Enantioselective Synthesis of (-)-LL-C10037α from Benzoquinone

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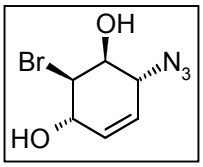
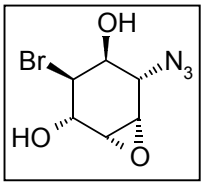
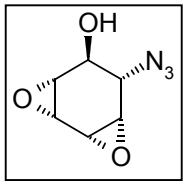
Supporting Information



(1*S*,2*R*,3*S*,6*R*)-6-Azido-2-bromo-4-cyclohexene-1,3-diol [(-)-6]. To a stirred solution of epoxide (+)-**5** (1.5 g, 7.9 mmol) in methanol (50 mL) was added $ZnSO_4 \cdot 7H_2O$ (2.3 g, 7.9 mmol) and NaN_3 (1.5 g, 24 mmol). After stirring under N_2 for 3.5 h, the mixture was filtered through a pad of Celite and concentrated in vacuo. The resulting material was taken up in water (50 mL) and saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (4 _ 30 mL). The combined organics were dried with $MgSO_4$ and concentrated in vacuo to provide azide **6** (1.75 g, 95%) as a white solid. Flash chromatography (7:3 hexanes:ethyl acetate) led to slight decomposition and no overall increase in purity. Mp 83-84 °C; $[\alpha]^{25}_D$ -225 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.83 (dd, *J* = 10.0, 2.5 Hz, 1H), 4.59 (br s, 1H), 4.31 (dd, *J* = 5.7, 2.3 Hz, 1H), 4.13 (br s, 1H), 4.04 (m, 1H), 2.45 (d, *J* = 5.5 Hz, 1H), 2.22 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3 (CH), 125.4 (CH), 71.3 (CH), 70.1 (CH), 61.0 (CH), 58.0 (CH); HRMS (EI) calcd for $C_6H_8O_2Br$ (M-N_3) 190.9708, found 190.9709.

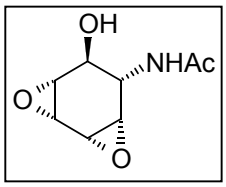


(1*S*,2*S*,3*S*,4*R*,5*S*,6*S*)-4-Azido-2-bromo-5,6-epoxycyclohexane-1,3-diol [(-)-7]. To a solution of azide **6** (1.4 g, 6.1 mmol) in dichloromethane (40 mL) and ethyl acetate (4 mL) was added ca. 70% MCPBA (3.0 g, 12.2 mmol) and the solution stirred under N_2 for 56 h. The solution was poured into saturated $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate (3 _ 50 mL). The combined organics were dried with $MgSO_4$, concentrated in vacuo and purified by flash chromatography (2:1 hexanes:ethyl acetate) to provide epoxide **7** (1.43 g, 94%) as a white solid: mp 86-90 °C; $[\alpha]^{23}_D$ -125 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 4.98 (d, *J* = 5.6 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, 1H), 4.43 (ddd, *J* = 7.2, 4.4, 4.0 Hz, 1H), 4.13 (ddd, *J* = 4.4, 2.4, 0.8 Hz, 1H), 4.07 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.97 (ddd, *J* = 6.8, 5.6, 2.4 Hz, 1H), 3.61 (dd, *J* = 4.0, 2.8 Hz, 1H), 2.48 (ddd, *J* = 4.0, 4.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 70.5 (CH), 69.7 (CH), 62.7 (CH), 59.2 (CH), 55.9 (CH), 55.1 (CH); MS (CI) *m/z* 250 (M+H), 252 (M+H); HRMS (EI) calcd for $C_6H_8O_3N_3$ (M-Br) 170.0566, found 170.0569.



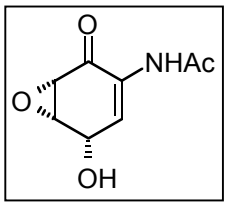
(1*S*,2*S*,3*S*,4*S*,5*R*,6*R*)-2-Azido-3,4:5,6-diepoxycyclohexan-1-ol [(-)-8]. To a solution of epoxide **7** (1.3 g, 5.3 mmol) in THF (20 mL) at 0 ºC was added dropwise a solution of 86% KOH (0.37 g, 5.5 mmol) in 5 mL of methanol. The solution was stirred at 0 ºC for 1.5 h and then poured into saturated NH_4Cl solution (25 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 _ 20 mL). The combined organics were dried with $MgSO_4$, concentrated in vacuo and purified by flash chromatography (1:1 hexanes:ethyl acetate) to provide diepoxide **8** (0.764 g, 89%) as a white solid: mp 119-121 °C; $[\alpha]^{24}_D$ -12.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, acetone-d_6) δ 5.15 (d, *J* = 6.0 Hz, 1H), 3.90 (d, *J* = 9.6 Hz, 1H), 3.75 (ddd, *J* = 9.6, 6.0, 1.6 Hz, 1H), 3.49 (dd, *J* = 4.0, 2.2 Hz, 1H), 3.41 (dd, *J* = 4.0, 2.2 Hz, 1H), 3.29 (d, *J* = 4.0 Hz, 1H), 2.99 (dd, *J* = 4.0, 1.6 Hz, 1H); ^{13}C NMR

(100 MHz, acetone-d_6) δ 70.3, 64.6, 56.1, 55.7, 49.5, 48.5; MS (CI) *m/z* 170 (M+H); HRMS (EI) calcd for $C_6H_7O_3$ (M-N_3) 127.0395, found 127.0399.

(1*S*,2*S*,3*S*,4*S*,5*R*,6*R*)-2-Acetamido-3,4,5,6-diepoxycyclohexan-1-ol [(-)-10]. 

A mixture of diepoxide **8** (710 mg, 4.2 mmol) and palladium, sulfided, on carbon (71 mg) in dry THF (20 mL) was stirred under an atmosphere of H_2 for 43 h. Methanol (20 mL) was added to dissolve the precipitate and the mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo to provide amine **9** (597 mg, 99%) as a light tan solid. Since the amine **9** is highly polar, the crude was used in the next step without further purification. ^{1}H NMR (500 MHz, CD_3OD) δ 3.56 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.44 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.42 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.18 (dd, *J* = 4.0, 2.0 Hz, 1H), 3.08 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.00 (dd, *J* = 4.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 71.3 (CH), 56.3 (CH), 55.6 (CH), 53.6 (CH), 50.2 (CH), 49.4 (CH); MS (CI) *m/z* 144 (M+H); HRMS (EI) calcd for $C_6H_{10}NO_3$ (M+H) 144.0661, found 144.0660.

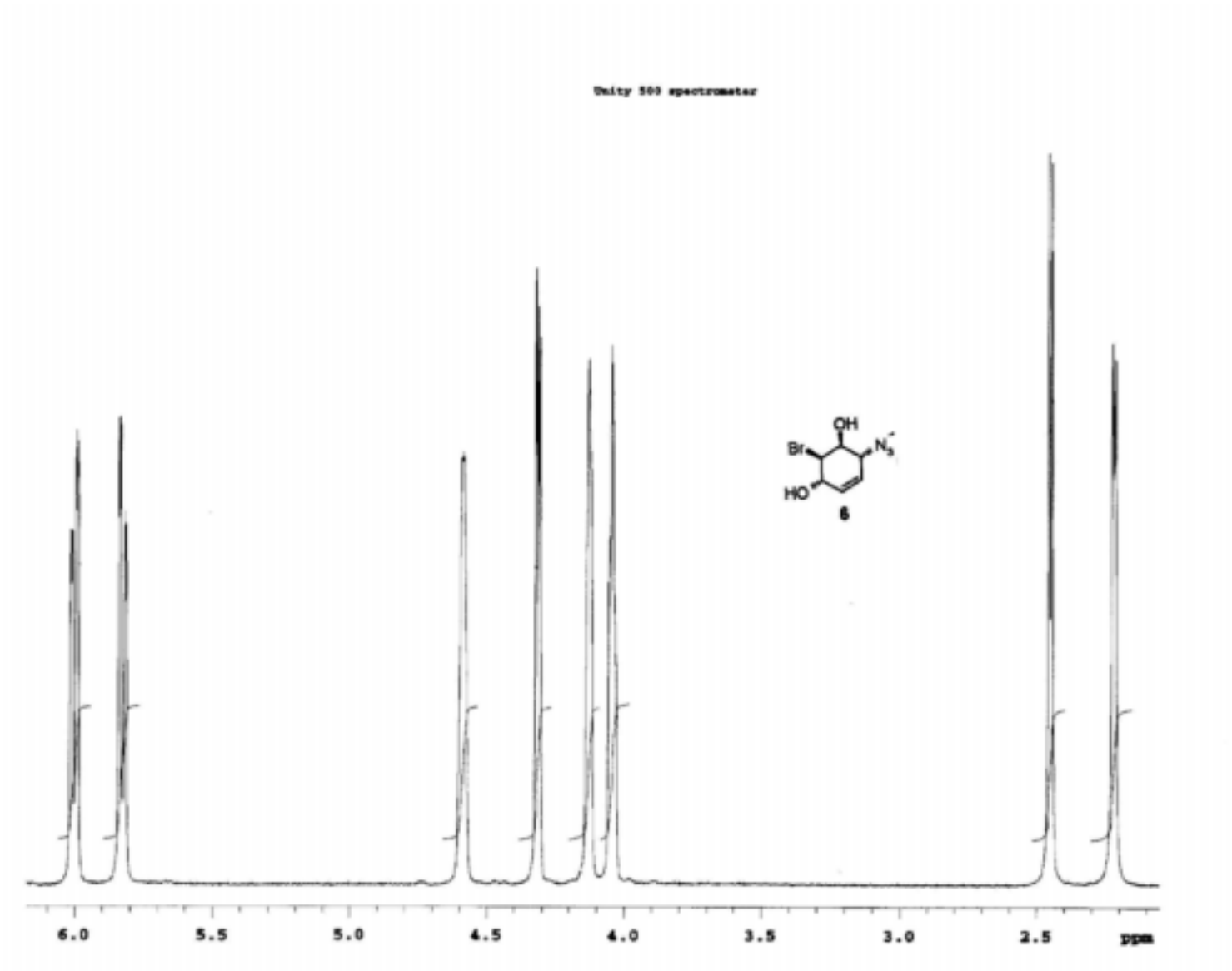
To a solution of amine **9** (100 mg, 0.70 mmol) in methanol (5 mL) at 0 ºC was added dropwise triethyl amine (120 μL, 0.86 mmol) and acetic anhydride (80 μL, 0.85 mmol). The solution was stirred at 0 ºC for 15 min and then concentrated in vacuo. The brown oil was purified by flash chromatography (1:1 dichloromethane:acetone) to provide acetamide **10** (110 mg, 85%) as a white solid: mp 159-160 °C; $[\alpha]^{22}_D$ -97 (*c* 0.7, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 4.26 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.69 (dd, *J* = 8.6, 1.5 Hz, 1H), 3.47 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.45 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.19 (dd, *J* = 4.0, 2.0 Hz, 1H), 3.04 (dd, *J* = 4.0, 1.5 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 173.8, 68.7 (CH), 55.5 (CH), 52.0 (CH), 50.0 (CH), 49.5 (CH), 22.7 (CH_3); MS (CI) *m/z* 186 (M+H); HRMS (EI) calcd for $C_8H_{12}NO_4$ (M+H) 186.0766, found 186.0771.

(-)-LL-C10037α (1). 

To a solution of acetamide **10** (110 mg, 0.59 mmol) in dry acetonitrile (10 mL) was added ca. 90% Dess-Martin periodinane (280 mg, 0.59 mmol). The solution was stirred for 30 min and filtered through a pad of Celite. The filtrate was concentrated with added Celite and then charged to a silica gel column and purified by flash chromatography (5:1 dichloromethane:acetone) to provide (-)-LL-C10037α (**1**) (95 mg, 87%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.21 (dd, *J* = 2.8, 2.4 Hz, 1H), 4.82 (dd, *J* = 2.8, 2.8 Hz, 1H), 3.80 (ddd, *J* = 4.1, 2.8, 2.4 Hz, 1H), 3.51 (d, *J* = 4.1 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 50 ºC) δ 189.3, 169.1, 128.2, 128.1 (CH), 63.2 (CH), 53.5 (CH), 51.9 (CH), 23.4 (CH_3); HRMS (EI) calcd for $C_8H_9NO_4$ 183.0532, found 183.0532.

A portion was recrystallized from methanol for comparison to the natural product: mp 149-151 °C; $[\alpha]^{22}_D$ -201 (*c* 0.34, MeOH) [lit.[1] mp 153 ºC; lit.[2] $[\alpha]^{20}_D$ -202 (*c* 0.334, MeOH).

(1) Lee, M. D.; Fantini, A. A.; Morton, G. O.; James, J. C.; Borders, D. B.; Testa, R. T. *J. Antibiot.* **1984**, *37*, 1149-1152.
(2) Shen, B.; Whittle, Y. G.; Gould, S. J.; Keszler, D. A. *J. Org. Chem.* **1990**, *55*, 4422-4426.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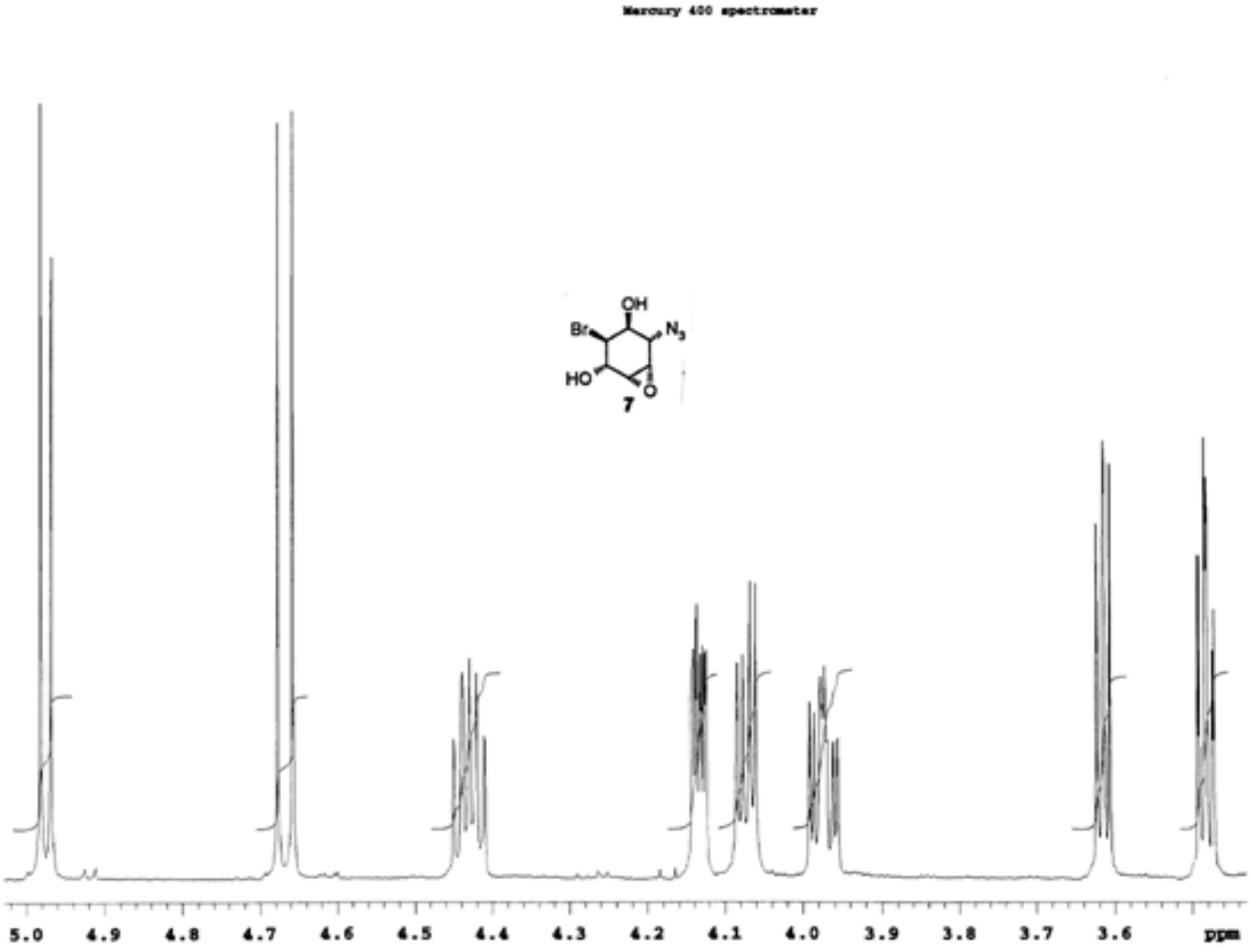
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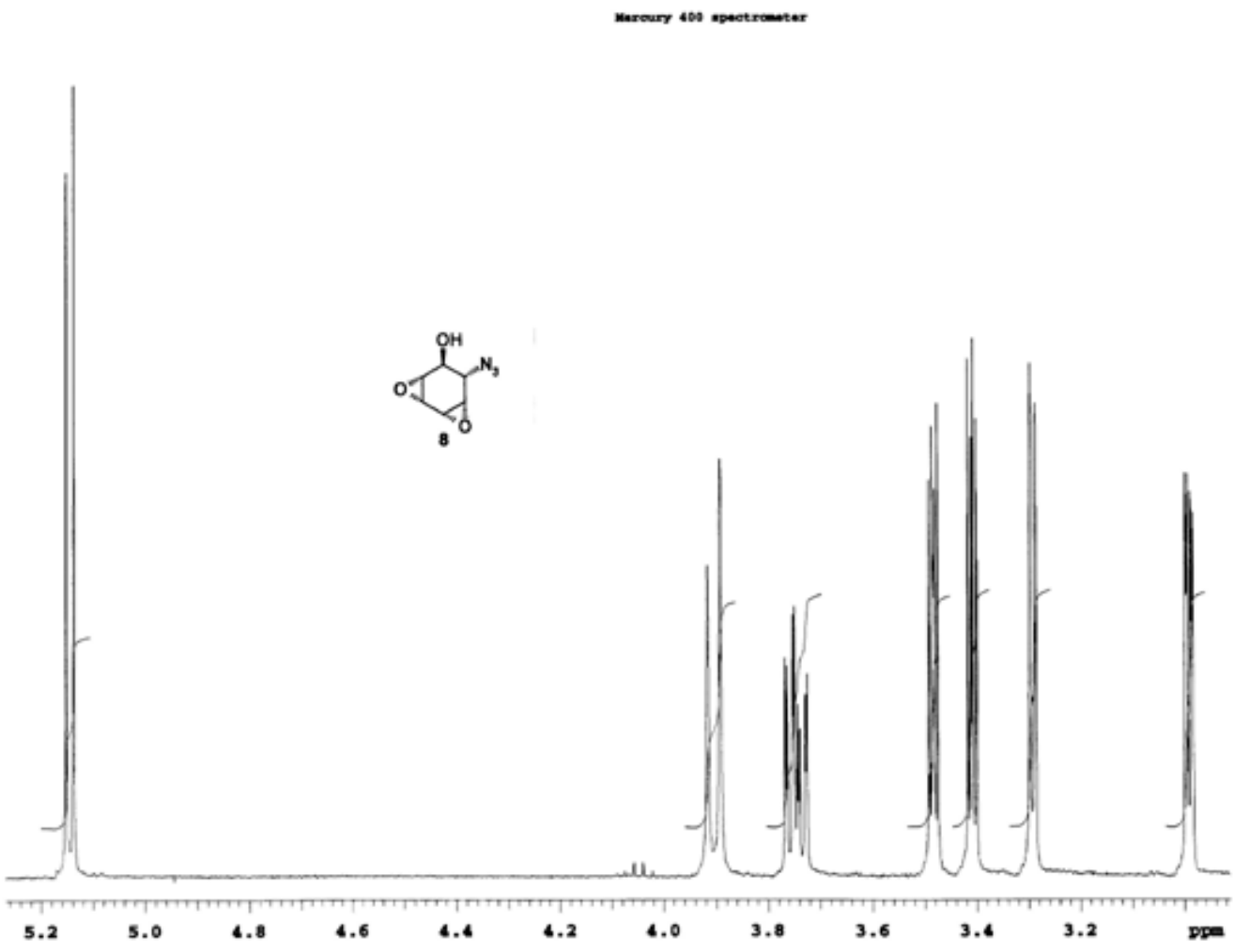
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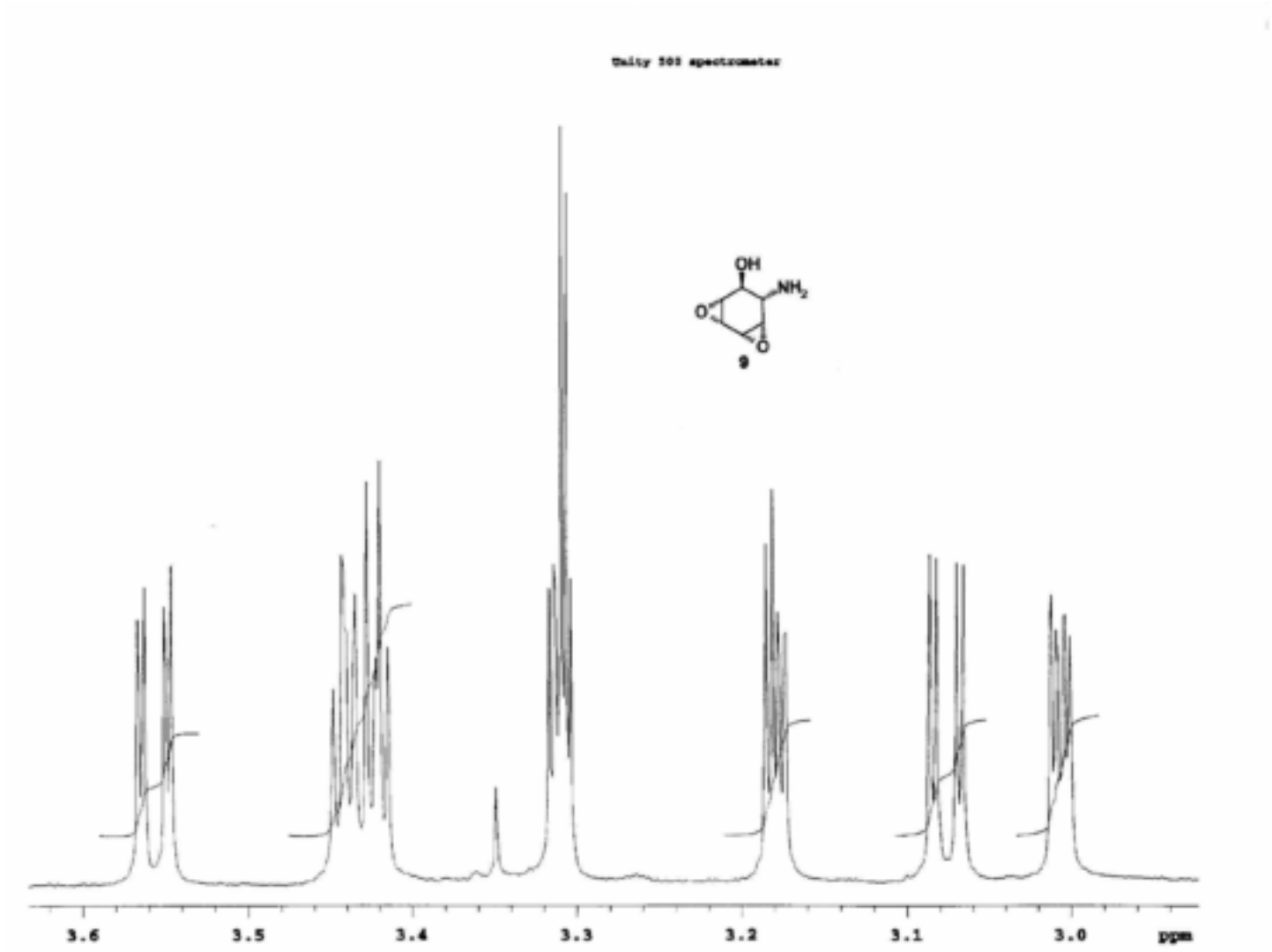
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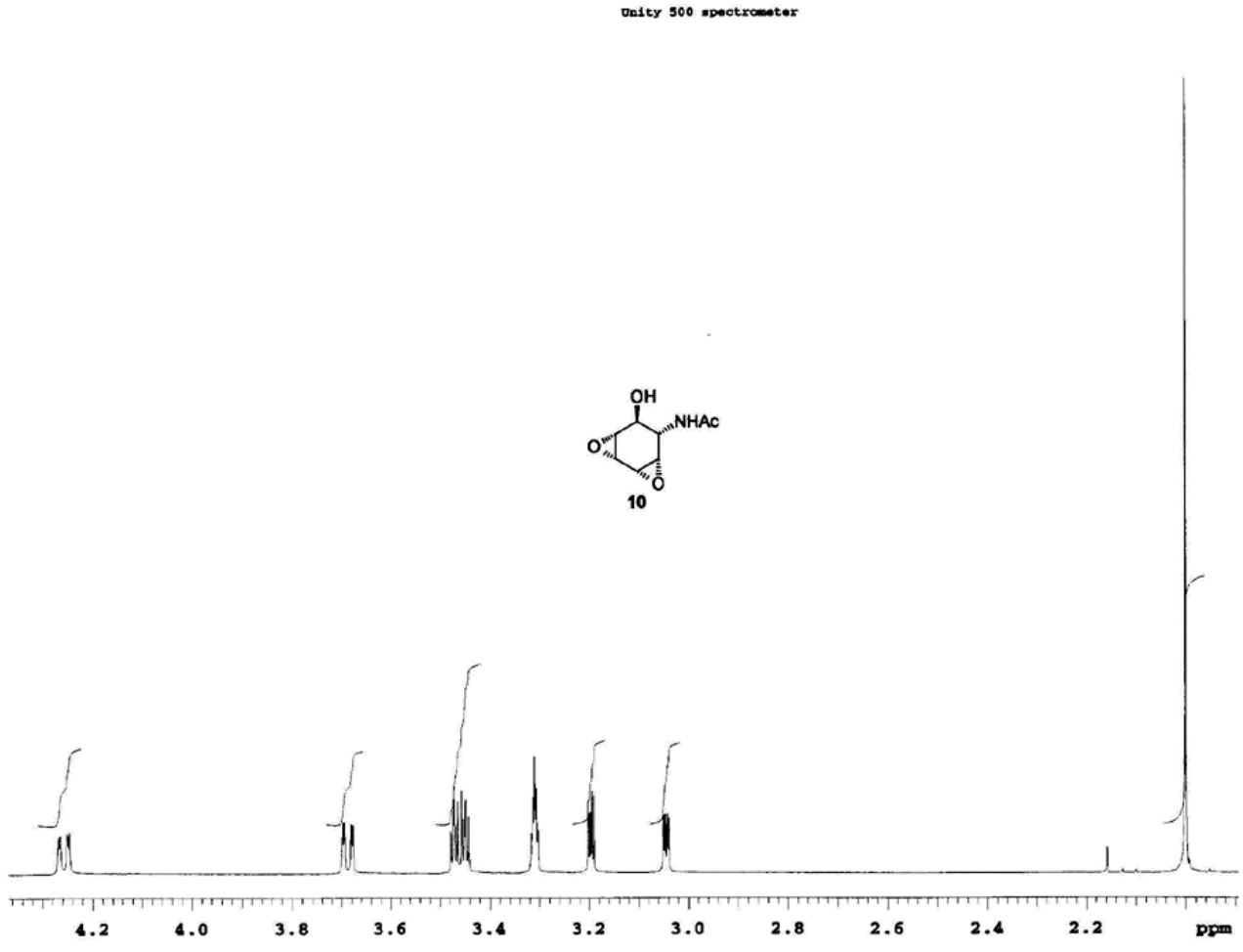
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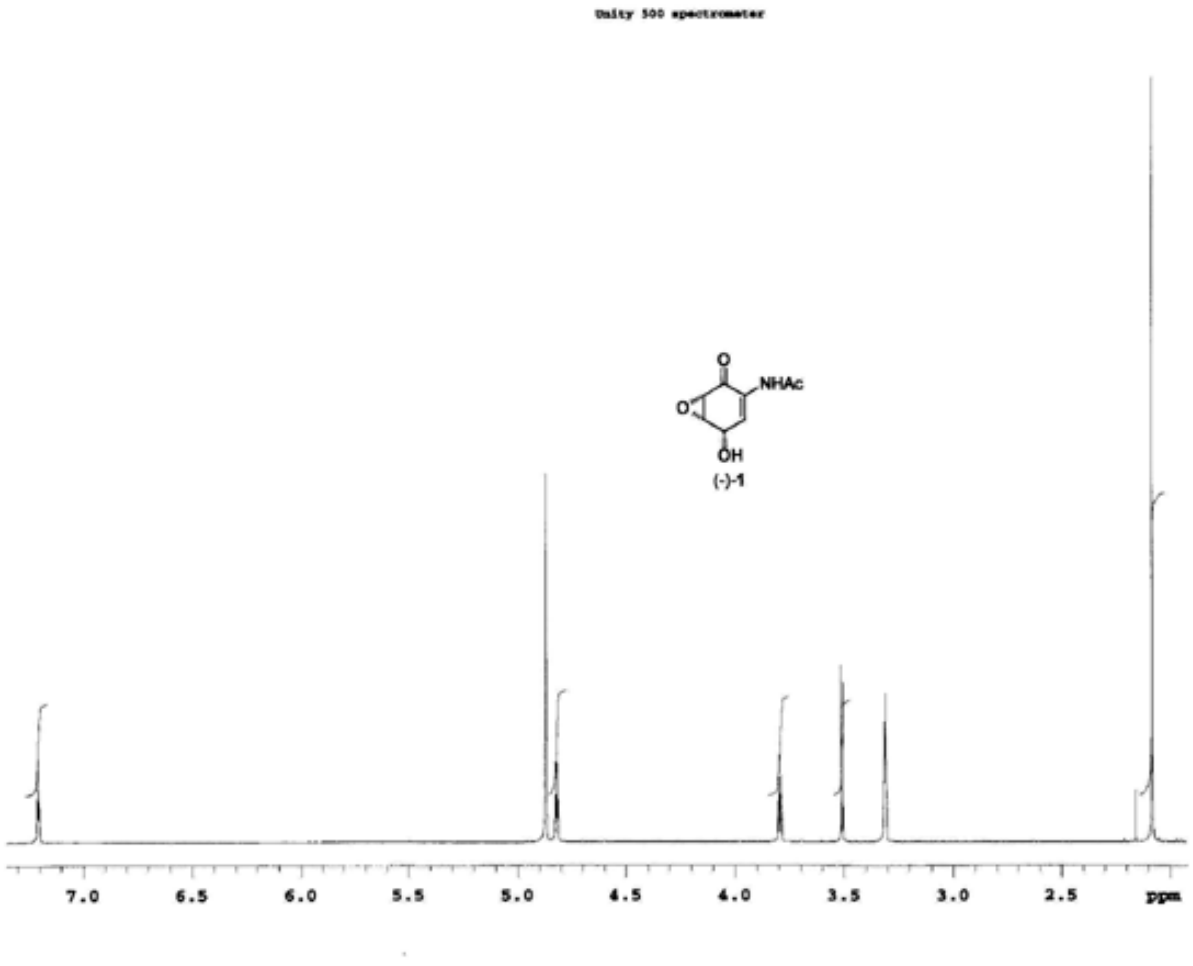
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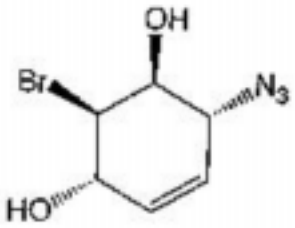
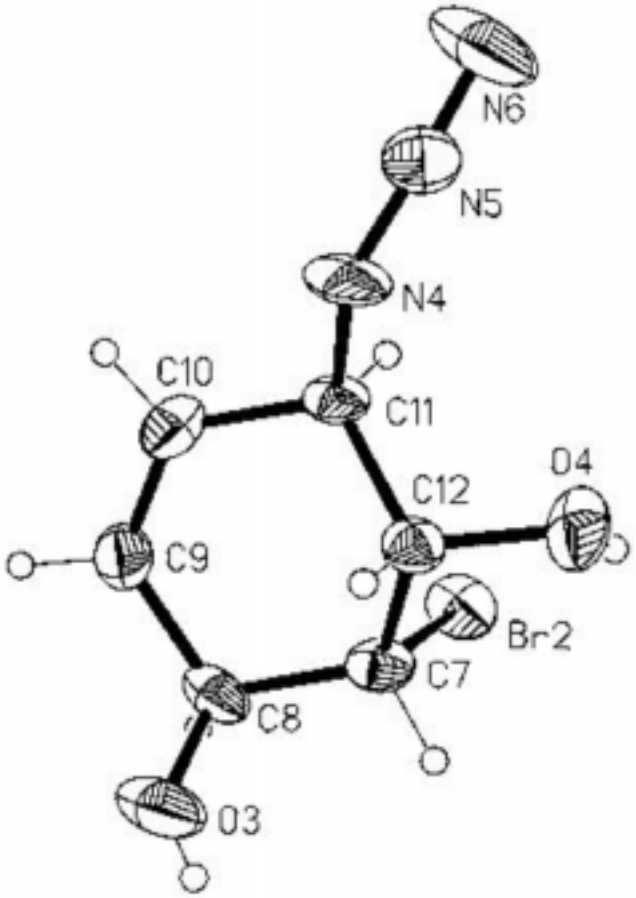
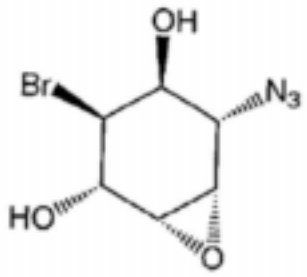


(±)-6





(±)-**7**