

Assembling Polycyclic Bisguanidine Motifs Resembling Batzelladine Alkaloids by Double Tethered Biginelli Condensations

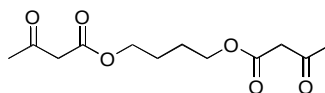
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Supporting Information:

Experimental procedures and characterization data for bis-b-ketoesters **6**, **10–15**; double Biginelli products **9**, **16–21**, **25** and **27**; copies of ^1H and ^{13}C spectra for these new compounds, selected minor double Biginelli products and **23** ($\text{R} = n\text{-C}_7\text{H}_{15}$) (33 pages).

General Experimental. All reactions were carried out under a N_2 or Ar atmosphere in oven-dried and base-washed glassware. Tetrahydrofuran (THF), diethyl ether, and dichloromethane were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; activated under a flow of Ar at 350 °C for 3h) to remove water.¹ Toluene (PhMe) was degassed with argon, passed through one 4 x 36 inch column of Q-5 reactant (activated under a flow of 5% hydrogen/nitrogen at 250 °C for 3h) to remove oxygen and then through one 4 x 36 inch column of anhydrous alumina to remove water.¹ Silica gel (0.040–0.063 mesh) was used for flash chromatography unless otherwise stated. Molarities of organolithium reagents were established by titration with diphenylacetic acid. Trifluoroethanol (TFE) was purchased from Aldrich and used without further purification. ^1H NMR chemical shifts are reported as δ values in ppm relative to CHCl_3 or MeOH. ^1H NMR coupling constants are reported in Hz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet); d (doublet); q (quartet); m (multiplet); app d (apparent doublet); app t (apparent triplet); dd (doublet of doublets); ddd (doublet, doublet of doublets); dddd (doublet, doublet, doublet of doublets); br s (broad singlet). ^1H NMR spectra of guanidine double Biginelli products show few resolved signals; these spectra are not tabulated, but the original spectra are reproduced. The IR spectra absorptions are recorded as wavenumbers (cm^{-1}).

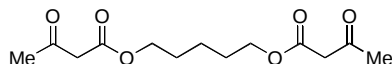


3-Oxobutyric acid 4-(3-oxobutyryloxy)butyl ester (10). General procedure for preparing bis-b-ketoesters using the Taber protocol.² A solution of DMAP (677 mg, 5.55 mmol), methyl

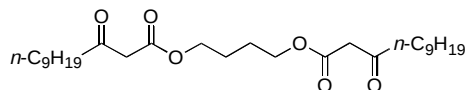
¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

² Taber, D. F.; Amedio, J.C.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

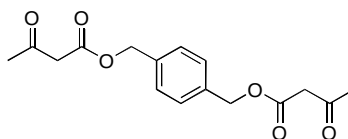
acetoacetate (1.8 mL, 17 mmol), 1,4-butanediol (500 mg, 5.5 mmol) and toluene (10 mL) was heated to 110 °C for 18 h. The reaction was allowed to cool to room temperature and then was concentrated in vacuo. The residue was purified by chromatography (1:4 ethyl acetate:hexanes) to afford 1.29 g (90%) of **10** as a yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 4.04–4.02 (m, 4H), 3.36 (s, 4H), 2.13 (s, 6H), 1.62–1.59 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.25, 166.6, 64.2, 49.42, 29.65, 24.6; IR (thin film) 2964, 1737, 1713, 1648, 1412, 1316, 1175, 1038, 955 cm^{-1} ; HRMS (CI^+) m/z 259.1180 (259.1181 calcd for $\text{C}_{12}\text{H}_{19}\text{O}_6$ [$\text{M}+\text{H}$] $^+$).



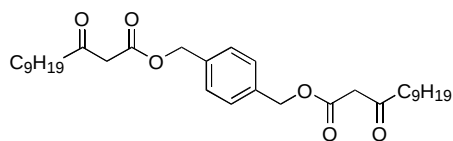
3-Oxododecanoic acid 4-(3-oxododecanoyloxy)butyl ester (6). Purification by chromatography (5:1–1:1 hexanes:EtOAc) afforded 85% of **6** as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 4.2–4.1 (m, 4H), 3.46 (s, 4H), 2.27 (s, 6H), 1.72–1.65 (m, 4H), 1.47–1.41 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 167.1, 65.0, 50.0, 30.2, 28.0, 22.2; IR (thin film) 2957, 1741, 1717, 1319, 1152 cm^{-1} ; HRMS (CI^+) m/z 273.1339 (273.1340 calcd for $\text{C}_{13}\text{H}_{21}\text{O}_6$, MH^+).



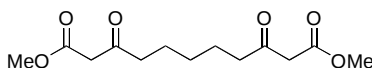
3-Oxododecanoic acid 4-(3-oxododecanoyloxy)butyl ester (11). Purification by chromatography (10:1 hexanes:EtOAc) afforded 48% of **11** as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 4.20–4.18 (m, 4H), 3.43 (s, 4H), 2.52 (dt, J = 10.0, 1.8 Hz, 4H), 1.71–1.63 (m, 2H), 1.61–1.56 (m, 4H), 1.45–1.39 (m, 2H), 1.30–1.18 (m, 24H), 0.90 (t, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.6, 167.06, 64.4, 48.9, 42.9, 31.7, 29.25, 29.2, 29.1, 28.9, 23.3, 22.5, 13.9; IR (thin film) 2920, 1738, 1413, 1321, 1267, 1159, 1050, 965, 733 cm^{-1} ; HRMS (CI^+) m/z 483.3686 (483.3685 calcd for $\text{C}_{29}\text{H}_{50}\text{O}_6$, MH^+).



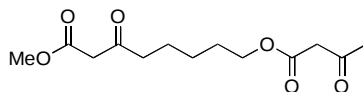
3-Oxobutyric acid 4-(3-oxobutyryloxymethyl)benzyl ester (12). Purification by chromatography (5:1 hexanes:EtOAc) afforded 70% of **12** as a colorless powder: ^1H NMR (500 MHz, CDCl_3) δ 7.42 (s, 4H), 5.23 (s, 4H), 3.56 (s, 4H), 2.31 (s, 6H); ^{13}C (125 MHz, CDCl_3) δ 200.5, 167.1, 135.8, 128.8, 66.9, 50.21, 30.4; IR (thin film) 2960, 1742, 1713, 1410, 1316, 1268, 1148, 1032, 808 cm^{-1} ; HRMS (CI^+) m/z 324.1447 (324.1447 calcd for $\text{C}_{16}\text{H}_{18}\text{O}_6$, [$\text{M}+\text{NH}_4$] $^+$).



3-Oxododecanoic acid 4-(3-oxododecanoyloxymethyl)benzyl ester (13). Purification by chromatography (4:1 hexanes:EtOAc) afforded 61% of **13** as a colorless oil that solidifies at 0 °C: ^1H NMR (500 MHz, CDCl_3) δ 7.35 (s, 4H), 5.16 (s, 4H), 3.47 (s, 4H), 2.50 (t, J = 7.3 Hz, 4H), 1.58–1.56 (m, 4H), 1.28–1.24 (m, 24H), 0.87 (t, J = 5.8 Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 202.6, 167.0, 135.5, 128.4, 88.6, 66.5, 49.1, 43.1, 31.8, 29.3, 29.3, 29.2, 28.9, 23.3, 22.6, 14.0; IR (thin film) 2927, 2858, 1746, 1406, 1220, 911 cm^{-1} ; HRMS (ESI) m/z 553.3497 (553.3505 calcd for $\text{C}_{32}\text{H}_{50}\text{O}_6$, $[\text{M}+\text{Na}]^+$).



3,9-Dioxoundecanedioic acid dimethyl ester (14). Following the general procedure of Weiler,³ NaH (413 mg, 60% dispersion, 10.4 mmol) was added slowly to a solution of methyl acetoacetate (1.0 g, 8.62 mmol) and THF (15 mL) at 0 °C. The opaque reaction mixture was stirred for 10 min at 0 °C, then *n*-BuLi (3.1 mL, 9.5 mmol) was added dropwise. The resulting yellow reaction mixture was stirred for an additional 10 minutes at 0 °C before 1,3-diiodopropane (500 μL , 4.3 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 30 min and then was quenched by the addition of 0.1 N HCl (~2 mL). Silica gel was added, the reaction mixture was concentrated and the residue purified by chromatography (4:1 hexanes:EtOAc) to afford 1.82 g (77 %) of **14** as a pale yellow liquid: ^1H NMR (400 MHz, CDCl_3) δ 3.48 (s, 6H), 3.24 (s, 4H), 2.33 (t, J = 7.1 Hz, 4H), 1.39–1.32 (m, 4H), 1.11–1.04 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.1, 167.1, 51.5, 48.3, 41.9, 27.6, 22.4; IR (thin film) 2954, 2923, 2854, 1744, 1717, 1457, 1320, 1156, 908 cm^{-1} ; HRMS (CI^+) m/z 273.1333 (273.1338 calcd for $\text{C}_{13}\text{H}_{21}\text{O}_6$, MH^+).

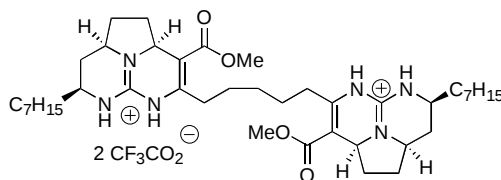


3-Oxo-8-(3-oxobutyryloxy)octanoic acid methyl ester (15). Following the general procedure of Weiler,³ NaH (413 mg, 60% dispersion, 10.43 mmol) was added slowly to a solution of methyl acetoacetate (1.00 g, 8.62 mmol) and THF (15 mL) at 0 °C. The opaque reaction mixture was stirred for 10 min at 0 °C, then *n*-BuLi (3.1 mL, 9.5 mmol) was added dropwise. The resulting yellow reaction mixture was stirred for an additional 10 min at 0 °C before *tert*-butyl(4-iodobutoxy)dimethylsilane (2.2

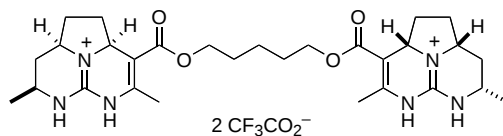
³ Weiler, L. *J. Am. Chem. Soc.* **1970**, 92, 6702–6704.

mL, 8.62 mmol) was added dropwise. The reaction was allowed to warm to room temperature over 30 min and then was quenched by the addition of 0.1 N HCl (~2 mL). Silica gel was added, the reaction mixture was concentrated and the residue was purified by chromatography to yield 3-oxo-8-(*tert*-butyldimethylsiloxy)octanoic acid methyl ester as a colorless liquid (2.41 g, 93 %).

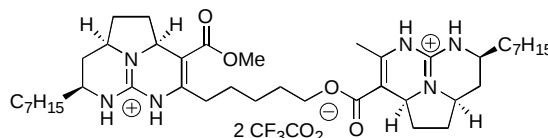
A portion of this liquid (150 mg, 0.49 mmol) was dissolved in MeOH (2 mL) and DOWEX-50 (300 mg) was added. This mixture was stirred at room temperature for 2 d, after which it was filtered and concentrated. The resulting residue was azeotroped with benzene (3x, 25 mL) and the residue was dissolved in Et₂O (20 mL). Diketene was added (60 μ L, 7.4 mmol) and the reaction mixture was stirred for 18 h at room temperature. Silica gel was added, the reaction mixture was concentrated and the residue was purified by chromatography (4:1 hexanes:EtOAc) to afford 81 mg (60%) of **15** as a yellow liquid: ¹H NMR (400 MHz, CDCl₃) δ 4.13 (app t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 2.55 (app t, *J* = 4.0 Hz, 2H), 2.26 (s, 3H), 1.67–1.58 (m, 8H), 1.38–1.34 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 202.4, 167.6, 167.1, 65.1, 52.3, 50.0, 49.0, 42.7, 30.1, 28.2, 25.2, 22.9; IR (thin film) 2941, 1744, 1713, 1360, 1150, 1017, 999 cm⁻¹; HRMS (CI⁺) *m/z* 273.1333 (273.1338 calcd for C₁₃H₂₁O₆, MH⁺).



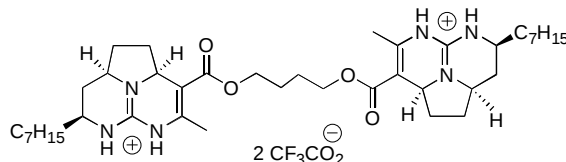
General procedure for double tethered Biginelli cyclizations. Preparation of (2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-7-heptyl-4-[5-(7'-heptyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazacacenaphthylene-3'-carboxylic acid methyl ester 4'-yl)pentyl]-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazacacenaphthylene-3-carboxylic acid methyl ester bistrifluoroacetate (16**).** Bis-b-ketoester **14** (15 mg, 0.06 mmol) was added to a stirring mixture of guanidine aldehyde **4** (65 mg, 0.21 mmol), morpholinium acetate (80 mg, 0.6 mmol), Na₂SO₄ (80 mg, 0.5 mmol) and MeOH (2 mL, 0.1 M) (In general, morpholine and AcOH can be added as liquids or as the morpholinium acetate salt). The reaction mixture was heated to 60 °C and stirred for 72 h. Concentration and purification of the residue by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 18 mg (35%) of **16** and 12 mg (23%) of C₁-symmetric isomer **22**, both as nearly colorless oils. Characterization data for **16**: ¹³C NMR (125 MHz, CD₃OD) δ 166.7, 148.1, 147.5, 102.9, 58.3, 57.2, 51.9, 51.5, 34.9, 34.0, 33.9, 32.9, 31.4, 30.4, 30.2, 29.9, 28.8, 27.5, 26.2, 23.7, 14.4; IR (thin film) 2921, 1686, 1457, 1185, 899 cm⁻¹; HRMS (ESI⁺) *m/z* 707.5226 (707.5224 calcd for C₄₁H₆₈O₄N₆, M⁺); [α]₅₈₉²⁷ -43.2, [α]₅₇₇²⁷ -42.1, [α]₅₄₆²⁷ -46.6, [α]₄₃₅²⁷ -83.0, [α]₄₀₅²⁷ -98.9 (c 1.0, MeOH). Characterization data for **22**: ¹³C NMR (125 MHz, CD₃OD) 166.7, 148.0, 147.5, 58.2, 57.2, 56.7, 56.1, 53.5, 51.9, 51.8, 51.5, 48.5, 36.0, 34.9, 34.0, 33.9, 33.6, 32.9, 32.8, 32.5, 31.5, 31.4, 30.5, 30.4, 30.3, 29.9, 29.0, 28.8, 27.5, 26.3, 26.2, 23.7, 14.4; HRMS (ESI⁺) *m/z* 707.5224 (707.5224 calcd for C₄₁H₆₈O₄N₆).



Preparation of (2a*S*,7*S*,8a*S*,2a'*S*,7*S'*,8a'*S*)-7-Methyl-4-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylene-3-carboxylic acid 4-(7'-methyl-4'-methyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazaacenaphthylene-3'-carboxy)butyl ester bistrifluoroacetate (9**).** Purification by preparative HPLC (Phenomenex C-18, 210 nm, 30% MeCN: 60% 0.1% TFA in H₂O) gave 24 mg (41%) of the C₂-symmetric product **9** as a nearly colorless oil: ¹³C NMR (125 MHz, CD₃OD) δ 166.2, 146.8, 143.9, 102.9, 65.3, 58.2, 57.1, 47.2, 36.1, 34.0, 29.4, 27.6, 23.9, 19.9, 17.8; HRMS (FAB) *m/z* 539.3217 (539.3346 calcd for C₂₉H₄₃O₄N₆); [α]_D²⁵ -93.6, [α]₅₄₆²⁵ -112, [α]₄₃₅²⁵ -207, [α]₄₀₅²⁵ -246 (c 0.7, MeOH).

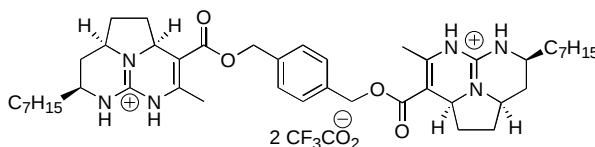


(2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-4-(5-(7'-Heptyl-4-methyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triaza-acenaphthylene-3'-carboxy)pentyl)-7-heptyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triaza-acenaphthylene-3-carboxylic acid methyl ester bistrifluoroacetate (17**).** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 26 mg (39%) of **17** and 24 mg (37%) of a stereoisomer that was contaminated with **17**, both as nearly colorless oils. Characterization data for **17**: ¹³C NMR (125 MHz, CD₃OD) δ 166.7, 166.6, 148.1, 147.4, 147.3, 144.7, 103.5, 102.6, 65.4 (2C), 58.3, 58.25, 57.21, 57.2, 51.9, 51.5, 34.9, 33.9, 33.9, 32.9, 31.4, 30.5, 30.3, 29.3, 28.7, 27.5, 27.4, 26.8, 26.3, 26.2, 23.7, 17.8, 14.4; HRMS (ESI⁺) *m/z* 707.5224 (707.5202 calcd for C₄₁H₆₈O₄N₆); [α]₅₈₉²⁷ -14.7, [α]₅₇₇²⁷ -15.9, [α]₅₄₆²⁷ -17.9, [α]₄₃₅²⁷ -44.1, [α]₄₀₅²⁷ -57.2 (c 1.2, MeOH).

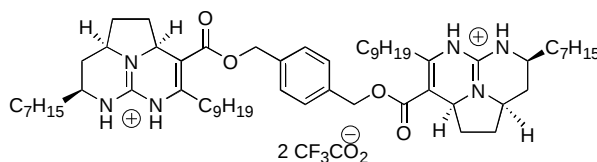


(2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-7-Heptyl-4-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triaza-acenaphthylene-3-carboxylic acid 4-(7'-heptyl-4'-methyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazaacenaphthylene-3'-carboxy)-butyl ester bistrifluoroacetate (18**)** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90%

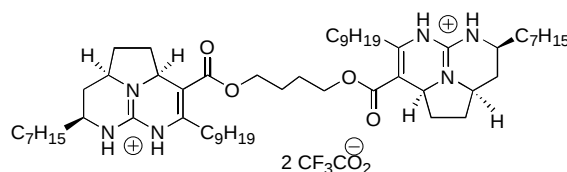
MeCN: 0.1% TFA in H₂O over 20 min) gave 20 mg (42%) of the C₂-symmetric product **18** and 10 mg (22%) of a C₁-symmetric product that was contaminated with **18**, both as nearly colorless oils. Characterization data for **18**: ¹³C NMR (125 MHz, CD₃OD) δ 166.5, 147.4, 144.2, 103.2, 65.2, 58.4, 57.2, 51.2, 34.9, 33.9, 32.9, 30.4, 30.3, 27.5, 26.6, 26.2, 23.7, 17.8, 14.4; IR (thin film) 2929, 1686, 1200, 1077, 721 cm⁻¹; HRMS (ESI⁺) *m/z* 693.5056 (693.5067 calcd for C₄₀H₆₆O₄N₆); [α]₅₈₉²⁷ -55.5, [α]₅₇₇²⁷ -58.0, [α]₅₄₆²⁷ -61.9, [α]₄₃₅²⁷ -86.3, [α]₄₀₅²⁷ -95.8 (*c* 0.5, MeOH).



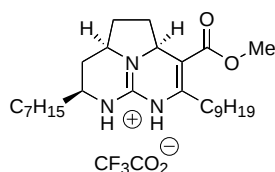
(2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-7-Heptyl-4-methyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triaza-acenaphthylene-3-carboxylic acid 4-(7'-heptyl-4'-methyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazacacenaphthylene-3'-carboxy)methylbenzyl ester bistrifluoroacetate (19**).** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 13 mg (25%) of the C₂-symmetric product **19** and 7 mg (13%) of a C₁-symmetric product that was contaminated with some **19**, both as nearly colorless oils. Characterization data for **19**: ¹³C NMR (125 MHz, CD₃OD) δ 163.2, 144.7, 141.2, 135.9, 129.8, 103.0, 67.0, 58.3, 57.2, 51.5, 35.0, 33.9, 33.0, 33.4, 30.3, 27.5, 26.2, 23.8, 17.9, 14.5; IR (thin film) 2927, 2858, 1684, 1197, 1135, 718 cm⁻¹; HRMS (ESI⁺) *m/z* 741.5063 (741.5067 calcd for C₄₄H₆₆O₄N₆).



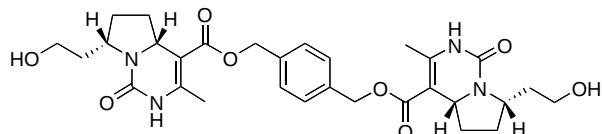
(2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-7-Heptyl-4-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triaza-acenaphthylene-3-carboxylic acid 4-(7'-heptyl-4'-nonyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazacacenaphthylene-3'-carboxy)methylbenzyl ester bistrifluoroacetate (20**).** This reaction was carried out by the general procedure using trifluoroethanol as the solvent. Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 17 mg (34%) of the C₂-symmetric product **20** and 12 mg (25%) of a C₁-symmetric product that was contaminated with some **20**, both as nearly colorless oils. Characterization data for **20**: ¹³C NMR (125 MHz, CD₃OD) δ 166.0, 148.2, 147.3, 137.6, 129.9, 103.0, 67.1, 58.3, 57.2, 51.5, 35.0, 34.0, 33.9, 33.0, 32.9, 32.0, 30.6, 30.4 (4C), 30.3, 29.3, 27.5, 26.3, 23.7, 23.7, 14.5, 14.4; IR (thin film) 2932, 2856, 1583, 1479, 1438, 1250 cm⁻¹; HRMS (ESI⁺) *m/z* 483.3817 (483.3819 calcd for C₆₀H₉₈O₄N₆); [α]₅₈₉²⁷ -38.8, [α]₅₇₇²⁷ -37.6, [α]₅₄₆²⁷ -43.6, [α]₄₃₅²⁷ -96.1, [α]₄₀₅²⁷ -120 (*c* 0.5, MeOH).



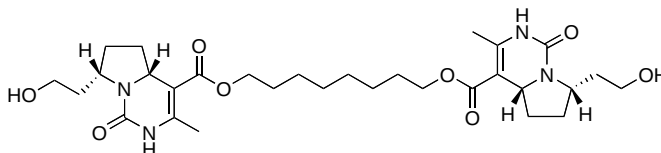
(2a*S*,7*S*,8a*R*,2a'*S*,7*S'*,8a'*R*)-7-Heptyl-4-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylene-3-carboxylic acid 4-(7'-heptyl-4'-nonyl-1',2',2a',5',6',7',8',8a'-octahydro-5',6',8b'-triazazaacenaphthylene-3'-carboxy)butyl ester bistrifluoroacetate (21**).** This reaction was carried out by the general procedure using trifluoroethanol as the solvent. Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 16 mg (33%) of the C₂-symmetric product **21** and 5 mg (11%) of a C₁-symmetric product that was contaminated with some **21**, both as nearly colorless oils. Characterization data for **21**: ¹³C NMR (125 MHz, CD₃OD) δ 165.8, 147.6, 146.6, 102.3, 67.2, 57.2, 56.3, 51.5, 43.4, 35.0, 34.0, 33.0, 32.9, 31.8, 30.6, 30.5, 30.4, 30.44, 30.3, 29.2, 27.5, 26.6, 26.3, 23.8, 23.7, 14.4; IR (thin film) 3352, 2927, 2495, 1671, 1686, 1459, 1202 cm⁻¹; HRMS (ESI⁺) *m/z* 459.3835 (459.3819 calcd for C₅₆H₉₈O₄N₆ [M]²⁺); [α]₅₈₉²⁷ -41.3, [α]₅₇₇²⁷ -50.7, [α]₅₄₆²⁷ -72.4, [α]₄₃₅²⁷ -123.1, [α]₄₀₅²⁷ -159.2 (c 0.5, MeOH).



(2a*S*,7*S*,8a*R*)-7-Heptyl-4-nonyl-1,2,2a,5,6,7,8,8a-octahydro-5,6,8b-triazaacenaphthylene-3-carboxylic acid methyl ester trifluoroacetate (23** R = *n*-C₇H₁₅).** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 45 mg (77%) of **23** as a nearly colorless oil: ¹H NMR (500 MHz, CD₃OD) δ 4.59–4.55 (m, 1H), 3.86–3.82 (m, 1H), 3.77 (s, 3H), 3.58–3.49 (m, 1H), 2.84–2.76 (m, 1H), 2.75–2.66 (m, 1H), 2.61–2.53 (m, 1H), 2.49–2.44 (m, 1H), 2.22–2.17 (m, 1H), 1.74–1.55 (m, 6H), 1.53–1.38 (m, 25H), 0.96–0.92 (m, 6H); ¹³C NMR (125 MHz, CD₃OD) δ 166.7, 148.2, 147.5, 102.8, 58.3, 57.2, 51.9, 51.5, 34.9, 34.0, 33.9, 33.0, 32.9, 31.6, 30.6, 30.4, 30.4, 30.3 (2C), 30.3, 29.2, 27.5, 26.2, 23.7, 23.7, 14.4, 14.3; IR (thin film) 2927, 2858, 1686, 1436, 1202, 1140, 906, 727 cm⁻¹; HRMS (ESI) *m/z* 446.3764 (446.3747 calcd for C₂₇H₄₈O₂N₃); [α]₅₈₉²⁷ -6.75, [α]₅₇₇²⁷ -6.92, [α]₅₄₆²⁷ -7.91, [α]₄₃₅²⁷ -17.0, [α]₄₀₅²⁷ -20.1 (c 3.8, MeOH).



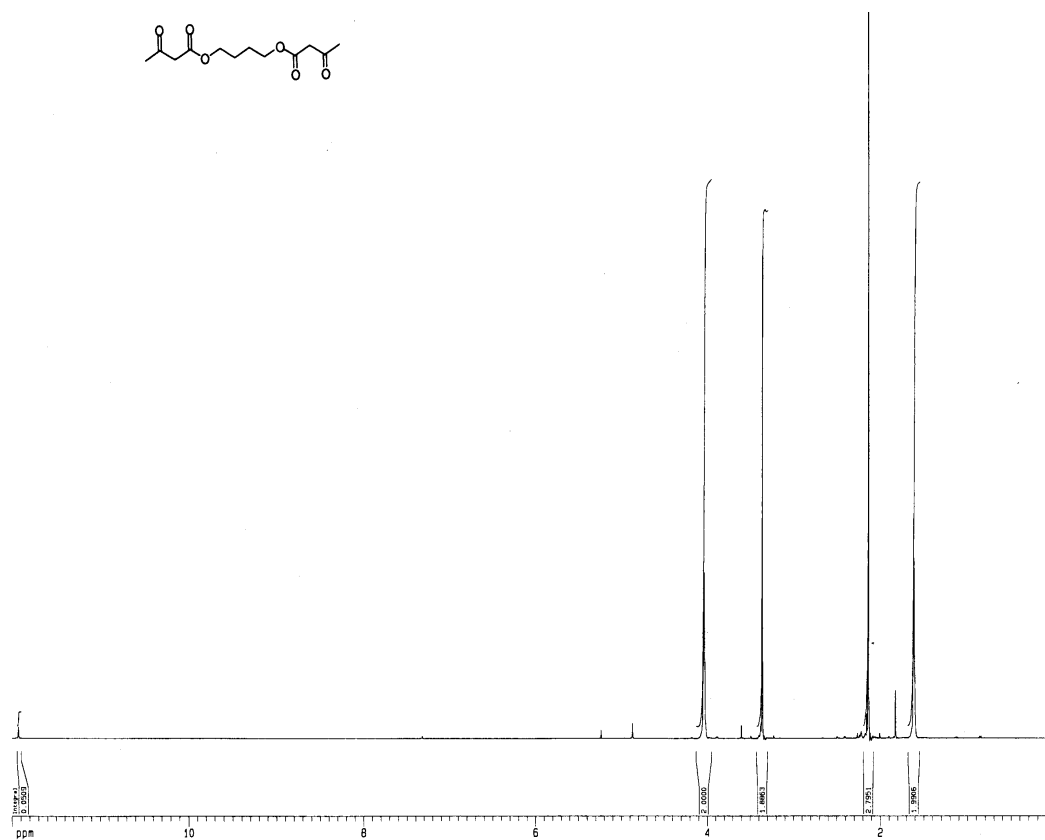
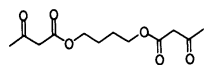
(2*S*,4*aR*,2'*S*,4*a'R*)-7-(2-Hydroxy-ethyl)-3-methyl-1-oxo-1,2,4*a*,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid 4-(7'-(2'-hydroxyethyl)-3'-methyl-1'-oxo-1',2',4*a'*,5',6',7'-hexahydropyrrolo[1',2'-*c*]pyrimidine-4'-carboxy)-methylbenzyl ester (25).** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10% MeCN: 0.1% TFA in H₂O to 90% MeCN: 0.1% TFA in H₂O over 20 min) gave 21 mg (69%) of the C₂-symmetric product **25** and 7 mg (23%) of a less pure sample of a C₁-symmetric isomer, both as pale yellow films. Characterization data for **25**: ¹H NMR (500 MHz, CDCl₃) (trace amounts of MeOH added to solubilize **25**) δ 7.61 (br s, 1H), 7.41 (s, 2H), 5.25 (d, *J* = 2.5 Hz, 1H), 5.18 (d, *J* = 2.5 Hz, 1H), 4.33–4.30 (m, 1H), 4.21–4.17 (m, 1H), 3.65–3.55 (m, 1H), 2.25 (s, 3H), 2.13–2.08 (m, 1H), 1.93–1.65 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.5, 154.4, 148.8, 136.2, 128.7, 102.5, 65.7, 59.2, 58.5, 52.4, 50.9, 39.5, 30.8, 29.9, 18.4; IR (thin film) 2950, 1676, 1630, 1437, 1313, 1251, 1112, 1074 cm⁻¹; HRMS (ESI) *m/z* 605.2572 (605.2587 calcd for C₃₀H₃₈O₈N₄); [α]₅₈₉²⁷ -39.7, [α]₅₇₇²⁷ -40.5, [α]₅₄₆²⁷ -46.0, [α]₄₃₅²⁷ -98.9, [α]₄₀₅²⁷ -110.1 (c 1, MeOH).



(2*S*,4*aR*,2'*S*,4*a'R*)-7-(2-Hydroxyethyl)-3-methyl-1-oxo-1,2,4*a*,5,6,7-hexahydro-pyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid 4-(7'-(2'-hydroxyethyl)-3'-methyl-1'-oxo-1',2',4*a'*,5',6',7'-hexahydropyrrolo[1',2'-*c*]pyrimidine-4'-carboxy)octyl ester (27).** Purification by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN: 0.1% TFA in H₂O to 90 % MeCN: 0.1% TFA in H₂O over 20 min) gave 20 mg (61%) of the C₂-symmetric product **27** and 7 mg (20%) of a less pure sample of a C₁-symmetric isomer, both as pale yellow films the former of which slowly solidified upon standing at 0 °C. Characterization data for **27**: ¹H NMR (500 MHz, CDCl₃) δ 7.54 (m, 1H), 4.31 (ddd, *J* = 11.2, 5.0, 1.2 Hz, 1H), 4.23–4.16 (m, 2H), 4.16–4.11 (m, 1H), 3.70–3.58 (m, 2H), 2.58–2.53 (m, 1H), 2.28 (s, 3H), 2.19–2.10 (m, 1H), 1.95–1.87 (m, 1H), 1.82–1.76 (m, 3H), 1.76–1.68 (m, 4H), 1.39–1.37 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 165.9, 154.5, 148.1, 103.0, 64.2, 59.2, 58.2, 52.4, 39.6, 30.9, 29.9, 29.1, 28.7, 26.0, 18.2; IR (thin film) 3236, 2927, 2858, 1738, 1645, 1452, 1321, 1251, 1081 cm⁻¹; HRMS (ESI⁺) *m/z* 613.3217 (613.3214 calcd for C₃₀H₄₆O₈N₄); [α]₅₈₉²⁷ -57.3, [α]₅₇₇²⁷ -57.6, [α]₅₄₆²⁷ -64.0, [α]₄₃₅²⁷ -145.4, [α]₄₀₅²⁷ -188.7 (c 0.5, MeOH).

^1H and ^{13}C NMR Spectra

A. β -Ketoesters



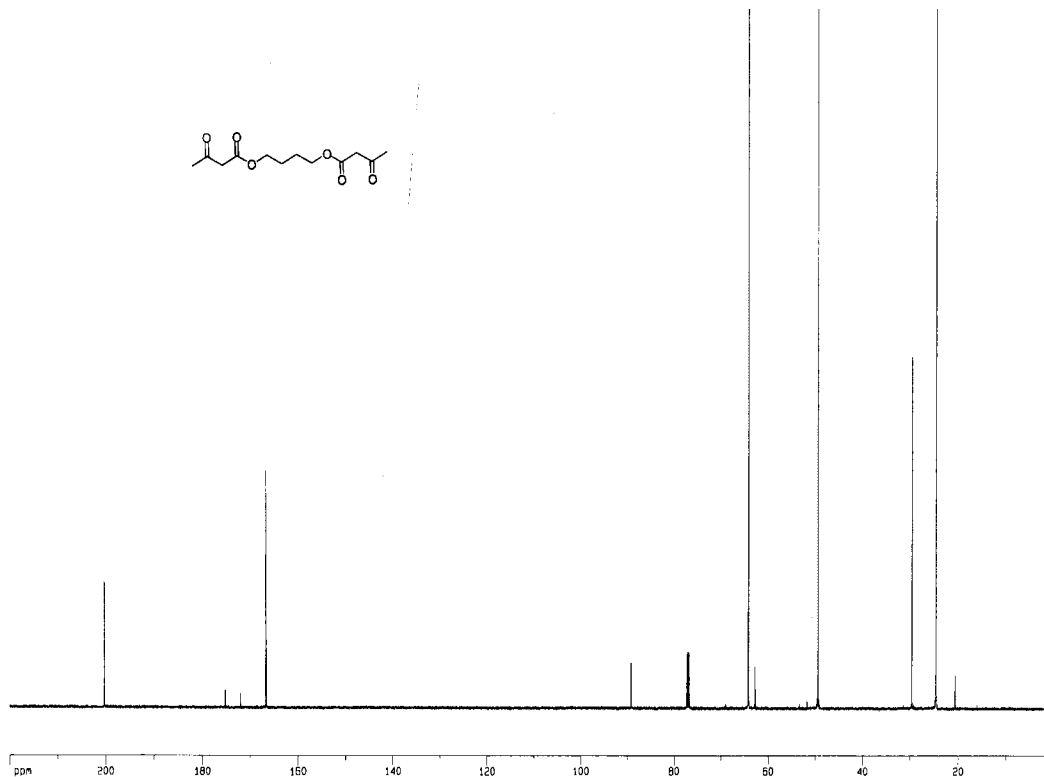
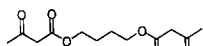
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 F2 0.00 Hz
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Current Data Parameters
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 NAME sc-111-109a
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 PROCNO 1

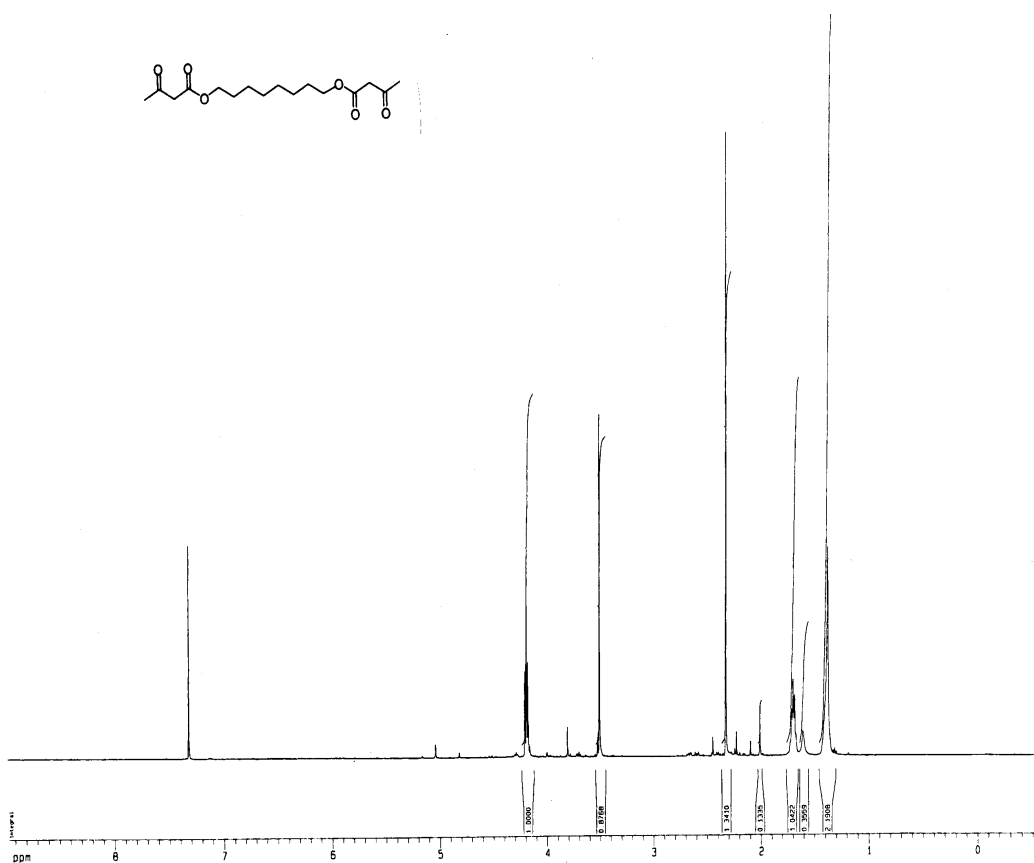
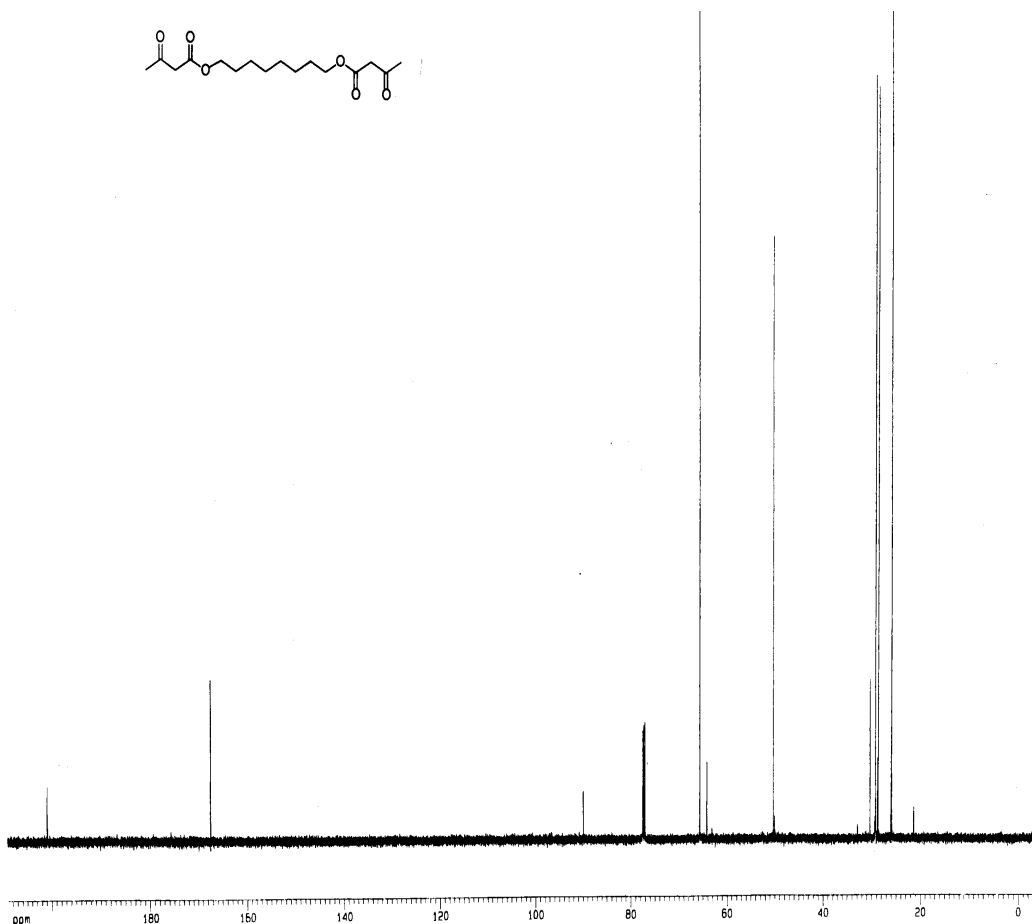
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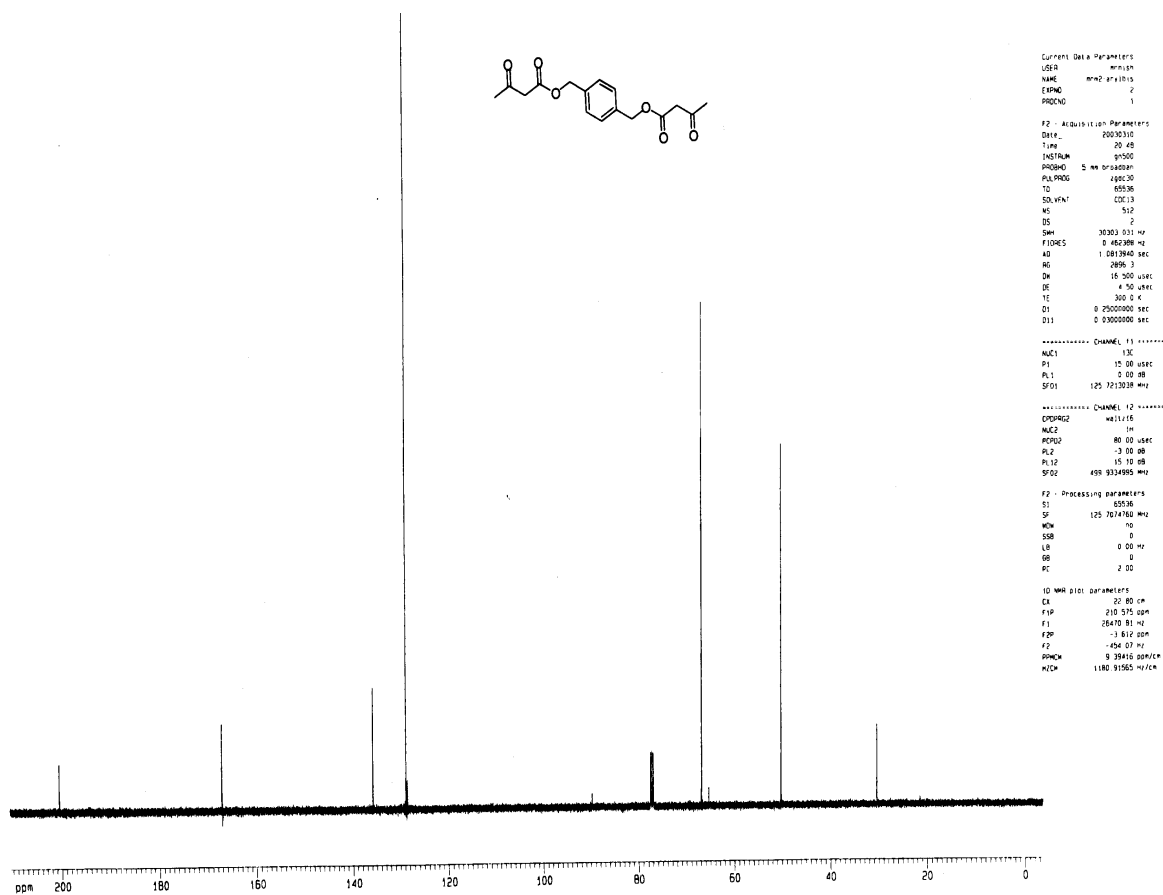
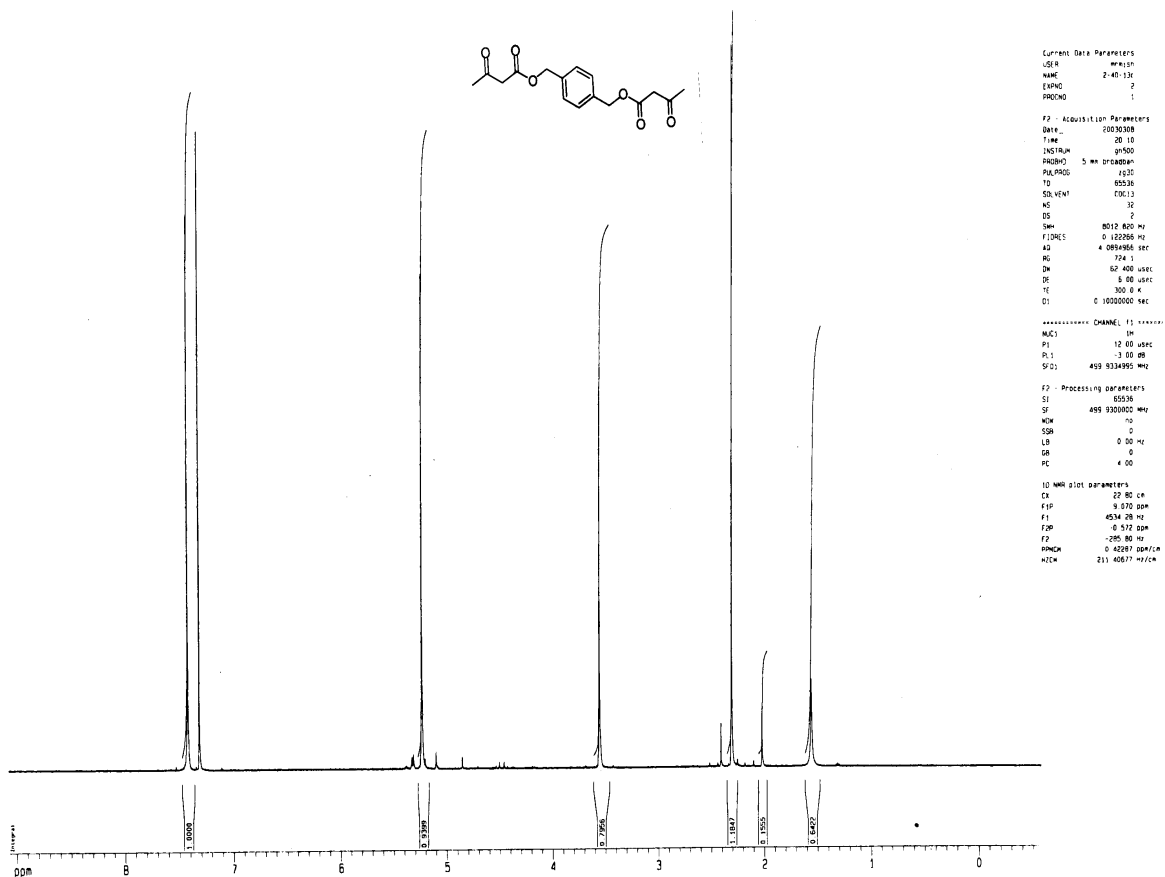
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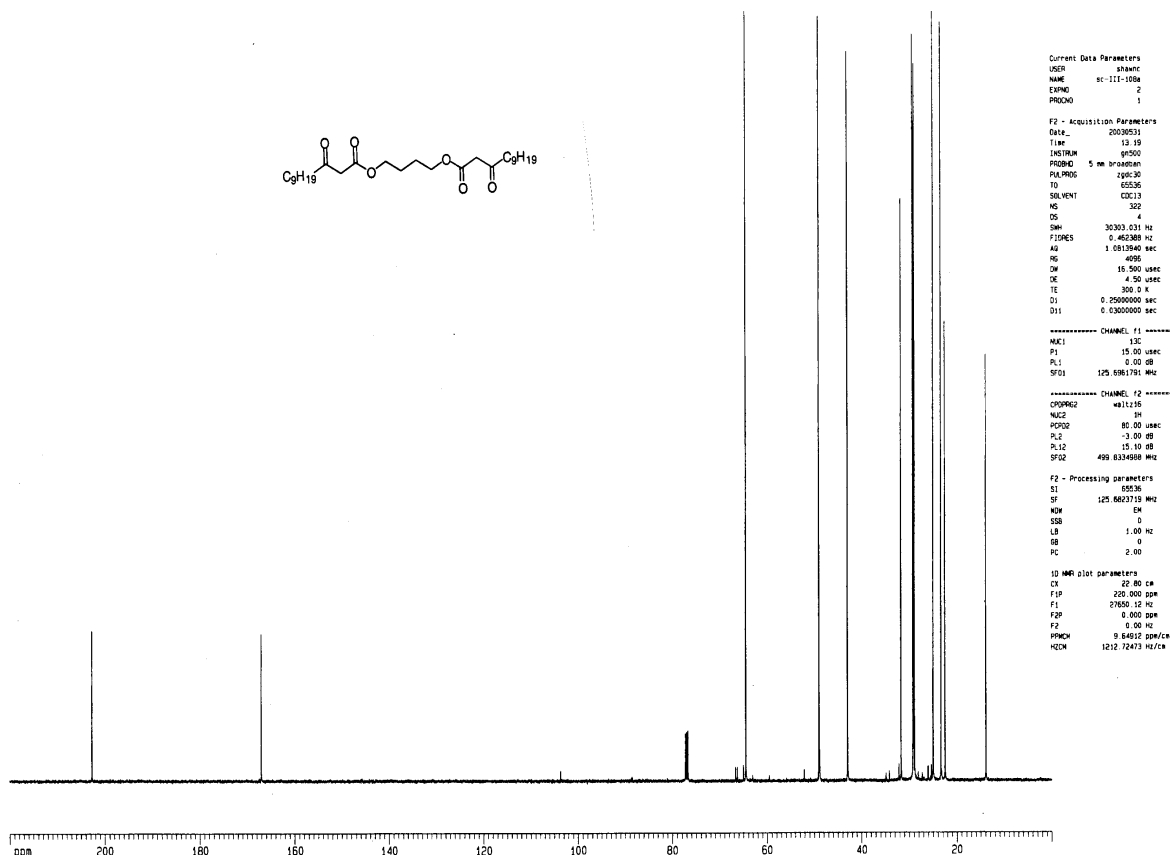
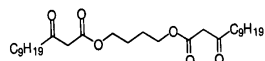
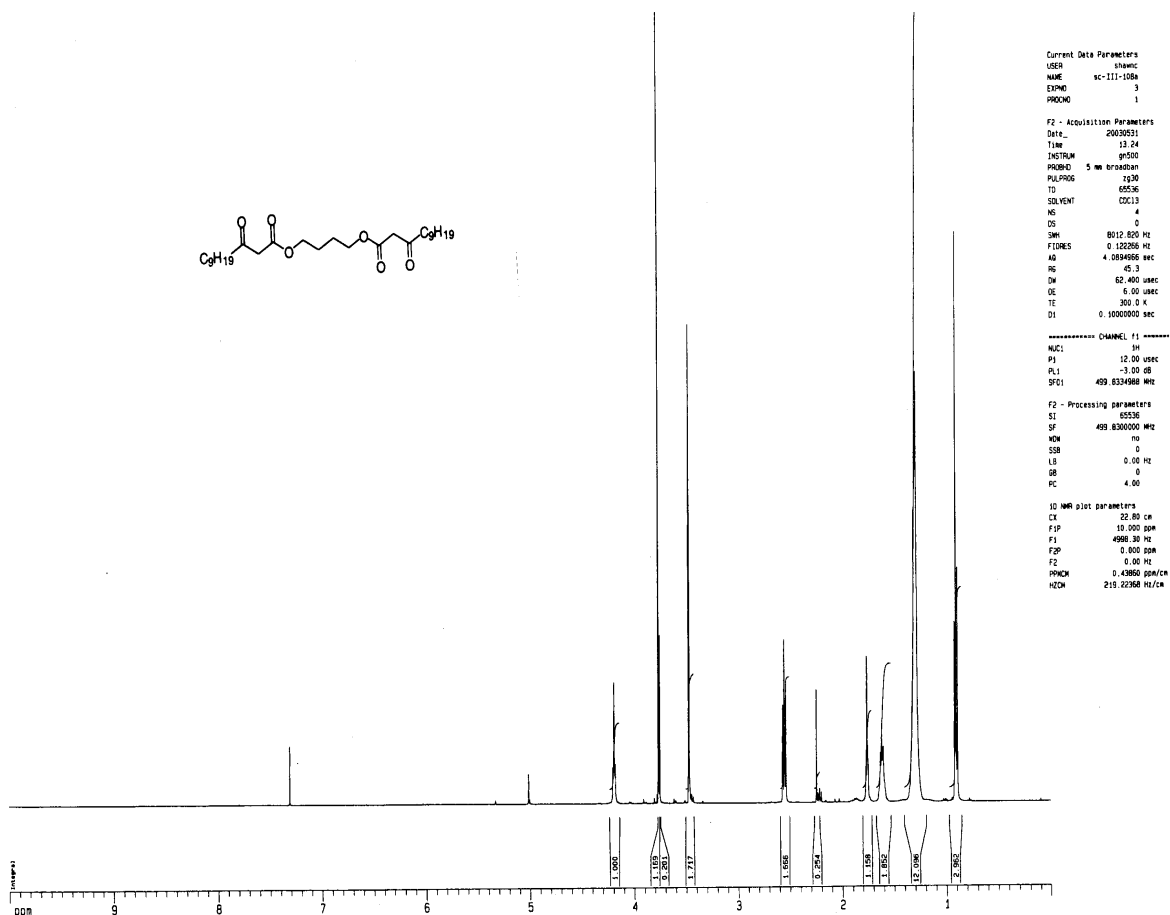
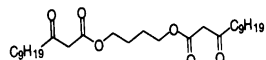
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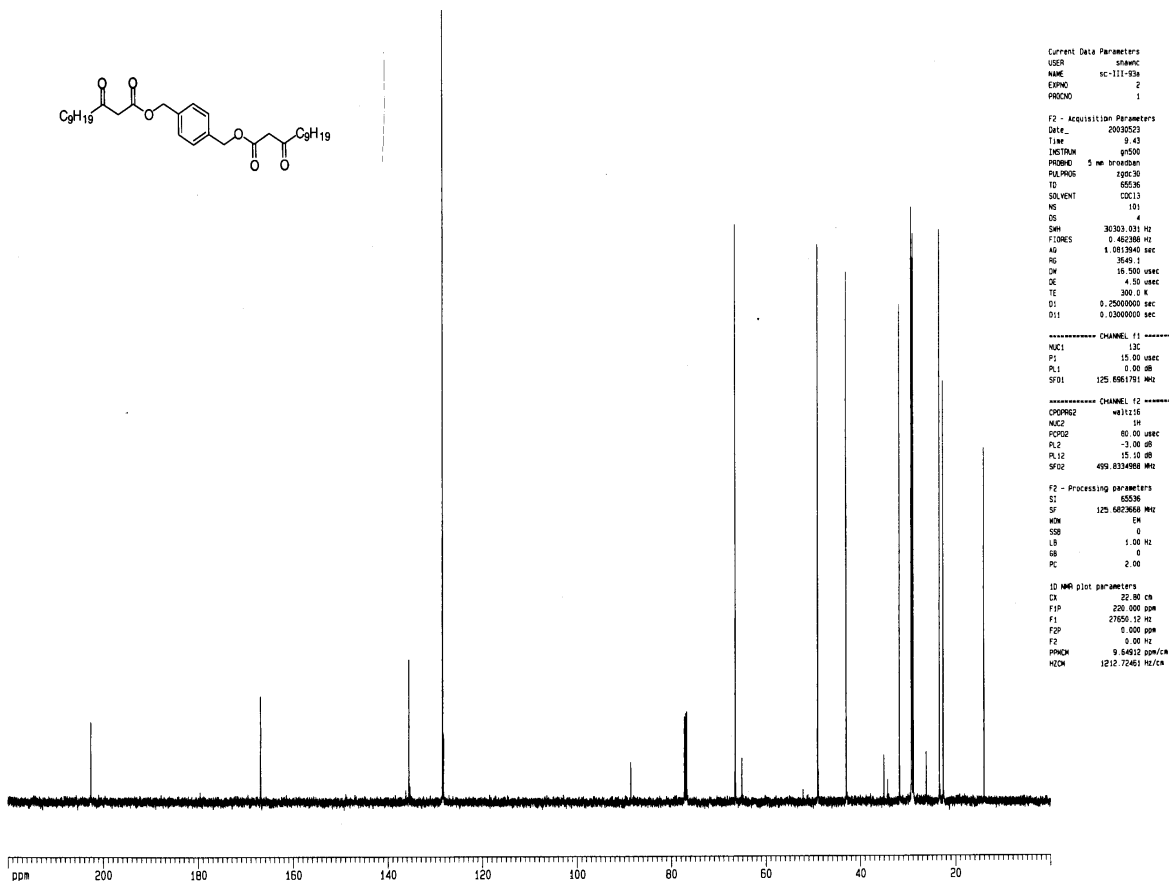
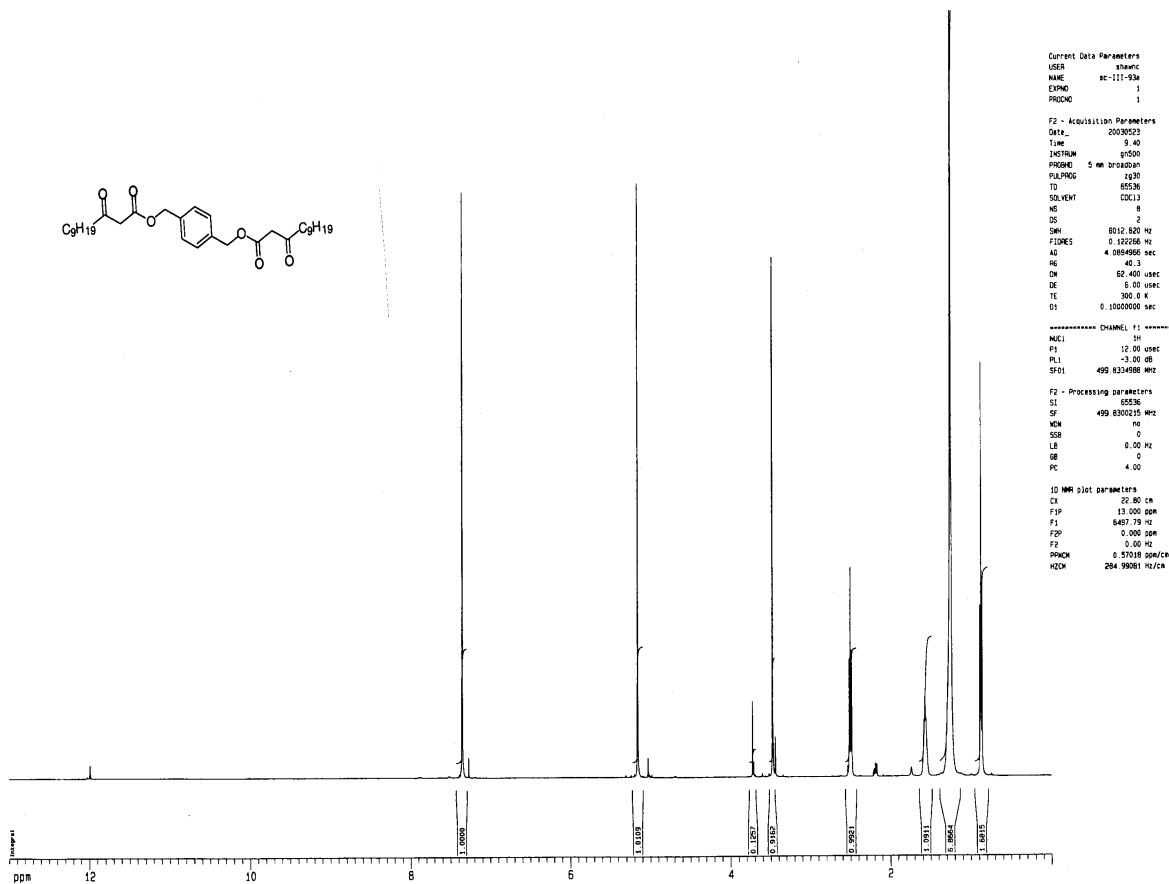
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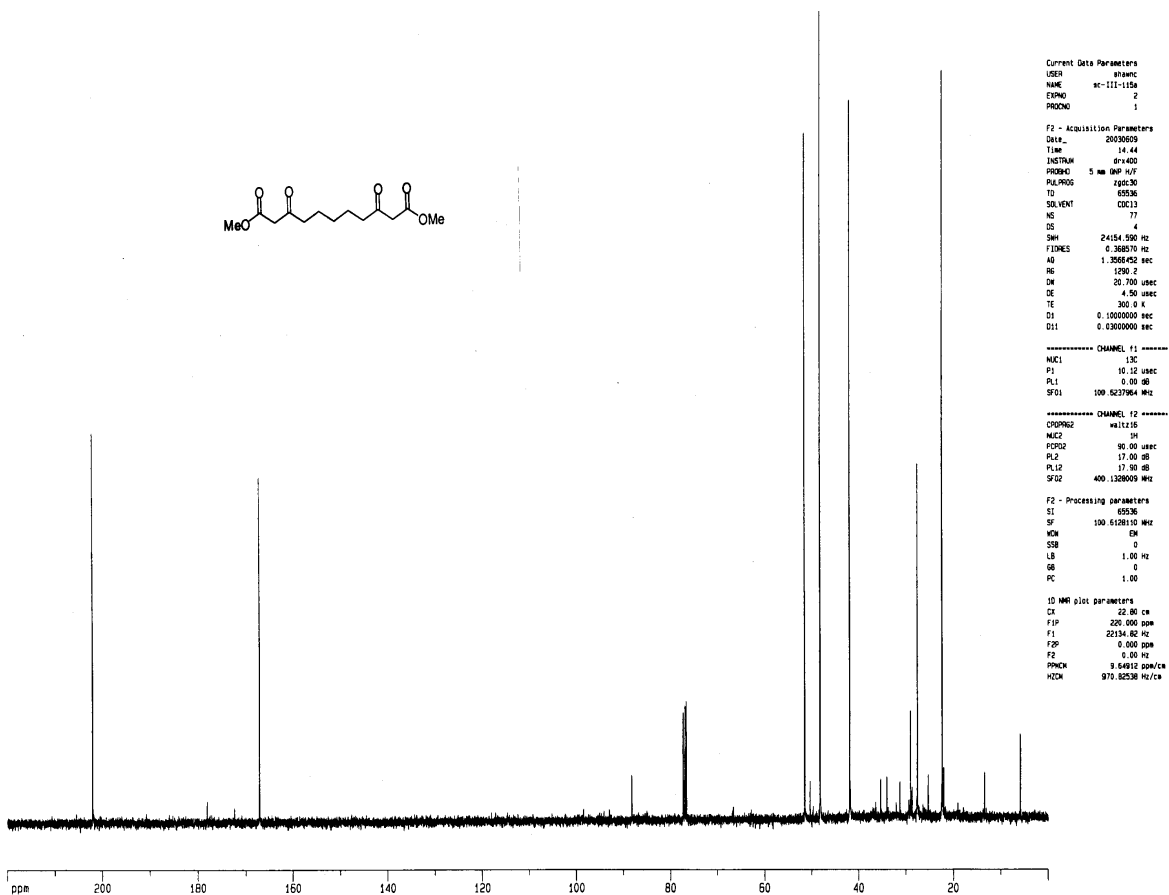
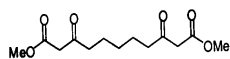
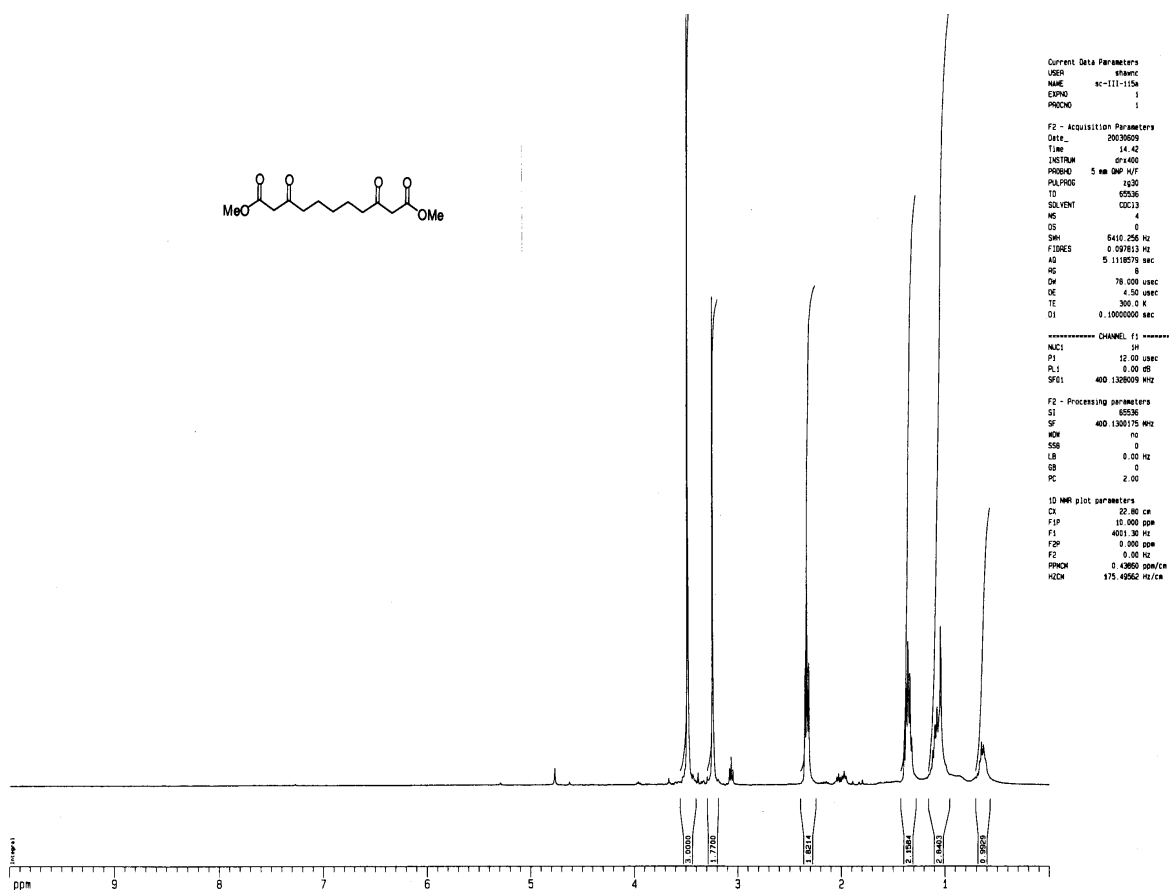
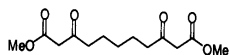
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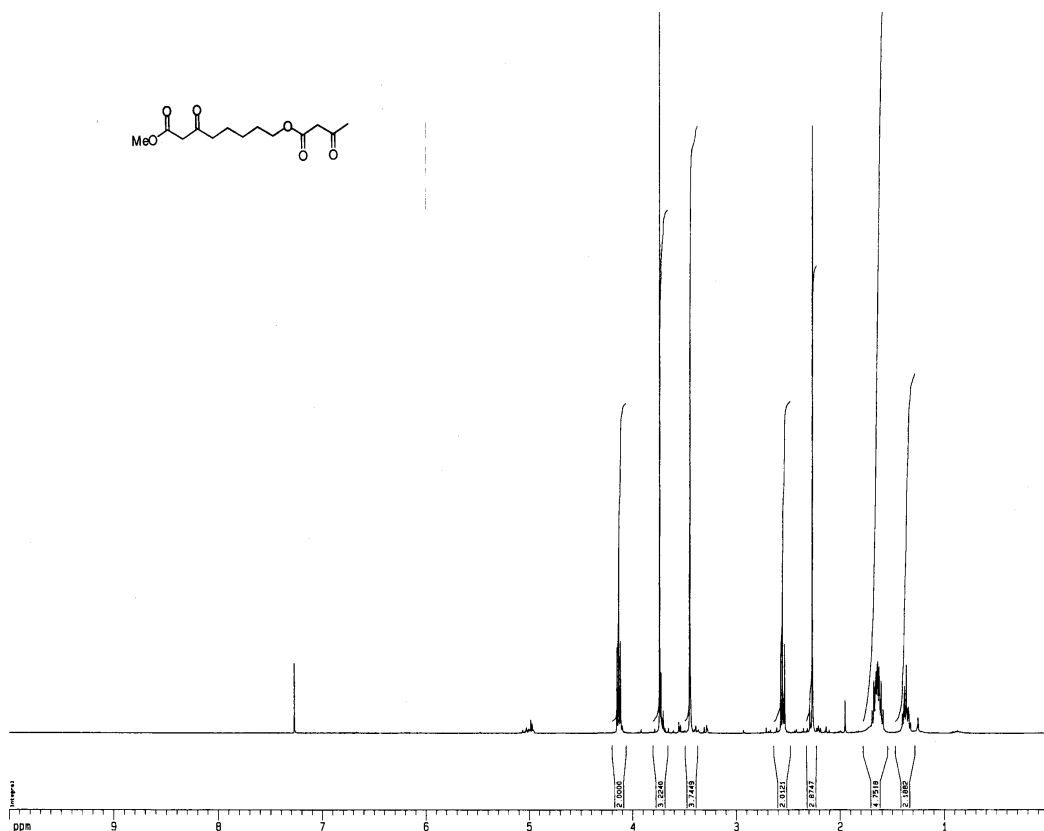
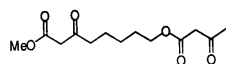
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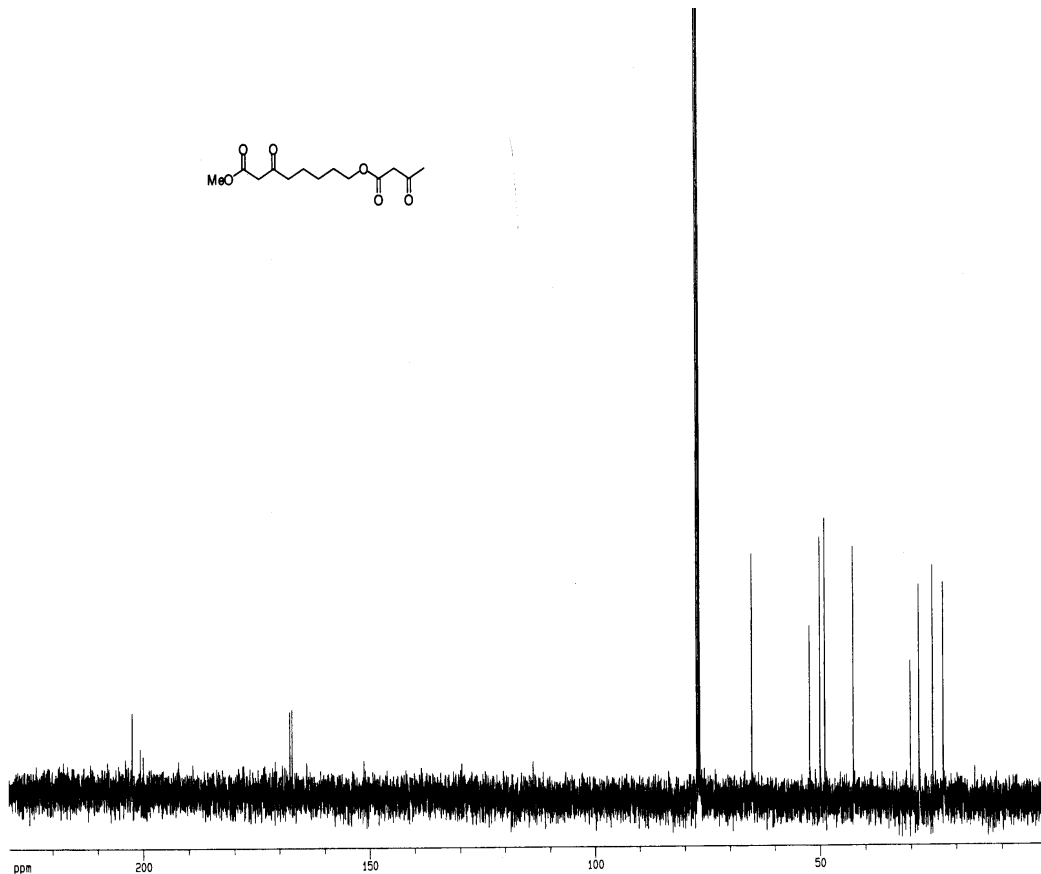
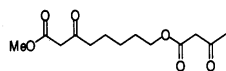








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^1H and ^{13}C NMR Spectra

B. C_2 -Symmetric Bisguanidine and Bisureas

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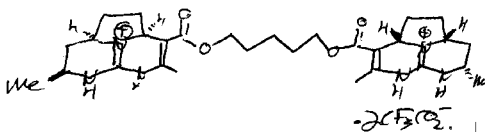
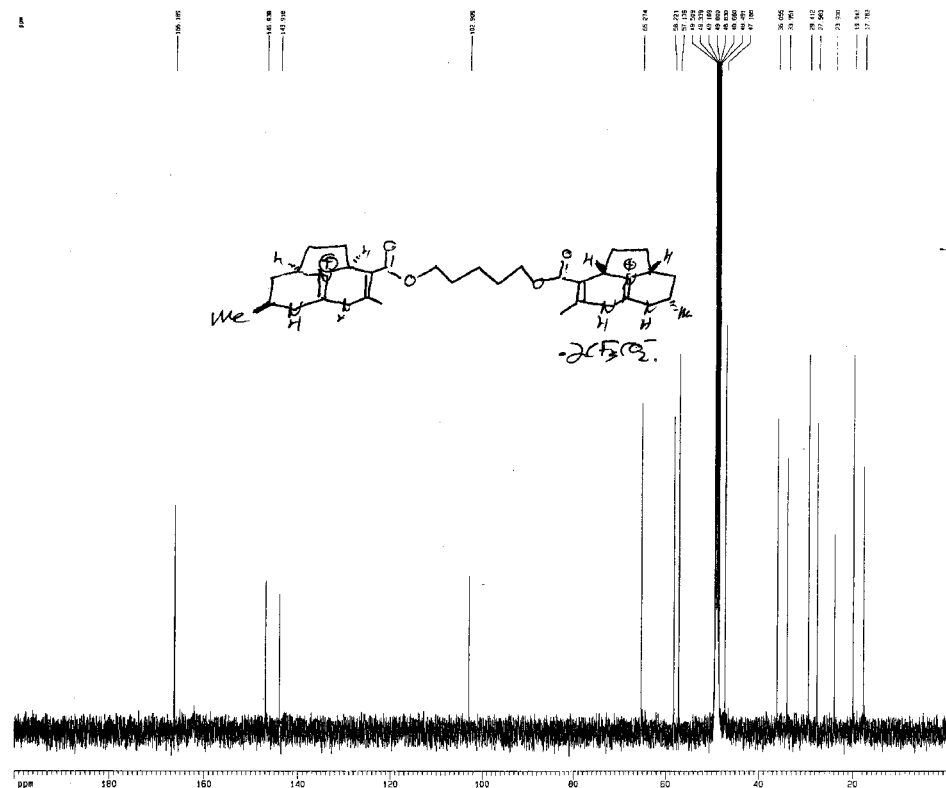
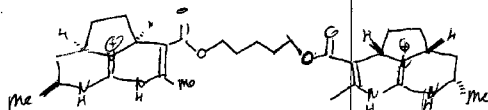
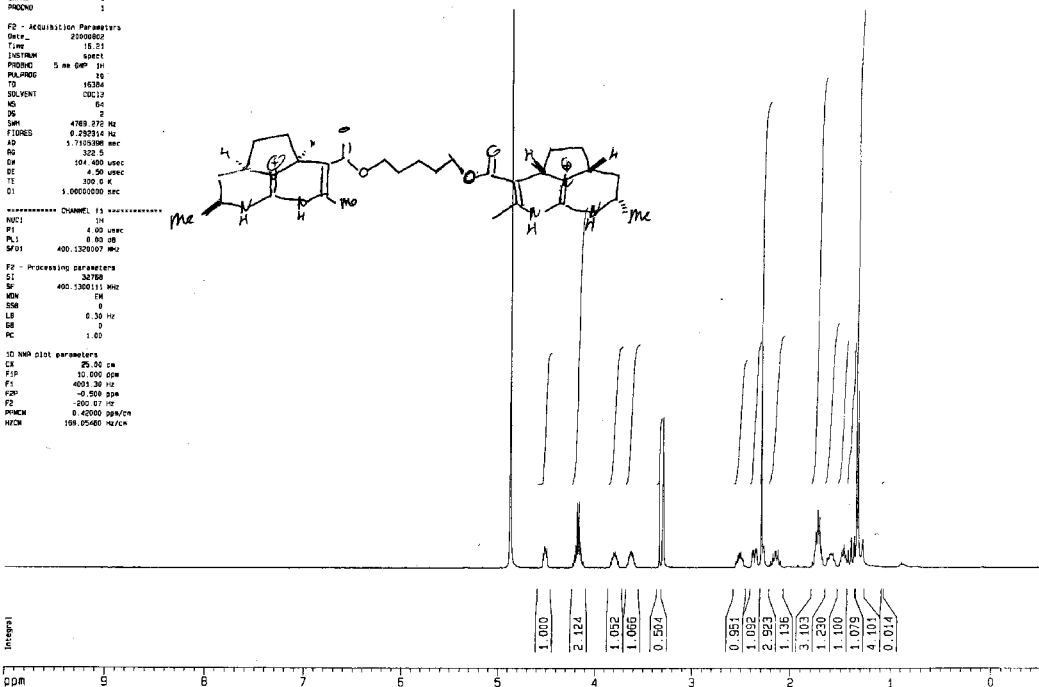
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• 245000

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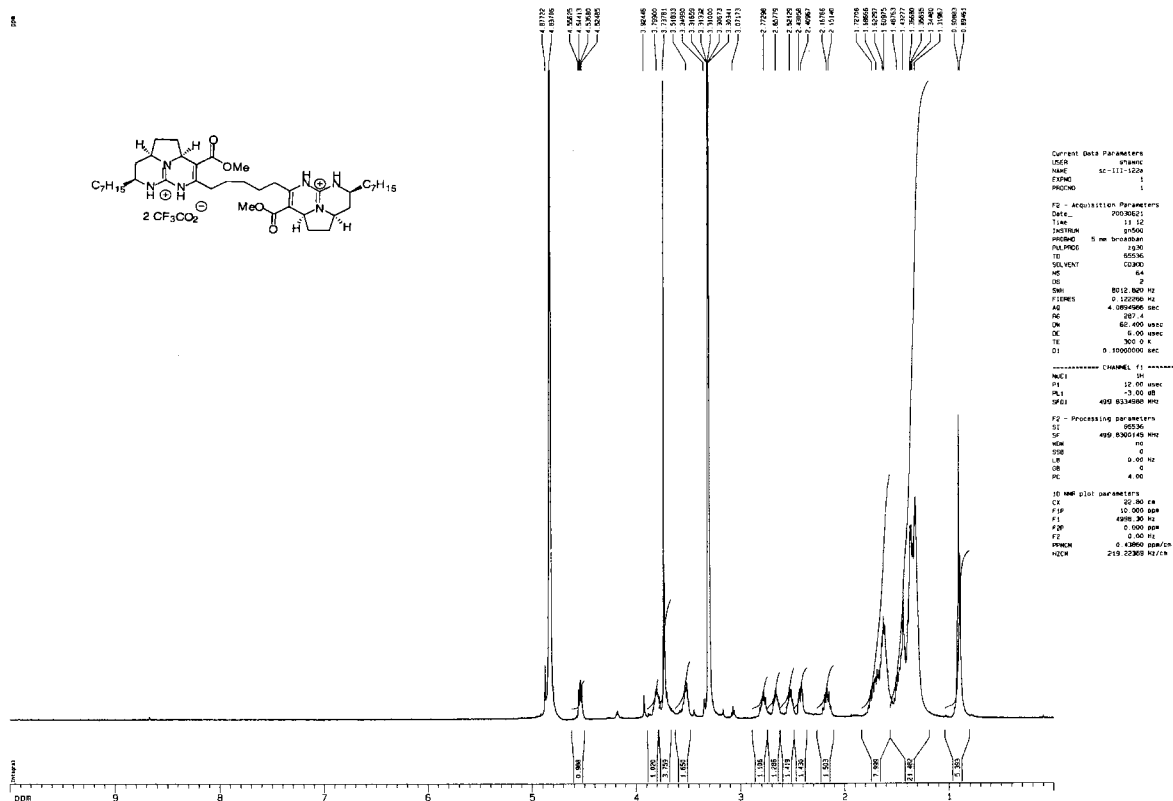
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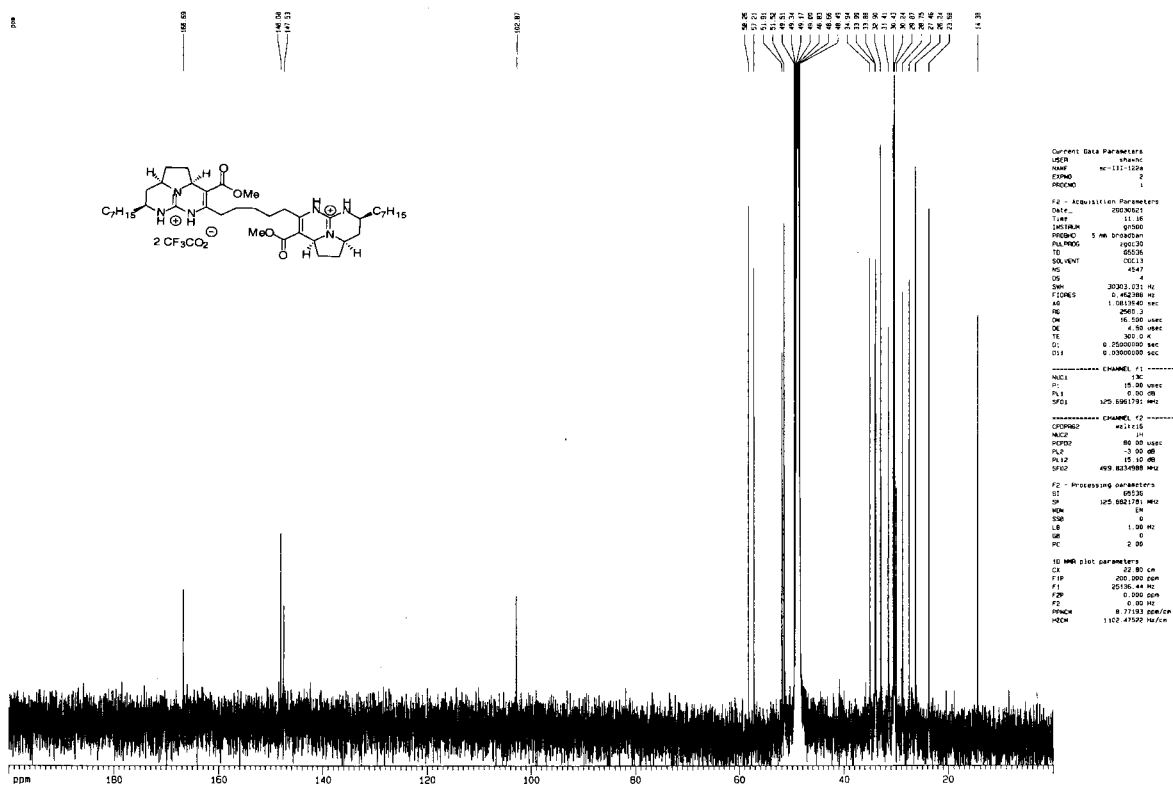
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¹H spectrum



¹³C spectrum with ¹H decoupling



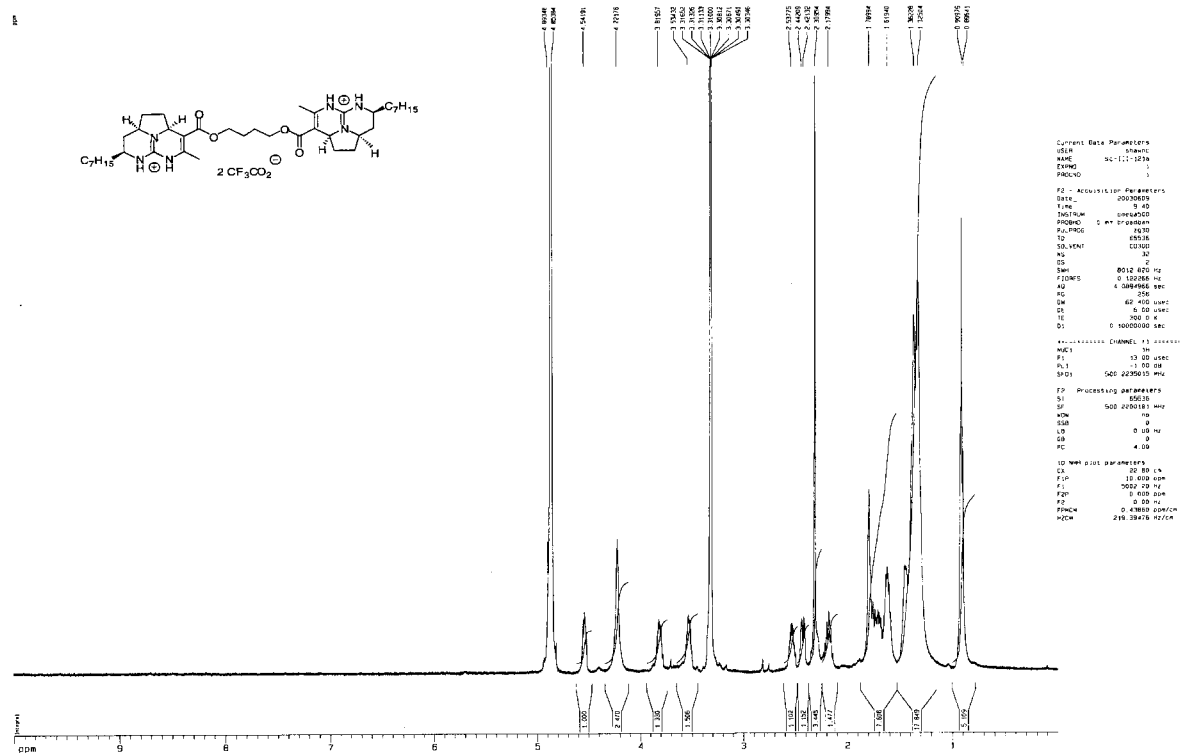
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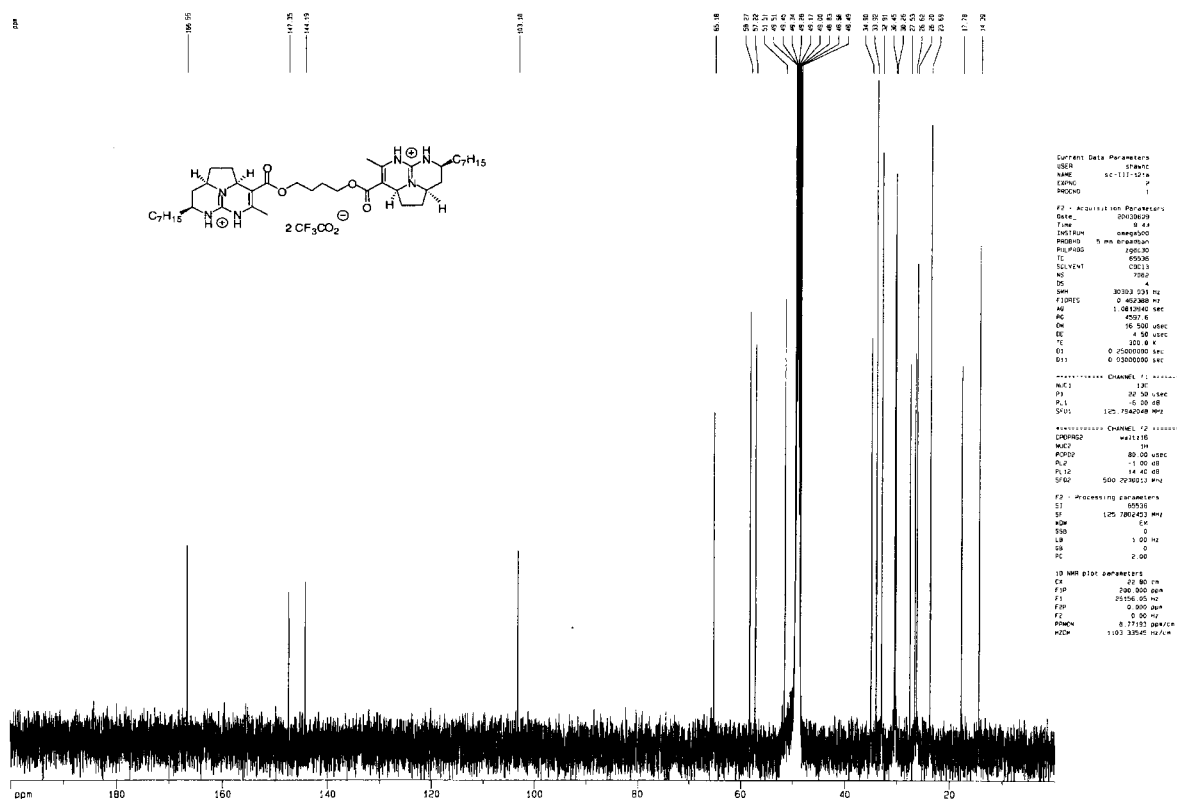
10



¹H spectrum



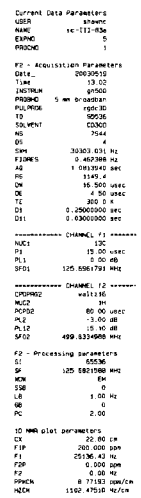
¹³C spectrum with ¹H decoupling



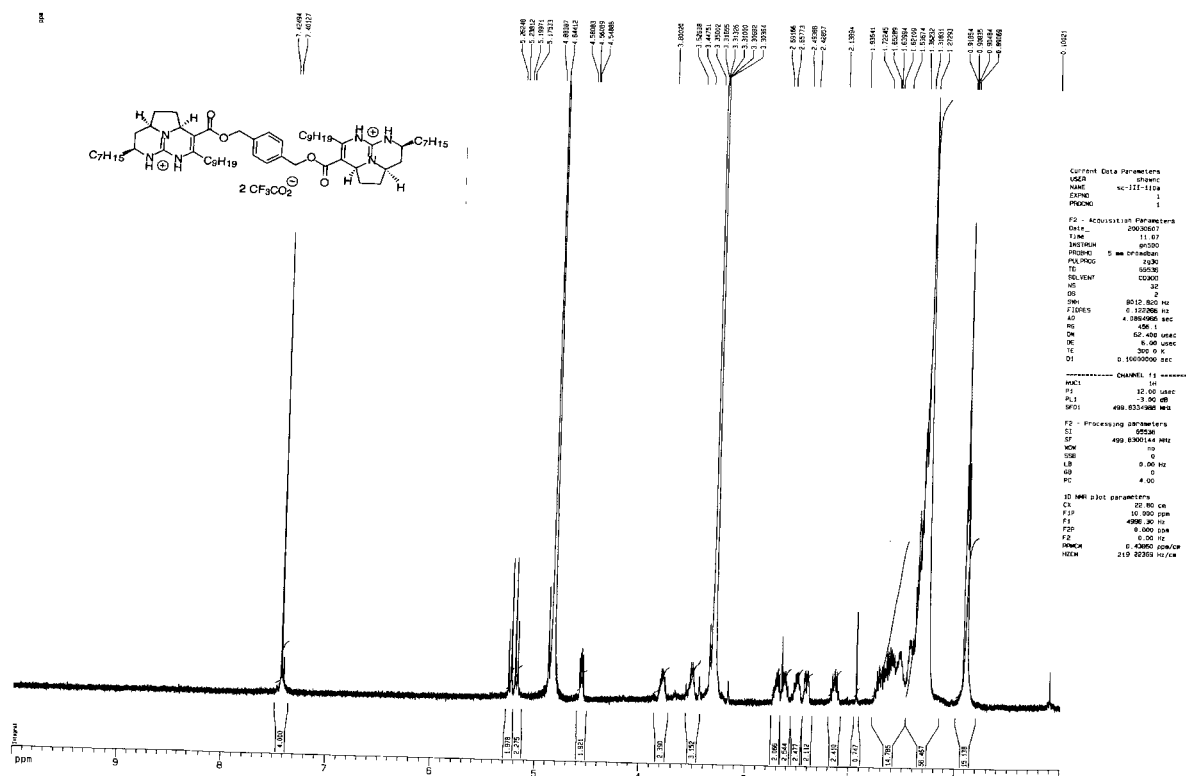
22



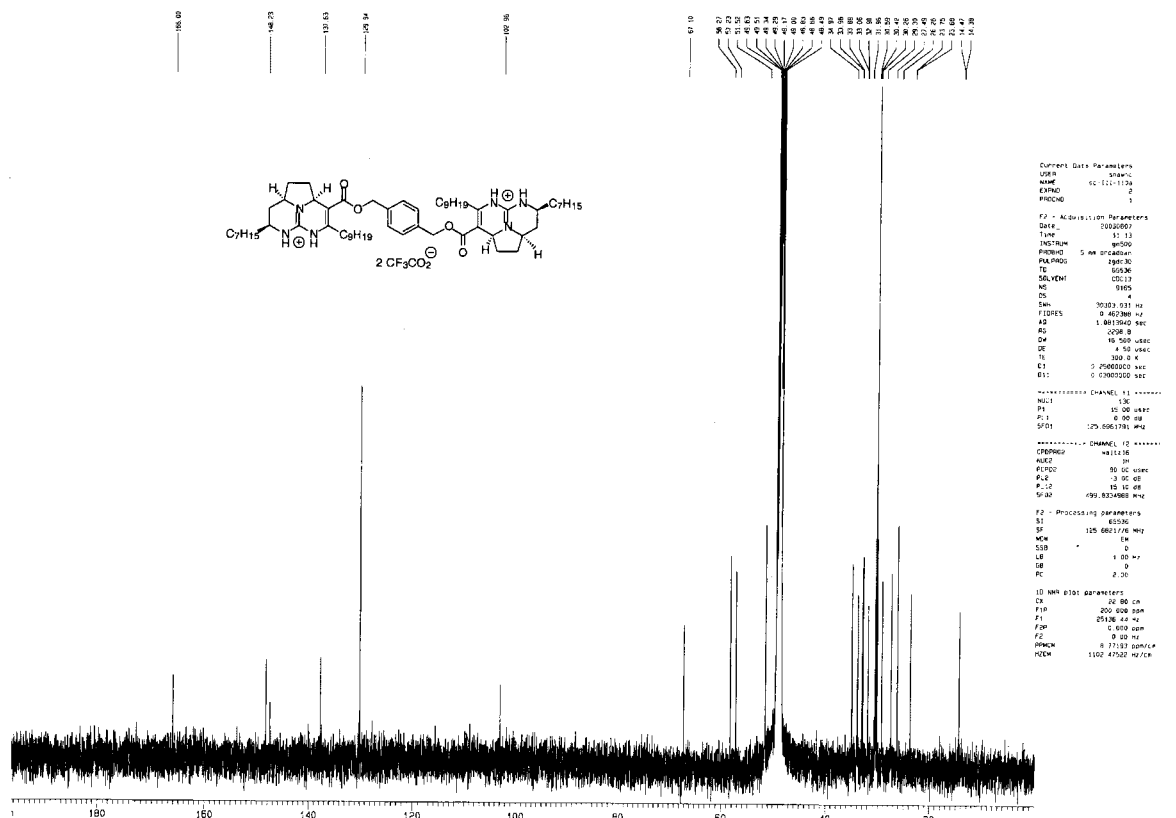
346



¹H spectrum

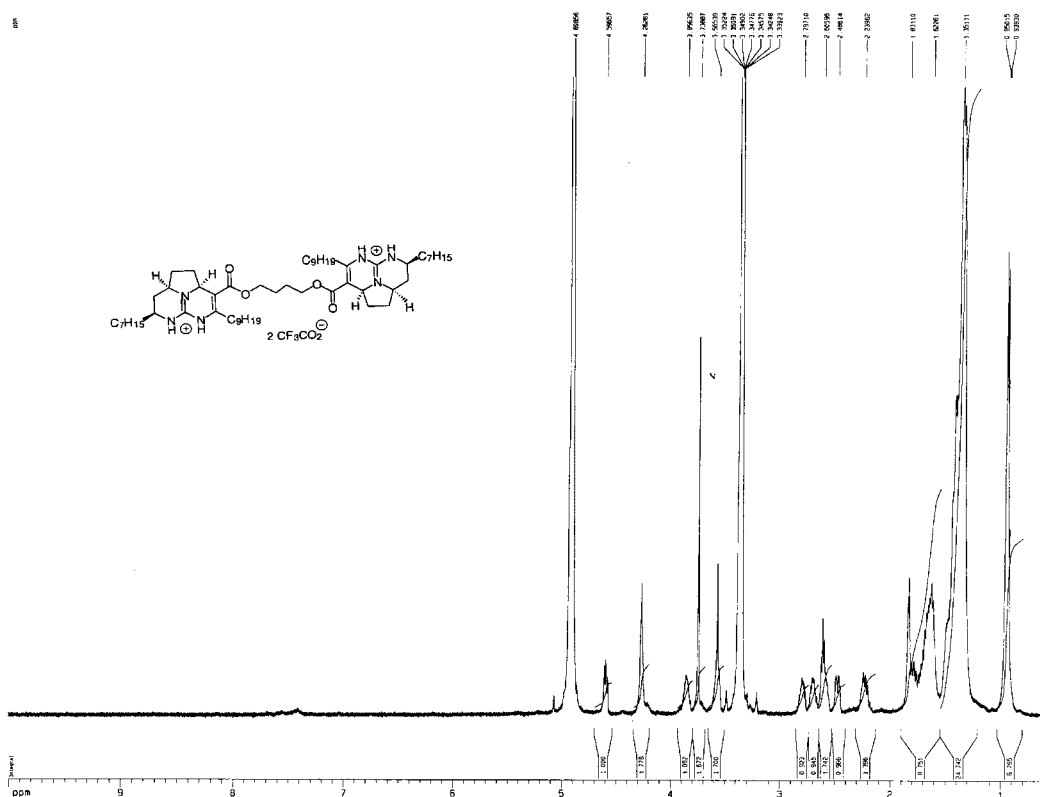


¹³C spectrum with ¹H decoupling



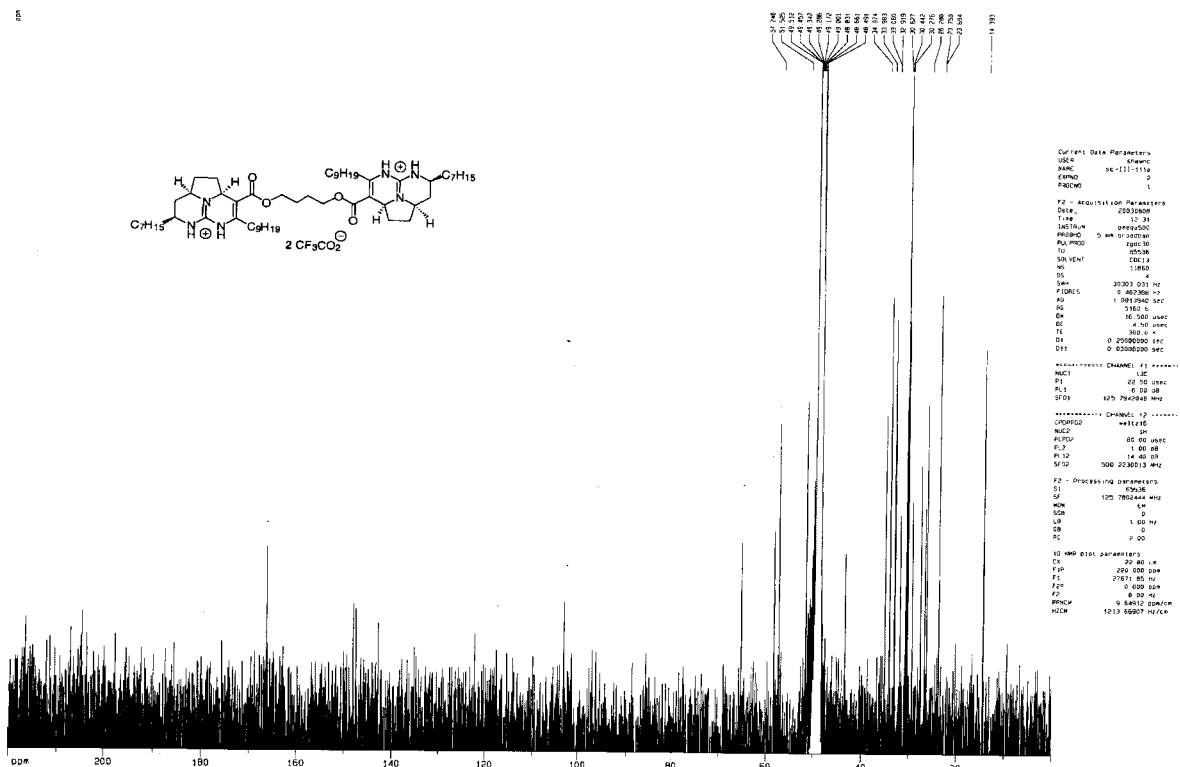
¹H spectrum

8

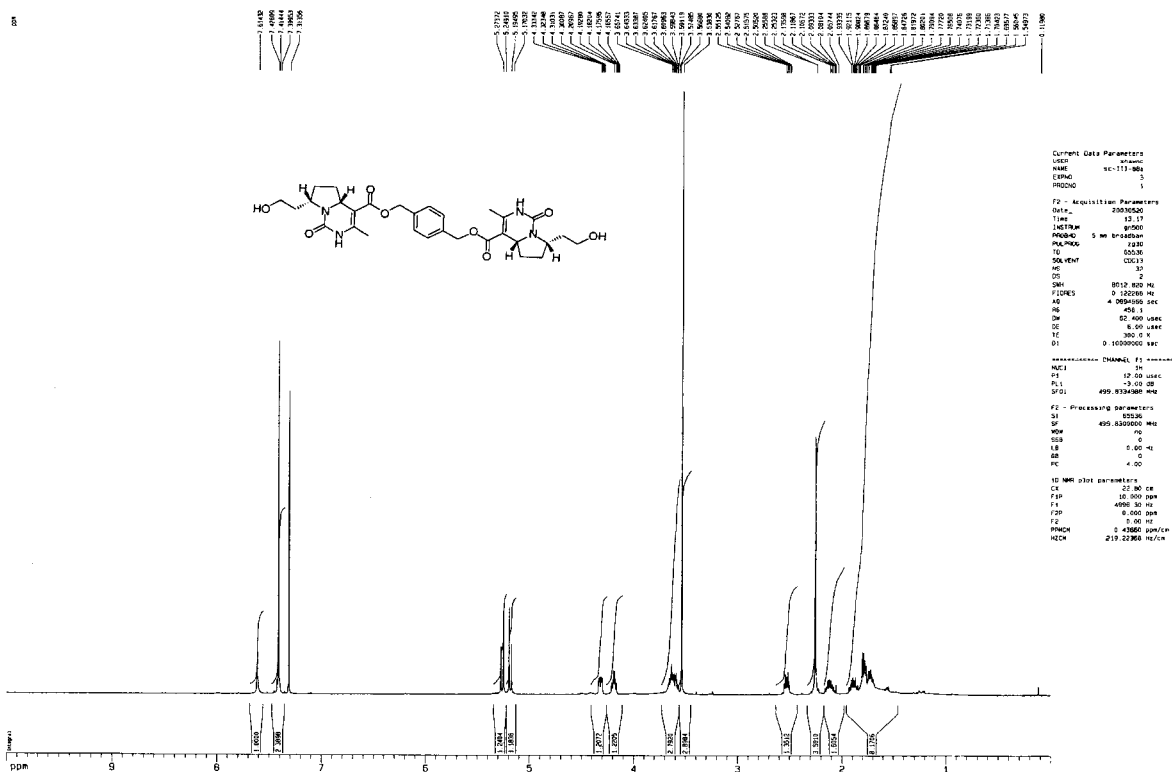


¹³C spectrum with ¹H decoupling

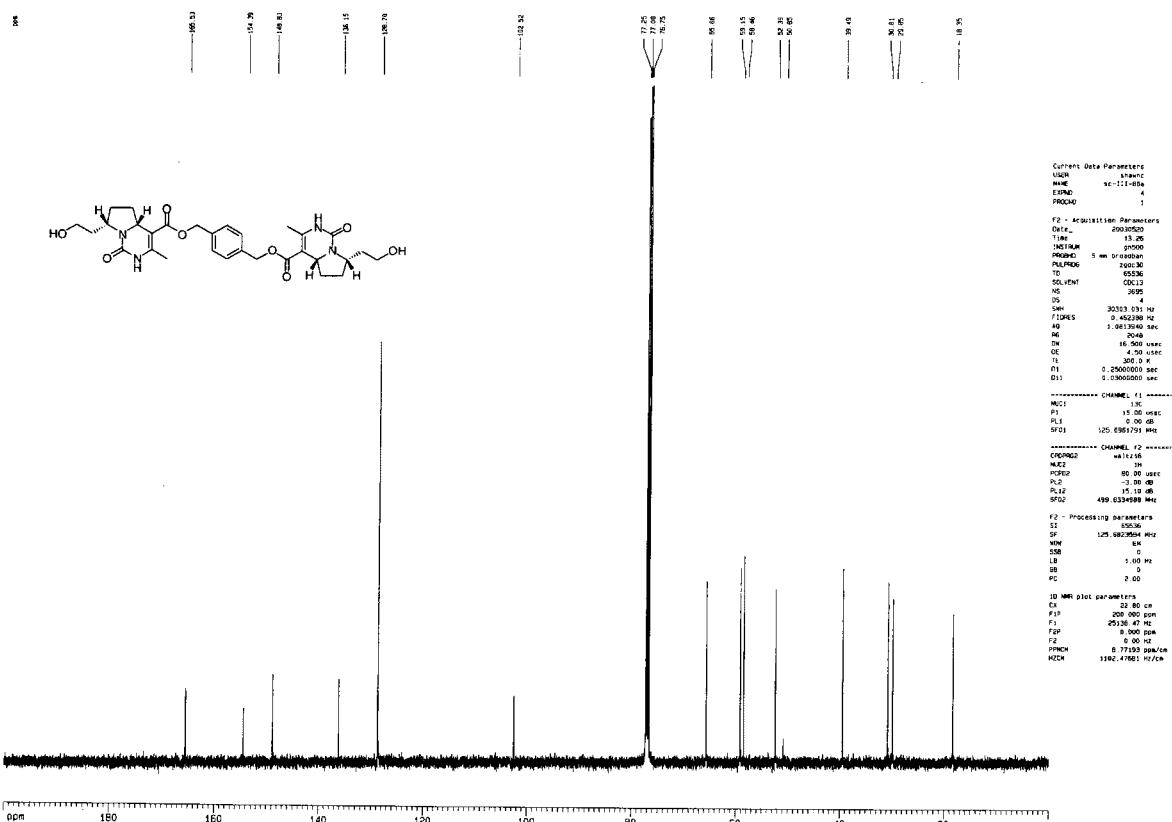
9



¹H spectrum



¹³C spectrum with ¹H decoupling

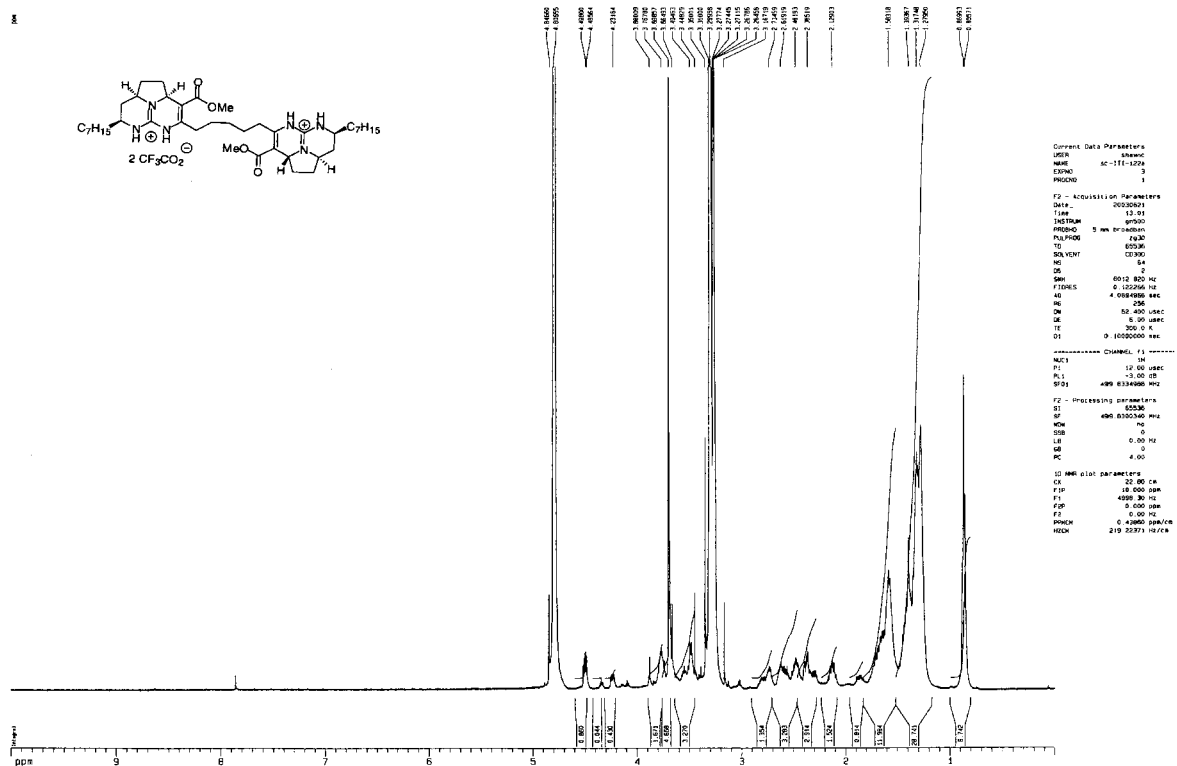


^1H and ^{13}C NMR Spectra

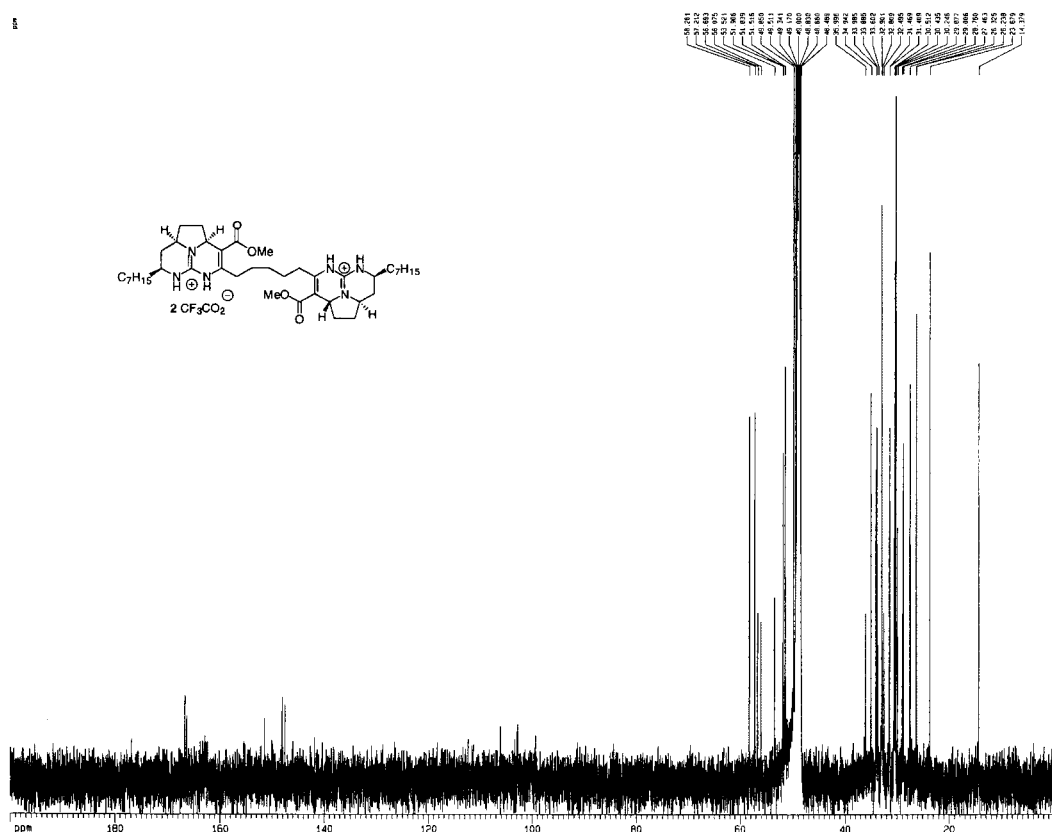
C. Minor Stereoisomers of Selected Double Biginelli Products

These samples are typically contaminated with some of the major C_2 -symmetric isomers.

¹H spectrum



¹³C spectrum with ¹H decoupling



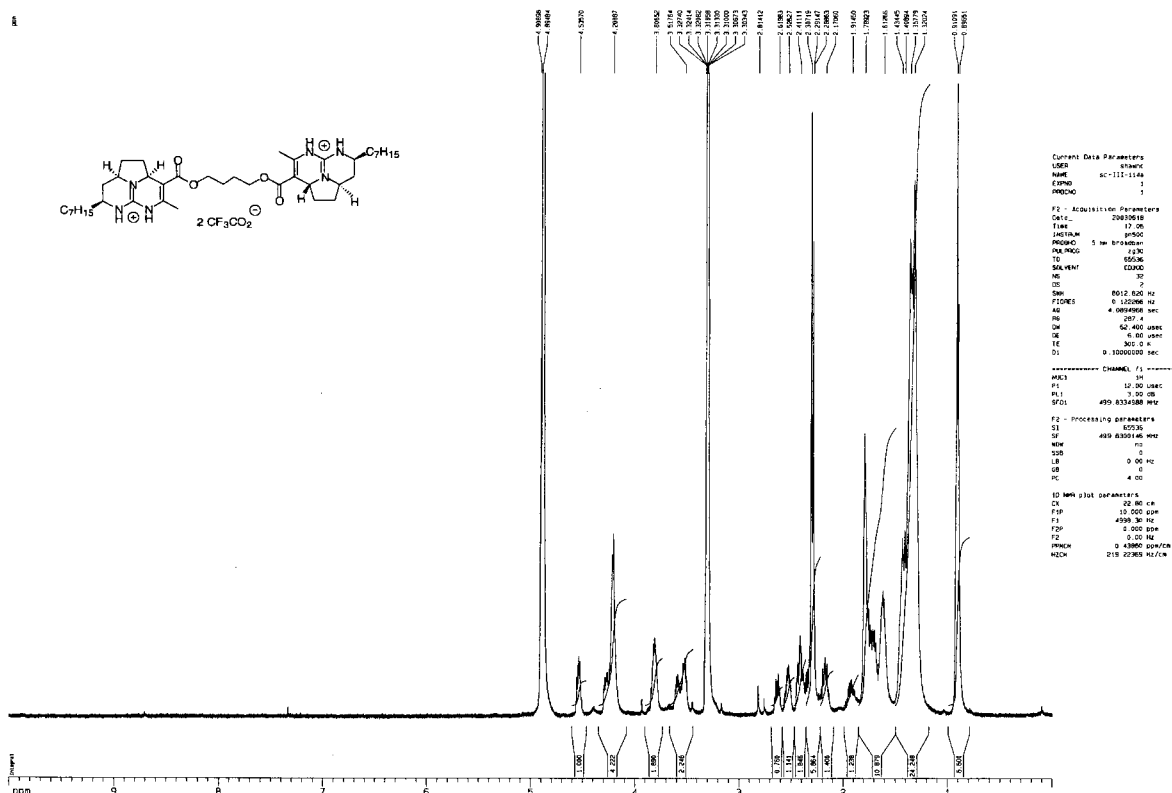
33



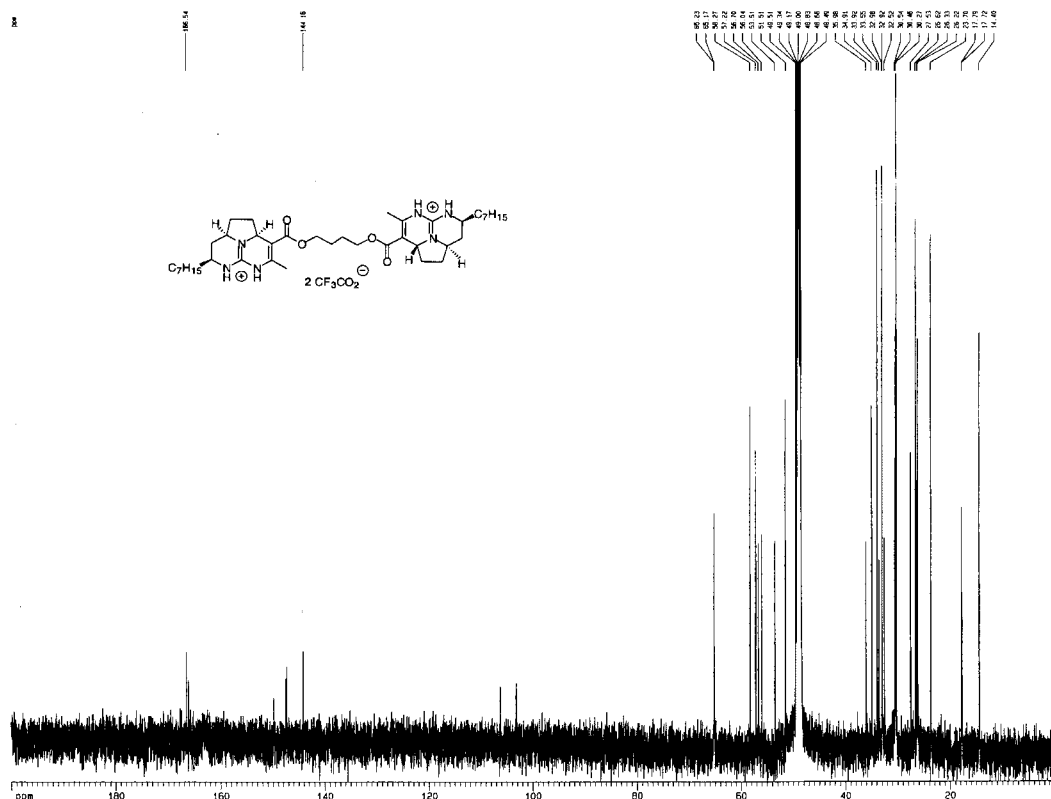
100



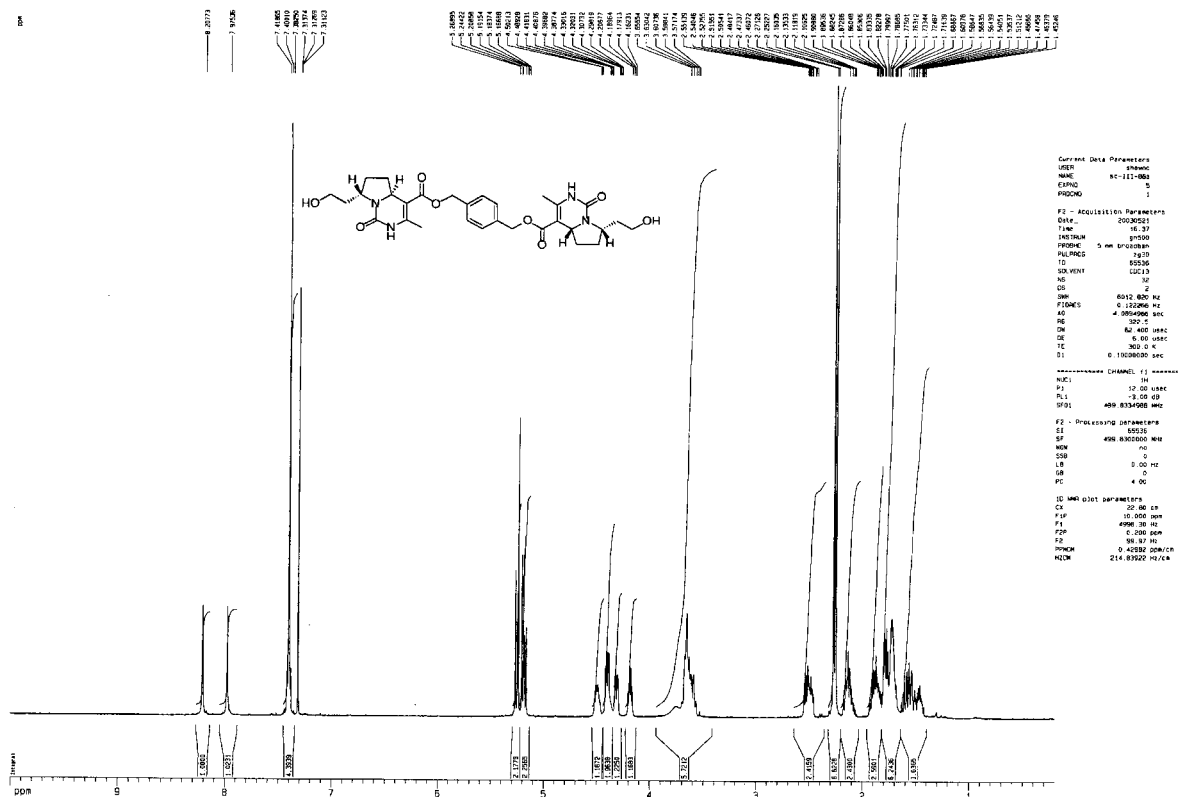
¹H spectrum



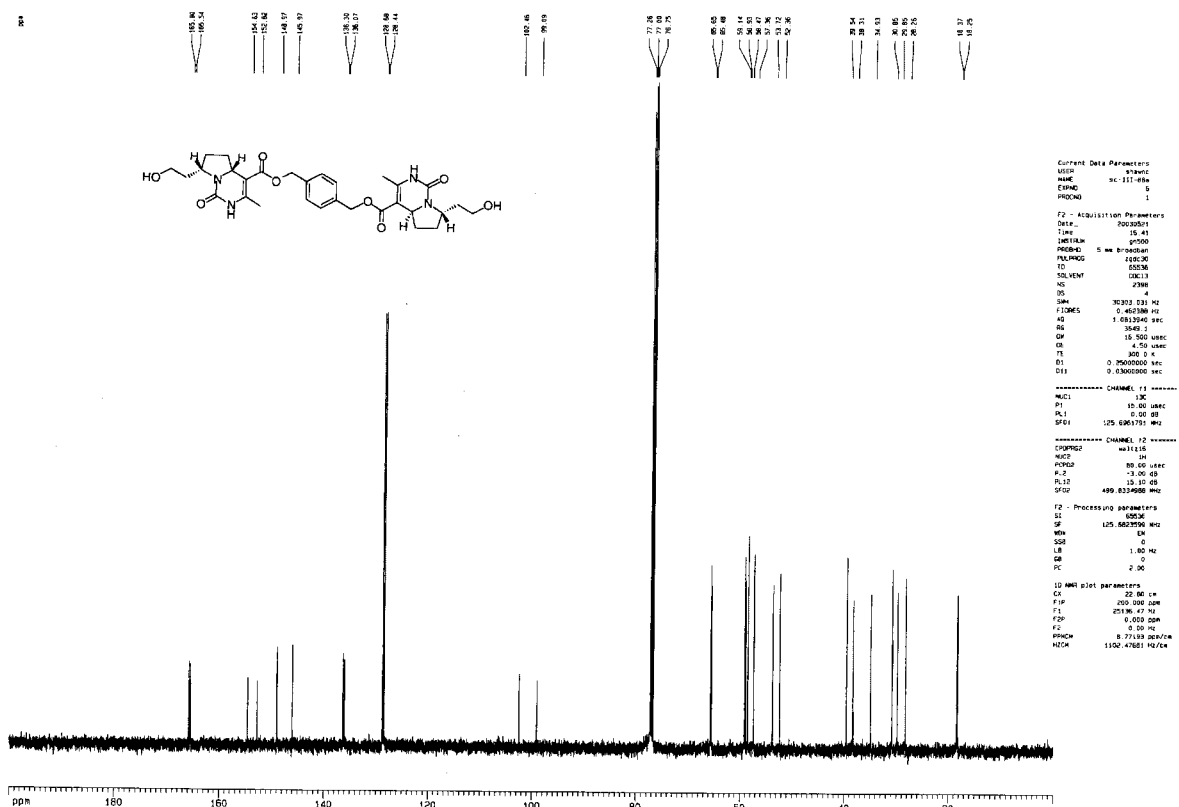
¹³C spectrum with ¹H decoupling



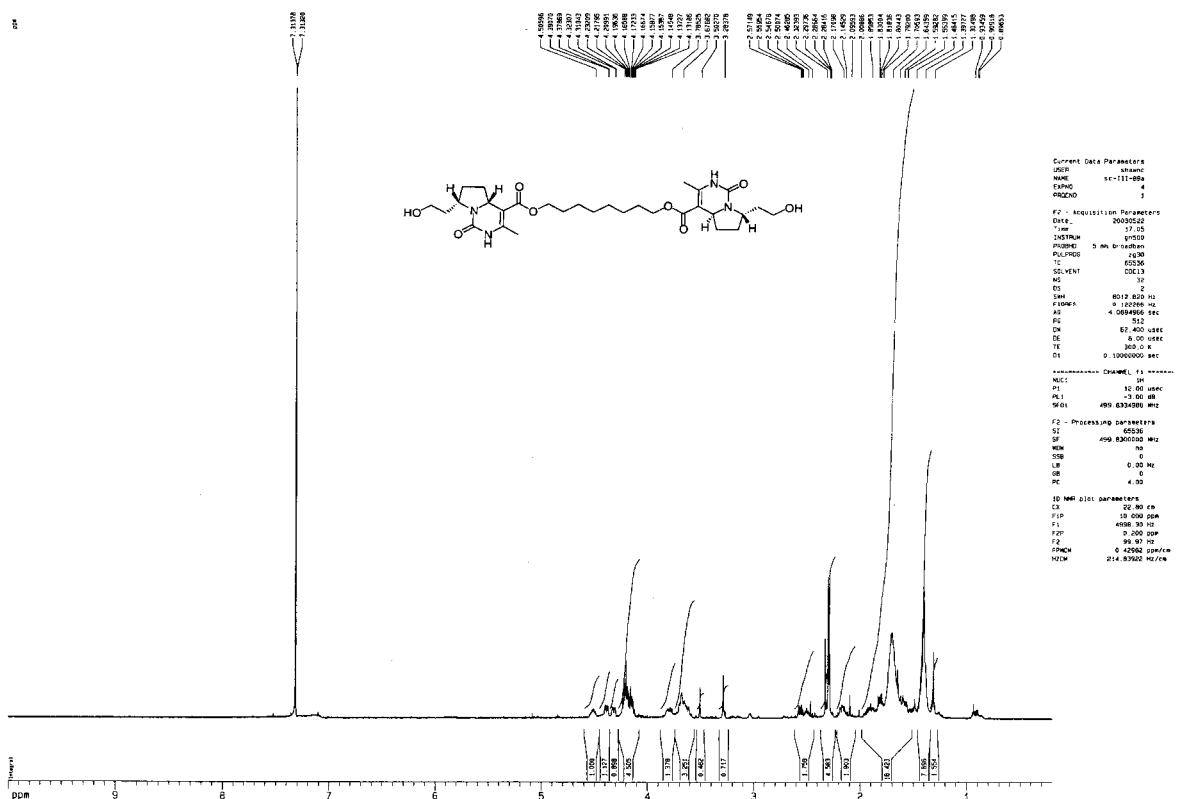
¹H spectrum



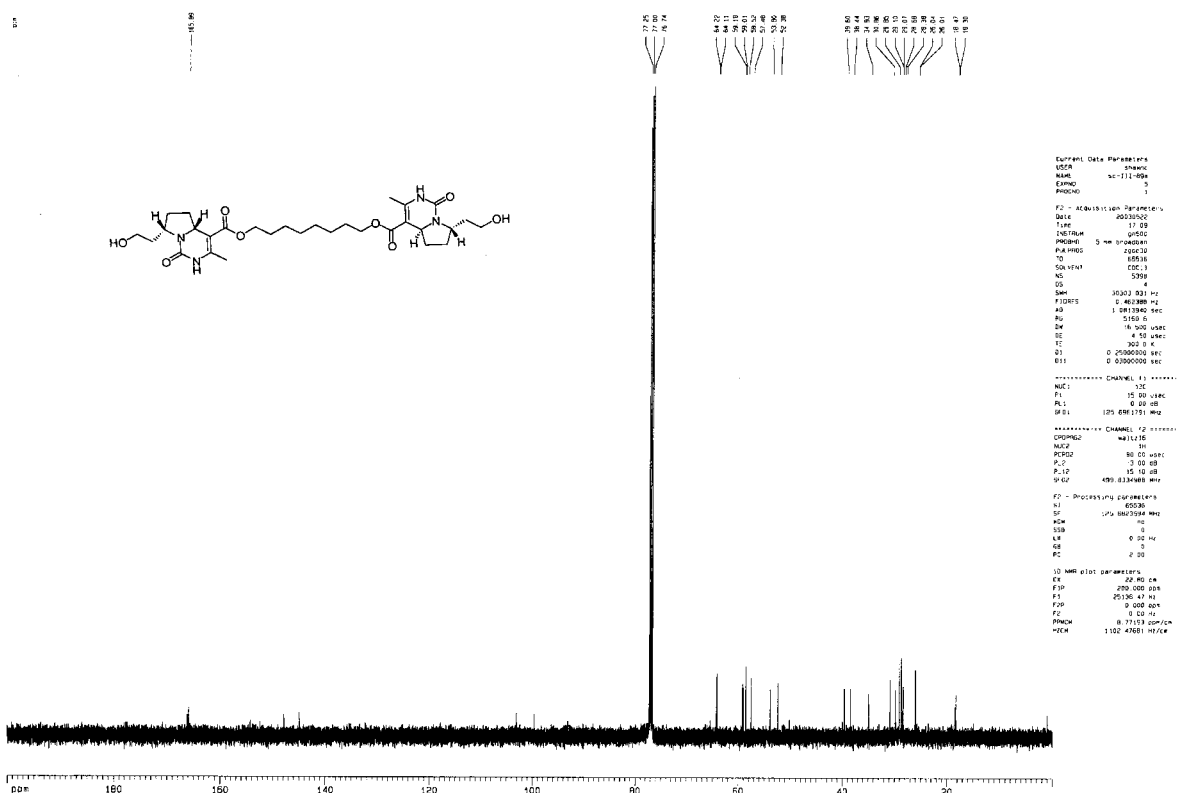
¹³C spectrum with ¹H decoupling



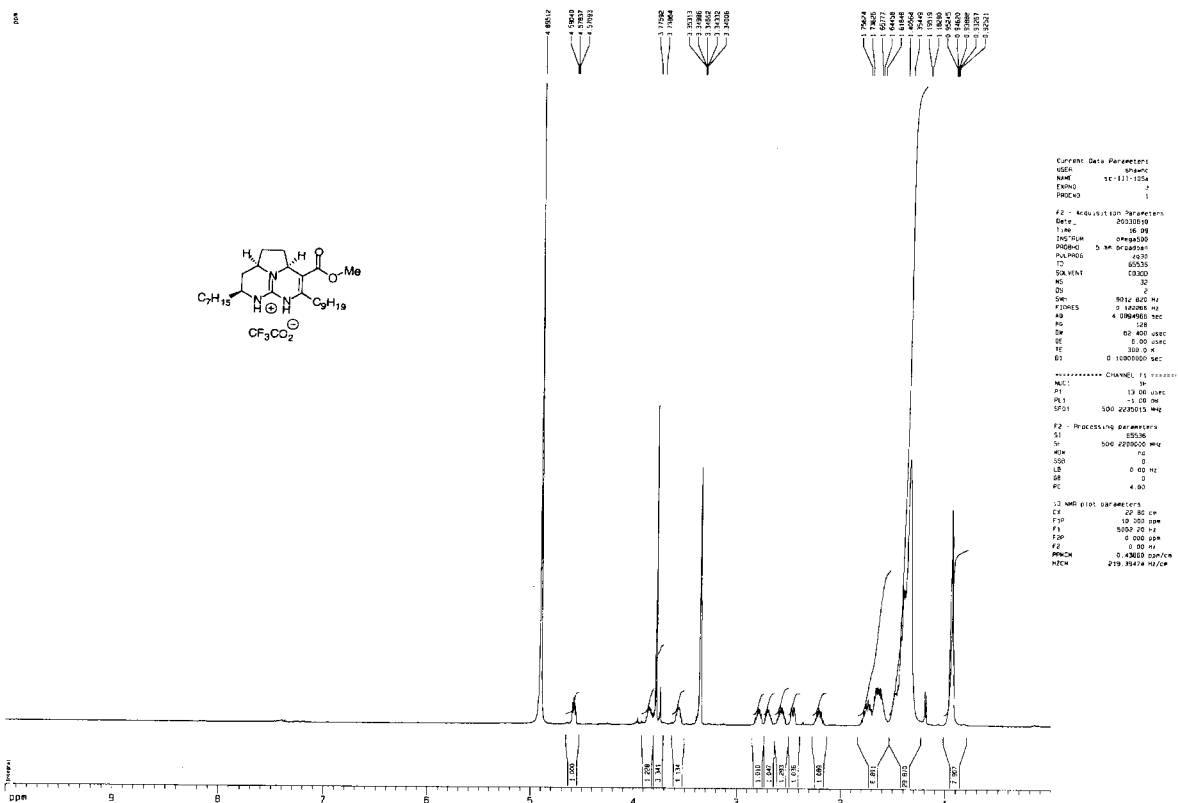
¹H spectrum



¹³C spectrum with ¹H decoupling



¹H spectrum



¹³C spectrum with ¹H decoupling

