

Investigation on the Regioselectivities of Intramolecular Oxidation of Unactivated C–H Bonds by Dioxiranes Generated *in Situ*

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SUPPORTING INFORMATION

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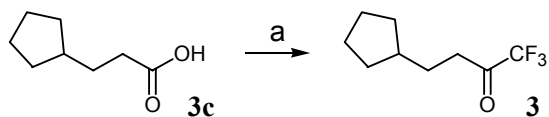
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General Methods. All reactions were performed in oven-dried apparatus. Air and moisture-sensitive compounds were introduced via syringes through a rubber septum. Diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone. Dichloromethane, toluene, pyridine, triethylamine and *N,N*-dimethylformamine were distilled over calcium hydride. Flash column chromatography was performed using the indicated solvent system on E. Merck silica gel 60 (230–400 mesh ASTM).

The preparations of ketones **1**, **2** and **12** were reported in the previous communication: Yang, D.; Wong, M.-K.; Wang, X.-C.; Tang, Y.-C. *J. Am. Chem. Soc.* **1998**, *120*, 6611.

Preparation of ketone **3**.

Ketone **3** was synthesized from 3-cyclopentylpropionic acid according to a literature procedure (Boivin, J.; Kaim, L. E.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 1285).



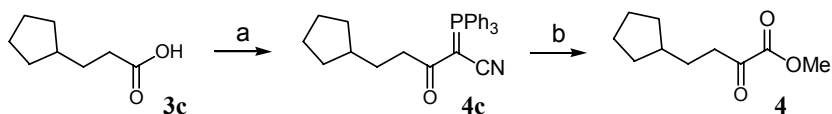
(a) i, oxalyl chloride, CH₂Cl₂; ii, (CF₃CO)₂O, pyridine, CH₂Cl₂.

To a solution of 3-cyclopentylpropionic acid (2.0 g, 14.1 mmol) in CH₂Cl₂ (20 mL) was added oxalyl chloride (2.5 mL, 28.2 mmol) at room temperature under nitrogen atmosphere. Stirring was continued for 2 h. The solvent and excess oxalyl chloride were evaporated off under reduced pressure. The resulting acid chloride was dissolved in CH₂Cl₂ (40 mL) and treated successively with trifluoroacetic anhydride (12 mL, 84.6 mmol) and pyridine (9.2 mL, 112.8 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature under nitrogen for 2 h and quenched slowly with water at 0 °C. Then the mixture was diluted with CH₂Cl₂, washed with diluted hydrochloric acid and saturated NaHCO₃ solution. The organic layer was dried over

anhydrous Na₂SO₄, and concentrated. The residue was purified by vacuum distillation (b.p. 56 °C at ca. 3 mmHg) to afford ketone **3** (0.84 g, 0.47 mmol, 34% yield) as a colourless liquid. ¹H NMR (300 MHz, CDCl₃) δ 2.73 (t, *J* = 7.5 Hz, 2H), 1.47–1.84 (m, 9H), 1.07–1.13 (m, 2H); ¹³C NMR (125.76 MHz, CDCl₃) δ 191.77 (q, ²*J*_{C,F} = 34.6 Hz), 115.83 (q, ¹*J*_{C,F} = 292.2 Hz), 39.47, 35.82, 32.51, 28.69, 25.22; IR (CH₂Cl₂) 1731 cm⁻¹; EIMS (20 eV) *m/z* 194 (*M*⁺, 5); HRMS (EI) for C₉H₁₃OF₃ (*M*⁺), calcd 194.0918, found 194.0929.

Preparation of ketone **4**.

Ketone **4** was synthesized from 3-cyclopentylpropionic acid according to a literature procedure (Wong, M.-K.; Yu, C.-W.; Yuen, W.-H.; Yang, D. *J. Org. Chem.* **2001**, *66*, 3606).



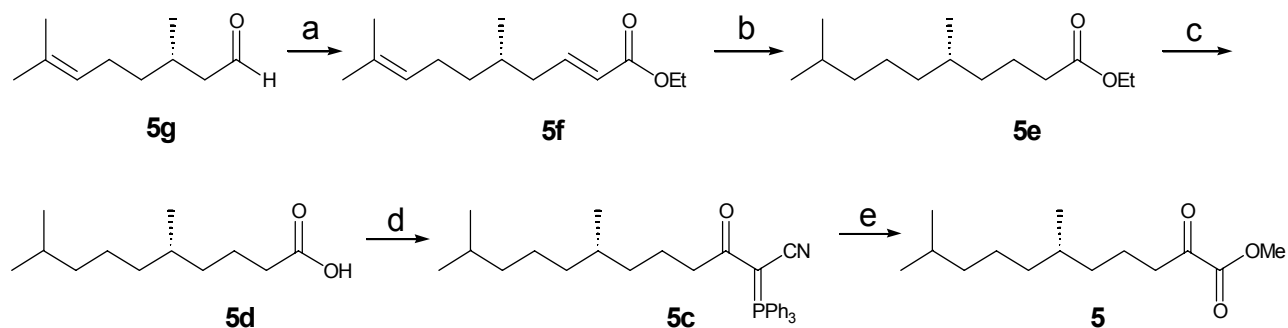
(a) Ph₃P=CHCN, EDCl, DMAP, CH₂Cl₂; (b) dimethyldioxirane, MeOH, CH₂Cl₂.

To a solution of **3c** (1.4 g, 10 mmol) in dry CH₂Cl₂ (50 mL) was added Ph₃P=CHCN (3.6 g, 12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.5 g, 13 mmol) and 4-dimethylaminopyridine (0.12 g, 1.0 mmol) under N₂ at room temperature. After stirring overnight, the reaction mixture was diluted with CH₂Cl₂ and washed successively with 5% NaHCO₃ solution, brine, and water. The organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% EtOAc in hexane) to give **4c** as a white solid (1.3 g, 1.5 mmol, 30% yield). M.p. 130 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, *R_f* = 0.4; ¹H NMR (270 MHz, CDCl₃) δ 7.46–7.64 (m, 15 H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.47–1.85 (m, 9H), 1.13–1.26 (m, 2H); ¹³C NMR (67.80 MHz, CDCl₃) δ 197.57, 133.47 (d, *J* = 10.1 Hz, 6C), 132.87, 128.95 (d, *J* = 12.9 Hz, 6C), 123.44 (d, *J* = 93.5 Hz, 3C), 122.62 (d, *J* = 16.0 Hz, CN), 48.07 (d, *J* = 127.1 Hz), 39.82, 38.87 (d, *J* = 6.7 Hz), 32.44,

31.66, 25.09; IR (CH₂Cl₂) 2174, 1538 cm⁻¹; EIMS (20 eV) *m/z* 425 (M⁺, 22), 356 (10), 328 (26); HRMS (EI) for C₂₈H₂₈NOP (M⁺), calcd 425.1908, found 425.1907.

To a solution of **4c** (0.5 g, 1.2 mmol) in dry MeOH (24 mL) was added dimethyldioxirane (0.04 M in acetone, 60 mL, 2.4 mmol) at room temperature. After 20 min, TLC analysis indicated the disappearance of starting materials. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give **4** as a colourless oil (0.15 g, 0.82 mmol, 68% yield). Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, *R_f* = 0.7; ¹H NMR (270 MHz, CDCl₃) δ 3.87 (s, 3H), 2.85 (t, *J* = 7.5 Hz, 2H), 1.52–1.79 (m, 9H), 1.47–1.85 (m, 9H), 1.07–1.11 (m, 2H); ¹³C NMR (75.48 MHz, CDCl₃) δ 194.46, 161.63, 53.40, 39.46, 38.67, 32.43, 29.08, 25.09; IR (CH₂Cl₂) 1731 cm⁻¹; EIMS (20 eV) *m/z* 184 (M⁺, 4), 153 (100), 125 (78); HRMS (EI) for C₁₀H₁₆O₃ (M⁺), calcd 184.1099, found 184.1096.

Preparation of ketone **5**.



(a) ethyl (triphenylphosphoranylidene)acetate, CH₂Cl₂, rt, overnight; (b) H₂, 10% Pd-C, MeOH, rt, 3 h; (c) LiOH·H₂O, THF/EtOH/H₂O, rt, overnight; (d) Ph₃P=CHCN, EDCI, DMAP, CH₂Cl₂, rt, N₂, overnight; (e) dimethyldioxirane, MeOH, rt, 20 min.

To a solution of **5g** (76% e.e. determined by optical rotation measurement, 1.2 mL, 6.5 mmol) in dry CH₂Cl₂ (50 mL) was added ethyl (triphenylphosphoranylidene)acetate (2.5 g, 7.1 mmol) at room temperature. After stirring overnight, the reaction mixture was concentrated to give a white solid, which was then dissolved in CH₂Cl₂ and passed through a short pad of silica gel to remove

Ph₃P=O. The pad of celite was further washed with 50% EtOAc in hexane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (5% EtOAc in hexane) to give **5f** as a yellow oil (1.2 g, 5.4 mmol, 83% yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, $R_f = 0.63$; $[\alpha]_D^{20} +3.33^\circ$ (c 1.0, CH₂Cl₂); ¹H NMR (270 MHz, CDCl₃) δ 6.93 (quintet, $J = 7.7$ Hz, 1H), 5.80 (d, $J = 15.4$ Hz, 1H), 5.08 (t, $J = 7.3$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 2.09–2.24 (m, 1H), 1.93–2.06 (m, 3H), 1.64 (d, $J = 11.2$ Hz, 6H), 1.19–1.45 (m, 2H), 0.86–1.02 (m, 1H), 0.91 (d, $J = 6.7$ Hz, 3H); ¹³C NMR (67 MHz, CDCl₃) δ 166.63, 148.16, 131.44, 124.41, 122.40, 60.10, 39.63, 36.68, 32.08, 25.68, 25.49, 19.48, 17.62, 14.26; IR (CH₂Cl₂) 1711 cm⁻¹; EIMS (20 eV) m/z 224 (M⁺, 27), 181 (27), 151 (5), 136 (100); HRMS (EI) for C₁₄H₂₄O₂ (M⁺), calcd 224.1776, found 224.1777. (ref: Balu, N.; Bhat, S. V. *J. Chem. Soc., Chem. Commun.* **1994**, 7, 903).

To a solution of **5f** (3 g, 13.3 mmol) in MeOH (50 mL) was added 10% Pd/C (0.15 g) at room temperature. After stirring under hydrogen atmosphere for 3 h, the reaction mixture was filtered through a short pad of celite to remove Pd/C. The silica gel pad was further washed with MeOH and EtOAc. Concentration of the filtrate under reduced pressure provided **5e** as a colourless oil (2.9 g, 12.7 mmol, 98% yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, $R_f = 0.68$; $[\alpha]_D^{20} +0.16^\circ$ (c 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 4.14 (dd, $J = 7.2$ Hz, 2H), 2.27 (t, $J = 7.2$ Hz, 2H), 1.06–1.69 (m, 12H), 1.26 (d, $J = 7.2$ Hz, 3H), 0.86 (d, $J = 6.5$ Hz, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 176.42, 59.88, 39.25, 37.06, 36.42, 34.49, 32.49, 27.89, 24.68, 22.59, 22.48, 19.44, 14.14; IR (CH₂Cl₂) 1727 cm⁻¹; EIMS (20 eV) m/z 228 (M⁺, 7), 185 (100); HRMS (EI) for C₁₄H₂₈O₂ (M⁺) calcd 228.2089, found 228.2079. (ref: Kikumasa, S.; Shioji, M.; Masao, H. *J. Org. Chem.* **1976**, 32, 177).

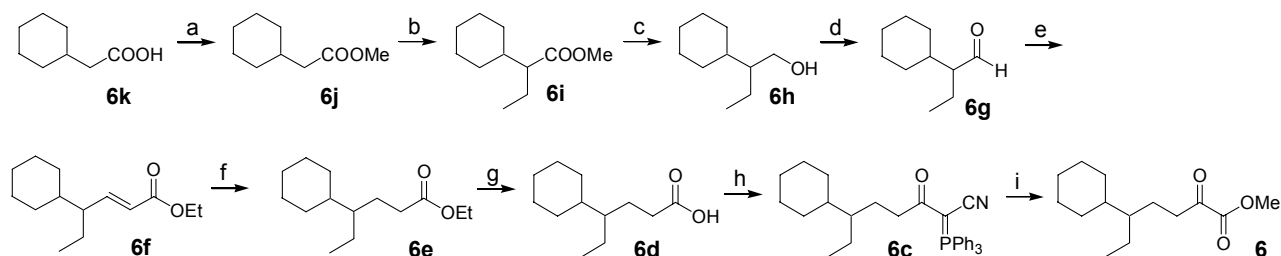
To a solution of **5e** (2.5 g, 11 mmol) in THF / EtOH / H₂O (30 mL / 7.5 mL / 7.5 mL) was added LiOH·H₂O (0.92 g, 21.9 mmol) at 0 °C. After stirring at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure, acidified with hydrochloric acid to pH 2–3 at 0

°C, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in hexane) to provide **5d** as a colourless oil (2.1 g, 10.5 mmol, 98% yield). Analytical TLC (silica gel 60), 25% EtOAc in n-hexane, $R_f = 0.40$; $[\alpha]_D^{20} +0.93^\circ$ (c 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 2.33 (t, $J = 7.5$ Hz, 2H), 1.10–1.65 (m, 12H), 0.86 (d, $J = 6.5$ Hz, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 180.73, 39.45, 37.22, 36.54, 34.59, 32.69, 28.12, 24.88, 22.85, 22.75, 22.42, 19.66; IR (CH₂Cl₂) 1731 cm⁻¹; EIMS (20 eV) m/z 200 (M⁺, 10), 157 (77); HRMS (EI) for C₁₂H₂₄O₂ (M⁺), calcd 200.1776, found 200.1775. (ref: Kazuaki, A.; Keiichiro, I.; Hiroshi, O. *Bunseki Kagaku*, **1999**, 48, 1085).

5c: prepared from **5d** following the procedure for **4c**, as a white solid (4.6 g, 9.5 mmol, 95% yield). M.p. 95–96 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, $R_f = 0.68$; $[\alpha]_D^{20} +0.83^\circ$ (c 1.0, CH₂Cl₂); ¹H NMR (270 MHz, CDCl₃) δ 7.59 (m, 15H), 2.67 (t, $J = 7.4$ Hz, 2H), 1.07–1.68 (m, 12H), 0.85 (d, $J = 6.7$ Hz, 9H); ¹³C NMR (67 MHz, CDCl₃) δ 197.59, 133.60 (d, $J = 10.2$ Hz, 6C), 133.05 (s, 3C), 129.16 (d, $J = 12.8$ Hz, 6C), 123.48 (d, $J = 93.6$ Hz, 3C), 122.86 (d, $J = 16.7$ Hz, CN), 48.48 (d, $J = 126.6$ Hz), 39.85 (d, $J = 6.8$ Hz), 39.37, 37.28, 36.77, 32.76, 27.97, 24.80, 23.21, 22.78, 22.67, 19.69; IR (CH₂Cl₂) 2173, 1733 cm⁻¹; FABMS m/z 484 (M⁺+1); HRMS (EI) for C₃₂H₃₈NOP (M⁺), calcd 483.2691, found 483.2687.

5: prepared from **5c** following the procedure for **4**, as a colourless oil (0.2 g, 0.8 mmol, 82% yield). Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.56$; $[\alpha]_D^{20} +0.69^\circ$ (c 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 3.86 (s, 3H), 2.81 (t, $J = 7$ Hz, 2H), 1.62 (m, 2H), 1.32 (m, 6H), 1.09 (m, 4H), 0.86 (d, $J = 6.5$ Hz, 9H); ¹³C NMR (67 MHz, CDCl₃) δ 194.44, 161.72, 52.95, 39.72, 39.39, 37.15, 36.36, 32.06, 28.06, 24.80, 22.79, 22.70, 20.65, 19.57; IR (CH₂Cl₂) 1729 cm⁻¹; EIMS (20 eV) m/z 242 (M⁺, 3), 183 (55), 165 (65); HRMS (EI) for C₁₄H₂₆O₃ (M⁺), calcd 242.1881, found 242.1878.

Preparation of ketone 6



(a) MeOH, concentrated H₂SO₄, reflux; (b) LDA, DMPU, EtI, THF, -78 °C to rt, 15 h; (c) DIBALH, CH₂Cl₂, 0 °C to rt; (d) PDC, celite, CH₂Cl₂, rt, 1 h; (e) Ph₃P=CHCO₂Et, CH₂Cl₂, rt; (f) H₂, 10% Pd-C, MeOH; (g) LiOH·H₂O, THF/EtOH/H₂O, rt; (h) Ph₃P=CHCN, DMAP, EDCI, CH₂Cl₂, rt, overnight; (i) dimethyldioxirane, MeOH, rt, 6 h.

To a solution of **6k** (8.0 g, 56 mmol) in MeOH (50 mL) was added concentrated sulfuric acid (2 drops). After refluxing overnight, the reaction mixture was concentrated under reduced pressure to give a white solid, which was then dissolved in Et₂O, washed with 5% NaHCO₃ solution, brine, and H₂O. The organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc in hexane) to give **6j** as a yellow oil (8 g, 51 mmol, 91% yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, *R_f* = 0.63; ¹H NMR (270 MHz, CDCl₃) δ 3.65 (s, 3H), 2.18 (d, *J* = 6.9 Hz, 2H), 1.59–1.80 (m, 6H), 0.87–1.32 (m, 5H); ¹³C NMR (67 MHz, CDCl₃) δ 173.59, 51.33, 42.01, 34.93, 33.08, 26.19, 26.08; IR (CH₂Cl₂) 1700 cm⁻¹. (ref: Inokuchi, T; Sugimoto, T; Kusumoto, M; Torii, S. *Bull. Chem. Soc. Jpn.* **1992**, 65, 3200)

To a solution of diisopropylamine (1.9 mL, 13.8 mmol) in dry THF (10 mL) at -78 °C was added n-BuLi (1.38 M in hexane, 10 mL, 13.8 mmol) under nitrogen atmosphere. After stirring for 1 h, the mixture was warmed to 25 °C for 10 min, and then cooled to -78 °C, followed by the addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (14 mL, 12 mmol) and a solution of **6j** (2 g, 12 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at -78 °C. After addition of EtI (2.0 g, 12 mmol), the reaction mixture was stirred for 2 h at -78 °C and then warmed

up to room temperature for 12 h. The reaction mixture was quenched with brine. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous MgSO_4 . The crude residue was purified by flash column chromatography (5% EtOAc in n-hexane) to afford **6i** as a colourless oil (2.2 g, 11.9 mmol, 95 % yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, R_f = 0.64; ^1H NMR (270 MHz, CDCl_3) δ 3.46 (s, 3H), 2.01–2.18 (m, 1H), 1.45–1.80 (m, 8H), 0.80–1.29 (m, 5H), 0.85 (t, J = 7 Hz, 3H); ^{13}C NMR (67 MHz, CDCl_3) δ 175.12, 53.13, 39.53, 30.53, 30.15, 25.91, 25.83, 21.94, 11.47; IR (CH_2Cl_2) 1733 cm^{-1} ; EIMS (20 eV) m/z 184 (M^+ , 10), 153 (32), 125 (62); HRMS (EI) for $\text{C}_{11}\text{H}_{20}\text{O}_2$ (M^+), calcd 184.1463, found 184.1454. (ref: Metzger, J. O.; Klenke, K.; Hartmanns, J.; Eisermann, D. *Chem. Ber.* **1986**, *119*, 508).

To a solution of **6i** (5.7 g, 31 mmol) in CH_2Cl_2 (20 mL) was added diisobutylaluminum hydride (1 M in toluene, 93 mL, 93 mmol) at 0 °C. After stirring at room temperature overnight, the reaction mixture was quenched with H_2O slowly, and acidified with diluted hydrochloric acid to pH 2 at 0 °C. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc in n-hexane) to afford **6h** as a yellow oil (4.0 g, 25.6 mmol, 83% yield). Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.51; ^1H NMR (300 MHz, CDCl_3) δ 3.52–3.65 (m, 2H), 1.90 (br.s, 1H), 1.60–1.74 (m, 5H), 0.96–1.47 (m, 9H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 63.04, 47.90, 38.26, 30.33, 30.11, 27.00, 26.96, 26.88, 20.71, 12.33; IR (CH_2Cl_2) $3618, 3465\text{ cm}^{-1}$. EIMS (20 eV) m/z 138 ($\text{M}^+ - \text{H}_2\text{O}$), 109 (68); HRMS (EI) for $\text{C}_{10}\text{H}_{18}$ ($\text{M}^+ - \text{H}_2\text{O}$), calcd 138.1408, found 138.1397. (ref: Choi, J. H.; Lee, S. J.; Joo, C. R.; Kim, J. S. Beak, D. J. *Bull. Korean Chem. Soc.* **1999**, *20*, 1384).

To a solution of **6h** (3.5 g, 22 mmol) in CH_2Cl_2 (50 mL) were added PDC (7.2 g, 33 mmol) and celite (7.2 g) at room temperature. After stirring for 1 h, the reaction mixture was filtered through

celite, and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in n-hexane) to afford **6g** as a yellow oil (2.77 g, 17.7 mmol, 81% yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, R_f = 0.40; ^1H NMR (300 MHz, CDCl_3) δ 9.60 (d, J = 3.7 Hz, 1H), 1.92–2.61 (m, 1H), 1.49–1.81 (m, 7H), 0.91–1.38 (m, 7H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.36, 59.53, 38.03, 30.98, 30.31, 26.48, 19.15, 12.15. (ref: Lai, R.; Ucciani, E. C. R. *Acad. Sci., Ser. C* **1973**, 276, 425).

To a solution of **6g** (2.5 g, 16 mmol) in toluene (50 mL) was added ethyl (triphenylphosphoranylidene)acetate (6.2 g, 18 mmol). After refluxing overnight, the reaction mixture was diluted with brine, and extracted with CH_2Cl_2 . The combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc in n-hexane) to give **6f** as a yellow oil (3.2 g, 14.3 mmol, 88% yield). Analytical TLC (silica gel 60), 5% EtOAc in n-hexane, R_f = 0.65; ^1H NMR (300 MHz, CDCl_3) δ 6.67 (dd, J = 15.5, 9.9 Hz, 1H), 5.75 (d, J = 15.5 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 1.81–1.91 (m, 1H), 1.51–1.74 (m, 6H), 1.24–1.38 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.90–1.20 (m, 5H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.00, 152.24, 121.94, 60.08, 50.47, 41.34, 31.13, 29.93, 26.57, 26.53, 26.52, 24.03, 14.27, 12.05; IR (CH_2Cl_2) 1706, 1650, 1449 cm^{-1} ; EIMS (20 eV) m/z 224 (M^+), 151 (20), 142 (100); HRMS (EI) for $\text{C}_{14}\text{H}_{24}\text{O}_2$ (M^+), calcd 224.1776 found 224.1777.

To a solution of **6f** (3.16 g, 14 mmol) in MeOH (50 mL) was added 10% Pd/C (0.15 g) at room temperature. After stirring under H_2 overnight, the reaction mixture was filtered through a pad of celite to remove Pd/C. The pad of celite was further washed with MeOH and EtOAc. Concentration of the filtrate provided **6e** as a colourless oil (2.3 g, 10.2 mmol, 74% yield). Analytical TLC (silica gel 60), 8% EtOAc in n-hexane, R_f = 0.33; ^1H NMR (300 MHz, CDCl_3) δ 4.11 (d, J = 7.1 Hz, 2H), 2.24–2.31 (m, 2H), 0.90–1.75 (m, 16H), 1.25 (t, J = 7.1 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.40, 60.32, 44.72, 39.76, 32.95, 29.97, 29.78, 27.06, 26.99, 25.64, 22.96,

14.41, 12.13; IR (CH₂Cl₂) 1726, 1650, 1449 cm⁻¹; EIMS (20 eV) *m/z* 197 (M⁺-C₂H₅); HRMS (EI) for C₁₂H₂₁O₂ (M⁺-C₂H₅), calcd 197.1543, found 197.1527.

To a solution of **6e** (2.27 g, 10 mmol) in THF / EtOH / H₂O (40 mL / 10 mL / 10 mL) was added LiOH·H₂O (2.3 mg, 55 mmol) at 0 °C. After stirring at room temperature overnight, the reaction mixture was concentrated under reduced pressure. The reaction mixture was acidified with hydrochloric acid to pH 2 at 0 °C, and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in hexane) to provide **6d** as a yellow oil (1.9 g, 9.6 mmol, 95% yield). Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, *R_f* = 0.66; ¹H NMR (300 MHz, CDCl₃) δ 2.28–2.40 (m, 2H), 0.95–1.78 (m, 16H), 0.90 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 180.95, 44.62, 39.73, 32.67, 29.98, 29.75, 27.03, 25.36, 22.92, 12.08 cm⁻¹; IR (CH₂Cl₂) 3496, 1744, 1708 cm⁻¹; EIMS (20 eV) *m/z* 198 (M⁺, 2), 139 (29), 115 (100); HRMS (EI) for C₁₂H₂₂O₂ (M⁺), calcd 198.1619, found 198.1615.

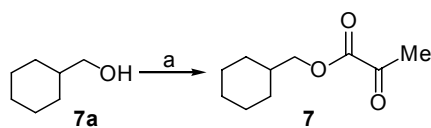
6c: prepared from **6d** following the procedure for **4c**, as a white solid (4.0 g, 8.3 mmol, 87% yield). M.p. 131–132 °C. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, *R_f* = 0.56; ¹H NMR (300 MHz, CDCl₃) δ 7.45–7.64 (m, 15H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.00–1.73 (m, 16H), 0.86 (d, *J* = 7 Hz, 3H); ¹³C NMR (67 MHz, CDCl₃) δ 198.15, 133.73 (d, *J* = 10.2 Hz, 6C), 133.12 (s, 3C), 129.22 (d, *J* = 12.8 Hz, 6C), 124.10 (d, *J* = 93.6 Hz, 3C), 122.95 (d, *J* = 14.5 Hz, CN), 48.32 (d, *J* = 127.16 Hz), 44.87, 39.77, 38.23, 29.90 (d, *J* = 9.3 Hz), 27.10, 26.31, 23.06, 12.27; IR (CH₂Cl₂) 2173, 1733 cm⁻¹; FABMS *m/z* 482 (M⁺+1, 100); HRMS (EI) for C₃₂H₃₆NOP (M⁺), calcd 481.2534, found 481.2543.

6: prepared from **6c** following the procedure for **4**, as a colourless oil (0.50g, 2.3 mmol, 76% yield). Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, *R_f* = 0.44; ¹H NMR (300 MHz, CDCl₃) δ 3.86 (s, 3H), 2.80 (t, *J* = 7.9 Hz, 2H), 1.00–1.75 (m, 16H), 0.87 (d, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 194.67, 161.69, 52.90, 44.54, 39.69, 37.87, 29.87, 29.70, 26.92, 23.43,

22.91, 11.99; IR (CH₂Cl₂) 1728, 1606 cm⁻¹; EIMS *m/z* 240 (M⁺), 163 (10); HRMS (EI) for C₁₄H₂₄O₃ (M⁺), calcd 240.1725, found 240.1730.

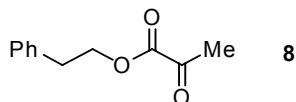
Preparation of ketones 7–10.

Ketones 7–10 were synthesized by coupling of pyruvic chloride with the corresponding alcohols. The preparation of pyruvic chloride follows a literature procedure (Ottenheim, H. C. J; de Man, J. H. M. *Syn. Comm.* **1975**, 5, 163). The preparation of ketone 7 was given as an example.

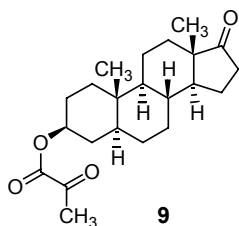


a) CH₃COCOCl, pyridine, CH₂Cl₂, rt

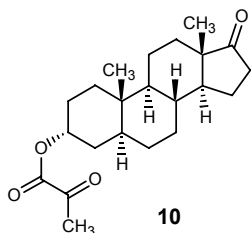
α,α -Dichloromethyl methyl ether (3.3 mL, 37 mmol) was added dropwise to pyruvic acid (3.2 g, 37 mmol) at room temperature. The reaction mixture was heated at 50 °C for 45 min. Then the crude acid chloride was added dropwise to a solution of 7a (0.84 g, 7.3 mmol) and pyridine (5 mL) in CH₂Cl₂ (70 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was diluted with CH₂Cl₂. The organic layer was washed with diluted aqueous HCl, saturated aqueous NaHCO₃, dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in n-hexane) to give 7 (0.49 g, 2.66 mmol, 36% yield) as a colourless oil. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, *R_f* = 0.5; ¹H NMR (270 MHz, CDCl₃) δ 4.05 (t, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 1.47–1.77 (m, 6H), 0.88–1.37 (m, 5H); ¹³C NMR (75.48 MHz, CDCl₃) δ 191.44, 160.52, 70.39, 36.55, 29.14, 26.22, 25.87, 25.20; IR (CH₂Cl₂) 1731 cm⁻¹; EIMS (20 eV) *m/z* 184 (M⁺, 1), 113 (100); HRMS (EI) for C₁₁H₁₂O₃ (M⁺), calcd 184.1098, found 184.1099.



8 (45% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.5; as a colourless oil; ^1H NMR (300 MHz, CDCl_3) δ 7.14–7.31 (m, 5H), 4.41 (t, J = 7.1 Hz, 2H), 3.00 (t, J = 7.1 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 191.63, 160.55, 136.97, 128.93, 128.61, 126.82, 66.64, 34.75, 26.64; IR (CH_2Cl_2) 1750, 1733 cm^{-1} ; EIMS (20 eV) m/z 192 (M^+ , 2); HRMS (EI) for $\text{C}_{11}\text{H}_{12}\text{O}_3$ (M^+), calcd 192.0786, found 192.0786.



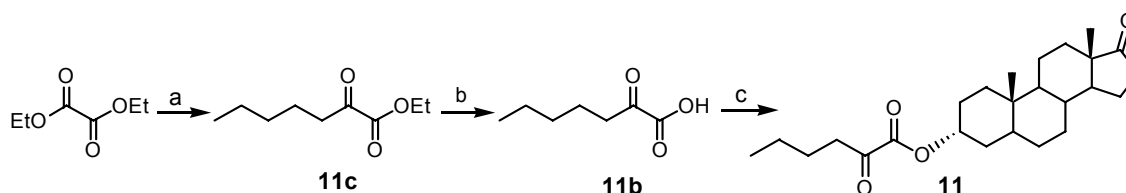
9 (36% yield). A white solid. M.p. 165 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.65; ^1H NMR (270 MHz, CDCl_3) δ 4.78–4.89 (m, 1H), 2.46 (s, 3H), 2.40–2.49 (m, 1H), 0.68–2.07 (m, 21H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 221.04, 192.38, 160.40, 76.18, 54.22, 51.31, 47.72, 44.63, 36.58, 35.78, 35.60, 34.97, 33.52, 31.48, 30.73, 28.18, 27.06, 26.62, 21.73, 20.43, 13.77, 12.17; IR (CH_2Cl_2) 1750, 1733 cm^{-1} ; EIMS (20 eV) m/z 360 (M^+ , 8), 272 (100); HRMS (EI) for $\text{C}_{22}\text{H}_{32}\text{O}_4$ (M^+), calcd 360.2301, found 360.2307.



10 (45% yield) as a white solid. M.p. 164 °C. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.29; ^1H NMR (270 MHz, CDCl_3) δ 5.16–5.30 (m, 1H), 2.48 (s, 3H), 0.90–2.40 (m,

22H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 221.07, 192.39, 160.51, 72.99, 54.17, 51.46, 47.77, 40.02, 35.96, 38.81, 35.02, 32.74, 32.60, 31.53, 30.63, 27.96, 26.79, 25.94, 21.73, 20.07, 13.82, 11.34; IR (CH_2Cl_2) 1750, 1733 cm^{-1} ; EIMS (20 eV) m/z 360 (M^+ , 2), 272 (100); HRMS (EI) for $\text{C}_{22}\text{H}_{32}\text{O}_4$ (M^+), calcd 360.2301, found 360.2300.

Preparation of ketone 11.



a) Pentylmagnesium bromide, ether, 10 $^{\circ}\text{C}$, N_2 ; b) 1M HCl, reflux; c) i) CHCl_2OMe , CH_2Cl_2 , 50 $^{\circ}\text{C}$, ii) Epiandrosterone, pyridine CH_2Cl_2 , DMAP

To a solution of diethyl oxalate (5.48 mL, 40 mmol) in Et_2O (30 mL) was added pentylmagnesium bromide (2 M in ether, 10 mL, 20 mmol) at -10 $^{\circ}\text{C}$ under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 h, then quenched with brine and extracted with Et_2O . The combined organic layers were dried over anhydrous MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (3% EtOAc in n-hexane) to furnish ketone **11c** (0.96 g, 5.6 mmol, 28% yield) as a colourless oil. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, R_f = 0.48; ^1H NMR (400 MHz, CDCl_3) δ 4.31 (q, J = 7.3 Hz, 3H), 2.82 (t, J = 7.3 Hz, 2H), 1.64 (t, J = 7.3 Hz, 3H), 1.25–1.42 (m, 8H), 0.90 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100.61 MHz, CDCl_3) δ 194.81, 161.30, 62.32, 39.22, 31.08, 22.65, 22.31, 13.98, 13.82; IR (CH_2Cl_2) 1723 cm^{-1} . (ref: Barry, J.; Kagan, H. B. *Synthesis* **1981**, 6, 453).

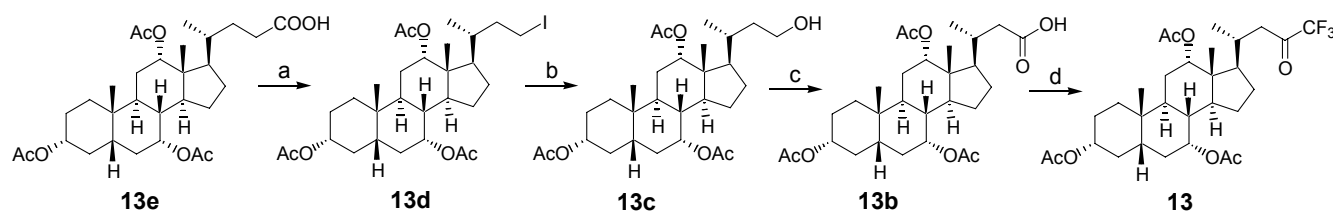
A solution of ketone **11c** (0.38 g, 2.2 mmol) in 1 M HCl was heated to reflux for 6 h. The reaction mixture was extracted with EtOAc , dried over anhydrous MgSO_4 and concentrated under reduced pressure to furnish acid **11b** (0.29 g, 2.0 mmol, 91% yield) as a colourless oil; ^1H NMR (400 MHz, CDCl_3) δ 2.93 (t, J = 7.1 Hz, 2H), 1.65–1.68 (m, 2H), 1.21–1.35 (m, 4H), 0.91 (t, J =

6.0 Hz, 3H); ^{13}C NMR (100.61 MHz, CDCl_3) δ 195.98, 159.79, 37.38, 31.01, 22.73, 22.27, 13.78; IR (CH_2Cl_2) 3536, 1722 cm^{-1} . (ref: Barry, J.; Kagan, H. B. *Synthesis* **1981**, 6, 453).

α,α -Dichloromethyl methyl ether (0.26 mL, 2.2 mmol) was added dropwise to **11c** (0.29 g, 2.0 mmol) at room temperature. The reaction mixture was heated at 50 °C for 45 min. Then the crude acid chloride was added dropwise to a solution of epiandrosterone (0.58 g, 2.0 mmol) and pyridine (1.6 mL) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 15 min, the reaction mixture was diluted with CH_2Cl_2 . The organic layer was washed with diluted aqueous HCl, saturated aqueous NaHCO_3 , dried over anhydrous MgSO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in n-hexane) to furnish ketone **11** (0.18 g, 22% yield) as a white solid. M.p. 167 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.63; ^1H NMR (400 MHz, CDCl_3) δ 5.16–5.18 (m, 1H), 2.81 (t, J = 7.3 Hz, 3H), 0.83–2.48 (m, 36H); ^{13}C NMR (100.61 MHz, CDCl_3) δ 221.25, 195.30, 160.73, 72.79, 70.14, 54.14, 51.42, 47.77, 40.00, 39.40, 35.93, 35.82, 34.98, 32.73, 32.58, 31.50, 30.76, 28.00, 27.94, 26.08, 25.93, 22.78, 21.73, 20.05, 13.81, 11.34; IR (CH_2Cl_2) 1735 cm^{-1} ; EIMS m/z 272 ($\text{M}^+ - \text{C}_7\text{H}_{12}\text{O}_3$, 100); HRMS (EI) for $\text{C}_{19}\text{H}_{29}\text{O}$ ($\text{M}^+ - \text{C}_7\text{H}_{12}\text{O}_3$), calcd 272.2139, found 272.2131.

Preparation of ketone 13.

Alcohol **13c** was prepared from acid **13e** according to a literature procedure (Gargiulo, D.; Blizzard, T. A.; Nakanishi, K. *Tetrahedron* **1989**, 45, 5423.)



a) hv, iodosobenzene diacetate (IBDA), I_2 , 70 °C; b) Ag_2CO_3 , aq. acetone, 50 °C; c) PDC, DMF, rt; d) i, oxalyl chloride, CH_2Cl_2 ; ii, $(\text{CF}_3\text{CO})_2\text{O}$, pyridine, CH_2Cl_2 .

13d (64% yield). ^1H NMR (300 MHz, CDCl_3) δ 4.95–5.05 (m, 1H), 4.89–4.93 (m, 1H), 4.52–4.63 (m, 1H), 3.07–3.29 (m, 2H), 2.14 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 0.95–2.05 (m, 24H), 0.92 (s, 3H), 0.81 (d, $J = 6.0$ Hz, 3H), 0.75 (s, 3H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 170.50, 170.46, 170.34, 75.34, 74.07, 70.66, 47.29, 45.15, 43.39, 40.91, 40.04, 37.72, 36.42, 34.68, 34.60, 34.33, 31.23, 28.87, 27.21, 26.89, 25.56, 22.78, 22.56, 21.62, 21.49, 21.45, 17.05, 12.23, 4.66.

13c (81% yield). ^1H NMR (300 MHz, CDCl_3) δ 5.10–5.12 (m, 1H), 4.89–4.92 (m, 1H), 4.52–4.63 (m, 1H), 3.60–3.70 (m, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 0.94–2.01 (m, 24H), 0.92 (s, 3H), 0.85 (d, $J = 6.4$ Hz, 3H), 0.75 (s, 3H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 170.55, 170.40, 75.45, 74.12, 70.73, 60.72, 47.99, 45.15, 43.43, 40.95, 38.69, 37.76, 34.72, 34.62, 34.36, 32.18, 31.28, 28.91, 27.41, 26.91, 25.59, 22.86, 22.58, 21.64, 21.51, 21.47, 18.06, 12.24.

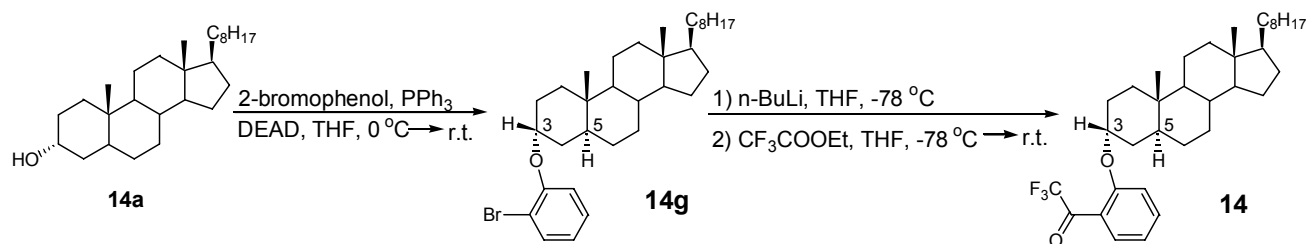
To a solution of alcohol **13c** (2.2 g, 4.3 mmol) in DMF (45 mL) was added freshly prepared pyridinium dichromate (16.5 g, 44 mmol). After stirring at room temperature overnight, the reaction mixture was poured into H_2O , and extracted with diethyl ether. The organic phase was separated, washed with brine, dried over anhydrous MgSO_4 , and concentrated under reduced pressure to give acid **13b** (1.8 g, 3.4 mmol, 80% yield) as a white solid. M.p. 123–125 °C. ^1H NMR (270 MHz, CDCl_3) δ 5.05–5.12 (m, 1H), 5.88–4.95 (m, 1H), 4.47–4.72 (m, 1H), 2.45 (dd, $J = 15, 3$ Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 0.98–1.98 (m, 22H), 0.92 (s, 6H), 0.77 (s, 3H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 178.73, 170.62, 170.52, 170.45, 75.25, 74.10, 70.69, 47.25, 45.15, 43.47, 40.97, 40.92, 37.74, 34.70, 34.61, 34.35, 32.91, 31.25, 28.88, 27.38, 26.89, 25.56, 22.79, 22.57, 21.65, 21.51, 21.42, 18.70, 12.22; IR (CH_2Cl_2) 3687, 1726 cm^{-1} . (ref: Gao, H. W.; Dias, J. R. *Syn. Comm.* **1997**, 27, 757.)

To a solution of acid **13b** (1.3 g, 2.5 mmol) in CH_2Cl_2 (30 mL) was added oxalyl chloride (2.2 mL, 25 mmol). The resulting mixture was stirred at room temperature overnight. Then the solvent and excess oxalyl chloride were evaporated off under reduced pressure. The resulting acid chloride was dissolved in CH_2Cl_2 (30 mL), and treated with trifluoroacetic anhydride (2.1 mL, 15 mmol) and

pyridine (1.6 ml, 20 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 h, quenched slowly with H₂O at 0 °C, and extracted with CH₂Cl₂. The organic layer was separated, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc in n-hexane) to furnish trifluoromethyl ketone **13** (0.46 g, 0.82 mmol, 32% yield) as a white solid. M.p. 73–75 °C. ¹H NMR (300 MHz, CDCl₃) δ 5.08–5.09 (m, 1H), 4.90–4.92 (m, 1H), 4.53–4.63 (m, 1H), 2.70–2.77 (m, 1H), 2.45–2.55 (m, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 0.99–2.07 (m, 20H), 0.93 (s, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.78 (s, 3H); ¹³C NMR (67.94 MHz, CDCl₃) δ 191.14 (q, ²*J*_{C,F} = 34.3 Hz), 170.54, 170.45, 170.34, 115.46 (q, ¹*J*_{C,F} = 293 Hz), 75.10, 74.06, 70.62, 46.88, 45.23, 43.52, 42.95, 40.94, 37.76, 37.73, 34.73, 34.64, 34.36, 31.26, 31.23, 28.88, 27.46, 26.91, 25.58, 22.80, 22.55, 21.61, 21.48, 21.42, 18.70, 12.18; IR (CH₂Cl₂) 1726 cm⁻¹; CIMS *m/z* 572 (M⁺, 10), 513 (100); HRMS (EI) for C₂₆H₃₅O₃F₃ (M⁺–2×CH₃COOH), calcd 452.2538, found 452.2539.

Preparation of ketone **14**.

The preparation of ketone **14** followed literature procedures: (a) Marchand, A. P.; Dave, P. R. *J. Org. Chem.* **1989**, *54*, 2775. (b) Baldwin, J. E.; Jesudason, C. D.; Moloney, M. G.; Morgan, D. R.; Pratt, A. J. *Tetrahedron*, **1991**, *47*, 5603. (c) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.

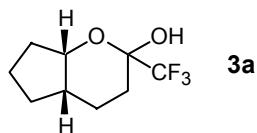


To a solution of **14a** (3.00 g, 7.72 mmol) and triphenylphosphine (2.00 g, 7.70 mmol) in tetrahydrofuran (50 mL) under nitrogen atmosphere at 0 °C, diethyl azodicarboxylate (1.21 mL, 7.70 mmol) was added in a dropwise fashion at a rate such that the reaction temperature was maintained below 10 °C. Upon completion of the addition, the temperature was increase to room temperature. After stirring overnight, the reaction mixture was concentrate under reduced pressure. The residue was purified by flash column chromatography (10 % EtOAc in n-hexane) to furnish **14g** (3.6 g, 6.62 mmol, 86% yield) as a white solid. M.p. 135 °C. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.73; ^1H NMR (300 MHz, CDCl_3) δ 7.50 (dd, J = 7.8, 1.4 Hz, 1H), 7.17 (dt, J = 7.1, 1.4 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.75 (dt, J = 7.6, 1.0 Hz, 1H), 4.56 (br s, 3H), 1.96 (br d, J = 11.6 Hz, 1H), 0.90–1.90 (m, 30H), 0.90 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 1H), 0.86 (d, J = 6.6 Hz, 1H), 0.81 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 154.0, 133.4, 128.1, 121.4, 115.1, 113.8, 73.5, 56.4, 56.2, 54.2, 42.5, 40.0, 39.5, 39.4, 36.2, 35.8, 35.7, 35.5, 32.7, 32.6, 31.9, 28.4, 28.2, 28.0, 25.7, 24.1, 23.8, 22.8, 22.6(2C), 20.8, 18.7, 12.1, 11.5; IR (CH_2Cl_2) 1476 cm^{-1} . EIMS (20 eV) m/z 542 (M^+ , 1), 370 (100); HRMS (EI) for $\text{C}_{33}\text{H}_{51}\text{BrO}$ (M^+), calcd 542.3123, found 542.3121.

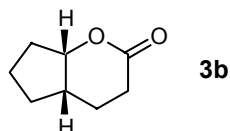
To a solution of **14g** (2.72 g, 5.00 mmol) in tetrahydrofuran (50 mL) under nitrogen atmosphere at –78 °C was added slowly n-butyl lithium (1M in hexane, 6 mL, 6.00 mmol). After stirring for 30 mins, ethyl trifluoroacetate (0.90 mL, 6.00 mmol) was added to the above reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight, then quenched with brine and extracted with Et_2O . The residue was purified by flash column chromatography (15% EtOAc in n-hexane) to furnish ketone **14** (2.0 g, 3.60 mmol, 72% yield) as a white solid. M.p. 74–76 °C. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, R_f = 0.64; ^1H NMR (300 MHz, CDCl_3) δ 7.62 (d, J = 6.7 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 6.98 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 4.67 (br s, 3H), 1.96 (br d, J = 9.5 Hz, 1H), 0.85–1.90 (m, 30H), 0.90 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 1H), 0.86 (d, J = 6.6 Hz, 1H), 0.82 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ

183.6 (q, $J = 36.4$ Hz, C=O), 158.2, 135.3, 131.4, 122.5, 119.8, 116.2 (q, $J = 291.5$ Hz, CF₃), 113.4, 73.9, 56.4, 56.3, 54.1, 42.6, 40.0, 39.6, 39.2, 36.2, 35.9, 35.6, 35.5, 32.5, 32.4, 31.9, 28.5, 28.3, 28.0, 25.8, 24.2, 23.9, 22.9, 22.6, 20.9, 18.7, 12.1, 11.4; IR (CH₂Cl₂) 2356, 1715, 1597 cm⁻¹. EIMS (20 eV) m/z 560 (M⁺, 1), 370 (100); HRMS (EI) for C₃₅H₅₁F₃O₂ (M⁺), calcd 560.3841, found 560.3827.

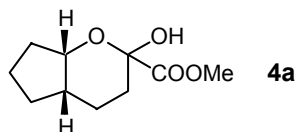
Characterization Data of Hemiketals



Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, R_f = 0.22; as an oil; ^1H NMR (300 MHz, CDCl_3) δ 4.29–4.32 (m, 1H), 2.73 (d, J = 2.0 Hz, 1H), 2.00–2.19 (m, 1H), 1.53–1.97 (m, 10H); ^{13}C NMR (67.94 MHz, CDCl_3) δ 122.98 (q, $^1J_{\text{C,F}}$ = 285.5 Hz), 94.36 (q, $^2J_{\text{C,F}}$ = 32.1 Hz), 75.09, 37.82, 32.97, 26.85, 22.89, 21.85, 18.93; IR (CH_2Cl_2) 1741 cm^{-1} ; EIMS (20 eV) m/z 210 (M^+ , 17), 181 (100); HRMS (EI) for $\text{C}_9\text{H}_{13}\text{O}_2\text{F}_3$ (M^+), calcd 210.0868, found 210.0853.



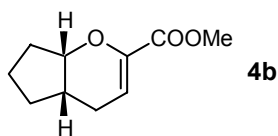
Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.31; ^1H NMR (300 MHz, CDCl_3) δ 4.71–4.76 (m, 1H), 1.46–2.62 (m, 11H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 173.67, 83.40, 36.97, 33.65, 30.98, 28.78, 23.62, 23.04. (ref: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111.)



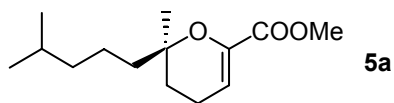
As a white solid. M.p. 113–114 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.4; ^1H NMR (300 MHz, CDCl_3) δ 4.36 (t, J = 7.5 Hz, 1H), 3.81 (s, 3H), 3.58 (s, 1H), 1.50–2.17 (m, 11H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 171.60, 94.75, 74.48, 53.00, 38.18, 33.05, 27.39, 25.73, 23.00, 19.73; IR (KBr) $3539, 1740\text{ cm}^{-1}$; EIMS (20 eV) m/z 182 ($\text{M}^+ - \text{H}_2\text{O}$, 100), 153 (100), 125 (78); HRMS (EI) for $\text{C}_{10}\text{H}_{16}\text{O}_4$ ($\text{M}^+ - \text{H}_2\text{O}$), calcd 182.0943, found 182.0950.

Preparation of 4b.

Ester **4b** was synthesized from **4a** according to a literature procedure (Norbeck, D. W.; Kramer, J.B.; Lartey, P. A. *J. Org. Chem.* **1987**, 52, 2174).

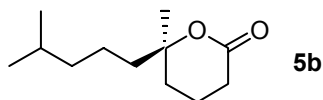


To a solution of **4a** (80 mg, 0.40 mmol) in CH₂Cl₂ (4 mL) were added triethylamine (0.3 mL) and methanesulfonyl chloride (0.13 mL) at room temperature. After 4 h the reaction was poured into 10% aqueous NaHCO₃, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc in hexane) to give **4b** as a colourless oil (60 mg, 0.33 mmol, 82% yield). Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, *R_f* = 0.5; ¹H NMR (270 MHz, CDCl₃) δ 6.05 (dd, *J* = 6.3, 3.3 Hz, 1H), 4.22 (br s, 1H), 3.79 (s, 3H), 1.68–2.49 (m, 9H); ¹³C NMR (75.48 MHz, CDCl₃) δ 163.65, 142.65, 109.50, 79.34, 52.06, 36.48, 32.11, 28.60, 22.61, 21.36; IR (CH₂Cl₂) 1728, 1652 cm⁻¹; EIMS (20 eV) *m/z* 182 (M⁺, 86), 151 (18), 123 (35); HRMS (EI) for C₁₀H₁₄O₃ (M⁺), calcd 182.0943, found 182.0939.

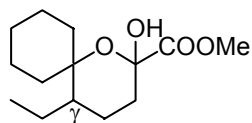


As an oil. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, *R_f* = 0.58; [α]_D²⁰ +8.50° (*c* 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 6.03 (t, *J* = 4.3 Hz, 1H), 3.77 (s, 3H), 2.13–2.19 (m, 2H), 1.51–1.67 (m, 6H), 1.30–1.38 (m, 2H), 1.25 (s, 3H), 1.14–1.20 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 164.11, 142.79, 109.67, 77.30, 52.10, 39.41, 39.07, 30.15, 27.92,

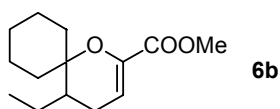
23.58, 22.68, 21.53, 18.80; IR (CH₂Cl₂) 1726, 1604 cm⁻¹; EIMS (20 eV) *m/z* 240 (M⁺, 6), 181 (17), 171 (83); HRMS (EI) for C₁₄H₂₄O₃ (M⁺), calcd 240.1725, found 240.1733.



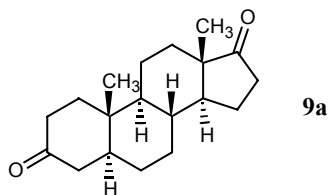
As an oil. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, *R_f* = 0.33; [α]_D²⁰ -2.38 (*c* 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 2.57–2.64 (m, 2H), 1.95–2.11 (m, 2H), 1.17–1.66 (m, 9H), 1.38 (s, 3H), 0.87 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 177.00, 87.09, 41.32, 39.20, 33.11, 29.31, 27.98, 25.74, 22.68, 21.76; IR (CH₂Cl₂) 1730 cm⁻¹; EIMS (20 eV) *m/z* 199 (M⁺+1, 52), 169 (57), 136 (95); HRMS (EI) for C₁₂H₂₂O₂ (M⁺), calcd 198.1619, found 198.1612.



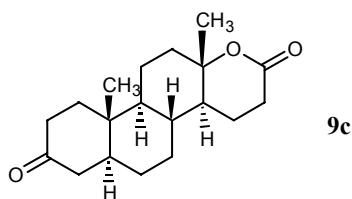
As a white solid. M.p. 77–79 °C. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, *R_f* = 0.31 and 0.30 (γ-substituted 4 : 1); ¹H NMR (300 MHz, CDCl₃) δ 3.80 (s, 4/5×3H), 3.79 (s, 1/5×3H), 3.67 (d, *J* = 2 Hz, 4/5×1H), 3.64 (d, *J* = 2 Hz, 1/5×1H), 1.96–2.07 (m, 2H), 0.88–1.08 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 172.14, 94.98, 78.80, 53.05, 47.48, 37.48, 31.46, 29.93, 26.51, 24.14, 21.96, 20.18, 17.62, 12.75; IR (CH₂Cl₂) 3600, 1738 cm⁻¹; EIMS *m/z* 256 (M⁺), 328 (51), 200 (10); HRMS (EI) for C₁₄H₂₄O₄ (M⁺), calcd 256.1674, found 256.1667.



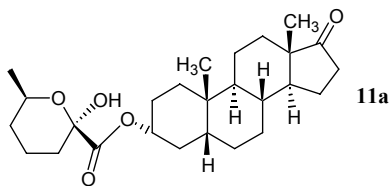
As a yellow oil. Analytical TLC (silica gel 60), 10% EtOAc in n-hexane, $R_f = 0.42$; ^1H NMR (300 MHz, CDCl_3) δ 6.02 (t, $J = 4$ Hz, 1H), 3.77 (s, 3H), 2.31 (dt, $J = 19.0, 5.0$ Hz, 1H), 0.90–1.89 (m, 13H), 0.92 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.19, 142.02, 110.41, 78.86, 52.09, 41.36, 34.17, 28.00, 26.16, 23.84, 22.72, 21.59, 21.47, 14.26, 12.51; IR (CH_2Cl_2) 1728 cm^{-1} ; EIMS m/z 238 (M^+ , 24), 123 (10); HRMS (EI) for $\text{C}_{14}\text{H}_{22}\text{O}_3$ (M^+), calcd 238.1568, found 238.1518.



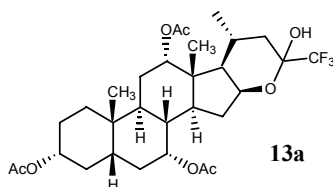
Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.18$; ^1H NMR (300 MHz, CDCl_3) δ 1.22–2.50 (m, 20H), 0.76–1.08 (m, 2H), 1.04 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75.48 MHz, CDCl_3) δ 220.87, 211.53, 53.85, 51.20, 47.69, 46.57, 44.54, 38.40, 38.03, 35.77, 34.92, 31.45, 30.50, 28.58, 21.74, 20.67, 13.76, 11.42; EIMS (20 eV) m/z 288 (M^+ , 100); HRMS (EI) for $\text{C}_{19}\text{H}_{28}\text{O}_2$ (M^+), calcd 288.2089, found 288.2084. (ref: Reich, H. J.; Jautelat, M.; Messe, M. T.; Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 7445.)



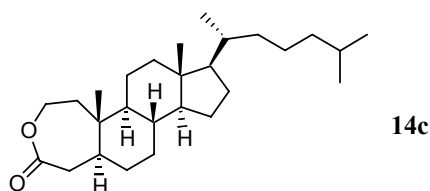
As a white solid. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, $R_f = 0.25$; ^1H NMR (400 MHz, CDCl_3) δ 3.03 (t, $J = 7.5$ Hz 2H), 0.78–2.72 (m, 26H); ^{13}C NMR (75 MHz, CDCl_3) δ 221.26, 171.37, 83.09, 52.52, 46.11, 45.91, 44.28, 39.15, 38.18, 37.78, 37.44, 35.64, 30.27, 28.48, 28.32, 22.18, 20.11, 19.81, 11.32 (ref: Hanson, J. R.; Hunter, A. C. *Phytochemistry* **1998**, *49*, 2349).



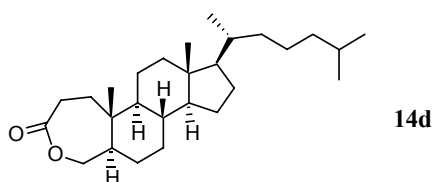
As a white solid. M.p. 170 °C. Analytical TLC (silica gel 60), 30% EtOAc in n-hexane, R_f = 0.44; ^1H NMR (400 MHz, CDCl_3) δ 5.08 (br s, 1H), 4.07–4.14 (m, 1H), 3.63 (dd, J = 9.6, 1.8 Hz, 1H), 0.77–2.49 (m, 37H); ^{13}C NMR (75 MHz, CDCl_3) δ 221.25, 170.51, 94.69, 72.23, 67.17, 54.37, 51.41, 47.75, 40.03, 35.78, 34.97, 32.83, 32.43, 31.49, 30.72, 29.93, 27.93, 26.86, 25.75, 22.59, 21.77, 21.68, 20.04, 18.48, 13.77, 11.32; IR (CH_2Cl_2) 1735cm^{-1} ; EIMS (20 eV) m/z 414 ($\text{M}^+ - \text{H}_2\text{O}$, 6), 272 (66); HRMS (EI) for $\text{C}_{26}\text{H}_{38}\text{O}_4$ ($\text{M}^+ - \text{H}_2\text{O}$), calcd 414.2770, found 414.2764.



As a white solid. M.p. 105–108 °C. Analytical TLC (silica gel 60), 50% EtOAc in n-hexane, R_f = 0.54; ^1H NMR (500 MHz, CDCl_3) δ 4.89–1.96 (m, 2H), 4.55–4.61 (m, 1H), 4.31–4.35 (m, 1H), 3.37–4.21 (m, 1H), 3.23 (s, OH), 2.13 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 0.90–2.21 (m, 20H), 0.94 (s, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.88 (s, 3H); ^{13}C NMR (125.75 MHz, CDCl_3) δ 170.58, 170.35, 170.25, 123.35 (q, $^1J_{\text{C},\text{F}}$ = 286 Hz), 95.51 (q, $^2J_{\text{C},\text{F}}$ = 31.3 Hz), 74.69, 71.42, 70.75, 50.74, 44.57, 40.94, 40.27, 37.32, 36.03, 34.78, 34.69, 74.06, 34.48, 31.75, 31.28, 29.17, 26.90, 25.45, 23.95, 22.54, 21.49, 21.44, 21.31, 20.83, 14.81; IR (CH_2Cl_2) $3555, 1725\text{ cm}^{-1}$; CIMS m/z 589 ($\text{M}^+ + 1$, 2), 469 (89), 409 (100); HRMS (EI) for $\text{C}_{26}\text{H}_{35}\text{O}_4\text{F}_3$ ($\text{M}^+ - 2 \times \text{CH}_3\text{COOH}$), calcd 468.2487, found 468.2480.

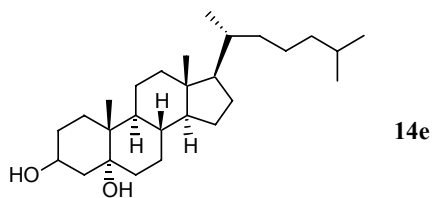


Analytical TLC (silica gel 60), as a white solid, 20% EtOAc in n-hexane, $R_f = 0.5$; ^1H NMR (300 MHz, CDCl_3) δ 4.29 (t, $J = 12.4$ Hz, 1H), 4.14 (ddd, $J = 11.4, 5.4, 1.9$ Hz, 1H), 2.86 (dd, $J = 14.2, 11.3$ Hz, 1H), 2.10 (d, $J = 14.3$ Hz, 1H), 1.98 (dt, $J = 12.5, 3.2$ Hz, 1H), 0.93–1.94 (m, 25H), 0.92 (s, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.5$ Hz, 1H), 0.86 (d, $J = 6.5$ Hz, 1H), 0.75 (tt, $J = 11.0, 3.8$ Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 176.0, 64.7, 56.2 (2C), 53.8, 43.4, 42.3, 41.7, 39.8, 39.5, 37.9, 37.6, 36.1, 35.8, 34.6, 31.9, 30.6, 28.2, 28.0, 24.1, 23.8, 22.8, 22.6 (2C), 21.3, 18.6, 12.1, 12.0; IR (CH_2Cl_2) 1729 cm^{-1} ; EIMS (20 eV) m/z 402 (M^+ , 100); HRMS (EI) for $\text{C}_{27}\text{H}_{46}\text{O}_2$ ($\text{M}^+ + 1$), calcd 403.3532, found 403.3531 (ref: Dave, V.; Stother, J. B.; Warnhoff, E. W. *Can. J. Chem.* **1984**, 62, 1965).

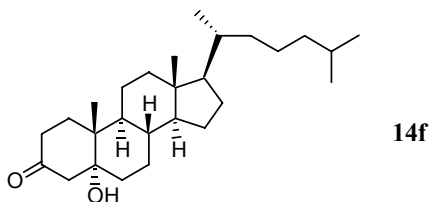


As a white solid. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.5$; ^1H NMR (300 MHz, CDCl_3) δ 4.28 (dd, $J = 13.0, 8.8$ Hz, 1H), 3.68 (d, $J = 13.0$ Hz, 1H), 2.69 (t, $J = 13.3$ Hz, 1H), 2.50 (dd, $J = 13.4, 6.8$ Hz, 1H), 1.98 (dt, $J = 12.5, 3.2$ Hz, 1H), 0.93–1.94 (m, 25H), 0.92 (s, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.87 (d, $J = 6.5$ Hz, 1H), 0.86 (d, $J = 6.5$ Hz, 1H), 0.75 (tt, $J = 11.0, 3.8$ Hz, 1H), 0.65 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 176.3, 70.1, 56.2 (2C), 53.6, 48.6, 42.3, 39.8, 39.5, 37.6, 36.2, 35.8, 35.5, 34.9, 31.6, 29.8, 28.2, 28.0, 26.3, 24.1, 23.8, 22.8, 22.6 (2C), 21.1, 18.6, 12.3, 12.0; IR (CH_2Cl_2) 1729 cm^{-1} ; EIMS (20 eV) m/z 402 (M^+ , 100); HRMS (EI) for

C₂₇H₄₆O₂ (M⁺+1), calcd 403.3532, found 403.3531 (ref: Dave, V.; Stother, J. B.; Warnhoff, E. W. *Can. J. Chem.* **1980**, *58*, 2666).

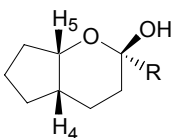
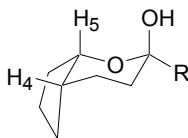
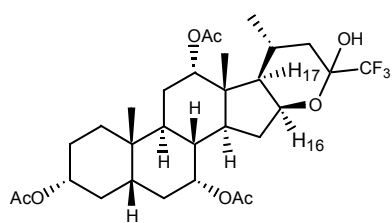
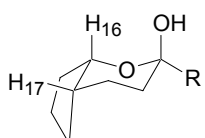


As a white solid. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.35$; ¹H NMR (300 MHz, CDCl₃) δ 4.07 (s, 1H), 3.21 (br s, 2H, OH), 1.99 (dt, $J = 10.9, 2.9$ Hz, 1H), 0.95–1.95 (m, 29H), 0.94 (s, 3H), 0.90 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 1H), 0.86 (d, $J = 6.5$ Hz, 2H), 0.66 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 75.2, 67.7, 56.3, 56.2, 45.8, 42.7, 40.0, 39.6, 39.5, 39.4, 36.2, 35.8, 34.8, 34.1, 29.2, 28.3, 28.0, 26.5, 25.5, 24.1, 23.9, 22.8, 22.6 (2C), 21.0, 18.7, 15.8, 12.2; IR (CH₂Cl₂) 3686, 3488 cm⁻¹ (ref: Mihailovic, M. L.; Lorenc, L.; Pavlovic, V. *Helv. Chim. Acta.* **1981**, *64*, 1032).



As a white solid. Analytical TLC (silica gel 60), 20% EtOAc in n-hexane, $R_f = 0.42$; ¹H NMR (300 MHz, CDCl₃) δ 2.67 (d, $J = 15.1$ Hz, 1H), 2.41–2.35 (m, 2H), 2.11 (dd, $J = 15.3, 1.2$ Hz, 1H), 2.01 (d, $J = 12.2$ Hz, 1H), 0.94–1.98 (m, 25H), 1.17 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.6$ Hz, 1H), 0.68 (s, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 210.9, 77.6, 56.3, 56.0, 51.9, 46.0, 42.7, 40.0, 39.5, 39.2, 37.9, 36.2, 35.8, 34.9, 34.5, 32.7, 28.3, 28.0, 26.3, 24.2, 23.9, 22.8, 22.6 (2C), 21.5, 18.7, 15.8, 12.1; IR (CH₂Cl₂) 1712 cm⁻¹ (ref: Collins, D. J.; Horn, C. M.; Welker, V. J. *Aust. J. Chem.* **1976**, *29*, 2077).

Table 1. 2D NOESY studies of cyclohemiketals **3a–4a**, and **13a**.^{a,b}

Cis-product	
 <p>3: R = COOMe 4: R = CF₃</p>	 <p>3a: R = COOMe 4a: R = CF₃</p> <p>NOE signal between H₄ and H₅</p>
 <p>13a</p>	 <p>NOE signal between H₁₆ and H₁₇ Only ring D and E was shown</p>

^a At the anomeric center C₁ the hydroxyl group prefers to be axial while the ester and trifluoromethyl groups prefer to be equatorial. For references regarding experimental and theoretical calculations of anomeric effect of tetrahydropyrans, see: (a) Booth, H.; Dixon, J. M.; Khedhair, K. A. *Tetrahedron* **1992**, 48, 6161. (b) Salzner, U.; Schleyer, P. von R. *J. Org. Chem.* **1994**, 59, 2138. (c) Cortes, F.; Tenorio, J.; Collera, O.; Cuevas, G. *J. Org. Chem.* **2001**, 66, 2918. ^b Only major product was shown.

HPLC Analysis of compound **5a**

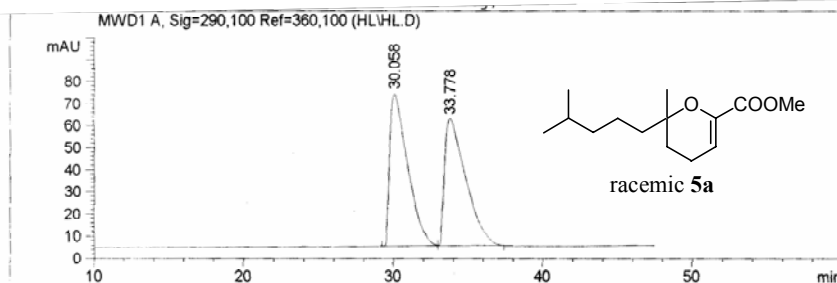
HPLC Conditions

Column: Chiral OD (Column No. OD00CE-AH045)

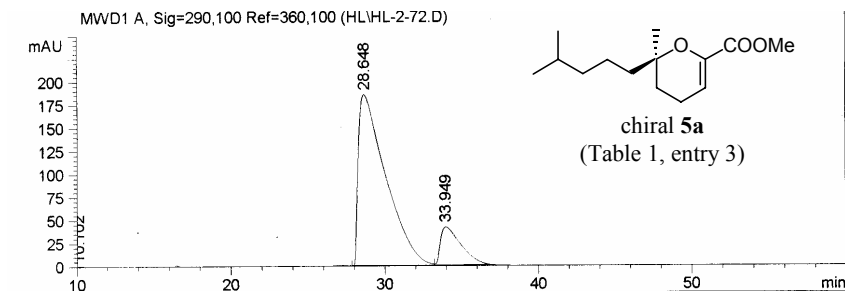
Solvents: n-Hexane/IPA (95.5/0.5)

Flowrate: 1.0 mL/min

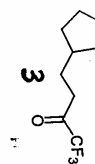
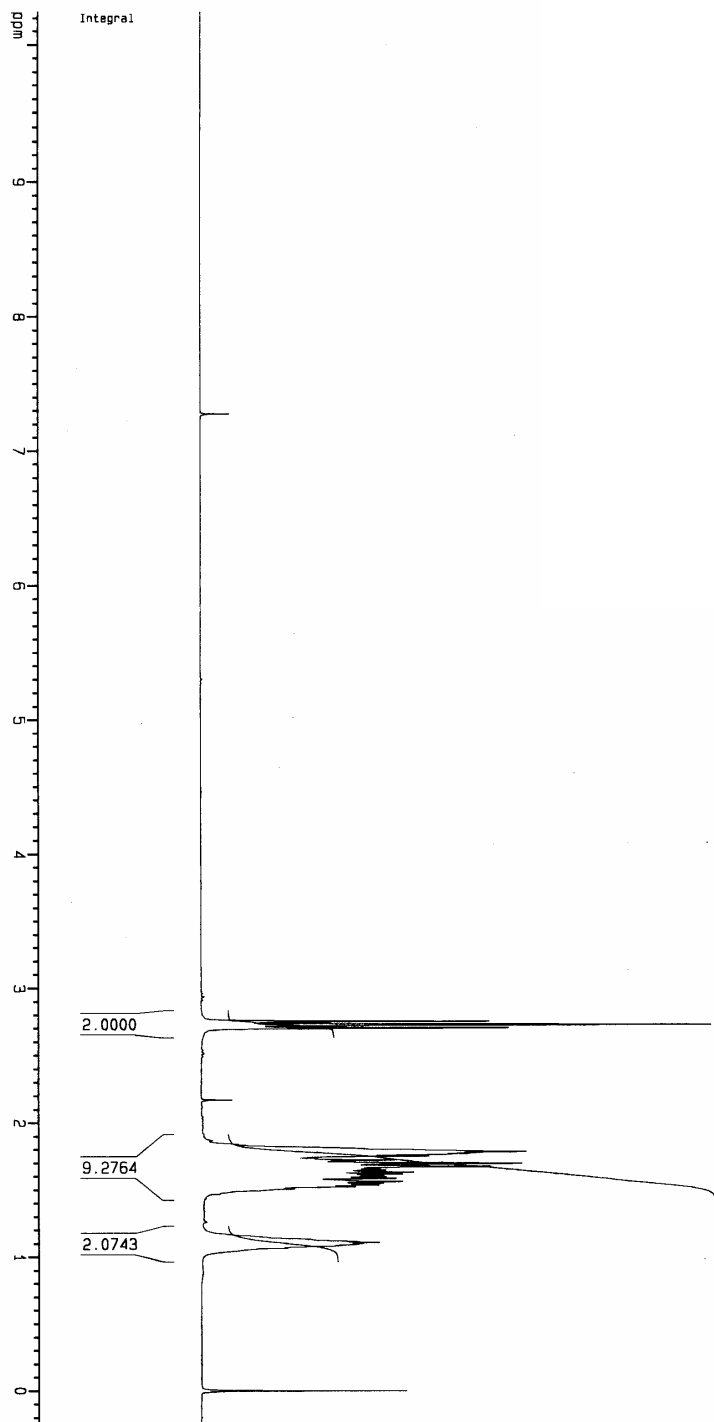
Detection: UV 289 nm

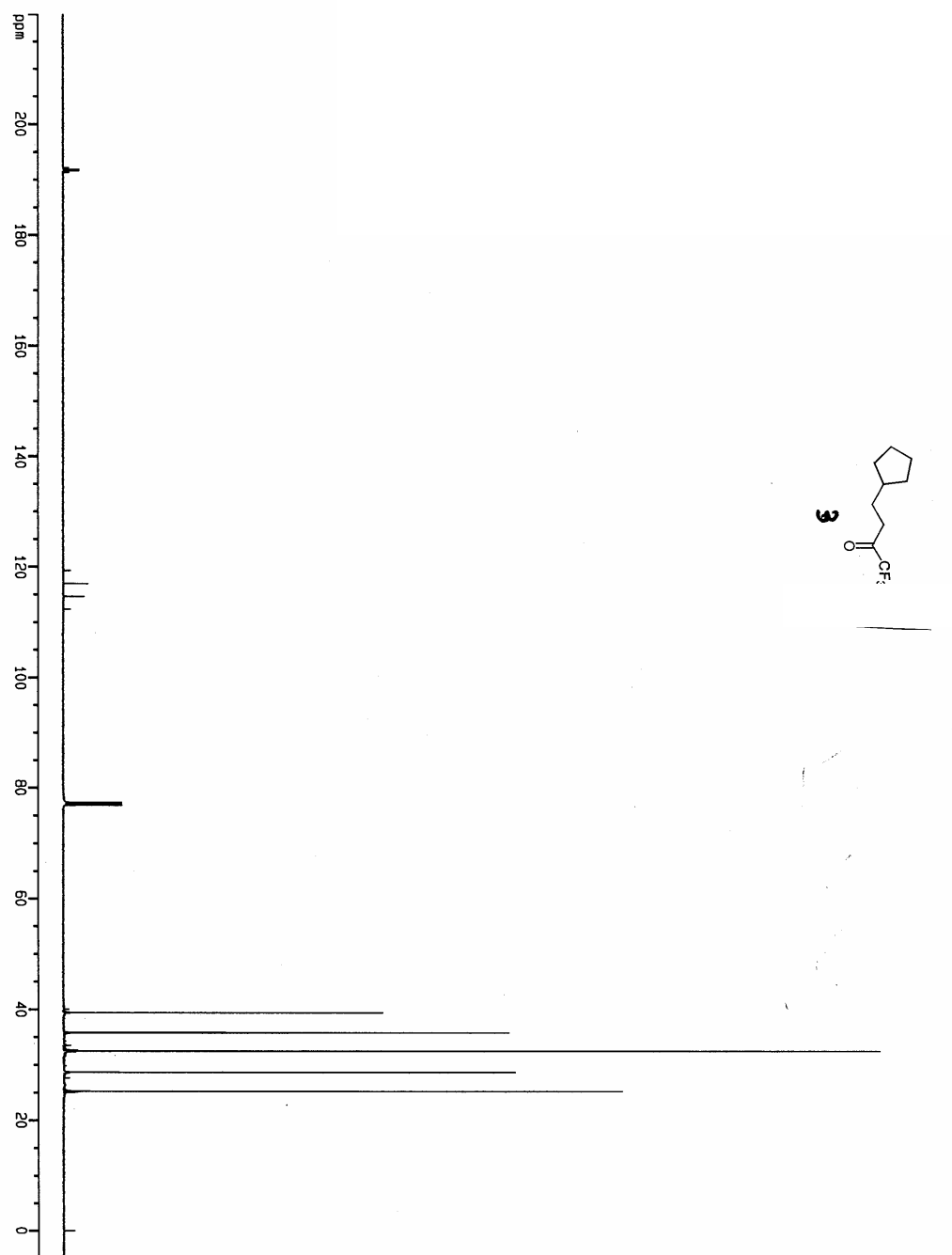


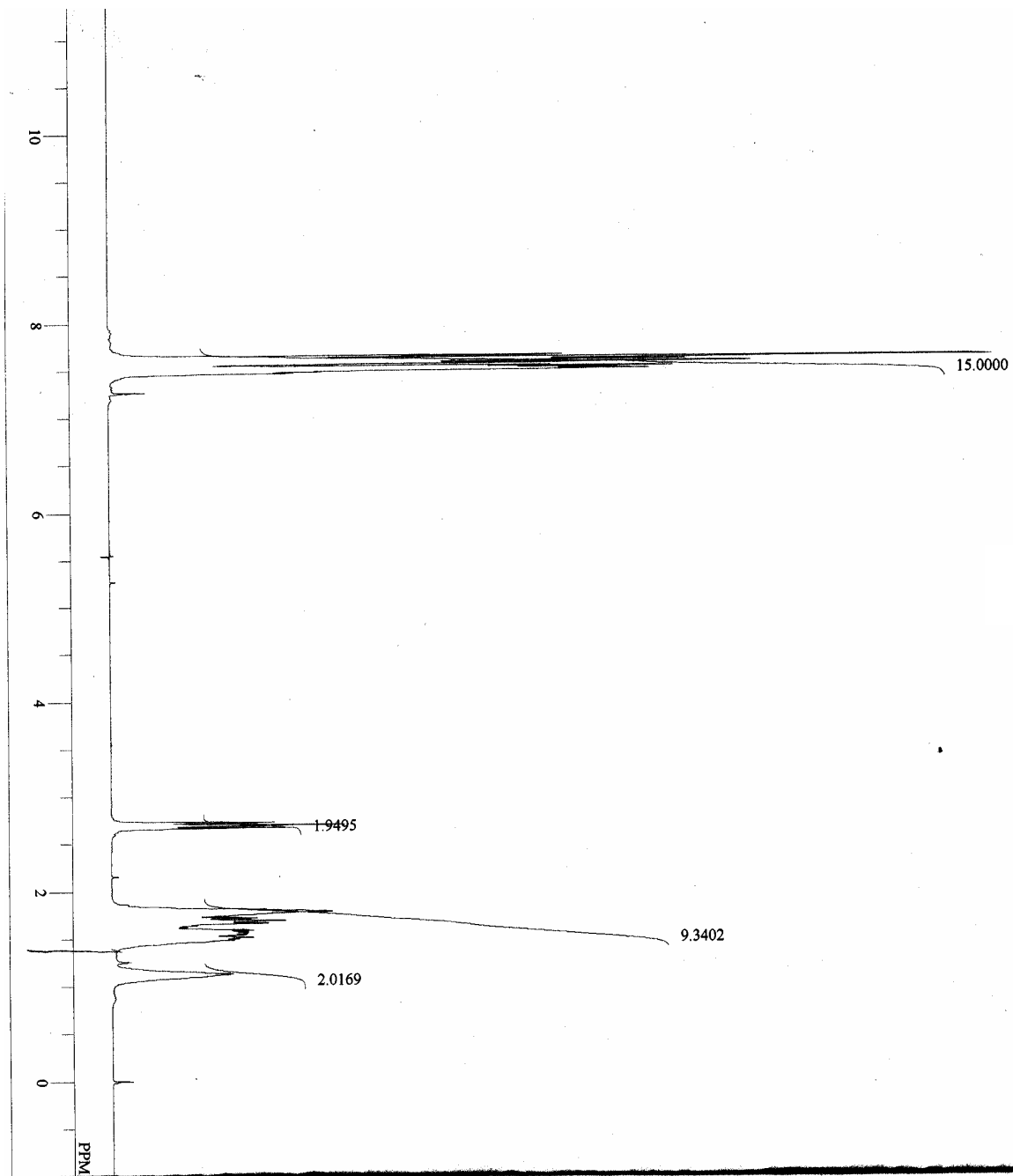
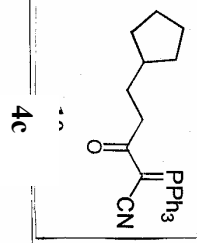
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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2	33.778	VB	1.1793	5685.16553	57.41090	49.7740

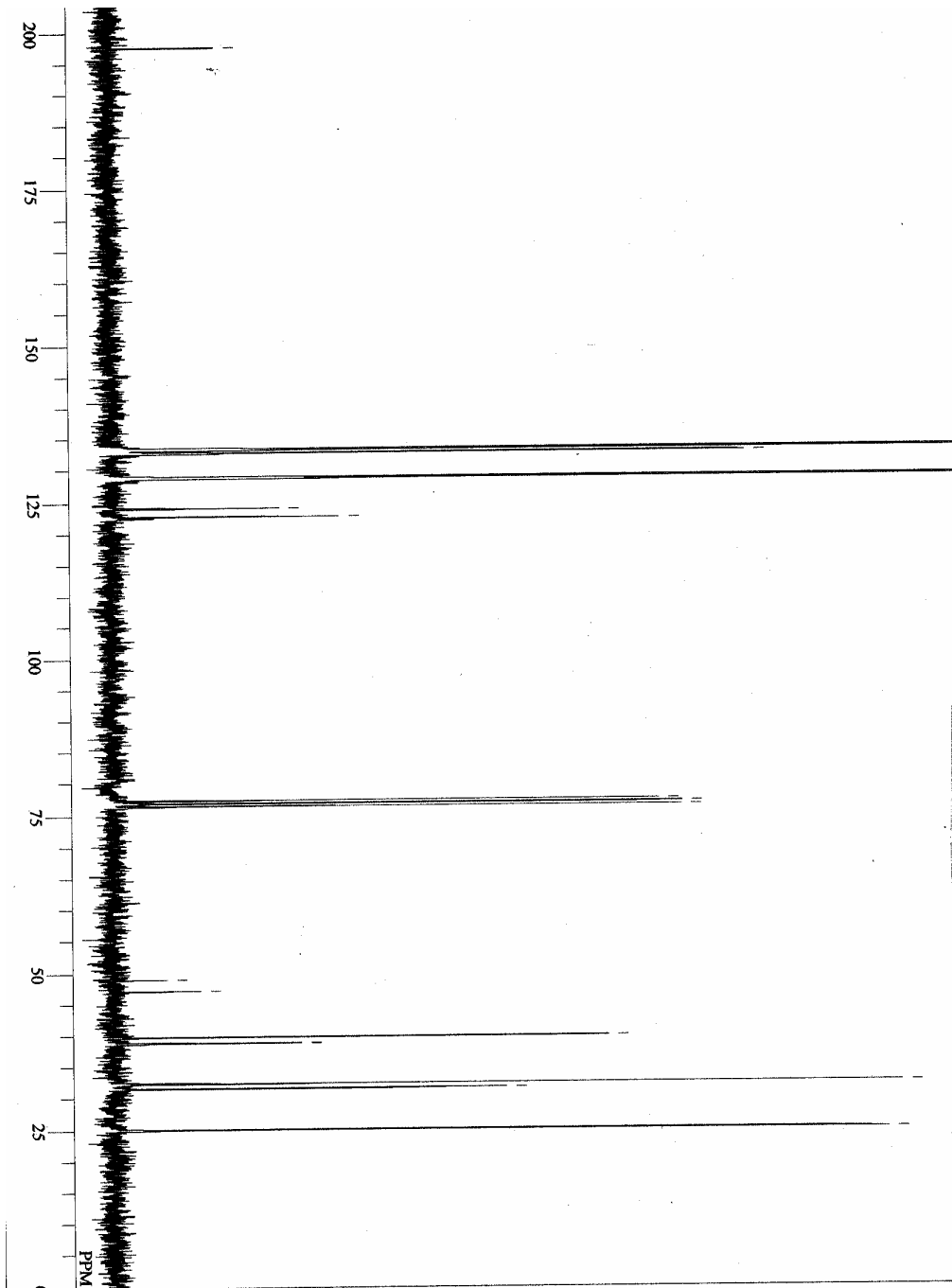
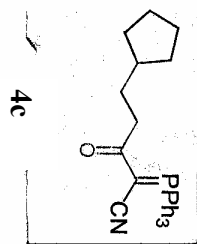


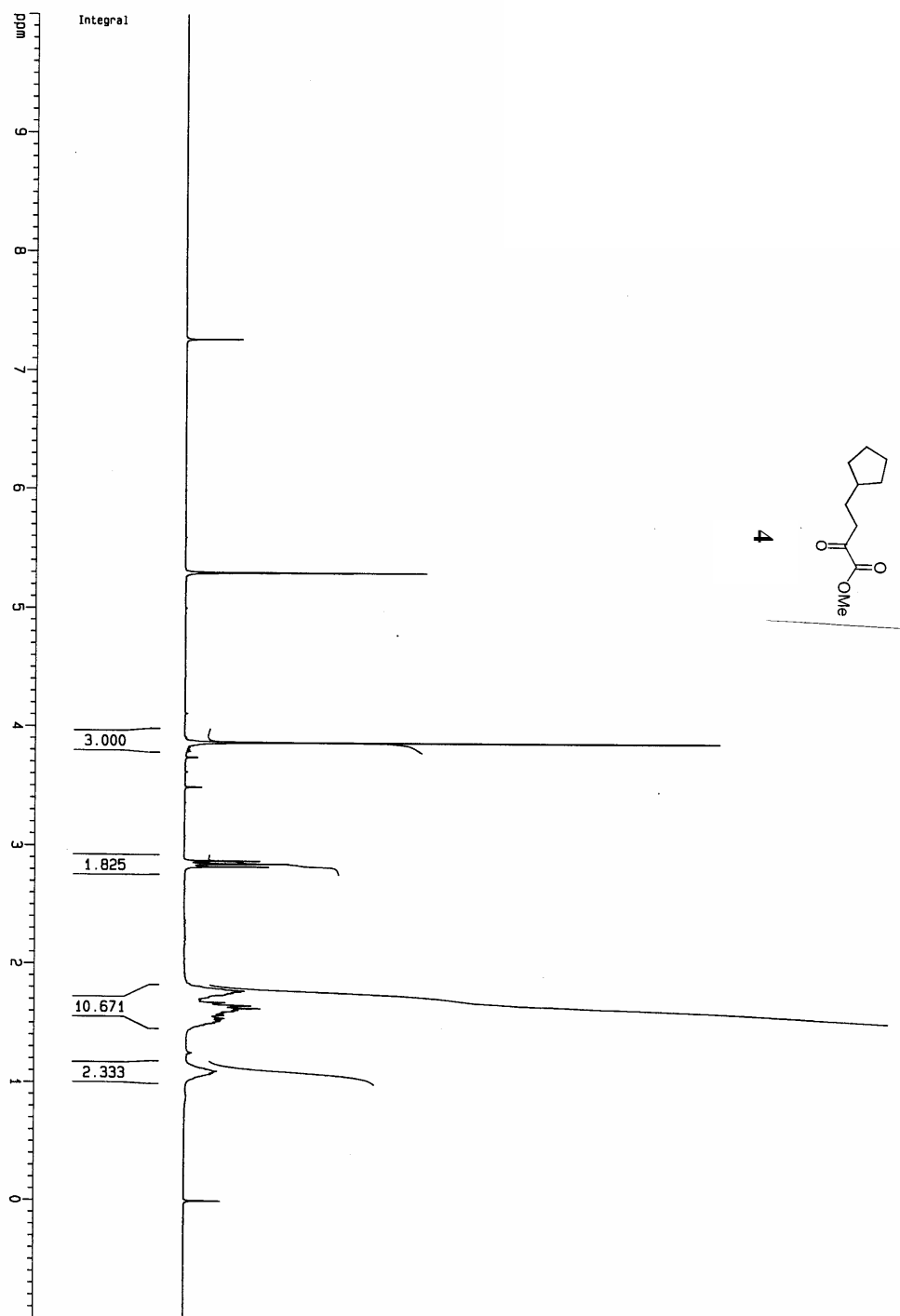
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.656	BV	0.1273	4.98914	5.52626e-1	0.0185
2	4.901	VV	0.1199	4.72600	6.13144e-1	0.0175
3	5.095	VV	0.1126	6.02060	8.30407e-1	0.0223
4	5.354	VB	0.2077	10.04083	7.33441e-1	0.0373
5	5.848	BV	0.1839	9.93431	8.65482e-1	0.0369
6	6.102	VP	0.1422	27.06237	2.81512	0.1004
7	7.131	BB	0.2455	8.81350	5.00453e-1	0.0327
8	10.102	PB	0.2040	4.39596	2.84960e-1	0.0163
9	28.648	BV	1.6333	2.30052e4	184.93938	85.3721
10	33.949	VB	1.2877	3865.78223	41.38974	14.3459

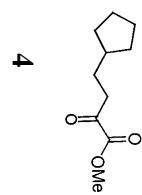




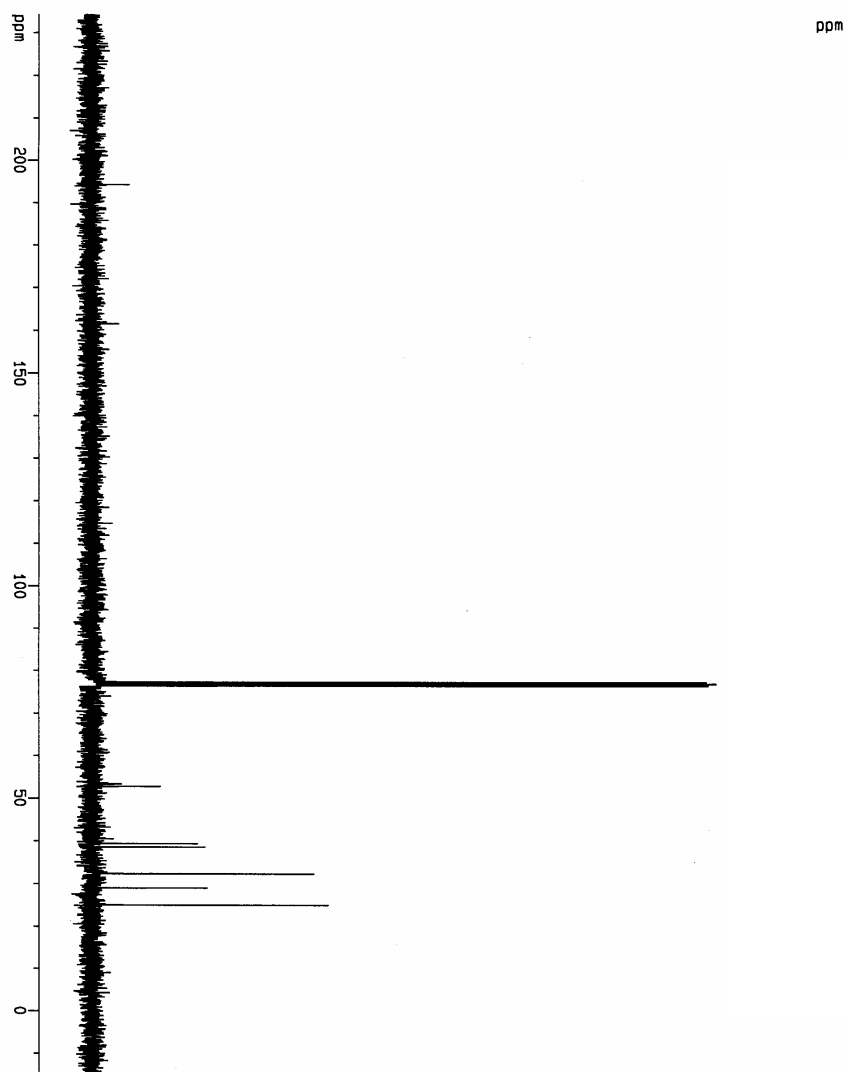


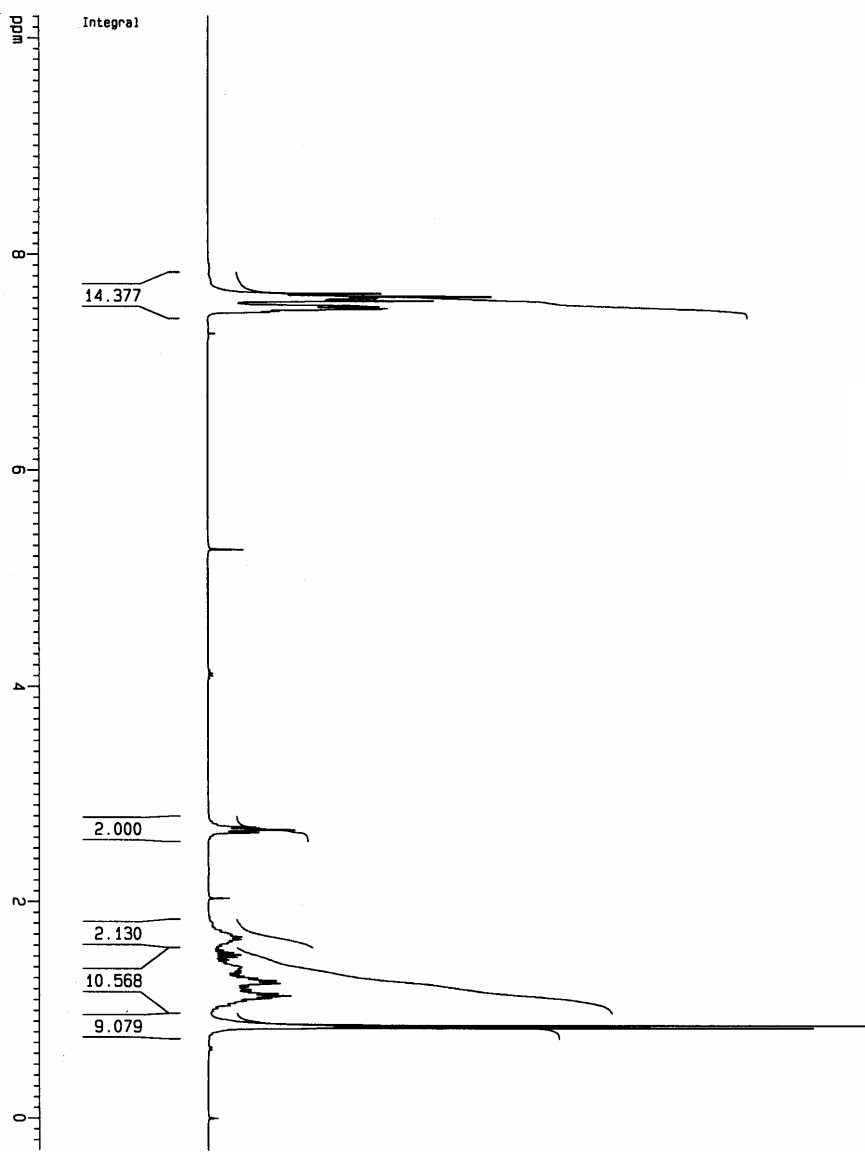
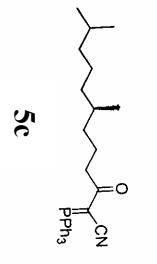


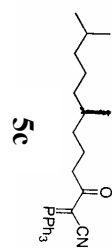




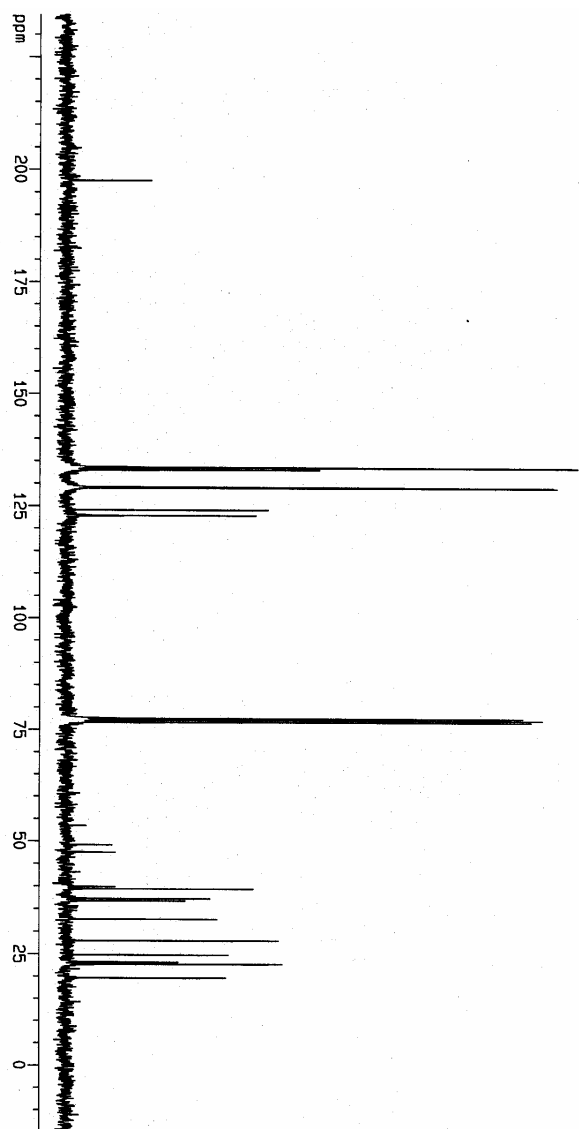
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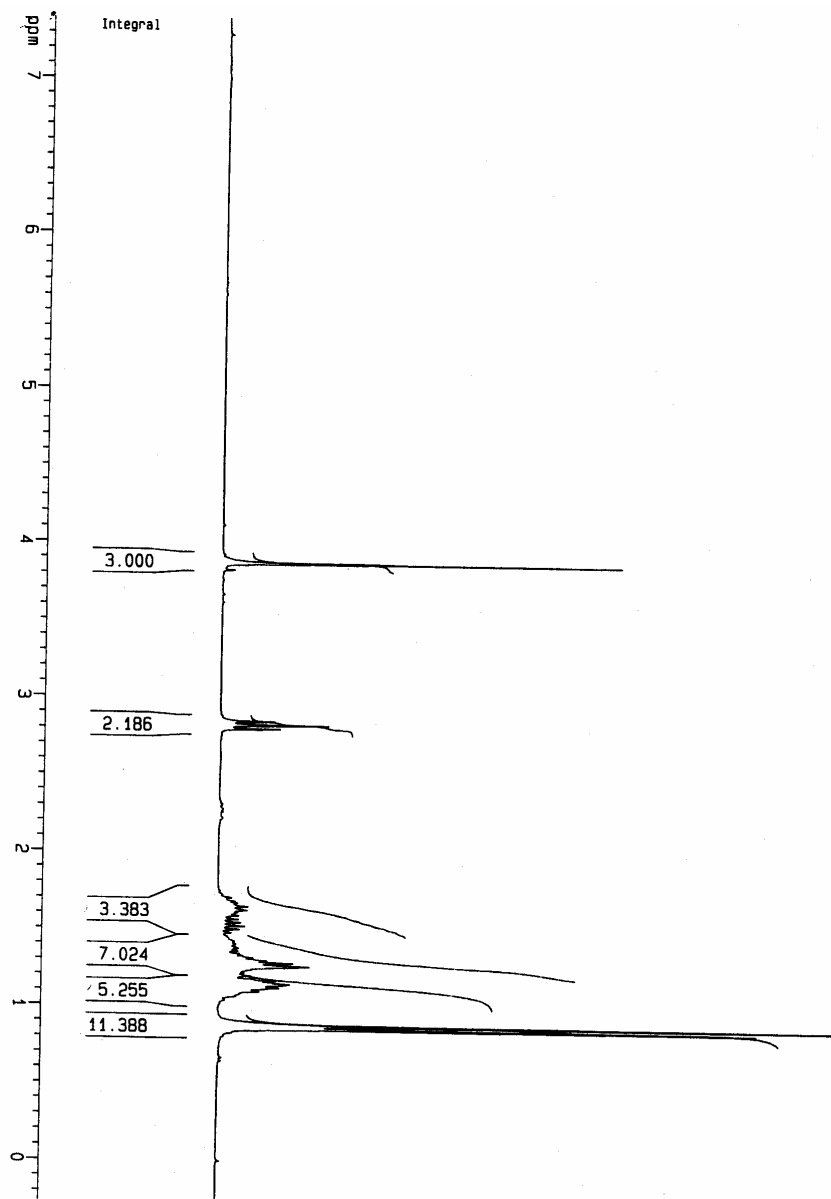
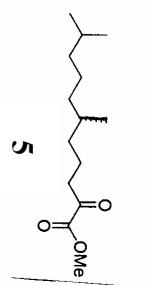


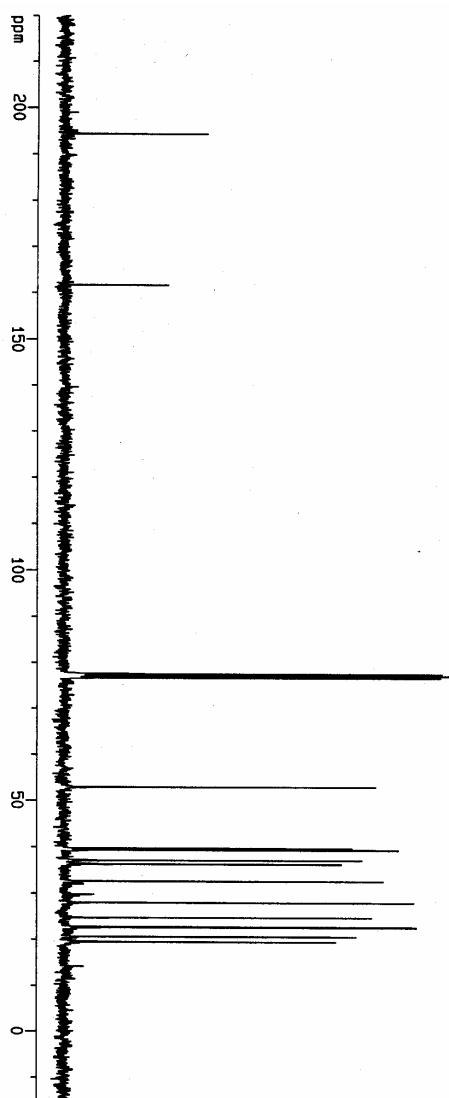
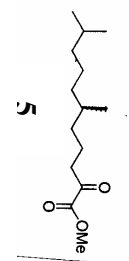


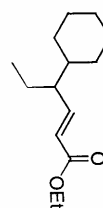


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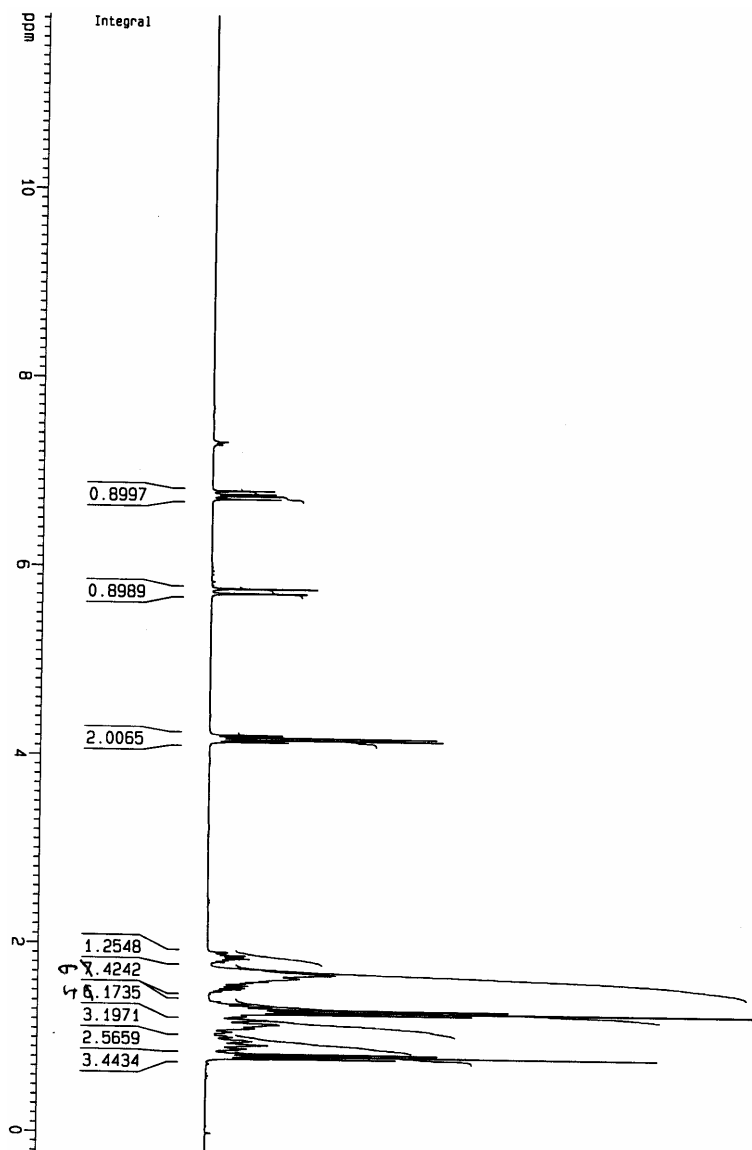


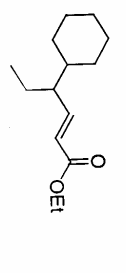




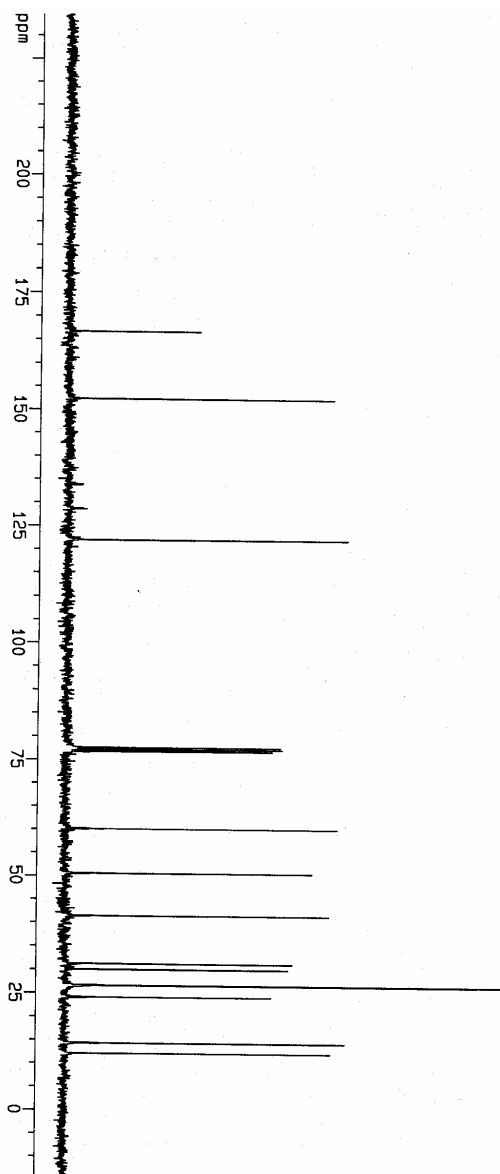


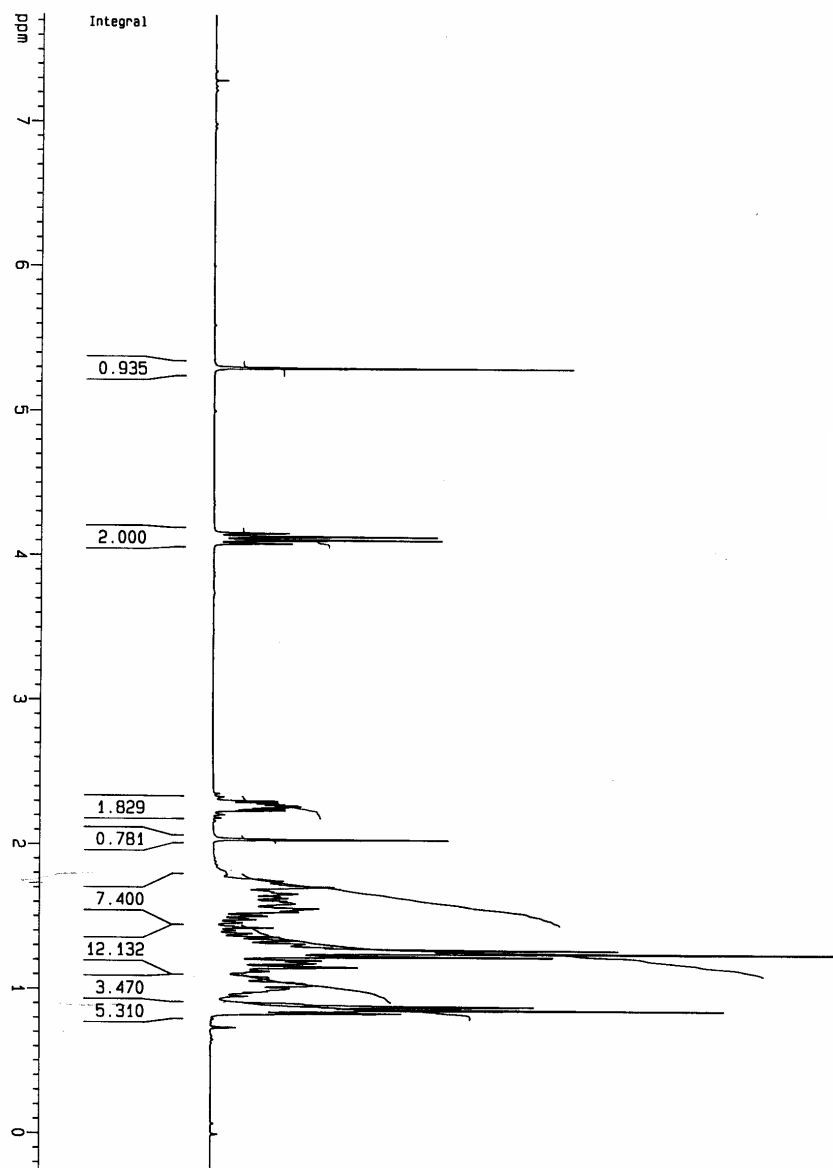
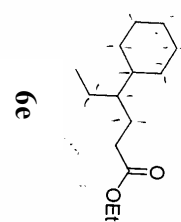
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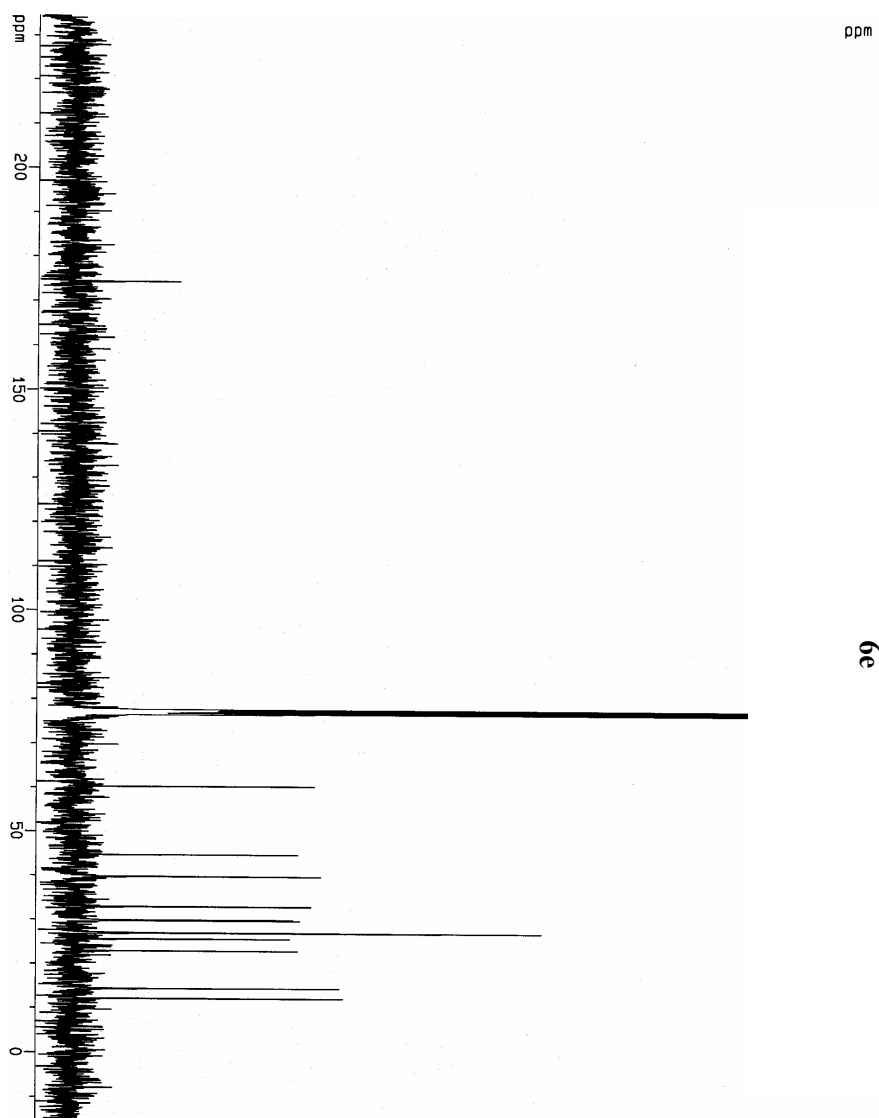




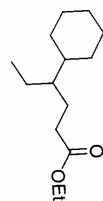
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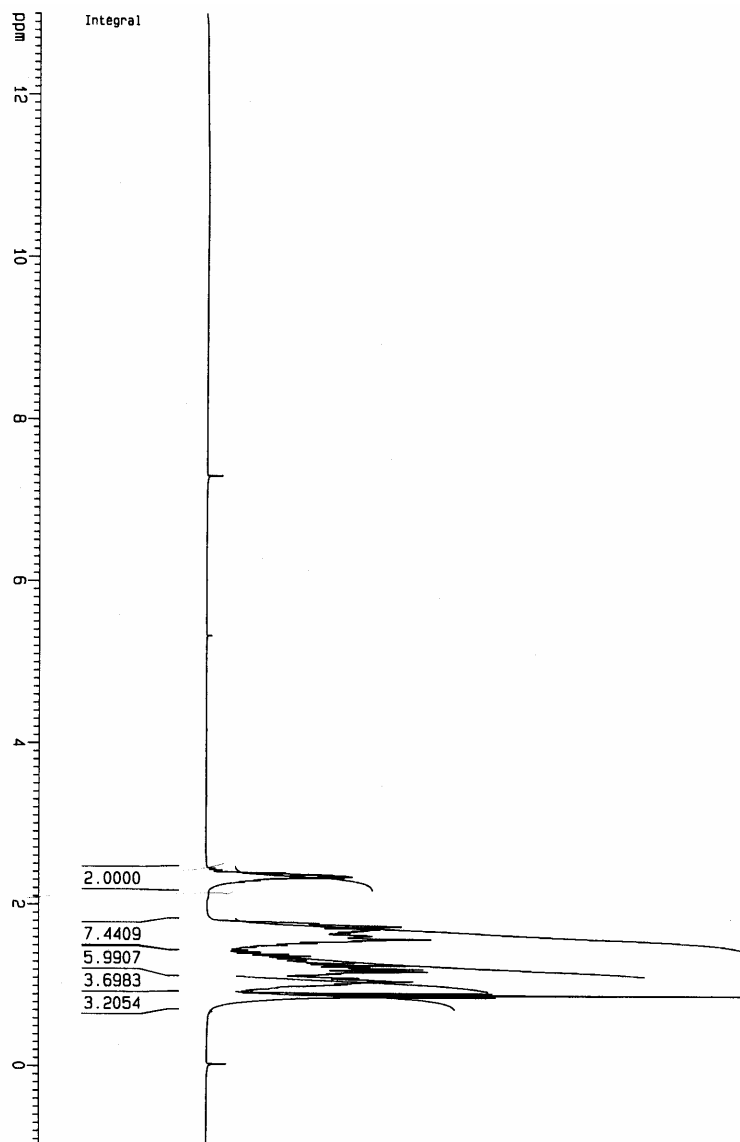
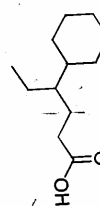


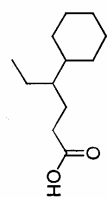


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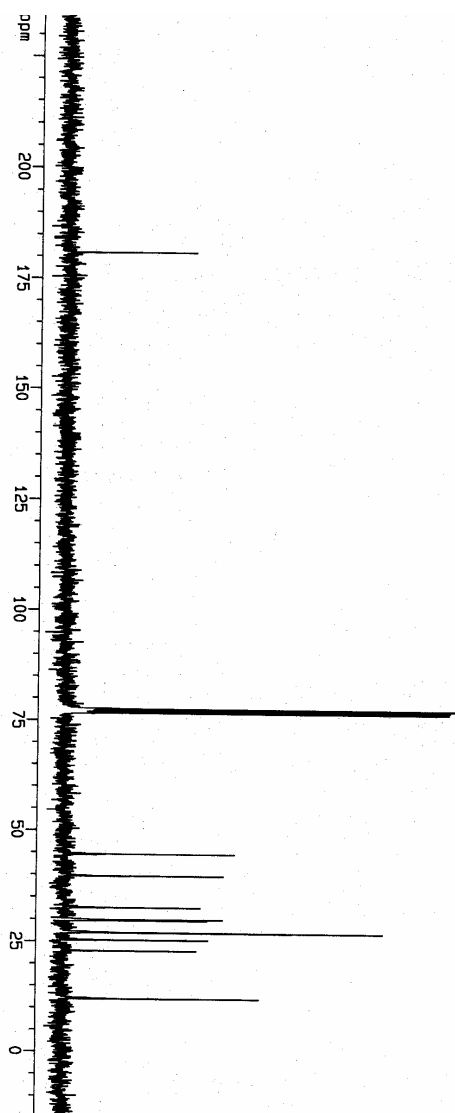


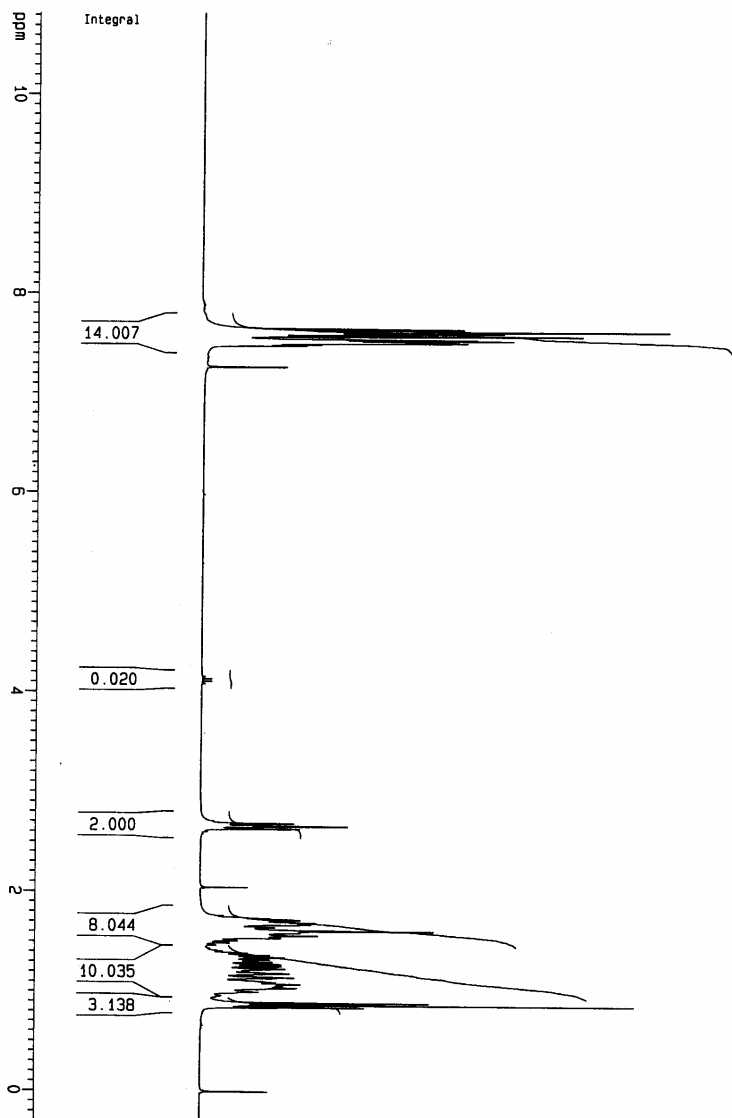
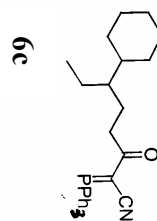
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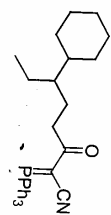




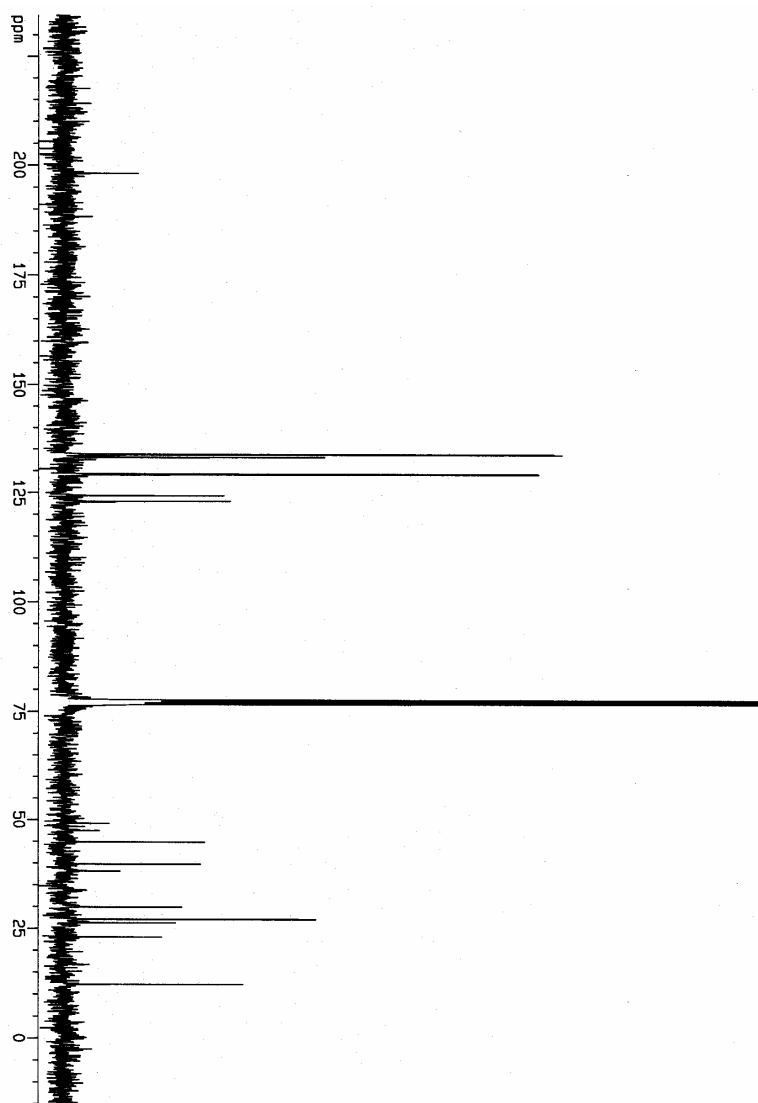
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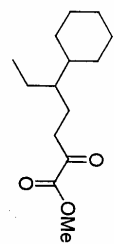




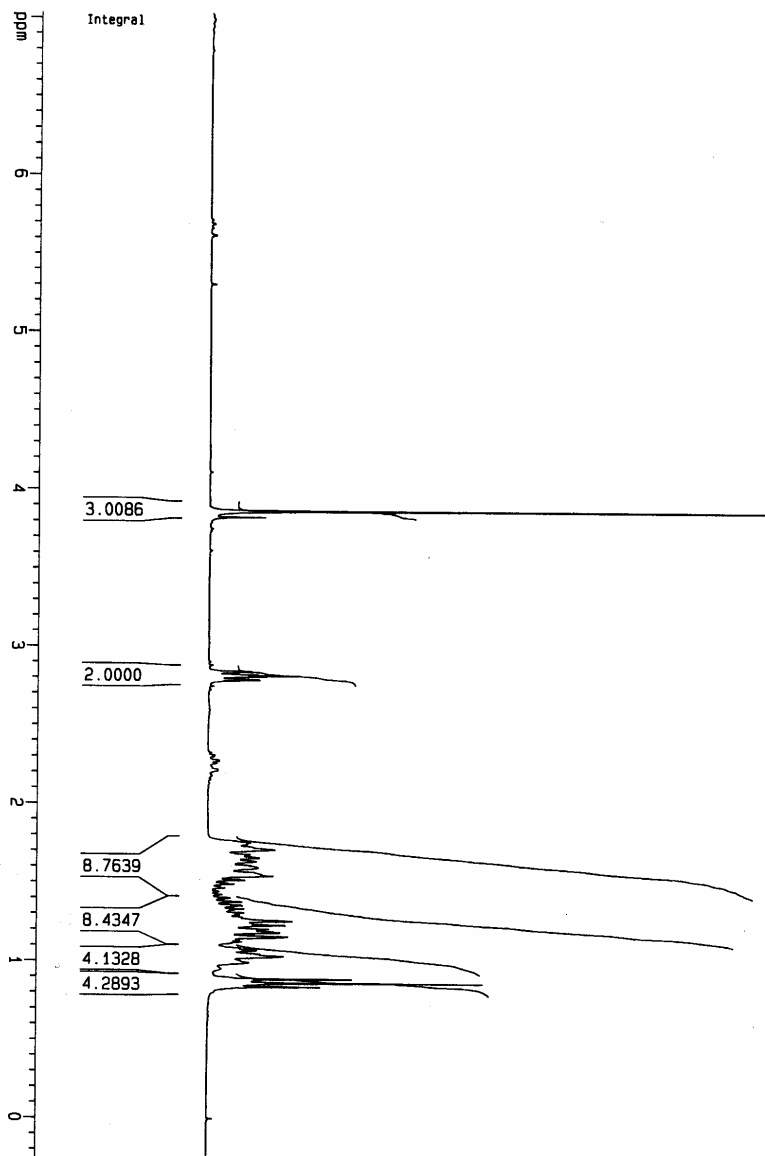


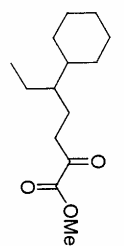
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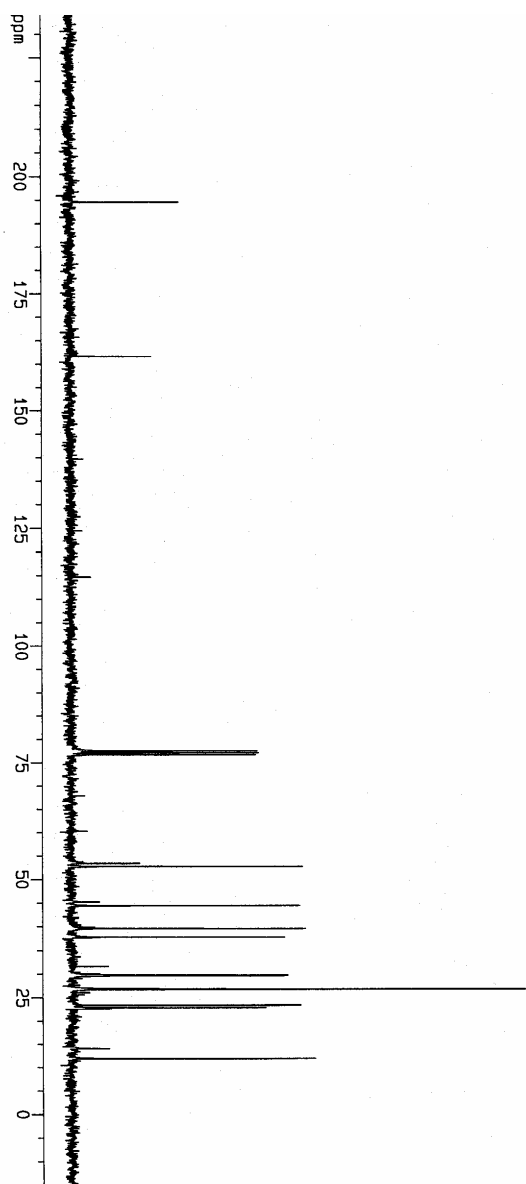


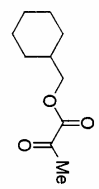
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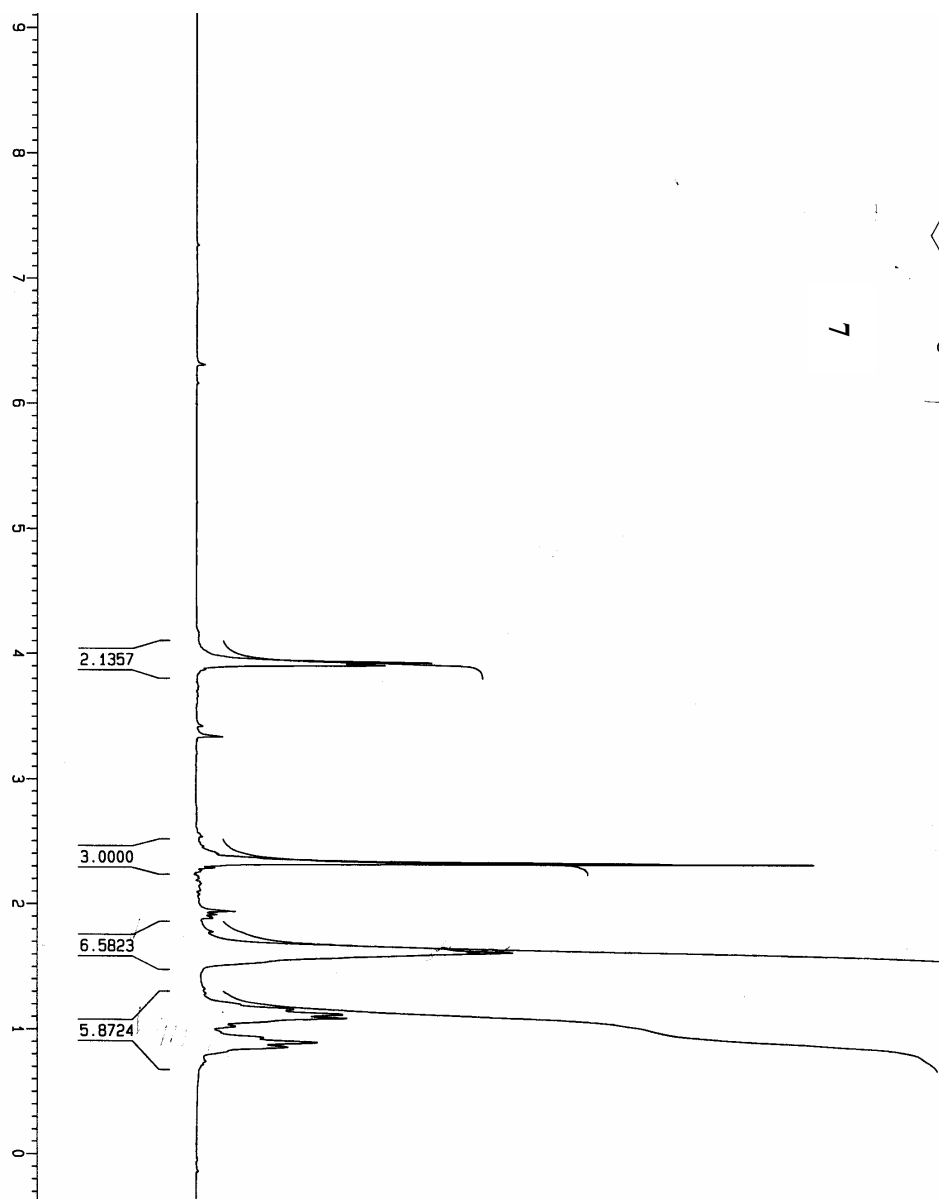


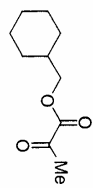
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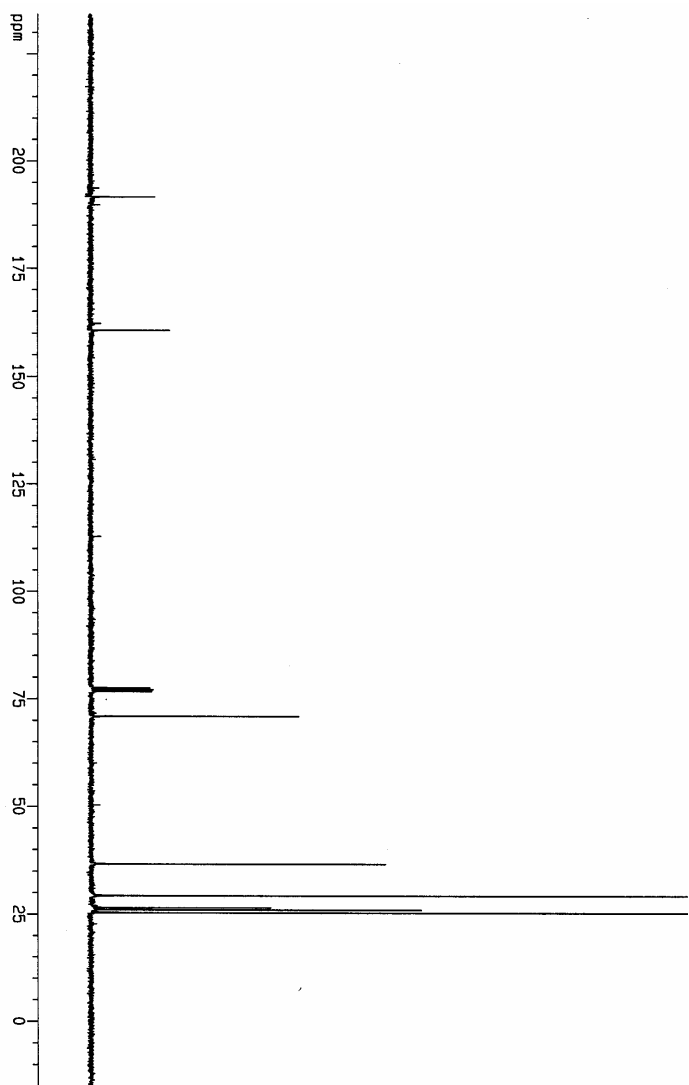


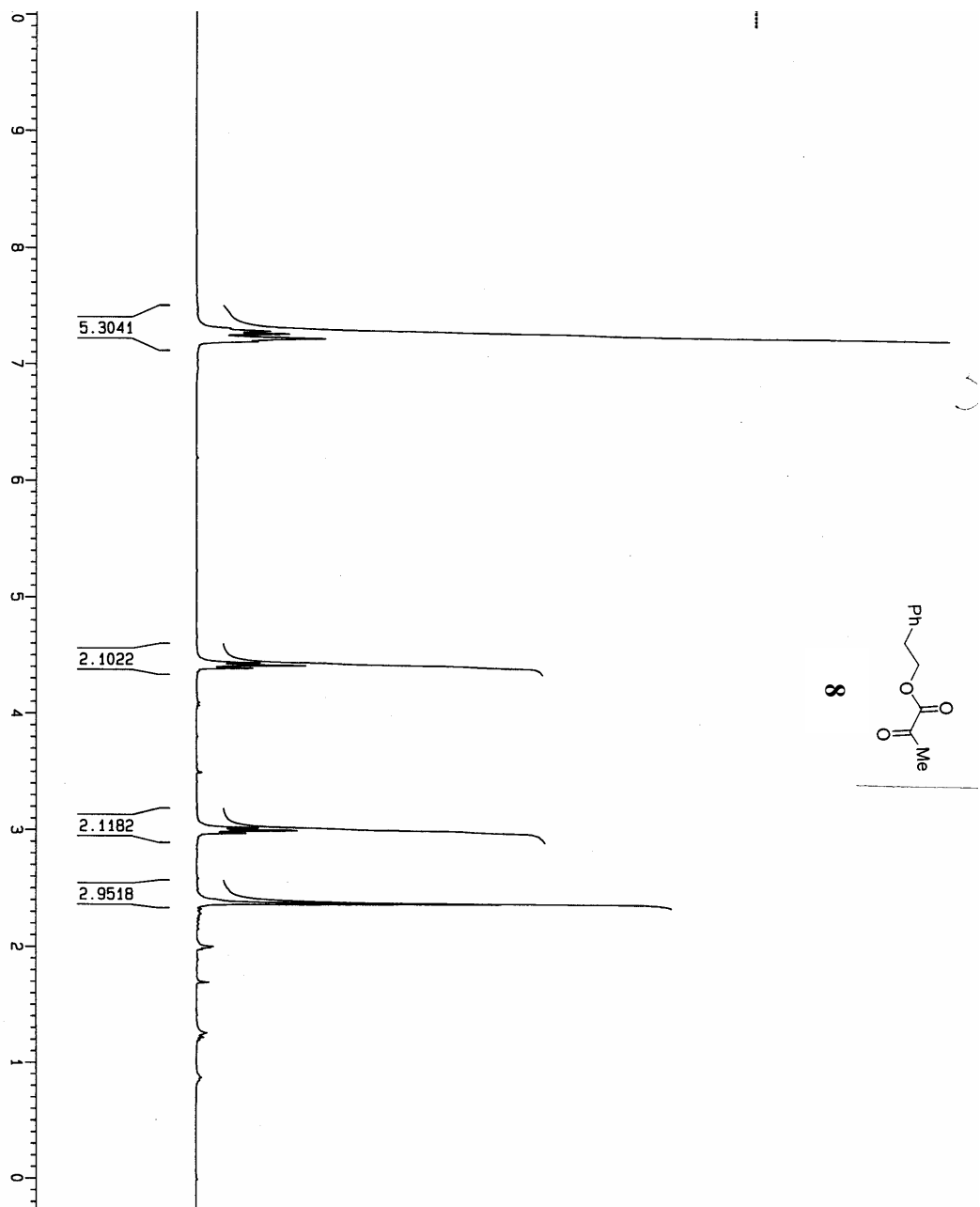
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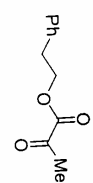




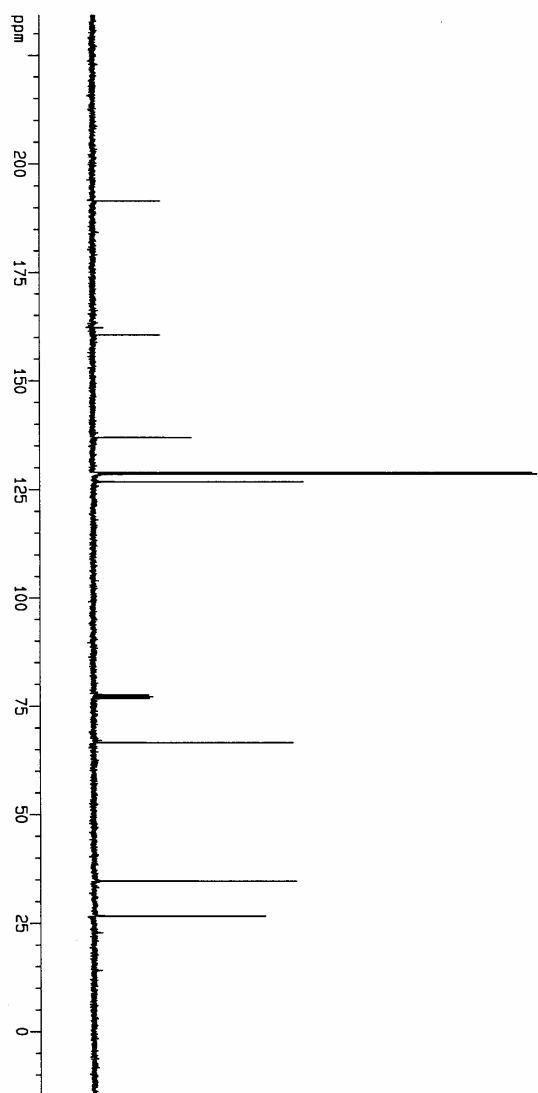
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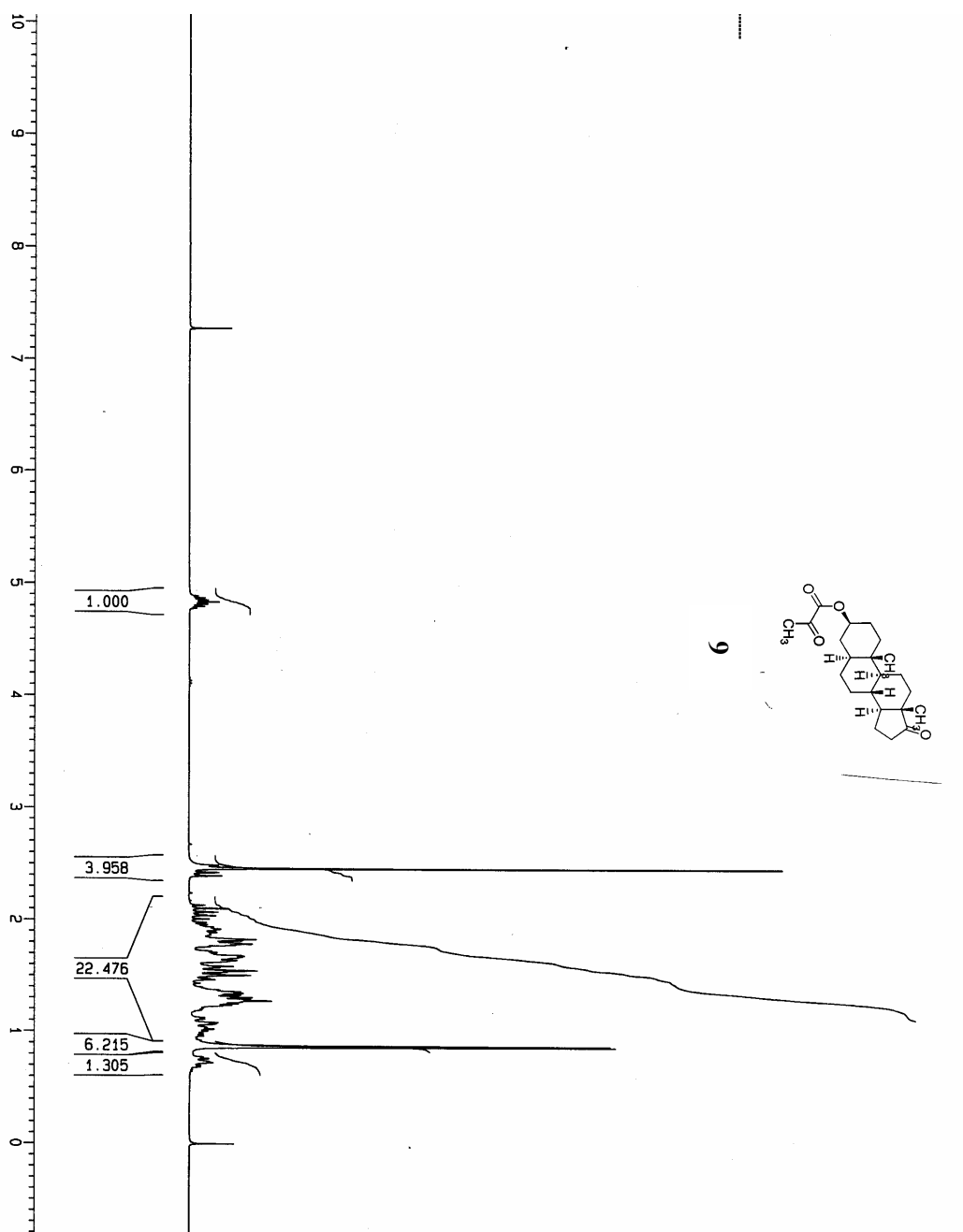


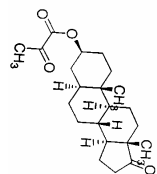




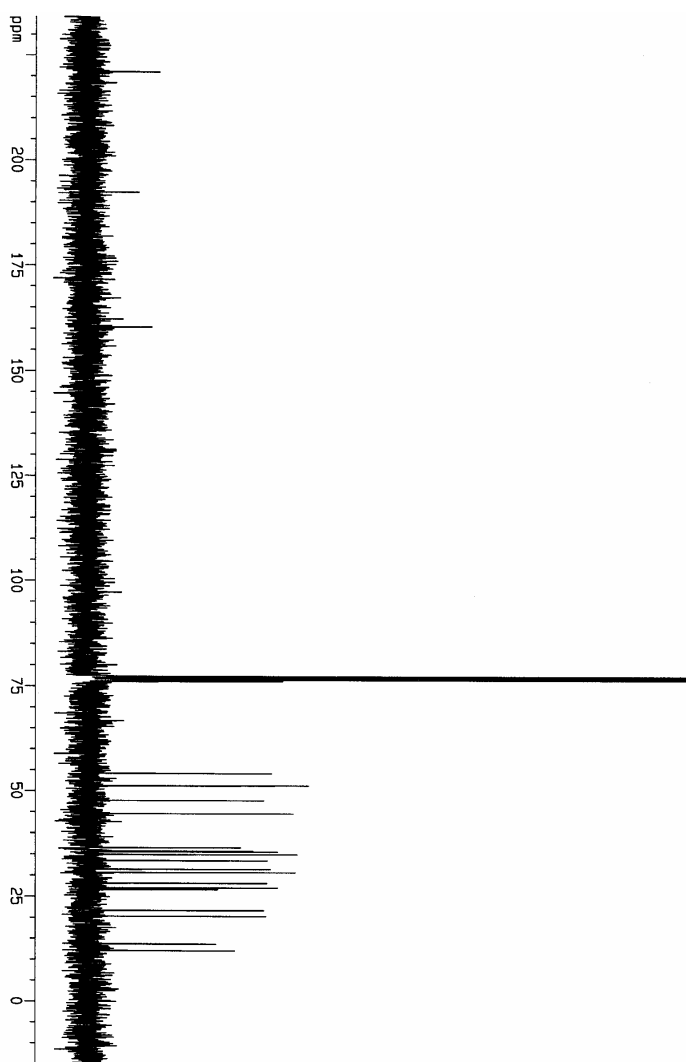
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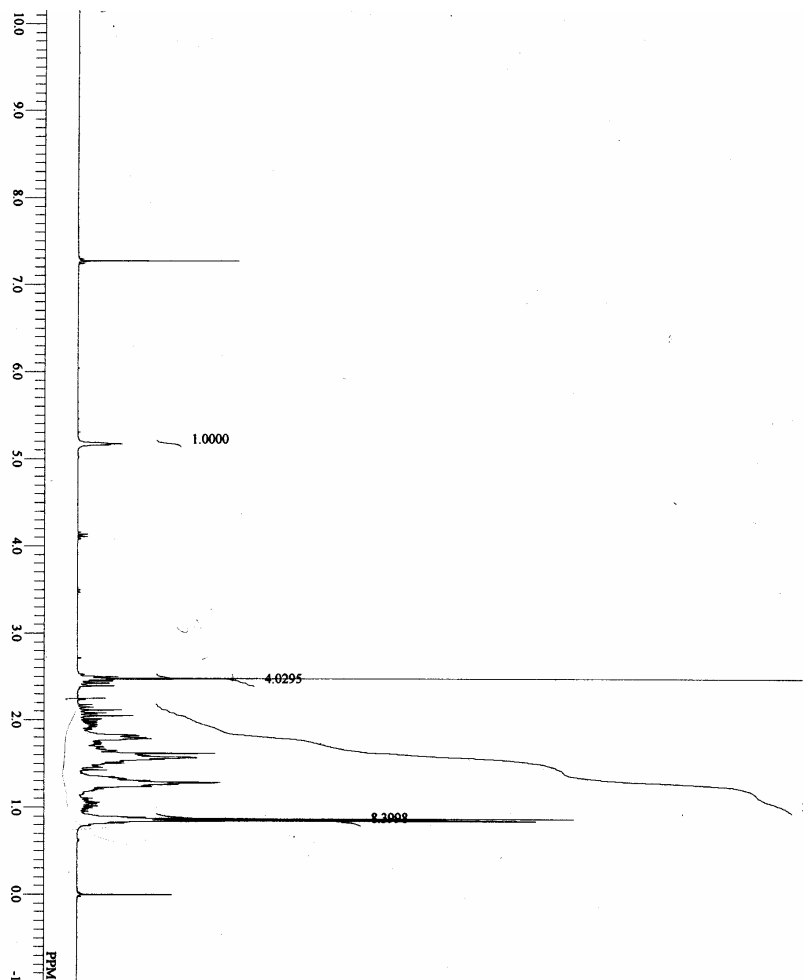


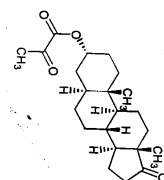
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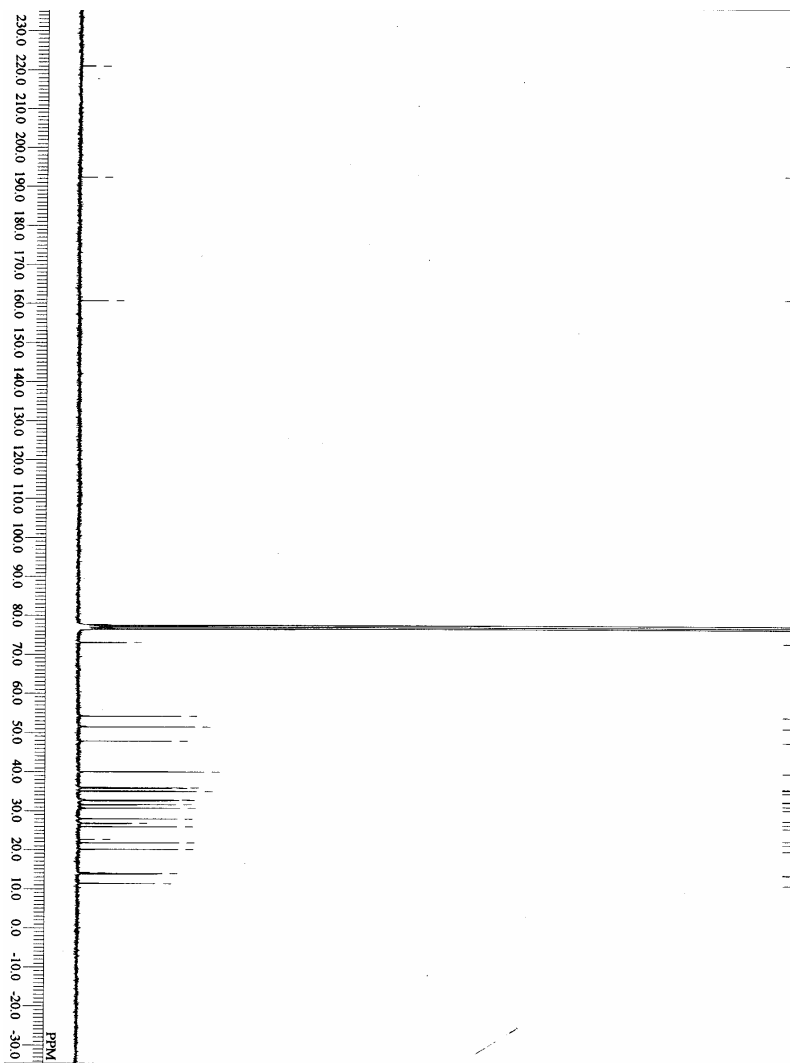


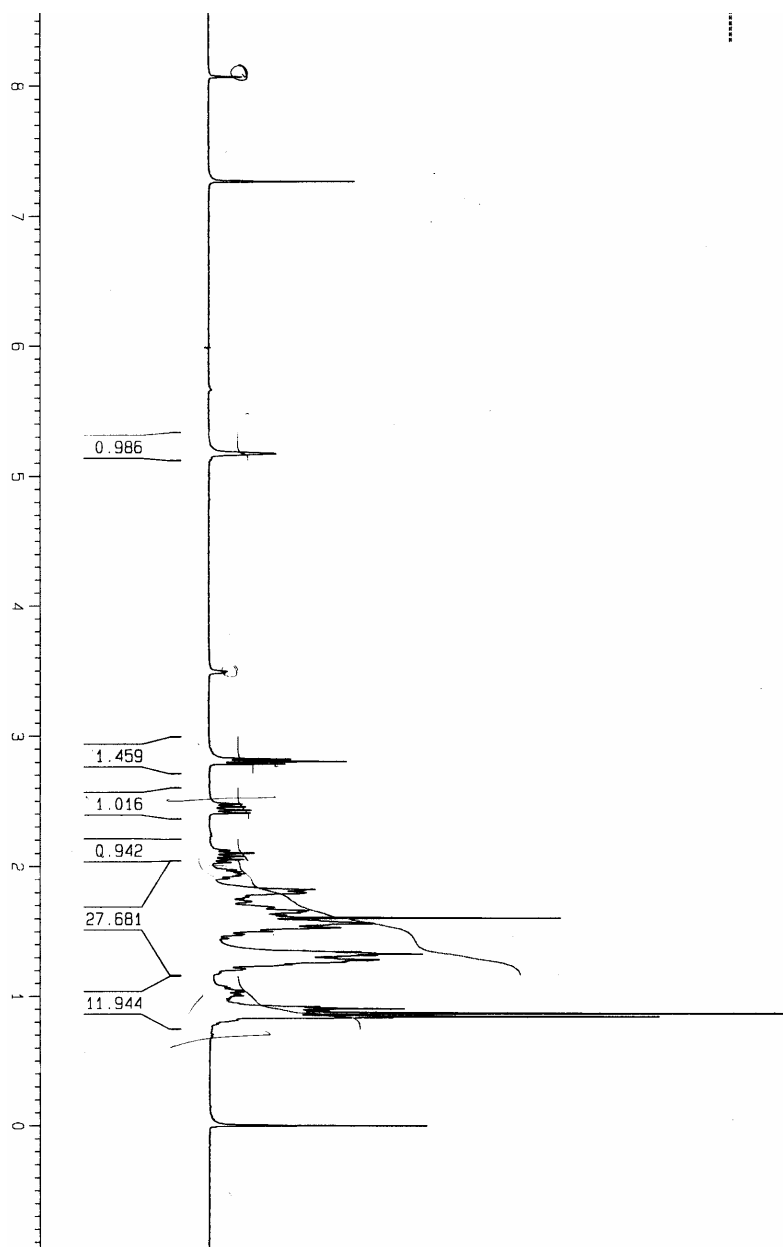
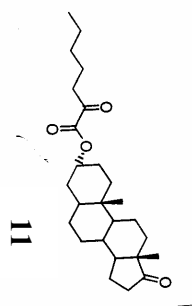
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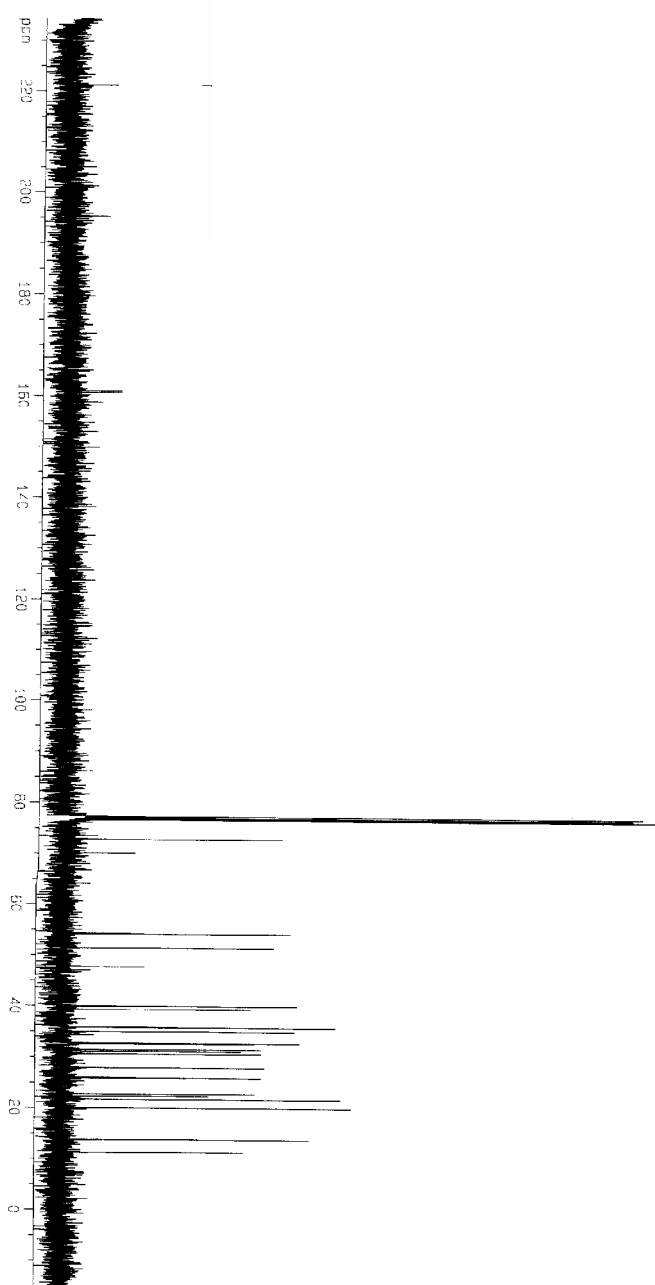
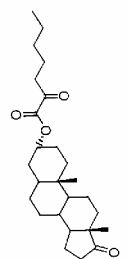


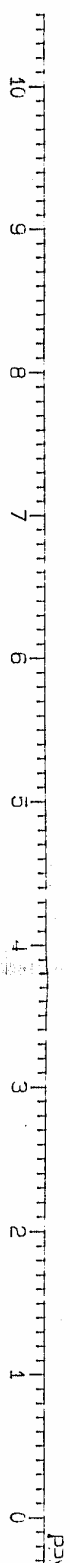
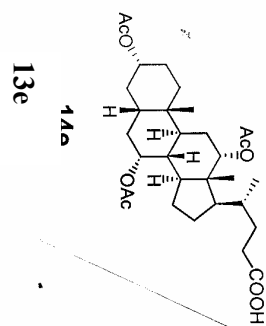
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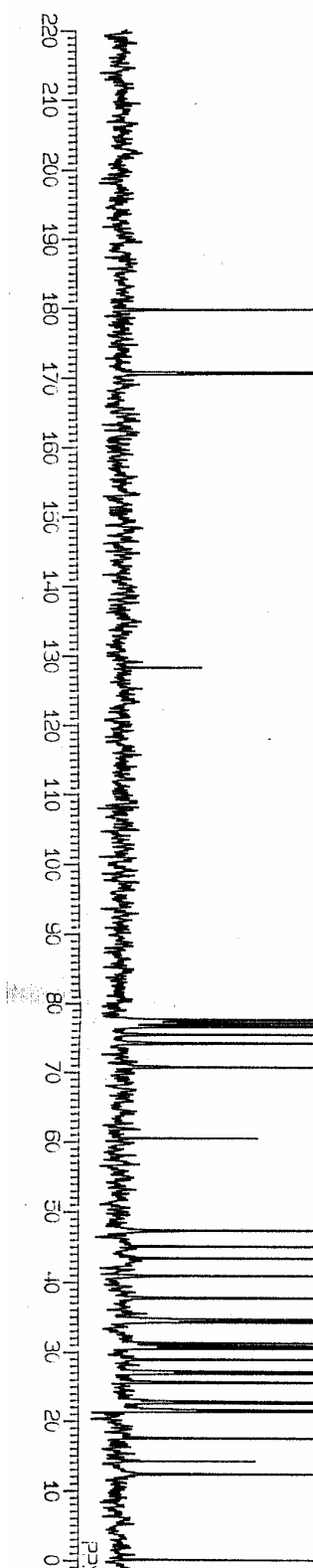
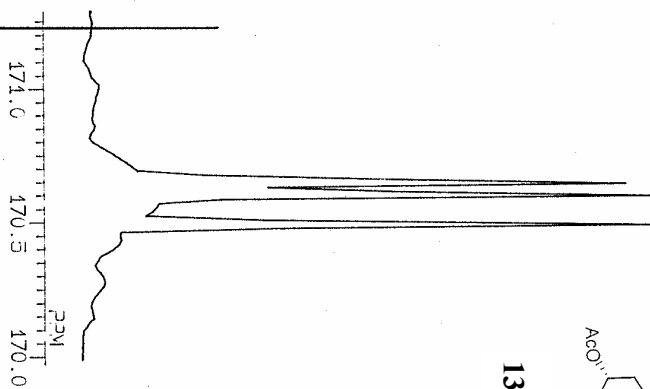
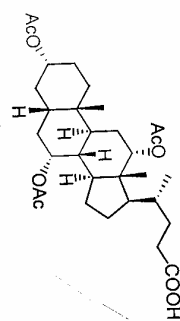


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13c



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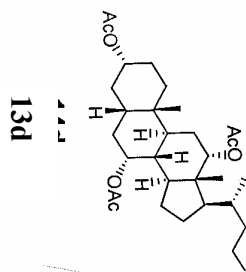
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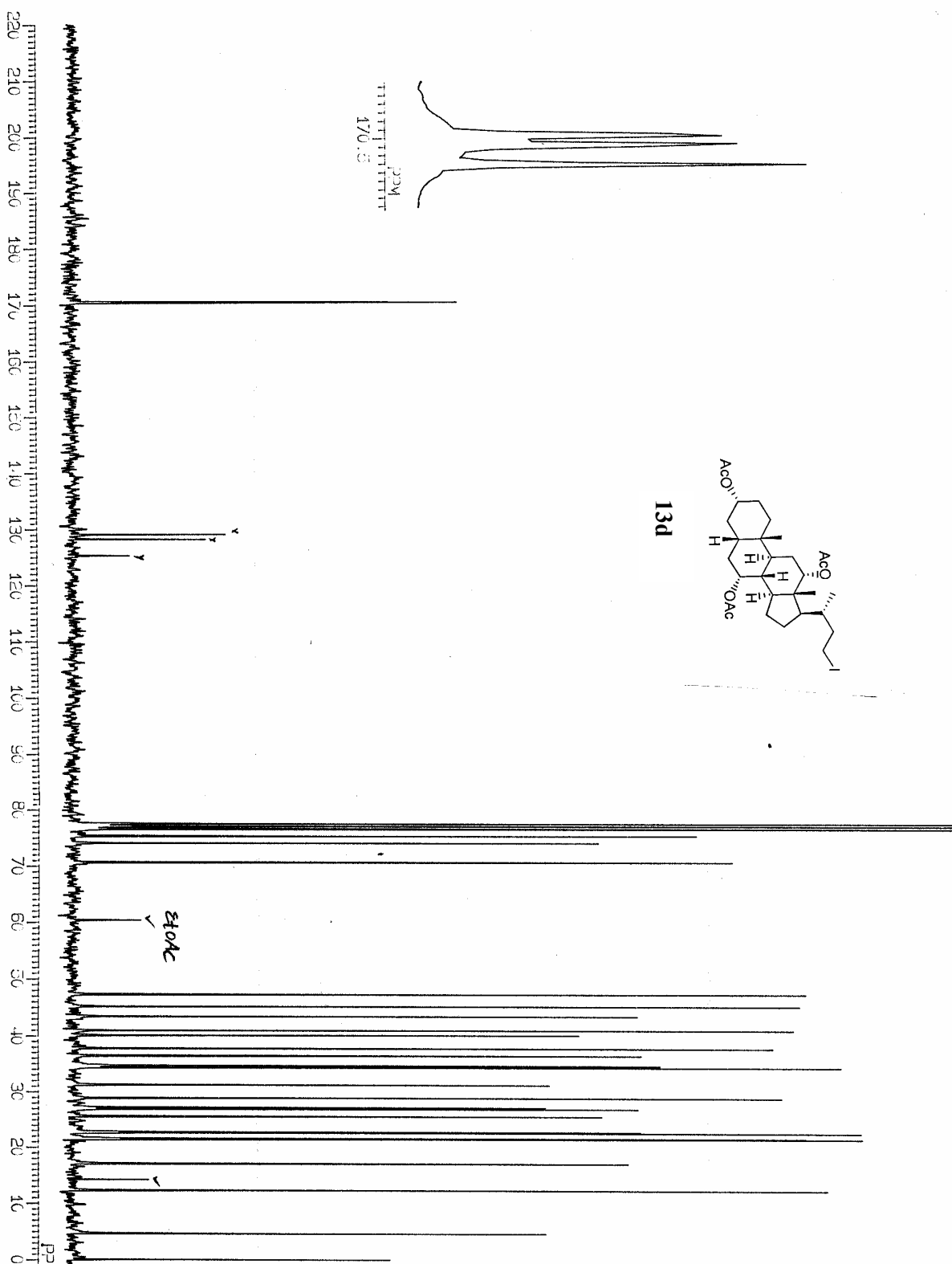
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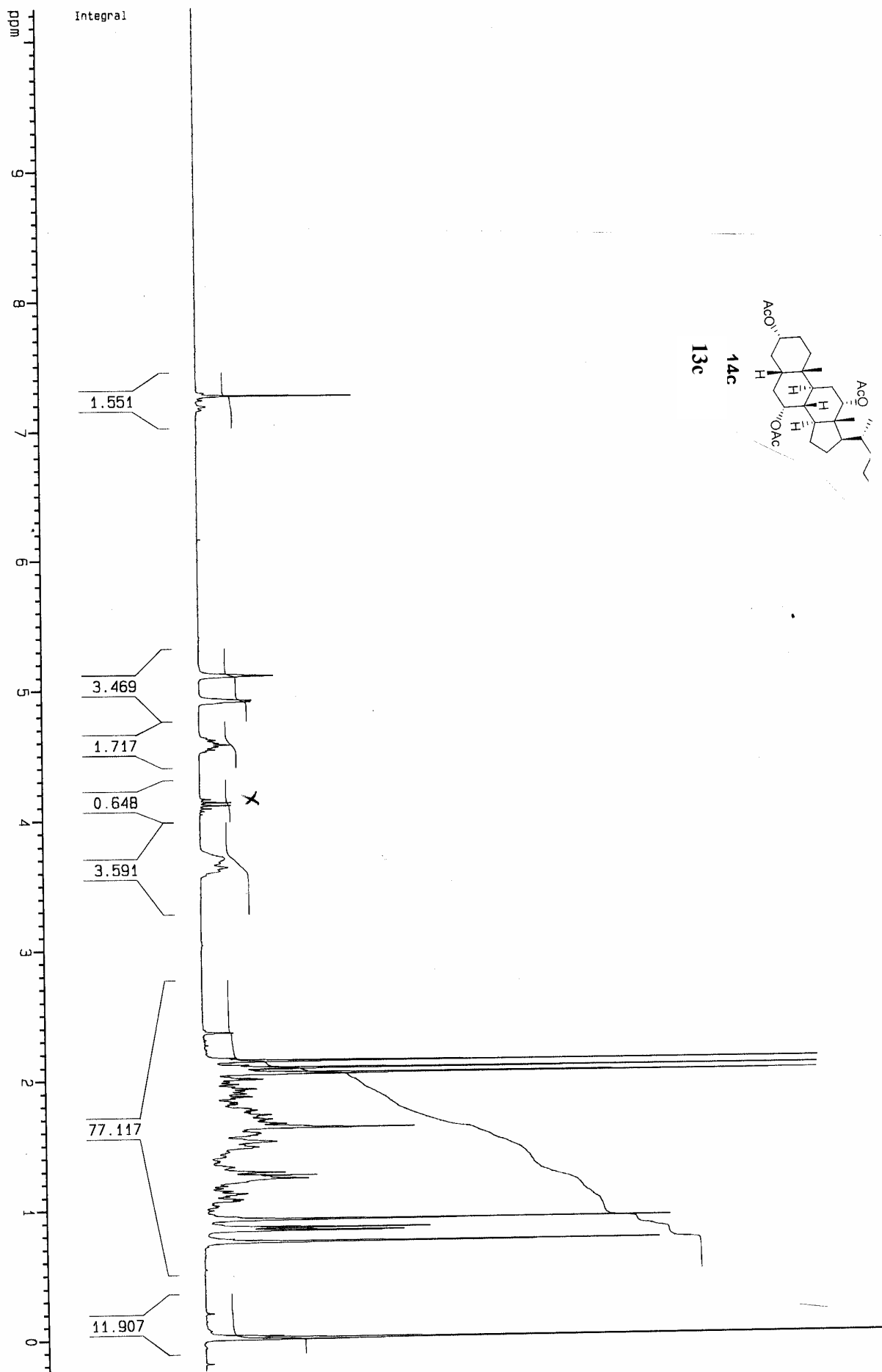
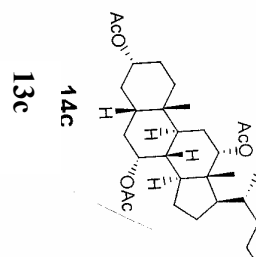
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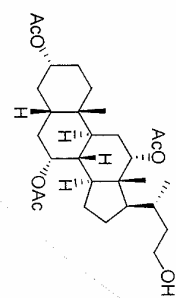
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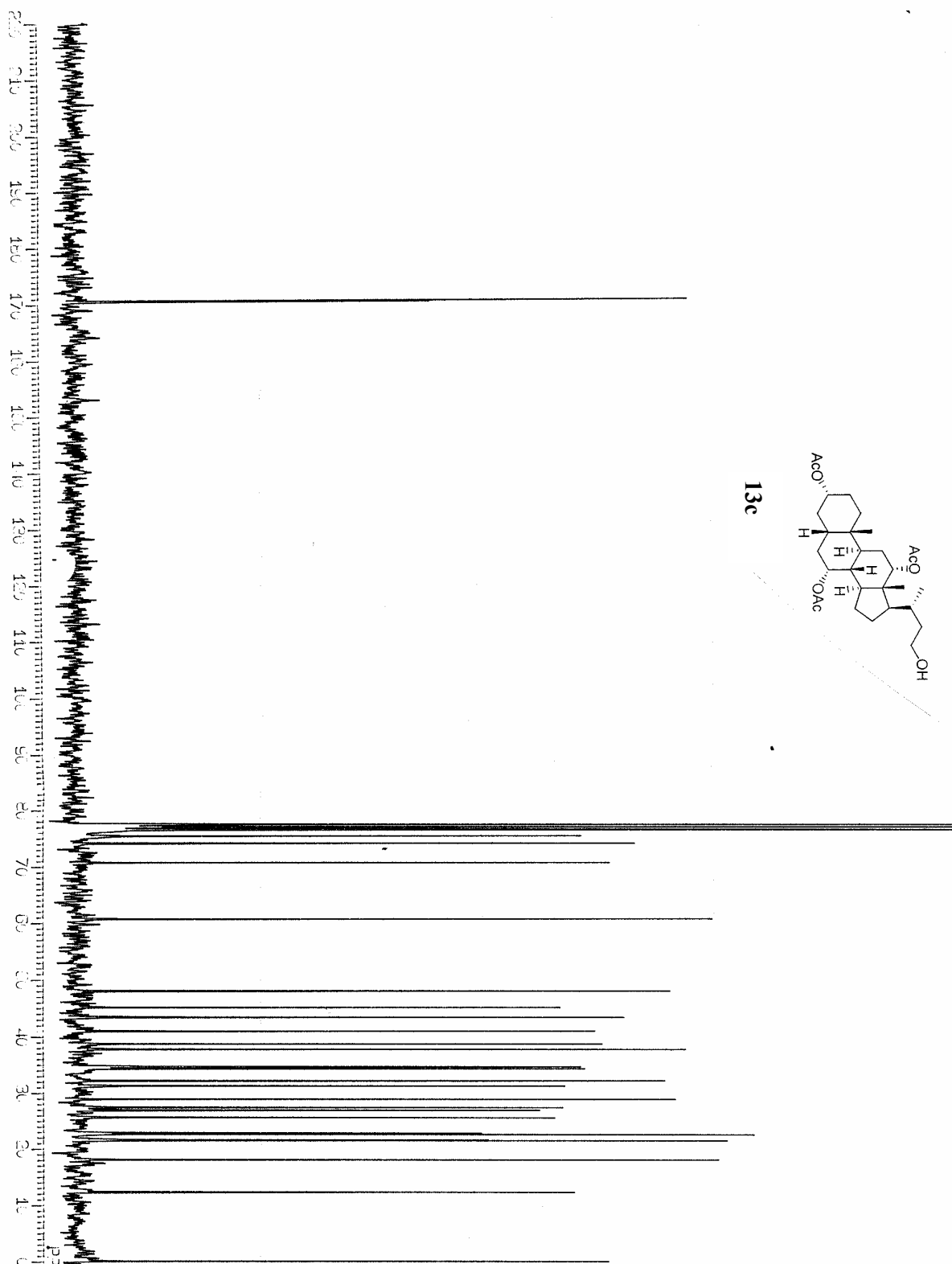


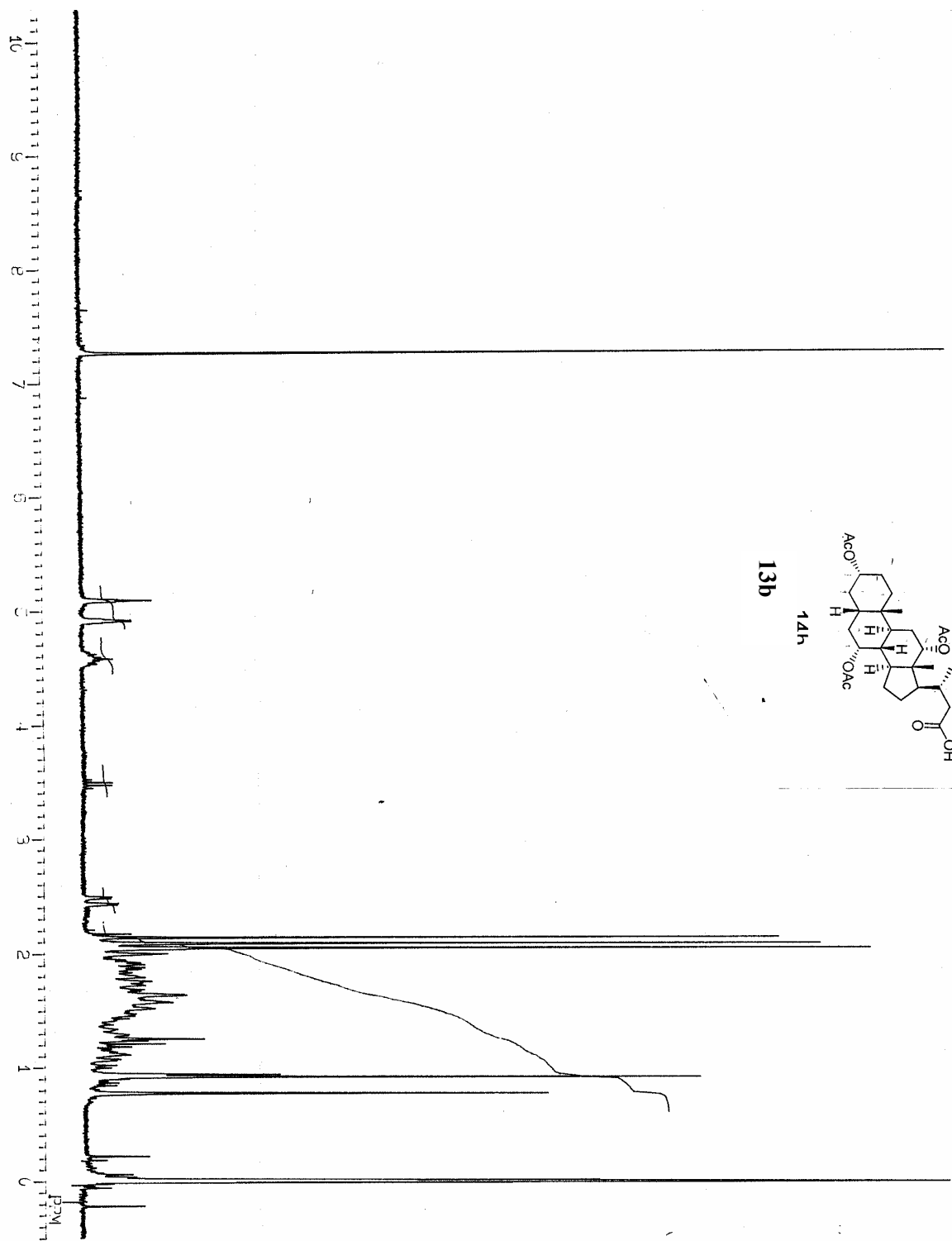


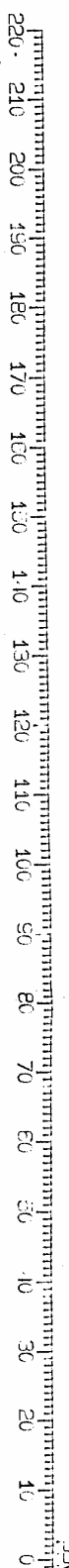
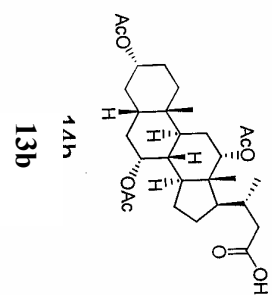




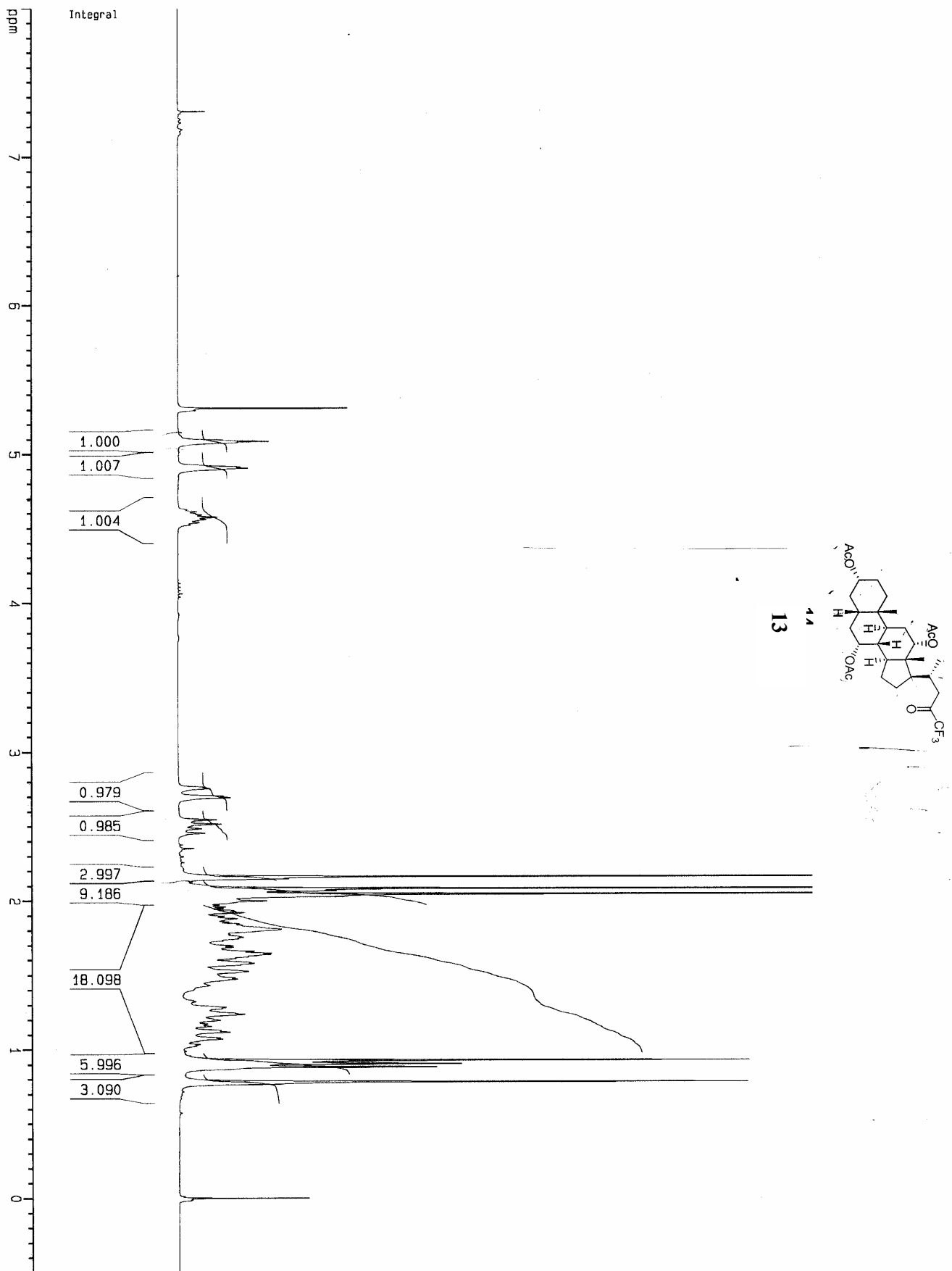
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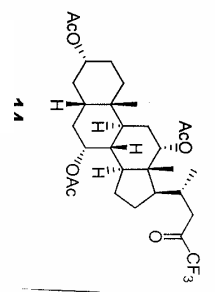




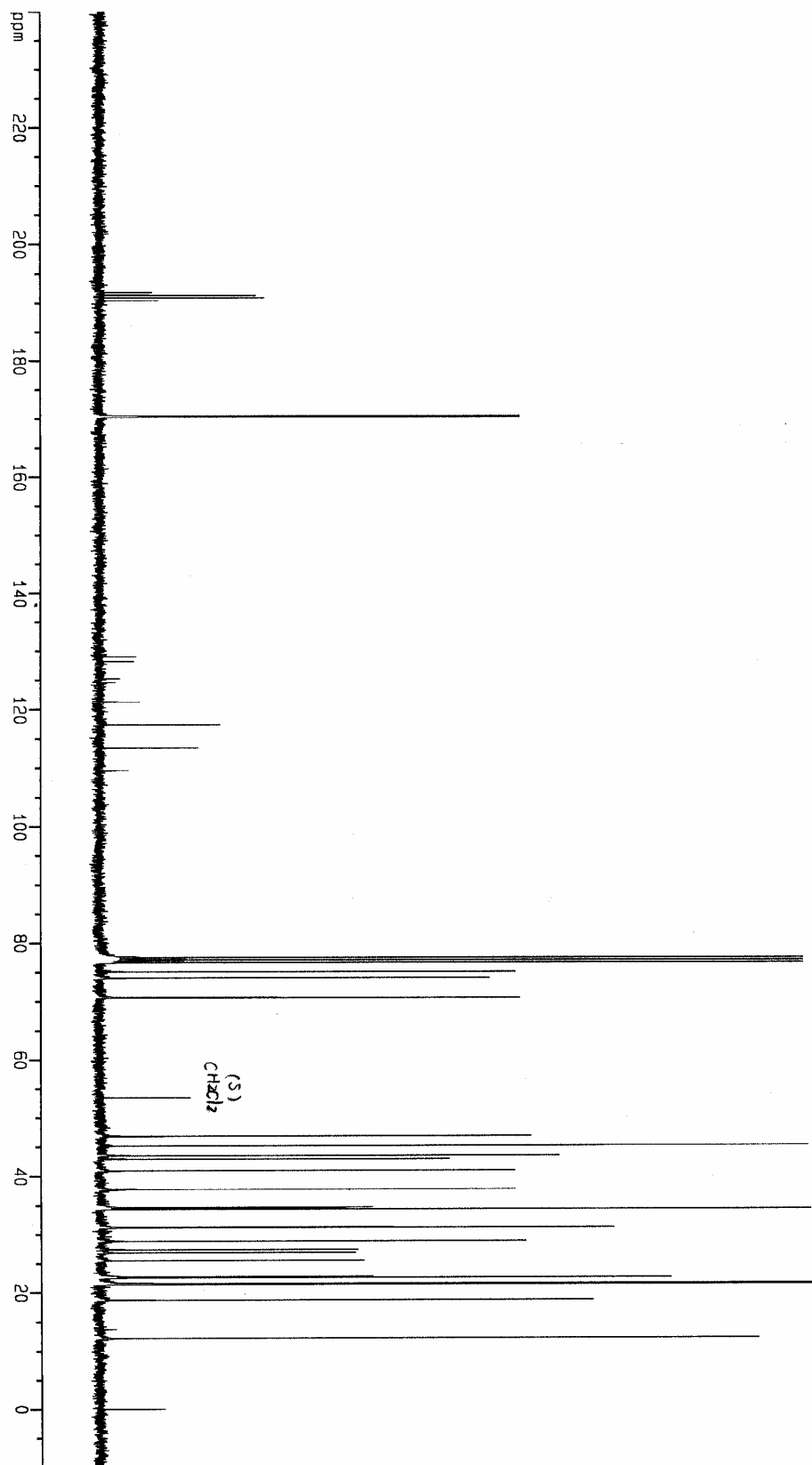


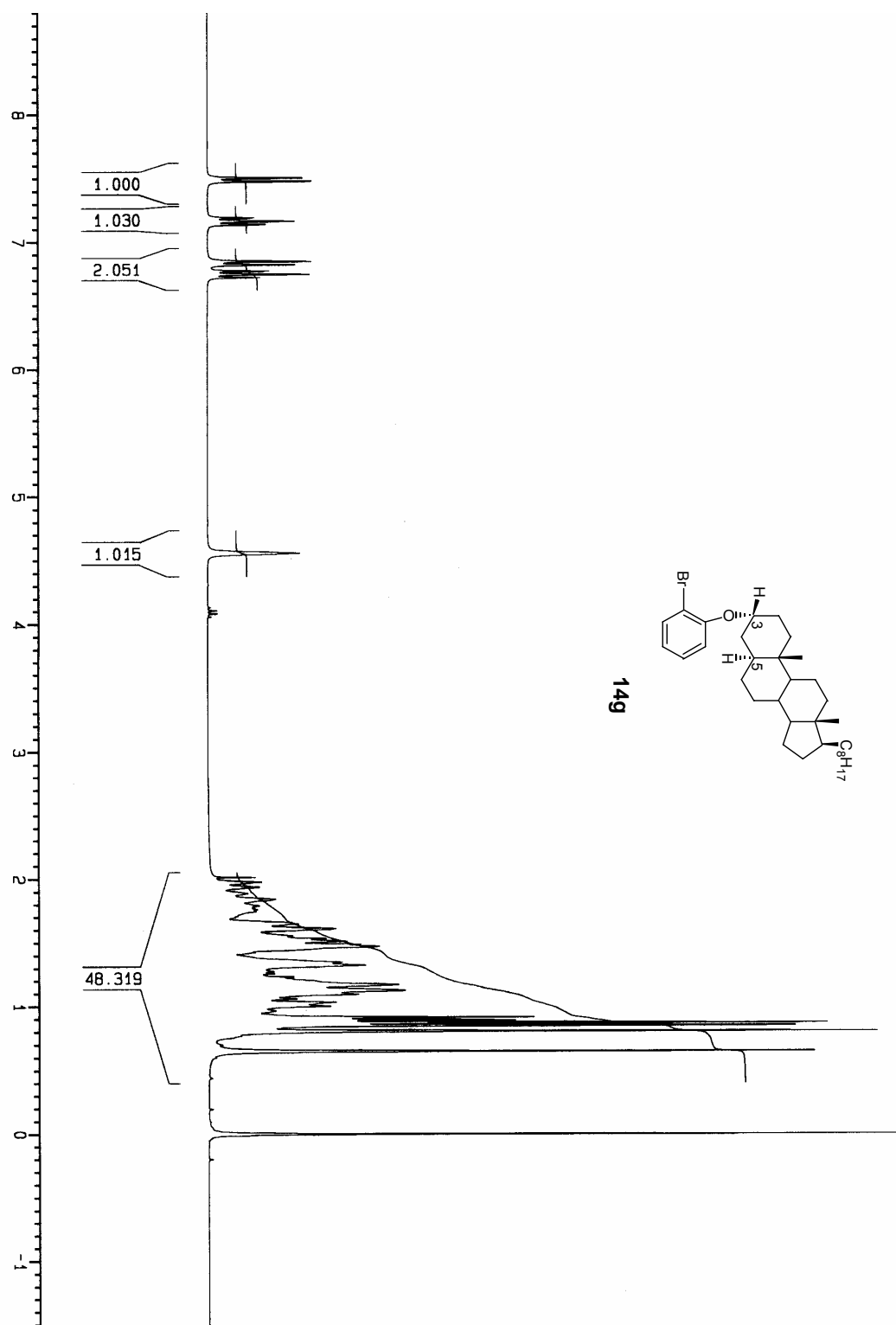
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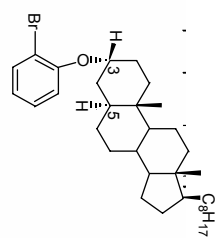




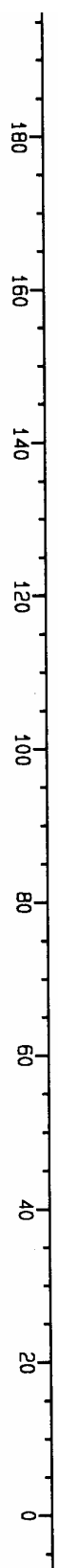
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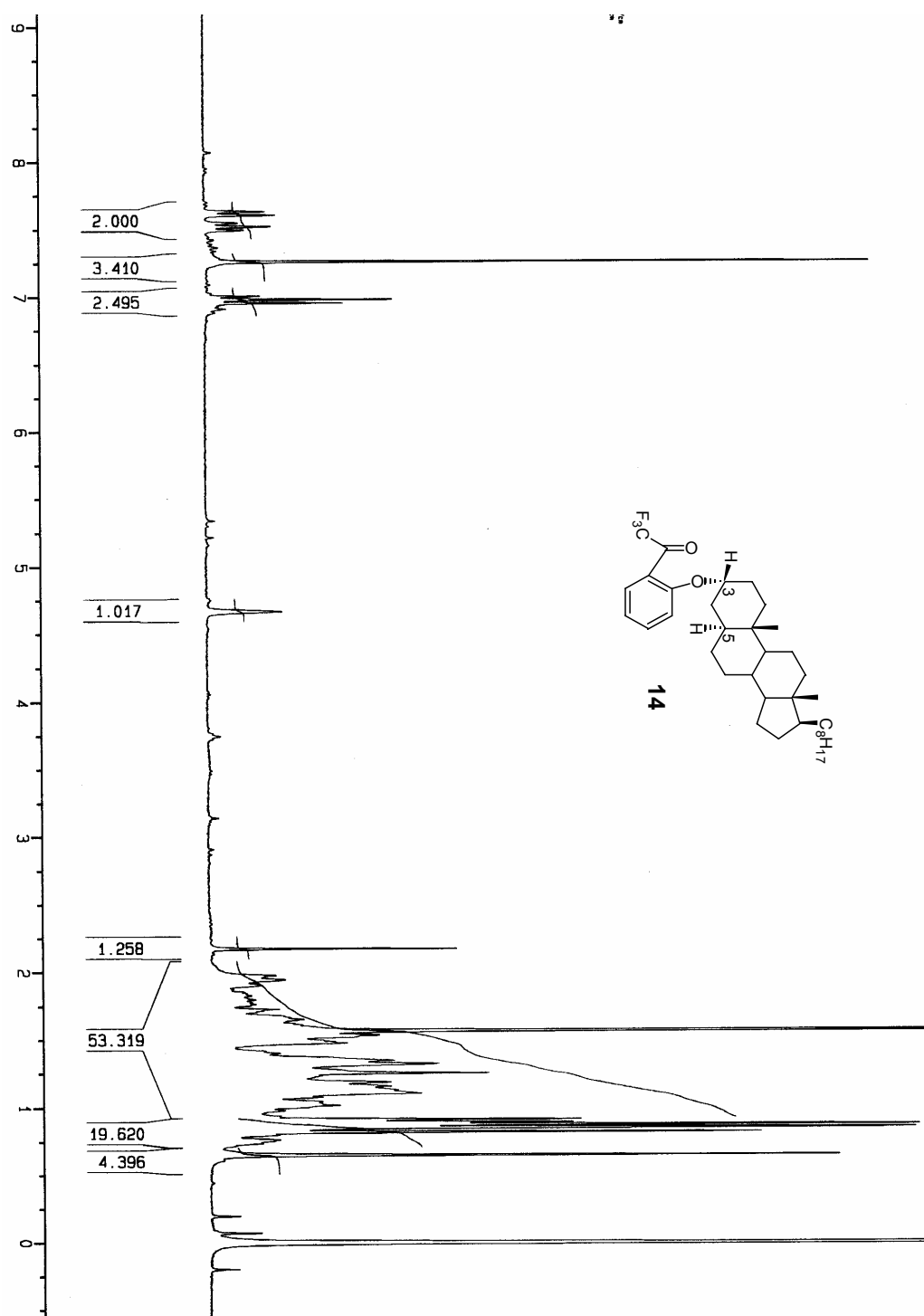


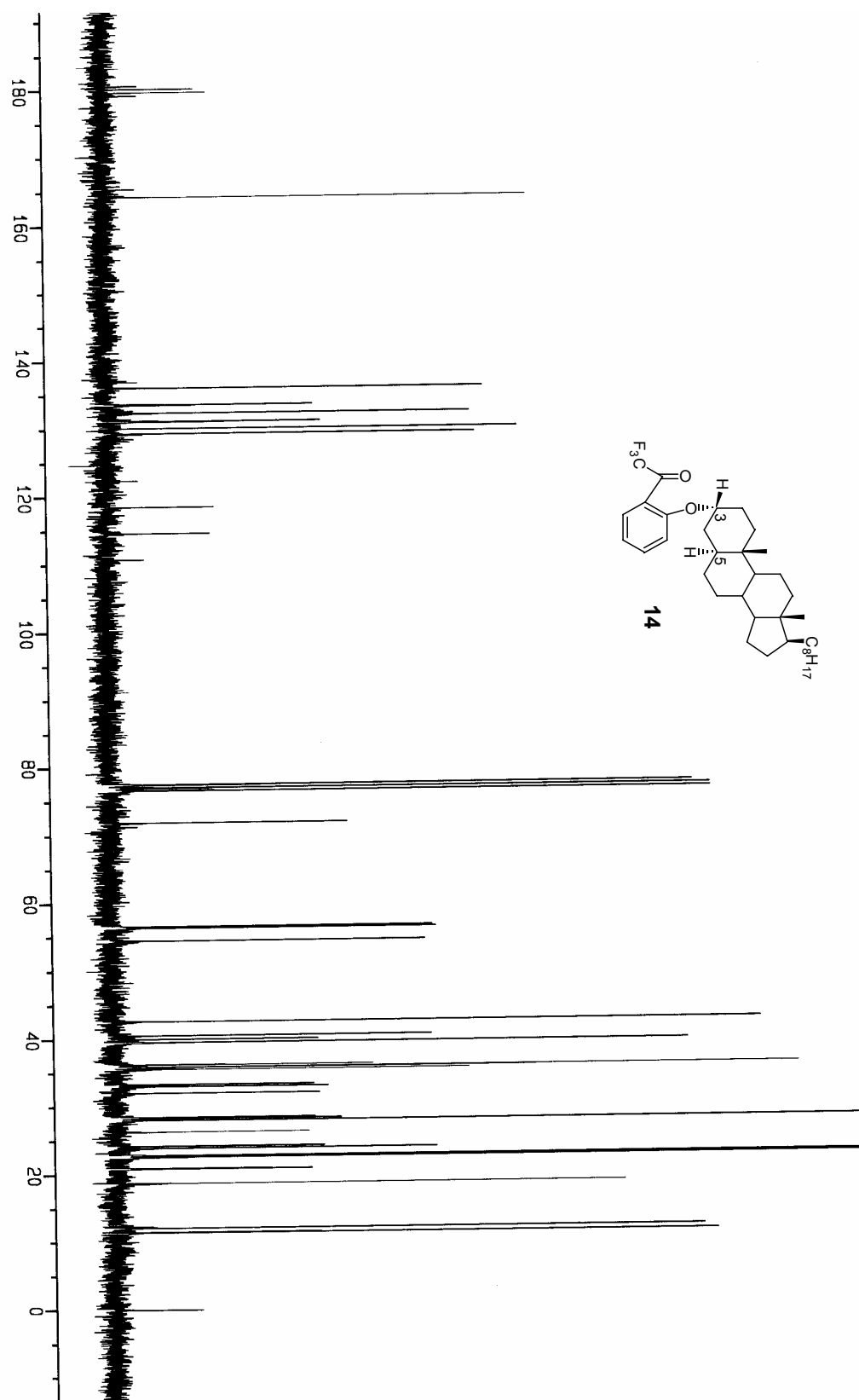


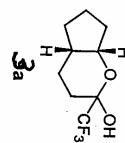
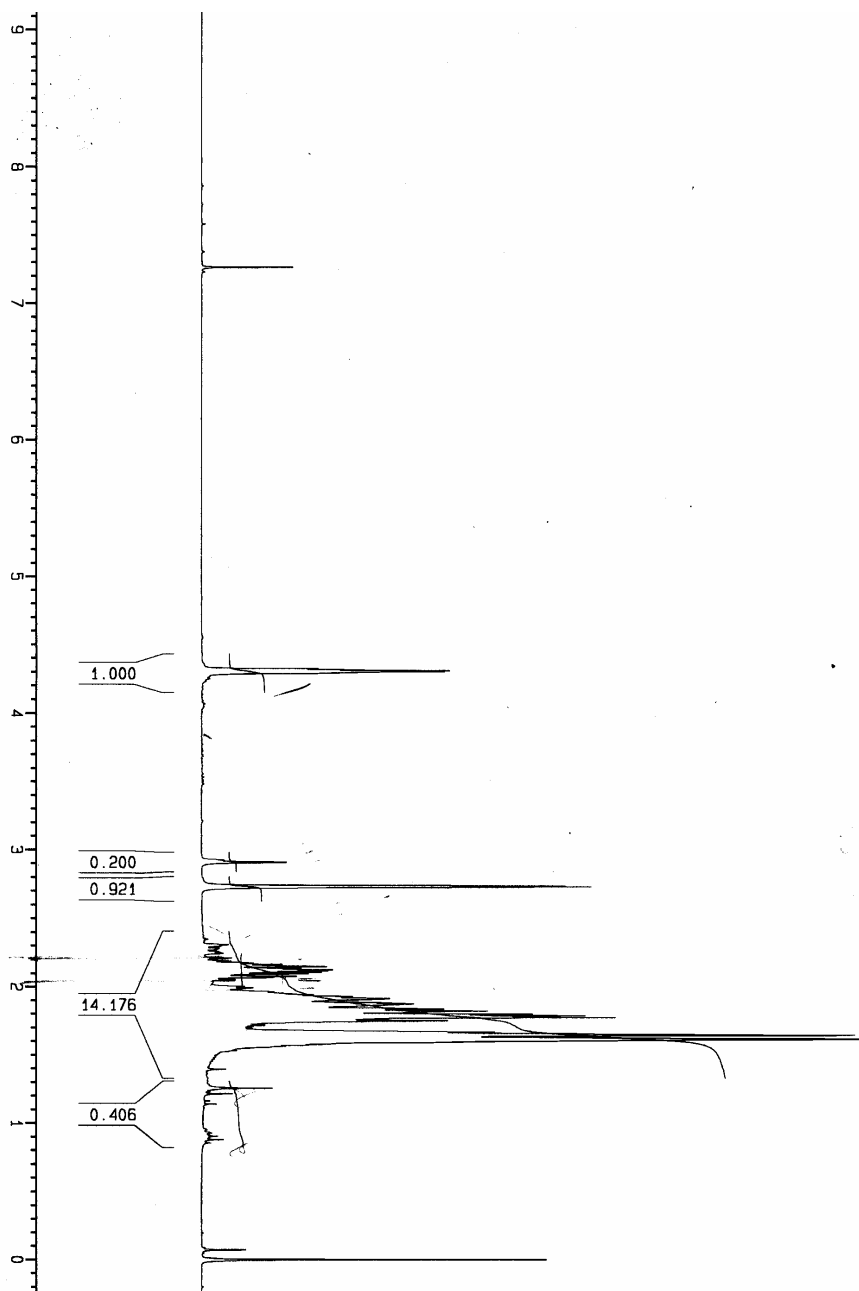


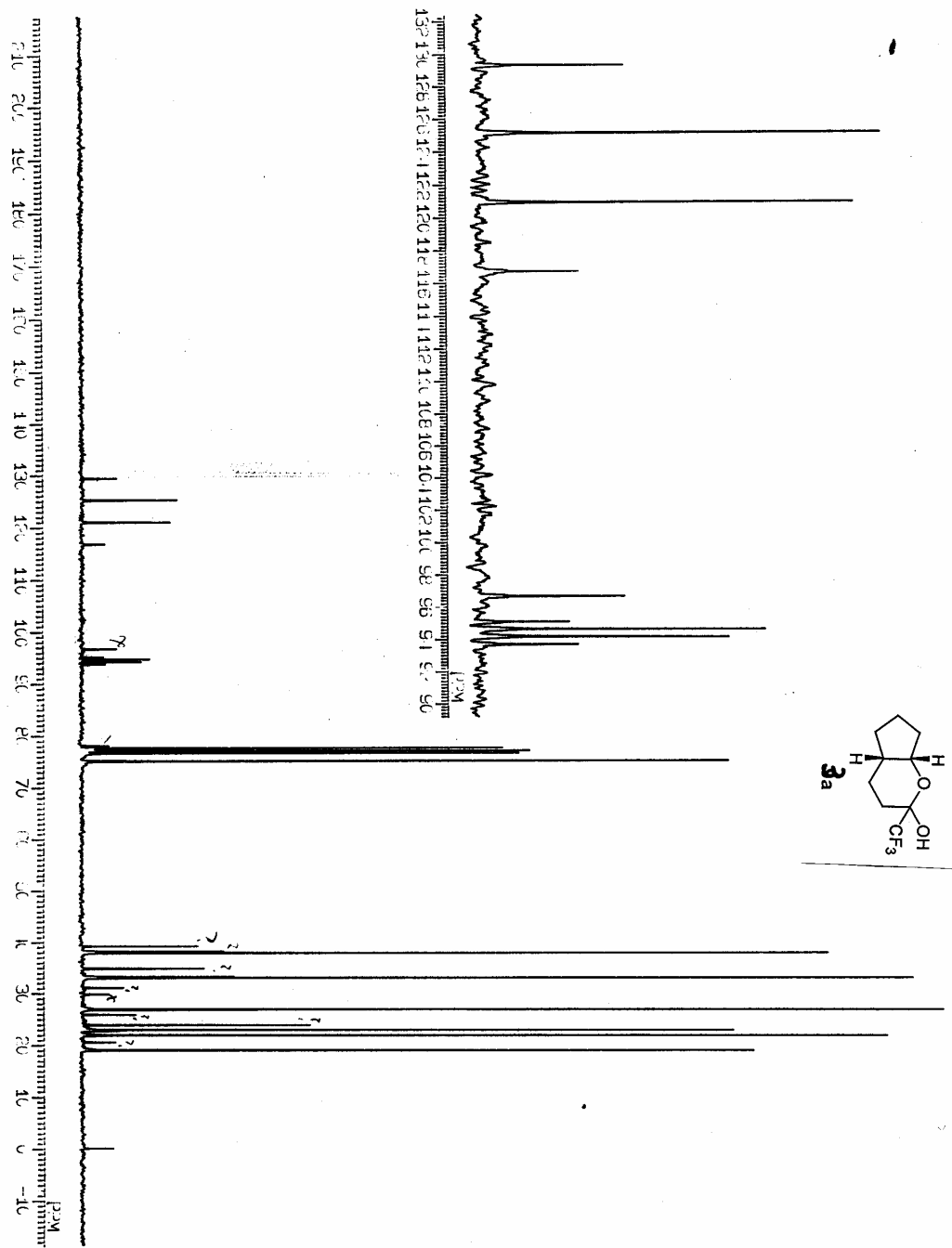
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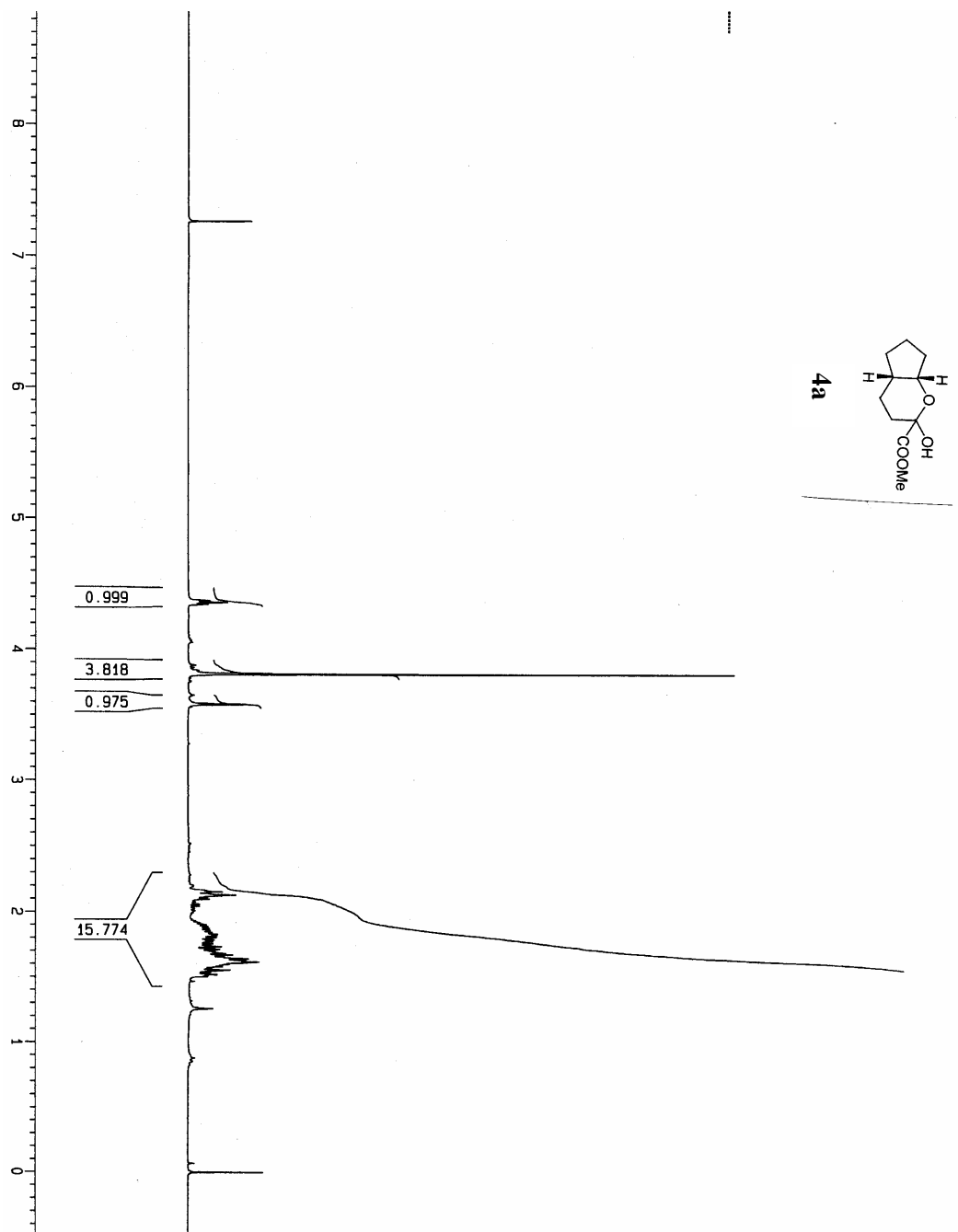


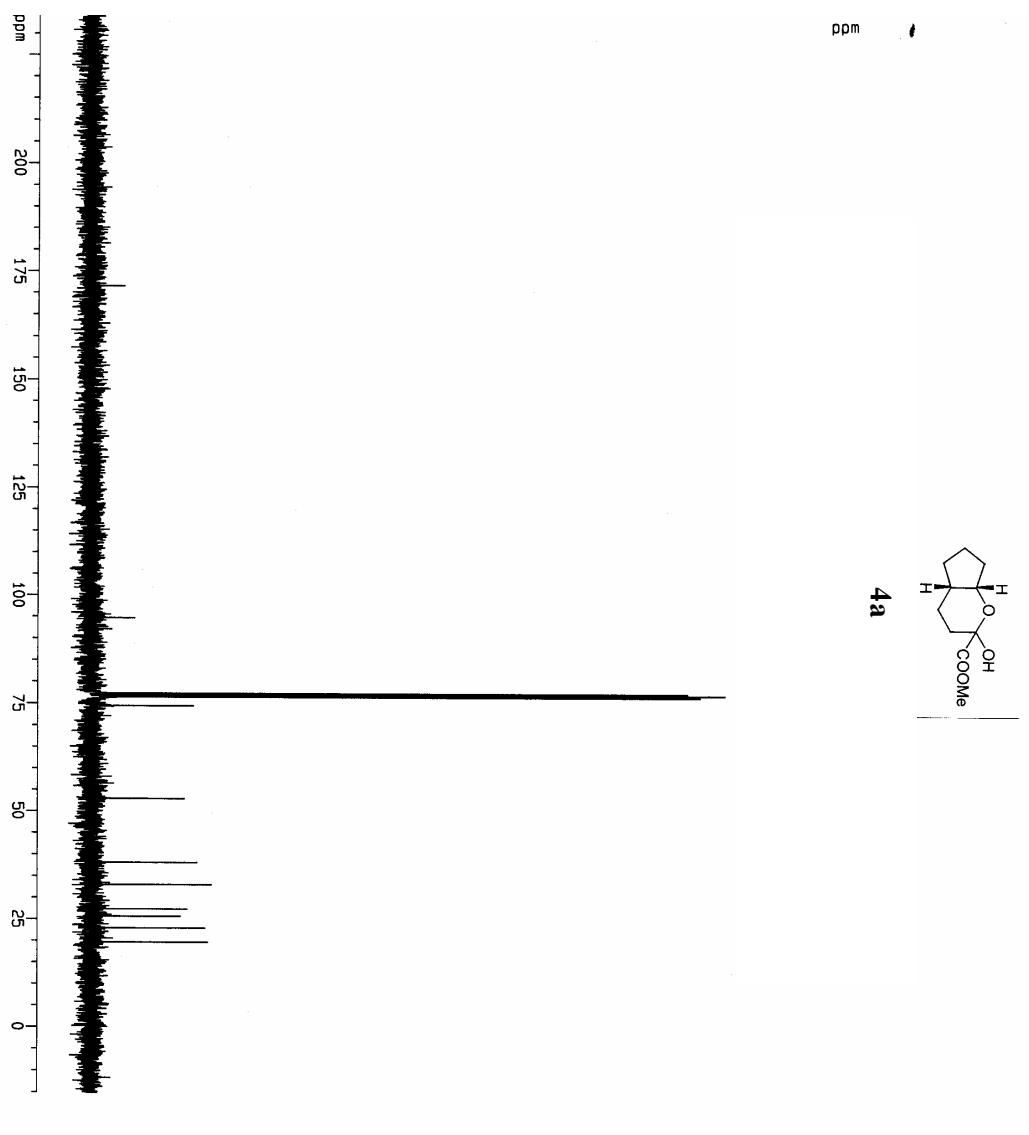


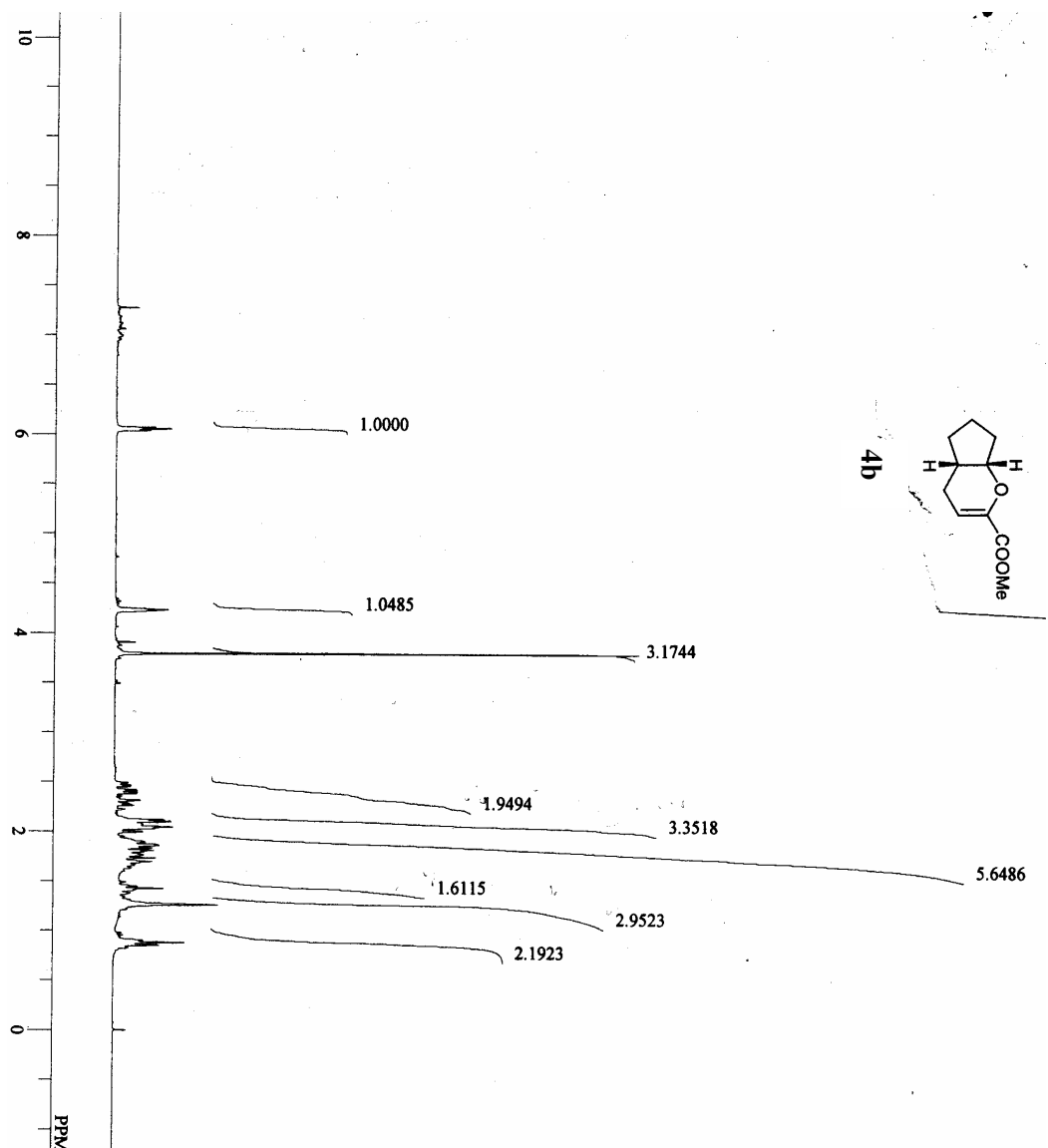


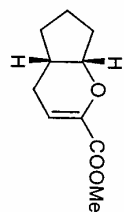




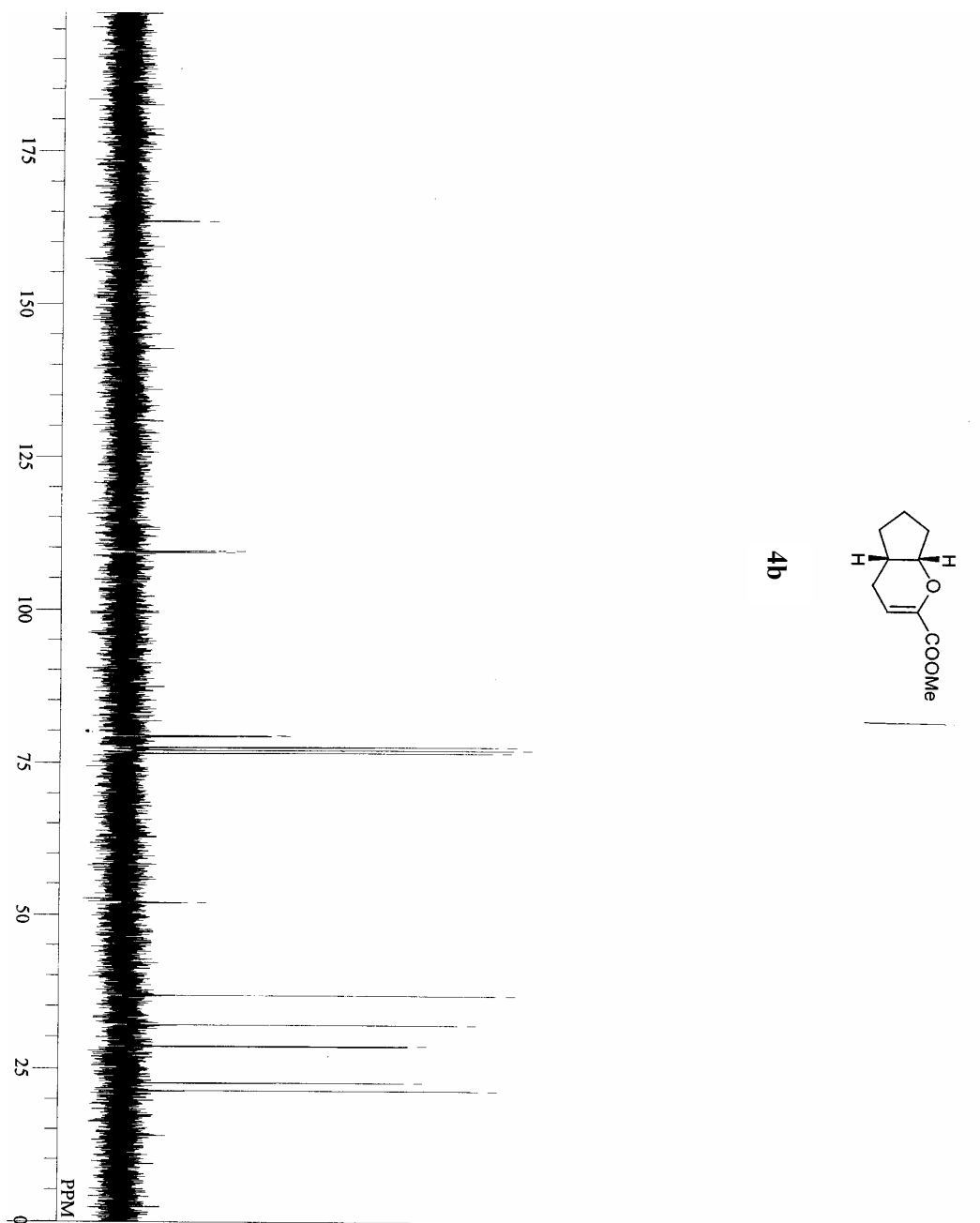


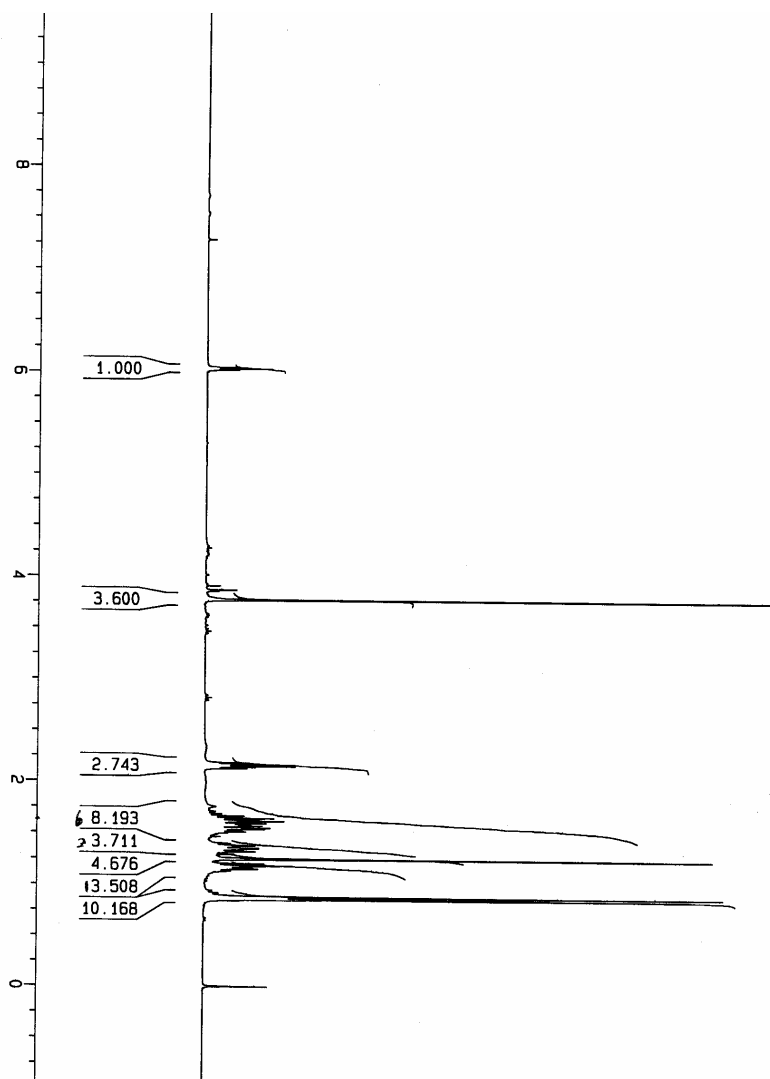
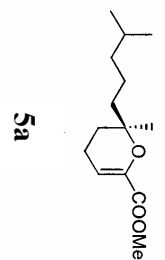


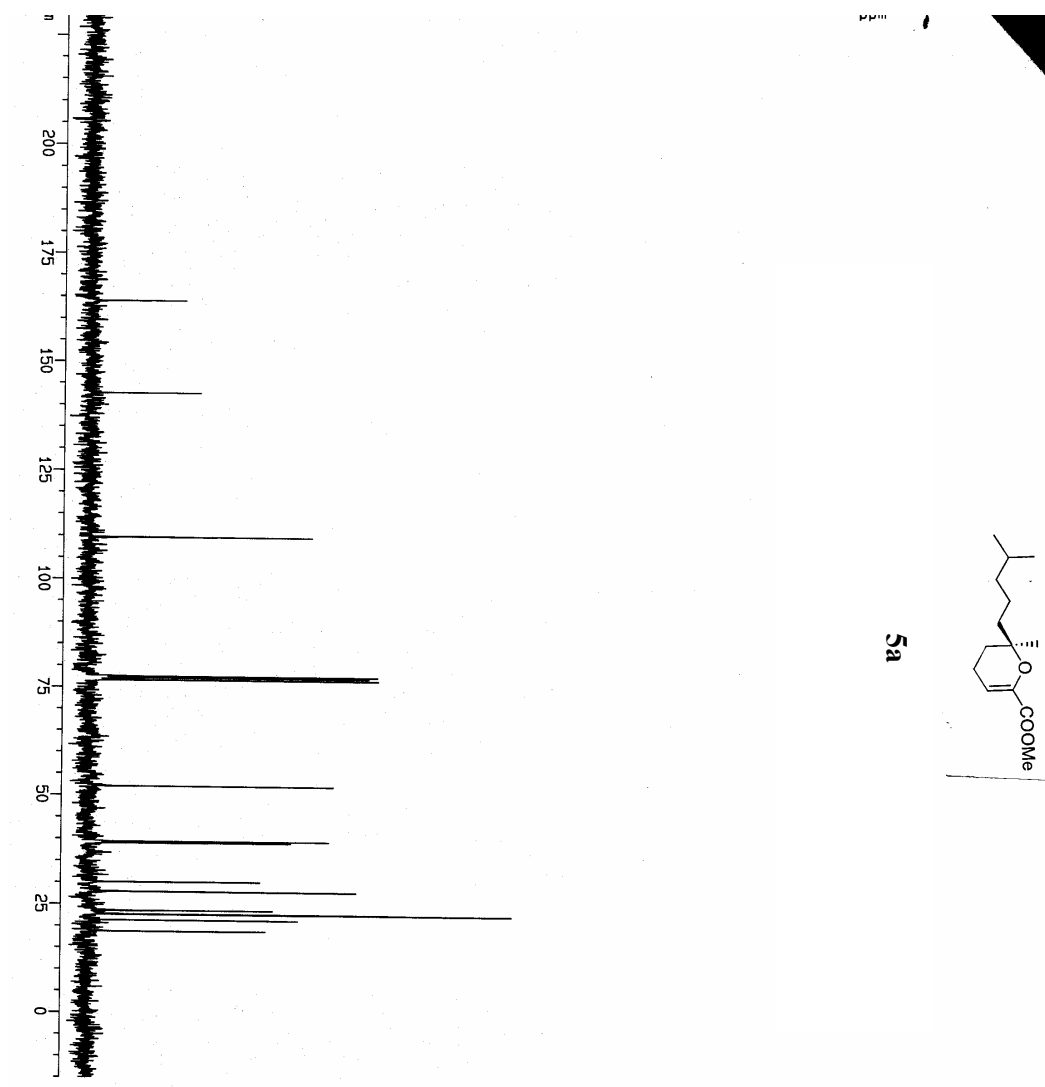


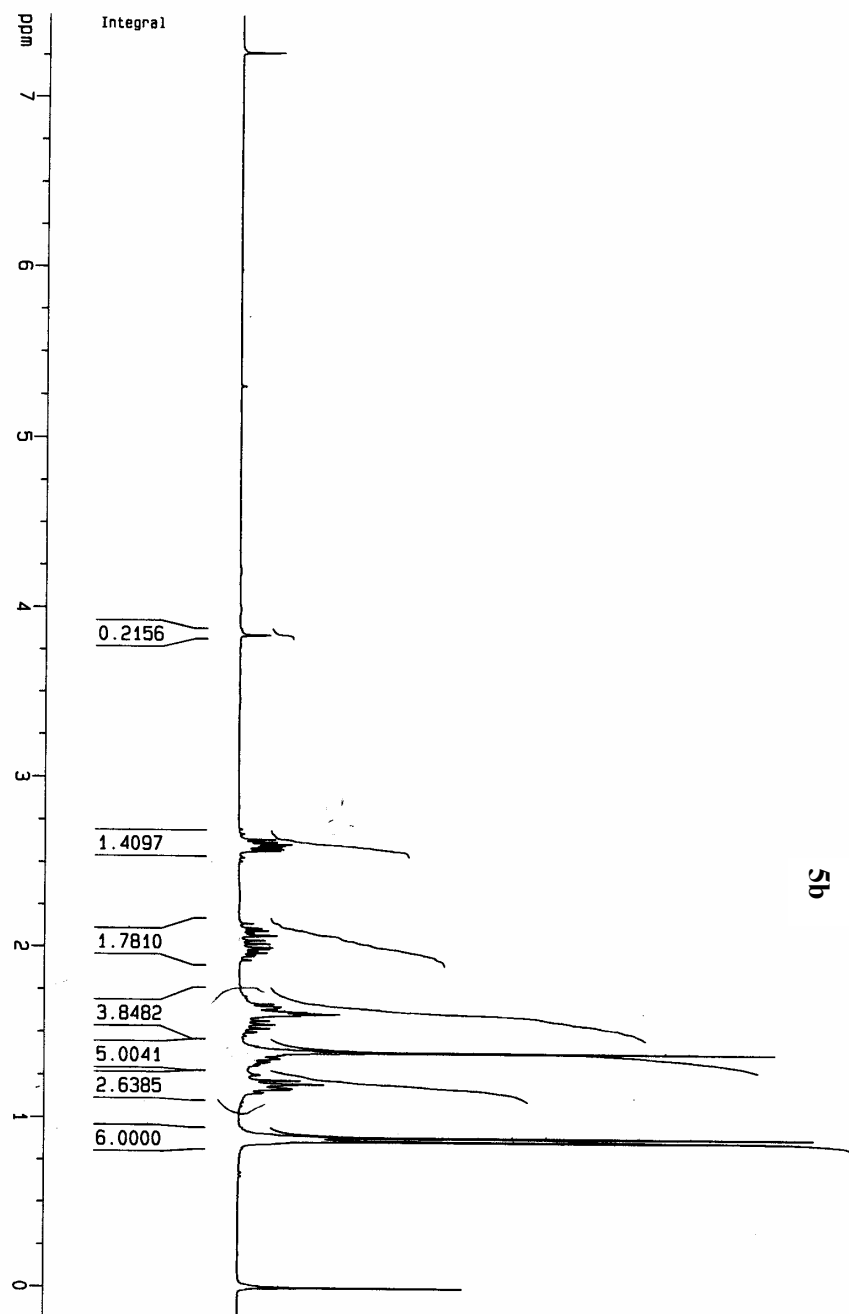


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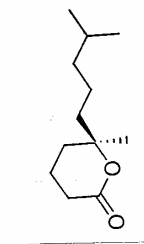


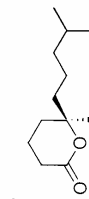






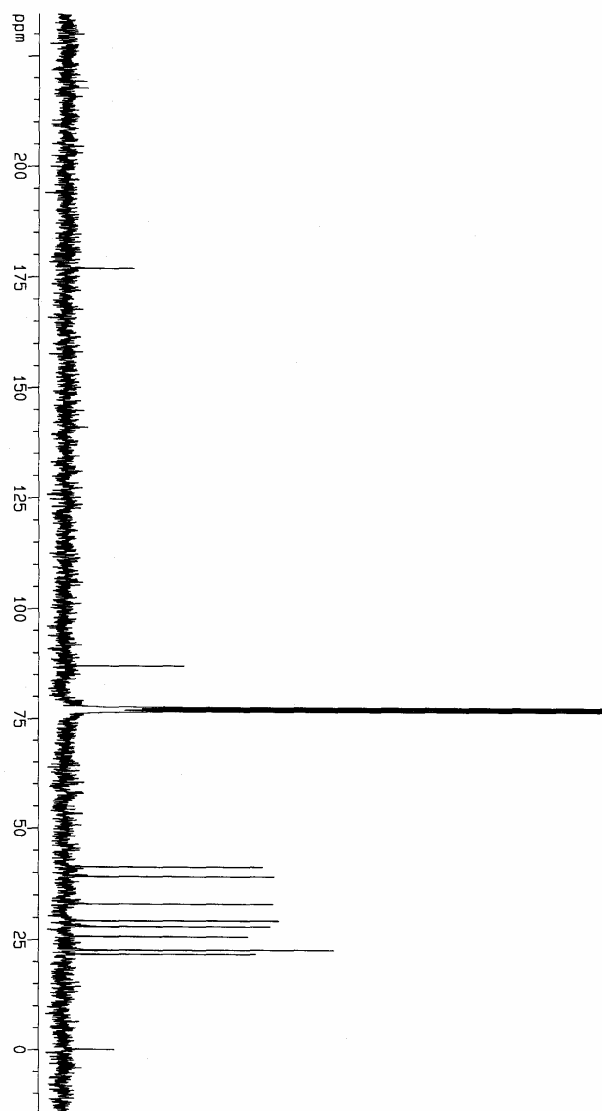
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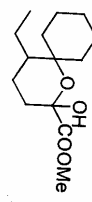




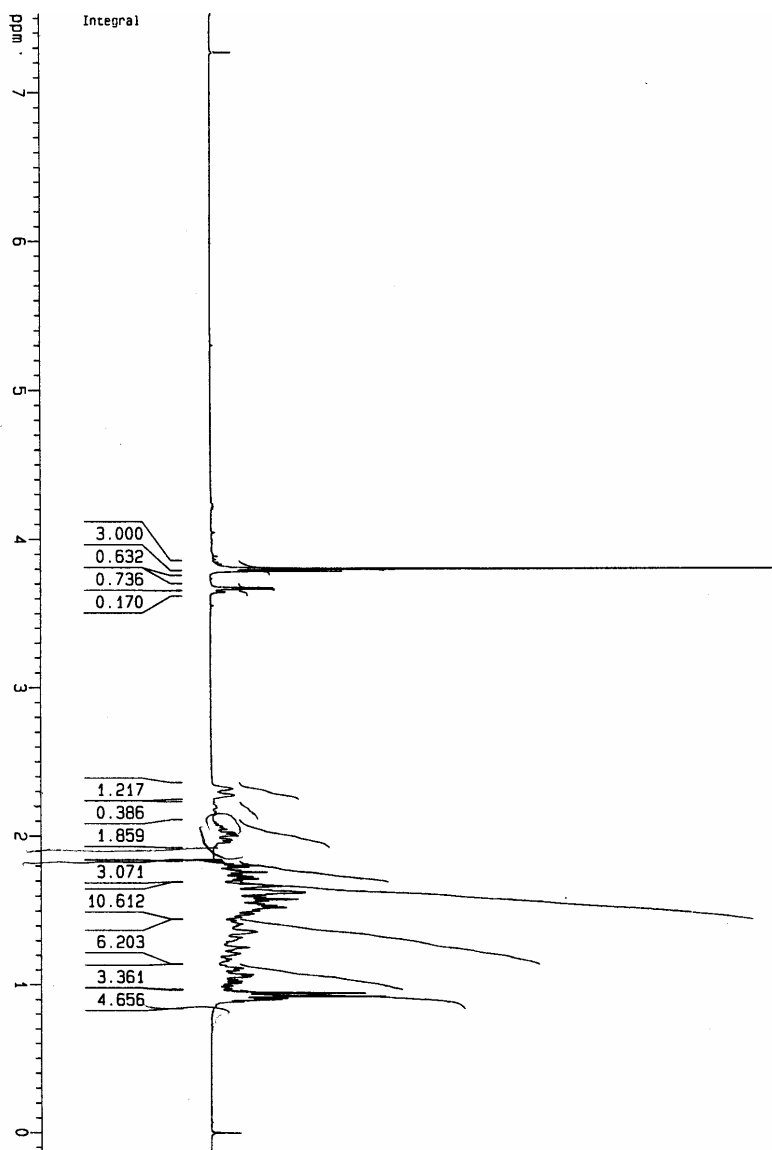
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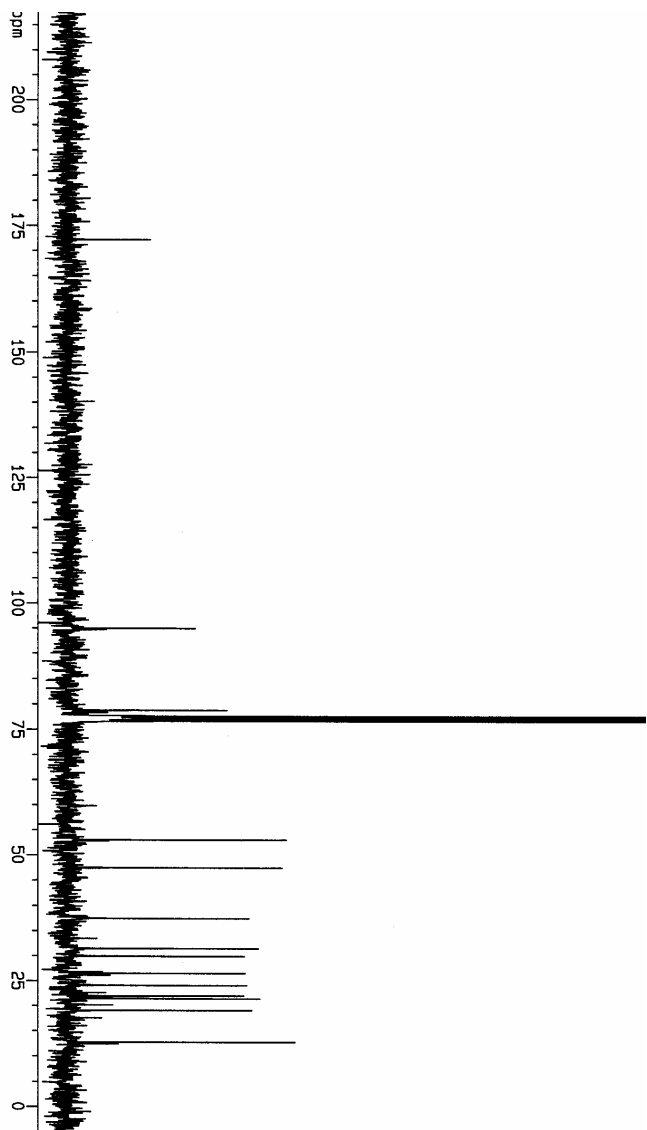
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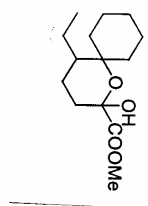
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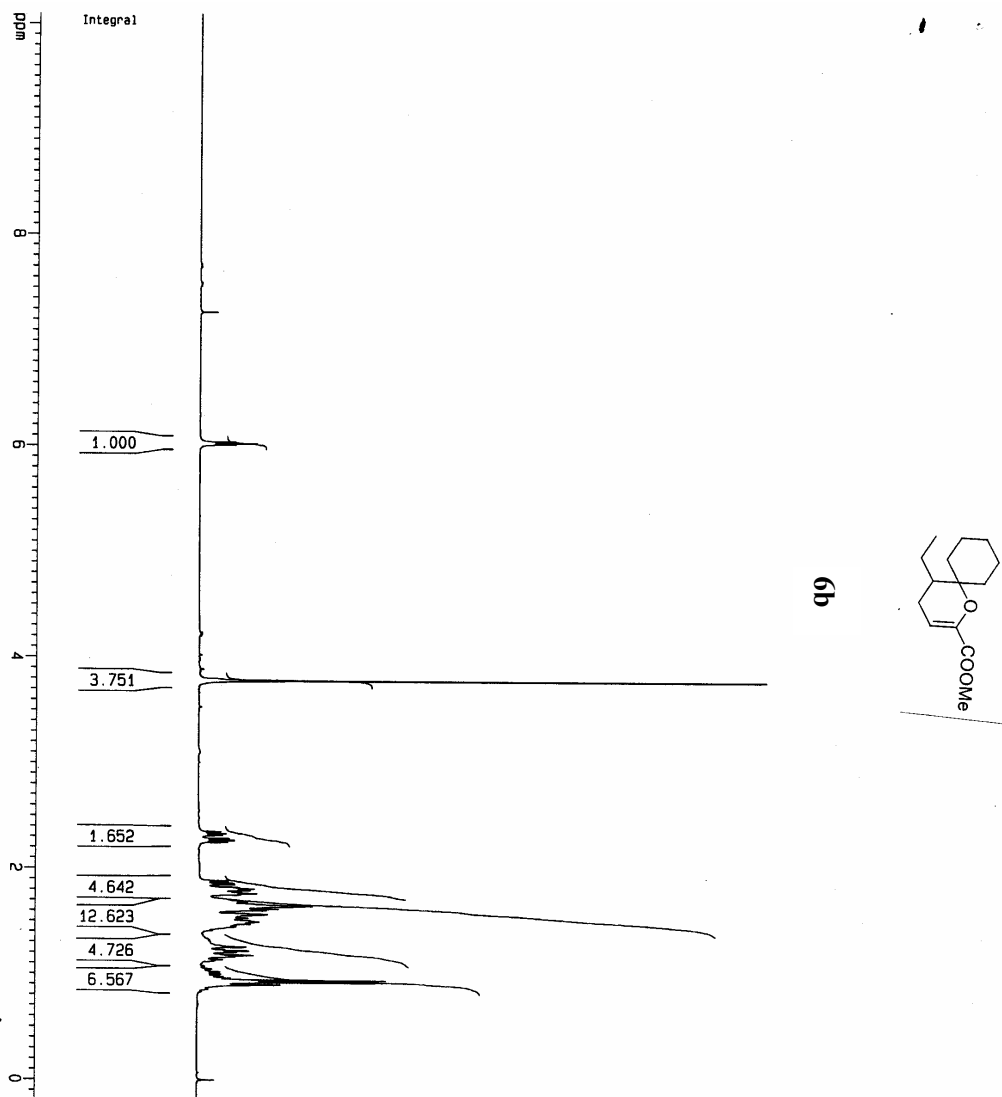


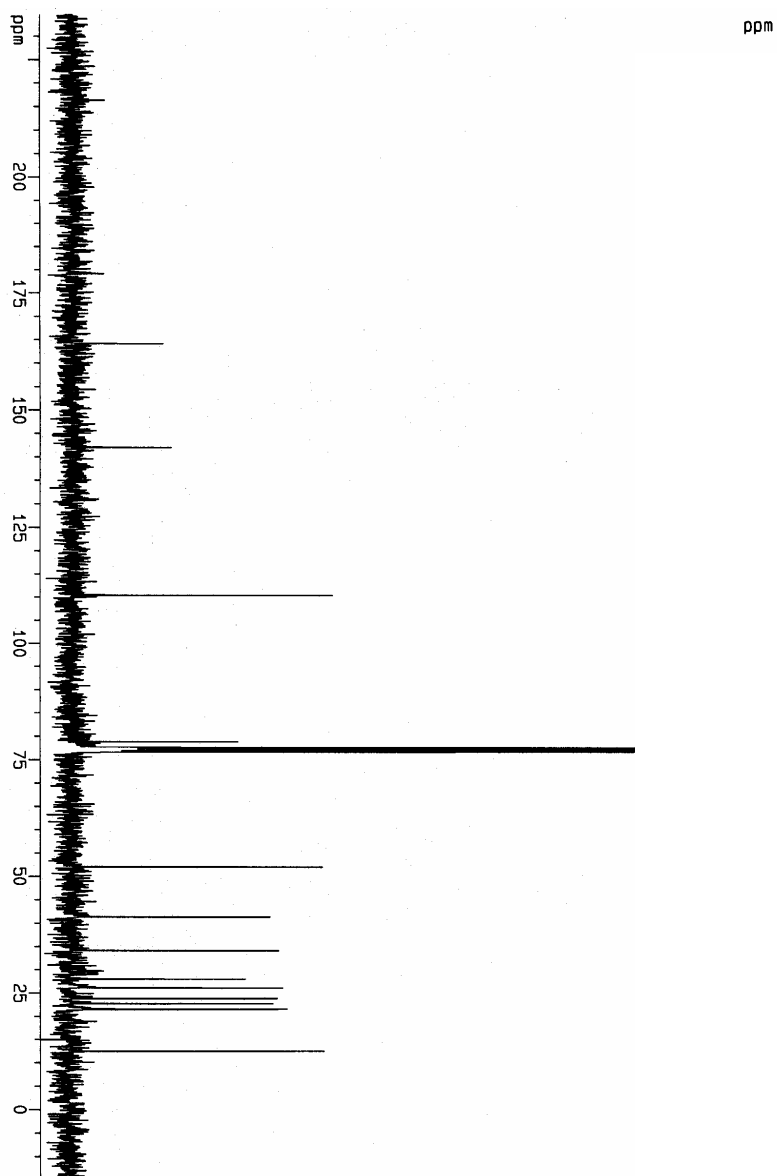
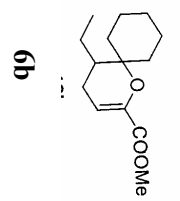


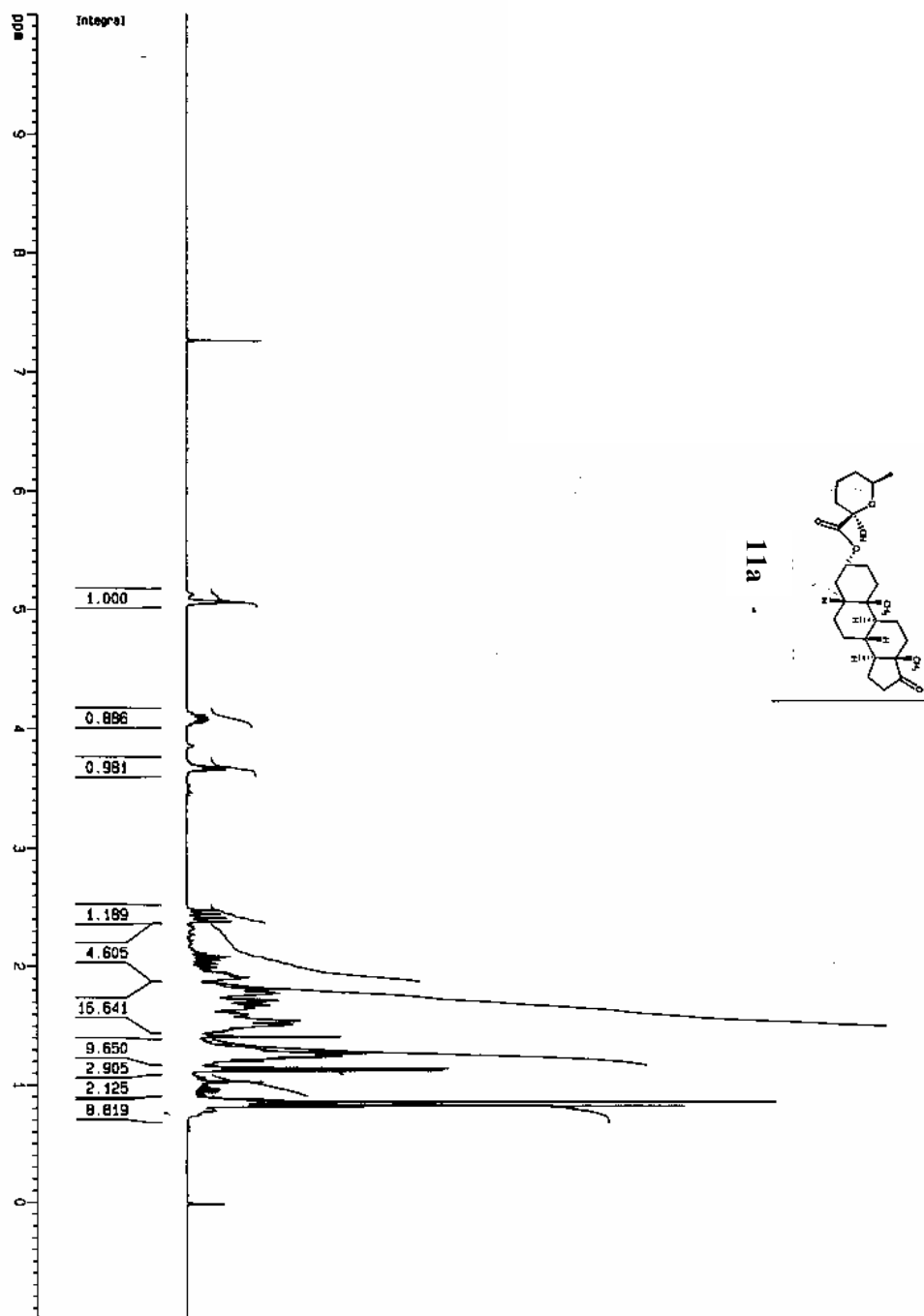
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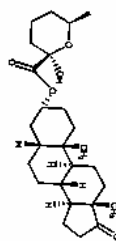
6a



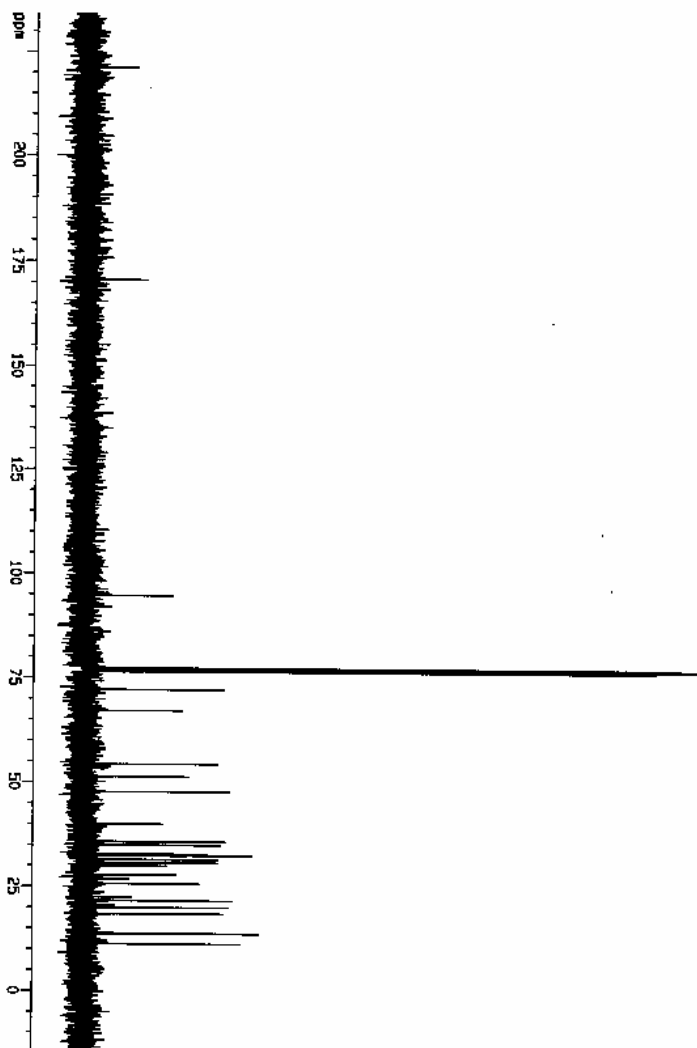


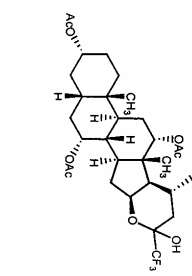




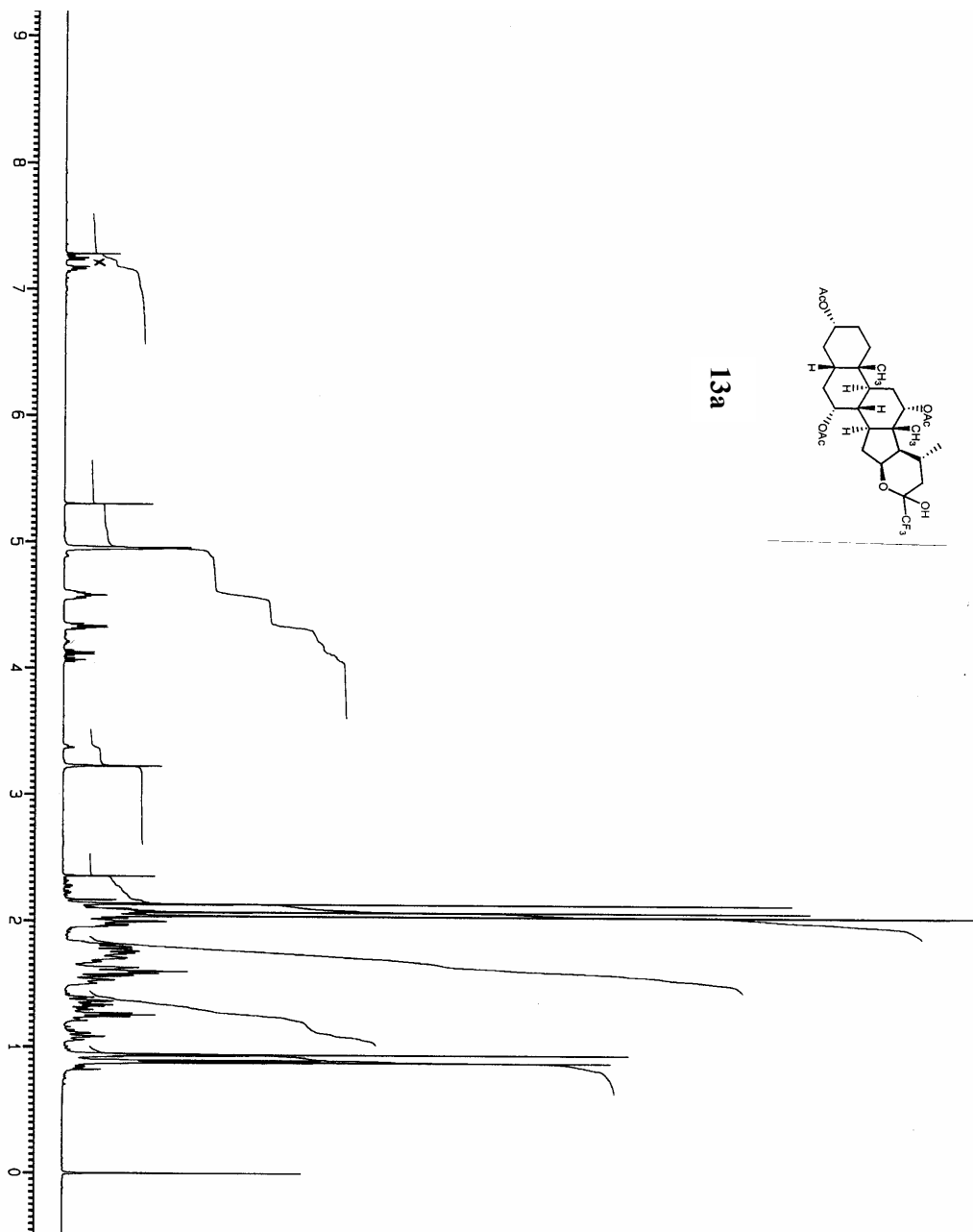


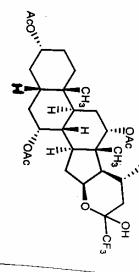
11a





13a





13a

