 H, H-8); Anal. Calcd for $C_{15}H_{16}Cl_2N_4O_4S$: C, 42.97; H, 3.85; N, 13.36; S, 7.65. Found C, 42.65; H, 4.11; N, 13.15; S, 7.34.

(*1S,2S,3R*)-2-(2,6-Dichloro-purin-9-yl)-tetrahydro-thiophene-3,4-diol (**15**).

Compound **12** (1.6 g, 4.6 mmol) was stirred with 2 *N* hydrochloric acid (10 mL) in THF (10 mL) at room temperature for 6 h. The mixture was carefully evaporated under reduced pressure. If the color of the solution turns to green, evaporation must be

immediately stopped. The resulting syrup was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 50/1) to give **15** (1.24g, 88%): UV (MeOH) λ_{max} 276.0 nm (pH 7); $[\alpha]_D^{25}$ +5.08 (*c* 0.46); ^{1}H NMR ($CDCl_3$) δ 3.14 (dd, 1 H, *J* = 2.8, 11.6 Hz, 4'-H_a), 3.57 (dd, 1 H, *J* = 4.0, 11.6 Hz, 4'-H_b), 3.77 (d, 1 H, *J* = 5.6 Hz, 2'-H), 4.63 (t, 1 H, *J* = 4.8 Hz, 3'-H), 5.98 (d, 1 H, *J* = 5.6 Hz, 1'-H), 8.45 (s, 1 H, H-8): ^{13}C NMR ($CDCl_3$) 35.5, 64.9, 74.1, 81.4, 145.3, 150.1, 152.6, 153.2, 153.2; Anal. Calcd for $C_9H_8Cl_2N_4O_2S$: C, 35.19; H, 2.63; N, 18.24; S, 10.44. Found C, 35.18; H, 2.85; N, 18.55; S, 10.31.

(*1R,2S,3R*)-2-(2,6-Dichloro-purin-9-yl)-3,4-bis-(tetrahydro-pyran-2-yloxy)-tetrahydro-thiophene-2-carboxylic acid methyl ester (**19**).

Compound **15** (3.0 g, 9.8 mmol) was taken in CH_2Cl_2 (50 mL) along with 3,4-dihydro-2*H*-pyran (8.91 mL, 97.6 mmol). To this stirring solution was added PPTS (1.22 g, 4.8 mmol) and the mixture was stirred at room temperature for 12 h until the mixture became completely homogeneous. The solution was evaporated at low temperature and The resulting syrup was purified by silica gel column chromatography (hexane/ethylacetate = 2/1) to give **18** (4.33 g, 93%) as a diastereomeric mixture.

The compound **18** (2.1 g, 4.42 mmol) was converted to a diastereomeric mixture of **19** (1.84 g, 78%) using LiHMDS (4.86 mL, 4.86 mmol), methyl chloroformate (1.025 mL, 13.26 mmol) in dry THF (100 mL) following the procedure for the synthesis of **13**: MS (FAB) *m/z* 555.0 ($M+Na^+$); UV (CH_2Cl_2) λ_{max} = 291 nm (pH 7); IR 1740 cm^{-1}; Anal. Calcd for $C_{21}H_{26}Cl_2N_4O_6S$: C, 47.28; H, 4.91; N, 10.50; S, 6.01. Found C, 47.65; H, 4.51; N, 10.89; S, 6.33.

(*1R,2S,3R*)-2-[2-Chloro-6-(3-iodobenzylamino)-purin-9-yl]-3,4-dihydroxy-tetrahydro-thiophene-2-carboxylic acid methylamide (**22**).

Compound **19** (250 mg, 0.47 mmol) was converted to N^6-3-iodobenzylamino derivative (281 mg, 82%) on treatment with 3-iodobenzylamine (152 mg, 0.56 mmol) and then N^6-3-iodobenzylamino derivative (281 mg, 0.38 mmol) was converted to **20** (146 mg, 52%) by treating with excess methylamine in THF at rt for 2 h. Finally, compound **20** (146 mg, 0.2 mmol) was converted to **22** (51 mg, 46%) according to the procedure used in the synthesis of **19**: MS (FAB) *m/z* 583.4 ($M+Na^+$); UV (MeOH) λ_{max} = 303 nm (pH 7); IR 1610 cm^{-1}; $[\alpha]_D^{25}$ +71.13 (*c* 0.197); ^{1}H NMR ($CDCl_3$) δ 2.85 (dd, 1 H, *J* = 2.4, 11.6 Hz, 4'-H_a), 2.91 (s, 3 H, CH_3-NH), 3.67 (dd, 1 H, *J* = 3.2, 11.2 Hz, 4'-H_b), 4.56 (m, 1 H, 2'-H), 4.73 (m, 2 H, Bn), 5.44 (dd, 1 H, *J* = 3.6, 7.6 Hz, 3'-H), 7.09 (m, 2 H, H-8 and Ph), 7.39 (d, 1 H, *J* = 7.6 Hz, Ph), 7.61 (m, 1 H, Ph), 7.78 (bs, 1H); ^{13}C NMR ($CDCl_3$) 26.4, 37.1, 44.4, 66.1, 75.3, 79.4, 95.1, 119.8, 128.3, 131.5, 137.6, 138.0, 142.8, 143.8, 152.9, 156.4, 157.3, 161.4; Anal. Calcd for $C_{18}H_{18}ClIN_6O_3S$: C, 38.55; H, 3.24; N, 14.99; S,

5.72 Found C, 38.86; H, 3.17; N, 14.59; S, 5.71.

(*1R,2S,3R*)-2-(2-Chloro-6-ethylamino-purin-9-yl)-3,4-dihydroxy-tetrahydro-thiophene-2-carboxylic acid methylamide (**23**).

Compound **19** (200 mg, 0.37 mmol) was converted to N^6-ethylamino derivative (158, 79%) on treatment with ethyl amine hydrochoride (36 mg, 0.44 mmol) and Et_3N (74 mg, 0.74 mmol). N^6-Eethylamino derivative (158 mg, 0.29 mmol) was converted to **21** (86 mg, 56%) by treating with excess methylamine in THF at rt for 2 h. Finally, compound **21** (86 mg, 0.16 mmol) was converted to **23** (30 mg, 51%) according to the procedure used in the synthesis of **19**: MS (FAB) *m/z* 395.1 ($M+Na^+$); UV (MeOH) λ_{max} = 302 nm (pH 7); IR 1620 cm^{-1}; $[\alpha]_D^{25}$ +89.12 (*c* 0.202); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.91 (m, 4 H, 4'-H_a and CH_3-NH), 3.58 (m, 2 H, CH_2-NH-C=O), 3.67 (dd, 1 H, *J* = 3.2, 11.2 Hz, 4'-H_b), 4.57 (dd, 1 H, *J* = 3.6, 5.6 Hz, 2'-H), 5.45 (dd, 1 H, *J* = 3.6, 7.6 Hz, 3'-H), 7.08 (d, 1 H, *J* = 7.2 Hz, H-8): ^{13}C NMR ($CDCl_3$) 14.9, 26.5, 36.6, 37.2, 66.1, 75.3, 79.5, 119.9, 143.4, 152.6, 156.5, 157.4, 161.5; Anal. Calcd for $C_{13}H_{17}ClN_6O_3S$: C, 41.88; H, 4.60; N, 22.54; S, 8.60 Found C, 41.82; H, 4.66; N, 22.59; S, 8.62.

(*1R,2S,3R*)-2-(2-Chloro-6-methylamino-purin-9-yl)-3,4-dihydroxy-tetrahydro-thiophene-2-carboxylic acid methylamide (**24**)**.**

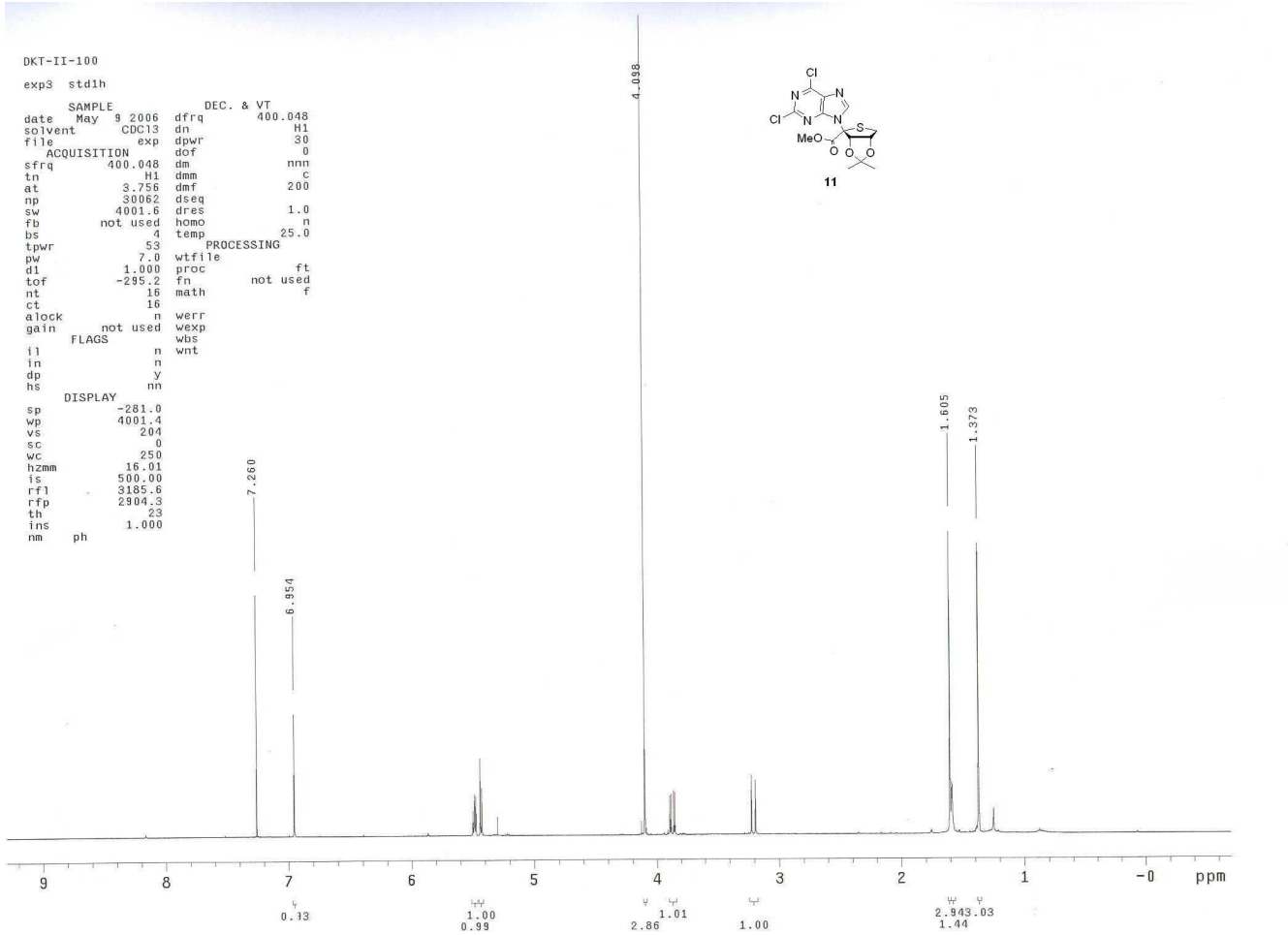
To a solution of **19** (250 mg, 0.47 mmol) in ethanol (2 mL) was added methyl amine solution in THF (10 mL) and the mixture was stirred at room temperature for 3 h and evaporated. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 100/1) to give N^6-methylamino derivative (106 mg, 43%).

N^6-methylamino derivative (106 mg, 0.2 mmol) was dissolved in a solution of CH_2Cl_2/MeOH = 50/1 (50 mL). To this stirring mixture was added p-toluenesulfonic acid (20 mg) and allowed to stir at room temperature for 30 min. The solution was evaporated under reduced pressure. The residue was purified by PTLC (CH_2Cl_2/MeOH = 20/1) to give **24** (35 mg, 49%): MS (FAB) *m/z* 381.1 ($M+Na^+$); UV (MeOH) λ_{max} = 302.5 nm (pH 7); IR 1625 cm^{-1}; $[\alpha]_D^{25}$ +79.44 (*c* 0.189); ^1H NMR (CD_3OD) δ 2.90 (dd, J=12.0, 2.0 Hz, 2H, 4'-H_a), 2.95 (s, 3H), 2.56 (s, 3H), 3.64 (dd, 1 H, *J* = 3.6, 10.6 Hz, 4'-H_b), 4.57 (m, 1 H, 2'-H), 5.44 (dd, 1 H, *J* = 4.0, 7.2 Hz, 3'-H), 7.06 (d, 1 H, *J* = 7.2 Hz, H-8); ^{13}C NMR (CD_3OD) 26.7, 28.0, 37.2, 65.9, 74.8, 79.0, 119.3, 143.6, 152.3, 156.1, 157.9, 161.0; Anal. Calcd for $C_{12}H_{15}ClN_6O_3S$: C, 40.17; H, 4.21; N, 23.42; S, 8.94 Found C, 40.19; H, 4.23; N, 23.47; S, 8.95.

(*1R, 2S, 3R*)-2-(6-Benzylamino-2-chloro-purin-9-yl)-3,4-dihydroxy-tetrahydro-thiophene-2-carboxylic acid benzylamide (**25**).

Compound **19** (185 mg) was converted to N^6-benzylamino derivative (156 mg, 49%)

using excess benzylamine in ethanol. N^6-Benzylamino derivative (156 mg, 0.23 mmol) was converted to **25** (50 mg, 43%) according to the procedure for the synthesis of **24**: MS (FAB) *m/z* 533.2 ($M+Na^+$); UV (MeOH) λ_{max} = 303 nm (pH 7); IR 1605 cm^{-1}; $[\alpha]_D^{25}$ +61.03 (*c* 0.112); ^1H NMR ($CDCl_3$) δ 2.88 (dd, 1 H, *J* = 2.0, 11.2 Hz, 4'-H_a), 3.65 (dd, 1 H, *J* = 3.6, 11.2 Hz, 4'-H_b), 4.57 (m, 2 H, C*H*$_2$-Ph), 4.76 (m, 1 H, 2'-H), 5.44 (dd, 1 H, *J* = 3.2, 6.8 Hz, 3'-H), 7.04 (d, 1 H, *J* = 6.8 Hz, H-8), 7.24-7.38 (m, 10 H, phenyl): ^{13}C NMR (CD_3OD) 37.2, 44.1, 45.1, 66.1, 75.3, 79.6, 128.5, 128.7, 128.9, 129.7, 129.74, 140.1, 142.1, 142.6, 160.2, 160.6, 169.2; Anal. Calcd for $C_{24}H_{23}ClN_6O_3S$: C, 56.41; H, 4.54; N, 16.45; S, 6.28 Found C, 56.72; H, 4.85; N, 16.25; S, 6.21.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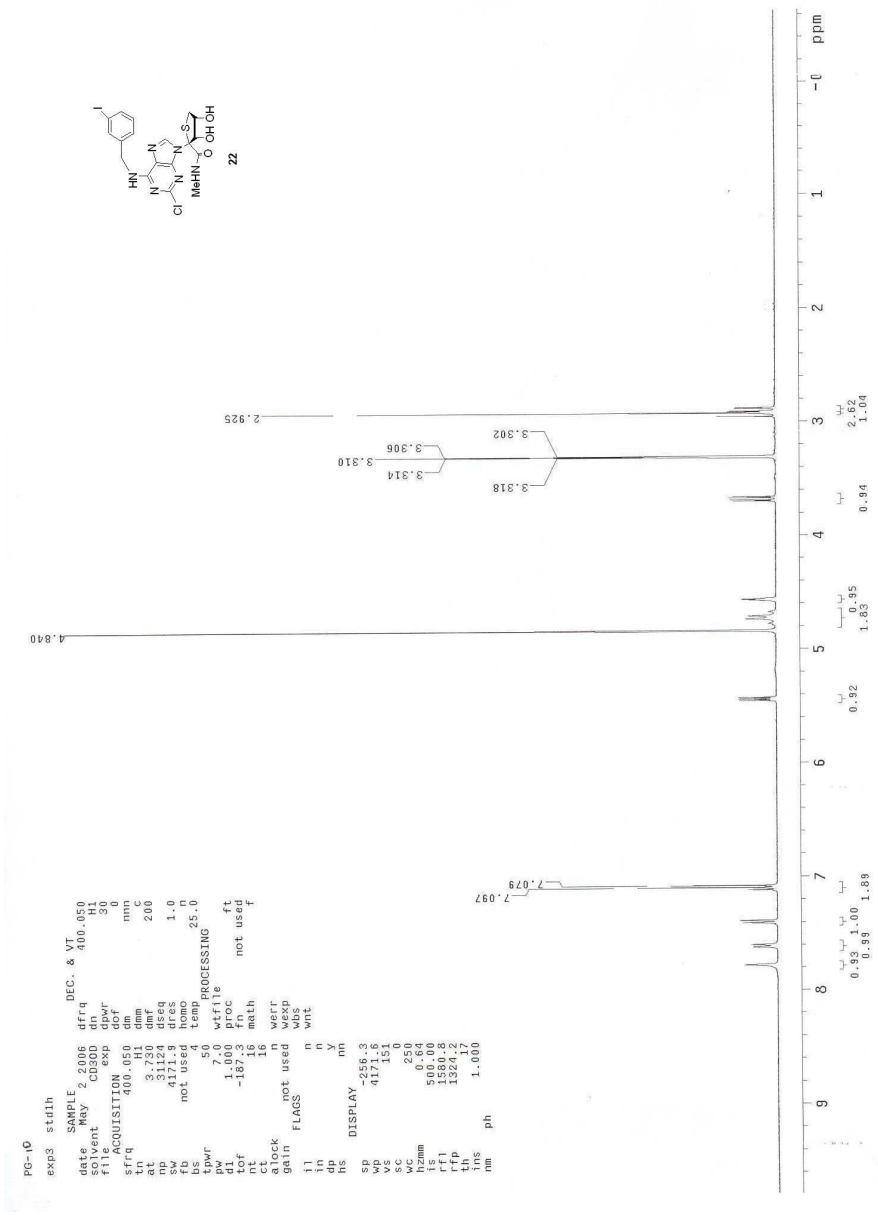
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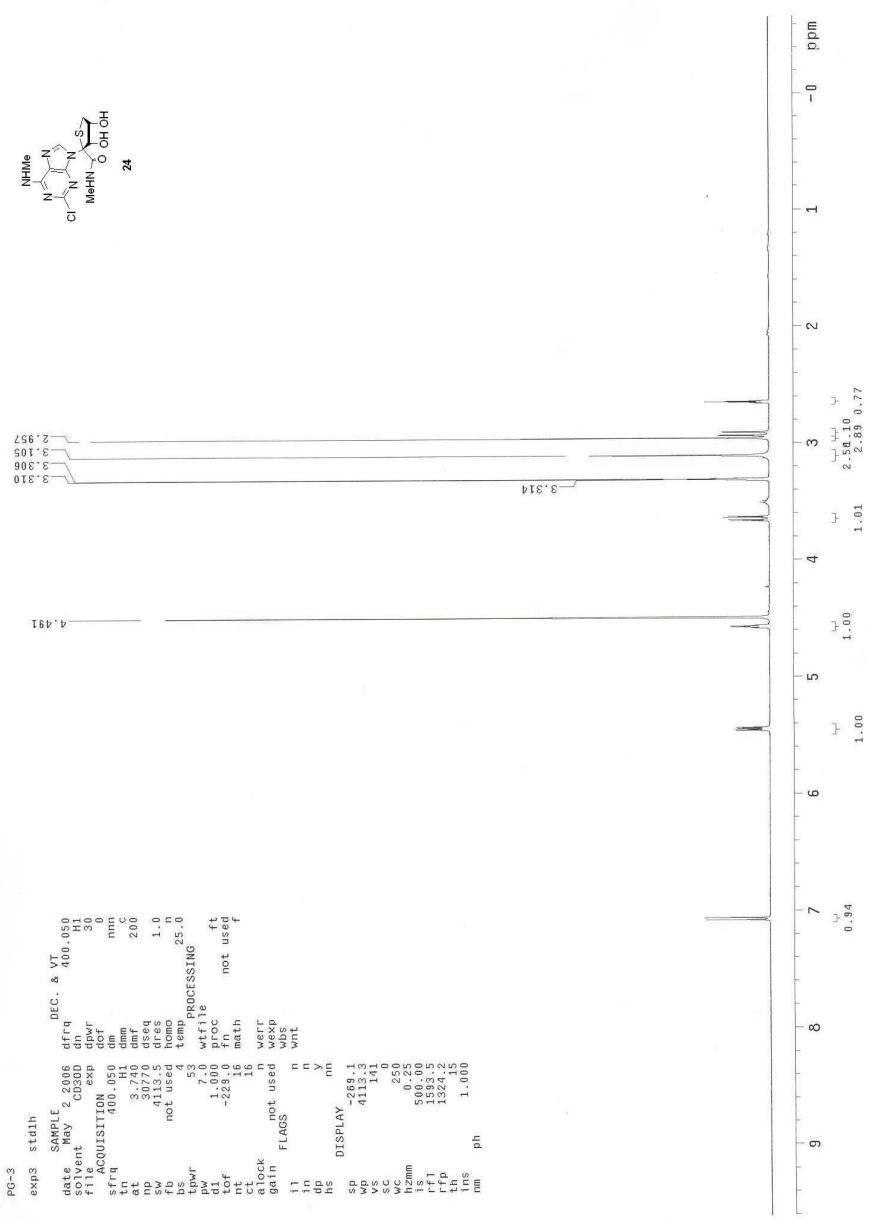
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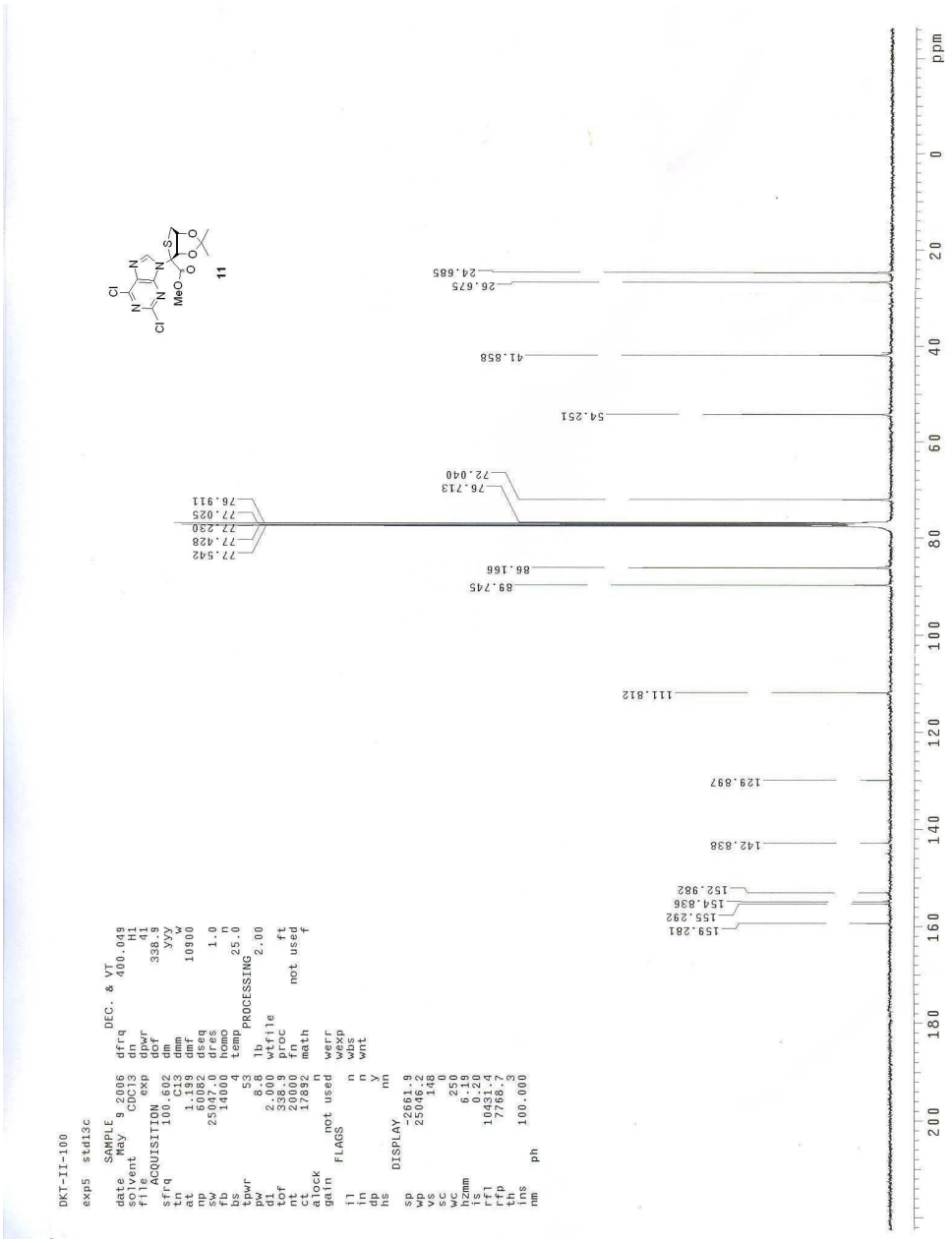
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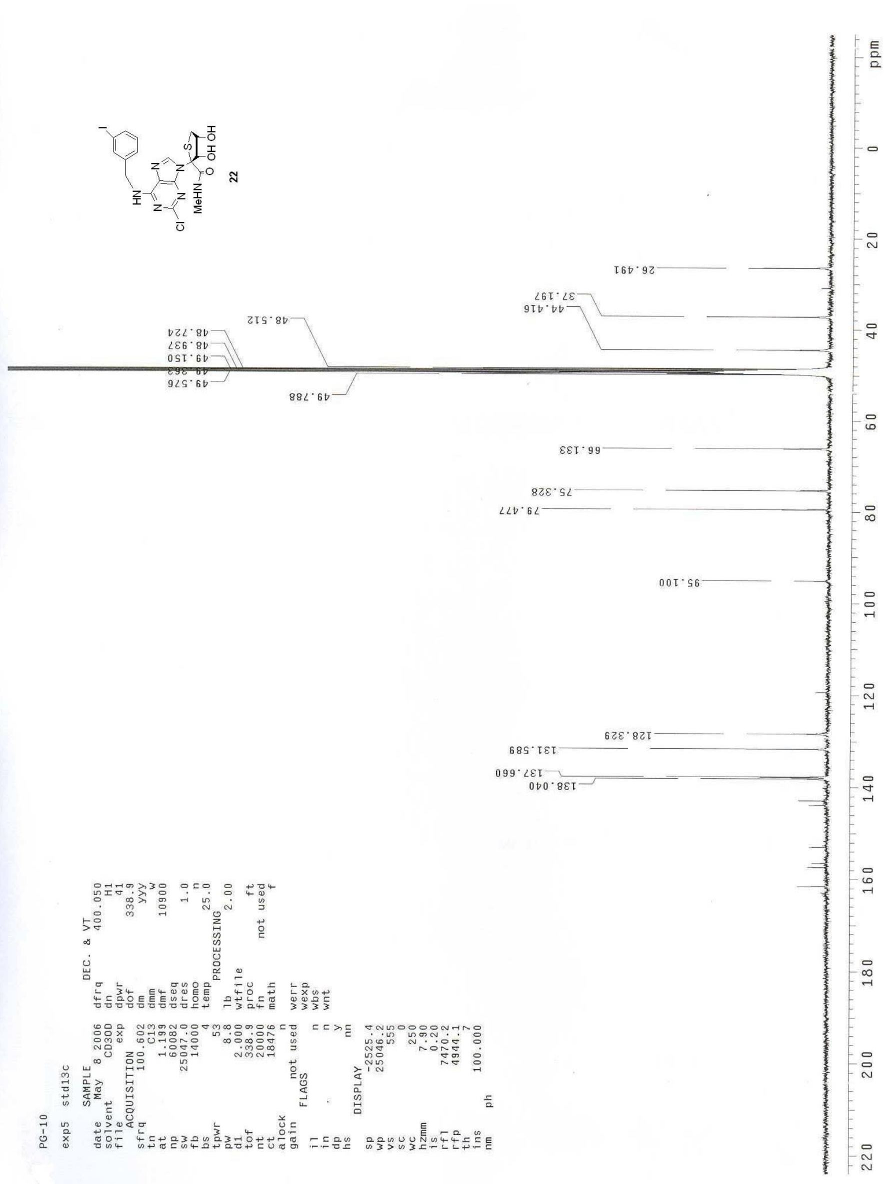
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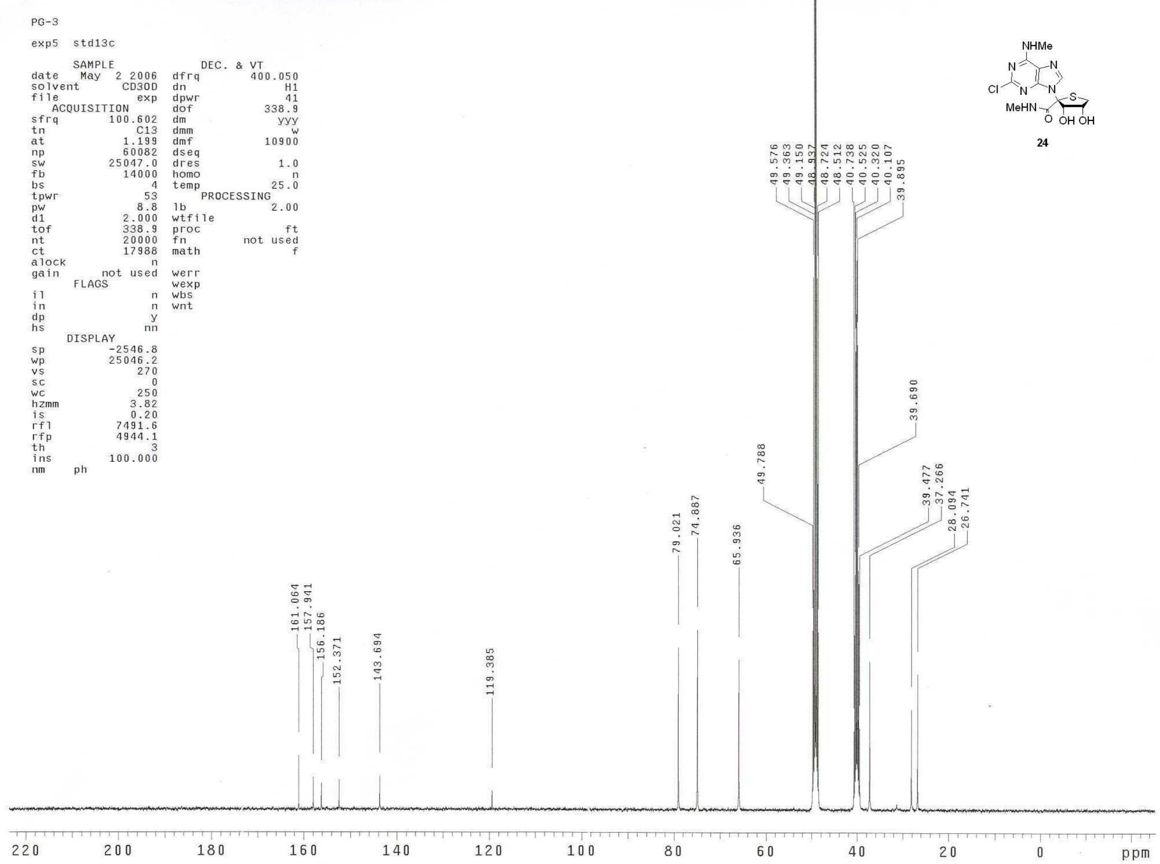

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in n
dp y
hs nn
DISPLAY
sp -2546.8
wp 25046.2
vs 270
sc 0
wc 250
hzmm 3.82
is 0.20
rfl 7491.6
rfp 4944.1
th 3
ins 100.000
nm ph
DEC. & VT
dfrq 400.050
dn H1
dpwr 41
dof 338.9
dm yyy
dmm w
dmf 10900
dseq
dres 1.0
homo n
temp 25.0
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
math f
werr
wexp
wbs
wnt
NHMe
N
N
Cl
N
N
S
MeHN
O
OH OH
24
161.064
157.941
156.186
152.371
143.694
119.385
79.021
74.887
65.936
49.788
49.576
49.363
49.150
48.937
48.724
48.512
40.738
40.525
40.320
40.107
39.895
39.690
39.477
37.266
28.094
26.741
220 200 180 160 140 120 100 80 60 40 20 0 ppm