Supporting Information

Highly Diastereoselective Synthesis of Nucleoside Adducts from the Carcinogenic Benzo[*a*]pyrene Diol Epoxide and a Computational Analysis

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Thin layer chromatography was performed on 250 μm silica plates and column chromatographic purifications were performed on 200-300 mesh silica gel. CH_2Cl_2 was routinely distilled over $CaCl_2$, and when needed was rendered anhydrous by distillation over CaH_2. CH_3CN, Et_3N and *N*,*N*-diisopropylethylamine were distilled over CaH_2. All other reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra were recorded either at 300, 500 or 600 MHz. When needed, $CDCl_3$ was deacidified by percolation through a bed of solid $NaHCO_3$ and basic alumina. Spectra were referenced to residual protonated solvent signal in the NMR solvent. Chemical shifts are reported in δ parts per million and coupling constants are in hertz. The sugar protons are numbered 1'–5' beginning at the anomeric carbon and proceeding via the carbon chain to the primary carbinol carbon. Proton assignments were made based upon ^1H–^1H COSY and analogy to known nucleoside derivatives.

Caution. Derivatives of benzo[*a*]pyrene could be potentially hazardous and should be handled in accordance with NIH guidelines (*NIH Guidelines for the Laboratory Use of Chemical Carcinogens*: NIH Publication No. 81-2385; U.S. Government Printing Office: Washington, DC, 1981).

(±)-7β,8α-Bis(*tert*-butyldimethylsilyloxy)-7,8-dihydrobenzo[*a*]pyrene (3).

To a suspension of dihydrodiol **2** (0.299 g, 1.04 mmol) in dry CH_2Cl_2 (15 mL) was added dry Et_3N (0.73 mL, 5.24 mmol) and the mixture was cooled to 0 ˚C in an ice bath. TBDMSOTf (1.2 mL, 5.22 mmol) was added, the mixture was allowed to stir at 0 ˚C for 15 min and then at rt for 1 h. The mixture was diluted with CH_2Cl_2, washed with sat aq $NaHCO_3$, dried over Na_2SO_4 and

evaporated. The crude product was directly crystallized from MeOH to yield 0.47 g (88%) of **3** as very pale yellow (almost whitish) needles. Recrystallization of the material left in the mother liquor yielded another 23.4 mg of material for a combined total of 0.49 g (92% yield) of **3**. Mp (MeOH) = 141-143 ˚C. R_f (silica/25% EtOAc-*n*-hexane): 0.79. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H, Ar-H), 8.31 (d, 1H, Ar-H, *J* = 9.1), 8.15 (d, 1H, Ar-H, *J* = 7.7), 8.14 (d, 1H, Ar-H, *J* = 7.7), 8.08 (d, 1H, Ar-H, *J* = 9.1), 8.05 (d, 1H, Ar-H, *J* = 8.9), 8.02 (d, 1H, Ar-H, *J* = 8.9), 7.97 (t, 1H, Ar-H, *J* = 7.7), 7.44 (d, 1H, H-7, *J* = 9.9), 6.22 (dd, 1H, H-10, *J* = 2.1, 10.2), 5.16 (d, 1H, H-9, *J* = 10.2), 4.66 (dt, 1H, H-8, *J* = 9.9, 2.1), 1.01, 0.97 (2s, 18H, *tert*-Bu), 0.28, 0.19, 0.14, 0.12 (4s, 12H, $SiCH_3$). Anal. Calcd for $C_{32}H_{42}O_2Si_2$: C, 74.67; H, 8.23. Found: C, 72.44; H, 8.39.

(±)-7β,8α-Bis(*tert*-butyldimethylsilyloxy)-9α,10α-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (8).

The silyl derivative **3** (0.252 mg, 0.49 mmol) was dissolved in pyridine (5 mL) and the solution cooled to 0 ˚C. A 0.5 M OsO_4 solution in *tert*-BuOH (1.07 mL, 1.1 molar equiv of OsO_4) was added and the mixture was allowed to stir at 0 ˚C for 1 h. Aq $NaHSO_3$ (1.12 g in 11.2 mL water) was added the mixture was stirred for an additional 1 h at rt and then extracted with EtOAc. The organic layer was sequentially washed with water, 10% aq HCl, sat aq $NaHCO_3$, then dried over Na_2SO_4 and evaporated. The crude product was chromatographed on a silica gel column packed in PhH by sequential elution with PhH and 10% CH_2Cl_2 in PhH. Recrystallization of the resulting product from MeOH yielded 0.156 g of **8** as yellow prisms. Recrystallization of the material left in the mother liquor yielded another 71.6 mg of material as a yellow powder for a combined total of 0.228 g (85% yield) of **8**. R_f (silica/20% EtOAc-*n*-hexane): 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, 1H, Ar-H, *J* = 9.4), 8.23 (d, 1H, Ar-H, *J* = 7.6), 8.22 (d, 1H, Ar-H, *J* = 9.4), 8.19 (d, 1H, Ar-H, *J* = 7.6), 8.07 (d, 1H, Ar-H, *J* = 9.0), 8.03 (d, 1H, Ar-H, *J* = 9.0), 8.02 (t, 1H, Ar-H, *J* = 7.6), 8.01 (s, 1H, Ar-H), 5.66 (dd, 1H, H-10, *J* = 3.9, 11.8), 5.17 (d, 1H, H-7, *J* = 3.9), 4.53 (dd, 1H, H-9, *J* = 3.9, 9.8), 4.41 (broad s, 1H, H-8), 3.48 (d, 1H, OH-9, *J* = 9.8), 3.17 (d, 1H, OH-10, *J* = 11.8), 0.84, 0.75 (2s, 18H, *tert*-Bu), 0.30, 0.23, 0.17 and 0.16 (4s, 12H, $SiCH_3$).

(±)-7β,8α-Bis(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyren-9α,10α-diyl-1,2-phenylboronate (9).

OsO_4 (64.9 mg, 0.255 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and $PhB(OH)_2$ (1.357 g, 11.1 mmol) was added. 4-Methylmorpholine-*N*-oxide (1.304 g, 11.1 mmol) was added to this mixture followed by addition of dihydrodiol dibenzoate **1** (5.00 g, 10.1 mmol) and dry CH_2Cl_2 (190 mL). The resulting dark brown solution was flushed with nitrogen and allowed to stir under a N_2

balloon for 5 h at rt. A 10% aq solution of $NaHSO_3$ (50 mL) was added and the mixture was allowed to stir at rt for 15 min. The mixture was transferred to a separatory funnel and diluted with additional CH_2Cl_2. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated. The resulting black tarry material was dissolved in a minimum volume of CH_2Cl_2 and precipitated into hexanes with sonication to produce a fine grey precipitate. Filtration yielded 5.29 g (85% yield) of the boronate ester **9** as a grey powder. R_f (silica/CH_2Cl_2): 0.1 (smears up from the origin). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (d, 1H, Ar-H, *J* = 9.2), 8.35 (d, 1H, Ar-H, *J* = 9.8), 8.31 (d, 1H, Ar-H, *J* = 7.3), 8.27 (s, 1H, Ar-H), 8.23 (d, 1H, Ar-H, *J* = 7.3), 8.10-8.06 (m, 4H, Ar-H), 8.02 (d, 1H, Ar-H, *J* = 9.3), 7.84-7.79 (m, 4H, Ar-H), 7.59-7.56 (m, 1H, Ar-H), 7.46-7.38 (m, 3H, Ar-H), 7.34 (t, 1H, Ar-H, *J* = 7.3), 7.30-7.27 (m, 2H, Ar-H), 7.17 (d, 1H, H-7, *J* = 6.8), 7.16-7.13 (m, 2H, 2Ar-H) 6.74 (d, 1H, H-10, *J* = 7.3), 6.02 (dd, 1H, H-8, *J* = 3.4, 6.8), 5.74 (dd, 1H, H-9, *J* = 3.4, 7.3). HRMS calcd for $C_{40}H_{27}BO_6$ (M^+) 614.1901, found 614.1884.

(±)-7β,8α-Bis(benzoyloxy)-9α,10α-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (6).

The boronate ester **9** (2 g, 3.25 mmol) was suspended in 2:1 EtOAc-acetone (250 mL) at rt and 50% aq H_2O_2 was added. After the mixture was stirred for about 15 min, its appearance changed from a greenish-gray suspension to an orange solution that became completely clear after 2 h. After 6.5 h at rt the reaction was complete at which time the mixture was diluted with EtOAc, washed with water, 10% aq Na_2SO_3 and water again. The organic layer was dried over Na_2SO_4 and evaporated. To remove origin material, using 5% EtOAc-CH_2Cl_2 as eluent, the crude product was passed through a short plug of silica gel that had been deactivated with 20% MeOH-CH_2Cl_2. The reddish foam obtained by this procedure was dissolved in a minimum volume of hot CH_2Cl_2 (ca 30 mL) and precipitated into hexanes (ca 500 mL) with sonication to produce a pinkish supernatent and a flocculent solid. Filtration yielded 1.30 g (75% yield) of the tetraol dibenzoate **6** as a pinkish solid. R_f (silica/10% EtOAc-CH_2Cl_2): 0.40. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, 1H, Ar-H, *J* = 9.3), 8.30 (d, 1H, Ar-H, *J* = 6.4), 8.27 (d, 1H, Ar-H, *J* = 6.3), 8.21 (d, 1H, Ar-H, *J* = 7.3), 8.09-8.00 (m, 6H, Ar-H), 7.86 (d, 2H, Ar-H, *J* = 7.8), 7.54 (t, 1H, Ar-H, *J* = 7.3), 7.48 (t, 1H, Ar-H, *J* = 7.3), 7.40 (t, 2H, Ar-H, *J* = 7.5), 7.32 (t, 2H, Ar-H, *J* = 7.8), 7.11 (d, 1H, H-7, *J* = 3.9), 5.98-5.94 (m, 2H, H8, H9), 4.92 (m, 1H, H-10), 3.67 (d, 1H, OH-10, *J* = 8.3), 2.65 (d, 1H, OH-9, *J* = 9.3). HRMS calcd for $C_{34}H_{24}O_6$ (M^+) 528.1573, found 528.1559.

(±)-10α-Azido-9α-acetoxy-7β,8α-bis(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyrene (11).

The tetraol dibenzoate **6** (0.394 g, 0.745 mmol) was placed in a flame-dried, round-bottomed flask that was flushed with N_2. Anhydrous MeCN (10 mL) was added and the mixture was

cooled to 0 ˚C in an ice bath. 1-Chlorocarbonyl-1-methylethylacetate (0.54 mL, 3.72 mmol) was added and the mixture was allowed to stir at 0 ˚C for 30 min. The ice bath was removed and the stirring was continued for 2.5 h at which time TLC indicated complete consumption of **6**. The mixture was diluted with Et_2O and washed twice with sat aq $NaHCO_3$. The organic layer was dried over Na_2SO_4, evaporated and dried under high vacuum for ca 10 min. To this crude product **10** were added NaN_3 (0.484 g, 7.45 mmol) and DMF (10 mL), the mixture was flushed with N_2 and then heated at 50 ˚C for 22 h. The mixture was cooled, diluted with EtOAc and washed with water, sat aq $NaHCO_3$ and then water. The organic layer was dried over Na_2SO_4 and evaporated. The crude product was initially chromatographed on silica gel using PhH as eluting solvent. Since minor polar impurities were still present, it was rechromatographed on silica gel using PhH to yield 0.271 g (61% yield) of the azido triacyl compound **11** as a yellow foam. Although this material contained a minor amount of some aliphatic impurity this product could be used for the subsequent reaction. This contaminant was not a consistent occurrence. R_f (silica/PhH): 0.22. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (d, 1H, Ar-H, *J* = 9.3), 8.34 (d, 1H, Ar-H, *J* = 9.3), 8.32 (s, 1H, Ar-H), 8.31 (d, 1H, Ar-H, *J* = 7.8), 8.26 (d, 1H, Ar-H, *J* = 7.3), 8.13-8.03 (m, 7H, Ar-H), 7.56 (t, 1H, Ar-H, *J* = 7.3), 7.52 (t, 1H, Ar-H, *J* = 7.3), 7.43 (t, 2H, Ar-H, *J* = 7.8), 7.37 (t, 2H, Ar-H, *J* = 7.8), 7.08 (d, 1H, H-7, *J* = 4.0), 6.22 (dd, 1H, H-9, *J* = 2.4, 5.0), 6.05 (dd, 1H, H-8, *J* = 2.4, 4.0), 6.00 (d, 1H, H-10, *J* = 5.0), 2.29 (s 3H, $OCOCH_3$). HRMS calcd for $C_{36}H_{25}N_3O_6$ (M^+) 595.1743, found 595.1747.

(±)-10α-Azido-7β,8α,9α-trihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (12).

To ammoniacal methanol (3 mL) was added the azido triacyl compound **11** (0.146 mg, 0.245 mmol). The flask was sealed and the mixture was allowed to stir at 40 ˚C, overnight. The mixture was cooled to rt, the flask was flushed with N_2 to remove excess ammonia and the mixture was evaporated to dryness. The product was dissolved in EtOAc (ca 100 mL) and washed twice with water. The organic layer was dried over Na_2SO_4 and evaporated. The product was washed with Et_2O to yield 84.3 mg (99% yield) of the azido triol **13** as a yellow solid. Alternatively, **12** can be chromatographed on a silca gel column using EtOAc as eluting solvent. However, solubility of **12** is a limitation and therefore washing with Et_2O is simpler. R_f (silica/EtOAc): 0.25. ^{1}H NMR (500 MHz, Acetone-d_6): δ 8.59 (d, 1H, Ar-H, *J* = 9.3), 8.42 (s, 1H, Ar-H), 8.35-8.34 (m, 2H, Ar-H), 8.31 (d, 1H, Ar-H, *J* = 7.8), 8.17 (AB_{quart}, 2H, Ar-H, *J* = 8.8), 8.09 (t, 1H, Ar-H, *J* = 7.6), 5.52 (d, 1H, H-10, *J* = 4.9), 5.34-5.32 (br m, 1H, H-7), 4.83 (d, 1H, OH-7, *J* = 4.8), 4.66-4.63 (m, 1H, H-9), 4.50 (d, 1H, OH-9, *J* = 7.8), 4.45 (broad s, 1H, OH-8), 4.24 (br m, 1H, H-8). HRMS calcd for $C_{20}H_{15}N_3O_3$ (M^+) 345.1113, found 345.1096.

(±)-10α-Amino-7β,8α,9α-trihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (13).

The azido triol **12** (0.359 g, 1.01 mmol) was dissolved in EtOH (77 mL) and 10% Pd-C (73.8 mg) was added. The mixture was allowed to stir under 1 atm H_2 pressure (balloon) for 2 h and 15 min at which time the reaction was complete as analyzed by TLC. The reaction mixture was filtered through Celite, and the flask and the residue were washed with MeOH. The combined filtrate was evaporated and the resulting product was washed with Et_2O with sonication to yield 0.277 g (83% yield) of the amino triol **13** as a whitish powder. R_f (silica/10% MeOH-CH_2Cl_2): 0.06. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.50 (d, 1H, Ar-H, *J* = 9.3), 8.31 (d, 1H, Ar-H, *J* = 7.8), 8.28-8.26 (m, 2H, Ar-H), 8.16-8.12 (m, 2H, Ar-H), 8.06 (t, 1H, Ar-H, *J* = 7.7), 5.56 (broad, exchangeable), 5.04 (broad s, 1H, H-7, this signal sharpens to a d upon D-exchange of the signal at 5.56 ppm and *J* = 2.5 is observed), 4.99 (d, 1H, H-10, *J* = 4.4), 4.24 (broad s, 1H, H-9), 4.12 (broad s, 1H, H-8). HRMS calcd for $C_{20}H_{18}NO_3$ (M^+ + H) 320.1287, found 320.1295.

The amino triol hydrochloride (**13**.HCl) was prepared by reduction of azido triol **12** (0.200 mg, 0.579 mmol) in EtOH (42 mL) using 10% Pd-C (40.6 mg) and 1 atm H_2 pressure (balloon) for 3 h, in the presence of 6 M HCl (184 μL). The product obtained by filtration of the reaction mixture through Celite and evaporation, was washed with Et_2O to yield 0.176 g (85% yield) of **13**.HCl as a tan solid.

(7*S*,8*R*,9*S*,10*S*)-*N*^{6}-[10-(7,8,9-Triacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine and (7*R*,8*S*,9*R*,10*R*)-*N*^{6}-[10-(7,8,9-Triacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (14b and 15b).

To a solution of the amino triol **13** (0.211 g, 0.66 mmol) and 6-fluoro-9-(2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-erythropentofuranosyl)purine (0.511 mg, 1.06 mmol) in DMSO (3.3 mL) were added *N*,*N*-diisopropylethylamine (1.15 mL, 6.6 mmol) and hexamethyldisiloxane (5.6 mL, 26.38 mmol). The biphasic mixture was flushed with N_2, capped and heated to 85 °C with vigorous stirring. After 6 h TLC indicated only a faint trace of the amino triol and the mixture was cooled to room temperature, diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc, the combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The product was carefully chromatographed on a silica gel column using CH_2Cl_2 followed by 3% MeOH-CH_2Cl_2 to yield 0.346 g (67% yield) of the diastereomeric adduct mixture (**14a** + **15a**) as a yellow foam. R_f (silica/5% MeOH-10% EtOAc-CH_2Cl_2): 0.51 (*less polar* diastereomer) and 0.47 (*more polar* diastereomer). The bulk of this mixture was triacetylated as follows.

The diastereomeric mixture of adducts **14a** + **15a** obtained above (0.156 g, 0.199 mmol) was dissolved in pyridine (10 mL), acetic anhydride (10 mL) and DMAP (catalytic) were added. The flask was flushed with N_2, capped and mixture was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc, washed twice with 1 M HCl and once with sat aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the crude acetylated adduct mixture on a silica gel column using 10% EtOAc-CH_2Cl_2 yielded 0.163 mg (90% yield) of the 2'-deoxyadenosine adduct triacetate **14b** + **15b** as a pale yellow solid. Small quantities of the pure diastereomers were obtained using preparative TLC (multiple developments of a 20 x 20 cm, 2000 μm silica gel plate, using 10% EtOAc-CH_2Cl_2 as developing solvent). The *faster-eluting* compound **14b** was the (7*S*,8*R*,9*S*,10*S*)-diastereomer and the *slower-eluting* isomer **15b** was the (7*R*,8*S*,9*R*,10*R*)-diastereomer. R_f of **14b** (silica/10% EtOAc-CH_2Cl_2): 0.15. ^{1}H NMR (600 MHz, $CDCl_3$) **14b**: δ 8.60 (s, 1H, Ar-H), 8.34 (d, 1H, Ar-H, *J* = 9.4), 8.23 (s, 1H, Ar-H), 8.19 (d, 1H, Ar-H, *J* = 7.6), 8.16 (d, 1H, Ar-H, *J* = 7.6), 8.10 (d, 1H, Ar-H, *J* = 9.1), 8.06 (d, 1H, Ar-H, *J* = 9.1), 8.04 (d, 1H, Ar-H, *J* = 9.4), 8.01 (t, 1H, Ar-H, *J* = 7.6), 7.98 (s, 1H, Ar-H), 7.15 (dd, 1H, H-10, *J* = 10.4, 5.3), 6.65 (d, 1H, H-7, *J* = 3.0), 6.46 (t, 1H, H-1', *J* = 6.7), 6.35 (d, 1H, NH, *J* = 10.4), 6.01 (dd, 1H, H-9, *J* = 5.3, 2.4), 5.74 (t, 1H, H-8, *J* = 2.4), 4.61 (app. quint, 1H, H3', *J* = 6.5, 3.6), 4.01 (app. q, 1H, H-4', *J* = 3.5), 3.84 (dd, 1H, H-5'a, *J* = 11.3, 4.5), 3.74 (dd, 1H, H-5'b, *J* = 11.3, 2.9), 2.67 (app. quint, 1H, H-2'β, *J* = 13.2, 6.6), 2.45 (ddd, 1H, H-2'α, *J* = 13.2, 6.2, 3.7), 2.23, 2.14, 1.83 (3s, 9H, $OCOCH_3$), 0.92, 0.86 (2s, 18H, *tert*-Bu), 0.11, 0.11, 0.04, 0.01 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_9Si_2$ (M^+ + H) 908.4086, found 908.4056. R_f of **15b** (silica/10% EtOAc-CH_2Cl_2): 0.12. ^{1}H NMR (600 MHz, $CDCl_3$) **15b**: δ 8.61 (s, 1H, Ar-H), 8.39 (d, 1H, Ar-H, *J* = 9.4), 8.24 (s, 1H, Ar-H), 8.20 (d, 1H, Ar-H, *J* = 7.5), 8.16 (d, 1H, Ar-H, *J* = 7.5), 8.08 (d, 1H, Ar-H, *J* = 9.1), 8.07 (d, 1H, Ar-H, *J* = 9.1), 8.04 (d, 1H, Ar-H, *J* = 9.4), 8.01 (t, 1H, Ar-H, *J* = 7.5), 8.03 (s, 1H, Ar-H), 7.16 (dd, 1H, H-10, *J* =10.5, 5.3), 6.66 (d, 1H, H-7, *J* = 3.0), 6.48 (t, 1H, H-1', *J* = 6.6), 6.34 (d, 1H, NH, *J* = 10.5), 6.00 (dd, 1H, H-9, *J* = 5.8, 1.2), 5.75 (t, 1H, H-8, *J* = 2.8), 4.60 (app. quint, 1H, H3', *J* = 6.5, 3.9), 4.00 (app. q, 1H, H-4', *J* = 3.5), 3.86 (dd, 1H, H-5'a, *J* = 11.3, 4.4), 3.77 (dd, 1H, H-5'b, *J* = 11.3, 3.3), 2.58 (app. quint, 1H, H-2'β, *J* = 13.2, 6.6), 2.43 (ddd, 1H, H-2'α, *J* = 13.2, 6.2, 3.7), 2.24, 2.14, 1.80 (3s, 9H, $OCOCH_3$), 0.91, 0.86 (2s, 18H, *tert*-Bu), 0.09, 0.08, 0.5, 0.04 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_9Si_2$ (M^+ + H) 908.4086, found 908.4081.

(7*S*,8*R*,9*S*,10*S*)-*N*^{2}-[10-(7,8,9-Triacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine and (7*R*,8*S*,9*R*,10*R*)-*N*^{2}-[10-(7,8,9-Triacetoxy-

7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (16b and 17b).

The amino triol hydrochloride **13**.HCl (0.142 g, 0.399 mmol) was suspended in *N*,*N*-diisopropylethylamine (693 μL, 3.99 mmol) and was allowed to stir for 15 min. After this DMSO (2 mL), hexamethyldisiloxane (3.3 mL, 15.53 mmol) and 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2-fluoro-2'-deoxyinosine (0.299 mg, 0.6 mmol) were added. The biphasic mixture was flushed with N_2, capped and heated to 85 °C with vigorous stirring. After ~8 h TLC indicated practically no trace of the amine and the mixture was cooled to room temperature, diluted with EtOAc and washed with water. The aqueous layer was extracted twice with EtOAc, the combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. R_f (silica/10% MeOH-CH_2Cl_2): 0.38 (mixture of diastereomers). The entire crude product mixture (**16a** + **17a**) was triacetylated as follows.

The diastereomeric mixture of adducts **16a** + **17a** obtained above (0.415 g crude material from the previous step) was dissolved in pyridine (2.6 mL), acetic anhydride (2.6 mL) and DMAP (catalytic) were added. The flask was flushed with N_2, capped and mixture was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc, washed twice with 1 M HCl and once with sat aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the crude acetylated adduct mixture on a silica gel column using 2% MeOH-40% CH_2Cl_2-58% EtOAc yielded 0.123 mg (33% yield over the two steps) of the 2'-deoxyguanosine adduct triacetate **16b** + **17b** as a tan solid. Small quantities of the pure diastereomers were obtained using preparative TLC (multiple developments of a 20 x 20 cm, 1000 μm silica gel plate, using 10% EtOAc-15% Acetone-75% CH_2Cl_2 as developing solvent). The *faster-eluting* compound **16b** was the (7*S*,8*R*,9*S*,10*S*)-diastereomer and the *slower-eluting* isomer **17b** was the (7*R*,8*S*,9*R*,10*R*)-diastereomer. R_f of **16b** (silica/10% MeOH-30% CH_2Cl_2-60% EtOAc): 0.48. ^{1}H NMR (500 MHz, DMSO-d_6) **16b**: δ 10.66 (s, 1H, ring NH), 8.36 (d, 1H, Ar-H, *J* = 7.6), 8.28 (d, 1H, Ar-H, *J* = 7.6), 8.26 (s, 1H, Ar-H), 8.25 (d, 1H, Ar-H, *J* = 9.1), 8.17 (d, 1H, Ar-H, *J* = 9.1), 8.12 (t, 1H, Ar-H, *J* = 7.6), 8.03 (s, 1H, Ar-H), 8.01 (d 1H, Ar-H, *J* = 7.6), 6.58 (dd, 1H, H-10, *J* = 9.7, 5.6), 6.52 (d, 1H, H-7, *J* = 3.6), 6.46 (d, 1H, NH, *J* = 9.7), 6.37 (t, 1H, H-1', *J* = 7.1), 5.80 (dd, 1H, H-9, *J* = 5.6, 2.4), 5.60 (dd, 1H, H-8, *J* = 3.6, 2.4), 4.56 (app. quint, 1H, H3', *J* = 5.9, 3.0), 3.93 (app. q, 1H, H-4', *J* = 2.6), 3.81 (dd, 1H, H-5'a, *J* = 11.0, 6.0), 3.77 (dd, 1H, H-5'b, *J* = 11.0, 4.6), 2.75 (app. quint, 1H, H-2'β, *J* =13.2, 6.9), 2.39 (ddd, 1H, H-2'α, *J* = 13.2, 6.2, 3.3), 2.14, 2.13, 1.83 (3s, 9H, $OCOCH_3$), 0.88, 0.86 (2s, 18H, *tert*-Bu), 0.11, 0.09, 0.08, 0.07 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_{10}Si_2$ (M^+ + H) 924.4035, found

924.4037. R_f of **17b** (silica/10% MeOH-30% CH_2Cl_2-60% EtOAc): 0.41. ^{1}H NMR (500 MHz, DMSO-d_6) **17b**: δ 10.79 (s, 1H, ring NH), 8.36 (d, 1H, Ar-H, *J* = 7.5), 8.31 (d, 1H, Ar-H, *J* = 7.5), 8.30 (s, 1H, Ar-H), 8.28 (d, 1H, Ar-H, *J* = 9.3), 8.24 (d, 1H, Ar-H, *J* = 9.1), 8.20 (d, 1H, Ar-H, *J* = 9.1), 8.14 (d, 1H, Ar-H, *J* = 9.3), 8.12 (t, 1H, Ar-H, *J* = 7.8), 8.01 (s 1H, Ar-H), 6.59 (dd, 1H, H-10, *J* = 9.7, 5.8), 6.53 (d, 1H, H-7, *J* = 3.6), 6.45 (d, 1H, NH, *J* = 9.7), 6.28 (dd, 1H, H-1', *J* = 8.7, 5.6), 5.84 (dd, 1H, H-9, *J* = 5.8, 2.4), 5.61 (t, 1H, H-8, *J* ~ 3.0), 4.56-4.60 (m, 1H, H3'), 3.88 (dd, 1H, H-5'a, *J* = 10.4, 4.6), 3.81 (app. t, 1H, H-4', *J* = 8.9), 3.72 (dd, 1H, H-5'b, *J* = 10.4, 4.1), 3.20 (ddd, 1H, H-2'β, *J* = 13.2, 9.2, 5.2), 2.25 (ddd, 1H, H-2'α, *J* = 13.2, 5.6, 2.1), 2.17, 2.10, 1.92 (3s, 9H, $OCOCH_3$), 0.89, 0.57 (2s, 18H, *tert*-Bu), 0.12, 0.10, –0.39 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_{10}Si_2$ (M^+ + H) 924.4035, found 924.3997.

Alternatively, to a solution of the amino triol **13** (14 mg, 43.8 μmol) and 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)-2-fluoro-2'-deoxyinosine (0.040 mg, 80.2 μmol) in DMSO (0.32 mL) were added *N*,*N*-diisopropylethylamine (40 μL, 0.227 mmol) and hexamethyldisiloxane (199 μL, 0.936 mmol). The biphasic mixture was flushed with N_2, capped and heated to 90 $^\circ$C with vigorous stirring for 3 h and 40 min. The mixture was cooled to room temperature, diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The entire crude product mixture (**16a** + **17a**) was triacetylated as follows.

The diastereomeric mixture of adducts **16a** + **17a** obtained above (0.035 g crude material from the previous step) was dissolved in pyridine (212 μL), acetic anhydride (492 μL) and DMAP (catalytic) were added. The flask was flushed with N_2, capped and mixture was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc, washed with 1 M HCl and then with sat aq $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography of the crude acetylated adduct mixture on a 1000 μm preparative silica gel plate using 2% MeOH-40% CH_2Cl_2-58% EtOAc yielded 0.0172 mg (42% over the two steps) of the 2'-deoxyguanosine adduct triacetate **16b** + **17b** as a yellow solid.

MM2 Computations on the Adducts

Models of the adducts were generated in Chem3D. Using the MM2 menu in Chem3D the structures were minimized and molecular dynamics run for 50,000 cycles in 2.0 fs step intervals by systematic heating and cooling. The resulting structures were energy minimized again and exported as pdb files for analysis.

Computational Analysis

To understand better the diastereoselectivities observed in the OsO_4-mediated reactions leading to either the major tetraol dibenzoate (**6** and its minor diastereomer **4**) or their boronate esters (**9** and its diastereomer), a computational analysis was undertaken. Starting structures were obtained by building in 2-dimension (2D), refined by minimization with the Merck Molecular Mechanics Force Field (MMFF94) converting to 3-dimension (3D) in PC Spartan Pro (Wavefunction, Inc.). The stereochemistry of the refined starting geometry was assigned by choosing configure labels from the Model menu and chirality checked from the dialog that appeared. This way the chiral centers were labeled using the *R*, *S* configuration. The refined molecular structure was then subjected to a Monte Carlo (MC) conformational search to establish the best conformer for the molecule. In the Setup calculation menu, conformer distribution and equilibrium geometry were chosen as the task to be accomplished. Molecular mechanics using MMFF94 force field was chosen as the type of calculation method. No constraints were applied and no frozen atoms were chosen. Symmetry was chosen and the calculation applied globally starting from the initial geometry. After establishing the best energy conformation (global minimum) or a structure close to it, an AM1 semi-empirical calculation was performed to establish the equilibrium geometry of this conformer. In setting up the quantum mechanical calculation, equilibrium geometry was chosen as the task to be performed while semi-empirical AM1 was chosen as the method. Again no constraints were applied and no frozen atoms chosen. In the compute menu, solvation energy was chosen for the tetraol dibenzoate isomers, but not for the boronate dibenzoate isomers because the method has not been parametrized for boron atom. Choosing the solvation energy in the compute menu ensured the calculation of the aqueous solvation energy using the SM5.4 procedure of Chambers et al. [Chambers, C. C.; Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. "Model for Aqueous Solvation Based on Class IV Atomic charges and First Solvation Shell Effects." *J. Phys. Chem.* **1996**, *100*, 16385-16398]. The solvation energies calculated are usually added to the gas-phase total energies obtained from AM1 calculations. Because the SM5.4 procedure of Chambers et al. has not been parameterized for the carbon-boron bond, solvation energy option was not chosen for the boronate dibenzoate derivatives. Frequency was also checked in the compute menu ensuring the calculation of second derivatives of energy leading to zero-point vibrational energies. Calculation of an electron density surface as well as the electron density surface onto which the value of the electrostatic potential had been mapped was performed.

The incorporation of MC conformational search method in PC SPARTAN Pro was important particularly for the treatment of large and flexible organic molecules with large numbers of degrees of freedom. First, an initial geometry was produced using the Builder menu in PC Spartan Pro and its structure was optimized by molecular mechanics energy minimization using the MMFF94 force field to obtain an initial strain energy. This initial refined structure was then submitted to the MC conformational search that located all readily accessible conformations with the goal of attaining the global minimum. The resulting minimum energy conformer was compared with previously found conformers to test for the possibility of duplication. If the newly generated conformer was a previously undiscovered conformer, then it was added to an accumulating list of unique conformers. The cycle was then repeated, and a new starting geometry was obtained and energy minimized. The search was terminated when new minima ceased to be found, and the lowest energy conformation was reported. Starting geometries were generated using random or pseudorandom variations of molecular geometry. Because no bonds were constrained the conformational search ran for a sufficiently long period of time covering all regions of conformational space. The probability of finding new conformers at any point in time depended upon the number of undiscovered conformers, in which case the number of new conformers decreased as the search progressed. The search began at an initial temperature of 5000 K, and this temperature was varied until the lowest energy conformation was found at 300 K.

At the end of the conformational search, similar molecules and high-energy conformers were discarded leaving only the best conformations (i.e., low-energy conformations). The best conformations, a maximum of 100 conformations, were retained and displayed on a spreadsheet. By sorting these conformations, the spreadsheet arranged them according to their potential energies in kcal/mol beginning with the lowest energy conformation. The lowest energy conformation was then saved in preparation for a semi-empirical AM1 calculation to determine the equilibrium geometry.

The semi-empirical AM1 calculation was used to obtain the heat of formation of the lowest energy conformer of one isomer relative to the other. In the AM1 calculation, the following menus were chosen in the Calculations dialog: Equilibrium Geometry, Semi-empirical, AM1 and MMFF conformer. The calculation was performed in the gas phase with a total molecular charge of 0 and spin multiplicity of 1.

The strain energies were obtained from the molecular mechanics (MM) calculations while the heats of formation were obtained from semi-empirical calculations using a restricted Hartree-Fock AM1 (RHF/AM1) model. The zero-point vibrational energies were obtained by checking the vibrational modes in the setup calculation menu. Standard thermodynamic quantities obtained at 298.15K and 1.00 atm included the translational, rotational, and vibrational enthalpies and entropies. The conformational enthalpies and entropies were calculated from the translational, rotational and vibrational enthalpies and entropies. The conformational free energies and Boltzmann weighting factors were determined using standard thermodynamic relationships [Atkins, P. W. *Physical Chemistry*, 5th Ed.; W. H. Freeman: NY, **1994,** p. 670].

The Boltzmann weighting factor or fractional statistical weight, P_i, of each isomer relative to the other was computed from the relationship

$$P_i = \frac{e^{-E_i / RT}}{\sum_{i=1}^{2} e^{-E_i / RT}} \qquad (1)$$

where E_i is the energy of the isomers in kcal/mol, R is the universal gas constant in kcal mol^{-1} deg^{-1} and T is the temperature in Kelvin. The free energy changes (ΔG) were then computed from the relationship

$$\Delta G = \Delta H - T\Delta S \qquad (2)$$

The flexible torsion angles, at the point of difference, for each isomer were measured using the Geometry model in PC Spartan Pro.

Table A. Lowest potential energies obtained by MC conformational searches at 298.15 K

Tetraol derivative	Potential Energy (kcal/mol)	ΔE (kcal/mol) between isomers	Boltzmann factor
B*a*P1	186.0	--	0.86
B*a*P2	187.1	1.1	0.14
B*a*PB1	125.5	--	0.99
B*a*PB2	128.1	2.6	0.01

Table B. Heats of formation by AM1 semi-empirical calculations

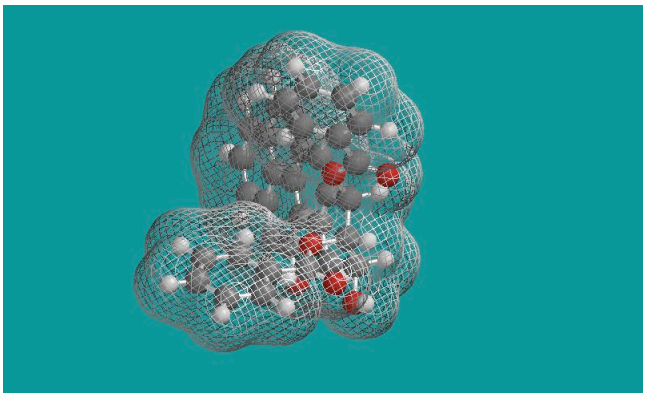
Tetraol derivative	H_f (kcal/mol)	ΔH_f (kcal/mol) between isomers	Boltzmann factor
B*a*P1	-125.2	--	0.95
B*a*P2	-123.4	1.8	0.05
B*a*PB1	-121.5	--	0.88
B*a*PB2	-120.3	1.2	0.12

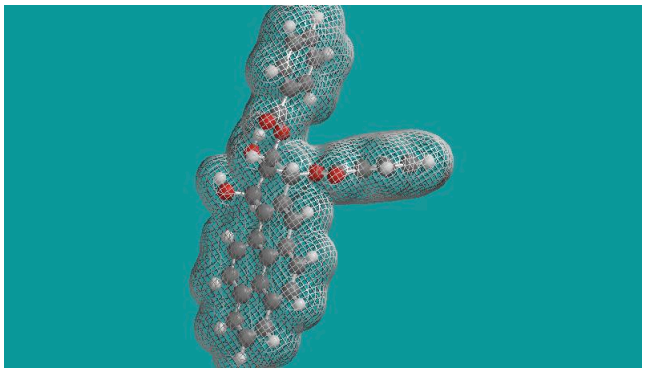
Table C. Thermodynamic Quantities at 298.15 K and 1.00 atm

Tetraol derivative	ΔG (kcal/mol)	G (kcal/mol)	H (kcal/mol)	TS (kcal/mol)
B*a*P1	--	284.9	344.3	59.4
B*a*P2	0.1	285.0	344.8	59.3
B*a*PB1	--	322.0	396.1	67.1
B*a*PB2	1.2	330.3	396.3	66.0

Table D. Solvation energies of tetraol dibenzoate isomers

Tetraol derivative	$E_{solvation}$ (kcal/mol)	$\Delta E_{solvation}$ between isomers	Boltzmann factor
B*a*P1	-13.4	--	0.96
B*a*P2	-11.5	1.9	0.04





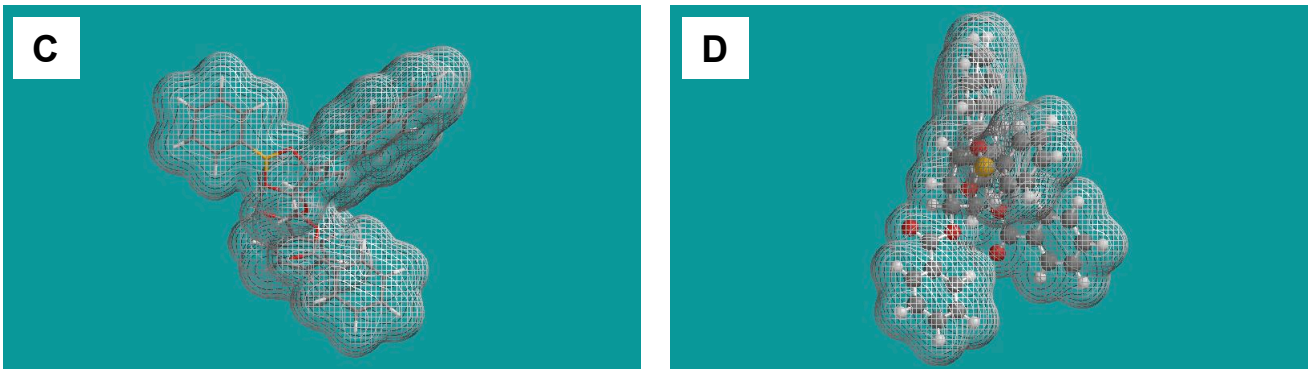
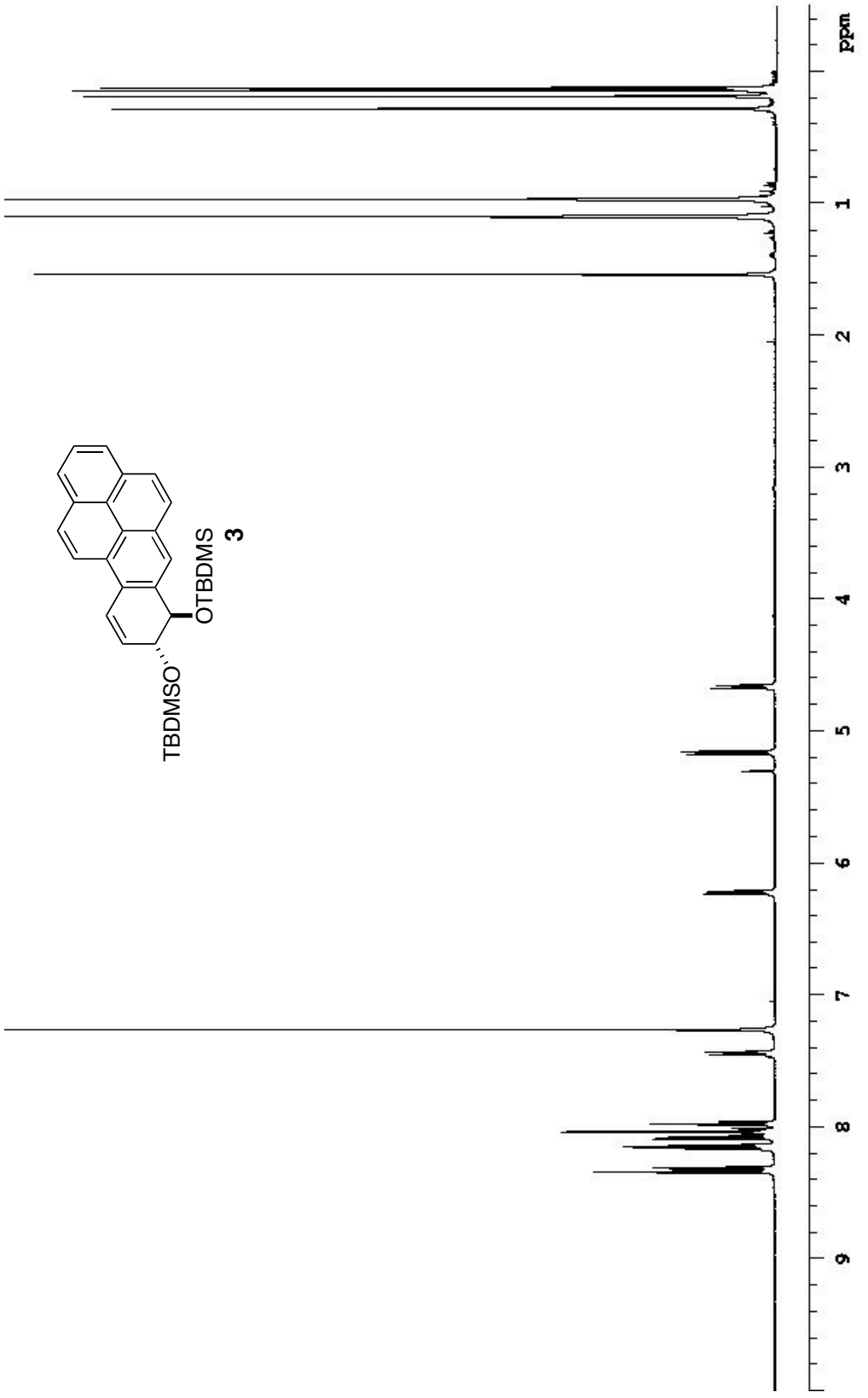


Figure 1. Structures of the tetraol dibenzoates **B*a*P1** (A), **B*a*P2** (B) as well as the corresponding boronate analogues **B*a*PB1** (C) and **B*a*PB2** (D), resulting from calculation of the electron density surface.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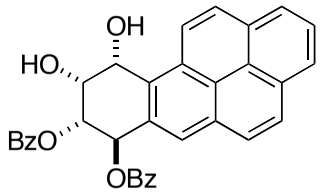

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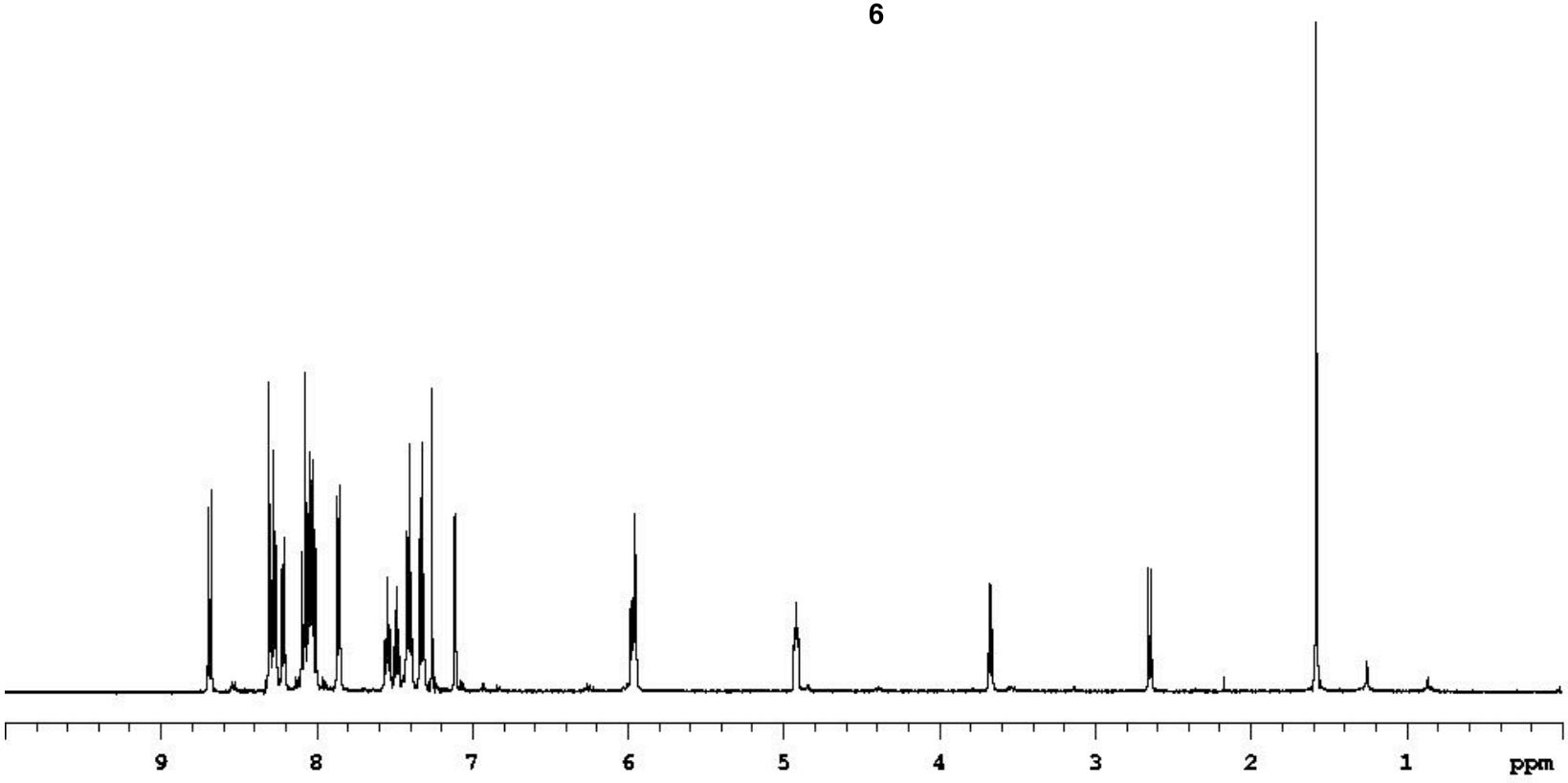

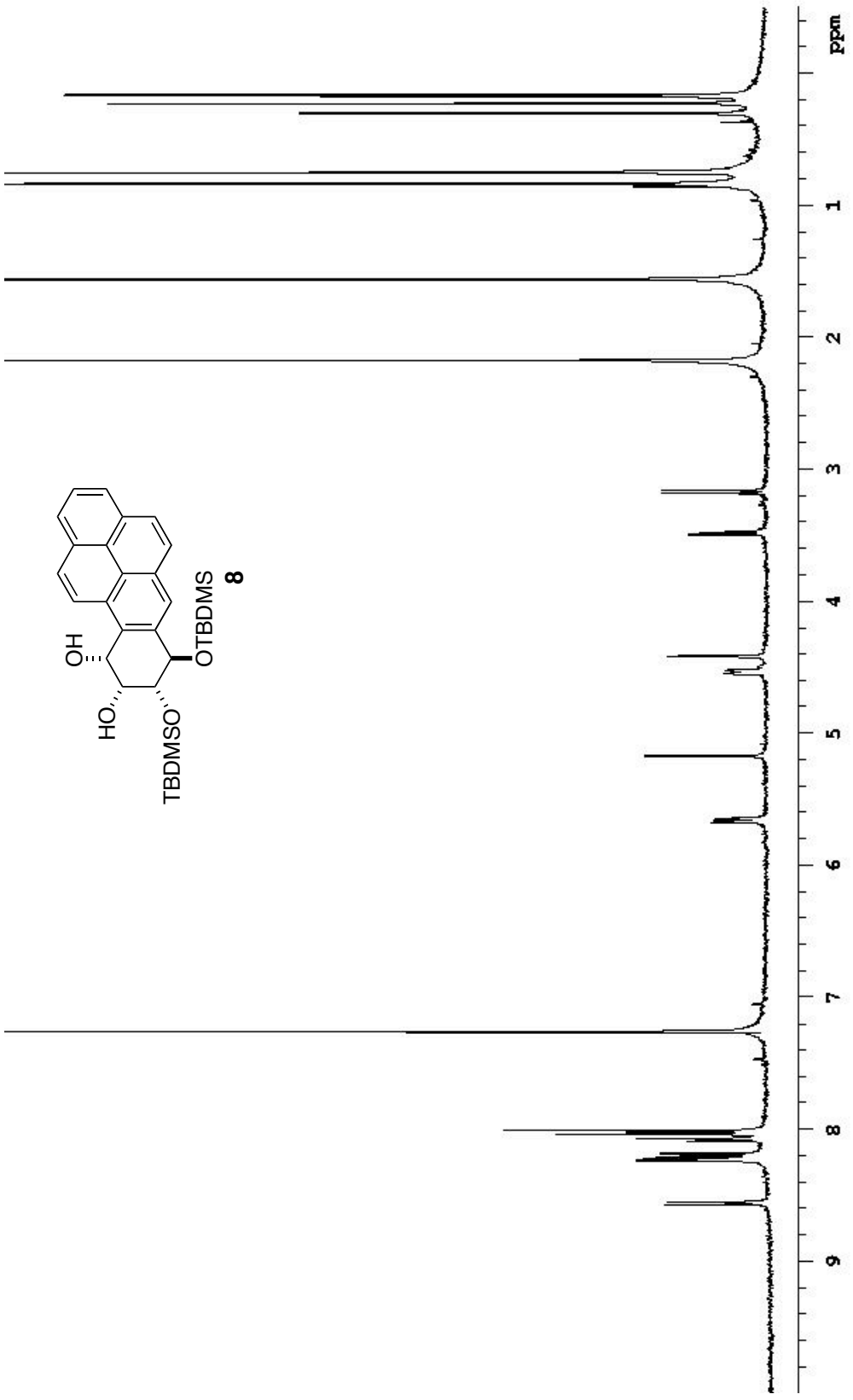
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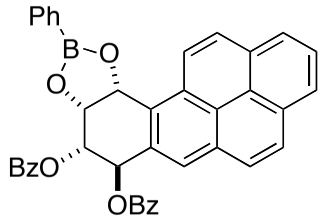

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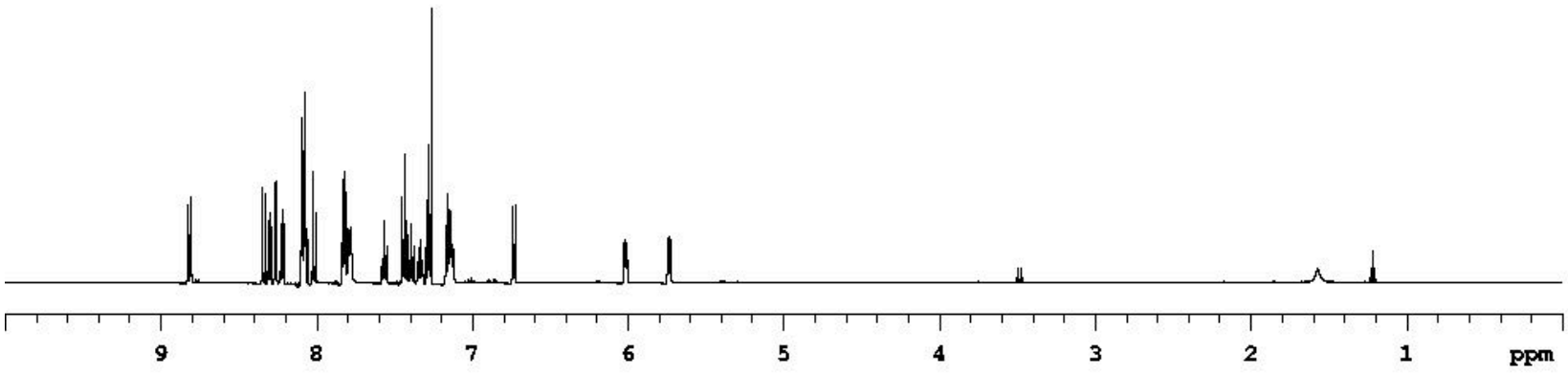

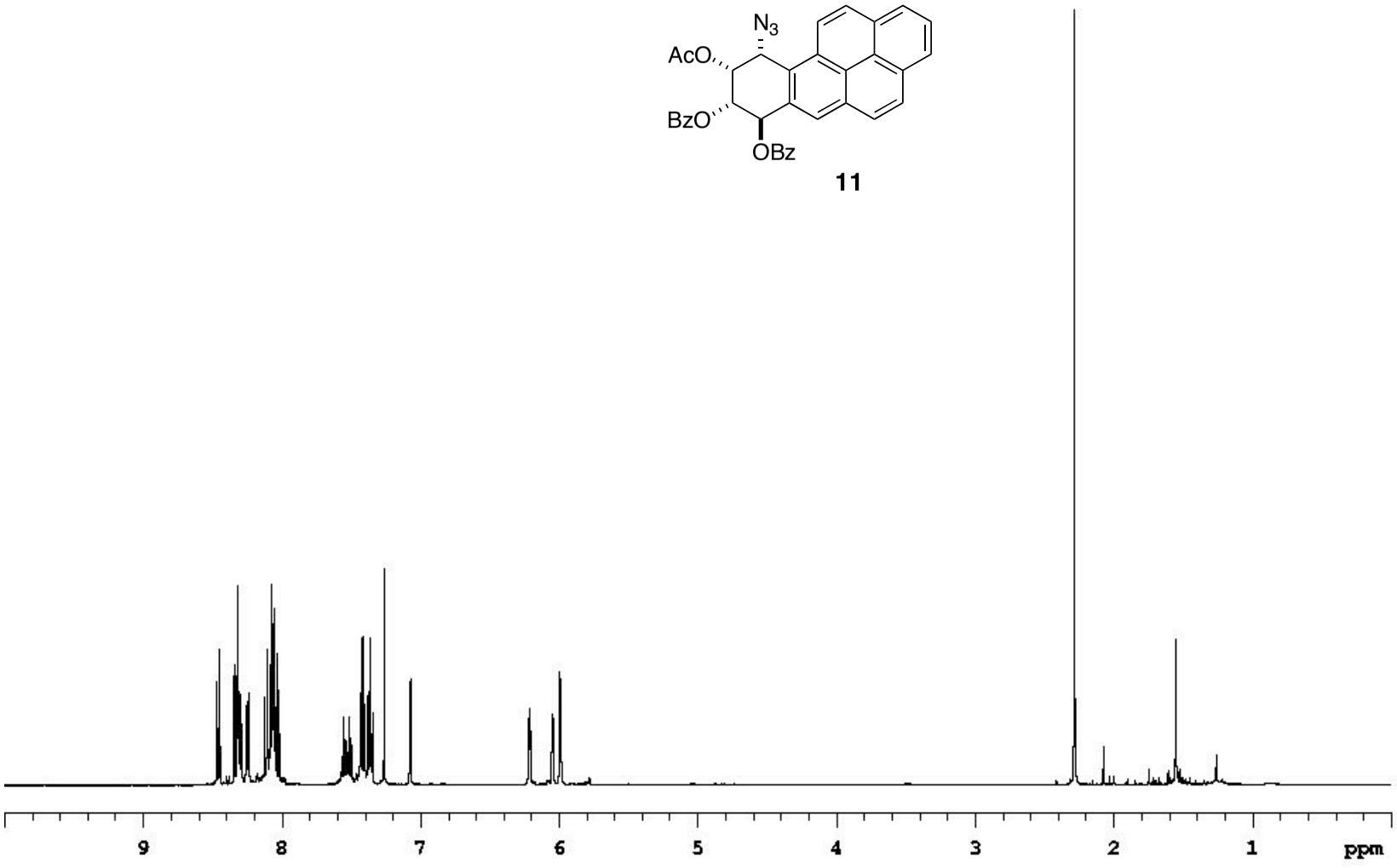
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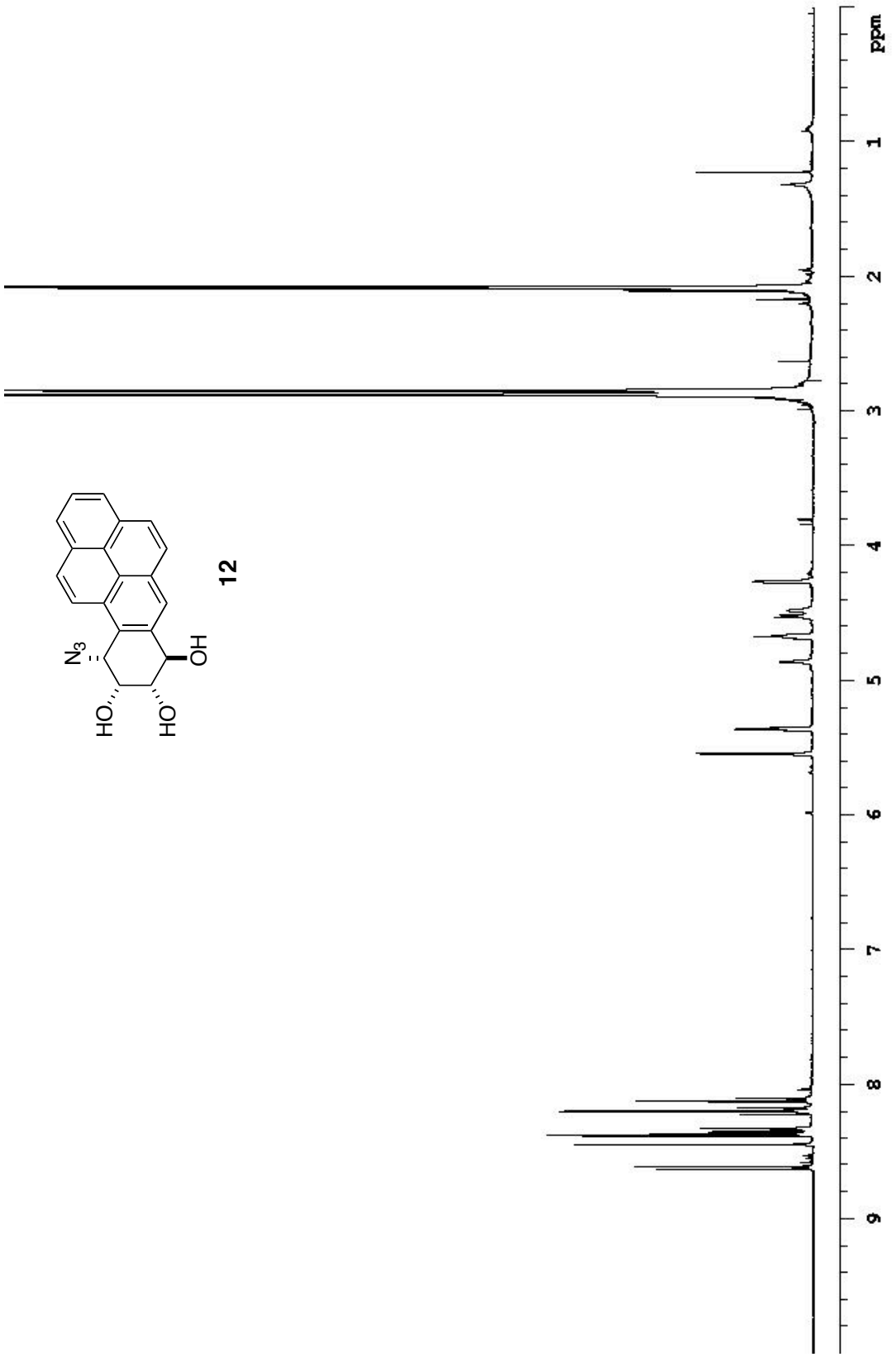

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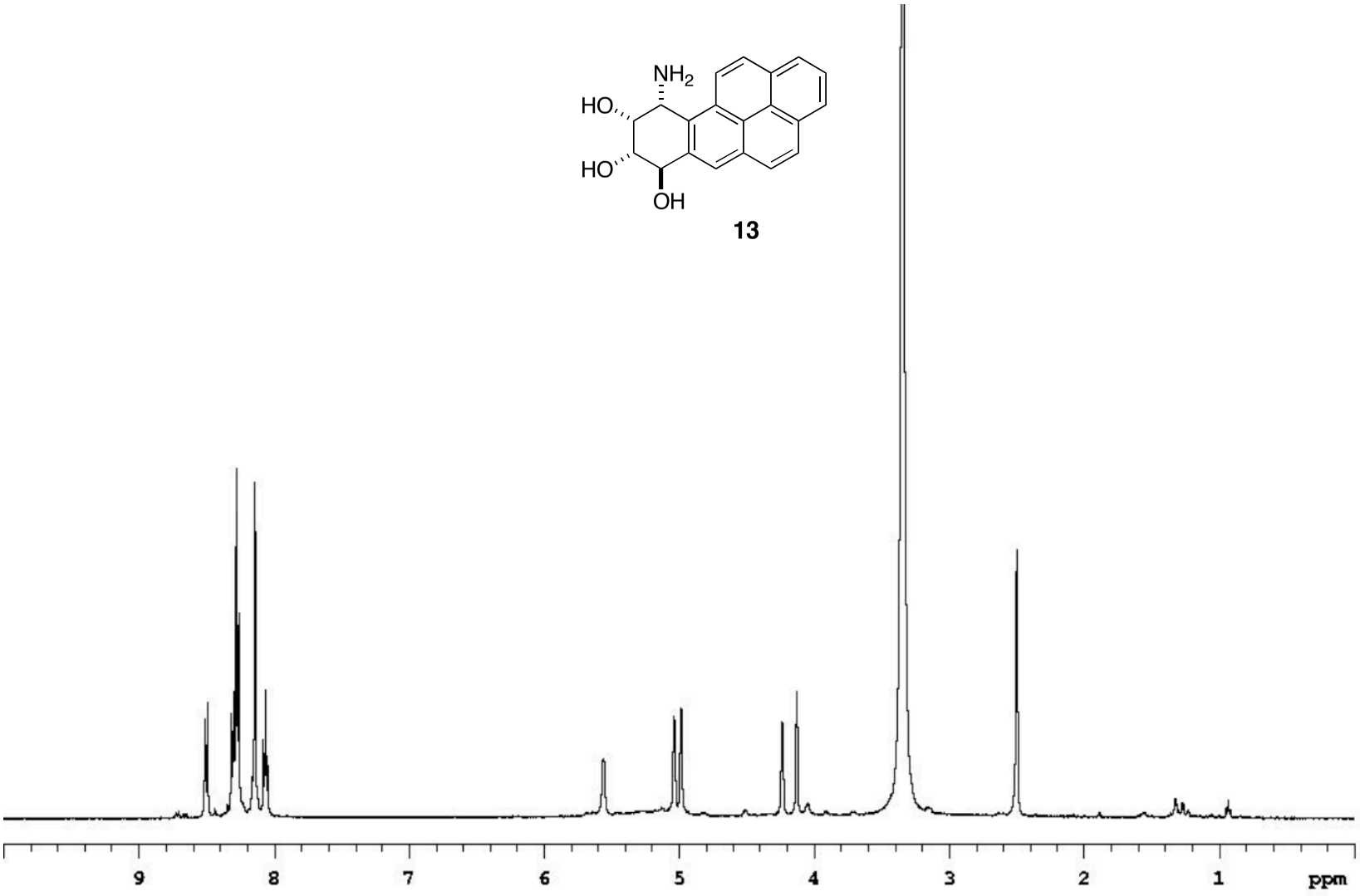

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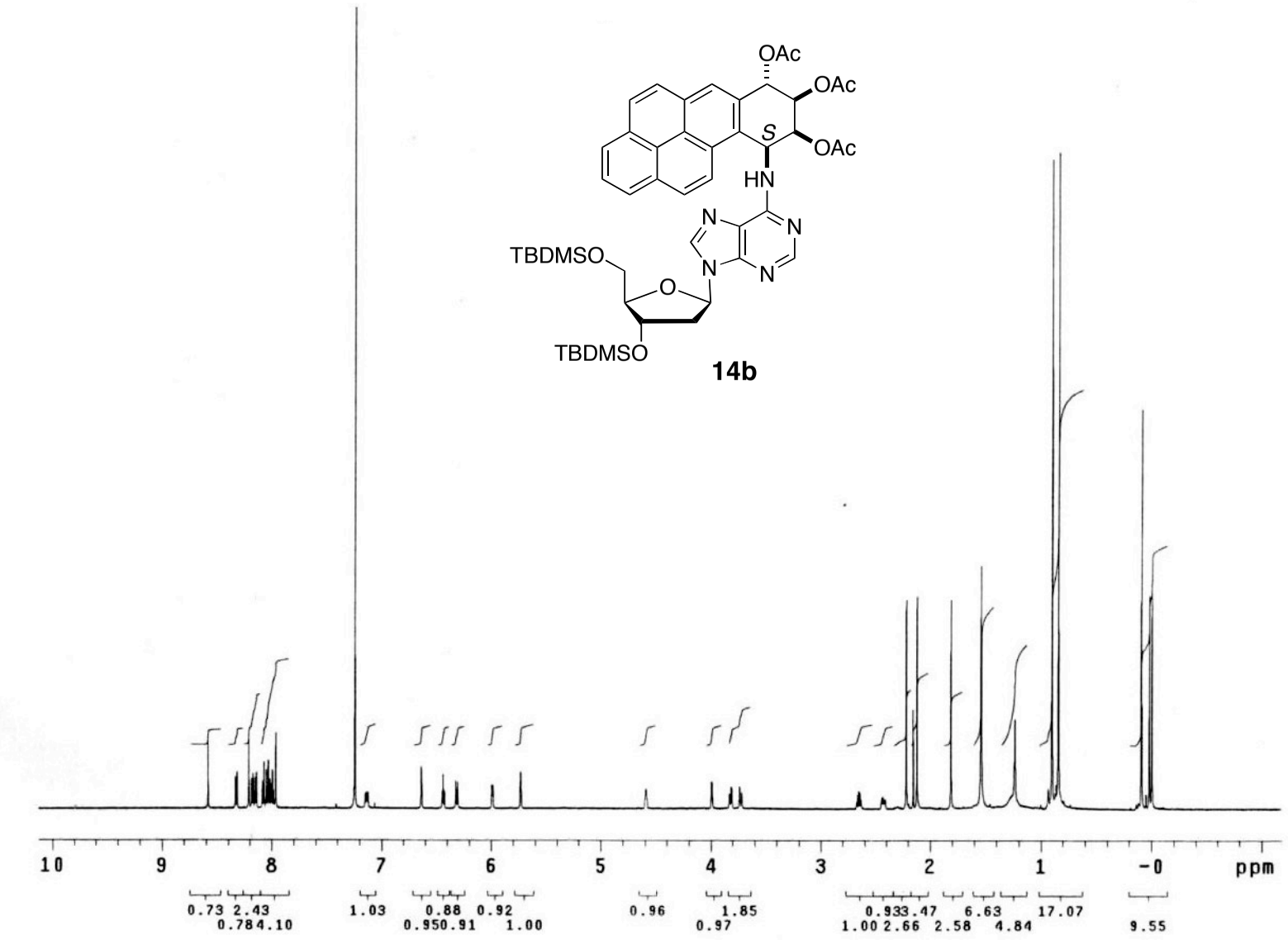
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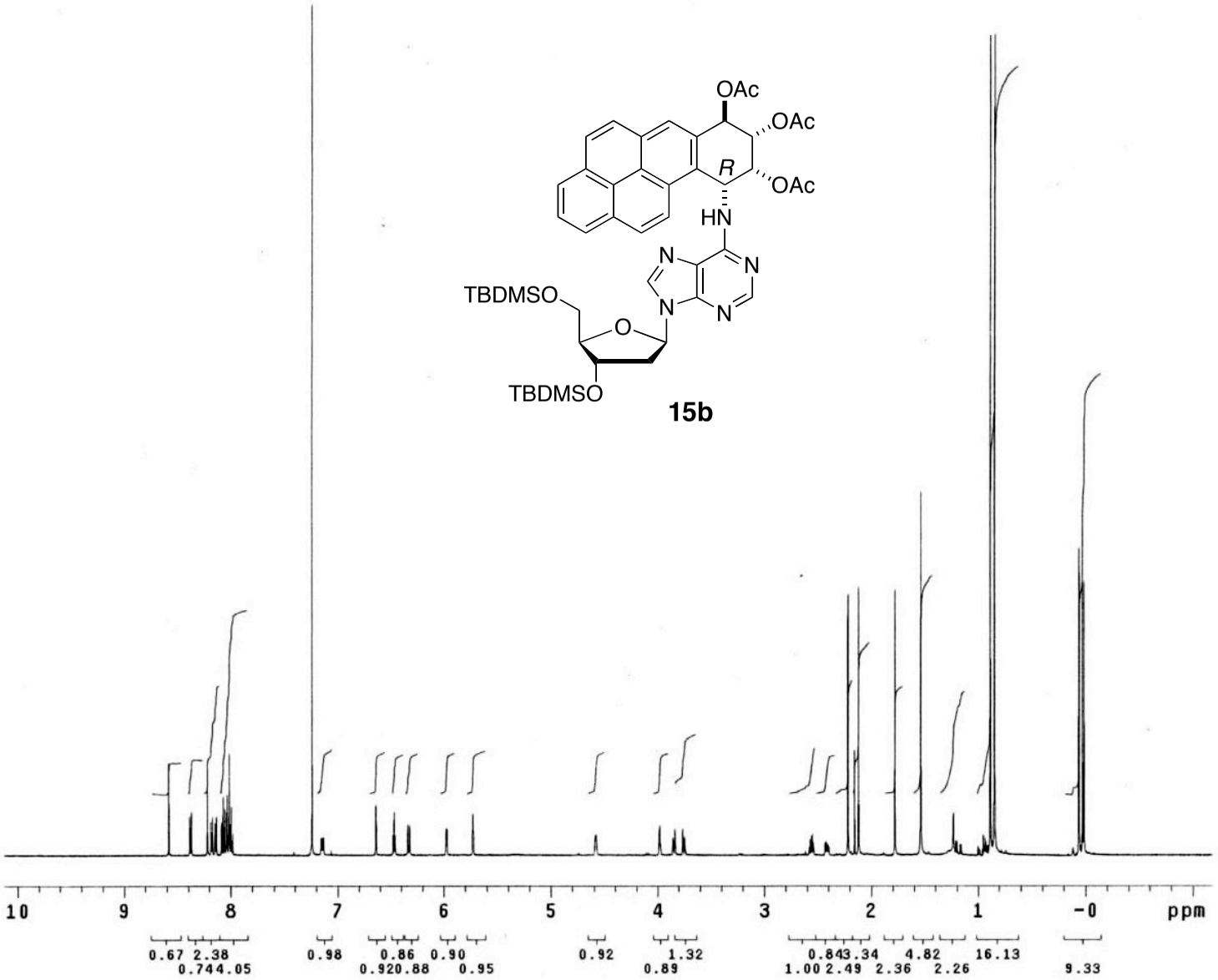
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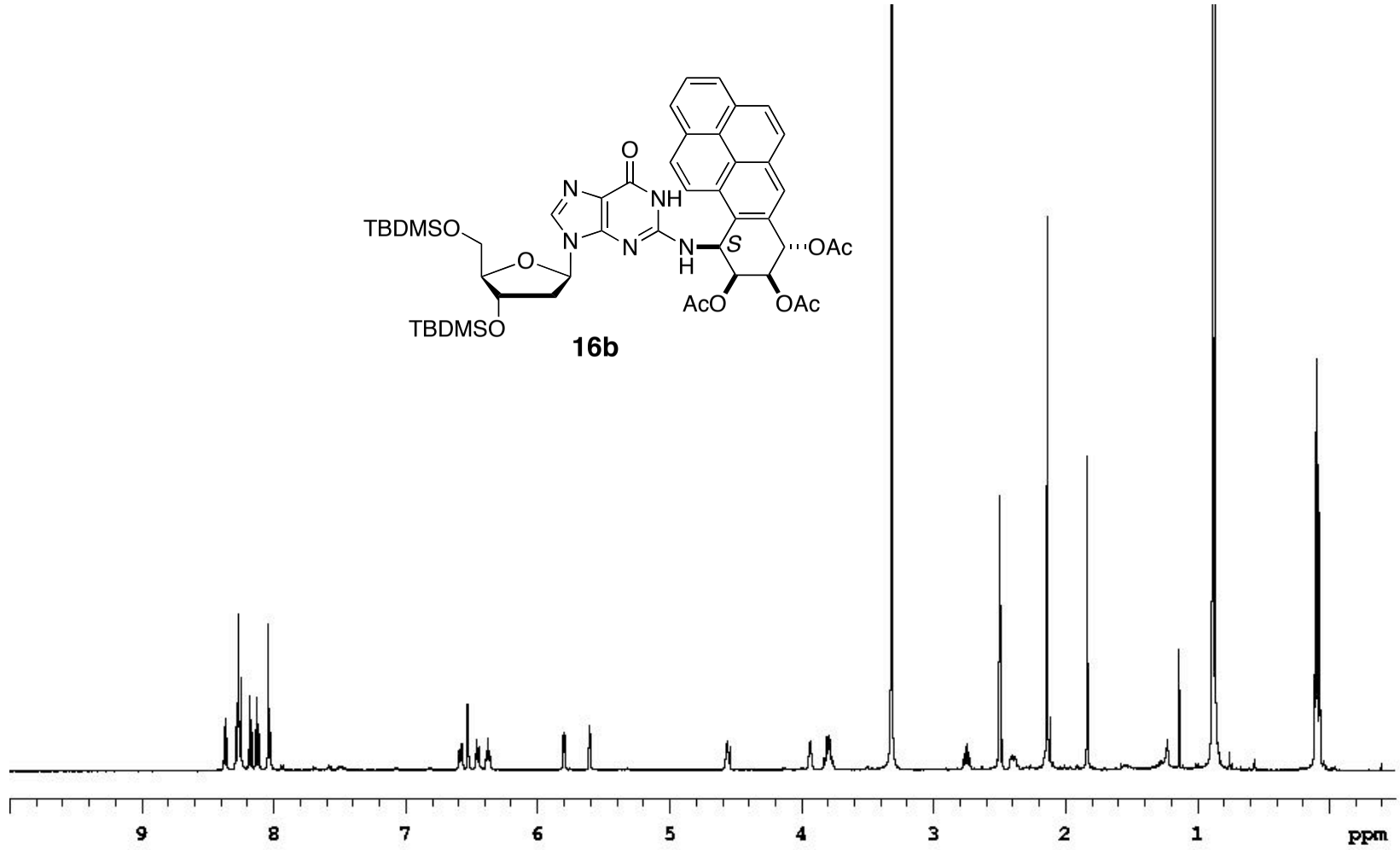
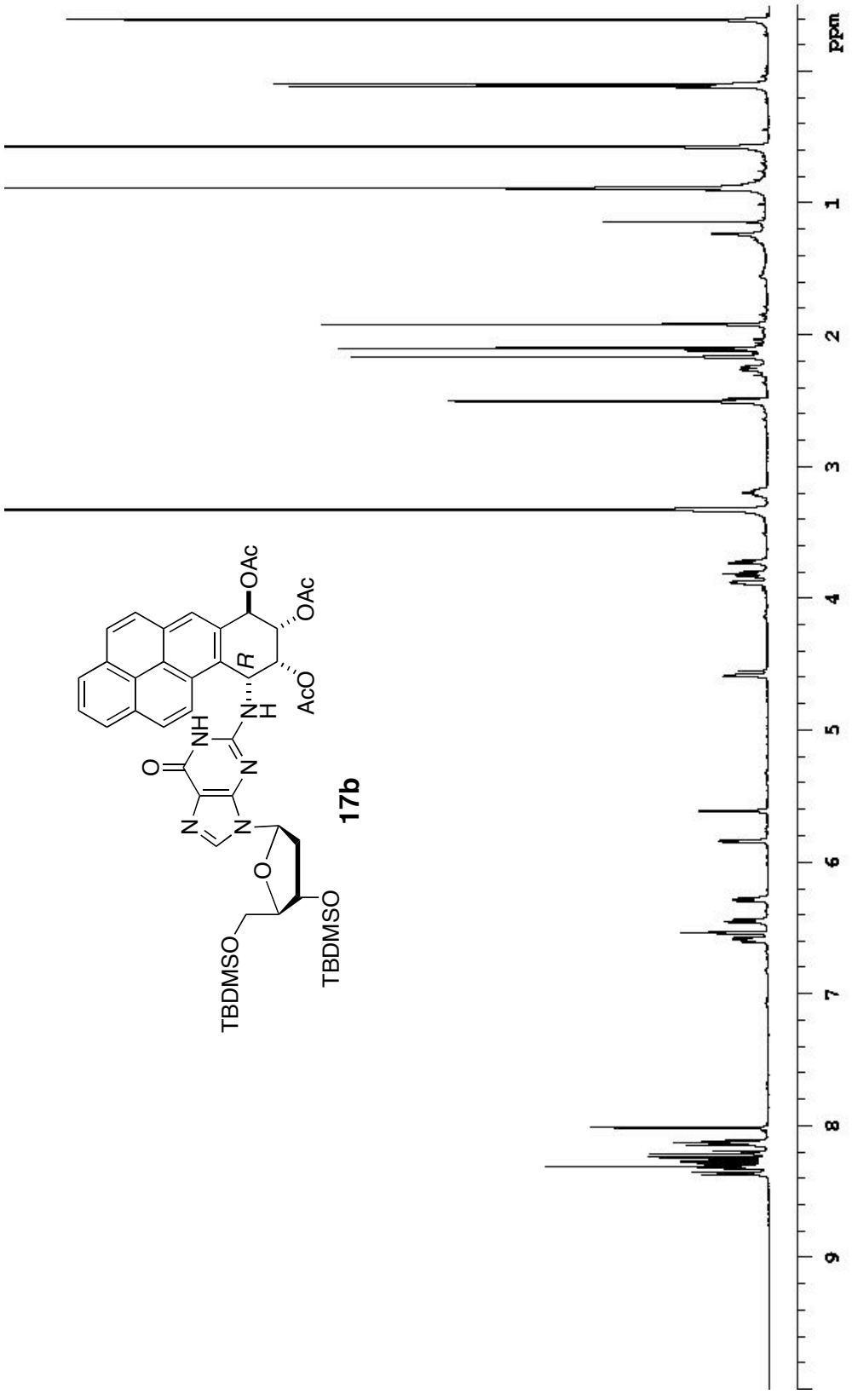


16b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