Supporting Information

Title: Practical Enantioselective Synthesis of Endothelin Antagonist S-1255 by Dynamic Resolution of 4-Methoxychromene-3-carboxylic Acid Intermediate

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1) Experimental details for reactions of **17a** and **17b** with **3** (Table 1, entry 4 and 5).

2) Melting point, ^{1}H and ^{13}C NMR, analytical data and HPLC data of **11**.

3) Copies of ^{1}H NMR spectra of **6**, **13** and **23**.

1) Experimental details for reactions of 17a and 17b with 3.

Reaction of Methyl Ester 17a with Grignard Reagent 3 (14a, Table 1, entry 4). A solution of 4-bromoanisole (701 mg, 3.75 mmol) in THF (7 mL) was added dropwise to a stirred mixture of Mg (96 mg, 3.94 mmol), 1,2-dibromoethane (35 mg, 0.188 mmol) and THF (1 mL) at room temperature. After being refluxed for 0.5 h, the mixture was added dropwise to a stirred solution of **17a** (500 mg, 1.25 mmol) in THF (7 mL) at 0 °C. The reaction solution was stirred at 0 °C for 0.5 h and poured into a mixture of 1 N HCl and ice-water. The resulting mixture was extracted with EtOAc, and the extract was washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography on silica gel (EtOAc/hexane, 1/4) to give methyl ester **14a** (381 mg, 64%) and ketone **18** (208 mg, 30%). **14a**: pale yellow crystals. mp. 98–99 °C. ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, *J* = 7.4), 1.30 (3H, d, *J* = 6.0), 1.31 (3H, d, *J* = 6.0), 1.43–1.69 (4H, m), 2.96–3.08(2H, m), 3.72 (3H, s), 4.36–4.44 (1H, m), 5.90 (2H, s), 6.11 (1H, s), 6.65–6.82 (5H, m), 6.95 (1H, d, *J* = 2.4). ^{13}C NMR ($CDCl_3$) δ 22.2, 22.4, 51.9, 55.6, 70.8, 75.4, 101.3, 108.3, 108.4, 113.8, 116.2, 117.7, 119.5, 121.6, 121.7, 125.0, 129.1, 130.2, 133.1, 145.1, 147.2, 147.9, 152.1, 159.5, 166.0. Anal. Calcd for $C_{25}H_{28}O_6 \cdot 0.15H_2O$: C, 70.29; H, 6.68. Found: C, 70.25; H, 6.91. **18**: pale yellow crystals. mp. 140–141 °C. ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, d, *J*= 6.0), 1.22 (3H, d, *J* = 6.0), 3.72 (3H, s), 3.76 (3H, s), 4.23–4.31 (1H, m), 5.89 (2H, s), 5.95 (1H, s), 6.49 (1H, d, *J* = 2.7), 6.67–6.86 (7H, m), 6.99–7.03 (2H, m), 7.09 (2H, d, *J* = 8.7), 7.68 (2H, d, *J* = 9.0). ^{13}C NMR ($CDCl_3$) δ 22.3, 22.4, 55.5, 55.7, 70.9, 77.5, 101.3, 108.2, 108.7, 113.6, 113.8, 115.4, 117.7, 118.5, 122.2, 124.5, 127.9, 129.9, 131.0, 131.7, 131.8, 132.7, 137.5, 147.4, 147.7, 147.8, 152.3, 159.6, 163.3, 195.1. Anal. Calcd for $C_{34}H_{30}O_7$: C, 74.17; H, 5.49. Found: C, 73.99; H, 5.66. HPLC: condition A ((MeCN/H_2O/TFA (75/25/0.1)) **14a**, 9.2 min; **18**, 7.0 min.

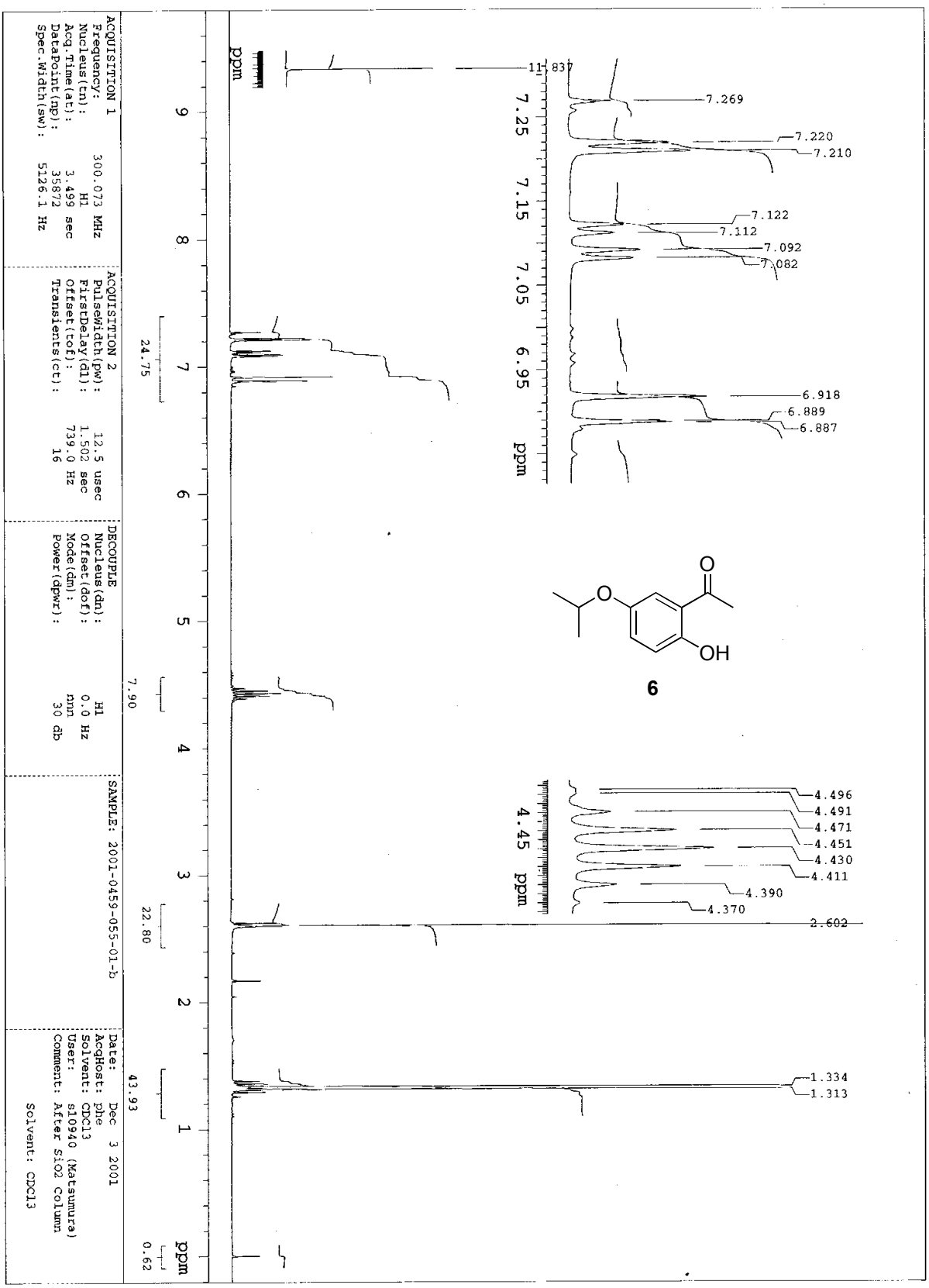
Reaction of Isopropyl Ester 17b with Grignard Reagent 3 (14b, Table 1, entry 5). Isopropyl ester **17b** was treated with 4.0 equiv. of **3** according to the same procedure used for **17a**, giving ester **14b** (82%) and ketone **18** (9%). **14b**: pale yellow crystals. mp 116–117.5 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 (3H,

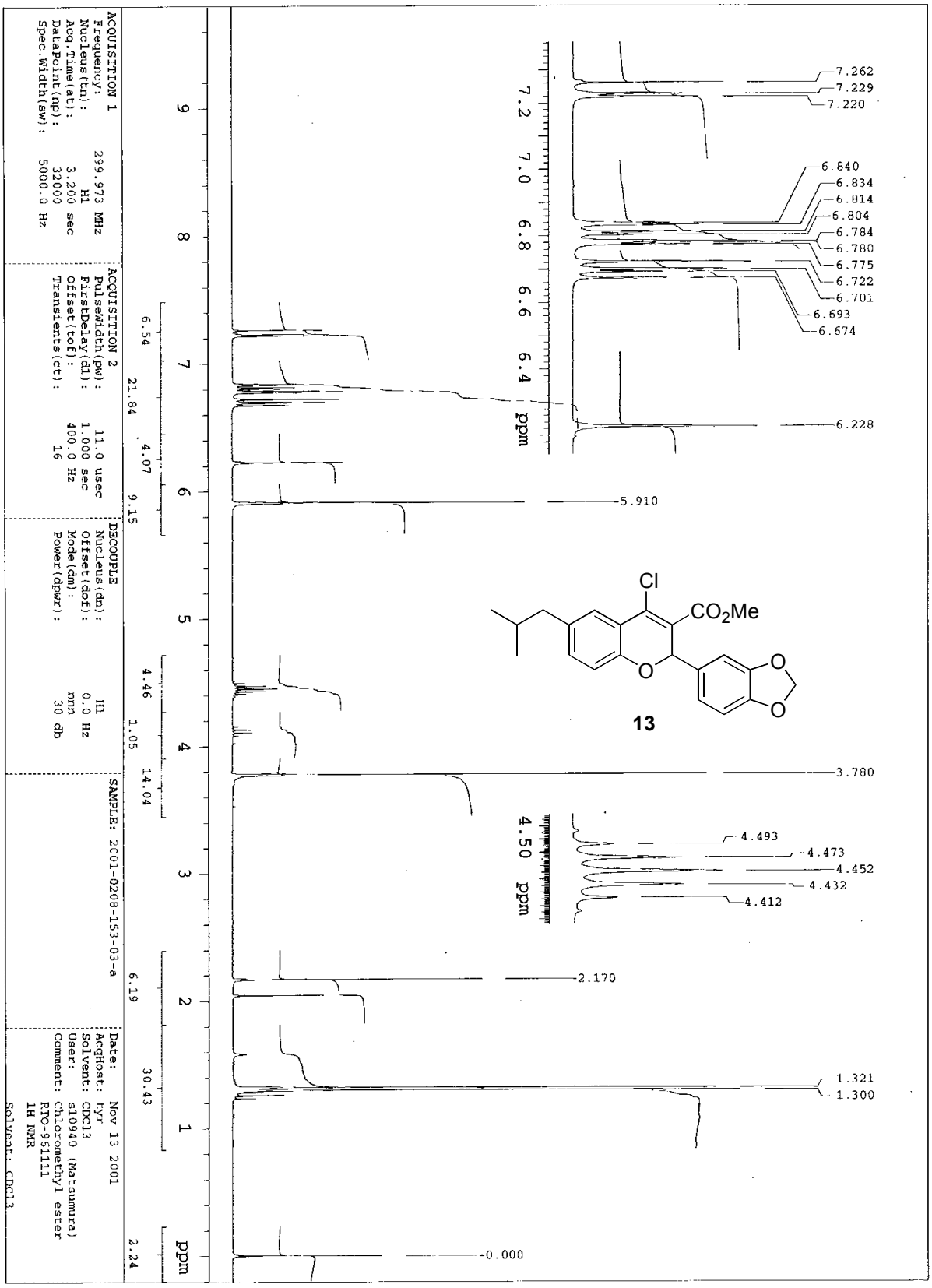
d, J =6.3), 0.93 (3H, d, J = 6.3), 1.17 (3H, d, J = 6.3), 1.19 (3H, d, J = 6.3), 3.86 (3H, 2), 4.17–4.26 (1H, m), 4.75–4.84 (1H, m), 5.91 (2H, s), 6.16 (1H, s), 6.31 (1H, d, J = 2.4), 6.72–6.74 (3H, m), 6.94–6.98 (4H, m), 7.17 (2H, br). ^{13}C NMR ($CDCl_3$) δ 21.7, 21.8, 22.3, 22.4, 55.7, 68.2, 70.8, 75.7, 101.3, 108.3, 108.4, 113.7, 116.1, 117.6, 119.2, 121.6, 123.1, 124.9, 129.4, 130.3, 133.4, 143.5, 147.2, 147.8, 147.8, 152.1, 159.5, 165.4. Anal. Calcd for $C_{30}H_{30}O_7$: C, 71.70; H, 6.02. Found: C, 71.63; H, 6.15. HPLC: condition A (($MeCN/H_2O$/TFA (75/25/0.1)) t_R 9.0 min.

2) Melting point, ^{1}H and ^{13}C NMR, analytical data and HPLC data of 11.

11: brown crystals. mp 100–102 °C. ^{1}H NMR ($CDCl_3$) δ 1.37 (6H, d, J = 6.0), 2.64 (3H, s), 4.53 (1H, m), 5.71 (1H, br), 6.85 (1H, d, J = 9.0), 6.98 (1H, dd, J = 3.3 and 9.0), 7.03 (1H, d, J = 3.3). ^{13}C NMR ($CDCl_3$) δ 22.5, 32.6, 71.6, 116.0, 116.5, 121.6, 129.4, 149.9, 151.7, 201.4. Anal. Calced for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.64; H, 7.19. HPLC: column, Cosmosil 5C18R AR 4.6 mm × 150 mm; solvent, $MeCN/H_2O$/TFA (75/25/0.1); flow rate, 1.0 mL/min; detection, 254 nm. t_R, 2.4 min.

3) Copies of ^{1}H NMR spectra of 6, 13 and 23.

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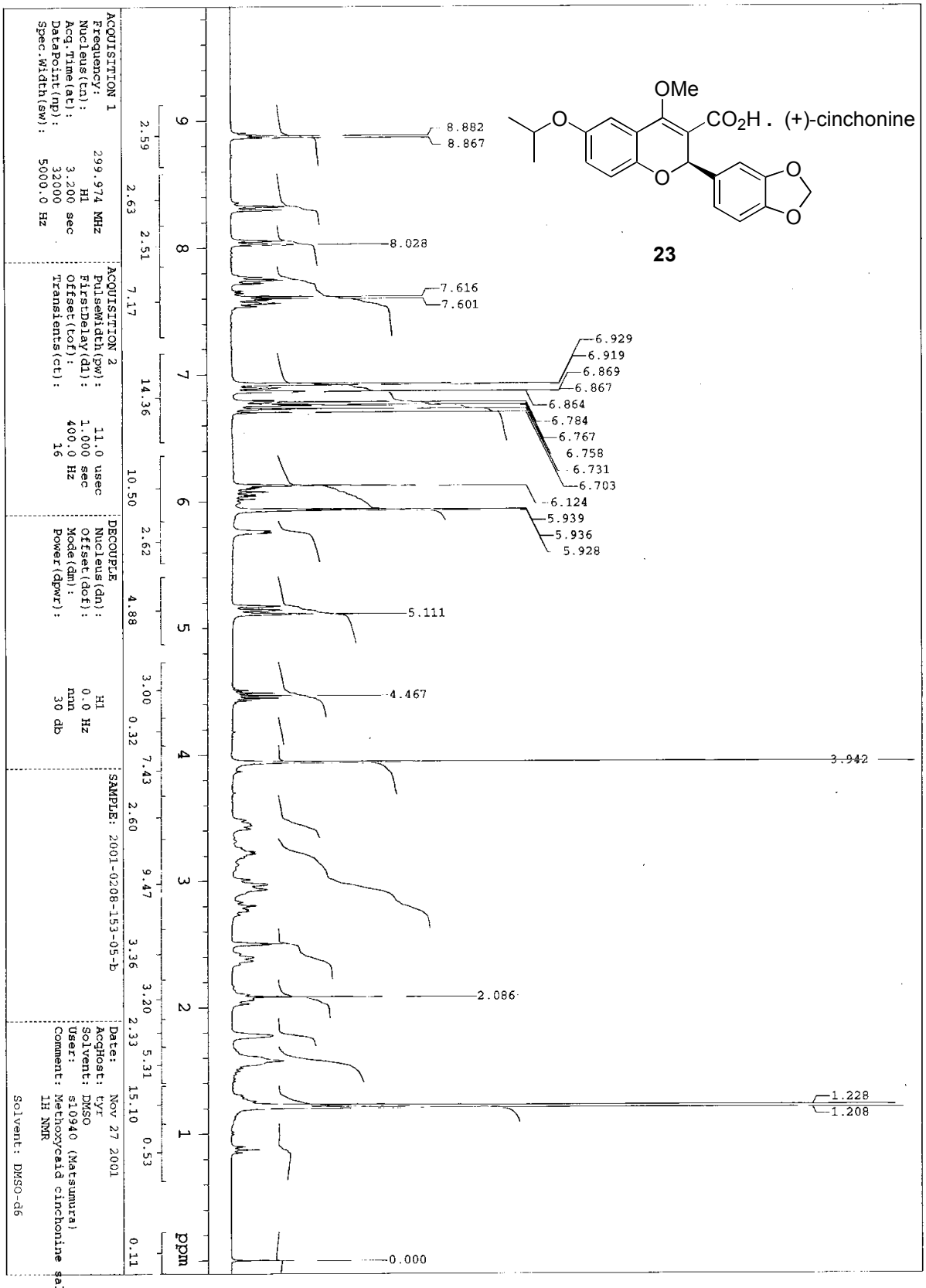
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