Supplementary Material: Experimental Procedures, Characterization Data and ^1H NMR spectra

Rapid Entry into the Cryptophycin Core via an Acyl-β-Lactam Macrolactonization: Total Synthesis of Cryptophycin-24

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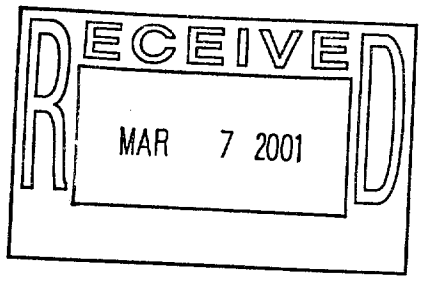
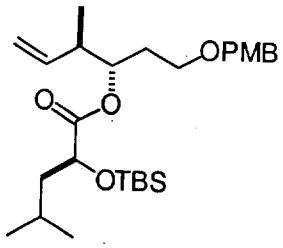


(1*S*,2*R*)-1-(2-(4-Methoxybenyloxy)ethyl)-2-methyl-3-butenyl (2*S*)-4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoate (10).



To (*tert*-Butyldimethylsilyl)oxy (2*S*)-4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoate (6.5 g, 18 mmol) in 30 mL CH_2Cl_2 was added 15 drops of DMF. The solution was cooled to 0 °C and oxalyl chloride (3.2 mL, 36 mmol) was added dropwise using an addition funnel. Vigorous bubbling was observed which gradually subsided. After addition was complete, the mixture was warmed to rt and stirred at rt for 4.5 h. The mixture was concentrated *in vacuo* and used in the next step.

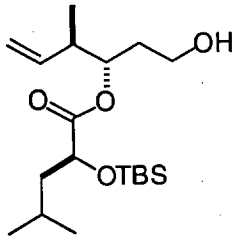
The crude acid chloride **6** was added dropwise to a solution of DMAP (2.2 g, 18 mmol) in CH_2Cl_2 (10 mL) at 0 °C. In a second flask, the alcohol (1.5 g, 6 mmol) was dissolved in CH_2Cl_2 (5 mL) and TEA (1.7 mL, 12 mmol) was added. The alcohol solution was added dropwise to the first. The reaction was stirred at 0 °C for 45 min at which time TLC indicated disappearance of alcohol **7**. The reaction was quenched with saturated aqueous $NaHCO_3$ and Et_2O. The aqueous layer was extracted with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes to 95:5 hexanes:EtOAc) provided ester **10** as an oil (2.22 g, 78%): $[\alpha]_D$ -42° (c 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.23 (d, J = 8 Hz, 2H), 6.87-6.85 (d, J = 8 Hz, 2H), 5.77-5.68 (m, 1H), 5.08-5.05 (m, 2H), 5.02-5.01 (d, 5 Hz, 1 H), 4.43-4.40 (d, J = 11.4 Hz, 1H), 4.37-4.34 (d, J = 11.4 Hz, 1H), 4.20-4.17 (dd, J = 9, 4 Hz, 1H), 3.79 (s, 3H), 3.48-3.36 (m, 2H), 2.43-2.38 (m, 1H), 1.85-1.83 (d, J = 7 Hz, 1H), 1.82-1.80 (d, J = 7Hz, 1H), 1.75 (m buried, 1H), 1.64-1.57 (ddd, J = 5, 9, 14 Hz, 1H), 1.50-1.44 (ddd, J = 4, 9, 14 Hz, 1H), 1.00-0.99 (d, J = 7 Hz, 3H), 0.924-0.907 (d, J = 7 Hz, 3H), 0.91

(buried, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 159.1, 139.0, 130.4, 129.2 (2C), 115.8, 113.7 (2 C), 74.3, 72.7, 70.7, 66.5, 55.2, 44.3, 41.6, 31.6, 25.7 (3C), 24.1, 23.4, 21.7, 18.2, 15.7, -4.6, -5.3; IR (film) 3050, 2920, 2820, 1730, 1625, 1590, 1570 cm^{-1}; MS (EI) *m/z* 477 (M-1, 25), 421 (15), 362 (50), 201 (50).

*Three step synthesis of **11** from **10**.*

*1. DDQ-deprotection of **10** to form intermediate alcohol **14**.*

(1*S*)-3-Hydroxy-1-[(1*R*)-1-methyl-2-propenyl)propyl] (2*S*)-4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoate (14).

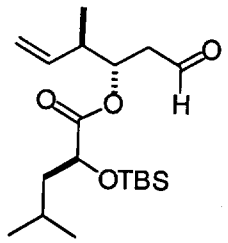


Ester **10** (276 mg, 0.577 mmol) was dissolved in CH_2Cl_2 (2 mL) and H_2O (0.1 mL).. The mixture was cooled to 0 °C and DDQ (144 mg, 0.635 mmol) was added. After 30 min at 0 °C, the bath was removed and the mixture was stirred an additional 90 min at rt. Additional CH_2Cl_2 was added and the organics were washed with saturated aqueous $NaHCO_3$ solution. The combined organics were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (hexanes to 85:15 hexanes:EtOAc) provided the desired alcohol **14** (176 mg, 85%) as an oil (often a mixture of alcohol and aldehyde by-product were utilized in the next reaction): ^1H NMR (400 MHz, $CDCl_3$) δ 5.76-5.68 (ddd, *J* = 8, 10, 17.8 Hz, 1H), 5.08-4.99 (m, 3H), 4.25-4.22 (dd, *J* = 4, 9 Hz, 1H), 3.65-3.60 (m, 1H), 3.51-3.45 (ddd, *J* = 4, 10, 11.5 Hz, 1H), 2.42-2.37 (m, 2H), 1.84-1.75 (m, 2H), 1.71-1.58 (m, 2H), 1.54-1.47 (ddd, *J* = 4, 9, 13.5 Hz, 1H), 1.03-1.01 (d, *J* = 7 Hz, 1H), 0.924-0.91 (d, *J* = 7 Hz, 3H), 0.916-0.90 (d, *J* = 7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 175.2, 139.0, 116.1, 74.5, 70.7, 58.5, 44.4, 41.9, 34.7, 25.7 (3 C), 24.2, 23.4, 21.7, 18.2, 16.2, -4.7, -5.3; IR (film) 3420, 3060, 2920, 2890, 2820, 1730 cm^{-1}.

*2. Oxidation of DDQ deprotected alcohol **14** to intermediate aldehyde **15**.*

(1*S*)-1-(1-Methyl-2-propenyl)-3-oxopropyl (2*S*)-4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoate (15).

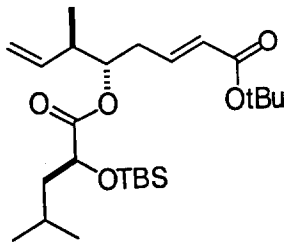


The alcohol **14** (95 mg, 0.265 mmol) was dissolved in CH_2Cl_2 (2.7 mL) and Dess-Martin periodinane (169 mg, 0.397 mmol) was added. After 2 h, a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and NH_4Cl solutions was added. After 10 min of vigorous stirring, the mixture was diluted with CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated. Product **15** was a colorless oil (76 mg, 81%): ^1H NMR (400 MHz, $CDCl_3$) δ 9.7 (dd, J = 2.5, 1.4 Hz, 1H), 5.76-5.67 (ddd, J = 17, 10.4, 8 Hz, 1H), 5.39-5.34 (dt, J = 8, 5 Hz, 1H), 5.11-5.09 (m, 1H), 5.10-5.06 (m, 1H), 4.19-4.16 (dd, J = 4, 9 Hz, 1H), 2.68-2.62 (ddd, J = 17, 8, 2.5 Hz, 1H), 2.62-2.56 (ddd, J = 17, 5, 1.4 Hz, 1H), 2.53-2.48 (m, 1H), 1.80-1.74 (m, 1H), 1.63-1.56 (ddd, J = 14, 9, 5 Hz, 1H), 1.48-1.42 (ddd, J = 14, 9, 4 Hz, 1H), 1.04-1.03 (d, J = 7 Hz, 3H), 0.92-0.89 (buried, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 173.7, 138.2, 116.9, 71.7, 70.7, 45.5, 44.2, 41.3, 25.7 (3 C), 24.1, 23.4, 21.7, 18.2, 15.5, -4.7, -5.4; IR (film) 3750, 2940, 2910, 2840, 1740, 1715 cm^{-1};

MS (EI) *m/z* 357 (M + 1, 100), 316, 303, 201, 189; HRMS (FAB) $C_{19}H_{37}O_4Si$ (M+H) calc'd for: 357.2461, found 357.2463.

*3. Wittig reaction of intermediate aldehyde **15** to form **11**.*

***tert*-Butyl (5*S*,6*R*,2*E*)-6-methyl-5-(4-methyl-(2*S*)-2-[(*tert*-butyldimethylsilyl)oxy] pentanoyloxy)octa-2,7-dienoate (11).**

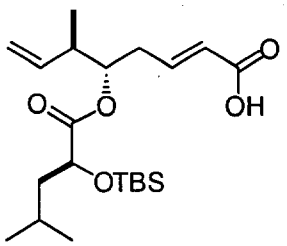


The aldehyde **15** (80 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2.2 mL) and cooled to 0 °C. (*tert*-Butoxycarbonylmethylene) triphenylphosphorane (101 mg, 0.27 mmol) was added. After 30 min at 0 °C and 90 min at rt, the reaction was concentrated and purified by flash chromatography (95:5 hexane:EtOAc) to provide **11** as a colorless oil (96 mg, 94 %): $[\alpha]_D$ -25° (c 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.77-6.69 (dt, *J* = 7, 15.5 Hz, 1H), 5.79-5.75 (d, *J* = 15.5 Hz, 1H), 5.75-5.66 (m, 1H), 5.08 (br s, 1H), 5.07-5.03 (m, 1H), 4.99-4.95 (app q, *J* = 6 Hz, 1H), 4.19-4.16 (dd, *J* = 4, 9 Hz, 1H), 2.45-2.38 (m, 3H), 1.81-1.74 (m, 1H), 1.63-1.57 (ddd, *J* = 5, 9, 13.5 Hz, 1H), 1.48-1.42 (buried, 1H), 1.45 (s, 9H), 1.02-1.00 (d, *J* = 7 Hz, 3H), 0.92-0.89 (buried, 6H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 165.3, 142.3, 138.6, 125.9, 116.3, 80.2, 75.3, 70.7, 44.3, 41.2, 34.1, 28.1 (3 C), 25.7 (3 C), 24.1, 23.4, 21.7, 18.2, 16.0, -4.6, -5.4; IR (film) 3070, 2935, 2910, 2840, 1740, 1700, 1645 cm^{-1}; MS (EI) *m/z* 399 (9), 341 (9), 267 (20), 201 (100), 189 (100); HRMS (FAB) calc'd for $C_{25}H_{47}O_5Si$ (M+H): 455.3193, found 455.3171.

*Two step synthesis of **12** from **11**.*

*1. Deprotection of ester **11** to intermediate acid **16**.*

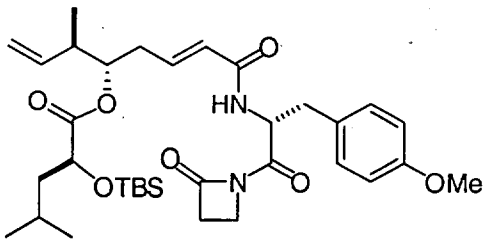
(5*S*,6*R*,2*E*)-6-Methyl-5-((2*S*)-4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoyloxy)octa-2,7-dienoic acid (16).



The *tert*-butyl ester **11** (40 mg, 0.088 mmol) was dissolved in 0.1 mL of CH_2Cl_2 and cooled to 0 °C. A TFA solution (1 M in CH_2Cl_2, 1.1 mL) was added via syringe. The ice bath was removed after 2 h and the reaction was continued with vigorous stirring. After 6 h, the reaction was found to be complete by TLC. Toluene (0.10 mL) was added and the reaction was concentrated under vacuum to provide acid **16** as a colorless oil (29 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99-6.92 (dt, J = 8, 15.5 Hz, 1H), 5.88-5.84 (br d, J = 15.5 Hz, 1H), 5.74-5.65 (ddd, J = 8, 10.5, 17 Hz, 1H), 5.09-4.99 (m, 3H), 4.19-4.16 (dd, J = 4, 9.5 Hz, 1H), 2.49-2.38 (m, 3H), 1.79-1.74 (m, 1H), 1.63-1.56 (ddd, J = 4.5, 9.5, 13.5 Hz, 1H), 1.45-1.38 (ddd, J = 4, 9.5, 13.5 Hz, 1H), 1.02-1.00 (d, J = 7 Hz, 3H), 0.91-0.90 (d, J = 4.5 Hz, 3H), 0.89-0.88 (d, J = 4.5 Hz, 3H), 16.52 (s, 9H), 6.05 (s, 3H), 5.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 146.7, 138.5, 123.3, 116.5, 75.0, 70.7, 44.4, 41.3, 34.5, 25.7 (3 C), 24.1, 23.4, 21.7, 18.2, 16.1, -4.7, -5.4; IR (film) 3060, 3000, 2930, 2900, 2840, 1740, 1715, 1680, 1640 cm^{-1}; MS (EI) *m/z* 399 (M+H, 3), 341 (3), 267 (4), 247 (10), 231 (30); HRMS (FAB) calc'd for (M+H) $C_{21}H_{39}O_5Si$: 399.2576, found 399.2559.

*2. Amide formation of **12** from acid **16** and salt **9**.*

(1*S*,3*E*)-4-(*N*-((1*R*)-1-((4-Methoxybenzyl)-2-oxo-2-(2-oxoazetidinyl)ethyl)carbamoyl)-1-((1*R*)-1-methyl-2-propenyl)but-3-enyl 4-methyl-2-[(*tert*-butyldimethylsilyl)oxy]pentanoate (12).



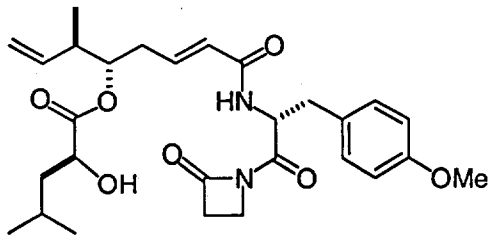
The *N*-Boc-4-methoxy (D)-phenylalanine (120 mg, 0.41 mmol) was dissolved in CH_3CN (4 mL) and cooled to 0 °C. 2-Azetidinone (50 mg, 0.69 mmol), DIEA (142 μL, 0.81 mmol) and HBTU (262 mg, 0.69 mmol) were added consecutively. After 20 min, the ice bath was removed and the mixture was stirred 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organics were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (80:20 to 50:50 hexanes:EtOAc) provided (2*R*)-(*tert*-butoxy)-*N*-((4-methoxyphenyl)methyl)-2-oxo-2-(2-oxoazetidinyl)ethyl)formamide as a cream colored solid (85 mg, 60%): $[\alpha]_D$ -56° (c 1.0, $CHCl_3$); m.p. 107-109°; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.10 (d, J = 8.6 Hz, 2H), 6.82-6.80 (d, J = 8.6 Hz, 2H), 5.05 (br s, 2H), 3.76 (s, 3H), 3.64-3.59 (m, 1H), 3.51-3.46 (m, 1H), 3.08-2.98 (m, 3H), 2.82-2.78 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.7, 159.4, 155.7, 130.8 (2C), 128.1, 114.3 (2C), 80.4, 56.2, 55.7, 37.5, 36.9, 36.4, 28.7 (3C); IR (film) 3390, 1790, 1705, 1690 cm^{-1}; MS(FAB) *m/z* 349 (M+H, 8), 293 (84), 249(25), 231 (76), 121 (100); HRMS (FAB, NBA) calc'd for $C_{18}H_{25}N_2O_5$ (M+H): 349.1763, found 349.1782.

This compound (150 mg, 0.431 mmol) was dissolved in 4N HCl in dioxane (4 mL) and stirred for 1.5 h. A precipitate formed and the reaction was concentrated to provide a light tan salt **9**.

Acid **16** (40 mg, 0.10 mmol) and salt **9** (40 mg, 0.140 mmol) were placed in a flask and CH_3CN (1 mL) was added. The solution was cooled to 0 °C and DIEA (52 mL, 0.30 mmol) was added. When solution was clear, HBTU (57 mg, 0.15 mmol) was added and the reaction stirred for 30 min at 0 °C and rt for 90 min. Saturated $NaHCO_3$ solution and

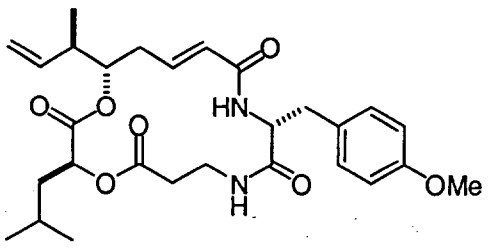
CH_2Cl_2 were added. The aqueous layer was further extracted with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered and concentrated. Flash chromatography (70:30 to 40:60 hexane/EtOAc) provided the product **12** as a thick oil (40 mg, 64%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.07 (d, *J* = 8.6 Hz, 2H), 6.82-6.80 (d, *J* = 8.6 Hz, 2H), 6.75-6.68 (dt, *J* = 7.5, 15 Hz, 1H), 5.98-5.96 (br d, *J* = 7.5 Hz, 1H), 5.82-5.78 (d, *J* = 15 Hz, 1H), 5.73-5.65 (m, 1H), 5.39-5.34 (app q, *J* = 7 Hz, 1H), 3.06-5.01 (m, 2H), 4.94-4.89 (app q, *J* = 6 Hz, 1H), 4.18-4.15 (dd, *J* = 4, 9 Hz, 1H), 3.77 (s, 3H), 3.64-3.59 (m, 1H), 3.53-3.48 (m, 1H), 3.15-3.10 (dd, *J* = 6, 14 Hz, 1H), 3.08-2.99 (m, 2H), 2.97-2.91 (dd, *J* = 7.5, 14 Hz, 1H), 2.43-2.39 (m, *J* = 7 Hz, 3H), 1.80-1.73 (m, 1H), 1.62-1.55 (ddd, *J* = 5, 9, 13.5 Hz, 1H), 1.47-1.41 (ddd, *J* = 4, 9, 13.5 Hz, 1H), 0.99-0.98 (d, *J* = 7 Hz, 3H), 0.91-0.89 (d, *J* = 7 Hz, 3H), 0.90-0.88 (d, *J* = 7 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.5, 164.7, 164.2, 158.8, 140.1, 138.6, 130.3 (2 C), 127.2, 125.6, 116.3, 114.0 (2 C), 75.4, 70.7, 55.2, 54.5, 44.3, 40.8, 36.7, 36.6, 36.0, 34.0, 25.7 (3 C), 24.1, 23.4, 21.7, 18.2, 16.3, -4.7, -5.4; IR (film) 3280, 3060, 2920, 2900, 2825, 1770, 1730, 1690, 1660, 1620 cm^{-1}; MS (EI) 629 (M+, 7), 572 (5), 457 (5), 383 (20), 284 (20), 231 (45), 121 (75); HRMS (FAB) calc'd for $C_{34}H_{52}N_2O_7Si$ 629.3622, found 629.3622.

(1*S*,3*E*)-4-(*N*-((1*R*)-1-((4-Methoxybenzyl)-2-oxo-2-(2-oxoazetidinyl)ethyl)carbamoyl)-1-((1*R*)-1-methyl-2-propenyl)but-3-enyl (2*S*)-2-hydroxy-4-methylpentanoate (5).



The silyl ether **12** (6.0 mg, 9.5 μmol) was dissolved in $CHCl_3$ (1 mL, dried over activated 4Å molecular sieves). $BF_3{\cdot}Et_2O$ (10 μL, 76.3 μmol) was added via syringe. After 1 h, $CHCl_3$ (5 mL) and saturated, aqueous $NaHCO_3$ (2 mL) were added. The organics were dried ($MgSO_4$), filtered and concentrated to provide clean **5** as an oil (4.4 mg, 88%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.08 (d, *J* = 8.6, 2H), 6.83-6.81 (d, *J* = 8.6, 2H), 6.71-6.63 (dt, J = 7.5, 15 Hz, 1H), 6.07-6.05 (br d, *J* = 7.5, 1H), 5.81-5.77 (d, *J* = 15, 1H), 5.71-5.62 (ddd, *J* = 8, 10.4, 17 Hz, 1H), 5.36-5.33 (app q, J = 6 Hz, 1H), 5.08-5.02 (m, 2H), 4.97-4.93 (app q, J = 6 Hz, 1H), 4.14-4.12 (br s, 1H), 3.77 (s, 3H), 3.64-3.61 (m, 1H), 3.54-3.49 (m, 1H), 3.16-3.11 (dd, *J* = 6, 14 Hz, 1H), 3.08-3.03 (m, 2H), 2.95-2.90 (dd, *J* = 8, 14 Hz, 1H), 2.45-2.40 (m, 3H), 1.91-1.84 (m, 1H), 1.52-1.48 (m, 2H), 1.00-0.99 (d, *J* = 6.9 Hz, 3H), 0.95-0.93 (d, *J* = 7 Hz, 3H), 0.94-0.92 (d, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.6, 164.9, 164.3, 158.8, 139.7, 138.4, 130.3 (2C), 127.2, 125.8, 116.6, 114.0 (2C), 76.4, 69.0, 55.2, 54.6, 43.5, 41.1, 36.6 (2C), 36.0, 34.1, 24.5, 23.3, 21.4, 16.2.

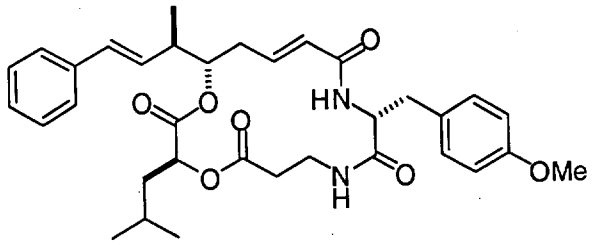
Dephenyldesepoxyarenastatin A (4).



Alcohol **5** (4.4 mg, 8.6 μmol) was dissolved in CH_2Cl_2 (2 mL). Bu_4NCN (21 mg, 77.0 μmol) was dissolved in CH_2Cl_2 (2 mL) and both were stirred with flame activated crushed 4 Å molecular sieves for 1 h. The Bu_4NCN solution was transferred via syringe dropwise to the solution of **5**. After 16 h, the reaction was filtered through celite and concentrated. Column chromatography (50:50 to 75:25 EtOAc:hexanes) provided clean product **4** (3.0 mg, 68%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.11-7.09 (d, *J* = 8.6 Hz, 2H), 7.05-7.02 (t, *J*

= 5.7 Hz, 1H), 6.81-6.79 (d, J = 8.6 Hz, 2H), 6.71-6.63 (ddd, J = 5, 10.3, 15 Hz, 1H), 5.84-5.82 (d, J = 8 Hz, 1H), 5.75-5.71 (d, J = 14 Hz, 1H), 5.69-5.65 (m, 1H), 5.08 (br s, 1H), 5.05-5.04 (d, J = 6 Hz, 1H), 5.02-4.97 (ddd, J = 2, 5, 11 Hz, 1H), 4.94-4.91 (dd, J = 4, 9.5 Hz, 1H), 4.72-4.66 (m, 1H), 3.76 (s, 3H), 3.54-3.47 (m, 1H), 3.47-3.40 (m, 1H), 3.16-3.11 (dd, J = 6, 14.4 Hz, 1H), 3.03-2.97 (dd, J = 7.6, 14.4 Hz, 1H), 2.44-2.28 (m, 2H), 1.76-1.66 (m, 1H), 1.48-1.40 (m, 1H), 1.04-1.02 (d, J = 7 Hz, 3H), 0.92-0.90 (d, J = 6.4 Hz, 3H), 0.88-0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.82, 170.76, 165.7, 158.5, 141.8, 138.6, 130.2 (2C), 128.5, 124.9, 116.5, 114.1 (2C), 76.8, 71.4, 55.2, 54.3, 42.4, 39.8, 36.1, 35.2, 34.2, 32.5, 24.5, 22.9, 21.5, 16.6; IR (film) 3420, 3300, 2990, 1740, 1675, 1525 cm^{-1}; MS (FAB) 515.3 (M+H); HRMS (FAB) calcd for $C_{28}H_{39}O_7N_2$ (M+H) 515.2757, found 515.2775.

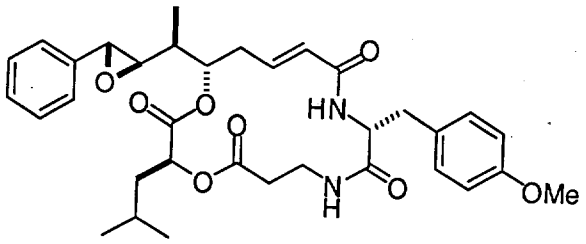
Desepoxyarenastatin A (13).



Olefin **4** (17 mg, 33 μmol) was dissolved in CH_3CN (0.33 mL) in a dry sealed tube. The solution was flushed with argon and iodobenzene (4.0 mL, 36 μmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol) and TEA (46 mL, 330 μmol) were added. The tube was sealed and placed in a 80-85 °C oil bath with vigorous stirring overnight. After 20 h, the solution was filtered and purified by silica gel chromatography to obtain product **13** as a solid (3 mg, 31% based on recovered starting material) and unreacted starting material **4** (6 mg): $[\alpha]_D^{20}$ +27° (c 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 7.11-7.09 (d, J = 8.6 Hz, 2H), 7.05-7.02 (t, J = 5.5 Hz, 1H), 6.81-6.78 (d, J = 8.6 Hz, 2H), 6.73-6.66 (ddd, J = 4.7, 10.5, 15 Hz, 1H), 6.41-6.37 (d, J = 15.8 Hz, 1H), 6.03-5.96 (dd, J = 8.8, 15.8 Hz, 1H), 5.77-5.75 (d, J = 7.9 Hz, 1H), 5.75-5.71 (d, J = 15 Hz, 1H), 5.06-5.01 (ddd, J =

2, 6.6, 11 Hz, 1H), 4.91-4.88 (dd, J = 3.6, 10 Hz, 1H), 4.73-4.67 (m, 1H), 3.76 (s, 3H), 3.54-3.48 (m, 1H), 3.46-3.39 (m, 1H), 3.15-3.11 (dd, J = 6, 14.4, 1H), 3.04-2.98 (dd, J = 7.5, 14.4 Hz, 1H), 2.57-2.52 (m, 3H), 2.39-2.30 (m, 1H), 1.78-1.57 (m, 3H), 1.35-1.27 (m, 1H), 1.13-1.11 (d, J = 6.8 Hz, 3H), 0.73-0.72 (d, J = 6.4 Hz, 3H), 0.70-0.69 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.9, 170.8, 165.6, 158.5, 141.7, 136.7, 131.8, 130.2 (2C), 128.6 (2C), 128.5, 127.5, 126.1 (2C), 125.0, 114.1 (2C), 76.6, 71.5, 55.2, 54.3, 42.2, 39.7, 36.4, 35.2, 34.2, 32.4, 24.3, 22.6, 21.2, 17.2; IR (film) 3365, 3260, 2940, 1725, 1710, 1665 cm^{-1}; MS (FAB) *m/z* 591.3 (M+H); HRMS (FAB) calcd for $C_{34}H_{43}N_2O_4$ (M+H) 591.3070, found 591.3069.

Arenastatin A (1).

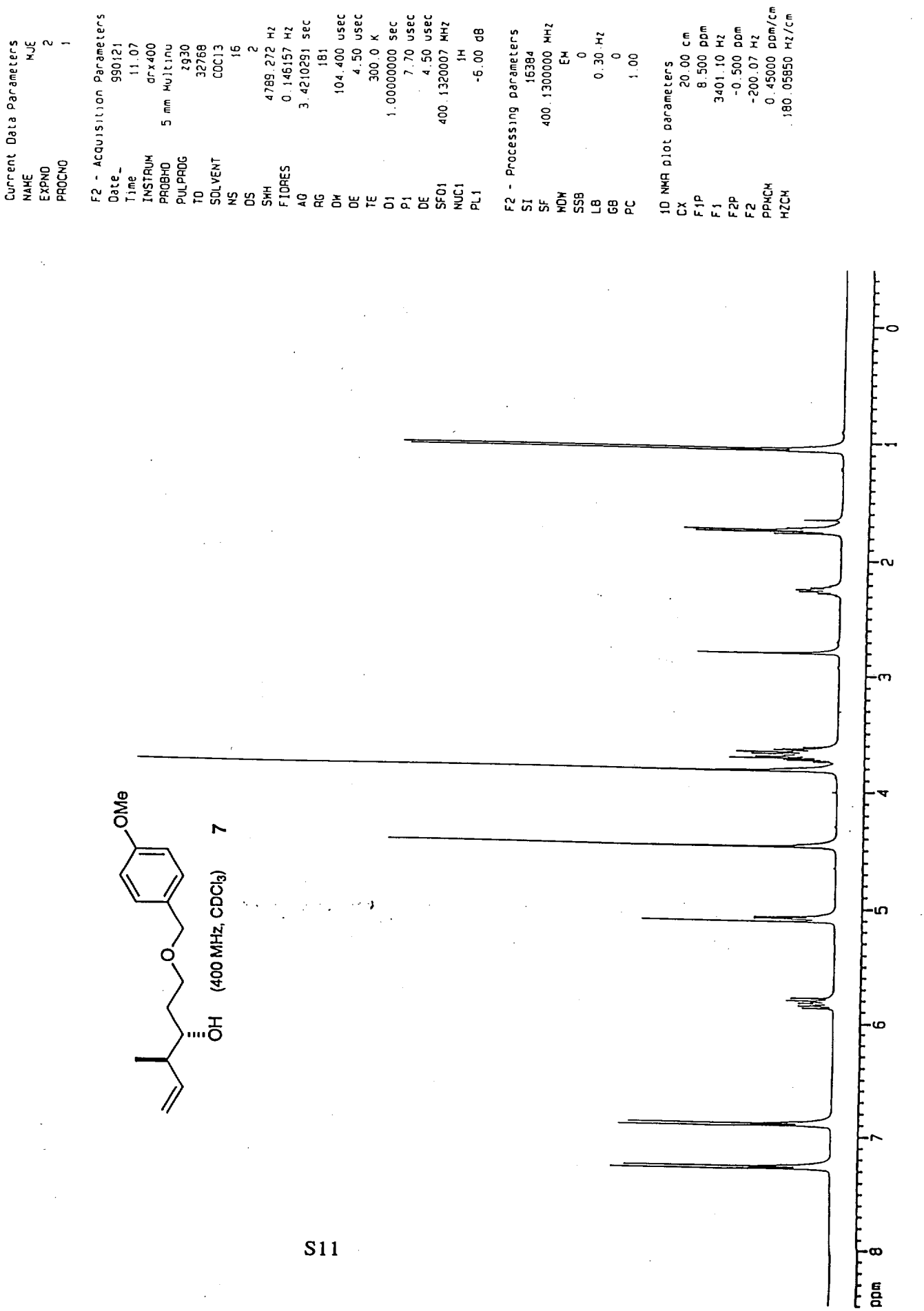


Olefin **13** (5.0 mg, 8.5 μmol) was reacted as previously reported[1] with dimethyldioxirane[2] to obtain a 2:1 mixture (*de was determined by HPLC Phenomenex Hypersil 5μ, C18, 150 x 3.2 mm, 254 nm, 3:2 CH_3CN: H_2O, 0.5 mL/min, retention time: β= 7.2 min, α = 7.9 min)* of epoxide diastereomers (3.9 mg, 76%): $[\alpha]_D^{20}$ +37° (*c* 0.10, $CHCl_3$).[1]

References:

(1) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206-6216.

(2) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.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PULPROG z930
TD 32768
SOLVENT CDCl3
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DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 181
DW 104.400 usec
DE 4.50 usec
TE 300.0 K
D1 1.00000000 sec
P1 7.70 usec
DE 4.50 usec
SFO1 400.1320007 MHz
NUC1 1H
PL1 -6.00 dB
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SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
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F1 3401.10 Hz
F2P -0.500 ppm
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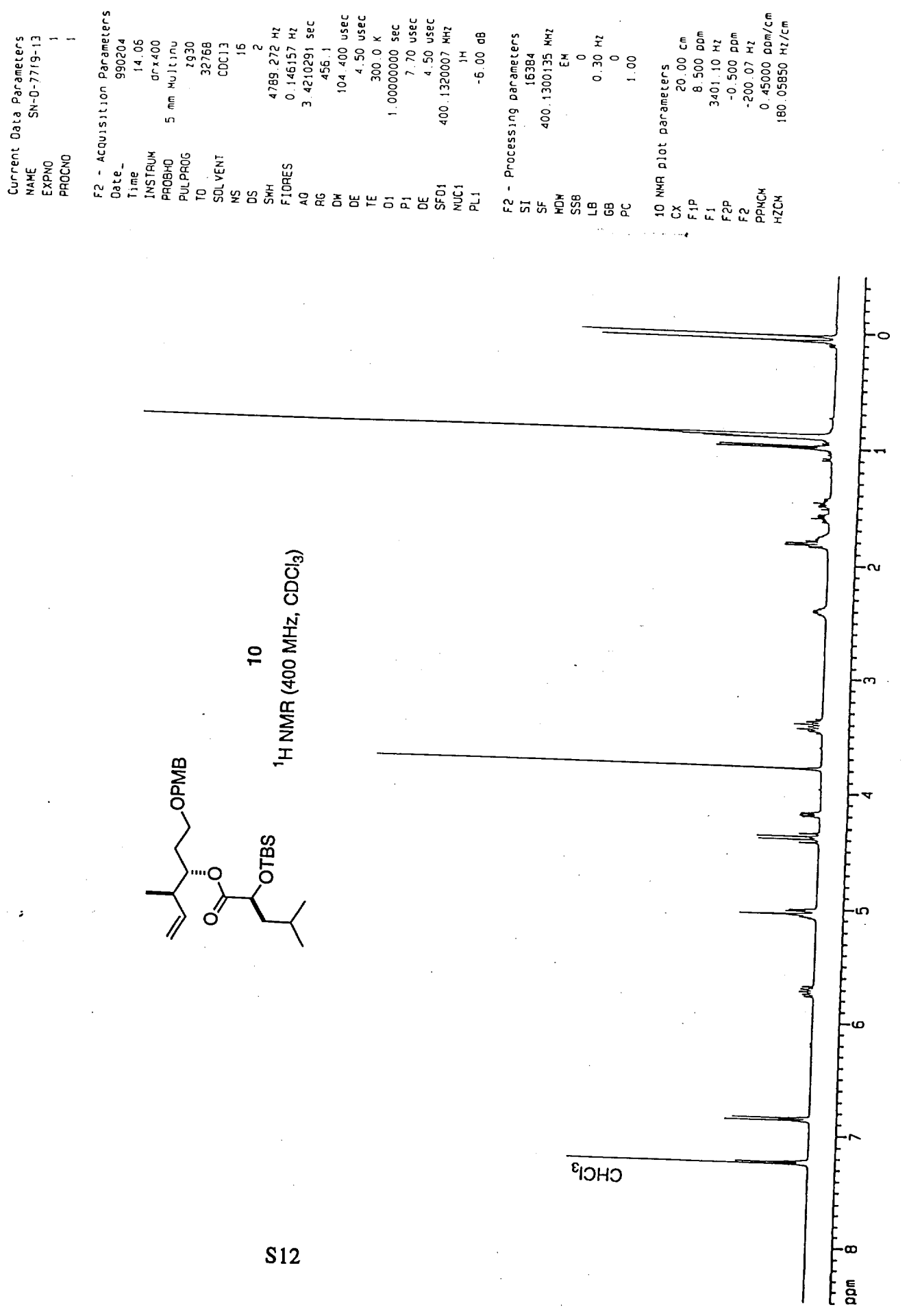
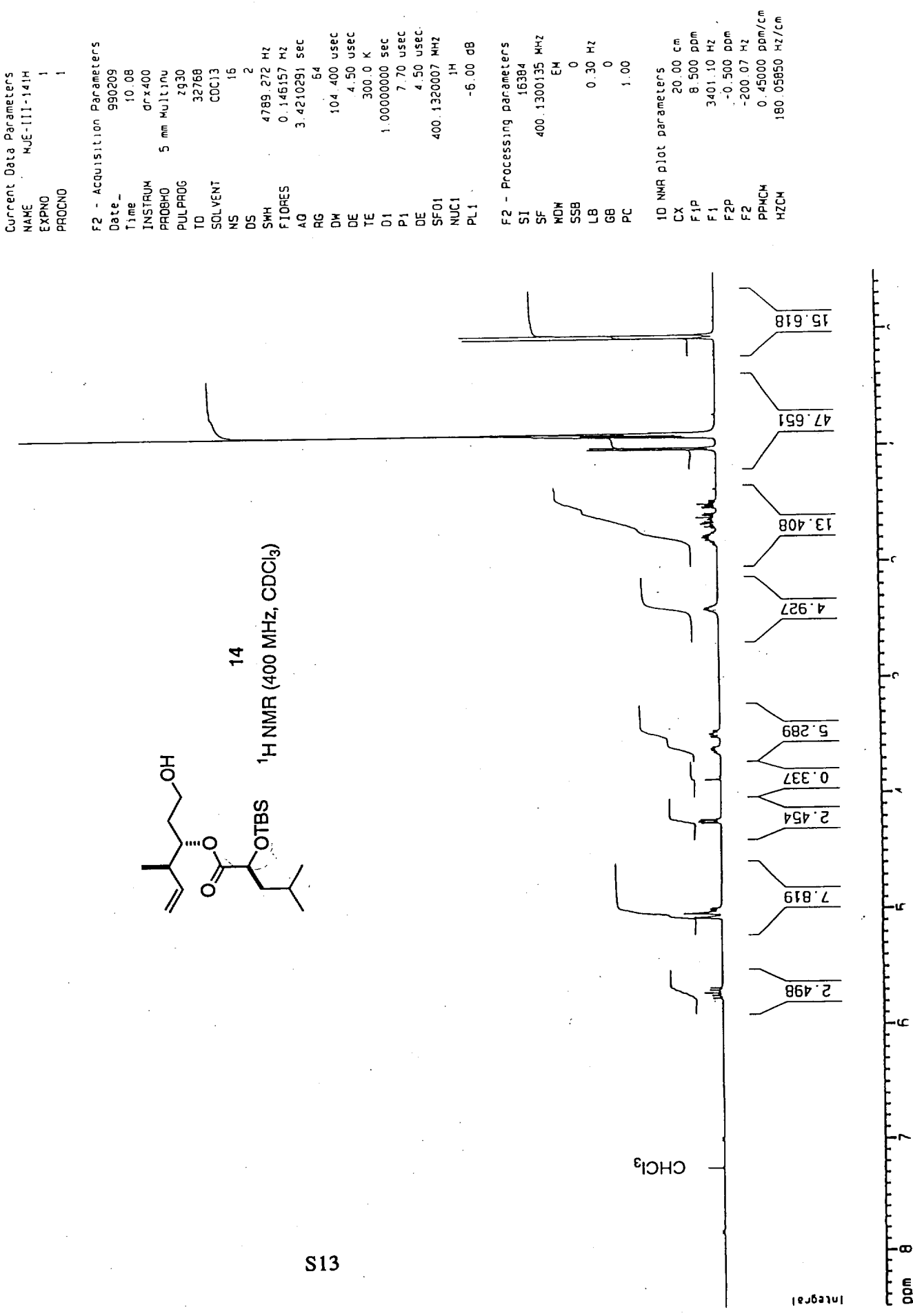
HZCM 180.05850 Hz/cm
OMe
OH
(400 MHz, CDCl3)
7
ppm





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TD              32768
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DS                  2
SWH          4789.272 Hz
FIDRES       0.146157 Hz
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RG                161.3
DW           104.400 usec
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TE             300.0 K
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P1             7.70 usec
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NUC1               1H
PL1              -6.00 dB

F2 - Processing parameters
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GB                  0
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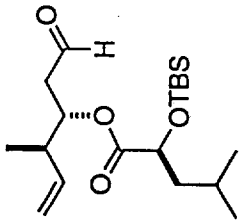
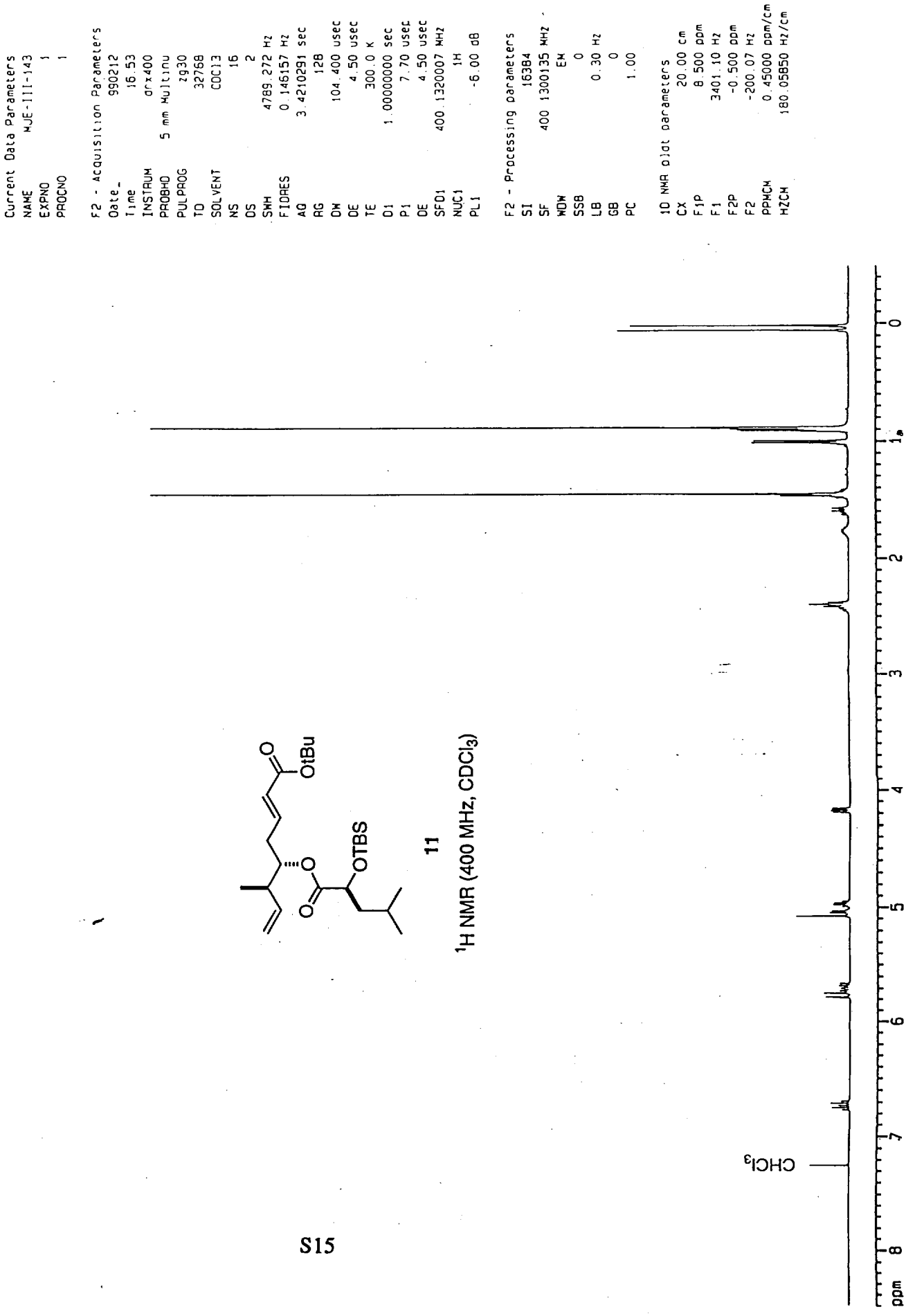


15

^{1}H NMR (400 MHz, $CDCl_3$)



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PROCNO            1

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PULPROG         zg30
TD             32768
SOLVENT        CDCl3
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DS                 2
SWH          4789.272 Hz
FIDRES       0.146157 Hz
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RG                512
DW           104.400 usec
DE             4.50 usec
TE             300.0 K
D1           1.00000000 sec
P1             7.70 usec
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NUC1               1H
PL1             -6.00 dB

F2 - Processing parameters
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WDW               EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00

1D NMR plot parameters
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HZCM         180.05850 Hz/cm
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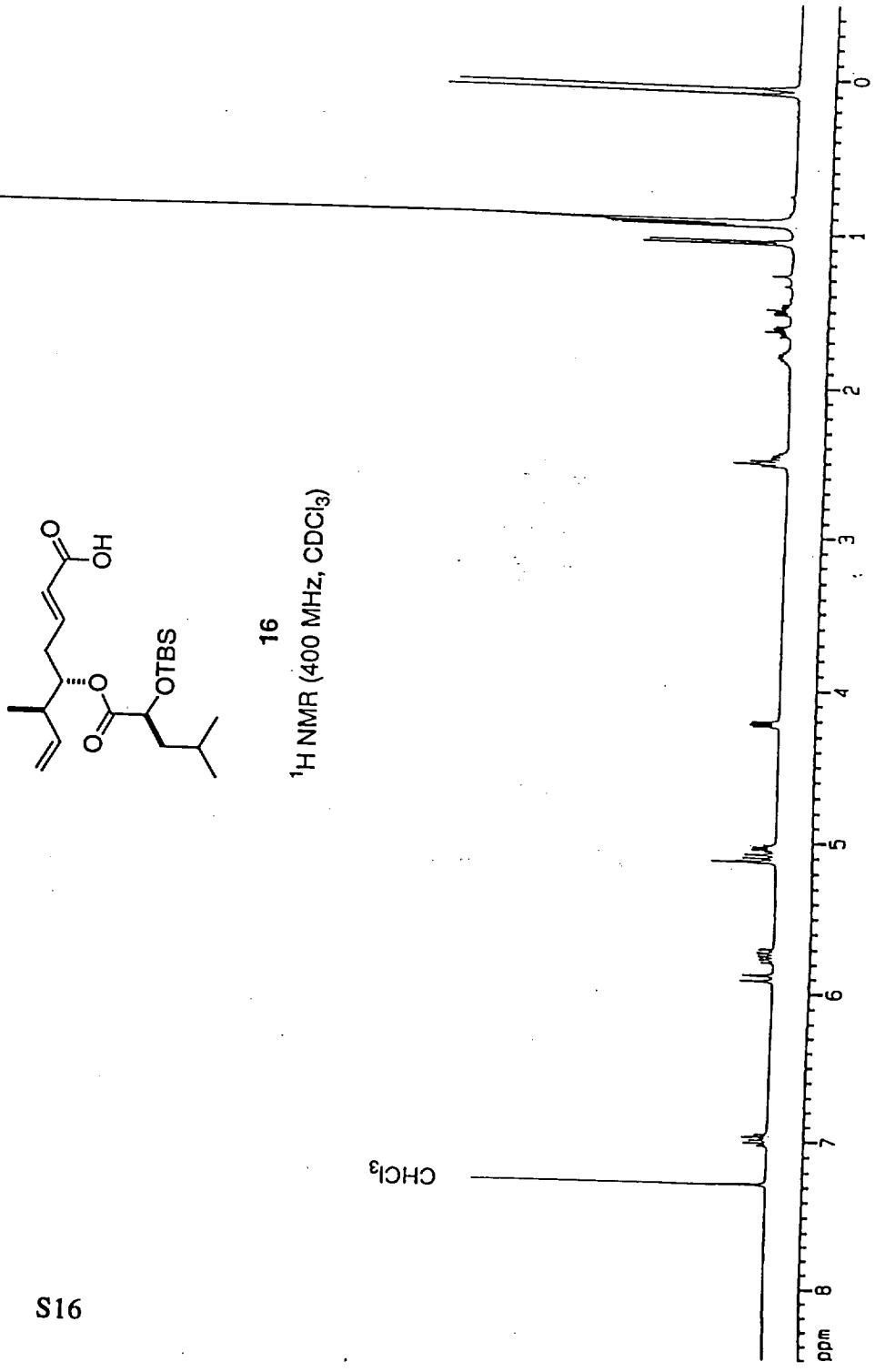
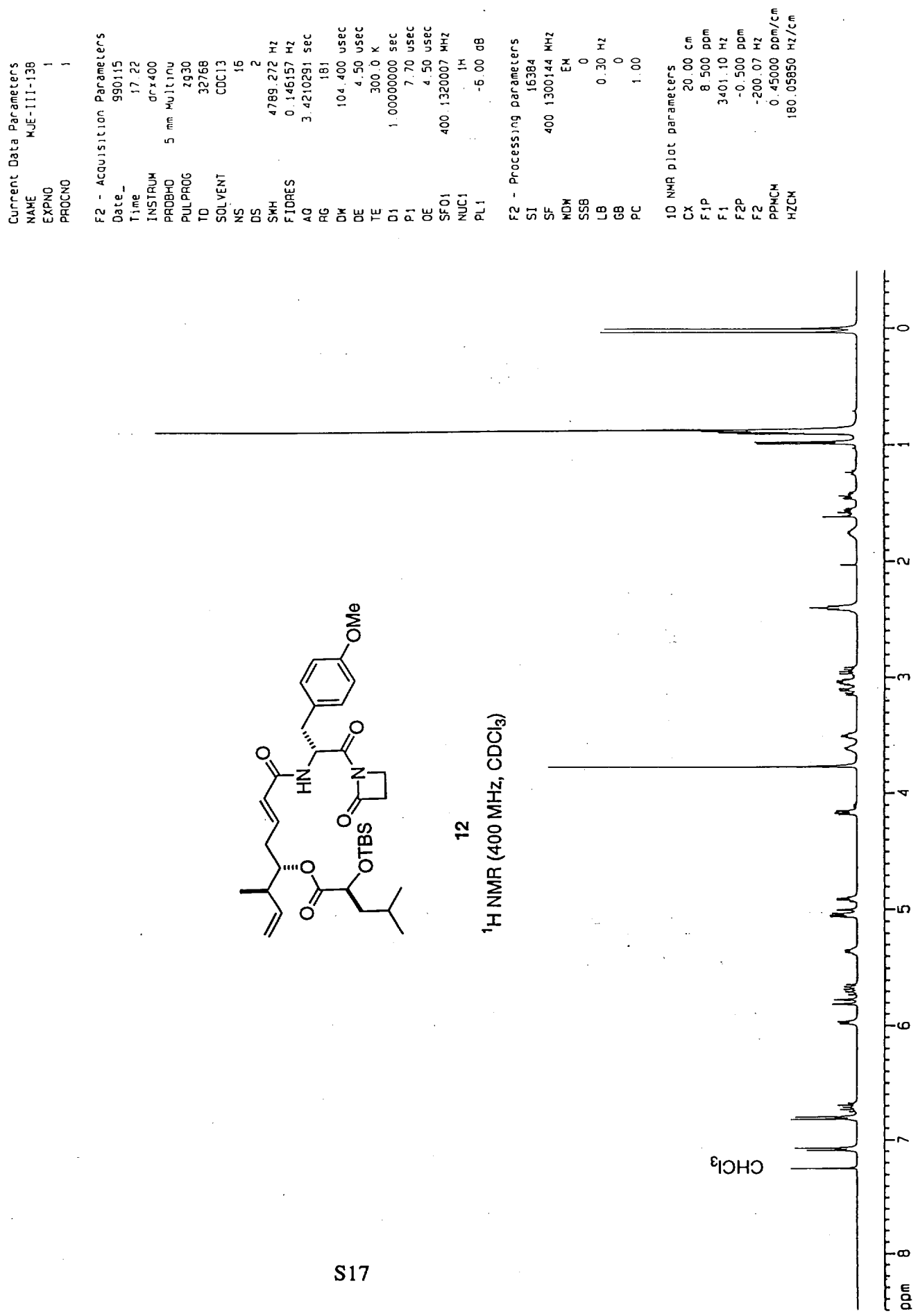


16

^{1}H NMR (400 MHz, $CDCl_3$)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PROCNO 1
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TD 32768
SOLVENT CDCl3
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FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 181
DW 104.400 usec
DE 4.50 usec
TE 300.0 K
D1 1.00000000 sec
P1 7.70 usec
DE 4.50 usec
SFO1 400.1320007 MHz
NUC1 1H
PL1 -6.00 dB
F2 - Processing parameters
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SF 400.1300144 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
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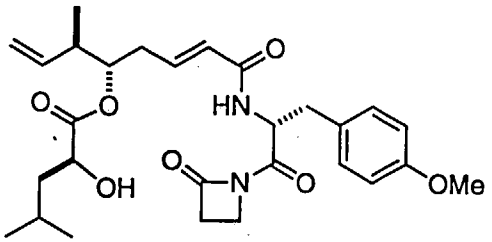
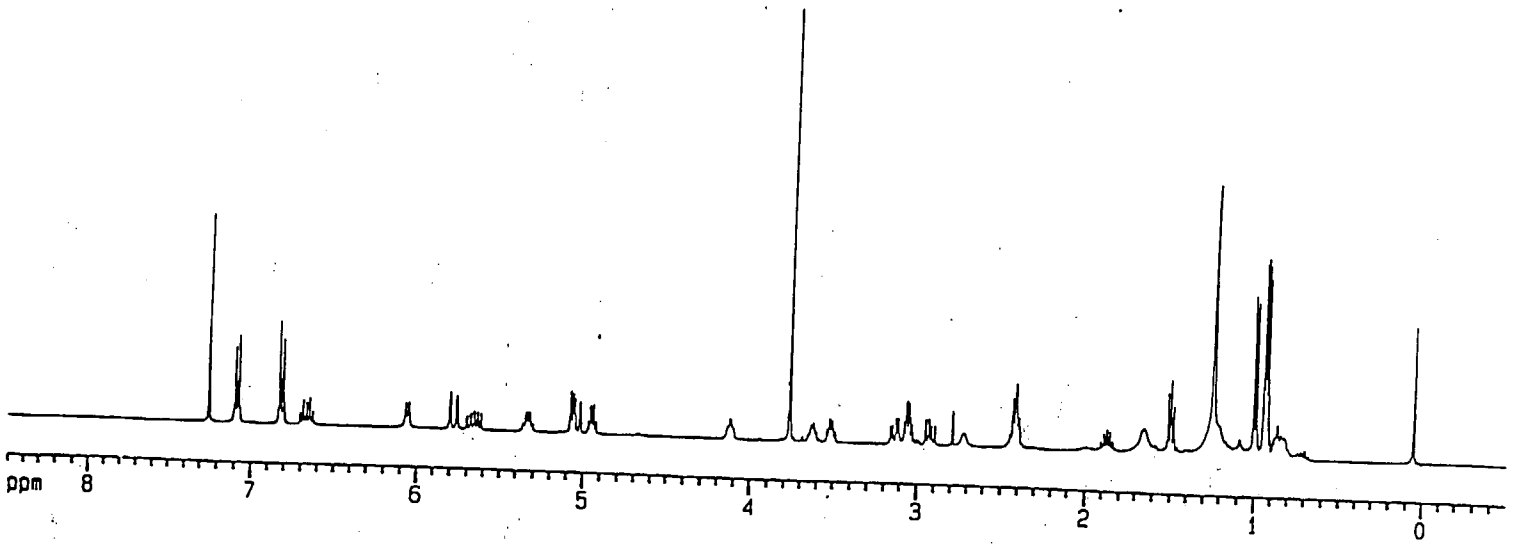
F1P 8.500 ppm
F1 3401.10 Hz
F2P -0.500 ppm
F2 -200.07 Hz
PPMCM 0.45000 ppm/cm
HZCM 180.05850 Hz/cm
OMe
HN
OTBS
12
^{1}H NMR (400 MHz, $CDCl_3$)
$CHCl_3$
ppm



5

^{1}H NMR (400 MHz, $CDCl_3$)

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PROCNO                      1

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PULPROG             zg30
TD                  32768
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DS                  2
SWH                 4789.272 Hz
FIDRES              0.146157 Hz
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NUC1                1H
PL1                 -6.00 dB

F2 - Processing parameters
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1D NMR plot parameters
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F2                  -200.07 Hz
PPMCM               0.45000 ppm/cm
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