A Ligand-Free Solid-Supported System for Sonogashira Couplings: Applications in Nucleoside Chemistry

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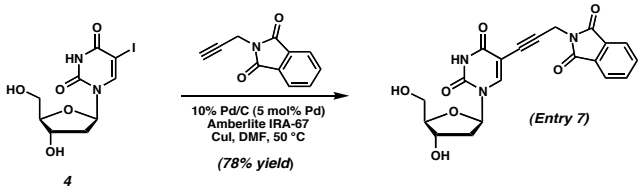
Electronic Supplementary Information (ESI) for Chemical Communications

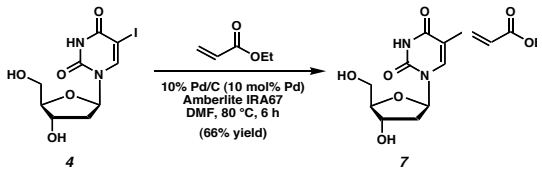
Materials and Methods. All commercially obtained reagents were used as received. Amberlite IRA-67, 10% palladium on charcoal, and CuI were obtained from Aldrich Chemical Company, Inc. DMF (DriSolv) was purchased from EMD Chemicals, Inc. Nucleoside substrates were obtained from Berry & Associates or Sigma. *N*-propargylphthalimide was purchased from GFS Chemicals, Inc. and *N*-propargyltrifluoroacetamide (**5**) was prepared following a literature protocol.[1] Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration.

Supplementary Material (ESI) for Chemical Communications

Representative Procedure for Resin-Based Sonogashira Coupling (Table 1, Entry 7 is used as an example):



A reaction tube was charged with 5-iodo-2'-deoxyuridine (**4**, 88.5 mg, 0.25 mmol), 10% palladium on charcoal (13.5 mg, 0.0125 mmol), CuI (9.5 mg, 0.05 mmol), *N*-propargylphthalimide (93 mg, 0.5 mmol), Amberlite IRA-67 (223 mg), and DMF (2.5 mL). The reaction mixture was sparged with argon for 2 min, and then capped with a rubber septum. The reaction vessel was evacuated and backfilled with N_2 (2x), sealed, then placed in a 50 °C oil bath. After 14 h, the reaction mixture was cooled to 23 °C, and filtered over a plug of SiO_2 topped with celite (5:1 CH_2Cl_2:MeOH eluent). After removal of solvents at reduced pressure with gentle heating (approximately 35 °C), the crude product was purified by flash chromatography (7:1 CH_2Cl_2:MeOH eluent) to afford the Sonogashira product (80.4 mg, 78% yield).



Heck Product 7. A reaction tube was charged with 5-iodo-2'-deoxyuridine (**4**, 88.5 mg, 0.25 mmol), 10% palladium on charcoal (27.0 mg, 0.025 mmol), Amberlite IRA-67 (223 mg), and DMF (2.5 mL). The reaction mixture was sparged with argon for 1 min, and then capped with a rubber septum. The reaction vessel was evacuated and backfilled with N_2 (2x), then ethyl acrylate (80 mL, 0.75 mmol) was added. The reaction tube was sealed and placed in a 50 °C oil bath. After 6 h, the reaction mixture was cooled to 23 °C, and filtered over a plug of SiO_2 topped with celite (5:1 CH_2Cl_2:MeOH eluent). After removal of solvents at reduced pressure with gentle heating (approximately 35 °C), the crude product was purified by flash chromatography (7:1 CH_2Cl_2:MeOH eluent) to afford the Heck product **7** (53.8 mg, 66% yield).

• ^{1}H NMR spectra for all compounds have been included below.[2]

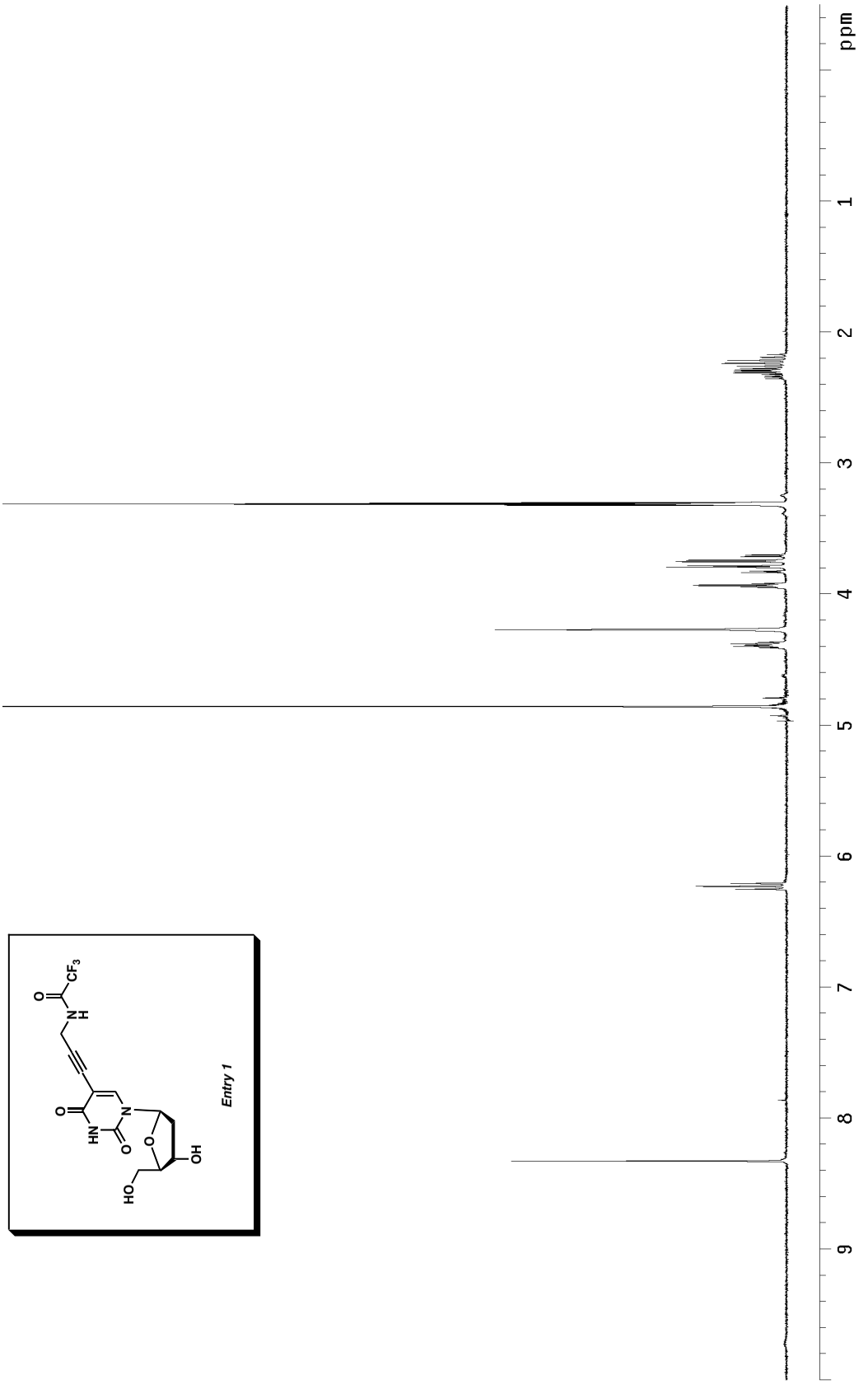


Figure SI.1 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 1*.[2a,b,c,d]

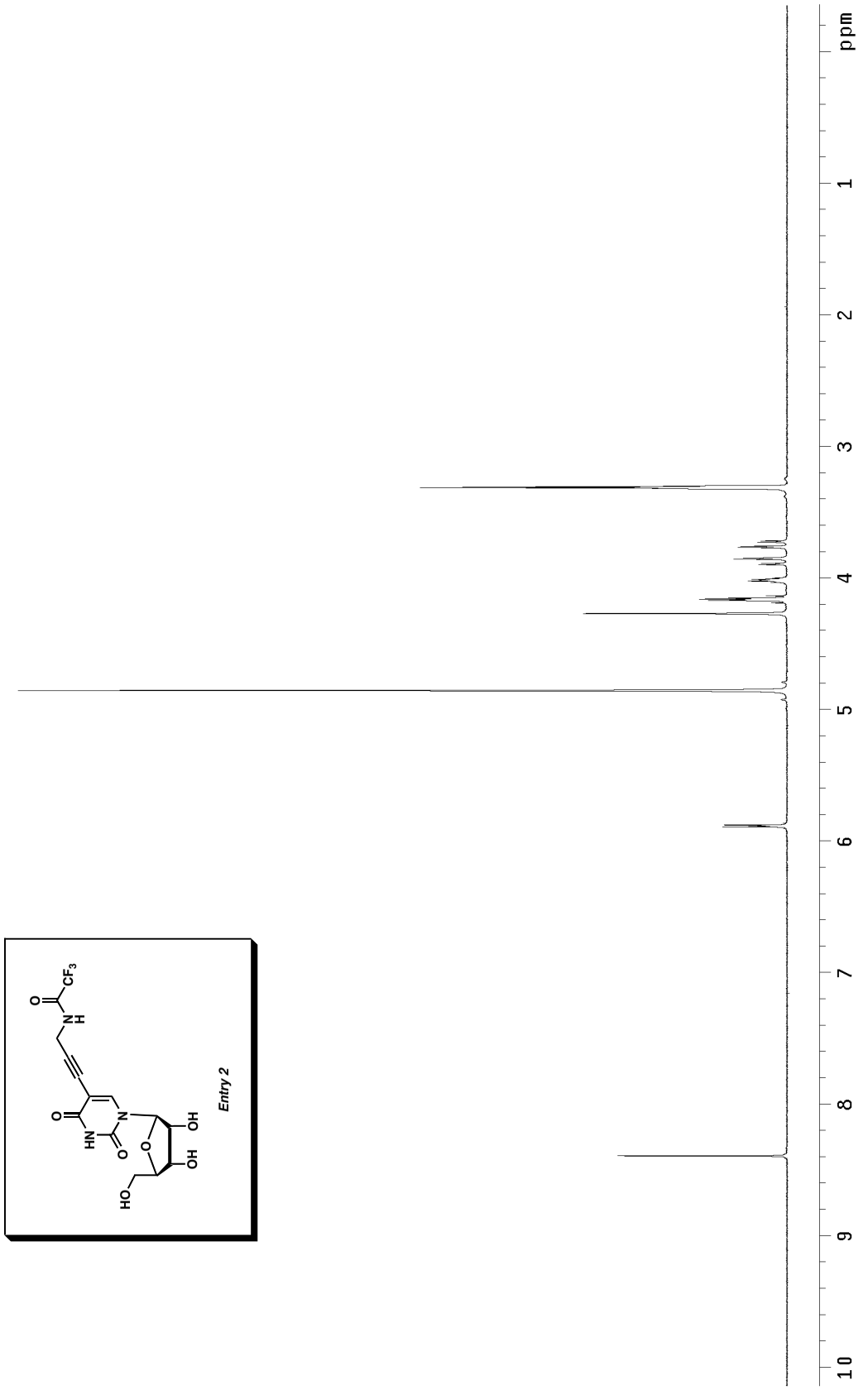
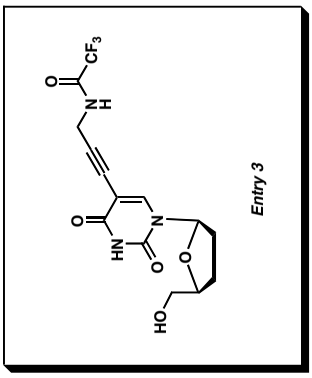


Figure SI.2 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 2*.[2a,e,f]



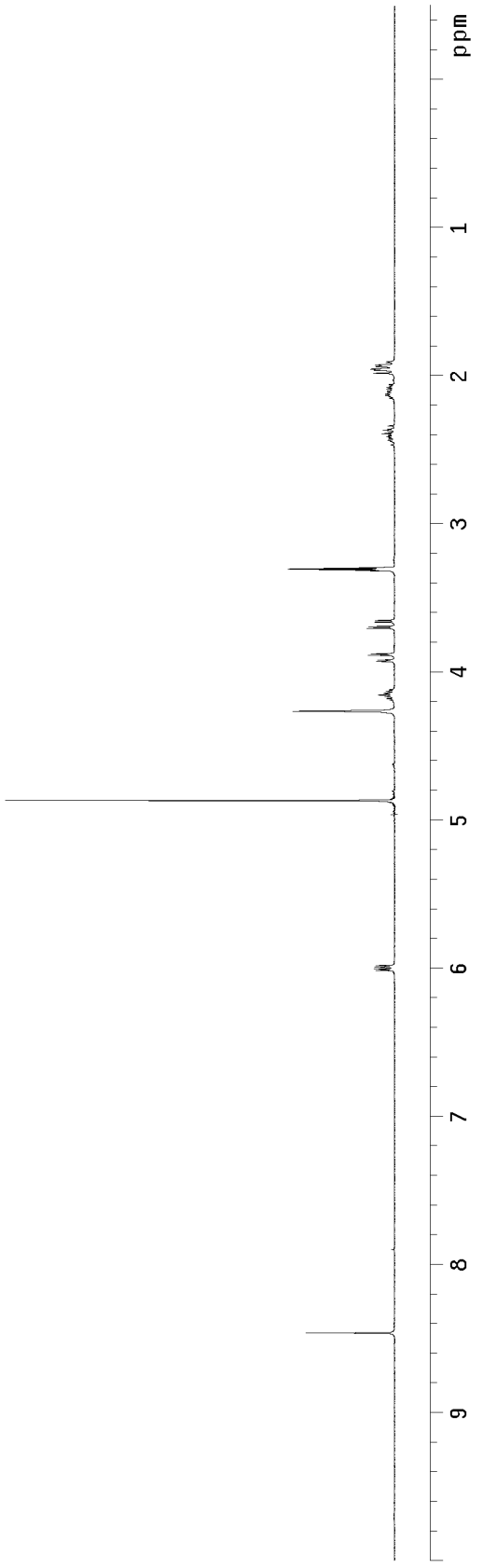


Figure SI.3 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 3*.[2a,g,h,i]

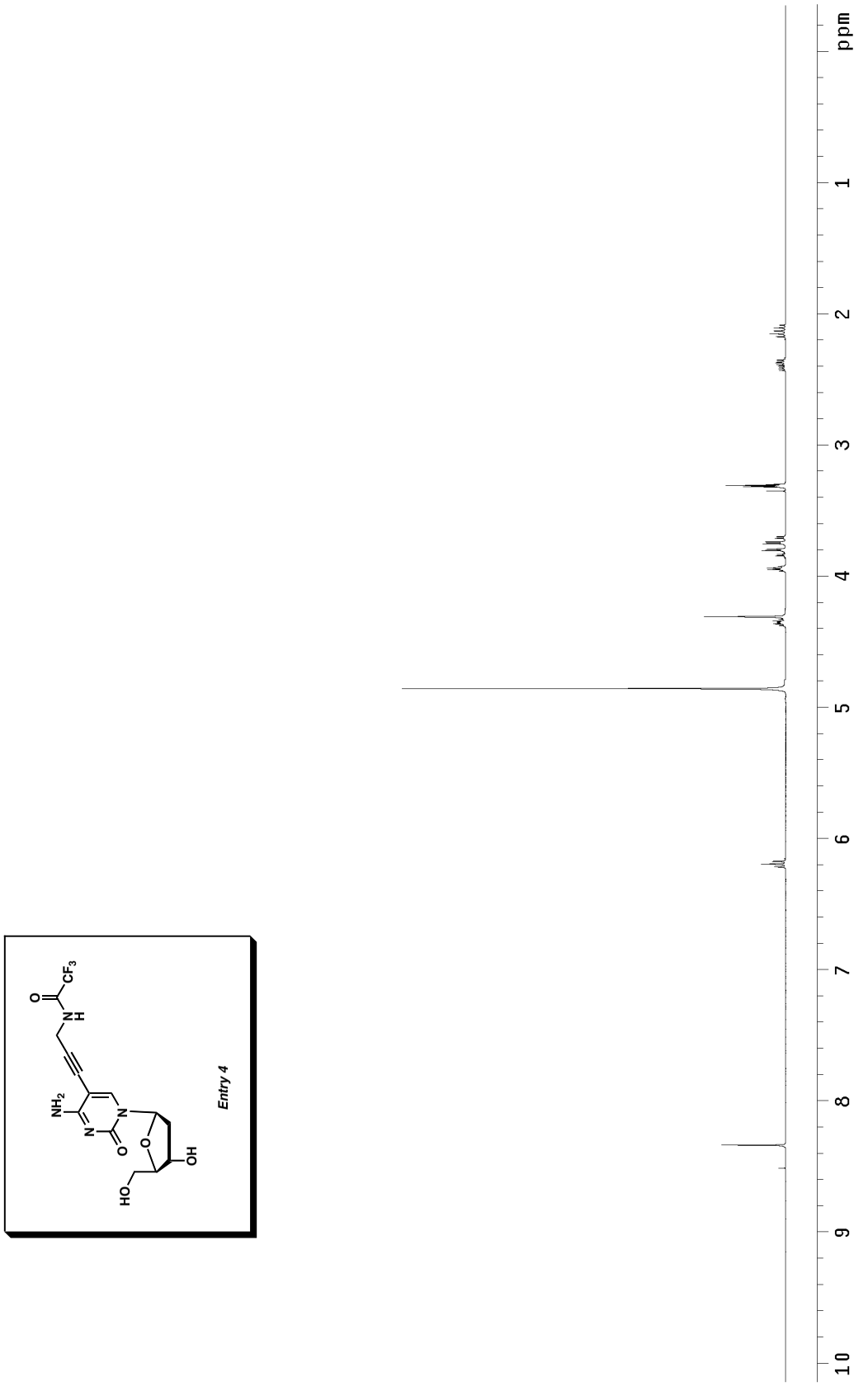


Figure SI.4 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 4*.[2a,d]

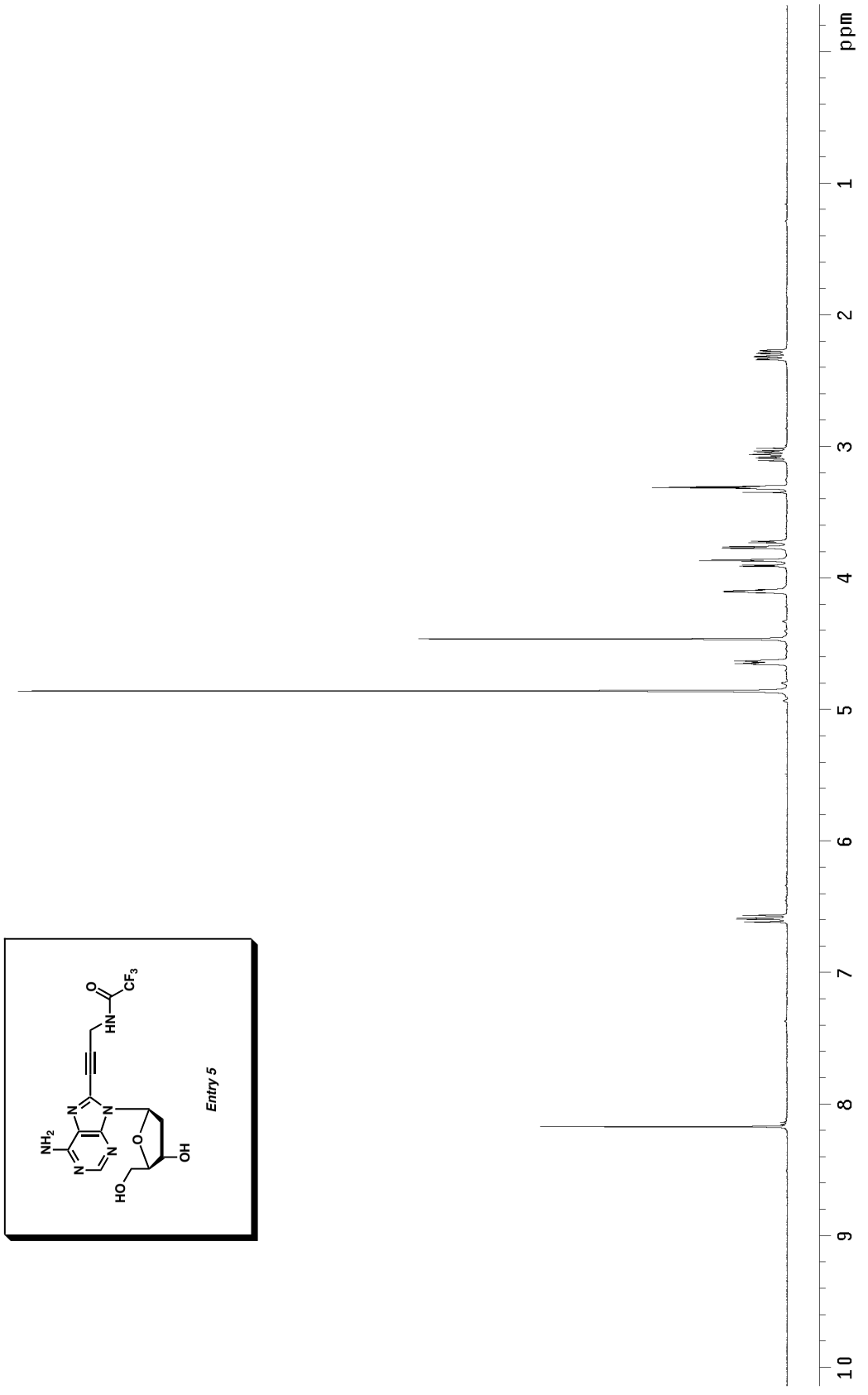


Figure SI.5 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 5*.

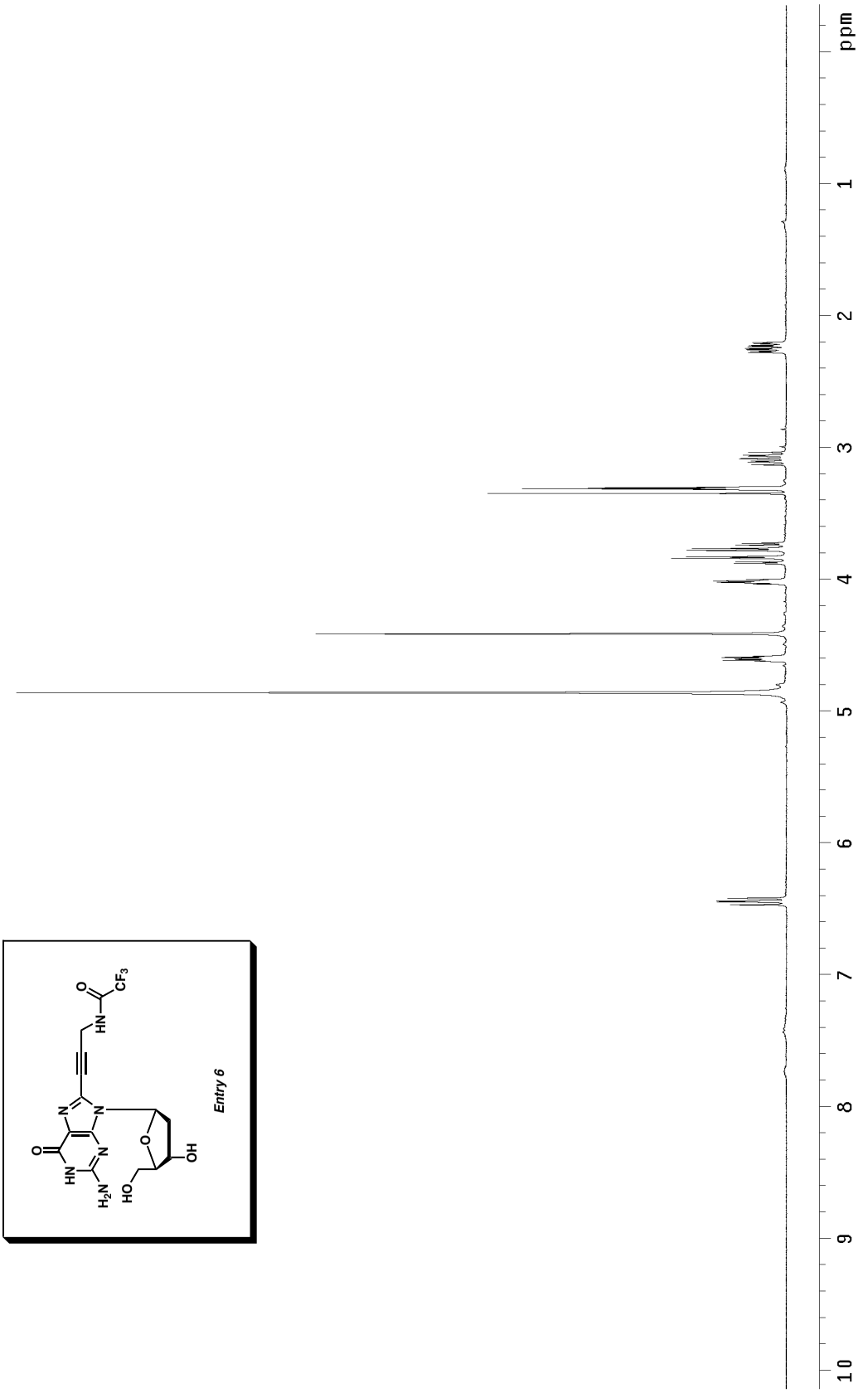


Figure SI.6 ^{1}H NMR (300 MHz, CD_3OD) of *Entry 6*.

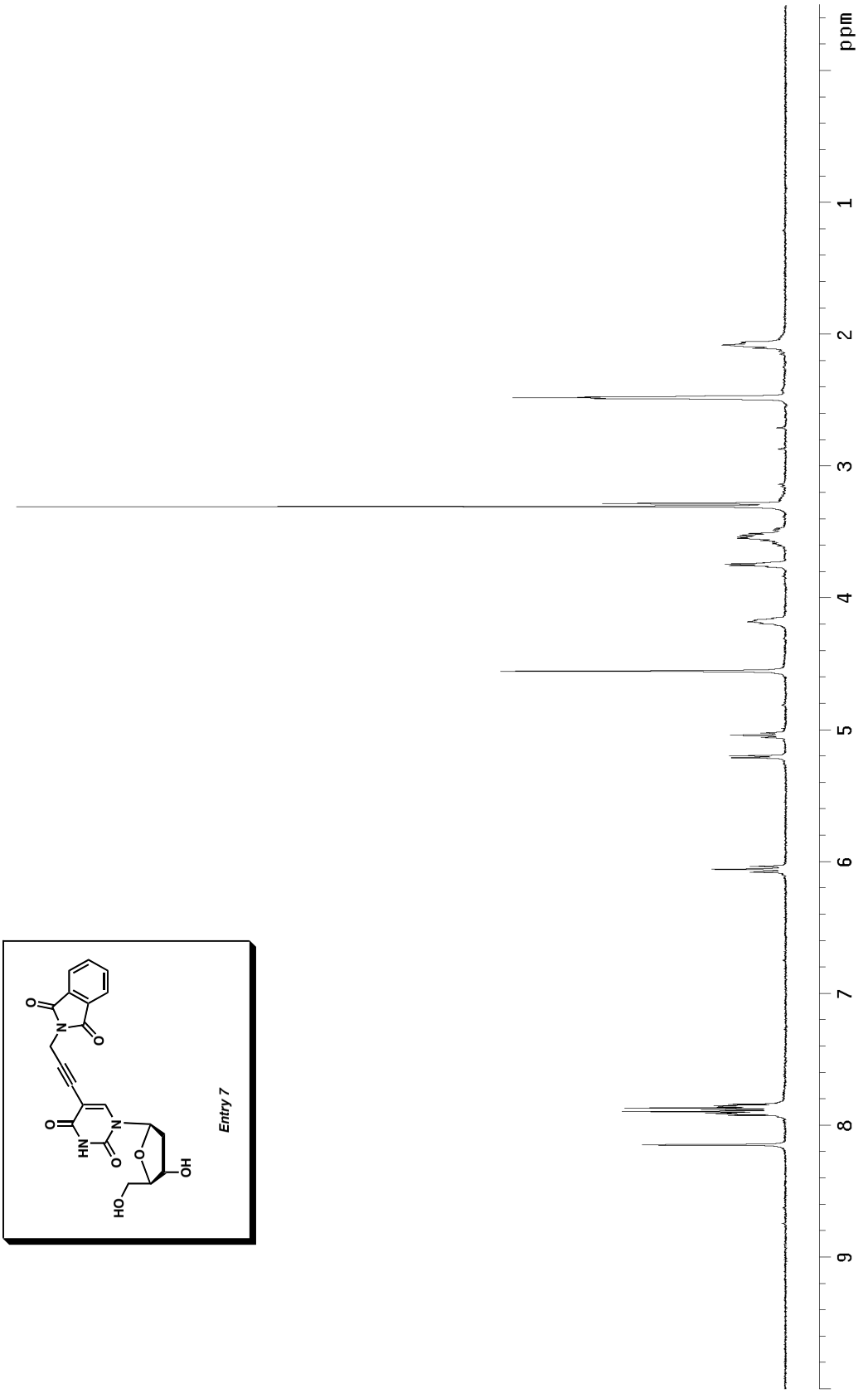


Figure SI.7 ^{1}H NMR (300 MHz, DMSO-d_6) of *Entry 7*.[2j,k]

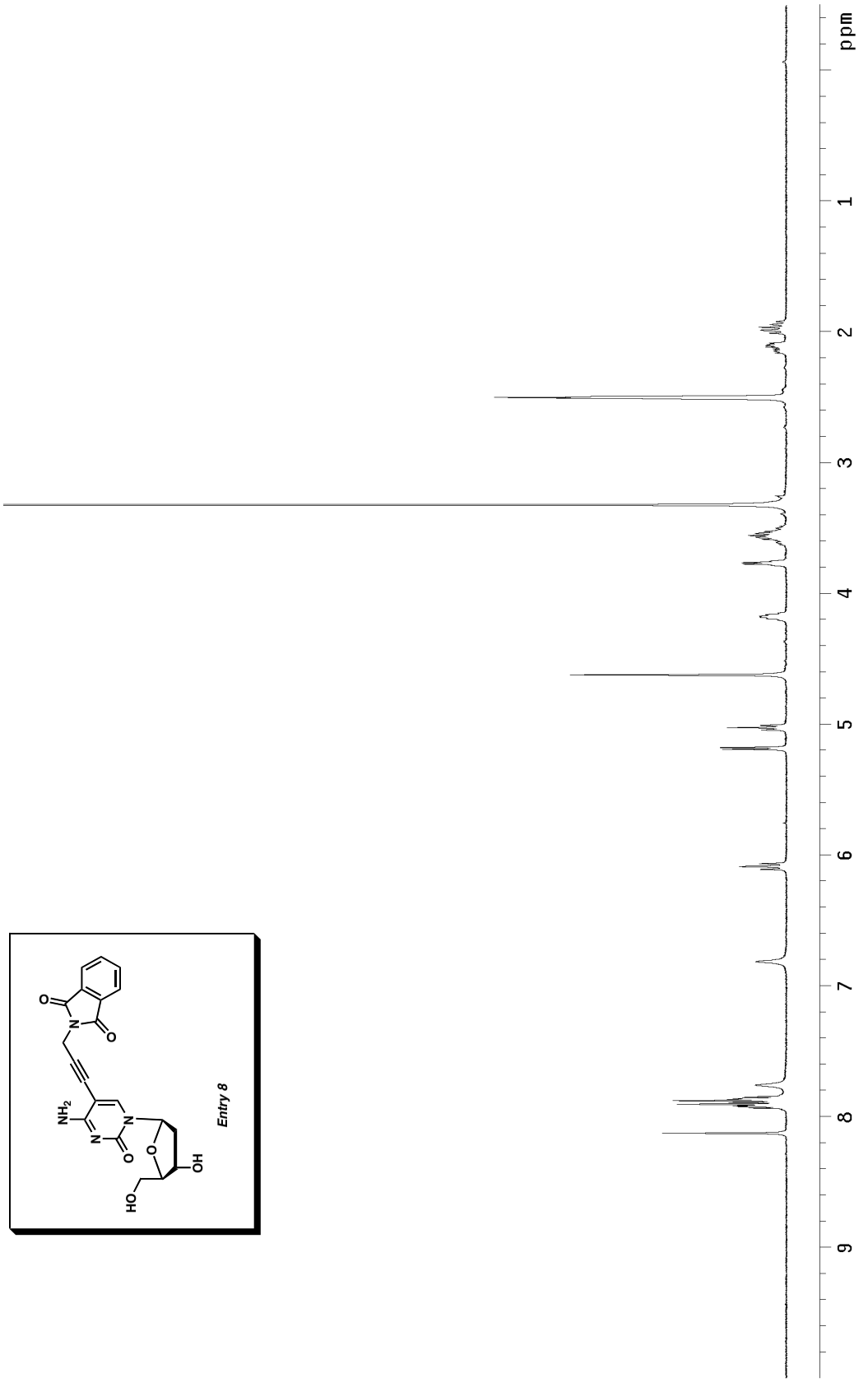


Figure SI.8 ^{1}H NMR (300 MHz, DMSO-d_6) of *Entry 8*.[21]

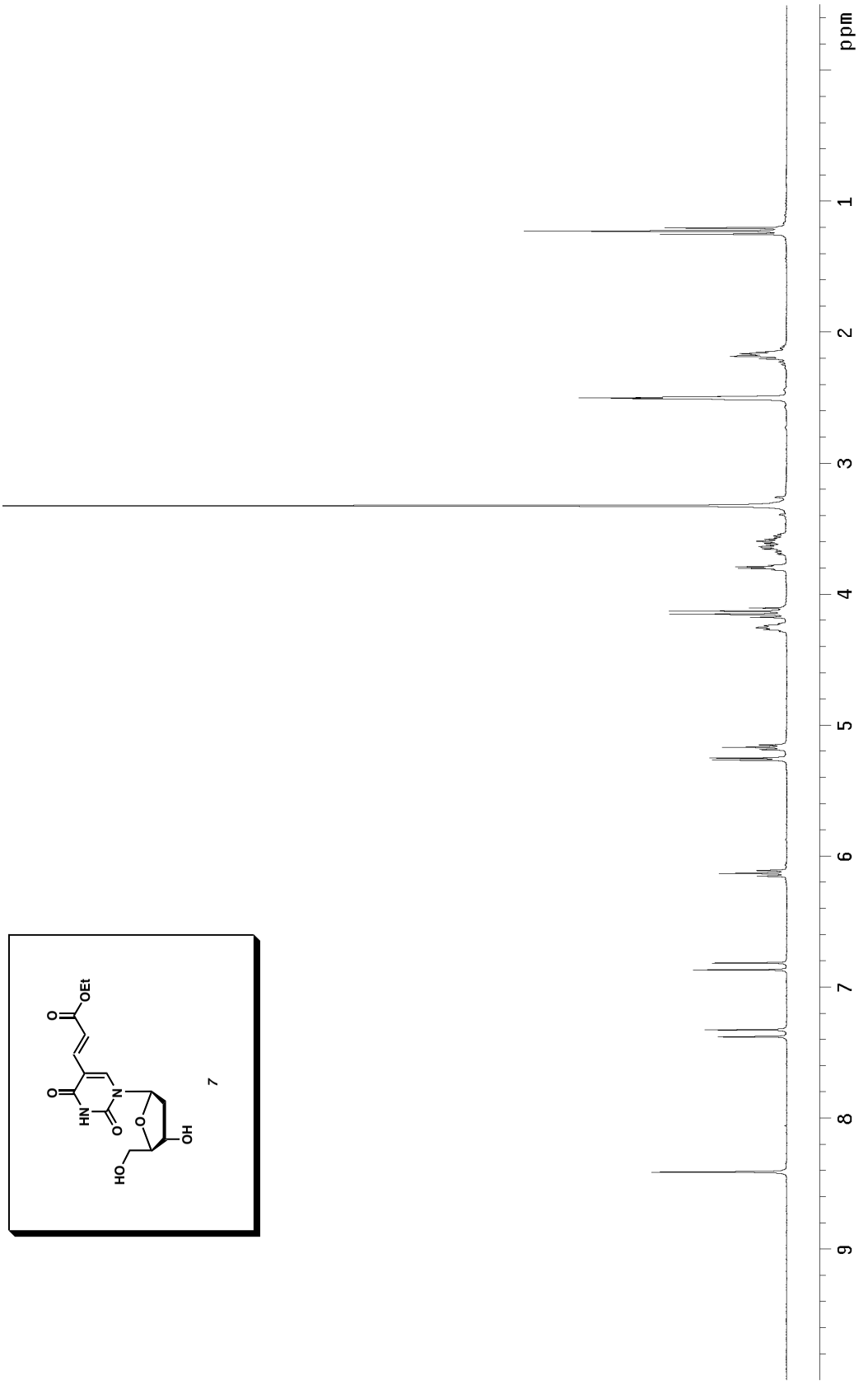


Figure SI.9 ^{1}H NMR (300 MHz, DMSO-d_6) of compound **7**.[2m,n]

References:

1 E. J. Trybulski, J. Zhang, R. H. Kramss and R. M. Mangano, *J. Med. Chem.*, 1993, **36**, 3533.

2 For previous syntheses, see: (*a*) F. W. Hobbs, *J. Org. Chem.*, 1989, **54**, 3420. (*b*) A. L. Casalnuovo and J. C. Calabrese, *J. Am. Chem. Soc.,* 1990, **112**, 4324. (*c*) T. R. Battersby, D. N. Ang, P. Burgstaller, S. C. Jurczyk, M. T. Bowser, D. D. Buchanan, R. T. Kennedy and S. A. Benner, *J. Am. Chem. Soc.,* 1999, **121**, 9781. (*d*) S. E. Lee, J. S. Vyle, D. M. Williams and J. A. Grasby, *Tetrahedron Lett.,* 2000, **41**, 267. (*e*) S. A. Benner, U.S. Patent 5,965,364, 1999. (*f*) P. V. Fisher, P. Vatta and S. H. Khan, PCT Int. Appl. WO 9818466, 2003. (*g*) J. M. Prober, R. J. Dam, C. W. Robertson, Jr., F. W. Hobbs, Jr. and G. L. Trainor, Eur. Pat. Appl. EP 252683, 1988. (*h*) P. N. Confalong, *J. Heterocycl. Chem.,* 1990, **27**, 31. (*i*) G. G.-Y. Shen and T. S. Dobashi, U.S. Patent 6,002,003, 1999. (*j*) K. J. Gibson and S. J. Benkovic, *Nuc. Acid. Res.,* 1987, **15**, 6455. (*k*) J. C. Tabone, M. R. Stamm, H. B. Gamper and R. B. Meyer, Jr., *Biochemistry,* 1994, **33**, 375. (*l*) F. Seela, N. Ramzeva, P. Leonard, Y. Chem, H. Debelak, E. Feiling, R. Kroeschel, M. Zulauf, T. Wenzel, T. Froehlich and M. Kostrzewa, *Nucleosides Nucleotides,* 2001, **20**, 1421. (*m*) A. S. Jones, G. Verhelst and R. T. Walker, *Tetrahedron Lett.*, 1979, **20**, 4415. (*n*) H. Griengl, W. Hayden, W. Schwarz, H. Bachmayer and B. Rosenwirth, *Eur. J. Med. Chem. Chim. Ther.*, 1985, **20**, 105.