New Nucleophiles for Palladium-Catalyzed Asymmetric Allylic Alkylation. Total Synthesis of Agelastatin A

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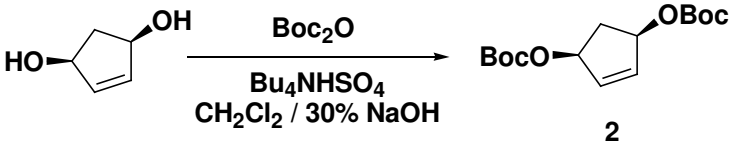
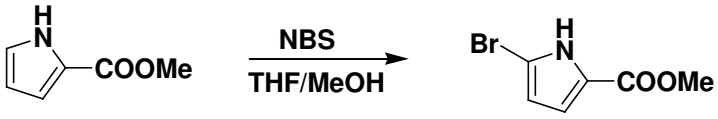
Supporting Information



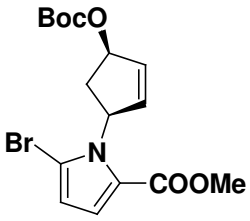
2

Compound 2: A 30% aqueous NaOH solution (8 ml) was added to a solution of cyclopent-4-ene-1,3-diol (1 g, 10 mmol), Boc_2O (5.45 g, 25 mmol) and $(n\text{-}Bu)_4NHSO_4$ (340 mg, 1 mmol) at 0 °C. After stirring vigorously for 12 hr, 1.5 g Boc_2O and 3 ml 30% aqueous NaOH were added at rt, then stirring continued for another 12 hr. Brine (20 ml) was added and the mixture was diluted with CH_2Cl_2. The organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the product was purified by silica gel flash column chromatography (petroleum ether / diethyl ether = 25/1, then 10/1). A white solid was obtained (2.4 g, 80%): mp: 59-60 °C; R_f: 3/7 (petroleum ether / ethyl acetate = 20/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.11 (s, 2H), 6.38 (dd, J = 7.5, 4.0 Hz, 2H), 2.94-2.88 (m, 1H), 1.87 (dt, J = 15, 4.0 Hz, 1H), 1.47 (s, 18H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 153.0,134.5, 82.2, 78.8, 37.0, 27.7; IR (film): 2981, 1738, 1459, 1395, 1370, 1339, 1272, 1253, 1159, 1087, 850 cm^{-1}; ESI ($C_{15}H_{24}O_6$): 323.2 $[M+Na]^+$.



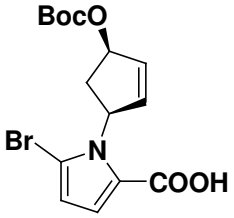
3

Compound 3: NBS (recrystallized, 0.49 g) was added to a solution of pyrrole-2-carboxylate methyl ester in THF (160 ml) and MeOH (80 ml) at 0 °C. After the solution was stirred at 0 °C for 30 min, a second portion of NBS (recrystallized, 0.63 g) was added and after 40 min, a third portion of NBS (recrystallized, 0.51 g) was added. After stirring for 2 hr, the solvent was removed under vacuum. Compound **3** was purified via silica gel flash column chromatography (petroleum ether / diethyl ether = 20/1, then 8/1) to give a white floppy solid (1.6 g, 50%): mp: 101-103 °C; R_f: 0.35 (petroleum ether / ether = 4/1); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.1 (br s, 1H), 6.82 (dd, J = 3.0, 3.5 Hz, 1H), 6.21 (dd, J = 3.0, 3.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.8, 123.7, 116.8, 112.7, 105.2, 51.8; IR (film): 3250, 2924, 2853, 1702, 1552, 1449, 1415, 1389, 1327, 1207 cm^{-1}; HRMS ($C_6H_6NO_2Br$): Calc'd. 202.958190 (M^+), Found 202.958096.



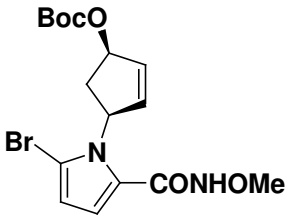
5

Compound 5: (eg. Table 1, entry 5) A solution of $[Pd(C_3H_5)Cl]_2$ (18.3 mg, 0.05 mmol) and (*R*,*R*)-**4** (103.5 mg, 0.15 mmol) in 15 ml degassed CH_2Cl_2, which had been stirring at rt for 10 min, was added to a mixture of compound **2** (750 mg, 2.5 mmol), compound **3** (512.5 mg, 2.5 mmol) and Cs_2CO_3 (815 mg, 2.5 mmol) under Ar. The mixture was stirred at rt for 2 to 3 hr, then filtered through a celite cake. After removing the solvent under vacuum, compound **5** was purified via silica gel flash column chromatography (petroleum ether / diethyl ether = 25/1) to give a light yellow oil (846 mg, 88%, 87% ee by HPLC OD column, 98:2 heptane: *i*-propanol, 1 ml/min). R_f: 0.5 (petroleum ether / ethyl acetate = 8/1); $[\alpha]^{22}_D$: -2.64 (CH_2Cl_2, c 0.94); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (d, *J* = 4.0 Hz, 1H), 6.58-6.54 (m, 1H), 6.19 (d, *J* = 4.0Hz, 1H), 6.11 (ddd, *J* = 2.0, 2.0, 5.5 Hz, 1H), 6.01 (ddd, *J* = 2.0, 2.5, 5.5 Hz, 1H), 5.57-5.54 (m, 1H), 3.80 (s, 3H), 3.10 (ddd, *J* = 8.0, 8.0 13.5 Hz, 1H), 2.29 (ddd, *J* = 6.5, 8.0, 13.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 153.1, 135.7, 130.8, 123.8, 119.1, 113.5, 109.7, 82.3, 79.7, 60.2, 51.3, 38.2, 27.8; IR (film):2981, 1736, 1708, 1522, 1441, 1410, 1369, 1339, 1275, 1255, 1224, 1156, 1131, 1094 cm^{-1}; HRMS ($C_{16}H_{20}NO_5Br$): Calc'd. 385.052484 (M^+), Found 385.051845.



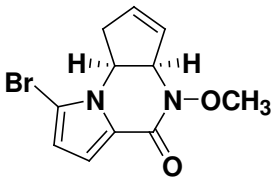
16

Compound 16: A solution of LiOH (1N, 4.7 ml) was added to a solution of compound **5** (605 mg, 1.57 mmol) in THF (15 ml) and H_2O (0.3 ml). The solution was stirred at rt for 48 hrs. The THF was removed under vacuum, and the aqueous phase was diluted with water and acidified to pH = 1-2 by aqueous HCl (3 N). Preformed white precipitate was collected and washed with 2 ml water twice, then dried under high vacuum. Compound **16** was obtained as a white powder (500 mg, 86%): mp: 119-121 ^oC; R_f: 0.5 (DCM / MeOH = 8/1); $[\alpha]_D$: +19.31 (CH_2Cl_2, c 0.72); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.11 (d, *J* = 4.4 Hz, 1H), 6.54 (td, *J* = 8.0, 2.0 Hz, 1H), 6.24 (d, *J* = 4.4 Hz, 1H), 6.14-6.12 (m, 1H), 6.04-6.01 (m, 1H), 5.57 (td, *J* = 1.6, 8.0 Hz, 1H), 3.17-3.10 (m, 1H), 2.33-2.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6, 153.2, 135.5, 131.0, 122.9, 121.2, 114.1, 111.3, 82.3, 79.6, 60.4, 38.2, 27.8; IR (film): 3200, 2981, 2926, 1736, 1670, 1523, 1448, 1403, 1276, 1254, 1162 cm^{-1}; HRMS ($C_{15}H_{18}NO_5Br$): Calc'd. 371.036834 (M^+), Found 371.036488.



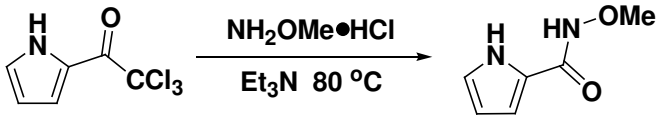
6

Compound 6: To a solution of compound **16** (100 mg, 0.27 mmol) in THF (2.7 ml), $(COCl)_2$ (36.8 mg, 0.29 mmol) and one drop of DMF were added. The resulting solution named A was then stirred for 1 hr at rt. In another separate operation, water (0.3 ml) was added to a mixture of $NH_2OMe•HCl$ (225.5 mg, 2.7 mmol) and K_2CO_3 (372.6 mg, 2.7 mmol). The resulting mixture was stirred at rt for 0.5 hr, before it was added to the above solution A. The resulting solution was stirred for 12 hr at rt and then extracted with ethyl acetate (10 ml) three times. The combined the organic phase was washed once with brine (10 ml) and then dried over $MgSO_4$. Compound **6** was purified by silica gel flash column chromatography (CH_2Cl_2, then CH_2Cl_2 / MeOH = 40/1) to give a yellow solid (87.7 mg, 85%): mp: 58-60 ^oC; R_f: 0.6 (CH_2Cl_2 / MeOH = 9/1); $[\alpha]_D$: +1.55 (CH_2Cl_2, c 0.74); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.47 (br, 1H) 6.50 (d, J = 4 Hz, 1H), 6.22-6.25 (m, 1H), 6.13 (d, J = 4 Hz, 1H), 6.11 (dt, J = 6, 2 Hz, 1H), 6.00 (dt, J = 6, 2 Hz, 1H), 5.49-5.23 (m, 1H), 3.81 (s, 3H), 3.14-3.08 (ddd, J = 13.5, 7.5 Hz, 1H), 2.30-2.25 (ddd, J = 13.5, 7.5, 6.5 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.9, 153.1, 135.5, 131.2, 124.7, 113.7, 112.8, 108.4, 82.3, 79.6, 64.4, 60.5, 38.2, 27.8; IR (film): 3244, 2979, 2933, 1738, 1651, 1530, 1416, 1340, 1277, 1161, 1096, 1055 cm^{-1}; HRMS ($C_{16}H_{21}N_2O_5Br$): Calc'd. 409.063383 (M^+), Found 400.064848.



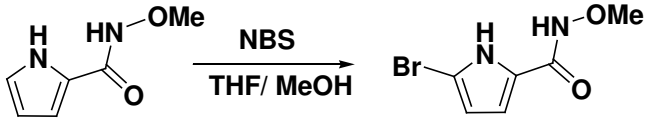
7

Compound 7: A solution of $Pd_2(dba)_3CHCl_3$ (2.29 mg, 0.00025 mmol) and (*R*,*R*)-**4** (5.18 mg, 0.00075 mmol) in CH_2Cl_2 (1 ml), which had been stirred at rt for 10 min, was added to a mixture of compound **6** (20 mg, 0.05 mmol) and Cs_2CO_3 (16.3 mg, 0.05 mmol) under Ar. The mixture was stirred at rt for 12 hr, then filtered through a celite cake. After removing the solvent under vacuum, compound **7** was purified via silica gel flash column chromatography (petroleum ether / ether = 8/1, then CH_2Cl_2 / MeOH = 40/1) to give a white solid (12.9 mg, 91.5%): mp: 107-109 ^oC; R_f: 0.6 (CH_2Cl_2 / MeOH = 9/1); $[\alpha]_D$: +164.7 (CH_2Cl_2, c 0.34); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.94 (dd, J = 1, 4 Hz, 1H), 6.30 (dd, J = 1, 4 Hz, 1H), 6.22-6.20 (m, 1H), 6.13-6.12 (m, 1H), 4.84-4.79 (m, 2H), 3.85 (s, 3H), 3.13-3.07 (m, 1H), 2.63-2-58 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.3, 135.5, 128.6, 123.7, 116.1, 106.8, 101.6, 64.1, 64.0, 57.2, 38.2; IR (film): 2927, 2853, 1668, 1545, 1418, 1358, 1334, 1310, 1027 cm^{-1}: HRMS ($C_{11}H_{11}N_2O_2Br$): Calc'd 282.000389 (M^+), Found 281.999714.



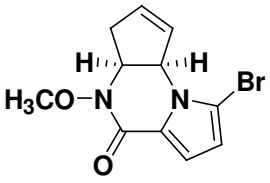
17

Compound 17: 2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)-ethanone (1.08 g, 5 mmol), NH_2OMe•HCl (625 mg, 7.5 mmol) and Et_3N (2.1 ml) were sealed in a tube. After the mixture was stirred at 80 °C overnight, Et_3N was removed under vacuum. The residue was then diluted with CH_2Cl_2. Compound **17** was purified by silica gel flash column chromatography (petroleum ether / ethyl acetate = 3/2, then 1/1) to give an off-white solid (687.5 mg, 98%): mp: 96-98 °C; R_f: 0.25 (petroleum ether / ethyl acetate = 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.28 (br, 1H), 9.90 (br, 1H), 6.93 (s, 1H), 6.82 (s, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4, 122.9, 122.4, 112.2, 110.0, 64.7; IR (film): 3240 (br), 2980, 1628, 1554, 1507, 1439, 1405, 1330, 1096, 1047cm^{-1}; HRMS ($C_6H_8N_2O_2$): Calc'd. 140.058578 (M^+), Found 140.058374.



17 **8**

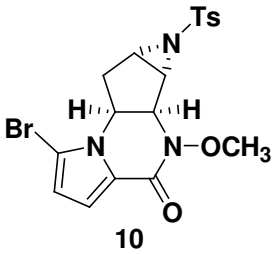
Compound 8: NBS (225 mg, 1.26 mmol) was added to a solution of compound **17** (446 mg, 3.19 mmol) in THF (35 ml) and MeOH (17 ml) at 0 °C. After the mixture was stirred for 30 min, another portion of NBS (314 mg, 1.76 mmol) was added. The resulting solution was allowed to warm to room temperature and stirred overnight. After removal of the solvent, compound **8** was purified by silica gel flash column chromatography (petroleum ether / ethyl acetate = 7/3, then 3/2) to give an off-white solid (662 mg, 95%): mp: 125-126 °C; R_f: 0.3 (petroleum ether / ethyl acetate = 1/1); ^{1}H NMR (CD_3OD, 400 MHz) δ 6.64 (d, *J* = 4.0 Hz, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 161.4, 125.5, 113.3, 112.5, 105.2, 64.6; IR (film): 3207 (br), 3002, 1622, 1553, 1505, 1411, 1327, 1046 cm^{-1}; HRMS ($C_6H_7N_2O_2Br$): Calc'd. 217.969089 (M^+), Found 217.969212.



9

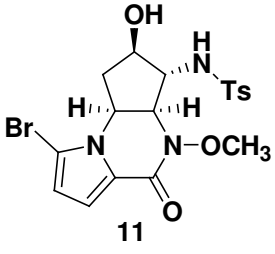
Compound 9: (eg. Table 2, entry 9) A solution of $Pd_2(dba)_3CHCl_3$ (5.2 mg, 0.005 mmol) and (*R*,*R*)-**4** (10.4 mg, 0.015 mmol) in degassed CH_2Cl_2 (0.5 ml), which had been stirring at 0 °C for 10 min, was added to a mixture of compound **8** (21.9 mg, 0.1 mmol), compound **2** (45 mg, 0.15 mmol) and HOAc (10 μl, 1M solution in CH_2Cl_2) under Ar. The mixture was stirred at rt for 3.5 hr, and then a solution of $Pd_2(dba)_3CHCl_3$ (5.2 mg, 0.005 mmol) and *Rac*-**4** (10.4 mg, 0.015 mmol) in degassed CH_2Cl_2 (0.5 ml), which had been stirring at rt for 10 min, was added. The resulting solution was stirred at rt for 3 hr. Compound **9** was purified via silica gel flash column chromatography (petroleum ether / ethyl acetate = 4/1, then 3/1) to give a colorless

solid (23.0 mg, 82%, 97.5% ee by HPLC OD column, 90:10 heptane: *i*-propanol, 0.8 ml/min): mp: 111-113 ^{o}C; R_f : 0.2 (petroleum ether / ethyl acetate = 4/1); $[\alpha]_D$: -120.2 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.91 (d, *J* = 5.0 Hz, 1H), 6.28 (d, *J* = 5.0 Hz, 1H), 6.02 (m, 1H), 5.95 (m , 1H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.65 (ddd, *J* = 8.0, 6.5, 2.5 Hz, 1H), 3.85 (s, 3H), 2.92 (d, *J* = 21.5 Hz, 1H), 2.71 (ddd, *J* = 21.5, 6.5, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 132.0, 129.0, 123.8, 114.7, 113.6, 104.8, 63.0, 61.6, 60.7, 36.4; IR (film): 2925, 2854, 1667, 1545, 1417, 1320, 1028 cm^{-1}; HRMS ($C_{11}H_{11}N_2O_2Br$): Calc'd. 282.000389 (M^+), Found 281.999491.



10

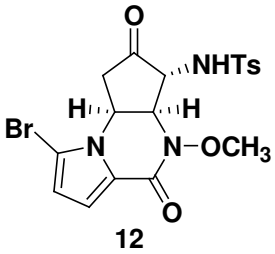
Compound 10: Benzene (1 ml) was added to a mixture of 4 Å molecular sieves (75 mg), compound **5** (20 mg, 0.071 mmol), PhI=NTs (132 mg, 0.355 mmol), and catalyst **14** (17.3 mg, 0.0355 mmol) under N_2. The resulting solution was stirred at rt for 4 hr, then filtered through a silica gel cake, and the cake was rinsed with ethyl acetate. After removing the solvent under vacuum, compound **10** was purified via alumina (neutral, activity 3) flash column chromatography (petroleum ether / ethyl acetate = 8/1, 4/1, then 3/1) to give a colorless foam (16.6 mg, 52%): R_f: 0.5 (petroleum ether / ethyl acetate=3/2); $[\alpha]_D$: +21.8 (c 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (dd, *J* = 1.5, 6.5 Hz, 2H), 7.40 (dd, *J* = 0.5, 8.5 Hz, 2H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.26 (d, *J* = 4.5 Hz, 1H), 4.50-4.44 (m, 2H), 3.97 (s, 3H), 3.88 (d, *J* = 5 Hz, 1H), 3.61 (dd, *J* = 2.5, 5.0 Hz, 1H), 2.77 (dd, *J* = 7.0, 14 Hz, 1H), 2.48 (s, 3H), 1.93 (ddd, *J* = 14.5, 9.0, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.2, 145.5, 134.8, 130.3, 128.2, 122.8, 116.2, 114.1, 106.2, 64.5, 61.3, 53.3, 44.7, 44.1, 32.9, 22.0; IR (film): 2925, 2855, 1682, 1543, 1433, 1416, 1325, 1163 cm^{-1}; HRMS ($C_{18}H_{21}N_3O_4SBr$): Calc'd. 451.020139 (M^+), Found 451.020921.



11

Compound 11: TFA (30 µl) was added to a solution of compound **10** (18 mg, 0.04 mmol) in dioxane (0.9 ml) and water (0.6 ml) under N_2. The resulting solution was heated in a microwave at 150 ^{o}C for 2.5 hr. The residue was diluted with ethyl acetate, washed with saturated $NaHCO_3$, washed with brine, and finally dried over $MgSO_4$. Compound **11** was purified via silica gel flash column chromatography (petroleum ether / ethyl acetate = 4/1, then 1/1) to give a colorless foam: R_f: 0.2 (petroleum ether / ethyl acetate = 1/1); $[\alpha]_D$: +36.2 (c 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, *J* = 8 Hz, 2H), 7.35 (d, *J* = 8 Hz, 2H), 6.91 (d, *J* = 4 Hz, 1H), 6.28 (d, *J* = 4 Hz, 1H), 5.68 (d, *J* = 3.5 Hz, 1H), 4.76-4.71 (m, 1H), 4.33 (dd, *J* = 7.5, 14 Hz, 1H), 4.23

(dd, J = 3.5, 7.0 Hz, 1H), 3.63 (dd, 1H), 3.54 (br, 1H), 2.89-2.84 (m, 1H), 2.44 (s, 3H), 2.10-2.04 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157. 2, 144.5, 135.3, 130.0, 127.4, 122.8, 115.7, 114.1, 105.8, 75.8, 65.7, 64.3, 63.0, 53.3, 38.6, 21.6; IR (film): 3435, 3238, 2828, 1652, 1540, 1415, 1338, 1160, 2093 cm^{-1}; HRMS ($C_{18}H_{20}N_3O_5SBr$): Calc'd. 471.028658 (M^+), Found 471.028806.

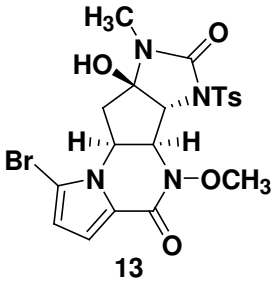


12

Compound 12:

a) From Compound **11**: Dess-Martin periodinane (13.5 mg, 0.032 mmol) was added to a solution of compound **11** (10 mg, 0.0213 mmol) and $NaHCO_3$ (5.4 mg, 0.0639 mmol) in 0.25 ml CH_2Cl_2. The resulting solution was stirred at rt for 30 min before being quenched with sat. aq. $Na_2S_2O_3$. Compound **12** was purified via silica gel flash column chromatography (petroleum ether / ethyl acetate = 3/1, then 3/2) to give a white solid (6-7 mg 70-80%).

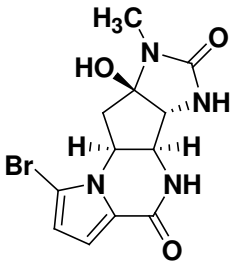
b) From Compound **10**: DMSO (1 ml) was added to a mixture of compound **10** (30 mg, 0,0665 mmol) and $In(OTf)_3$ (26 mg, 0.0462 mmol) at rt under N_2. The resulting solution was heated at 80 ^{o}C for 6 hr, before being diluted with ethyl acetate (30 ml). The solution was washed with brine. The aqueous phases were combined, and extracted with ethyl acetate. Finally, the organic phases were combined and dried over $MgSO_4$. After the solvent was removed under vacuum, compound **12** was purified via silica gel flash column chromatography (petroleum ether / ethyl acetate = 3/1, then 3/2) to give a white solid (28.3 mg, 91%): mp: 100-102 ^{o}C, R_f: 0.3 (petroleum ether / ethyl acetate = 1/1); $[\alpha]_D$: +57.8 (c 0.97, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 4.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 5.63 (d, J = 7.5 Hz, 1H), 5.23-5.18 (m, 1H), 5.00 (d, J = 2.5 Hz, 1H), 4.98 (d, J = 5.5 Hz, 1H), 4.00 (br, 1H), 3.84 (s, 3H), 3.02 (dd, J = 7.5, 18 Hz, 1H), 2.68 (dd, J = 11, 18 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) TBD; IR (film): 3252, 2924, 2854, 1768, 1652, 1548, 1416, 1338, 1162, 1093, 1025 cm^{-1}; HRMS ($C_{18}H_{18}N_3O_5SBr$): Calc'd. 469.013008 (M^+), Found 469.013016.



13

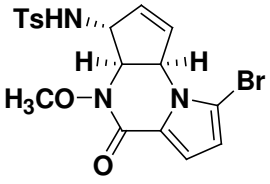
Compound 13: To a mixture of compound **12** (15 mg, 0.034 mmol) and Cs_2CO_3 (2.2 mg, 0.0068 mmol) in CH_2Cl_2 (0.5 ml) was added a solution of CH_3NCO (2.3

mg, in 0.85 ml benzene) during a period of 2 hr at room temperature. The resulting solution was stirred for another 2 hr before being quenched with KH_2PO_4 (5 ml, 1.0 M). The mixture was extracted with 5 ml $CHCl_3$ twice and then extracted with 5 ml ethyl acetate twice. The organic phases were combined, and dried over $MgSO_4$. Compound **13** was purified via silica gel column chromatography (petroleum ether / ethyl acetate = 4/1, then 2/3, then 1/1) to give a foam-like colorless solid (9.0 mg, 53%): R_f: 0.4 (petroleum ether / ethyl acetate = 2/3); $[\alpha]_D$: + 9.67 (c 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 4.0 Hz, 1H), 6.29 (d, *J* = 4.0 Hz, 1H), 5.76 (s, 1H), 5.04 (s, 1H), 4.65 (m, 2H), 3.95 (s, 3H), 2.88 (s, 3H), 2.67 (dd, *J* = 7.5, 13 Hz, 1H), 2.43 (s, 3H), 2.32 (dd, *J* = 13, 13 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.6, 152.8, 145.6, 135.3, 130.1, 128.2, 122.6, 116.9, 114.0, 106.3, 91.6, 66.4, 65.5, 62.0, 53.4, 38.9, 25.1, 21.8; IR (film): 3290 (br), 2924, 1743, 1651, 1545, 1414, 1344, 1305, 1175, 1092, 1026 cm^{-1}; HRMS ($C_{20}H_{21}N_4O_6SBr$): Calc'd. 524.036518 (M^+), Found 524.036512.



(+)-Agelastatin A (1)

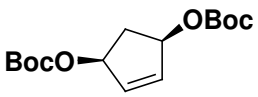
(+)-Agelastatin A (1): Freshly made SmI_2 (1.6 ml, 0.1 M in THF) was added to compound **13** (10.0 mg, 0.019 mmol) under argon at 0 °C. The resulting blue solution was allowed to gradually warm to rt and stirred for 2 hr before another 0.5 ml SmI_2 (0.1 M in THF) was added. After the solution was stirred at rt for 15 min, THF was removed under vacuum. The residue was first purified by silica gel chromatography (10% to 15% MeOH in CH_2Cl_2). A yellow solid was obtained, which was then dissolved in 15% MeOH in CH_2Cl_2 and filtered through charcoal. The (+)-Agelastatin A was further purified by another silica gel chromatography (10% to 15% MeOH in CH_2Cl_2) to give an off-white solid (6.0 mg, 88%): mp: 195 °C (decomposed); R_f: 0.25 (10% MeOH in CH_2Cl_2); $[\alpha]_D$: + 53.2 (c 0.13, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 6.91 (d, *J* = 4.0 Hz, 1H), 6.33 (d, *J* = 4.0 Hz, 1H), 4.60 (m, 1H), 4.09 (d, *J* = 5.5 Hz, 1H), 3.89 (s, 1H), 2.81 (s, 3H), 2.65 (dd, *J* = 6.5, 13 Hz, 1H), 2.10 (dd, *J* = 13, 13 Hz, 1H); ^{13}C NMR (CD_3OD, 150 MHz) δ 161.4, 161.1, 124.1, 116.0, 113.8, 107.2, 95.7, 67.4, 62.2, 54.4, 40.0, 24.2; IR (film): 3346 (br), 2923, 1685, 1644, 1555, 1424, 1380 cm^{-1}; ESI ($C_{12}H_{13}N_4O_3Br$): 341.0 $[M+H]^+$, 363.0 $[M+Na]^+$.



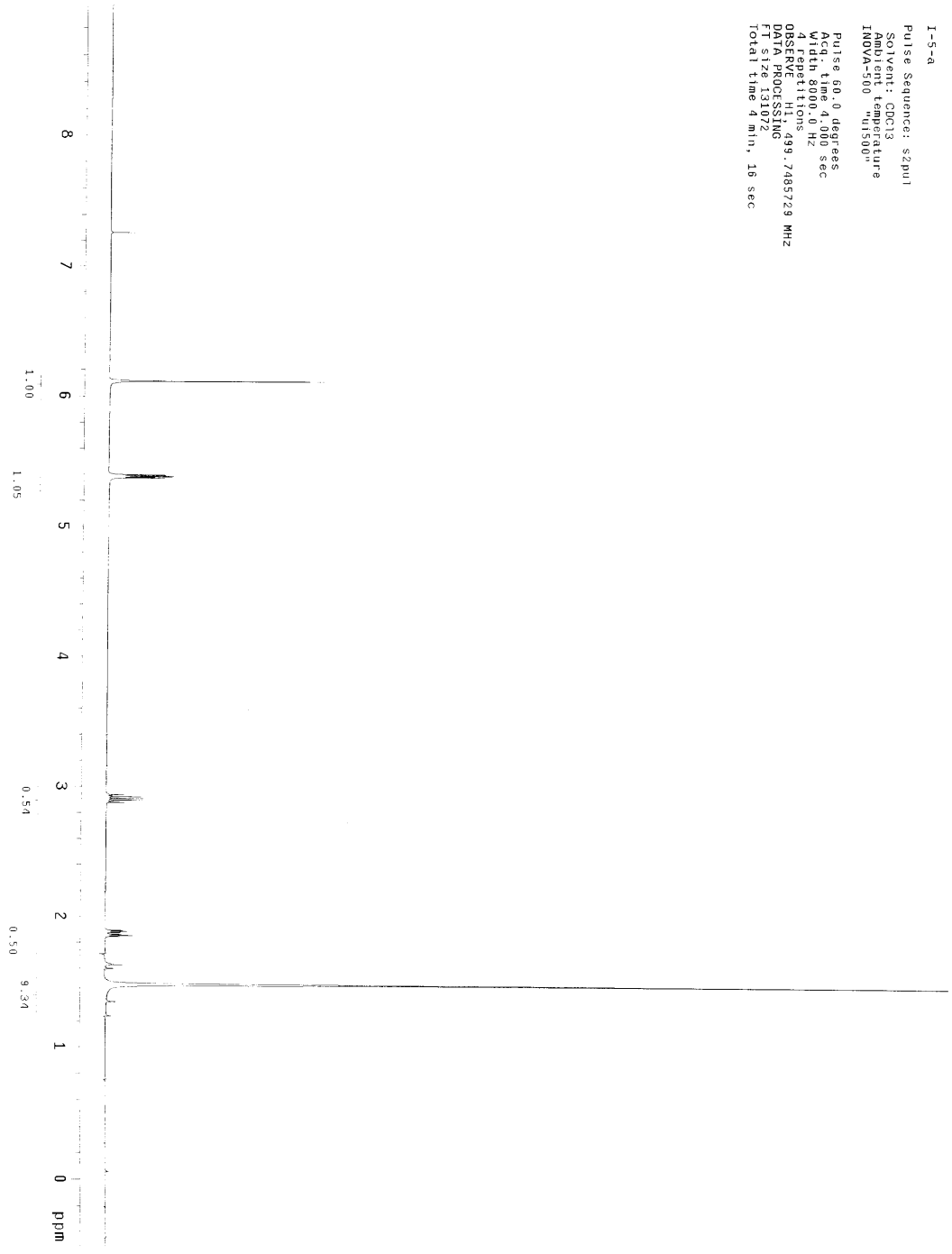
15

Compound 15: A solution of dry pyridine (0.001 ml) in dry benzene (0.01 ml) was added to a solution of *N*-sulfinyl-*p*-toluenesulfonamide (0.11 g) in dry benzene (0.19 ml) at rt. The resulting mixture was stirred at rt for 1 hr, and then it was diluted with 1

ml of toluene. The resulting suspension was added to compound **9** (22 mg) portionwise at rt. The suspension was heated at 100 ^{o}C for 40 hr. The solvents were removed under vacuum. Methanol (1.5 ml) and trimethyl phosphite (0.03 ml, 0.25 mmol) were added to the residue and the mixture was stirred at rt for 1 hr. The solvents were removed under vacuum and the residue was purified via silica gel flash column chromatography (petroleum ether / ethyl acetate = 4/1, then 3/1, then 2/1) to give an off-white foam (15 mg, 43%): $[\alpha]_D$: -111.7 (c 0.90, CH_2Cl_2); R_f : 0.2 (petroleum ether / ethyl acetate = 4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 4.0 Hz, 1H), 6.29 (d, *J* = 4.0 Hz, 1H), 6.02 (d, *J* = 5.5 Hz, 1H), 5.85(m, 1H), 5.55(d, *J* = 6.5 Hz, 1H), 4.91 (d, *J* = 6 Hz, 1H), 4.69 (m, 1H), 4.62 (d, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.4, 144.4, 136.4, 134.5, 130.9, 130.1, 127.4, 123.3, 115.3, 114.0, 105.4, 64.7, 62.3, 62.0, 59.5, 21.7; IR (film): 3189, 2926, 1651, 1548, 1428, 1334, 1161, 1094 cm^{-1}; HRMS ($C_{18}H_{18}N_3O_4SBr$): Calc'd. 451. 020139 (M^+), Found 451.020526.


OBoc
BocO

2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Pulse 60.0 degrees
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4 repetitions
OBSERVE H1, 499.7485729 MHz
DATA PROCESSING
FT size 131072
Total time 4 min, 16 sec
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0.50
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6
5
4
3
2
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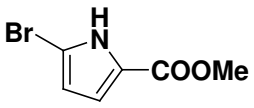
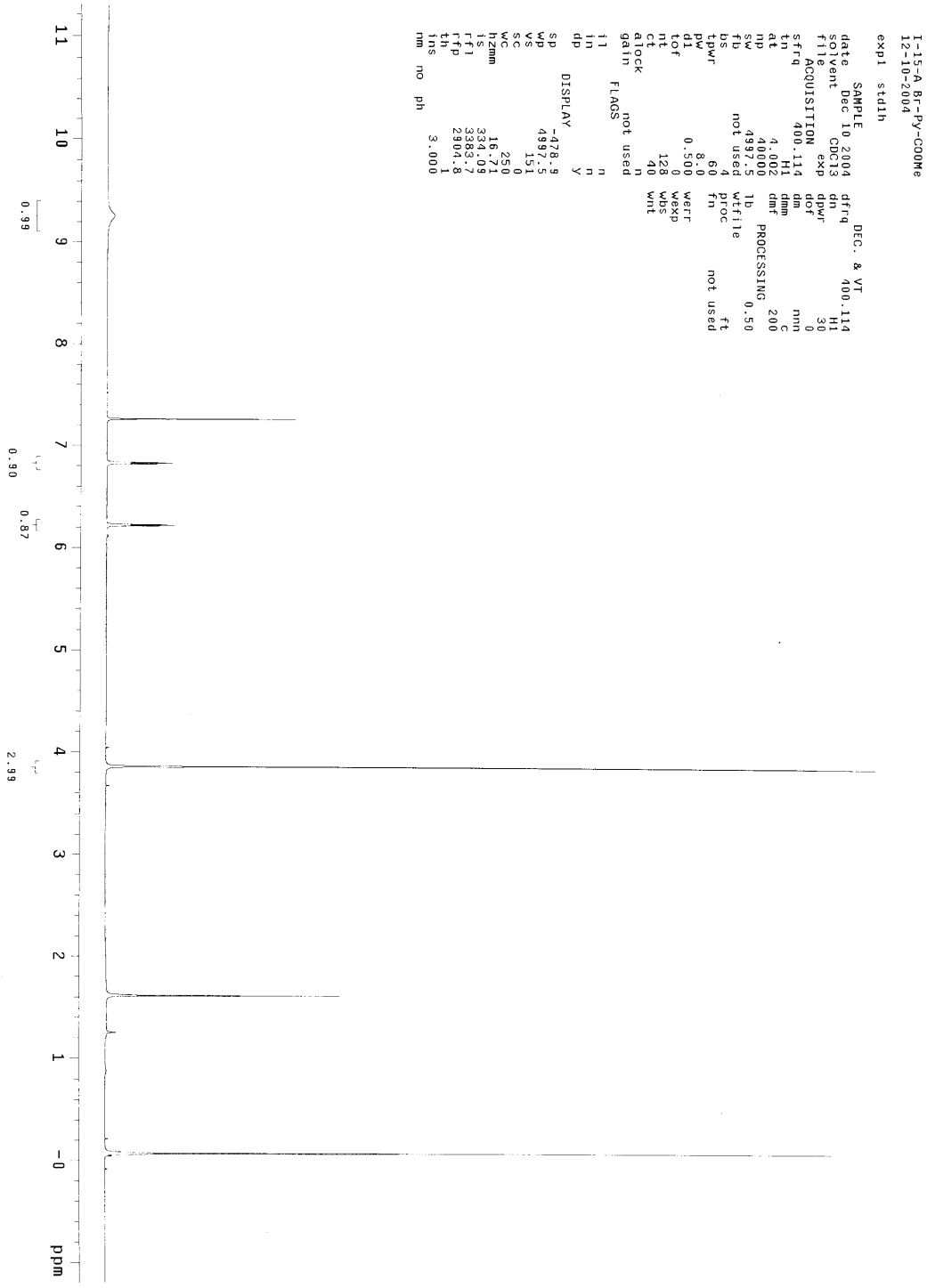
0
ppm


Br
H
N
COOMe

3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gain n
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dp y
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proc ft
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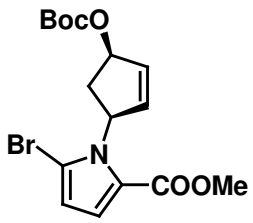
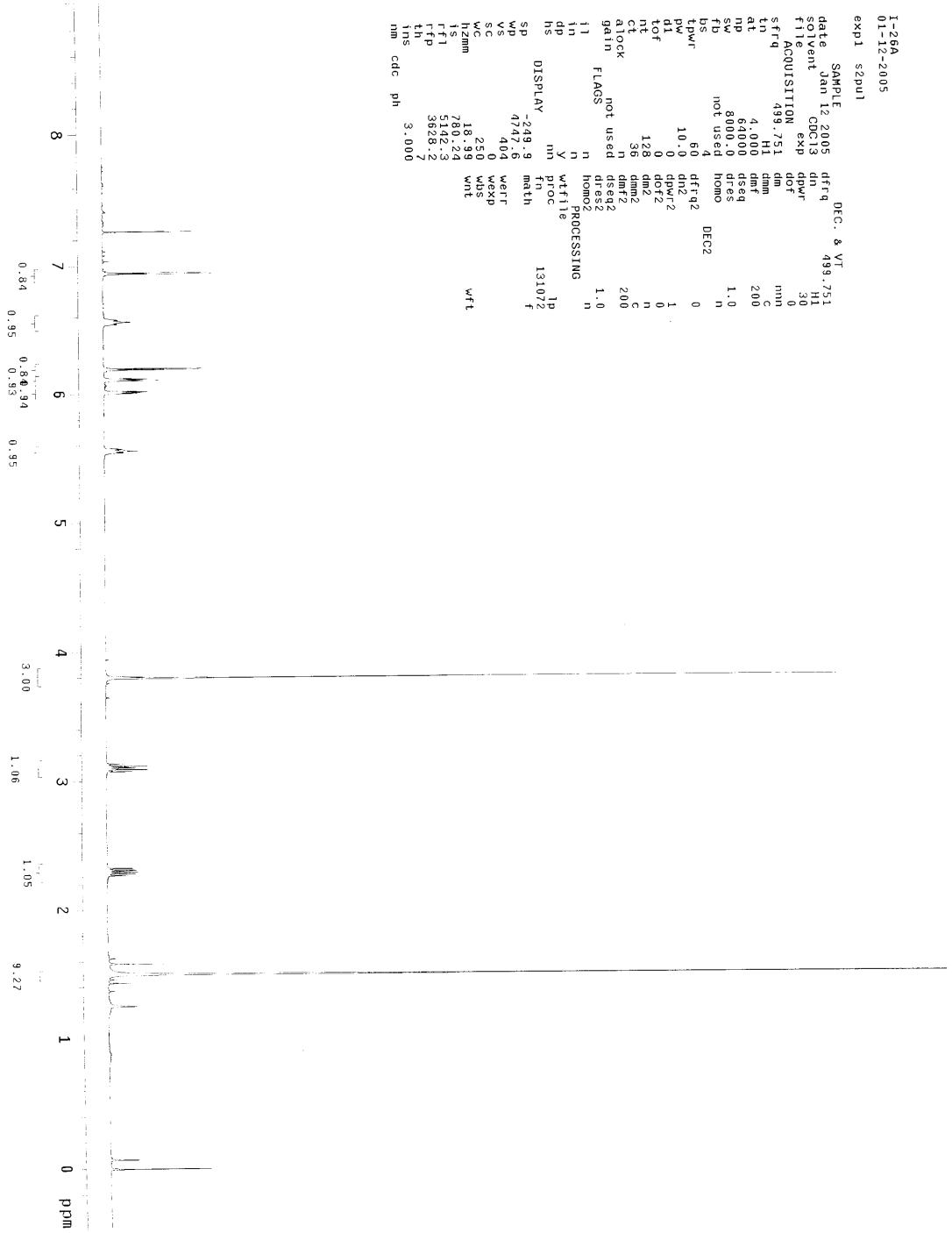

BocO
Br
N
COOMe

5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tof 0
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alock n
gain not used
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homo2 n
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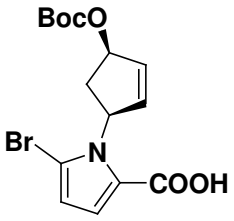
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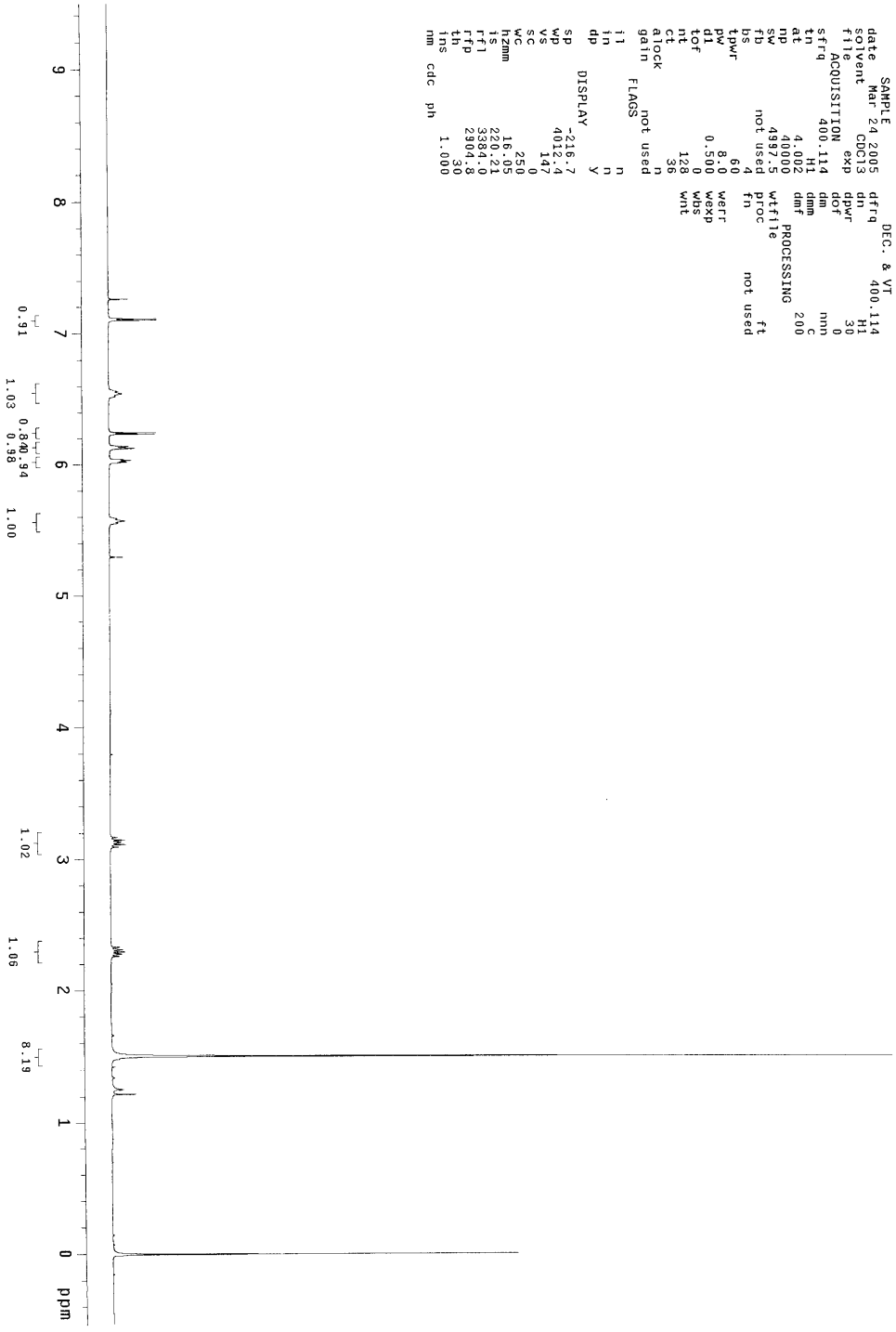
Br
N
COOH

16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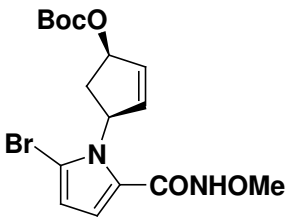
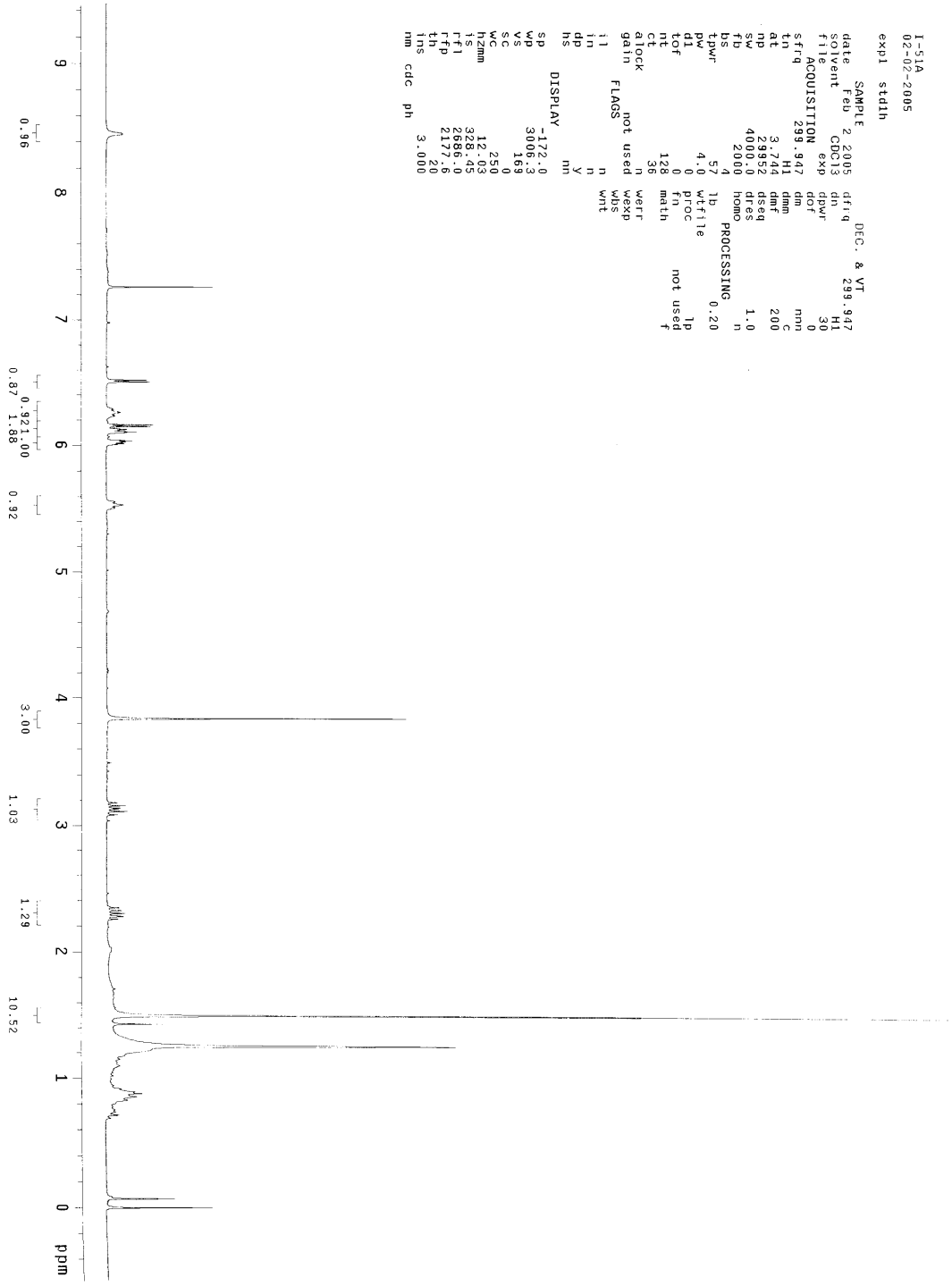

BocO
Br
N
CONHOMe

6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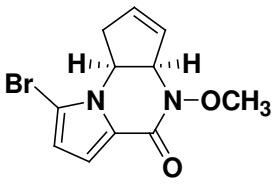
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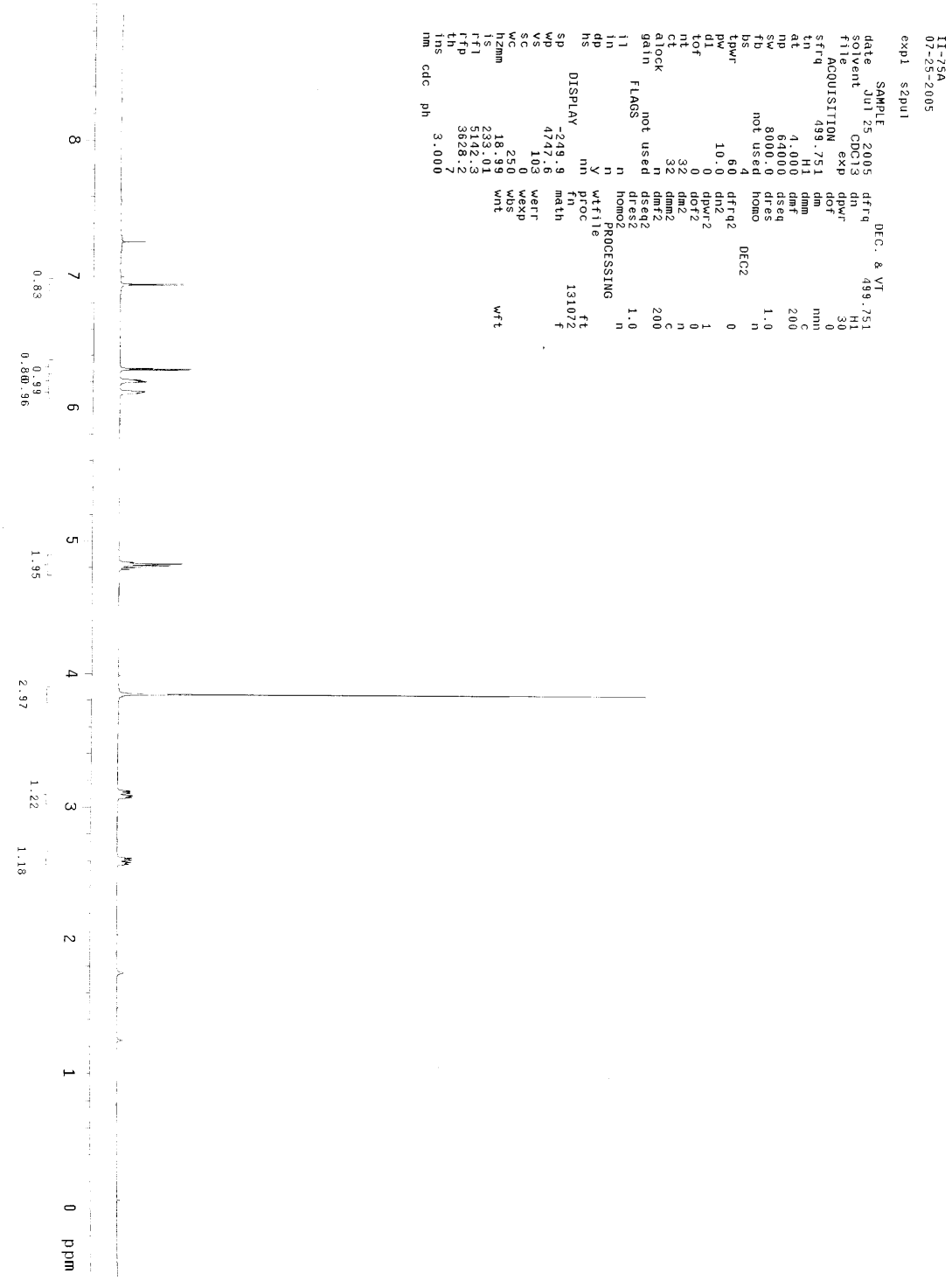
O

7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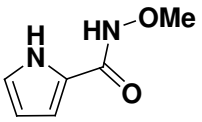
H
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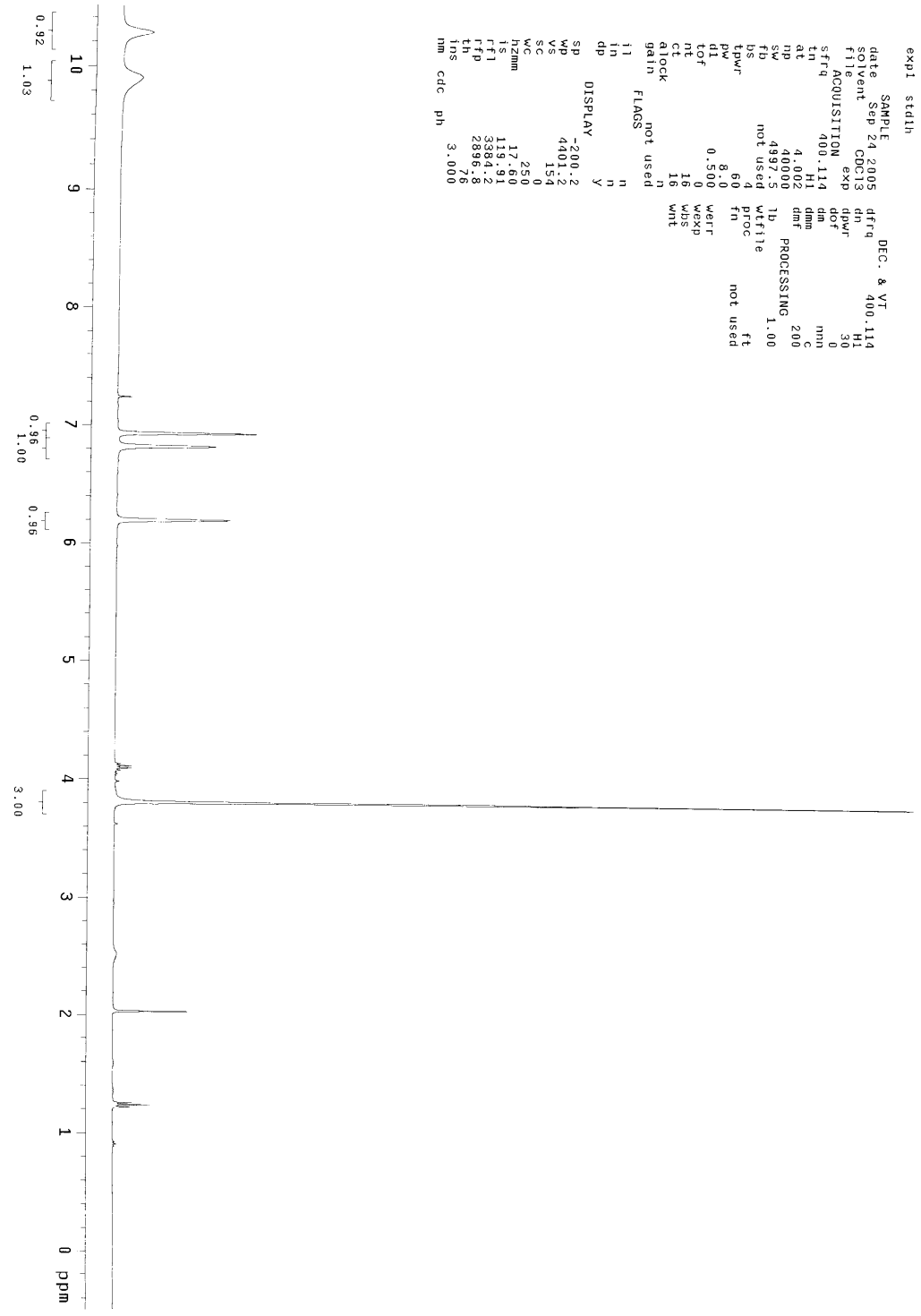
OMe
O

17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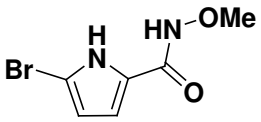
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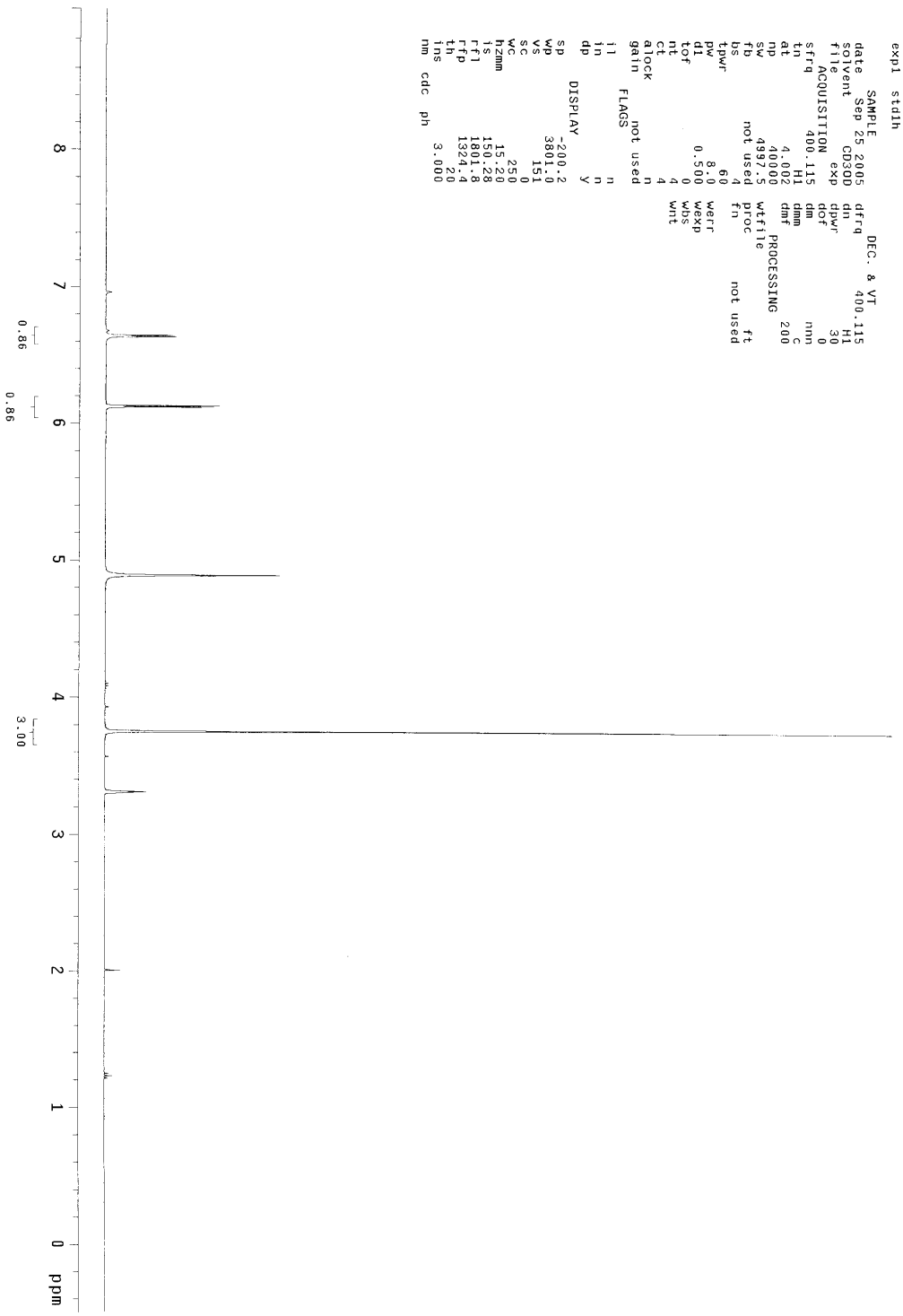
8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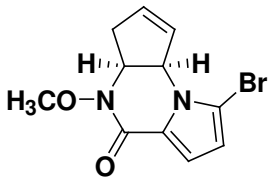
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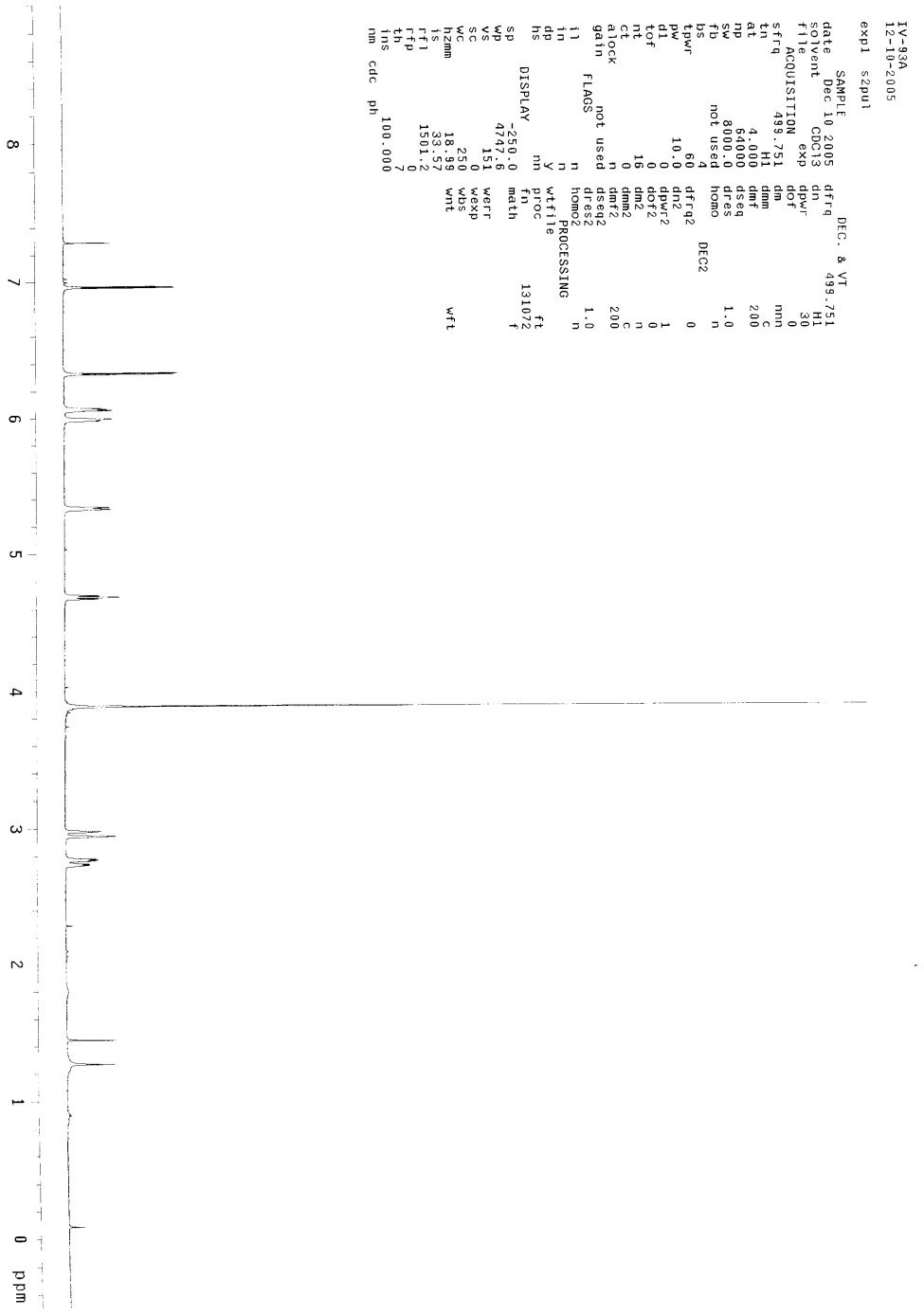
9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dseq
dres 1.0
homo n
DEC2
dfrq2
dn2
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dmm2 c
dmf2 200
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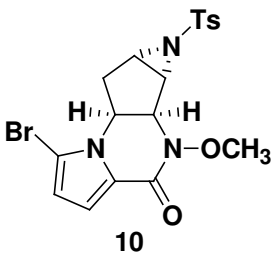
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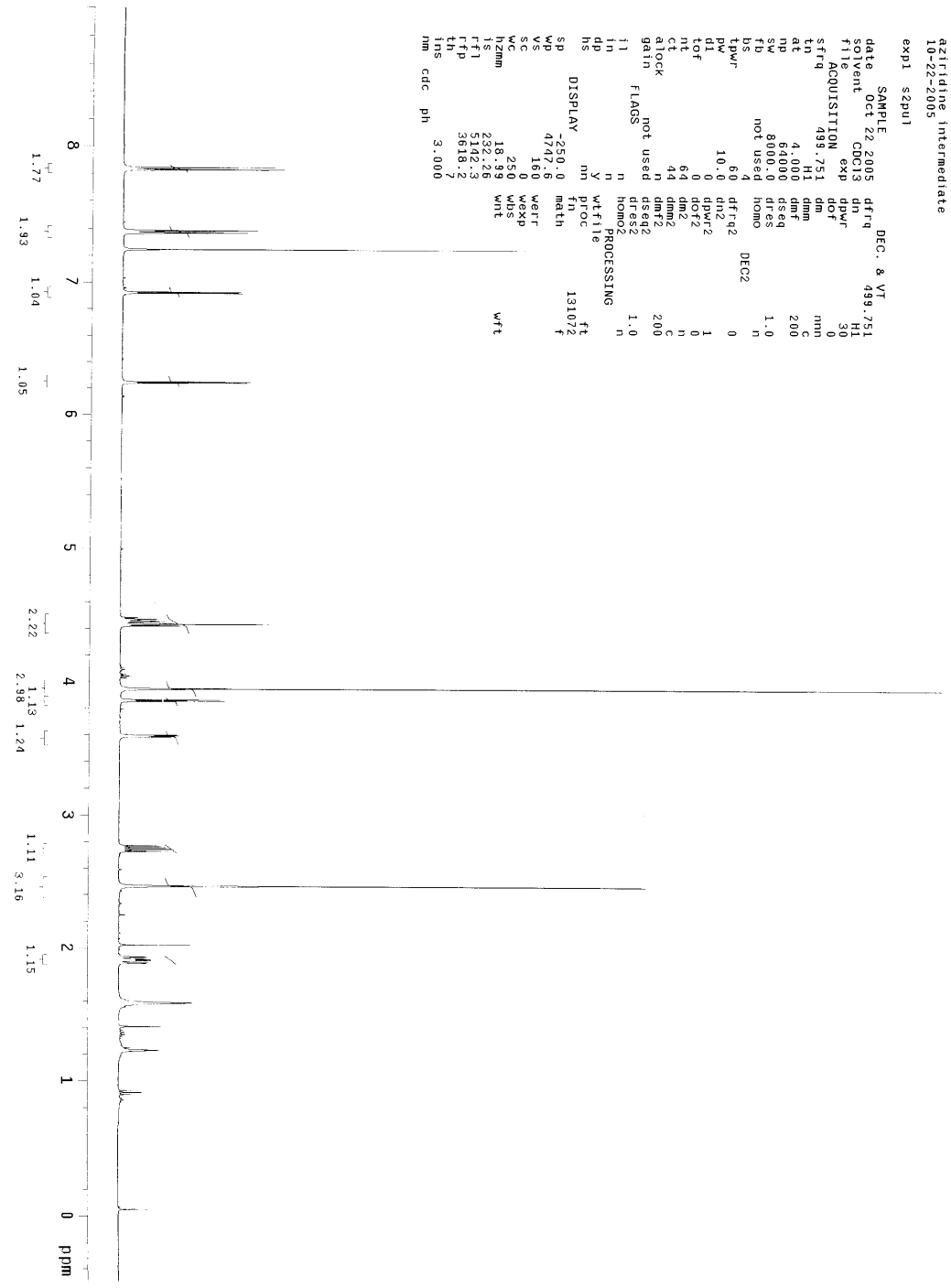
N
N–OCH3
O

10


aziridine intermediate
10-22-2005
exp1 s2pul
SAMPLE
date Oct 22 2005
solvent CDCl3
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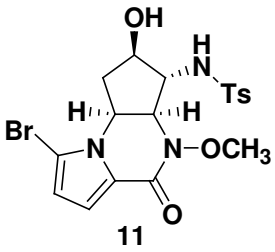
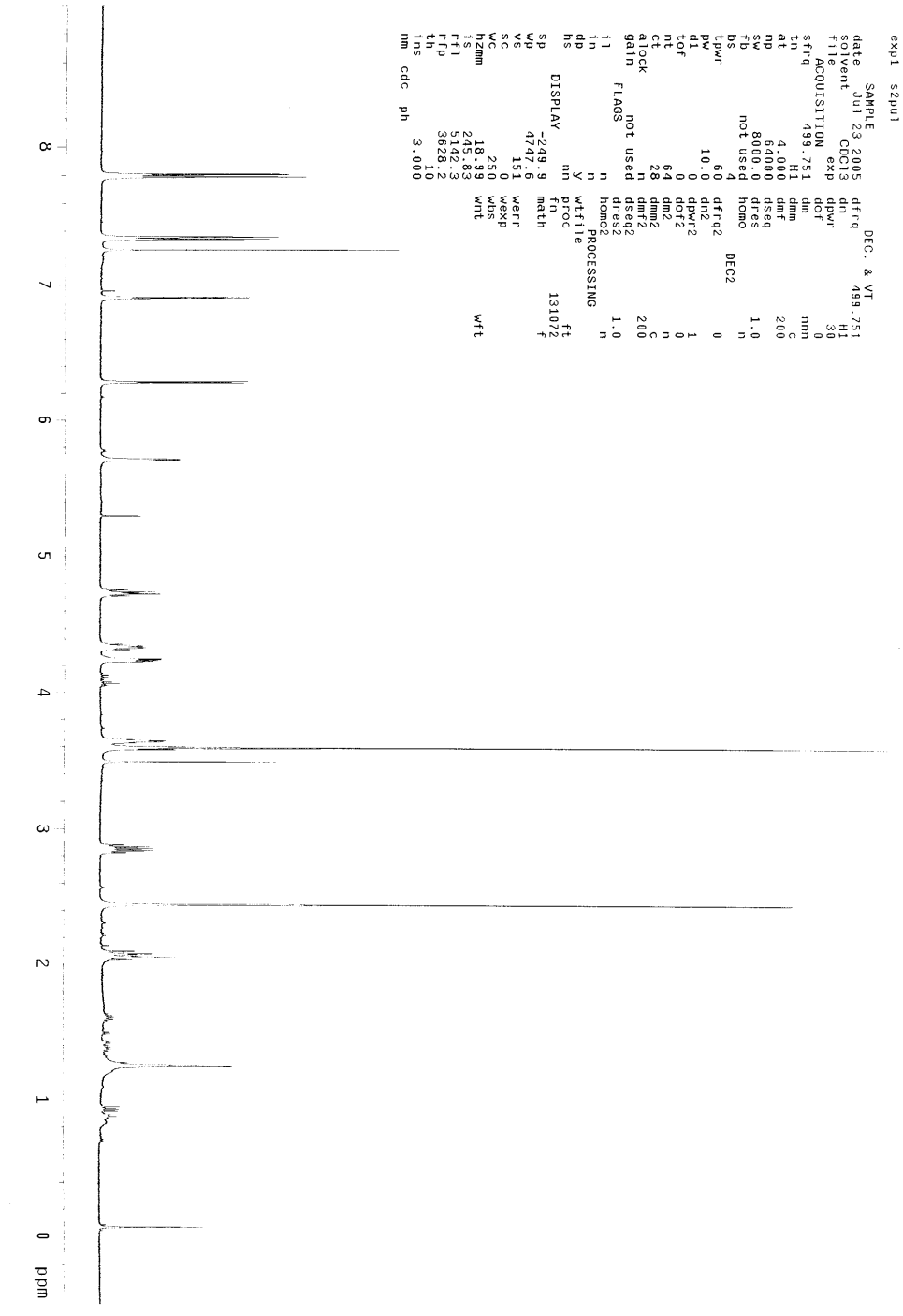
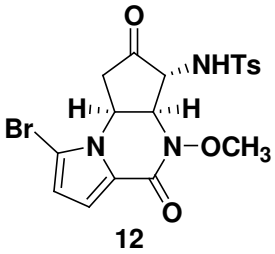
hzcm 232.226
ic 5142.23
rfl 3618.2
rfp 7
th
ins
nm cdc ph 3.000
dfrq DEC. & VT
dn 499.751
dpwr H1
dof 30
dmm 0
dmf nnn
dseq c
dres 200
homo 1.0
DEC2 n
dfrq2
dn2 0
dpwr2
dof2 1
dm2 0
dmm2 n
dmf2 c
dseq2 200
dres2
homo2 1.0
PROCESSING n
wtfile
proc
fn
math 131072
werr f
wexp
wbs
wnt wft
1.77
1.93
1.04
1.05
2.22
1.13
2.98
1.24
1.11
3.16
1.15
8
7
6
5
4
3
2
1
0
ppm

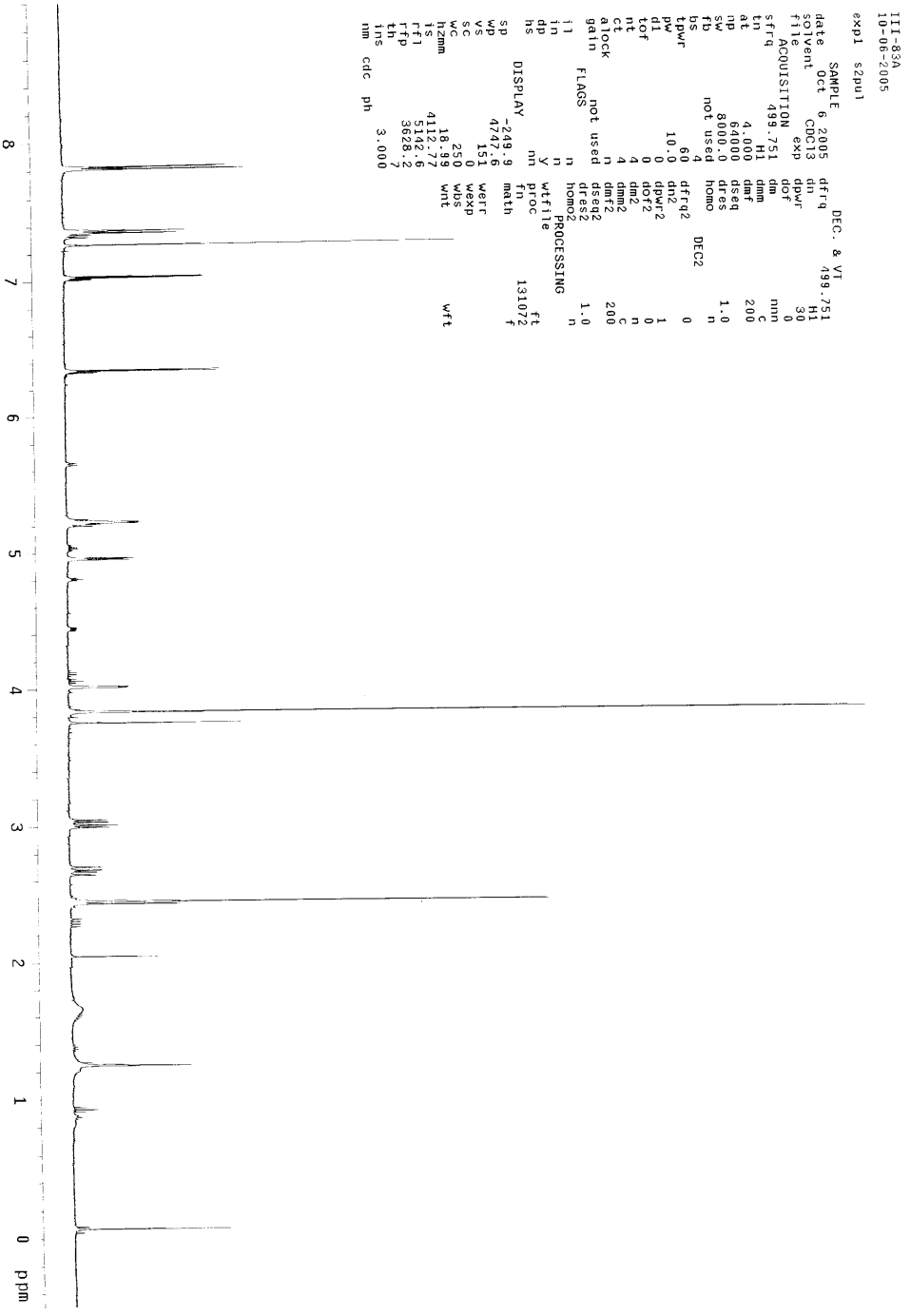

OH
H
N
Ts
H
H
Br
N
N–OCH3
O

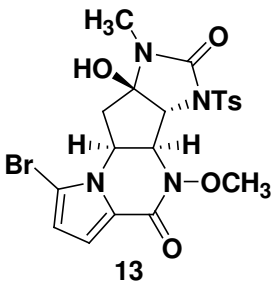
11


II-69A
07-23-2005
expl s2pul
SAMPLE
date Jul 23 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb
bs 4
tpwr 60
pw 10.0
dw
tof 0
nt 64
ct 28
alock n
gain
FLAGS not used
il n
in n
dp y
hs nn
DISPLAY
sp -249.9
wp 4747.6
vs 151
sc 0
wc 250
hzmm 18.99
is 245.83
rfl 5142.3
rfp 3628.2
th 10
ins
nm cdc ph 3.000
dfrq
dn
dpwr
dof
dm
dmm
dmf
dseq
dres
homo
DEC2
dfrq2
dn2
dpwr2
dof2
dm2
dmm2
dmf2
dseq2
dres2
homo2
PROCESSING
wtfile
proc
ft
fn 131072
math f
werr
wexp
wbs
wnt wft
DEC. & VT
499.751
H1
30
0
nnn
c
200
1.0
n
0
1
0
n
c
200
1.0
n
8
7
6
5
4
3
2
1
0
ppm

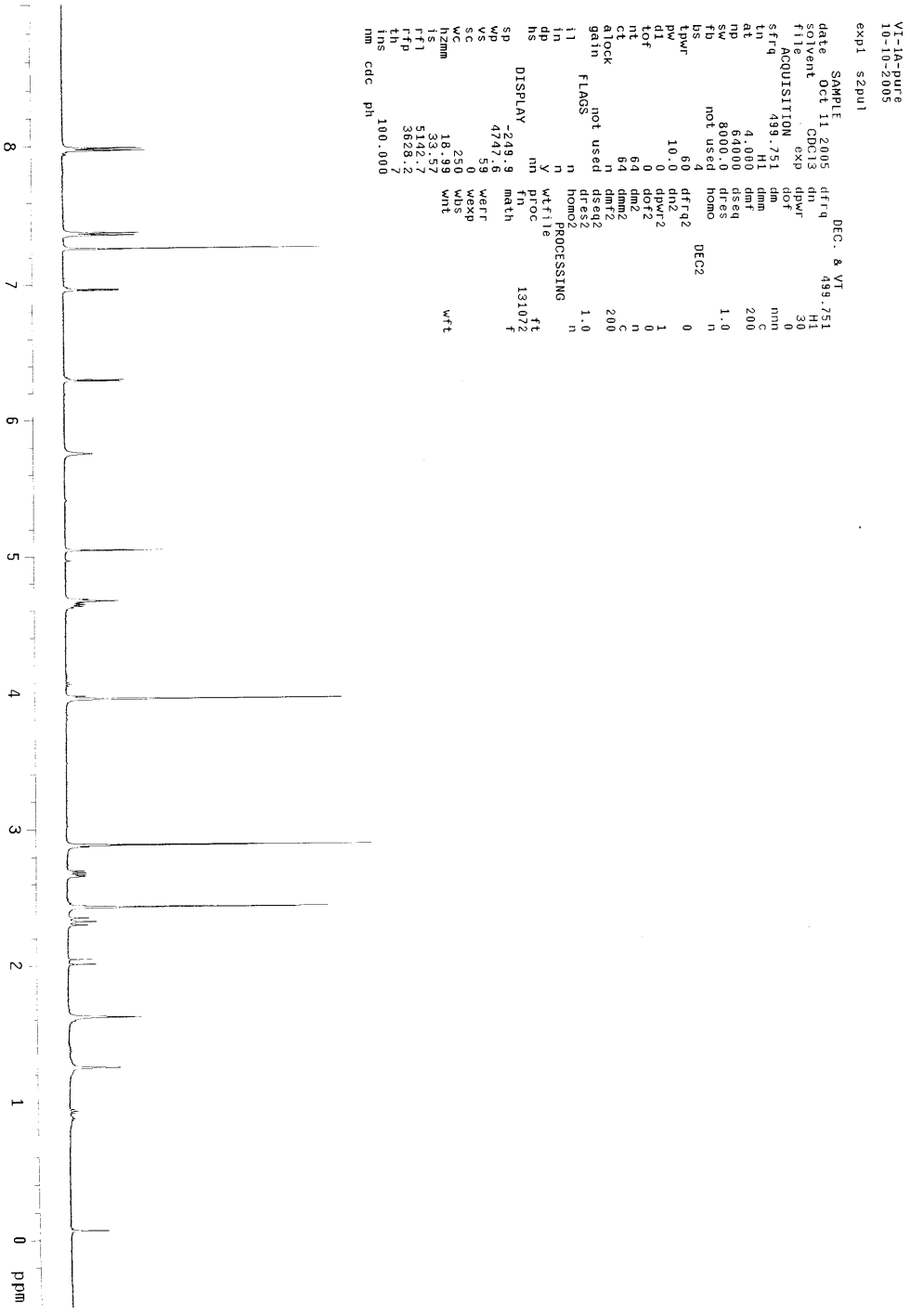

O
NHTs
H
H
Br
N
N–OCH3
O

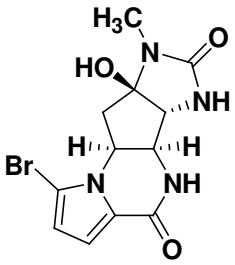
12


III-83A
10-06-2005
expl s2pul
date SAMPLE DEC. & VT
Oct 6 2005 dfrq 499.751
solvent CDCl3 dn H1
file exp dpwr 30
ACQUISITION dof 0
sfrq 499.751 dm nnn
tn H1 dmm c
at 4.000 dmf 200
np 64000 dseq
sw 8000.0 dres 1.0
fb not used homo n
bs 4 DEC2
tpwr 60 dfrq2 0
pw 10.0 dn2
d1 0 dpwr2 1
tof 0 dof2 0
nt 4 dm2 n
ct 4 dmm2 c
alock n dmf2 200
gain not used dseq2
FLAGS dres2 1.0
il n homo2 n
in n
dp y wtfile
hs nn proc ft
DISPLAY fn 131072
sp -249.9 math f
wp 4747.6
wp 151 werr
vs 0 wexp
sc 250 wbs
wc 18.99 wnt wft
hzmm 4112.77
is 5142.6
rfl 3628.2
rfp 7
th
ins
nm cdc ph
3.000
8
7
6
5
4
3
2
1
0 ppm

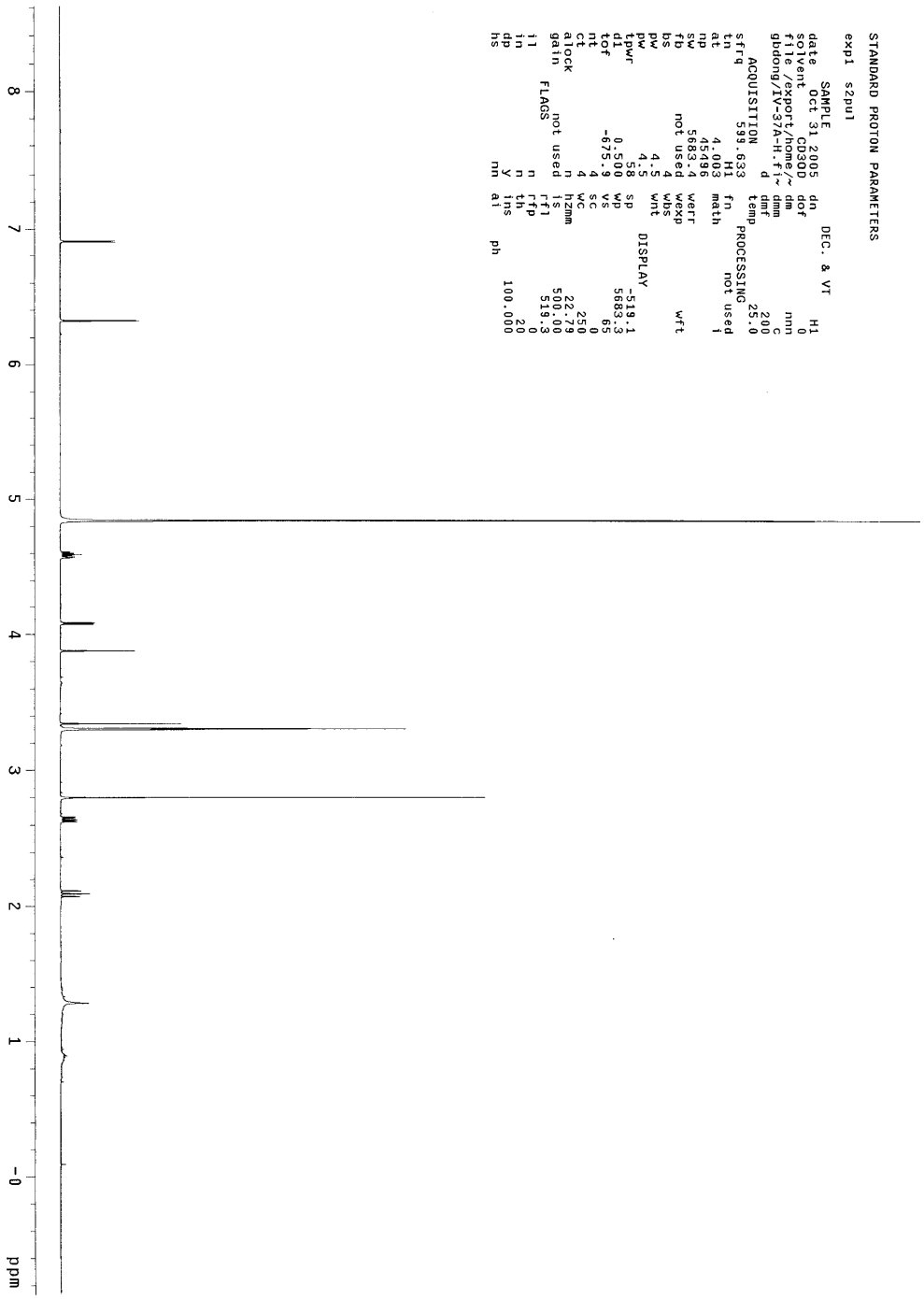

H3C
N
O
HO
NTs
H
H
Br
N
N–OCH3
O

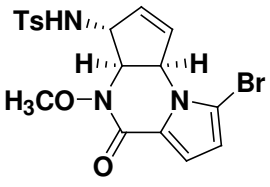
13


Vi-IA-pure
10-10-2005
expl s2pul
SAMPLE
date Oct 11 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb 4
bs 4
tpwr 60
pw 10.0
d1 0
tof 0
nt 64
ct 64
alock n
gain n
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -249.9
wp 4747.6
vs 59
sc 0
wc 250
hzmm 18.99
is 33.57
rfl 5142.7
rfp 3628.2
th 7
ins 1
nm cdc
ph 100.000
DEC. & VT
dfrq 499.751
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
wtfile
proc ft
fn 131072
math f
werr
wexp
wbs
wnt wft
8
7
6
5
4
3
2
1
0
ppm

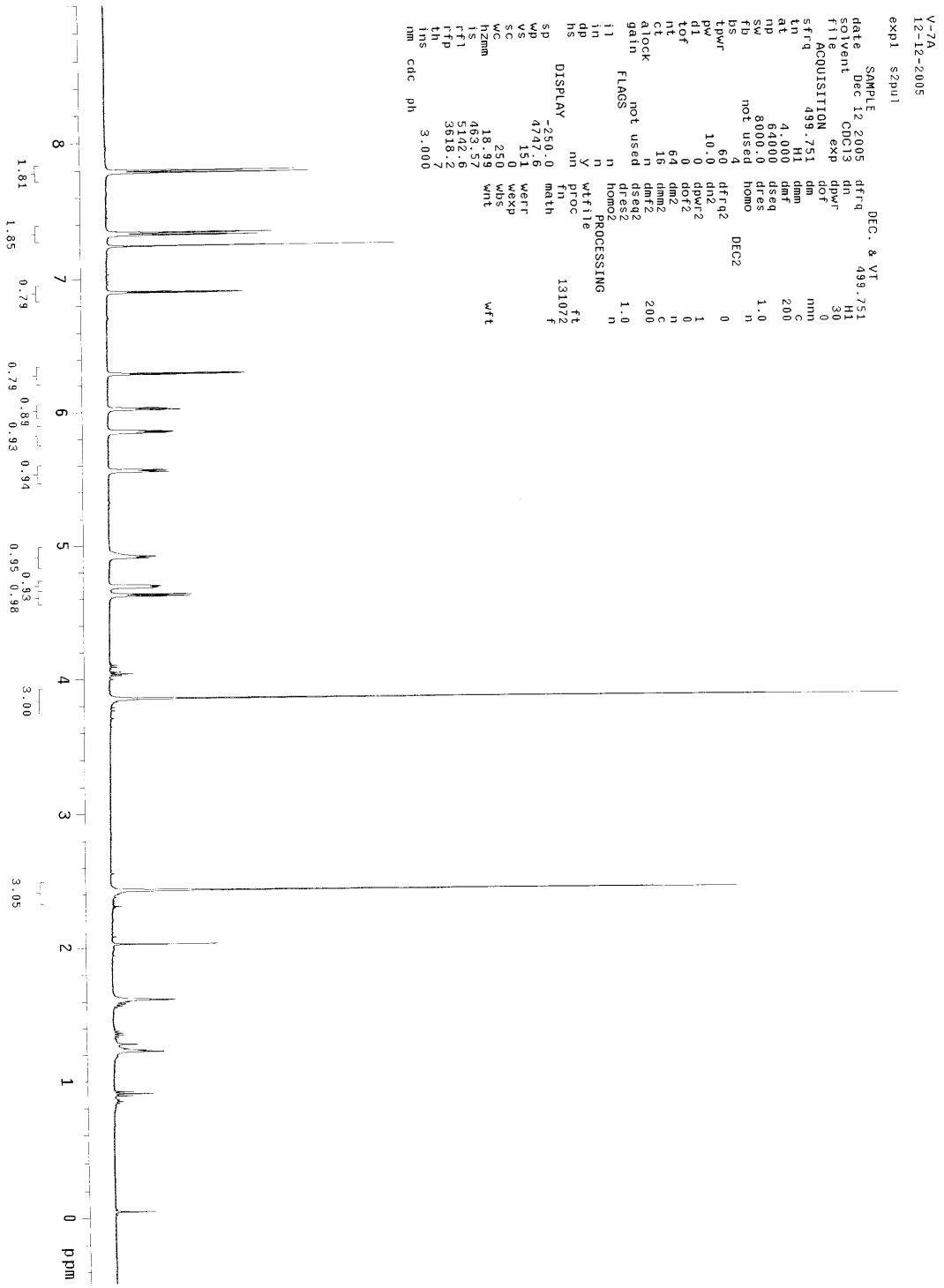


(+)-Agelastatin A (1)




TsHN
H
H
H3CO–N
N
Br
O

15


V-7A
12-12-2005
expl s2pul
SAMPLE
date Dec 12 2005
solvent CDCl3
file exp
ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb not used
bs 4
tpwr 60
pw 10.0
d1 0
tof 0
nt 64
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -250.0
wp 4747.6
vp 151
sc 0
wc 250
hzmm 18.99
is 463.57
rfl 5142.6
rfp 3618.2
th 7
ins
nm cdc ph 3.000
DEC. & VT
dfrq 499.751
dn H1
dpwr 30
dof 0
dm nnn
tm c
dmf 200
dseq
dres
homo
DEC2
dfrq2
dn2
dpwr2
dof2
dm2
dmm2
dmf2
dseq2
dres2
homo2
PROCESSING
wtfile
proc
fn
math
werr
wexp
wbs
wnt
ft
131072
f
wft
1.81
1.85
0.79
0.79
0.89
0.93
0.94
0.95
0.98
0.93
3.00
3.05
8
7
6
5
4
3
2
1
0
ppm