Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

SUPPORTING MATERIAL

Synthetic Access to the Chlorocylcopentane Cores of the Proposed Original and Revised Structures of Palau'amine.

Michael S. Bultman, Jun Ma, and David Y. Gin*

Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

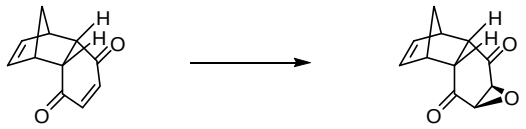
Experimental Procedures

General Procedures. Reactions were performed in flame-dried sealed-tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. Molecular sieves were activated at 350 °C and were crushed immediately prior to use, then flame-dried under vacuum. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230-400 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Dichloromethane, tetrahydrofuran, diethyl ether, hexane, toluene, and benzene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. Methanol was distilled from magnesium at 760 Torr. Triethylamine and pyridine were distilled from calcium hydride at 760 Torr. Isopropyl alcohol and dimethylformamide was dried over 4Å molecular sieves. All other chemicals were obtained from commercial vendors and were used without further purification unless noted otherwise.

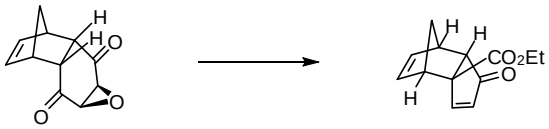
Instrumentation. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum BX spectrophotometer or a Bruker Tensor 27. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Varian 400, a Varian 500, a Varian

Inova 500, or a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent ($CHCl_3$: δ 7.26 for ^1H NMR, δ 77.16 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, ABq = AB non-first order spin system, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration, assignment.



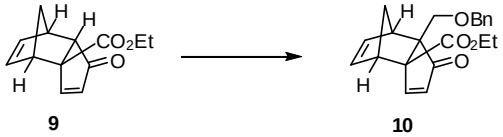
8 **S1**

6,7-epoxy-1,4,4a,6,7,8a-hexahydro-1,4-methano-naphthalene-5,8-dione S1. To a solution of dienone **8** (1.88 g, 0.0108 mol, 1 equiv) in ethanol (6 mL, 190 proof) and acetone (2.5 mL) at 0 ^oC was added a solution of hydrogen peroxide (30% in water, 4.0 mL, 0.039 mol, 3.5 equiv) and a solution of sodium carbonate (1.0 g, 0.0094 mol, 0.9 equiv) in water (4.0 mL) simultaneously. The reaction effervesced and formed an off-white precipitate over the course of 30 minutes, at which time no starting material was observed by TLC analysis. The solution was diluted with water (200 mL) and extracted with diethyl ether (3 x 100 ml). The combined organic layers were then dried (magnesium sulfate), filtered, and concentrated *in vacuo* to afford epoxide **S1** (1.95 g, 95%) as a white highly crystalline solid, which was of high purity (>95%) and could be used directly in the following step. R_f 0.70 (1:1 hexanes:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (br s, 2H, CHC*H*=C*H*CH), 3.52 (s, 2H, C*H*OC*H*), 3.44 (s, 2H, CHC*H*C*H*CH), 3.33 (br s, 2H, C*H*CH=CHC*H*), 1.49 (dt, 1H, J = 1.7, 8.7 Hz, CH_2), 1.29 (br d, 1H, J = 8.7 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 136.8, 58.0, 49.6, 46.5, 43.4; IR (neat film) 2983 (w), 2939 (w), 1709 (s), 1340 (w), 1287 (w), 1224 (s), 1042 (w), 800 (m), 737 (m) cm^{-1}; LRMS (ESI) m/z for $C_{11}H_9O_3$ $(M-H)^-$ 188.92. All spectra data matched that as previously reported.[1]



S1 9

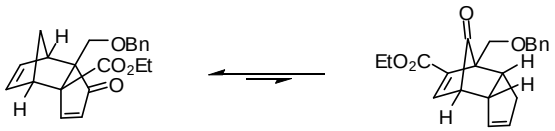
Ethyl 5-oxo-tricyclo[5.2.1.0]deca-3,8-diene-2-carboxylate 9. To a solution of epoxide **S1** (15.4 g, 0.081 mol, 1 equiv) in ethanol (200 proof, 390 mL) at 23 ^{o}C was added a solution of sodium hydroxide (1.62 g, 0.04 mol, 0.5 equiv) in ethanol (200 proof, 10 mL). The solution instantly turned deep purple and then dark brown. After stirring for 3 hours 2/3's of the volume of ethanol was removed *in vacuo*; the resulting solution was diluted with water (1 L) and extracted with diethyl ether (5 x 400 ml). The combined organic layers were then dried (magnesium sulfate), filtered, and concentrated *in vacuo* to afford enone **9** (10.39 g, 60%) as a brown oil, which was of high purity (>95%) and could be used directly in the following step. R_f 0.52 (1:1 benzene:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, 1H, J = 5.7, O=CH=C*H*)**,** 6.02 (dd, 1H, J = 2.8, 5.6 Hz, CHC*H*=CHCH), 5.95-5.93 (m, 2H, O=C*H*=CH, CHCH=C*H*CH), 4.22 (q, 2H, J = 7.2 Hz, OCH_2CH$_3$), 3.32 (s, 1H, C*H*CHCH=CHCH), 3.30 (br s, 1H, CHC*H*CH=CHCH), 3.22 (br s, 1H, CHCHCH=CHC*H*), 1.94 (br d, 1H, J = 8.8 Hz, CH_2), 1.74 (dt, 1H, J = 1.6, 8.8 Hz, CH_2), 1.30 (t, 3H, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 173.0, 161.8, 136.3, 134.9, 133.7, 64.6, 61.8, 54.3, 51.3, 49.8, 45.8, 14.3; IR (neat film) 2996 (w), 2966 (m), 2933 (w), 1714 (s), 1340 (w), 1190 (w), 847 (m), 736 (m) cm^{-1}; LRMS (ESI) m/z for $C_{13}H_{15}O_3$ $(M+H)^+$ 219.07. All spectra data matched that as previously reported.[2]



9 10

7a-Benzyloxymethyl-1-oxo-1,4,7,7a-tetrahydro-4,7-methano-indene-3a-carboxylic acid ethyl ester 10. A solution of lithium hexamethyldisilizane (2.5 g, 0.015 mol, 1.5 equiv) in tetrahydrofuran (35 mL) was prepared at –78 ^{o}C. To this was added via cannula a solution of ketone **9** (2.19 g, 0.1 mmol, 1 equiv) in tetrahydrofuran (36 mL) at -78 ^{o}C in

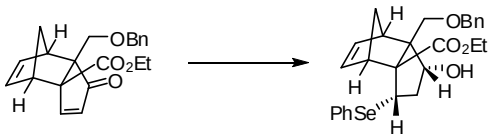
portions. After stirring for 45 minutes a solution of benzyloxymethyl chloride (2.6 mL, 0.017 mol, 1.7 equiv) in tetrahydrofuran (10 mL) at –78 °C was added via cannula. After 30 minutes the solution was allowed to warm to –20 °C, then quenched after 30 minutes with saturated ammonium chloride (500 mL), allowed to warm to 23 °C, and extracted with diethyl ether (3 x 250 ml). The combined organic layers were then dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (gradient 8:1 to 6:1 benzene:ethyl acetate) to afford enone **10** (1.84 g, 53%) as a yellow crystal. R_f 0.55 (5:1 benzene:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, J = 6.0 Hz, O=CCH=C*H*), 7.23 (m, 5H, $C_6H_5CH_2OCH_2$), 6.04 (dd, 1H, J = 3.1, 5.5 Hz, CHC*H*=CHCH), 6.01 (d, 1H, J = 6.0 Hz, O=CC*H*=CH), 5.92 (dd, 1H, J = 3.0, 5.5 Hz, CHCH=C*H*CH), 4.37 (ABq, 2H, J = 12.1, $C_6H_5CH_2OCH_2$), 4.11 (dq, 1H, J = 7.2, 10.8 Hz, OCH_2CH_3), 4.03 (d, 1H, J = 8.6 Hz, $C_6H_5CH_2OCH_2$), 3.91 (dq, 1H, J = 7.2, 10.8 Hz, OCH_2CH_3), 3.75 (d, 1H, J = 8.6 Hz, $C_6H_5CH_2OCH_2$), 3.06 (br s, 1H, C*H*CH=CHCH), 2.80 (d, 1H, J = 9.0 Hz, CH_2), 2.76 (br s, 1H, CHCH=CHC*H*), 1.71 (dt, 1H, J = 1.5, 9.0 Hz, CH_2), 1.13 (t, 3H, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 172.8, 163.0, 138.2, 135.8, 134.4, 128.2, 127.3, 127.1, 73.2, 72.7, 65.3, 63.1, 61.4, 51.0, 50.6, 48.6, 14.0; IR (neat film) 2977 (w), 2863 (w), 1712 (s), 1453 (m), 1235 (s), 1092 (m) cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{23}O_4$ $(M+H)^+$ 339.1596, observed 339.1600.



10 **11**

4-Benzyloxymethyl-8-oxo-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid ethyl ester 11. Crystalline enone **10** was stable to rearrangement at room temperature for several months, however, in solution **10** was found to exist in a dynamic equilibrium with 1,5 diene isomer **11** under a variety of conditions. It took 2 weeks for pure sample of **10** in *d*-benzene at 23 °C to achieve a stable ratio of 72:28 of **10**:**11** respectively. The same ratio was observed upon heating a pure sample of **10** in dichloromethane to 90 °C in a sealed tube for 15 min. The most enriched sample of **11**

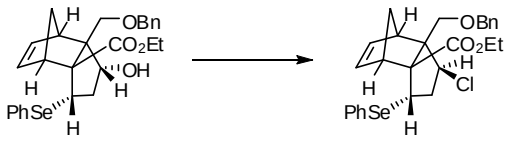
was obtained via column chromatography (8:1 gradient to 6:1 and then 2:1 benzene:ethyl acetate) as a 4:1 mixture of **11**:**10**, respectively. R_f 0.72 (5:1 toluene:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 5H, $C_6H_5CH_2OCH_2$), 7.01 (d, 1H, J = 4.0 Hz, C=C*H*CHCHCH), 5.69 (dq, 1H, J = 2.5, 6.0 Hz, CH_2CH=CH), 5.33 (dq, 1H, J = 2.5, 6.0 Hz, CH_2CH=C*H*), 4.65 (ABq, 2H, J = 12.0 Hz, $C_6H_5CH_2OCH_2$), 4.15 (dd, 1H, J = 7.4, 10.5 Hz, OCH_2CH_3), 4.08 (dd, 1H, J = 7.4, 10.5 Hz, OCH_2CH_3), 4.03 (d, 1H, J = 9.5 Hz, $C_6H_5CH_2OCH_2$), 3.93 (d, 1H, J = 10.0 Hz, $C_6H_5CH_2OCH_2$), 3.52-3.48 (m, 1H, C=CHCHC*H*CH), 3.20 (t, 1H, J = 4.3 Hz, C=CHC*H*CHCH), 2.65 (ddd, 1H, J = 3.8, 9.0, 9.9 Hz, C=CHCHCHC*H*), 2.29 (ddq, 1H, J = 2.1, 9.8, 17.6 Hz, CH_2CH=CH), 2.12-2.06 (m, 1H, CH_2CH=CH), 1.19 (t, 3H, J = 7.3 Hz, OCH_2CH_3); HRMS (ESI) m/z calcd for $C_{21}H_{23}O_4$ $(M+1)^+$ 339.1596, observed 339.1602.



10 **S2**

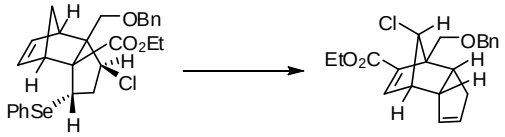
7a-Benzyloxymethyl-1-hydroxy-3-phenylselanyl-1,2,3,4,7,7a-hexahydro-4,7-methano-indene-3a-carboxylic acid ethyl ester S2. To a solution of diphenyldiselenide (4.4 g, 0.014 mol, 3.0 equiv) in ethanol (31 mL) was added sodium borohydride (2.4 g, 0.063 mol, 13 equiv) at 0 °C and the solution effervesced and turned tan. After 1 hour acetic acid (2.7 mL, 0.047 mol, 10 equiv) was added. The resulting solution was stirred for 30 minutes, at which point enone **10** (1.633 g, 4.8 mmol, 1 equiv) in ethanol (15 mL) was added via cannula and the solution was allowed to warm to 23 °C. After 52 hours sodium borohydride (1.8 g, 0.048 mol, 10 equiv) was added at 0 °C with much effervescence. After one hour the solution was diluted with water (500 mL), and extracted with diethyl ether (3 x 300 mL). The combined organic layers were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (4:1 hexane:ethyl acetate) to afford alcohol **S2** (1.669 g, 70%) as a clear oil. R_f 0.15 (4:1 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (m, 2H, C_6H_5Se), 7.30 (m, 8H, C_6H_5Se, $C_6H_5CH_2OCH_2$), 6.46 (dd, 1H, J = 3.0, 5.5 Hz, CHC*H*=CHCH), 6.37 (dd, 1H, J = 3.0, 5.5 Hz, CHCH=C*H*CH), 4.49 (q, 2H, J = 11.5

Hz, $C_6H_5CH_2OCH_2$), 4.16 (m, 2H, HOC*H*CH_2C*H*Se), 3.84 (q, 2H, J = 7.0 Hz, OC$H_2$$CH_3$), 3.63 (d, 1H, J = 8.5 Hz, $C_6H_5CH_2OCH_2$), 3.37 (br s, 1H, C*H*CH=CHCH), 3.35 (d, 1H, J = 8.5 Hz, $C_6H_5CH_2OCH_2$), 3.07 (br s, 1H, CHCH=CHC*H*), 2.38 (d, 1H, J = 2.5 Hz, *H*OCH), 2.28 (dt, 1H, J = 8.0, 12.5 Hz, HOCHCH_2CHSe), 2.07 (dt, 1H, J = 11.0, 13.0 Hz, HOCHCH_2CHSe), 1.85 (d, 1H, J = 9.0 Hz, CH_2), 1.55 (d, 1H, J = 9.0 Hz, CH_2), 1.04 (t, 3H, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 139.8, 136.9, 133.8, 127.9, 127.6, 127.0, 126.7, 126.6, 78.2, 77.1, 72.9, 66.5, 64.7, 60.1, 50.4, 49.1, 46.8, 45.4, 41.5, 13.0; IR (neat film) 3564 (w), 2979 (w), 2870 (w), 1713 (s), 1476 (m), 1231 (s), 1074 (m) cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{31}O_4Se$ $(M+H)^+$ 499.1388, observed 499.1388.



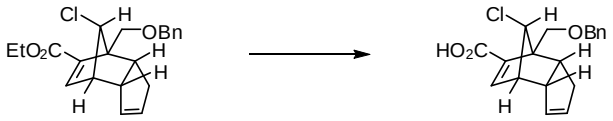
7a-Benzyloxymethyl-1-chloro-3-phenylselanyl-1,2,3,4,7,7a-hexahydro-4,7-methano-indene-3a-carboxylic acid ethyl ester 12. To a solution of alcohol **S2** (85 mg, 0.171 mmol, 1.0 equiv) in carbontetrachloride (1.4 mL) was added tributylphosphine (126 μL, 0.513 mol, 3 equiv) and the solution was heated to 90 ^{o}C. After 15 hours the reaction was diluted with dichloromethane (0.2 mL) and purified directly by silica gel flash chromatography (4:1 hexane:ethyl acetate) to afford chloride **12** (72 mg, 82%) as a clear oil. R_f 0.42 (4:1 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2H, C_6H_5Se), 7.43-7.30 (m, 8H, C_6H_5Se, $C_6H_5CH_2OCH_2$), 6.50 (dd, 1H, J = 3.0, 5.3 Hz, CHC*H*=CHCH), 6.28 (dd, 1H, J = 3.2, 5.4 Hz, CHCH=C*H*CH), 4.62 (dd, 1H, J = 8.2, 13.2, ClCHCH_2C*H*Se), 4.56 (d, 1H, J = 11.6 Hz, $C_6H_5CH_2OCH_2$), 4.40 (d, 1H, J = 11.5 Hz, $C_6H_5CH_2OCH_2$), 4.29 (d, 1H, J = 6.4 Hz, ClC*H*CH_2CHSe), 4.07 (d, 1H, J = 9.1 Hz, $C_6H_5CH_2OCH_2$), 3.94-3.82 (m, 2H, J = 7.0 Hz, OC$H_2$$CH_3$), 3.45 (br s, 1H, C*H*CH=CHCH), 3.35-3.33 (m, 2H, $C_6H_5CH_2OCH_2$, CHCH=CHC*H*), 2.61 (dt, 1H, J = 6.5, 14.6 Hz, ClCHCH_2CHSe), 2.39 (dt, 1H, J = 8.2, 14.7 Hz, ClCHCH_2CHSe), 1.98 (d, 1H, J = 9.3 Hz, CH_2), 1.54 (d, 1H, J = 9.4 Hz, CH_2), 1.08 (t, 3H, J = 7.0 Hz, OCH_2CH_3);

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 138.9, 138.5, 138.4, 134.6, 129.2, 128.9, 128.5, 127.7, 127.6, 127.5, 73.8, 73.1, 68.6, 67.8, 66.6, 61.1, 51.8, 51.3, 50.4, 48.7, 48.6, 13.9; IR (neat film) 2924 (s), 2853 (s), 1724 (s), 1455 (w), 1231 (s), 1093 (m) cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{30}ClO_3Se$ $(M+H)^+$ 517.1049, observed 517.1027.



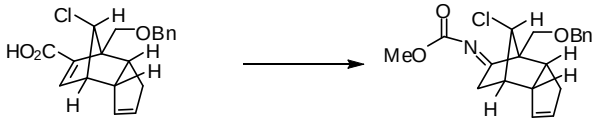
12 **14**

4-Benzyloxymethyl-8-chloro-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid ethyl ester 14. To a solution of chloride **12** (5.0 g, 9.7 mmol, 1.0 equiv) in dichloromethane (51 mL) at -20 ^oC was added *meta*-chloroperoxybenzoic acid (2.14 g, 9.6 mol, 0.99 equiv). After twenty minutes triethylamine (2.7 mL, 19.0 mmol, 2 equiv) was added and the solution was heated to 80 ^oC for 17 hours in a sealed tube. At this time the solvent was removed and the residue was purified directly by silica gel flash chromatography (dichloromethane) to afford chloride **14** (3.2 g, 92%) as a yellow oil. R_f 0.56 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, $C_6H_5CH_2OCH_2$), 6.86 (dd, 1H, J = 1.5, 3.5 Hz, C=C*H*CHCHCH), 5.57 (dq, 1H, J = 2.0, 5.5 Hz, CH_2CH=CH), 5.43 (dq, 1H, J = 2.0, 5.5 Hz, CH_2CH=C*H*), 4.61 (ABq, 2H, J = 12.0 Hz, $C_6H_5CH_2OCH_2$), 4.32 (d, 1H, J = 10.0 Hz, $C_6H_5CH_2OCH_2$), 4.15 (m, 3H, C*H*Cl, OCH_2CH_3), 3.90 (d, 1H, J = 10.0 Hz, $C_6H_5CH_2OCH_2$), 3.39 (m, 1H, C=CHCHC*H*CH), 3.21 (t, 1H, J = 3.5 Hz, C=CHC*H*CHCH), 3.09 (m, 1H, C=CHCHCHC*H*), 2.26 (ddq, 1H, J = 2.0, 8.5, 18.0 Hz, CH_2CH=CH), 1.87 (m, 1H, CH_2CH=CH), 1.26 (t, 3H, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 146.6, 138.7, 134.4, 134.0, 130.1, 129.2, 128.2, 127.5, 75.5, 73.4, 66.1, 63.2, 60.2, 52.5, 51.2, 38.2, 34.0, 14.1; IR (neat film) 2917 (w), 2852 (w), 1709 (s), 1454 (m), 1276 (s), 1090 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{24}O_3Cl$ $(M+H)^+$ 359.1424, observed 359.1414.



14 **S3**

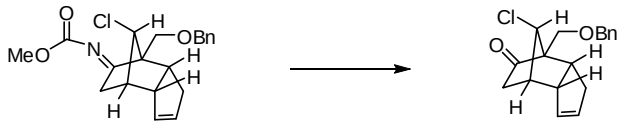
4-Benzyloxymethyl-8-chloro-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid S3. To a solution of chloride **14** (125 mg, 0.349 mmol, 1.0 equiv) in ethanol (3 mL) at 23 ^{o}C was added a sodium hydroxide solution (3 mL, 5.0 M). After 90 minutes the reaction was warmed to 30 ^{o}C. After 5 hours the reaction was diluted with hydrochloric acid (10 mL, 1 M) and extracted with ethyl acetate (3 x 10 mL), dried with sodium sulfate, and reduced *in vacuo* to afford acid **S3** (111.5 mg, 97%) as a clear oil. R_f 0.58 (2:1 ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H, $C_6H_5CH_2OCH_2$), 7.06-7.05 (m, 1H, C=C*H*CHCHCH), 5.59 (dq, 1H, J = 2.0, 5.7 Hz, CH_2CH=CH), 5.43 (dq, 1H, J = 2.2, 5.7 Hz, CH_2CH=C*H*), 4.62 (s, 2H, $C_6H_5CH_2OCH_2$), 4.28 (d, 1H, J = 10.2 Hz, $C_6H_5CH_2OCH_2$), 4.13 (s, 1H, C*H*Cl), 3.91 (d, 1H, J = 10.2 Hz, $C_6H_5CH_2OCH_2$), 3.43-3.40 (m, 1H, C=CHCHC*H*CH), 3.25 (t, 1H, J = 3.2 Hz, C=CHC*H*CHCH), 3.08 (m, 1H, C=CHCHCHC*H*), 2.31 (ddd, 1H, J = 1.5, 10.2, 18.1 Hz, CH_2CH=CH), 1.90 (dt, 1H, J = 2.2, 18.02 Hz, CH_2CH=CH); IR (neat film) 3049 (w), 2904 (w), 2676 (w), 1680 (s), 1454 (m), 1146 (s) cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 149.6, 137.5, 133.3, 132.8, 128.2, 127.5, 126.7, 126.6, 73.6, 72.6, 65.5, 62.1, 51.9, 50.5, 37.7, 33.4; HRMS (ESI) m/z calcd for $C_{19}H_{20}O_3Cl$ $(M+H)^+$ 331.1101, observed 331.1093.



S3 **S4**

Imine S4. To a solution of acid **S3** (139 mg, 0.421 mmol, 1.0 equiv) in toluene (8 mL) at 23 ^{o}C was added diphenylphosphorylazide (100 μL, 0.463 mmol, 1.1 equiv) and triethylamine (65 μL, 0.463 mmol, 1.1 equiv). After 15 minutes additional diphenyl phosphorylazide (15 μL, 0.070 mmol, 0.16 equiv) was added. After 5 hours TLC

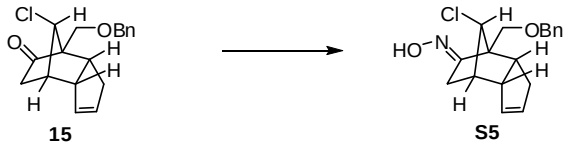
analysis showed complete conversion to the corresponding acyl azide, at which point methanol (70 μL, 1.68 mmol, 4.0 equiv) was added and the solution was heated to 80 ^{o}C. After 1 hour the solvent was reduced *in vacuo* to afford imine **S4** which was used without purification. R_f 0.42 (4:1 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H, $C_6H_5CH_2OCH_2$), 5.76 (dd, 1H, J = 2.1, 5.7 Hz, CH_2CH=CH), 5.45 (dd, 1H, J = 2.3, 5.7 Hz, CH_2CH=C*H*), 4.59 (d, 1H, J = 12.1 Hz, $C_6H_5CH_2OCH_2$), 4.54 (d, 1H, J = 12.1 Hz, $C_6H_5CH_2OCH_2$), 4.40 (t, 1H, J = 2.1 Hz, C*H*Cl), 3.77 (s, 3H, OCH_3), 3.69-3.64 (m, 1H, $C_6H_5CH_2OCH_2$), 3.34-3.30 (m, 1H, $CCH_2CHCHCH$), 3.19 (dt, 1H, J = 4.0, 9.7 Hz, CCH_2CHCH), 2.74 (t, 1H, J = 2.8 Hz, $CCH_2CHCHCH$), 2.62 (dd, 1H, J = 4.6, 18.0 Hz, $CCH_2CHCHCH$), 2.38 (dd, 1H, J = 2.4, 17.9 Hz, $CCH_2CHCHCH$), 2.28-2.24 (m, 2H, CH_2CH=CH); IR (neat film) 3043 (w), 2904 (w), 1733 (s), 1690 (s), 1253 (s) cm^{-1}; LRMS (ESI) m/z for $C_{20}H_{23}O_3ClN$ $(M+H)^+$ 360.06.



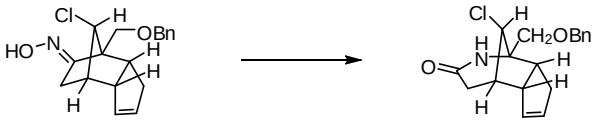
S4 **15**

Ketone 15. To a solution of imine **S4** (151 mg, 0.421 mmol, 1.0 equiv) in methanol (2 mL) at 23 ^{o}C was added concentrated hydrochloric acid (0.6 mL). After 12 hours the solution was diluted with saturated sodium chloride solution (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic layer was dried with sodium sulfate, and reduced *in vacuo.* The residue was purified via silica gel chromatography (4:1 gradient to 1:1 hexane:ethyl acetate) to yield ketone X (114 mg, 90% over two steps) as a clear oil. R_f 0.56 (4:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H, $C_6H_5CH_2OCH_2$), 5.73-5.71 (m, 1H, CH_2CH=CH), 5.52-5.50 (m, 1H, CH_2CH=C*H*), 4.59 (d, 1H, J = 12.1 Hz, $C_6H_5CH_2OCH_2$), 4.53 (d, 1H, J = 12.1 Hz, $C_6H_5CH_2OCH_2$), 4.43 (t, 1H, J = 2.4 Hz, C*H*Cl), 3.67 (d, 1H, J = 10.6 Hz, $C_6H_5CH_2OCH_2$), 3.63 (d, 1H, J = 10.6 Hz, $C_6H_5CH_2OCH_2$), 3.41-3.38 (m, 1H, $CCH_2CHCHCH$), 3.13 (dt, 1H, J = 3.8, 10.3 Hz, CCH_2CHCH), 2.87-2.85 (m, 1H, $CCH_2CHCHCH$), 2.49 (dd, 1H, J = 4.7, 18.2 Hz, $CCH_2CHCHCH$), 2.32 (ddd, 1H, J = 1.7, 10.4, 18.0 Hz, CH_2CH=CH), 2.13 (dd, 1H, J = 2.6, 18.2 Hz, $CCH_2CHCHCH$), 1.99-1.94 (m, 1H, CH_2CH=CH); ^{13}C NMR (125

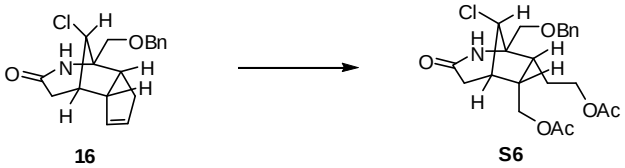
MHz, $CDCl_3$) δ 213.2, 138.5, 133.6, 130.3, 128.6, 127.8, 126.4, 73.8, 67.1, 66.5, 64.5, 52.8, 48.7, 43.1, 38.6, 38.4, 33.3; IR (neat film) 2929 (w), 2856 (w), 1745 (s), 1101 (m), 1070 (m) cm^{-1}; LRMS (ESI) m/z for $C_{18}H_{19}O_2ClNa$ $(M+Na)^+$ 324.87.



Oxime S5. To a solution of ketone **15** (35.1 mg, 0.116 mmol, 1.0 equiv) in ethanol (2 mL) and water (1 mL) was added hydroxylamine hydrochloric salt (80.6 mg, 1.162 mmol, 10 equiv) and pyridine (94 μL, 1.162 mmol, 10 equiv). The resulting mixture was then heated up to reflux for 68 hrs at which point ketone **15** could still be detected by TLC analysis. Another portion of hydroxylamine hydrochloric salt (80.6 mg, 1.162 mmol, 10 equiv) and pyridine (94 μL, 1.162 mmol, 10 equiv) was added the reaction was refluxed for another 68 hrs until the complete consumption of the starting material (by TLC analysis). The solution was diluted with ethyl acetate (30 mL), and washed with water (3 x 10 mL), brine (10 mL) dried (sodium sulfate), filtered, and concentrated *in vacuo* to afford oxime **S5** (33.6 mg, 91%) as highly crystalline white solid. R_f 0.44 (30% ethyl acetate in hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H, $C_6\mathit{H}_6CH_2O$), 7.33-7.26 (m, 1H, $C_6\mathit{H}_6CH_2O$), 5.73 (m, 1H, $CH_2C\mathit{H}$=CH), 5.45 (m, 1H, CH_2CH=C*H*), 4.60 (d, 1H, J = 12.1 Hz, Ph$C\mathit{H}_2O$), 4.54 (d, 1H, J = 12.1 Hz, Ph$C\mathit{H}_2O$), 4.32 (t, 1H, J = 1.9 Hz, C*H*Cl), 3.66 (d, 1H, J = 10.2 Hz, $C_6H_5CH_2OC\mathit{H}_2$), 3.61 (d, 1H, J = 10.3 Hz, $C_6H_5CH_2OC\mathit{H}_2$), 3.31-3.24 (m, 1H, $CCH_2CHC\mathit{H}CH$), 3.08 (dt, 1H, J = 3.6, 10.0 Hz, $CCH_2C\mathit{H}CHCH$), 2.67 (dt, 1H, J = 1.7, 4.6 Hz, $CCH_2CHCHC\mathit{H}$), 2.59 (dd, 1H, J = 4.4, 17.7 Hz, $CC\mathit{H}_2CHCHCH$), 2.37 (dd, 1H, J = 2.2, 17.6 Hz, $C\mathit{H}_2CH$=CH), 2.33-2.23 (m, 1H, $CC\mathit{H}_2CHCHCH$), 2.22-2.13 (m, 1H, $C\mathit{H}_2CH$=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 138.8, 133.5, 130.4, 128.7, 127.92, 127.89, 73.8, 67.6, 65.6, 61.3, 48.9, 43.7, 39.3, 33.4, 28.2; IR (neat film) 3333 (w), 2921 (m), 2856 (m), 1735 (m), 1684 (m). LRMS (ESI) m/z for $C_{18}H_{20}ClNO_2Na$ $(M+Na)^+$ 340.2.

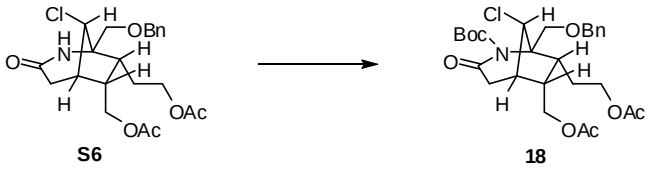


Lactam 16. To a solution of the oxime **S5** (12.6 mg, 0.0397 mmol, 1.0 equiv) in diethyl ether (1.2 mL) was added thionyl chloride (11.6 uL, 0.159 mmol, 4.0 equiv) and the resulting mixture was stirred at 23 ^{o}C for 20 h. The solution was then diluted with ethyl acetate (20 mL), washed with water (3 x 10 mL), brine (10 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo*. The residue was purified via silica gel chromatography (90: 10 gradient to 60:40 hexane:ethyl acetate) to yield the lactam **16** (6.8 mg, 54%) as a yellow solid. R_f = 0.14 (70:30 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H, $C_6H_6CH_2O$), 5.98 (s, 1H, N*H*), 5.80 (m, 1H, CH=C*H*CH_2CH), 5.58 (m, 1H, C*H*=CHCH_2CH), 4.54 (ABq, 2H, J = 12.0 Hz, PhCH_2O), 4.13 (d, 1H, J = 5.0 Hz, C*H*Cl), 3.58 (d, 1H, J = 9.0 Hz, CCH_2O), 3.50 (d, 1H, J = 8.9 Hz, CCH_2O), 3.41 (t, 1H, J = 1.0 Hz, CH=CHC*H*), 2.83 (dt, 1H, J = 3.2, 9.8 Hz, CH=CHCH_2C*H*), 2.75-2.65 (m, 2H, NHCOCH_2C*H*, NHCOCH_2), 2.57-2.45 (m, 2H, CH=CHCH_2), 2.29 (d, 1H, J = 17.9, NHCOCH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 137.8, 134.2, 129.9, 128.9, 128.3, 127.8, 74.0, 72.3, 65.0, 60.5, 50.5, 47.2, 40.4, 33.7, 31.7; IR (neat film) 3200 (br), 3062 (w), 2946 (w), 2860 (w), 1670 (s); LRMS (ESI) m/z for $C_{18}H_{21}ClNO_2$ $(M+H)^+$ 318.0



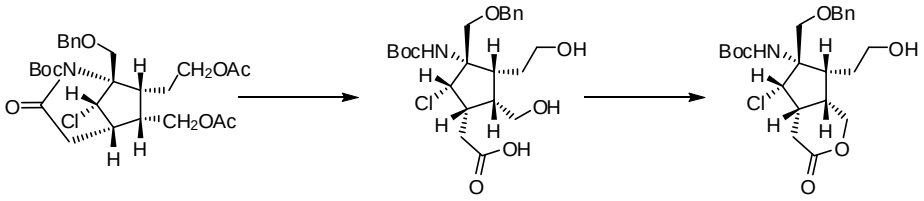
Diacetate S6. To a solution of the alkene **16** (18.1 mg, 0.0571 mmol, 1.0 equiv) in methanol (1.5 mL) and dichloromethane (1.5 mL) at -78 ºC was bubbled O_3 for 10 min, then argon was bubbled through for 3 minutes. After the cooling bath was removed sodium borohydride (10.8 mg, 5 equiv) was added. The solution warmed to 23 ^{o}C and stirred for 1 hr when the solution was quenched with a saturated Rochelle's salt solution

(2 mL), and stirred for 25 min. The mixture was then extracted with ethyl acetate (3 x 2 mL), and dichloromethane (3 x 2 mL). The organic layers were combined, dried (sodium sulfate), and concentrated *in vacuo*. The residue was then diluted with pyridine (2 mL) followed by addition of acetic anhydride (54 uL, 10 equiv) and stirred at 23 ^{o}C for 12 h. The solvent was then concentrated *in vacuo*, and the residue was purified via silica gel chromatography (80: 20 gradient to 30:70 hexane:ethyl acetate) to yield the diacetate **S6** (19.1 mg, 77%) as a white solid. R_f = 0.29 (50:50 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, $C_6H_6CH_2O$), 6.42 (s, 1H, N*H*), 4.54 (ABq, 2H, J = 11.8, PhCH_2O), 4.40 (dd, 1H, J = 5.7, 11.4 Hz, CHCH_2OAc), 4.24 (d, 1H, J = 4.0 Hz, C*H*Cl), 4.12-3.96 (m, 2H, CH_2CH_2OAc), 4.00 (dd, 1H, J = 9.2, 11.3 Hz, CHCH_2OAc), 3.53 (d, 1H, J = 9.4 Hz, $C_6H_5CH_2OCH_2$), 3.45 (d, 1H, J = 9.4 Hz, $C_6H_5CH_2OCH_2$), 2.83 (dd, 1H, J = 4.5, 17.6 Hz, CH_2CONH, 2.70-2.61 (m, 2H, C*H*CH_2OAc, CHClC*H*), 2.48-2.41 (m, 1H, C*H*CH_2CH_2OAc), 2.36 (d, 1H, J = 18.8, CH_2CONH), 2.05 (s, 3H, O_2CCH_3), 2.01 (s, 3H, O_2CCH_3), 1.89-1.81 (m, 1H, CH_2CH_2OAc), 1.74-1.67 (m, 1H, CH_2CH_2OAc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.0, 169.9, 136.7, 128.1, 127.6, 127.2, 73.3, 67.9, 65.4, 62.9, 61.8, 59.0, 40.6, 39.4, 37.0, 30.0, 24.1, 20.41, 20.38; IR (neat film) 3199 (w), 3089 (w), 3070 (w), 2955 (w), 1741 (s), 1674 (s), 1237 (s). LRMS (ESI) m/z for $C_{22}H_{28}ClNO_6Na$ $(M+Na)^+$ 460.04.



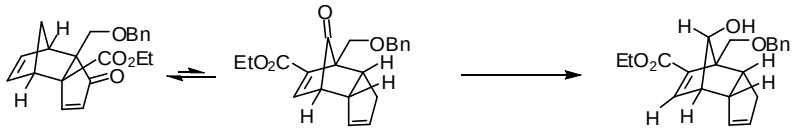
Imide 18. To a solution of lactam **S6** (19.1 mg, 0.0437 mmol, 1.0 equiv) in tetrahydrofuran (1.5 mL) was added di-*tert*-butyl carbonate (28.3 mg, 0.131. mmol, 3 equiv) and 4-dimethylamino pyridine (1 mg, 0.00874 mmol, 0.2 equiv). The resulting mixture was stirred at 23 ^{o}C for 1 h and then heated up to reflux for 30 minutes, at which point another portion of 4-dimethylamino pyridine (1 mg, 0.00874 mmol, 0.2 equiv) was added and heating was continued at reflux for 16 hr. The solvent was then removed *in vacuo*, and the residue was purified via silica gel chromatography (95:5 gradient to 70:30 hexane:ethyl acetate) to yield the imide **18** (24.0 mg, 99%) as yellow oil. R_f = 0.13

(70:30 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H, $C_6H_6CH_2O$), 7.32-7.28 (m, 3H, $C_6H_6CH_2O$), 4.56 (ABq, 2H, J= 11.8, PhCH_2O), 4.47 (d, 1H, J = 4.3 Hz, C*H*Cl), 4.40 (dd, 1H, J = 4.1, 11.0 Hz, CHCH_2OAc), 4.15-4.05 (m, 2H, CH_2CH_2OAc), 4.04-3.98 (m, 1H, CHCH_2OAc), 3.64 (d, 1H, J = 9.3 Hz, $C_6H_5CH_2OCH_2$), 3.57 (d, 1H, J = 9.3 Hz, $C_6H_5CH_2OCH_2$), 2.94 (dd, 1H, J = 4.7, 18.6 Hz, CH_2CONBoc), 2.63 (m, 3H, C*H*CH_2OAc, CHClC*H*, C*H*CH_2CH_2OAc), 2,43 (d, 1H, J = 18.7, CH_2CONBoc), 2.19-2.10 (m, 1H, CH_2CH_2OAc), 2.04 (s, 3H, O_2CCH_3), 2.01 (s, 3H, O_2CCH_3), 1.79-1.71 (m, 1H, CH_2CH_2OAc), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 170.9, 169.0, 152.5, 137.6, 128.8, 128.4, 128.0, 84.8, 74.0, 71.8, 66.1, 63.8, 62.5, 59.6, 40.0, 39.9, 37.9, 31.5, 27.7, 25.3, 21.22, 21.18; IR (neat film) 2980 (w), 2935 (w), 2874 (w), 1741 (s), 1680 (m), 1243 (s); LRMS (ESI) m/z for $C_{27}H_{36}ClNO_8Na$ $(M+Na)^+$ 560.10.



Lactone 19. To a solution of diacetate **18** (12.3 mg, 0.0229 mmol, 1.0 equiv) in methanol (1.3 mL) and water (0.6 mL) was added potassium carbonate (79.0 mg, 0.573 mmol, 25 equiv). The resulting mixture was stirred at 23 ^{o}C for 14 h, at which point the diacetate was completely consumed (by TLC analysis). The solution was then diluted with ethyl acetate (30 mL), water (5 mL) and hydrochloric acid (4.4 mL, 2 N). After partitioning, the organic layer was washed with water (10 mL), brine (10 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo* to yield the carboxylic acid **S7** (11.4 mg). Crude acid **S7** was dissolved in dichloromethane (2 mL) and *p*-toluenesulfonic acid monohydrate (1.0 mg, 0.00458 mmol, 0.2 equiv) was added. The resulting mixture was stirred at 23 ^{o}C for 3 hrs until the starting material was consumed (by TLC analysis). Potassium carbonate (6.3 mg, 0.0458 mmol, 2 equiv) was then added, and the reaction was stirred for 40 min, at which point it was diluted with ethyl acetate (25 mL) and water

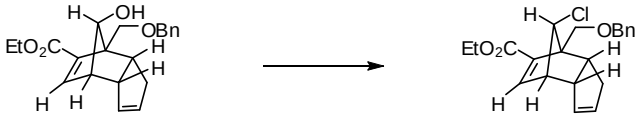
(5 mL). After partitioning, the organic layer was washed with water (10 mL), brine (10 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo*. The residue was purified via silica gel chromatography (95:5 gradient to 30:70 hexane:ethyl acetate) to yield the lactone **19** (10.0 mg, 96%) as a clear oil. R_f = 0.45 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H, $C_6H_6CH_2O$), 7.33-7.26 (m, 3H, $C_6H_6CH_2O$), 4.96 (s, 1H, N*H*Boc), 4.75 (d, 1H, J = 8.4 Hz, C*H*Cl), 4.54 (s, 2H, PhCH_2O), 4.42-4.33 (m, 2H, CH_2O_2C), 4.01 (d, 1H, J = 7.1 Hz, $C_6H_5CH_2OCH_2$), 3.79-3.73 (m, 1H, CH_2OH), 3.67-3.61 (m, 2H, $C_6H_5CH_2OCH_2$, CH_2OH), 2.85-2.77 (m, 1H, CHClC*H*), 2.86-2.67 (m, 1H, CHClCHCH_2), 2.67-2.58 (m, 2H, CHClCHCH_2, CHClCC*H*), 2.08-2.01 (m, 1H, CH_2CH$_2$OH), 1.79 (dd, 1H, J = 4.8, 5.8 Hz, CH$_2$O*H*), 1.72-1.64 (m, 1H, CH_2CH$_2$OH), 1.42 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 Hz, $CDCl_3$) δ 173.0, 155.3, 137.9, 128.9, 128.4, 128.1, 80.8, 73.8, 68.0, 67.6, 67.4, 65.2, 62.1, 40.1, 38.8, 36.3, 31.8, 29.6, 28.6; IR (neat film) 3404 (br), 3209 (w), 2975 (w), 2871 (w), 1733 (s), 1495 (s); LRMS (ESI) m/z for $C_{23}H_{32}ClNO_6Na$ $(M+Na)^+$ 476.1.



10 **11** **20**

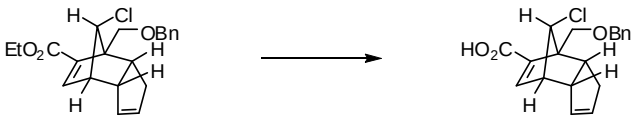
4-Benzyloxymethyl-8-hydroxy-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid ethyl ester 20. To a solution of ketone **10** (207 mg, 0.612 mmol, 1.0 equiv) in *iso*-propyl alcohol (1.2 mL) was added aluminum *iso*-propoxide (250 mg, 1.27 mmol, 2 equiv) and heated up to 90 ^{o}C. After heating for 5 hours the reaction was cooled and quenched with hydrochloric acid (25 mL, 1N). The solution was extracted with dichloromethane (3 x 25 mL) and the combined organic layers were then dried (sodium sulfate), filtered, and concentrated *in vacuo* to afford alcohol **20** (214 mg) as yellow oil which was of high purity (>95%) and could be used directly in the following step. R_f 0.49 (20% ethyl acetate in benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, $C_6H_6CH_2O$), 6.80 (d, 1H, J = 4.0 Hz, C=C*H*CHCH), 5.50 (m, 2H, C*H*=C*H*CH$_2$CH), 4.48 (q, 2H, J = 12.0 Hz, PhCH_2O), 4.20 (d, 1H, J = 9.5 Hz, CCH_2O), 4.15 (d, 1H, J = 10.0 Hz, CCH_2O), 4.13 (m, 2H, CH$_3$CH_2O), 3.85 (br s, 1H, C*H*OH), 3.74 (m, 1H,

C=CHCHC*H*), 3.25 (d, 1H, J = 1.5 Hz, CHO*H*), 3.16 (m, 1H, CH=CHCH$_2$C*H*), 2.90 (m, 1H, C=CHC*H*CH), 2.25 (m, 1H, CH=CHC*H*$_2$CH), 1.90 (m, 1H, CH=CHC*H*$_2$CH), 1.25 (t, 3H, J = 7.0 Hz, C*H*$_3$CH$_2$O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 146.5, 138.2, 135.7, 132.9, 130.2, 128.6, 127.8, 127.7, 87.6, 73.8, 60.2, 59.6, 54.0, 50.0, 39.1, 32.6, 14.3; IR (neat film) 3323 (w), 2930 (w), 1709 (s), 1235 (m), 1099 (s), 737 (m) cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{25}O_4$ $(M+1)^+$ 341.1753, observed 341.1763.

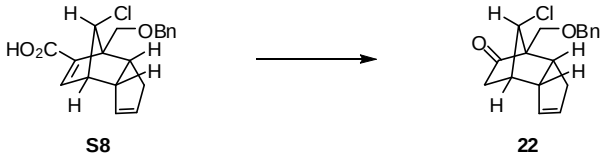


20 **21**

4-Benzyloxymethyl-8'-chloro-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid ethyl ester 21. To a solution of alcohol **20** (214 mg, 0.612 mmol, 1.0 equiv) in dichloromethane (20.0 mL) at was added thionyl chloride (140 μL, 1.2 mmol, 2.0 equiv) and the solution was heated up to 60 ^{o}C. After stirring for 24 hours the solvent was removed *in vacuo* to afford pure chloride **21** as a yellow solid (213 mg, 97% over two steps). R_f 0.47 (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H, C$_6$*H*$_5$CH$_2$OCH$_2$), 6.81 (d, 1H, J = 3.5 Hz, C=C*H*CHCHCH), 5.51 (dq, 1H, J = 2.0, 6.0 Hz, CH$_2$C*H*=CH), 5.47 (dq, 1H, J = 2.0, 5.5 Hz, CH$_2$CH=C*H*), 4.59 (d, 1H, J = 12.5 Hz, C$_6$H$_5$C*H*$_2$OCH$_2$), 4.51 (d, 1H, J = 12.0 Hz, C$_6$H$_5$C*H*$_2$OCH$_2$), 4.17 (m, 4H, C$_6$H$_5$CH$_2$OC*H*$_2$, OC*H*$_2$CH$_3$, C*H*Cl), 3.79 (m, 1H, C=CHCHC*H*CH), 3.66 (dd, 1H, J = 1.0, 9.5 Hz, C$_6$H$_5$CH$_2$OC*H*$_2$), 3.05 (m, 1H, C=CHC*H*CHCH), 2.78 (m, 1H, C=CHCHCHC*H*), 2.20 (ddq, 1H, J = 2.0, 10.0, 17.5 Hz, C*H*$_2$CH=CH), 2.23 (m, 1H, C*H*$_2$CH=CH), 1.26 (t, 3H, J = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 164.4, 144.7, 139.1, 137.6, 128.2, 73.4, 71.6, 66.6, 62.9, 60.0, 53.7, 50.3, 39.9, 32.4, 14.0; IR (neat film) 2917 (w), 2852 (w), 1713 (s), 1454 (w), 1272 (s), 1111 (s) cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{24}O_3Cl$ $(M+H)^+$ 359.1424, observed 359.1414.

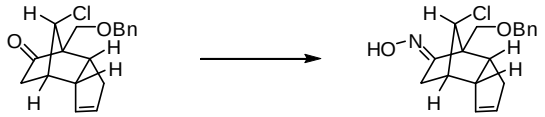


4-Benzyloxymethyl-8'-chloro-3a,4,7,7a-tetrahydro-3H-4,7-methano-indene-5-carboxylic acid S8. To a solution of chloride **21** (905 mg, 2.53 mmol, 1.0 equiv) in ethanol (12 mL, 190 proof) at 23 ^{o}C was added sodium hydroxide (12 mL, 30 wt % in water, 1:1 volume ratio). The brown solution formed a white precipitate that slowly dissolved over time. After 43 hours the reaction was diluted with ethyl acetate (80 mL), then hydrochloric acid (100 mL, 1.0 N), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 80 mL), and then the organic layers were combined, dried with sodium sulfate, and reduced *in vacuo* to afford pure carboxylic acid X (820 mg, 98%) as an orange crystal. R_f 0.49 (1:1 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.30 (m, 5H, $C_6H_6CH_2O$), 7.04 (d, 1H, J = 3.7 Hz, C=C*H*CHCH), 5.52 (m, 1H, CH=C*H*CH_2CH), 5.49 (m, 1H, C*H*=CHCH_2CH), 4.61 (d, 1H, J = 12.0 Hz, PhC*H*$_2$O), 4.54 (d, 1H, J = 12.0 Hz, PhC*H*$_2$O), 4.18 (d, 1H, J = 9.5 Hz, CC*H*$_2$O), 4.10 (d, 1H, J = 1.0 Hz, C*H*Cl), 3.82-3.80 (m, 1H, C=CHCHC*H*), 3.68 (d, 1H, J = 9.5 Hz, CC*H*$_2$O), 3.09 (dt, 1H, J = 1.7, 4.1 Hz, C=CHC*H*CH), 2.83-2.79 (m, 1H, CH=CHCH_2C*H*), 2.23 (ddd, 1H, J = 1.7, 10.3, 18.0 Hz, CH=CHC*H*$_2$CH), 1.98 (dd, 1H, J = 1.9, 18.0 Hz, CH=CHC*H*$_2$CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 149.0, 138.2, 136.6, 133.8, 129.2, 128.5, 127.8, 127.7, 73.7, 71.4, 66.8, 62.3, 53.8, 50.6, 40.2, 32.8; IR (neat film) 3088 (br), 2560 (w), 2859 (m), 1688 (s), 1593 (m), 1454 (m), 1277 (s), 1114 (s); LRMS (ESI) m/z for $C_{19}H_{18}ClO_3$ $(M-H)^-$ 328.85, $C_{19}H_{19}ClO_3Na$ $(M+Na)^+$ 352.86.



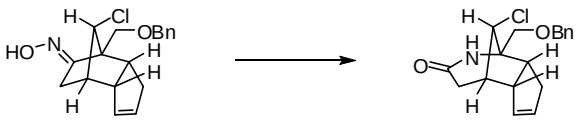
Ketone 22. To a solution of acid **S8** (25.6 mg, 0.78 mmol, 1.0 equiv) in toluene (2.0 mL) at 23 ^{o}C was added triethylamine (22 μL, 0.156 mmol, 2 equiv) and

diphenylphosphorylazide (17 μL, 0.082 mmol, 1.05 equiv). After 15 minutes ethanol (35 μL, 0.624 mmol, 8 equiv, dried under 4A mol sieves) was added and the solution was heated up to 80 ^{o}C. After 70 minutes the solvent was concentrated *in vacuo* and the residue was found to be a 2:1 mixture of enamine:imine by NMR analysis. The residue was then diluted with ethanol (1.0 mL) at 23 ^{o}C and concentrated hydrochloric acid (0.5 mL) was added, at which point a white precipitate formed. After 30 minutes the reaction was diluted with saturated sodium chloride (25 mL), extracted with dichloromethane (3 x 25 mL), dried with sodium sulfate, and reduced *in vacuo.* The residue was purified via silica gel chromatography (8:1 hexanes:ethyl acetate) to yield ketone X (22.2 mg, 94%) as a clear oil. R_f 0.69 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H, $C_6H_6CH_2O$), 5.63 (dq, 1H, J = 2.1, 6.1 Hz, CH=C*H*CH_2CH), 5.52 (dq, 1H, J = 2.3, 5.7 Hz, C*H*=CHCH_2CH), 4.60 (d, 1H, J = 12.3 Hz, PhCH_2O), 4.53-4.50 (m, 2H, PhCH_2O, C*H*Cl), 3.80-3.76 (m, 2H, CCH_2O, CH_2CHC*H*), 3.46 (d, 1H, J = 9.8 Hz, CCH_2O), 2.94 (dt, 1H, J = 3.3, 10.1 Hz, CH=CHCH_2C*H*), 2.82 (t, 1H, J = 4.53 Hz, CH_2C*H*CH), 2.34 (d, 1H, J = 18.2 Hz, CH_2CHCH), 2.23 (ddq, 1H, J = 2.1, 10.3, 18.0 Hz, CH=CHCH_2CH), 2.07 (dd, 1H, J = 4.4, 18.2 Hz, CH_2CHCH), 1.95 (dq, 1H, J = 2.4, 18.0 Hz, CH=CHCH_2CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 138.6, 133.3, 130.4, 128.6, 127.9, 127.8, 73.9, 68.7, 67.4, 65.5, 51.2, 43.1, 42.2, 41.1, 31.7; IR (neat film) 3049 (w), 2973 (m), 2912 (w), 2859 (w), 1751 (s), 1102 (s) cm^{-1}; LRMS (ESI) m/z for $C_{18}H_{19}ClO_2Na$ $(M+Na)^+$ 324.97.



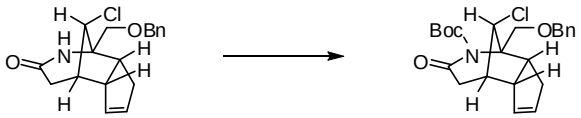
Oxime S9. To a solution of ketone **22** (1.69 g, 5.6 mmol, 1.0 equiv) in ethanol (37 mL) and water (19 mL) was added pyridine (4.5 mL, 56 mmol, 10 equiv) and hydroxylamine hydrochloride (3.89 g, 56 mmol, 10 equiv) and heated up to 95 ^{o}C. After 27 hours the reaction was diluted with ethyl acetate (150 mL), then saturated sodium chloride (100 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL) and then the combined organic layers were washed with water (5 x 100 mL),

dried with sodium sulfate, and reduced *in vacuo* to afford to yield pure oxime **S9** (1.72 g, 96%) as a white crystal. R_f 0.23 (4:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.28 (m, 5H, $C_6H_6CH_2O$), 6.91 (s, 1H, NO*H*), 5.66 (dq, 1H, J = 2.1, 5.2 Hz, CH=C*H*CH_2CH), 5.47 (dq, 1H, J = 2.3, 5.7 Hz, C*H*=CHCH_2CH), 4.64 (d, 1H, J = 12.5 Hz, PhC*H*$_2$O), 4.55 (d, 1H, J = 12.5 Hz, PhC*H*$_2$O), 4.34 (d, 1H, J = 1.1 Hz, C*H*Cl), 3.73 (d, 1H, J = 10.0 Hz, CC*H*$_2$O), 3.69-3.67 (m, 1H, CH_2CHC*H*), 3.56 (d, 1H, J = 10.0 Hz, CC*H*$_2$O), 2.90 (dt, 1H, J = 3.9, 9.7 Hz, CH=CHCH_2C*H*), 2.61 (t, 1H, J = 4.2 Hz, CH_2C*H*CH), 2.51 (d, 1H, J = 17.9 Hz, C*H*$_2$CHCH), 2.23-2.17 (m, 3H, CH=CHC*H*$_2$CH, C*H*$_2$CHCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.8, 133.2, 130.3, 128.6, 128.0, 127.8, 73.9, 69.5, 66.8, 60.6, 51.4, 43.0, 42.0, 32.1, 29.6; IR (neat film) 3274 (br), 3048 (w), 2913 (w), 1452 (s), 1100 (s) cm^{-1}; LRMS (ESI) m/z calcd for $C_{18}H_{21}ClNO_2$ $(M+H)^+$ 317.98, $C_{18}H_{20}ClNO_2Na$ $(M+Na)^+$ 339.90.

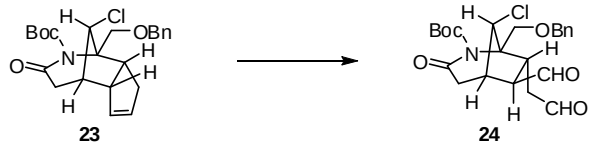


Lactam S10. To a solution of oxime **S9** (1.65 g, 5.2 mmol, 1.0 equiv) in diethyl ether (260 mL) at 23 ^{o}C was added thionyl chloride (6.0 mL, 52 mmol, 10 equiv). The solution turned yellow and a white precipitate formed. After 15 hours the reaction was diluted with diethyl ether (200 mL), and then poured into a solution of saturated sodium chloride (300 mL) and ice (100 mL). After partitioning of the layers, the aqueous layer was extracted with ethyl acetate (2 x 250 mL) and the combined organic layers were dried with sodium sulfate and concentrated *in vacuo.* The residue was purified via silica gel chromatography (2:1 to 1:2 hexanes:ethyl acetate) to afford to yield lactam **S10** (0.98 g, 59%) as a white solid. R_f 0.11 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H, $C_6H_6CH_2O$), 6.06 (s, 1H, N*H*), 5.76 (dd, 1H, J = 2.1, 5.6 Hz, CH=C*H*CH_2CH), 5.60 (dd, 1H, J = 2.3, 5.7 Hz, C*H*=CHCH_2CH), 4.54 (s, 2H, PhC*H*$_2$O), 4.34 (s, 1H, C*H*Cl), 3.82-3.78 (m, 1H, CH_2CHC*H*), 3.69 (d, 1H, J = 9.5 Hz, CC*H*$_2$O), 3.61 (d, 1H, J = 9.5 Hz, CC*H*$_2$O), 3.11 (dt, 1H, J = 7.2, 9.9 Hz, CH=CHCH_2C*H*), 2.73-2.71 (m, 1H, CH_2C*H*CH), 2.46-2.44 (m, 4H, CH=CHC*H*$_2$CH, C*H*$_2$CHCH); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 170.0, 137.4, 133.4, 129.8, 128.5, 128.0, 127.6, 73.6, 72.1, 68.5, 66.8, 52.7, 47.2, 43.3, 35.9, 32.0; IR (neat film) 3198 (w), 3066 (w), 2942 (w), 1669 (s), 1454 (w), 1106 (m), 696 (m) cm^{-1}; LRMS (ESI) m/z calcd for $C_{18}H_{21}ClNO_2$ $(M+H)^+$ 317.94.

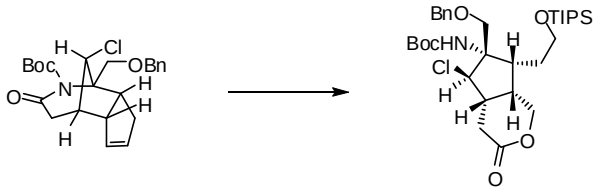


Imide 23. To a solution of lactam **S10** (0.85 g, 2.9 mmol, 1.0 equiv) in tetrahydrofuran (24 mL) was added di-*tert*-butyl carbonate (1.8 g, 8.0 mmol, 3 equiv), triethylamine (2.2 mL, 16.1 mmol, 6 equiv), and 4-dimethylamino pyridine (82 mg, 0.67 mmol, 0.25 equiv) and heated up to 90 ^oC. After 15 hours the reaction was diluted with ethyl acetate (250 mL), washed with hydrochloric acid (1.0 N, 3 x 100 mL), water (100 mL), and then saturated sodium chloride (100 mL). The organic layer was dried with sodium sulfate, reduced *in vacuo*, and purified via silica gel chromatography (4:1 gradient to 2:1 hexanes:ethyl acetate) to yield imide **23** (0.98 g, 94%) as a yellow film. R_f 0.72 (2:1 ethyl acetate:hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.18 (m, 5H, $C_6H_6CH_2O$), 5.69 (dd, 1H, J = 2.1, 5.7 Hz, CH=C*H*CH_2CH), 5,.48 (dd, 1H, J = 2.3, 5.7 Hz, C*H*=CHCH_2CH), 4.65 (s, 1H, C*H*Cl) 4.54 (d, 1H, J = 12.4 Hz, PhCH_2O), 4.30 (d, 1H, J = 12.3 Hz, PhCH_2O), 3.93 (d, 1H, J = 10.3 Hz, CCH_2O), 3.77 (d, 1H, J = 10.3 Hz, CCH_2O), 3.68-3.65 (m, 1H, CH_2CHC*H*), 2.85-2.75 (m, 2H, CH=CHCH_2C*H*), 2.67 (t, 1H, J = 4.7 Hz, CH_2C*H*CH), 2.55 (dd, 1H, J = 4.8, 17.4 Hz, CH_2CHCH), 2.37 (m, 2H, CH=CHCH_2CH, CH_2CHCH), 1.36 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 153.6, 137.8, 134.1, 129.2, 128.8, 128.4, 127.7, 127.4, 83.6, 74.8, 72.9, 69.2, 68.5, 52.9, 45.9, 43.6, 37.7, 32.1, 27.7; IR (neat film) 2980 (m), 2934 (m), 1734 (s), 1699 (s), 1454 (w), 1256 (s), 1157 (s), 1136 (m) cm^{-1}; LRMS (ESI) m/z calcd for $C_{23}H_{28}ClNO_4Na$ $(M+Na)^+$ 439.92.



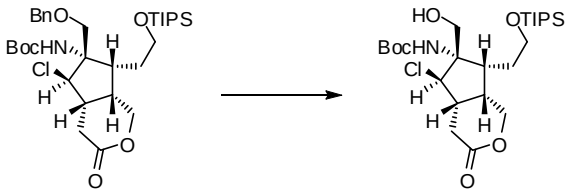
23 **24**

Dialdehyde 24. To a solution of alkene **23** (33 mg, 0.08 mmol, 1.0 equiv) in tetrahydrofuran (0.75 mL) and water (0.25 mL) at 23 ^{o}C was added osmium tetraoxide (2 mg, 0.008 mmol, 0.1 equiv), sodium periodate (71 mg, 0.4 mmol, 5 equiv), and 2,6-lutidine (25 μL, 0.16 mmol, 2 equiv). After 13 hours the reaction was diluted with saturated sodium thiosulfate (10 mL), and then extracted with ethyl acetate (3 x 10 mL). The organic layer was dried with sodium sulfate and concentrated *in vacuo* to afford a mixture aldehydes and hemiacetals. This residue was dissolved in ethyl acetate (14 mL) at 23 ^{o}C and triethylamine (1 mL) and silica gel (337 mg, 3:1 ratio Et_3N mL:SiO_2 g) were added. After 2 hours the solution was filtered though a plug of silica gel and purified twice via silica gel chromatography (8:1 hexanes:ethyl acetate with 5% triethylamine) to yield dialdehyde **24** (31 mg, 86%) as a white solid. R_f 0.41 (1:1 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H, C*H*O), 9.80 (s, 1H, C*H*O), 7.36-7.28 (m, 5H, $C_6H_6CH_2O$), 4.62 (s, 1H, C*H*Cl), 4.59 (d, 1H, J = 12.1 Hz, PhCH_2O), 4.39 (d, 1H, J = 12.1 Hz, PhCH_2O), 3.95 (d, 1H, J = 10.5 Hz, CCH_2O), 3.88 (d, 1H, J = 10.5 Hz, CCH_2O), 3.34 (dd, 1H, J = 5.3, 19.1 Hz, CH_2CHCH), 3.11 (dt, 1H, , J = 6.1, 8.6 Hz, CH_2C*H*CH), 3.00 (br s, 1H, C*H*CH_2CHO), 2.96 (dd, 1H, J = 4.8, 17.6 Hz, CHCH_2CHO), 2.67 (dd, 1H, J = 8.7, 19.1 Hz, CH_2CHCH), 2.56 (dd, 1H, J = 2.2, 17.6 Hz, CHCH_2CHO), 2.23 (d, 1H, J = 6.3 Hz, CH_2CHC*H*), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR δ (125 MHz, $CDCl_3$) δ 201.2, 200.4, 168.7, 137.4, 128.5, 128.0, 127.5, 84.5, 75.1, 73.2, 67.6, 66.0, 61.7, 46.1, 44.6, 42.0, 39.2, 27.9; IR (neat film) 2925 (m), 2853 (m), 2728 (w), 1732 (s), 1698 (s), 1368 (w), 1251 (m), 1143 (s). LRMS (ESI) m/z for $C_{23}H_{27}ClNO_6$ $(M-H)^-$ 448.19.



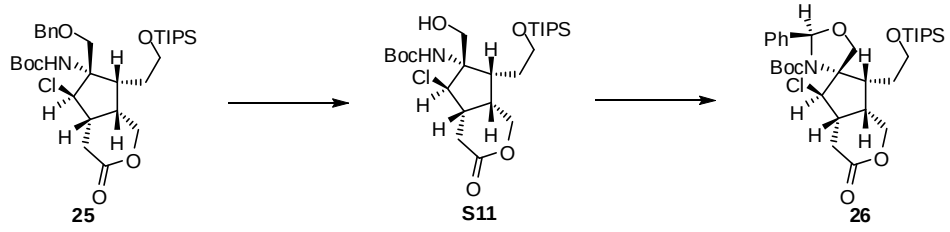
23 **25**

Lactone 25. To a solution of the alkene **23** (90.8 mg, 0.218 mmol, 1.0 equiv) in methanol (4.0 mL) and dichloromethane (4.0 mL) at -78 ºC was bubbled O_3 for 10 minutes until the blue color persisted, then argon was bubbled through for 3 mins. After the cooling bath was removed, sodium borohydride (41.2 mg, 1.090 mmol, 5 equiv) was added. The solution was warmed to 23 ^{o}C and stirring was continued for 50 minutes until the consumption of starting material by TLC. The solution was then quenched with a saturated Rochelle's salt solution (2 mL) and stirred at 23 ^{o}C for another 20 minutes. The mixture was then extracted with dichloromethane (3 x 2 mL) and the organic layers were combined, dried (sodium sulfate), and concentrated *in vacuo*. The resulting residue was then dissolved in dichloromethane (3 mL) at 23 ^{o}C followed by addition of *p*-toluenesulfonic acid monohydrate (4.1 mg, 0.0218 mmol, 0.1 equiv). The resulting mixture was stirred for 3 hrs until the consumption of starting material indicated by TLC (1:1 ethyl acetate:hexane). To this mixture was then added tri-*iso*propylsilyl chloride (93.3 uL, 0.436 mmol, 2 equiv) and imidazole (56.7 mg, 0.872 mmol, 4 equiv). The resulting mixture was stirred at 23 ^{o}C for 21 hrs, at which point it was diluted with ethyl acetate (50 mL), washed with water (20 mL), brine (20 mL), dried (sodium sulfate), filtered, and concentrated *in vacuo*. The residue was purified via silica gel chromatography (95:5 gradient to 80:20 hexane:ethyl acetate) to yield the lactone **25** (121.1 mg, 91%) as clear oil. R_f = 0.71 (50:50 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H, $C_6H_6CH_2O$), 5.16 (d, 1H, J = 3.5 Hz, C*H*Cl), 4.71 (s, 1H, N*H*Boc), 4.50 (ABq, 2H, J = 12.0, PhCH_2O), 4.54-4.47 (m, 1H, CO_2CH_2) 4.34 (dd, 1H, J = 5.4 11.6 Hz, CO_2CH_2), 3.91 (d, 1H, J = 9.3 Hz, $C_6H_5CH_2OCH_2$), 3.78-3.73 (m, 2H, CH_2OSi), 3.54 (d, 1H, J = 9.2 Hz, $C_6H_5CH_2OCH_2$), 2.83-2.78 (m, 2H, CH_2CO_2, C*H*CH_2CH_2OSi), 2.76-2.70 (m, 2H, CHClC*H*C*H*), 2.56 (dd, 1H, J = 7.0, 15.8 Hz, $CH_2CO_2CH_2$), 2.01-1.95 (m, 1H, CH_2CH_2OSi), 1.56-1.50 (m, 1H, CH_2CH_2OSi), 1.42 (s, 9H, $C(CH_3)_3$), 1.09-1.03 (m, 21H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.7, 138.1, 128.7, 128.0, 127.8, 80.5, 73.8, 73.6, 68.0, 66.9, 66.8, 63.0, 44.9, 43.2, 38.0, 33.5, 28.5, 28.4, 18.3, 12.1; IR (neat film) 3030 (m), 2891 (m), 1749 (m), 1714(m), 1497 (m), 1249 (m), 1165 (m), 1101 (m); LRMS (ESI) m/z for $C_{32}H_{53}ClNO_6$ $(M+H)^+$ 610.2.



25 **S11**

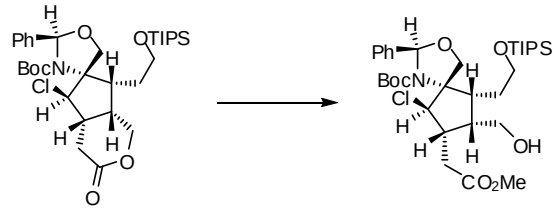
Alcohol S11. To a solution of the benzyl ether **25** (17.1 mg, 0.0281 mmol, 1.0 equiv) in tetrahydrofuran (1.0 mL) was added $Pd(OH)_2/C$ (11.8 mg, 0.00842 mmol, 0.3 equiv) and charged with a 1 atm hydrogen atmosphere via balloon. The resulting mixture was stirred at 23 ^oC for 14 h. The mixture was then filtered through a pad of celite and the solvent was concentrated *in vacuo*. The residue was purified via silica gel chromatography (90:10 gradient to 60:40 hexane:ethyl acetate) to yield the alcohol **S11** (13.1 mg, 90%) as clear oil. R_f = 0.13 (80:20 hexane:ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H, N*H*Boc), 4.87 (d, 1H, J = 7.5 Hz, C*H*Cl), 4.63 (dd, 1H, J = 9.0, 11.8 Hz, CO_2CH_2), 4.31 (dd, 1H, J = 5.0, 11.6 Hz, CO_2CH_2), 3.91 (dd, 1H, J = 6.2, 11.9Hz, CH_2OH), 3.78-3.72 (m, 2H, CH_2OSi), 3.64 (dd, 1H, J = 7.2, 11.9 Hz, CH_2OH), 3.19 (t, 1H, J = 6.7 Hz, OH), 2.84 (dd, 1H, J = 7.9, 16.6 Hz, CH_2CO_2), 2.77-2.72 (m, 1H, $CHCH_2CH_2OSi$), 2.72-2.66 (2H, m, $CHClCHCH$), 2.55 (dd, 1H, J = 5.4, 16.5 Hz, CH_2CO_2), 1.75-1.62 (m, 2H, CH_2CH_2OSi), 1.43 (s, 9H, $C(CH_3)_3$), 1.30-1.02 (m, 21H, $Si(CH(CH_3)_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 156.2, 81.0, 68.2, 67.9, 67.8, 67.0, 42.2, 42.0, 38.1, 32.7, 29.0, 28.6, 18.3, 12.2; IR (neat film) 3421 (br), 2942 (m), 2866 (m), 1741 (m), 1709 (m), 1505 (m), 1463 (m), 1251 (m), 1165(m); LRMS (ESI) m/z for $C_{25}H_{47}ClNO_6Si$ $(M+H)^+$ 520.3.



25 **S11** **26**

Lactone 26 (from 25 without purification of S11). To a solution of the benzyl ether **25** (713.8 mg, 1.172 mmol, 1.0 equiv) in tetrahydrofuran (40.0 mL) was added $Pd(OH)_2/C$ (160.0 mg, 1.139 mmol, 0.1 equiv) and charged with a 1 atm hydrogen atmosphere via balloon. The resulting mixture was stirred at 23 ^oC for 13 h. The mixture was then

filtered through a pad of celite and the solvent was concentrated *in vacuo*. The crude benzyl alcohol **S11** was dissolved in toluene (46.0 mL) and followed by addition of benzaldehyde dimethyl acetal (211 uL, 1.406 mmol, 1.2 equiv) and *p*-toluenesulfonic acid monohydrate (22.3 mg, 0.1172 mmol, 0.1 equiv). The resulting mixture was stirred at 23 ^{o}C for 3 hrs, and another portion of benzaldehyde dimethyl acetal (106 uL, 0.703 mmol, 0.6 equiv) was added. The resulting mixture was stirred for another 16 hrs and the solvent was removed *in vacuo.* The residue was purified via silica gel chromatography (95:5 gradient to 80:20 hexane:ethyl acetate) to yield the lactone **26** (438.5 mg, 62%) as white foam. R_f = 0.21 (80:20 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H, C_6H_5), 7.38-7.35 (m, 3H, C_6H_5), 5.74 (s, 1H, C_6H_5CH), 5.39 (d, 1H, J = 11.4 Hz, C*H*Cl), 4.82 (t, 1H, J = 11.5 Hz, PhCHOCH_2), 4.54 (d, 1H, J = 9.2 Hz, CO_2CH_2), 4.32 (dd, 1H, J = 3.9, 11.7 Hz, PhCHOCH_2), 3.80-3.74 (m, 2H, CH_2OSi), 3.65 (d, 1H, J = 9.2 Hz, CO_2CH_2), 2.96 (dd, 1H, J = 8.6, 17.2 Hz, C$H_2CO_2CH_2$), 2.62 (dd, 1H, J = 5.8, 8.9 Hz, CH_2CO_2), 2.62-2.50 (m, 2H, C*H*C*H*CH_2CH_2OSi), 2.47-2.42 (m, 1H, CHClC*H*), 1.77-1.72 (m, 2H, CH_2CH_2OSi), 1.43 (m, 30H, C(CH_3)$_3$), Si(C*H*(CH_3)$_2$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 152.9, 139.5, 129.4, 128.6, 127.6, 92.3, 81.4, 75.2, 72.5, 67.9, 67.8, 62.2, 44.8, 41.6, 38.2, 32.6, 29.4, 28.1, 18.4, 12.3; IR (neat film) 2942 (m), 2866 (m), 1749 (m), 1697 (s); LRMS (ESI) m/z for $C_{32}H_{51}ClNO_6Si$ $(M+H)^+$ 608.3



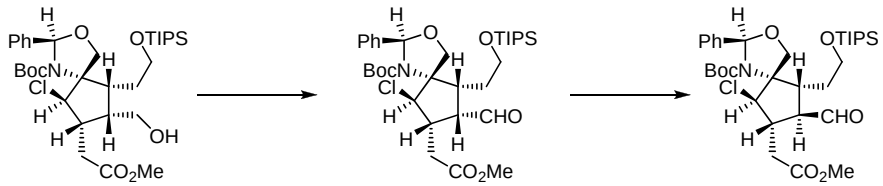
26 **S12**

Alcohol S12. To a solution of the lactone **26** (15.7 mg, 0.0258 mmol, 1.0 equiv) in methanol (3.0 mL) was added a sodium hydroxide aqueous solution (30%, 0.3 mL). The resulting mixture was stirred at 23 ^{o}C for 40 minutes, at which point the reaction was diluted with ethyl acetate (30 mL), water (10 mL), and hydrochloric acid (1.6 mL, 2.0 N). After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were dried (sodium sulfate) and concentrated *in*

vacuo. The resulting residue was then dissolved in benzene (1.5 mL) and methanol (0.5 mL), followed by addition of a trimethylsilyldiazomethane solution (2.0 M in diethyl ether, 26 uL, 0.0517 mmol, 2.0 equiv). The resulting solution was stirred at 23 ^{o}C for 30 minutes and reduced *in vacuo* to yield the alcohol **S12** (17.1 mg, 0.0267 mmol, 99%) as clear oil. This material was used directly into the next step without further purification. R_f = 0.62 (50:50 hexane:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H, C_6H_5), 7.36-7.34 (m, 3H, C_6H_5), 5.70 (s, 1H, C_6H_5CH), 5.14 (d, 1H, J = 12.0 Hz, C*H*Cl), 4.86 (dd, 1H, J = 2.1, 11.0 Hz, CH_2OH), 4.60 (d, 1H, J= 9.3 Hz, PhCHOCH_2), 3.93 (d, 1H, J = 13.3 Hz, CH_2OH), 3.80-3.76 (m, 1H, CH_2OSi), 3.71 (s, 3H, CO_2CH_3), 3.69 (d, 1H, J = 9.3 Hz, PhCHOCH_2) 3.68-3.62 (m, 2H, CH_2OH, CH_2OSi), 2.98-2.96 (m, 2H, CH_2CO_2), 2.42-2.37 (m, 3H, CHClC*H*C*H*C*H*), 2.08-2.03 (m, 1H, CH_2CH_2OSi) 1.81-1.75 (m, 1H, CH_2CH_2OSi), 1.10-1.06 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$), 1.02 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 154.0, 139.3, 129.4, 128.7, 127.9, 93.0, 82.1, 72.0, 67.9, 62.2, 58.6, 52.0, 45.2, 45.1, 41.9, 32.4, 29.7, 28.0, 18.4, 12.3; IR (neat film) 3425 (br), 2943 (m), 2866 (m), 1738 (m), 1698 (m), 1680 (m); LRMS (ESI) m/z for $C_{33}H_{55}ClNO_7Si$ $(M+H)^+$ 640.4

Cis Aldehyde S13. To a solution of the crude alcohol **S12** (17.1 mg, 0.0258 mmol, 1.0 equiv) in dichloromethane (2.0 mL) was added Dess-Martin periodinane (21.9 mg, 0.0516, 2.0 equiv). The resulting mixture was stirred at 23 ^{o}C for 1.5 h, at which point it was diluted with ethyl acetate (25 mL). The organic layer was then washed with a saturated sodium bicarbonate solution (3 x 10 mL), water (10 mL), brine (10 mL), dried (sodium sulfate), and reduced *in vacuo* to afford crude cis aldehyde **S13** (contaminated with Dess-Martin Periodane by-product). R_f = 0.58 (95:5 ethyl acetate:benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (d, 1H, J = 3.6 Hz, C*H*O), 7.62-7.58 (m, 2H, C_6H_5), 7.46-7.35 (m, 3H, C_6H_5), 5.79 (s, 1H, C_6H_5CH), 5.42 (d, 1H, J = 12.7 Hz, C*H*Cl), 4.74 (d,

1H, J = 9.4 Hz, PhCHOCH_2), 3.96-3.90 (m, 1H, CH_2OSi), 3.89-3.85 (m, 1H, CH_2OSi), 3.82 (m, 1H, PhCHOCH_2), 3.81 (s, 3H, CO_2CH_3), 3.04 (dd, 1H, J = 4.5, 16.5 Hz, CH_2CO_2), 3.06-3.01 (m, 1H, CHCH_2CO_2), 2.87 (dd, 1H, J = 10.7, 16.8 Hz, CH_2CO_2), 2.65-2.55 (m, 2H, CHCHO, CHCH_2CH_2OSi), 2.06-1.98 (m, 1H, CH_2CH_2OSi), 1.89-1.82 (m, 1H, CH_2CH_2OSi), 1.22-1.13 (m, 21H, Si(CH(CH_3)$_2$)$_3$), 1.10 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 172.6, 153.0, 139.3, 129.5, 128.5, 128.0, 92.6, 81.4, 75.4, 71.4, 66.7, 61.2, 52.2, 51.4, 45.7, 44.8, 32.8, 29.1, 28.0, 18.4, 12.3; IR (neat film) 2942, 2865, 1738, 1690; LRMS (ESI) m/z for $C_{33}H_{53}ClNO_7Si$ $(M+H)^+$ 638.4.



S12 **S13** **27**

Aldehyde 27 (from S12 without isolation of S13). To a solution of the crude alcohol **S12** (47.6 mg, 0.0745 mmol, 1.0 equiv) in dichloromethane (3.0 mL) was added Dess-Martin periodinane (63.6 mg, 0.0150, 2.0 equiv). After the mixture was stirred at 23 ^oC for 1 h, triethylamine (0.2 mL) and silica gel (100 mg) were added. The resulting mixture was stirred at 23 ^oC for 42 hrs, at which point the mixture was filtered through a pad of celite, and solvent was removed *in vacuo* to yield exclusively the trans aldehyde **27** by crude NMR analysis. The mixture was purified via silica gel chromatography (95:5 to 80:20 hexane:ethyl acetate) to yield trans aldehyde **27** (43.3 mg, 90% over 3 steps). R_f = 0.56 (95:5 ethyl acetate:benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, 1H, J = 4.3 Hz, CHO), 7.48-7.44 (m, 2H, C_6H_5), 7.38-7.34 (m, 3H, C_6H_5), 5.71 (s, 1H, C_6H_5CH), 5.10 (d, 1H, J = 10.9 Hz, CHCl), 4.64 (d, 1H, J = 9.4 Hz, PhCHOCH_2), 3.76 (d, 1H, J 9.4 Hz, PhCHOCH_2), 3.75-3.69 (m, 1H, CH_2OSi), 3.67 (s, 3H, CO_2CH_3), 3.65-3.59 (m, 1H, CH_2OSi), 3.05 (dt, 1H, J = 4.2, 10.5 Hz, CHCHO), 2.85 (d, 1H, J = 11.8 Hz, CH_2CO_2), 2.58-2.47 (m, 3H, CHCH_2CO_2, CHCH_2CH_2OSi), 1.86-1.72 (m, 2H, CH_2CH_2OSi), 1.08-1.04 (m, 21H, Si(CH(CH_3)$_2$)$_3$), 1.03 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 172.5, 153.0, 139.5, 129.4, 128.6, 127.8, 92.4, 81.2, 74.3, 71.7, 67.8, 61.0, 59.8,

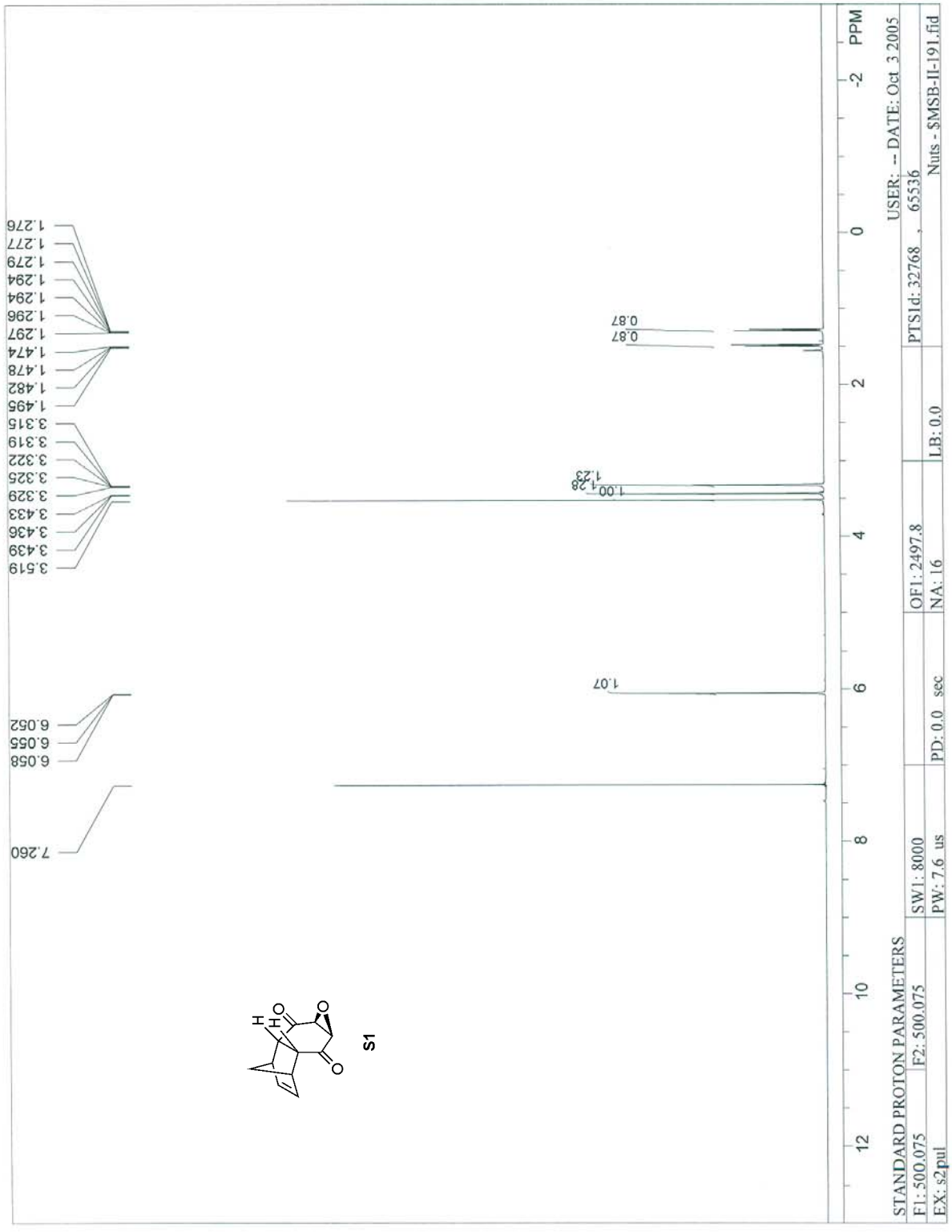
52.2, 45.2, 44.1, 35.8, 32.5, 28.1, 18.4, 12.3; IR (neat film) 2942 (m), 2866 (m), 1738 (m), 1694 (s); LRMS (ESI) m/z for $C_{33}H_{53}ClNO_7Si$ $(M+H)^+$ 638.4.

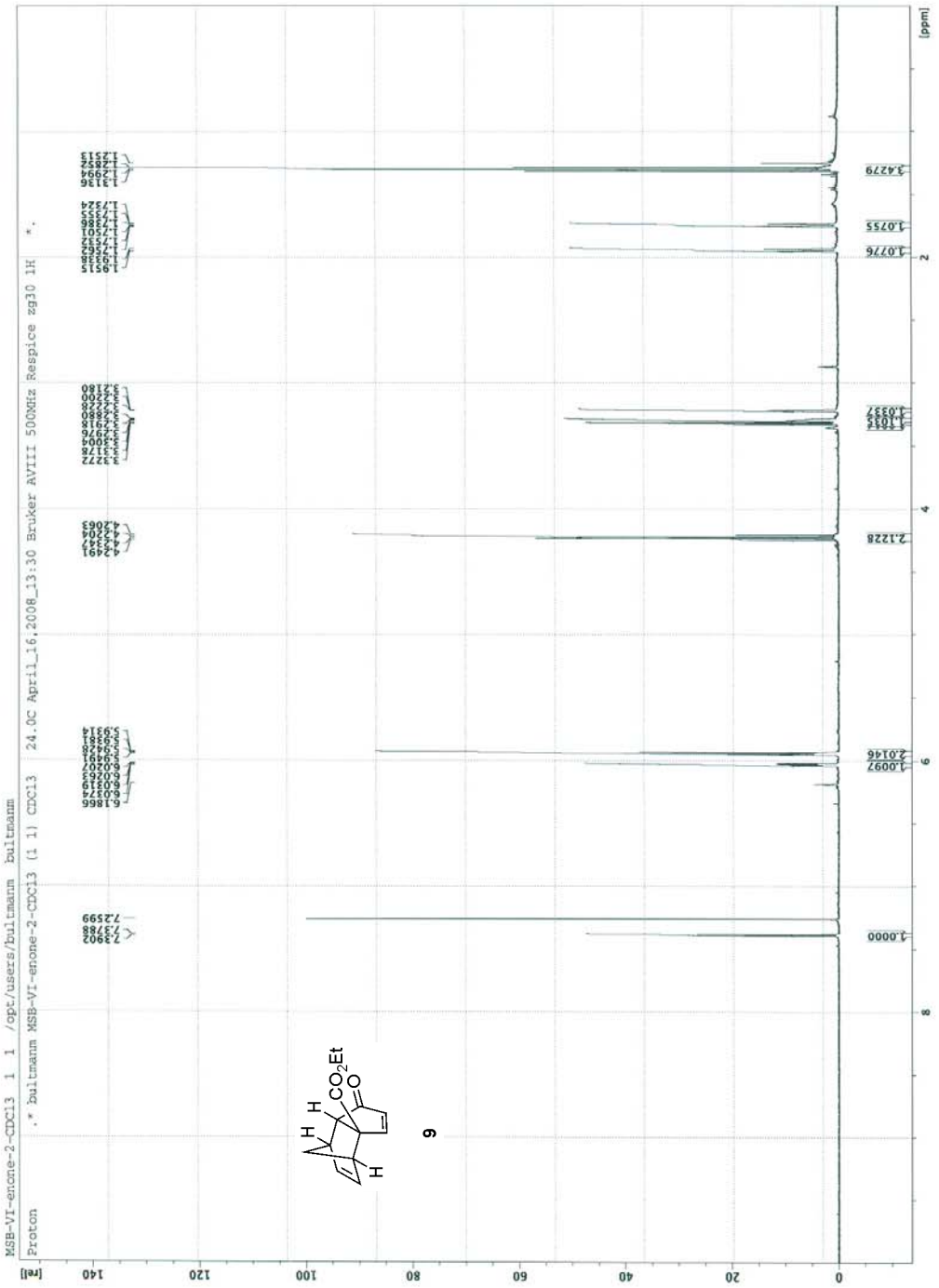
References

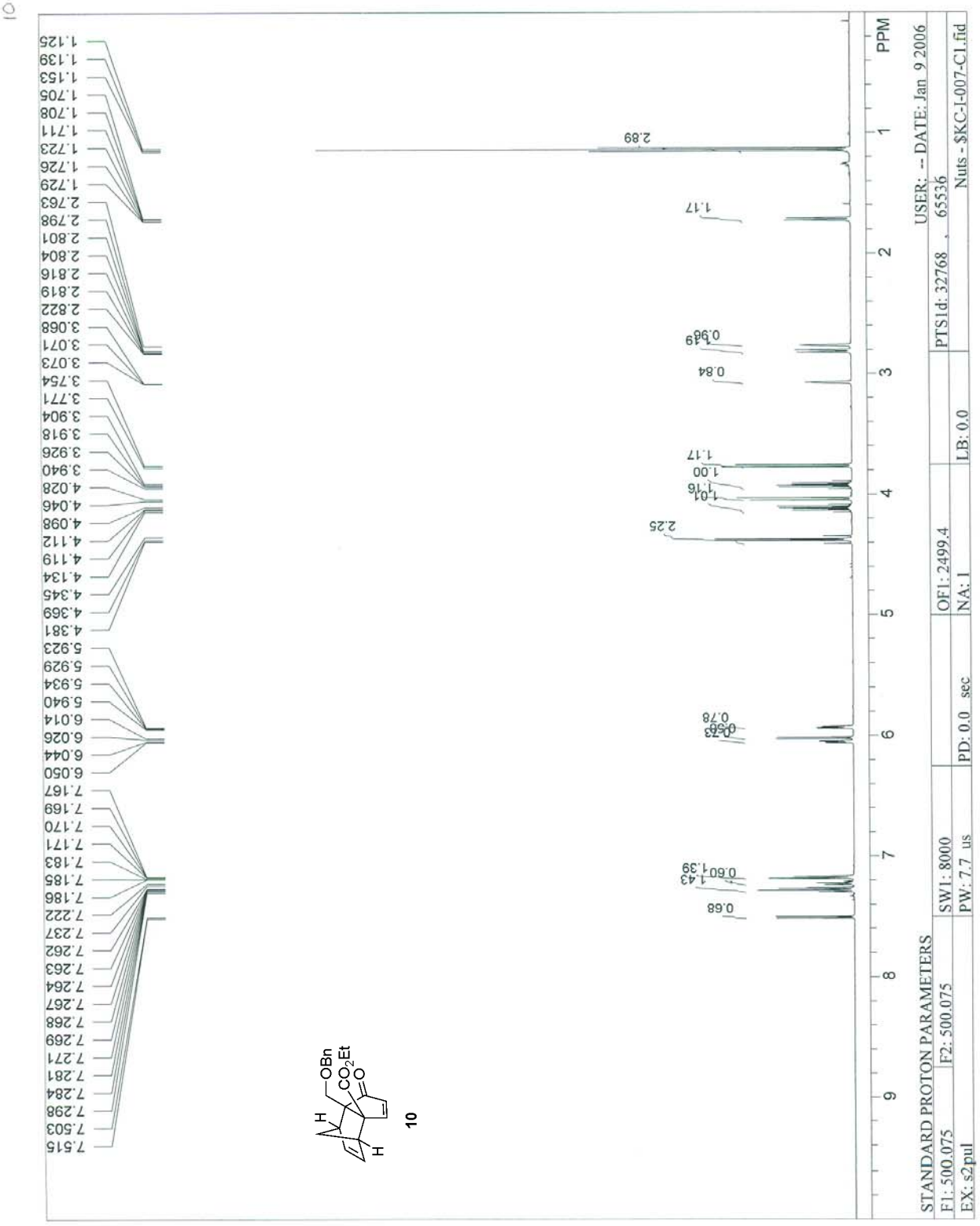
1. O'Brien, D. F.; Gates, J. W., Jr., *J. Org. Chem.* **1965**, *30*, 2593-2601.

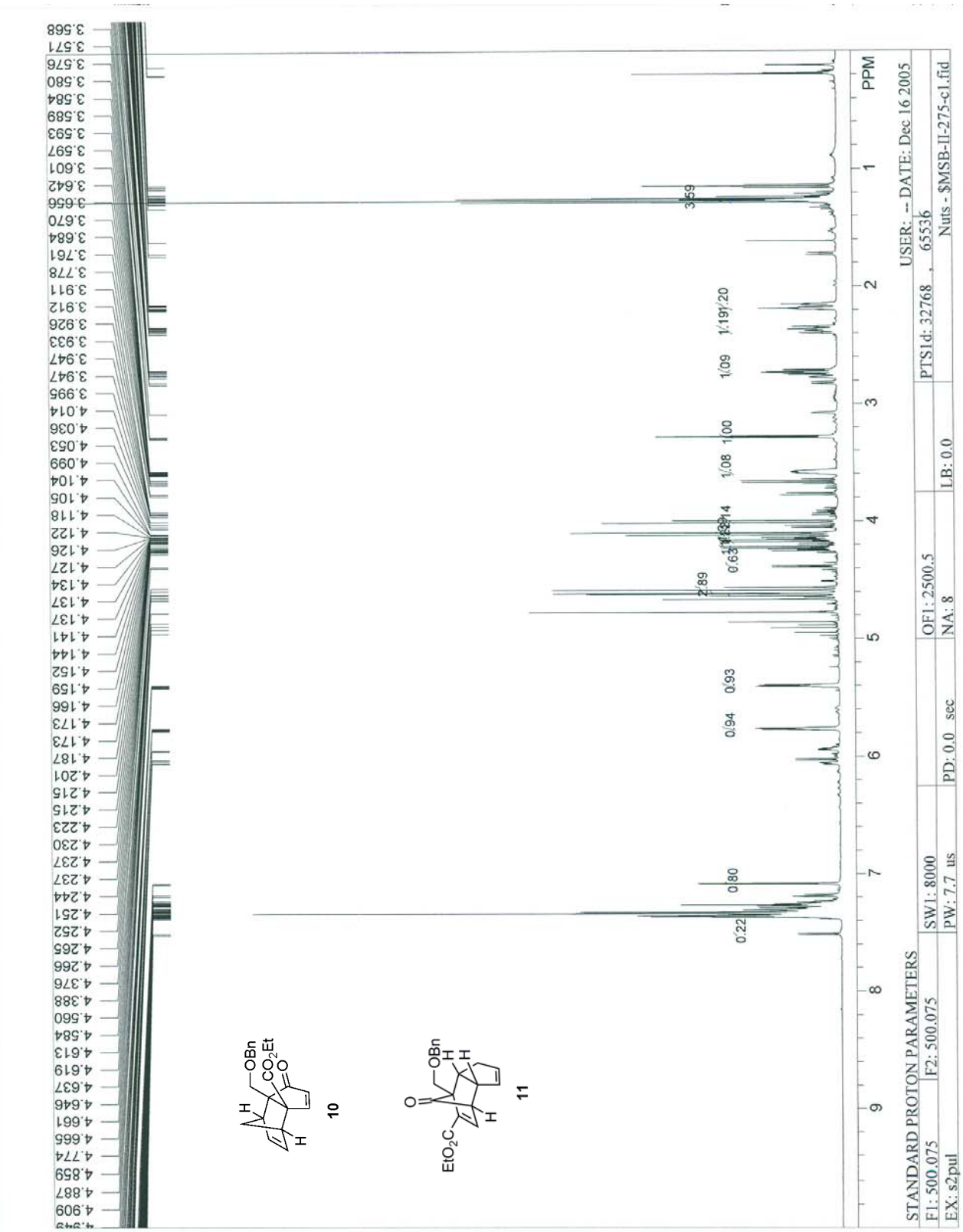
2. a) Yoshida, N.; Kamikubo, T.; Ogasawara, K., *Tetrahedron: Asymmetry* **1998**, *9*, 3325-3329.

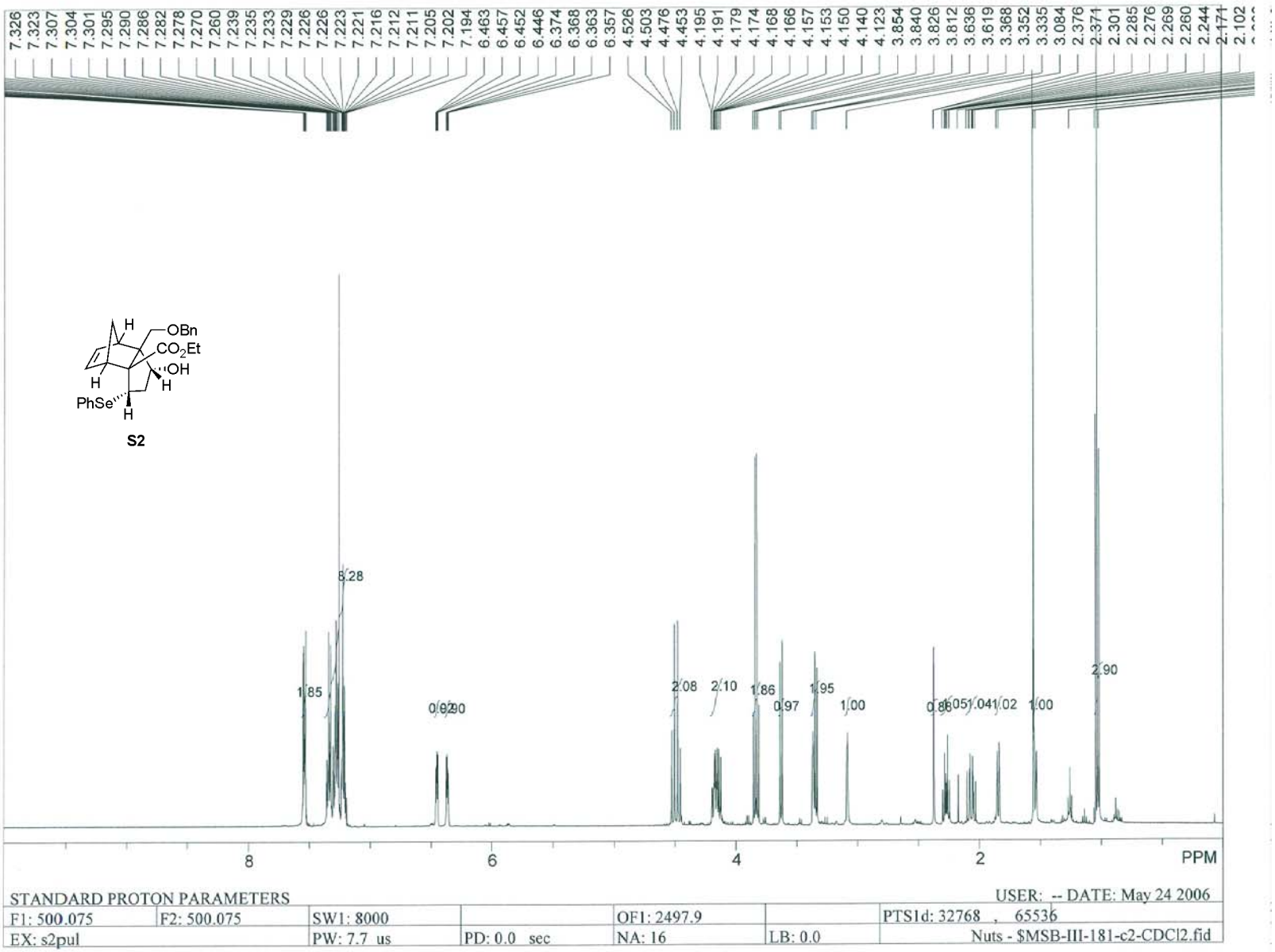
b) Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B., *Tetrahedron* **1991**, *47*, 1495-508.

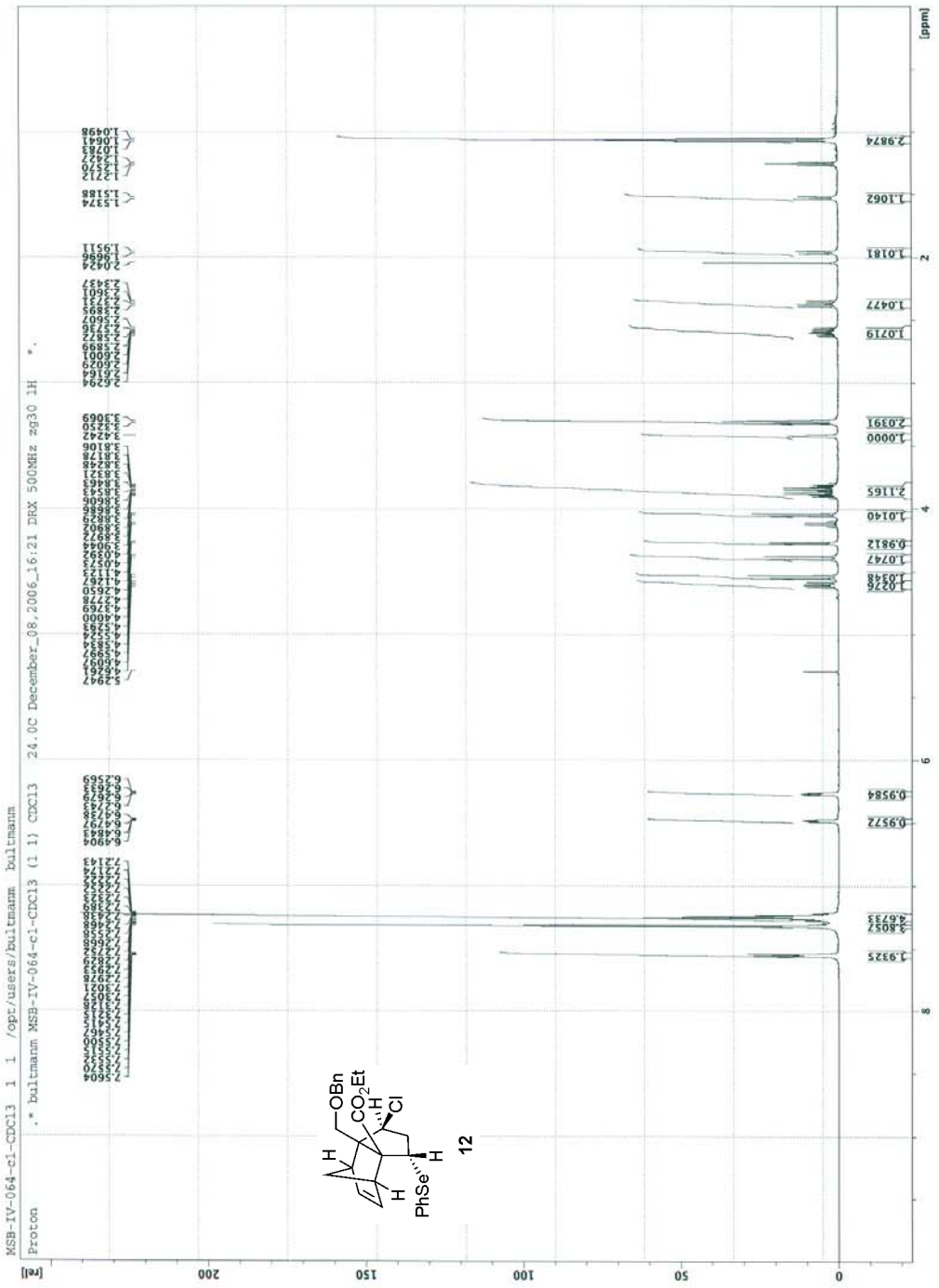

7.260
6.058
6.055
6.052
3.519
3.439
3.436
3.433
3.329
3.325
3.322
3.319
3.315
1.495
1.482
1.478
1.474
1.297
1.296
1.294
1.294
1.279
1.277
1.276
1.07
1.00
1.23
0.87
0.87
S1
STANDARD PROTON PARAMETERS
F1: 500.075
F2: 500.075
SW1: 8000
PW: 7.6 us
PD: 0.0 sec
OF1: 2497.8
NA: 16
LB: 0.0
PTS1d: 32768 , 65536
USER: -- DATE: Oct 3 2005
Nuts - $MSB-II-191.fid
PPM

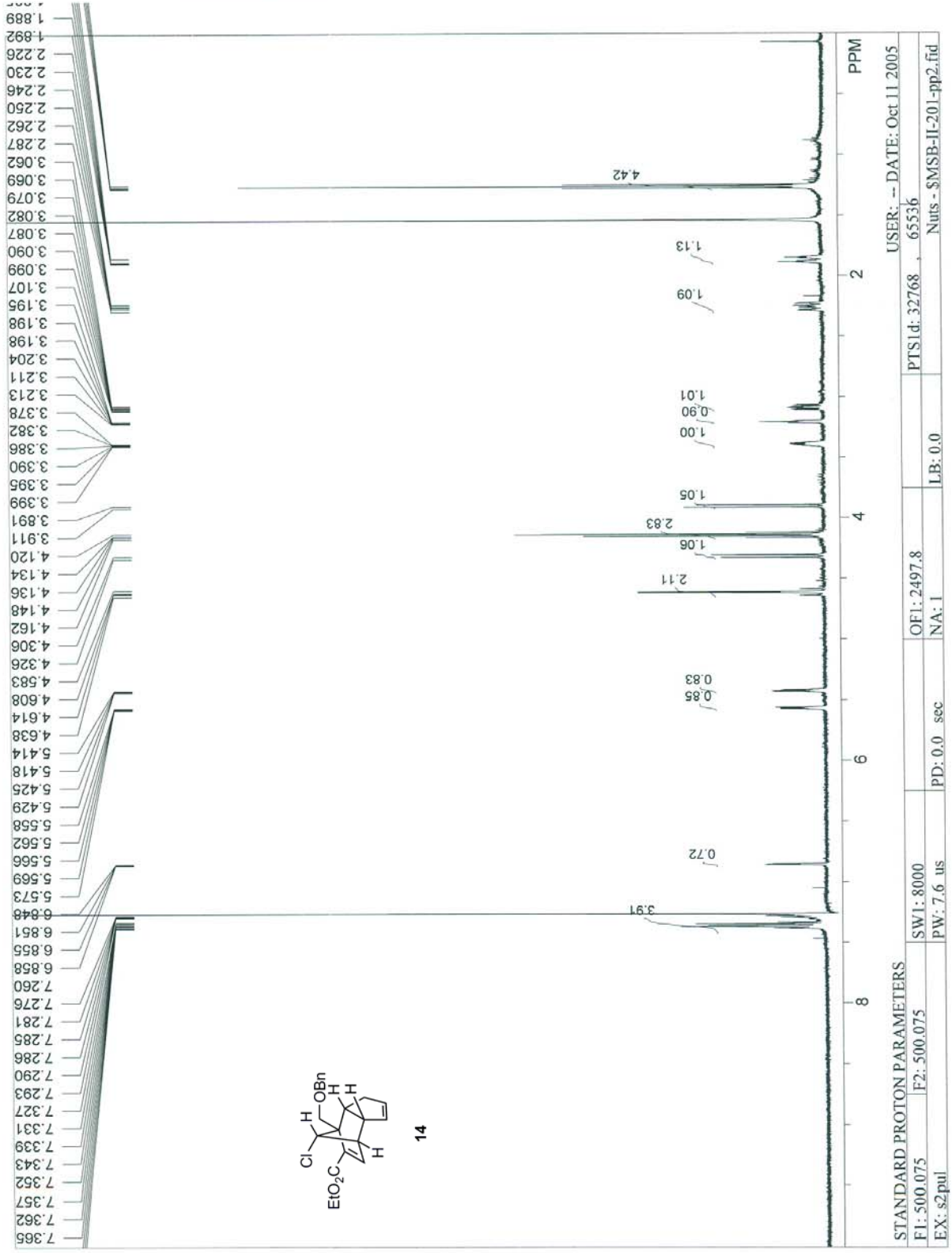

MSB-VI-enone-2-CDCl3 1 1 /opt/users/bultmann bultmann
Proton
.* bultmann MSB-VI-enone-2-CDCl3 (1 1) CDCl3 24.0C April_16,2008_13:30 Bruker AVIII 500Mz Respice zg30 1H *.
[rel]
[ppm]
1.0000
2.0146
1.0097
2.1228
1.0337
1.0755
1.0776
3.4279
CO2Et
O
H
H
9

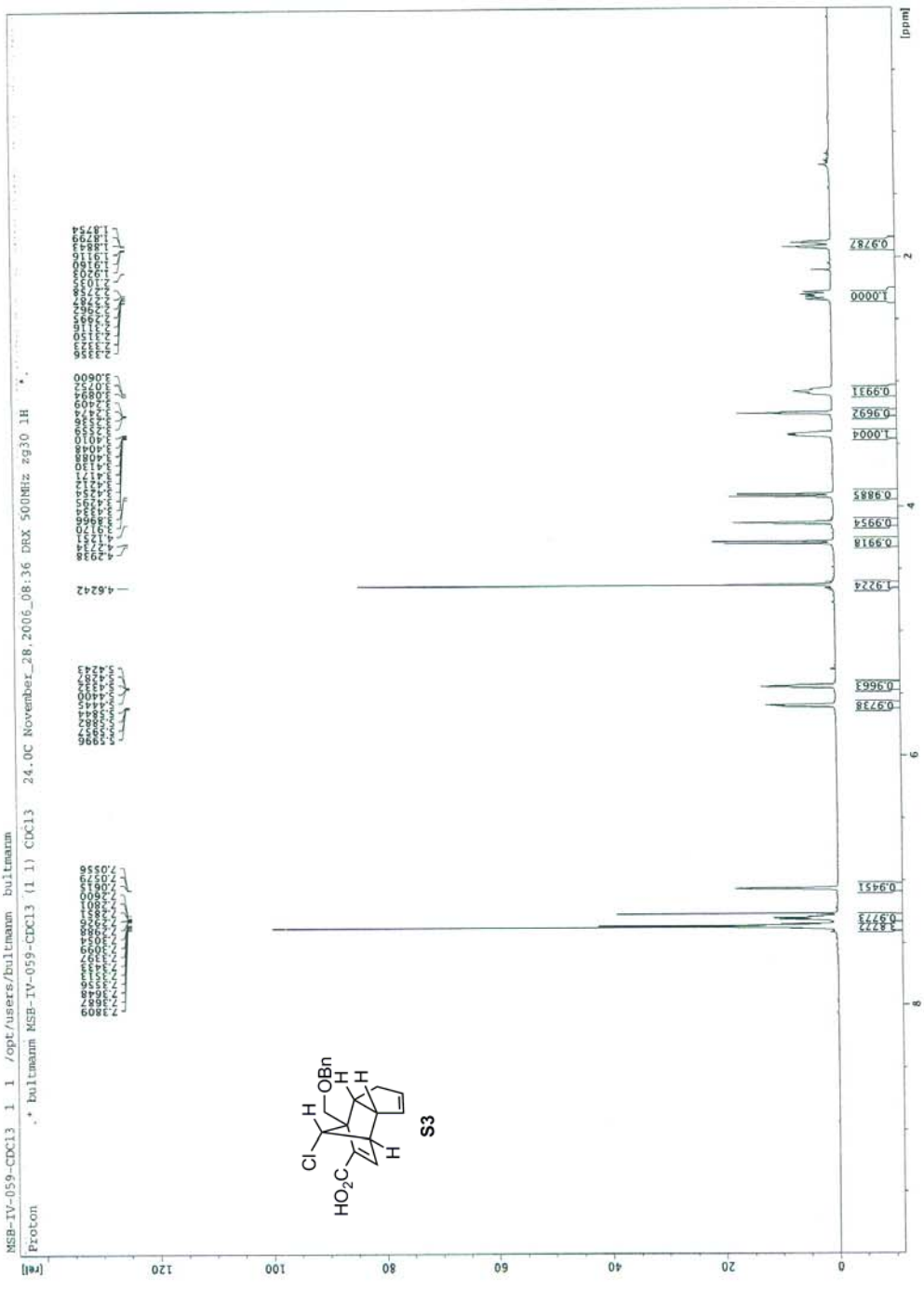

OBn
CO2Et
O
H
H
10
PPM
USER: -- DATE: Jan 9 2006
STANDARD PROTON PARAMETERS
F1: 500.075
F2: 500.075
EX: s2pul
SW1: 8000
PW: 7.7 us
PD: 0.0 sec
OF1: 2499.4
NA: 1
LB: 0.0
PTS1d: 32768 , 65536
Nuts - $KC-I-007-C1.fid

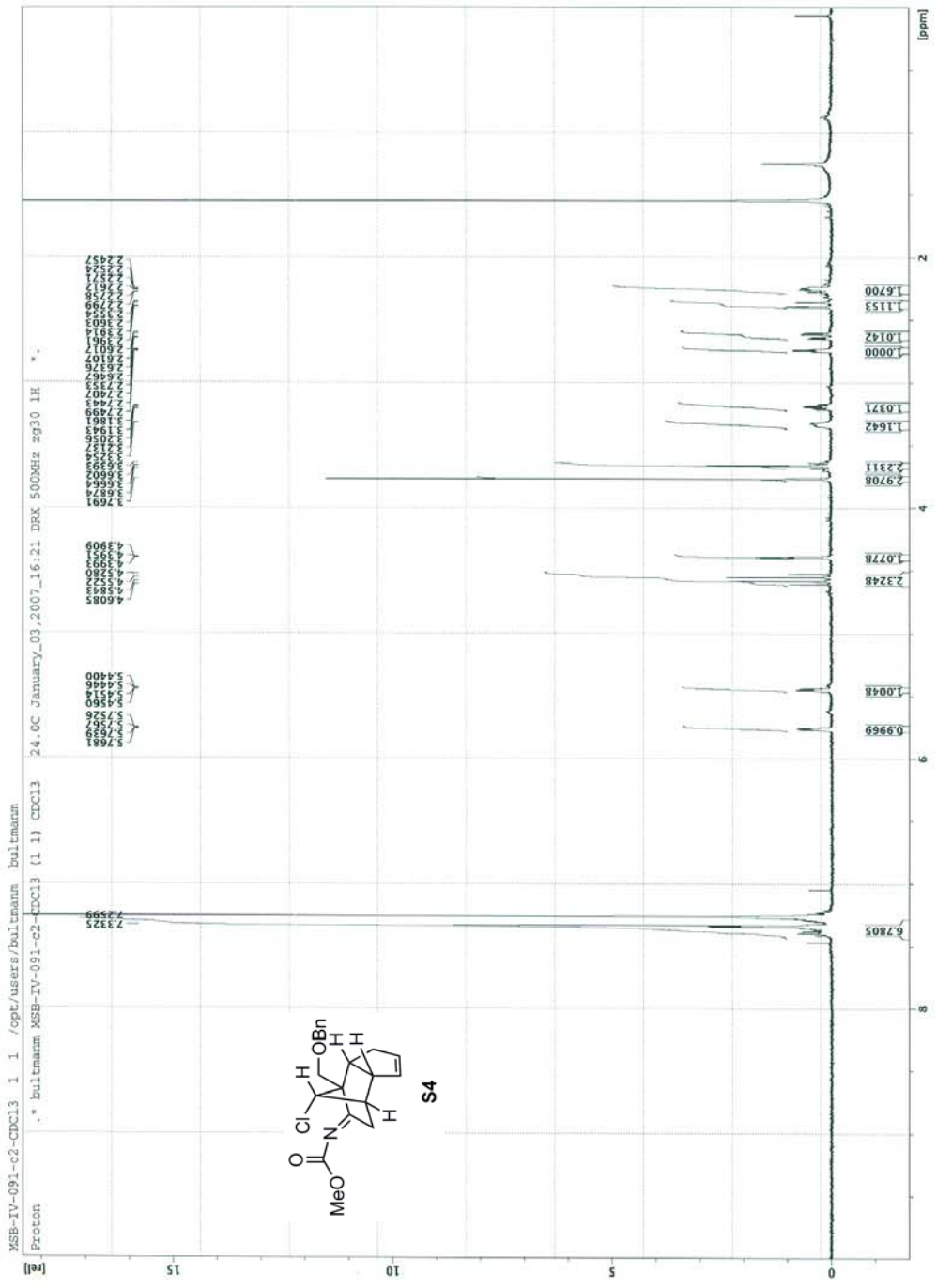

OBn
CO2Et
O
H
10
OBn
H
H
O
EtO2C
H
11
PPM
USER: -- DATE: Dec 16 2005
STANDARD PROTON PARAMETERS
F1: 500.075
F2: 500.075
EX: s2pul
SW1: 8000
PW: 7.7 us
PD: 0.0 sec
OF1: 2500.5
NA: 8
LB: 0.0
PTS1d: 32768
65536
Nuts - $MSB-II-275-c1.fid

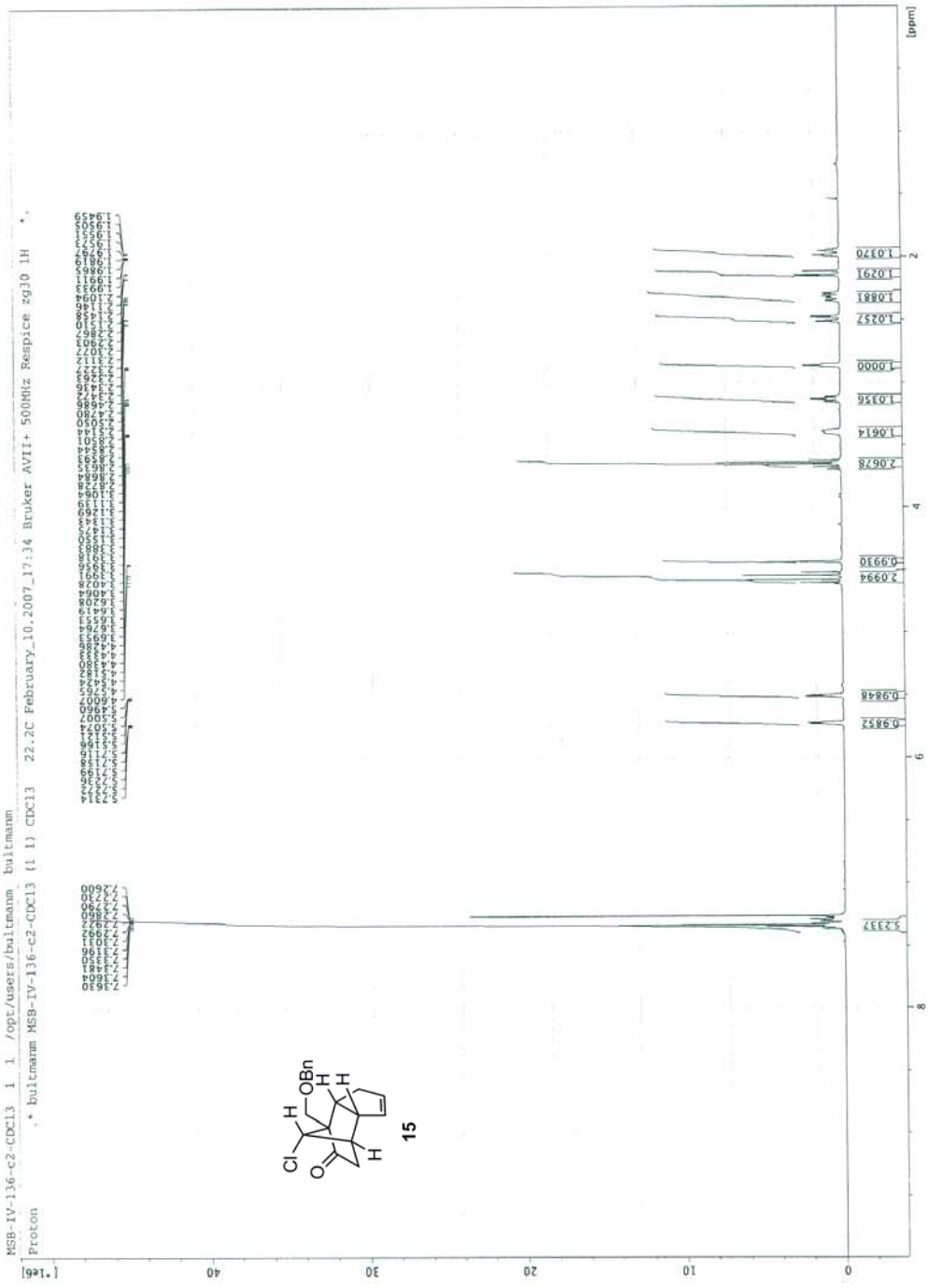

7.326 7.323 7.307 7.304 7.301 7.295 7.290 7.286 7.282 7.278 7.270 7.260 7.239 7.235 7.233 7.229 7.226 7.226 7.223 7.221 7.216 7.212 7.211 7.205 7.202 7.194 6.463 6.457 6.452 6.446 6.374 6.368 6.363 6.357 4.526 4.503 4.476 4.453 4.195 4.191 4.179 4.174 4.168 4.166 4.157 4.153 4.150 4.140 4.123 3.854 3.840 3.826 3.812 3.636 3.619 3.368 3.352 3.335 3.084 2.376 2.371 2.301 2.285 2.276 2.269 2.260 2.244 2.171 2.102
H
OBn
CO2Et
OH
H
H
PhSe
H
S2
8.28
1.85
0.90
2.08
2.10
1.86
0.97
1.95
1.00
0.86
0.51
1.04
1.02
1.00
2.90
8
6
4
2
PPM
STANDARD PROTON PARAMETERS
USER: -- DATE: May 24 2006
F1: 500.075
F2: 500.075
SW1: 8000
OF1: 2497.9
PTS1d: 32768 , 65536
EX: s2pul
PW: 7.7 us
PD: 0.0 sec
NA: 16
LB: 0.0
Nuts - $MSB-III-181-c2-CDCl2.fid

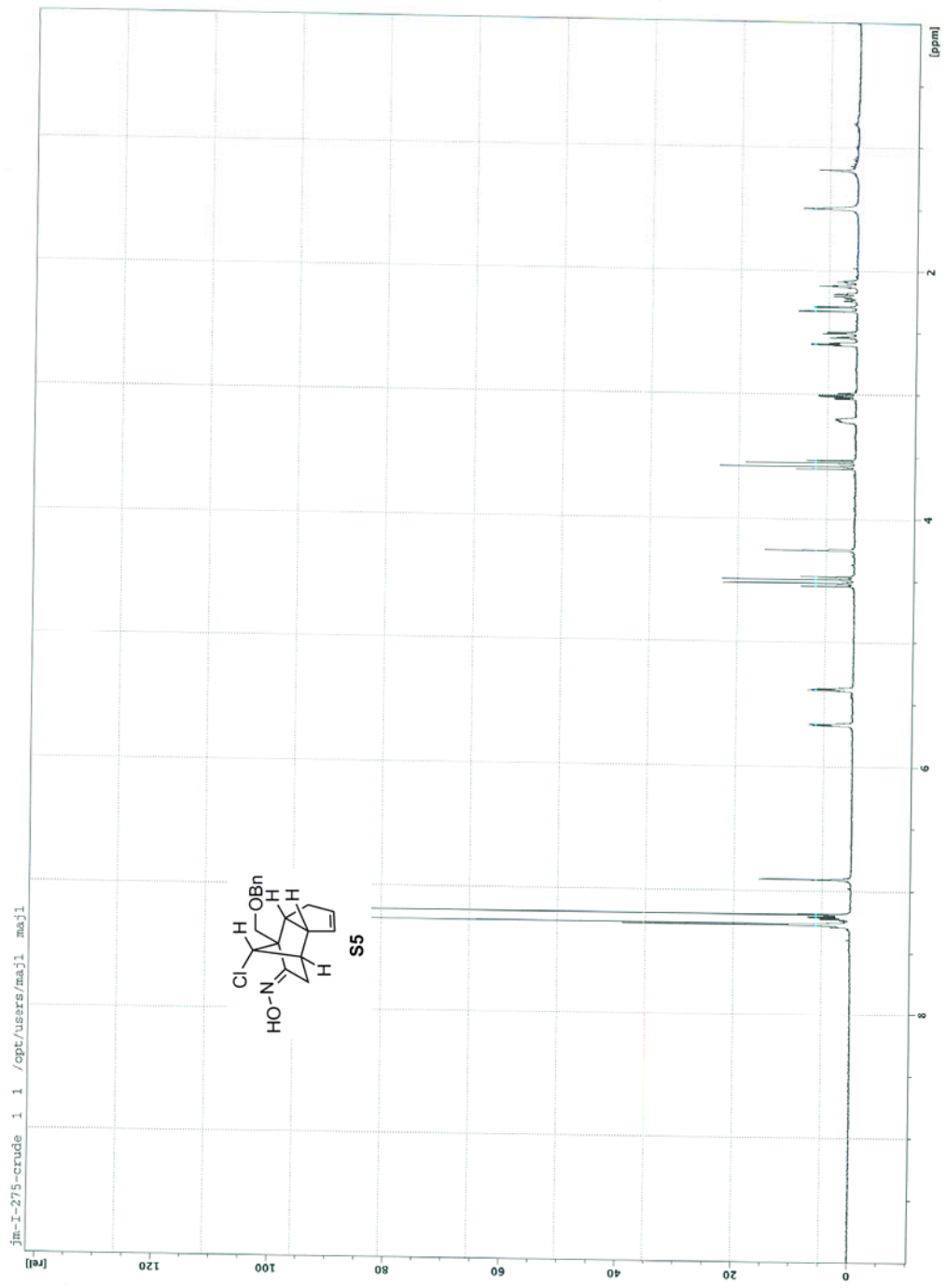

MSB-IV-064-c1-CDCl3 1 1 /opr/users/bultmann bultmann
Proton
.* bultmann MSB-IV-064-c1-CDCl3 (1 1) CDCl3 24.0C December 08.2006_16:21 DRX 500MHz zg30 1H *.
[rel]
[ppm]
OBn
CO2Et
H
Cl
H
H
PhSe
H
12

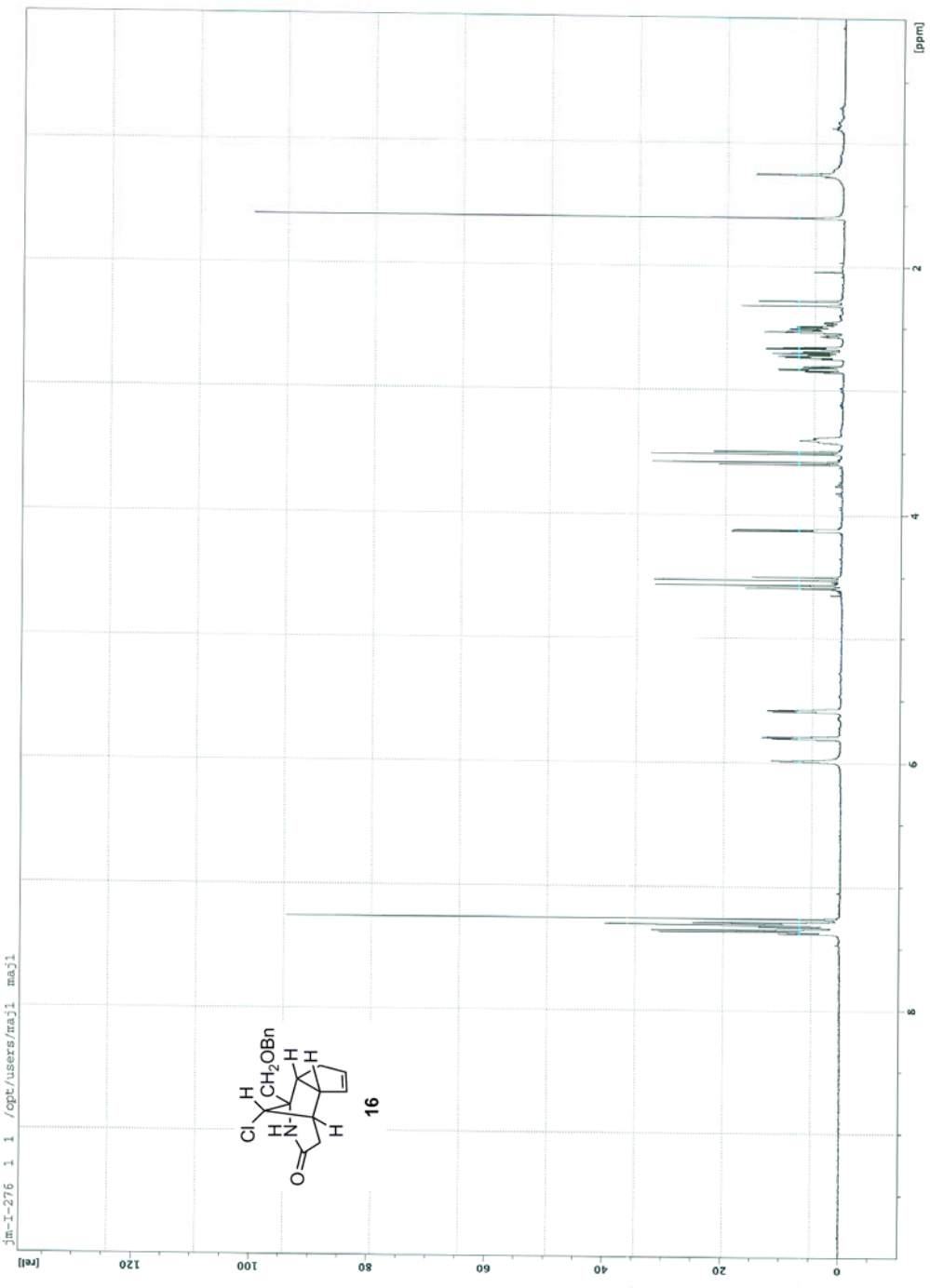

14
PPM
STANDARD PROTON PARAMETERS
F1: 500.075
F2: 500.075
EX: s2pul
SW1: 8000
PW: 7.6 us
PD: 0.0 sec
OF1: 2497.8
NA: 1
LB: 0.0
PTS1d: 32768 , 65536
USER: -- DATE: Oct 11 2005
Nuts - $MSB-II-201-pp2.fid

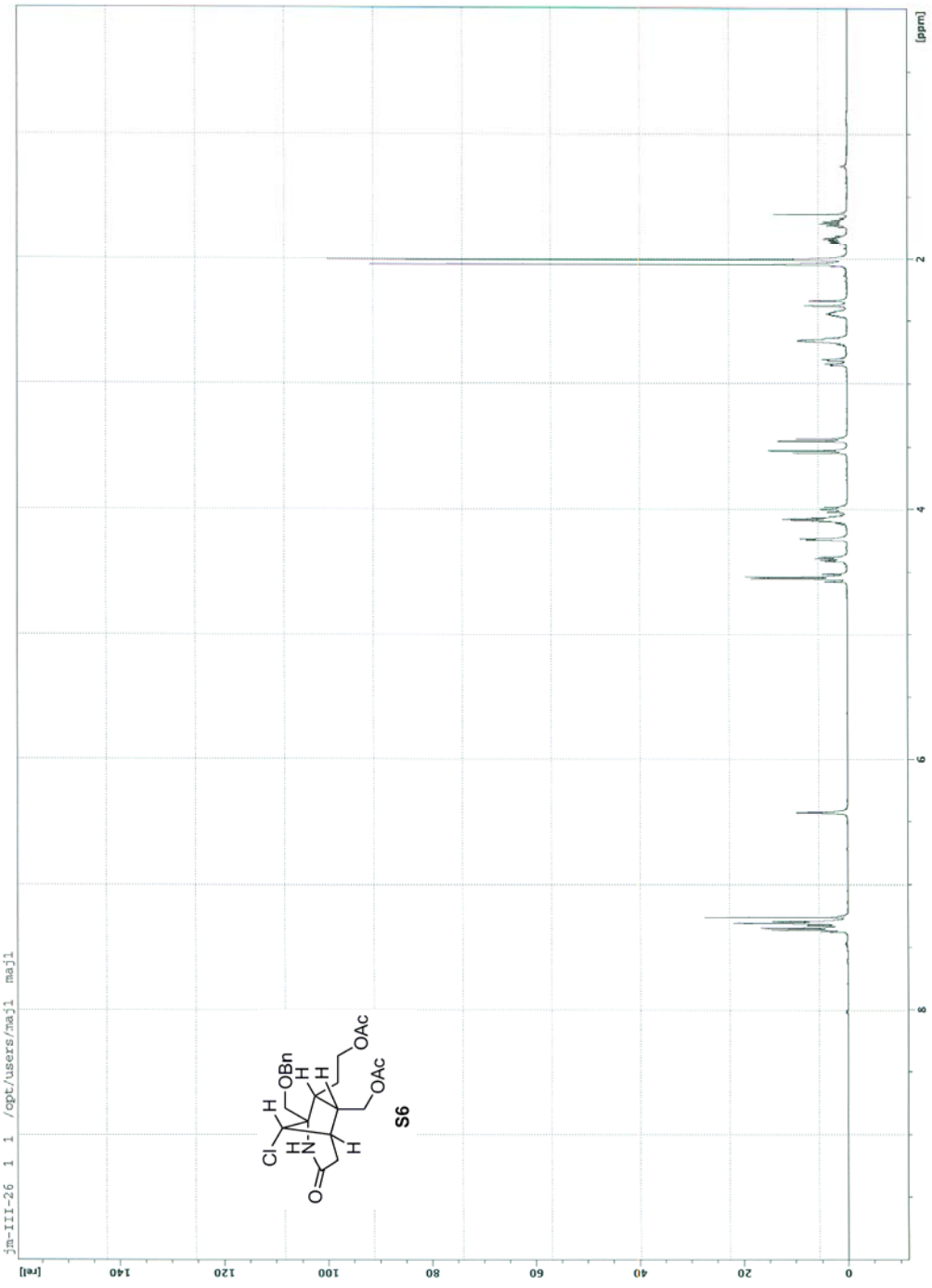

MSB-IV-059-CDCl3 1 1 /opt/users/bultmann bultmann
Proton .* bultmann MSB-IV-059-CDCl3 (1 1) CDCl3 24.0C November_28,2006_08:36 DRX 500MHz zg30 1H
[rel]
[ppm]
0.9787
1.0000
0.9931
0.9692
1.0004
0.9885
0.9954
0.9918
1.9224
0.9738
0.9663
0.9451
0.9773
3.8777
4.6242
3.0600
Cl
OBn
H
H
H
H
HO2C
S3

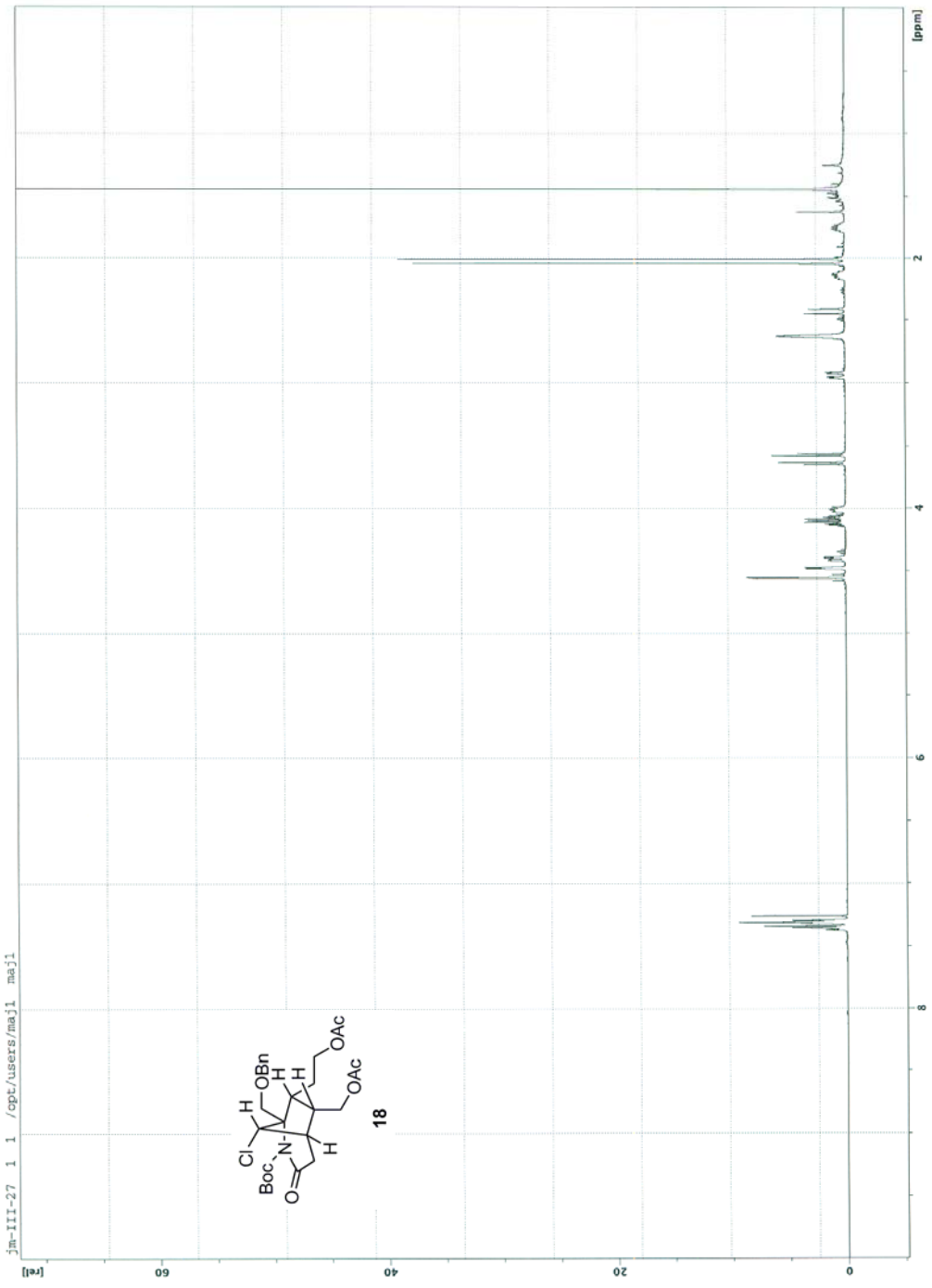

MSB-IV-091-c2-CDCl3 1 1 /opt/users/bultmann bultmann
Proton . * bultmann MSB-IV-091-c2-CDCl3 (1 1) CDCl3 24.0C January_03,2007_16:21 DRX 500MHz zg30 1H *.
[rel]
[ppm]
S4
OBn
Cl
MeO
N
O
H
1.6700
1.1153
1.0142
1.0000
1.0371
1.1642
2.2311
2.9708
2.3248
1.0778
1.0048
0.9969
6.7805

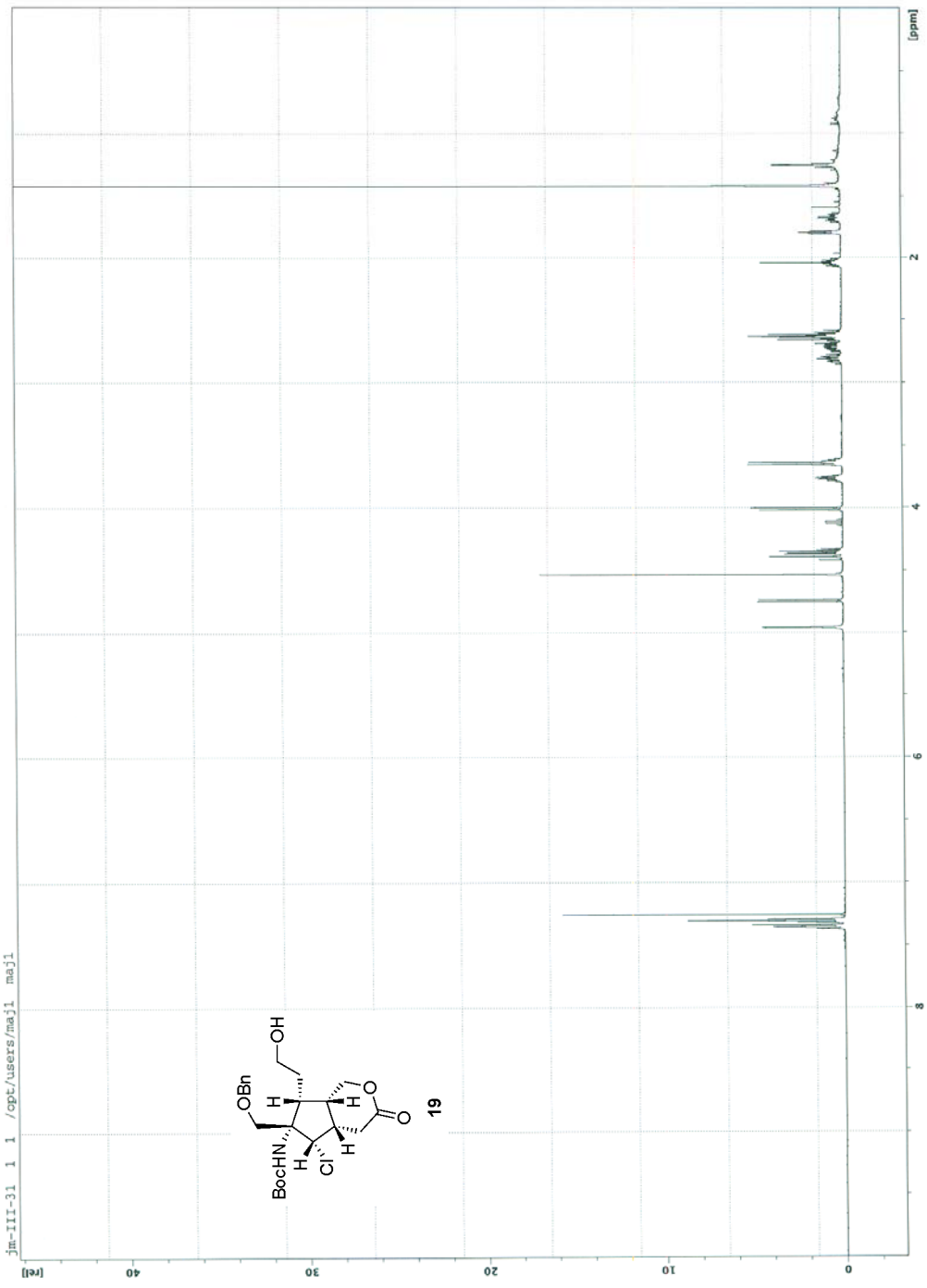

MSB-IV-136-c2-CDCl3 1 1 /opt/users/bultmann bultmann
Proton * bultmann MSB-IV-136-c2-CDCl3 (1 1) CDCl3 22.2C February_10.2007_17:34 Bruker AVII+ 500MHz Respice zg30 1H
OBn
H
H
H
Cl
O
15
[ppm]
5.2137
0.9852
0.9848
2.0994
0.9930
2.0678
1.0614
1.0356
1.0000
1.0257
1.0881
1.0291
1.0370

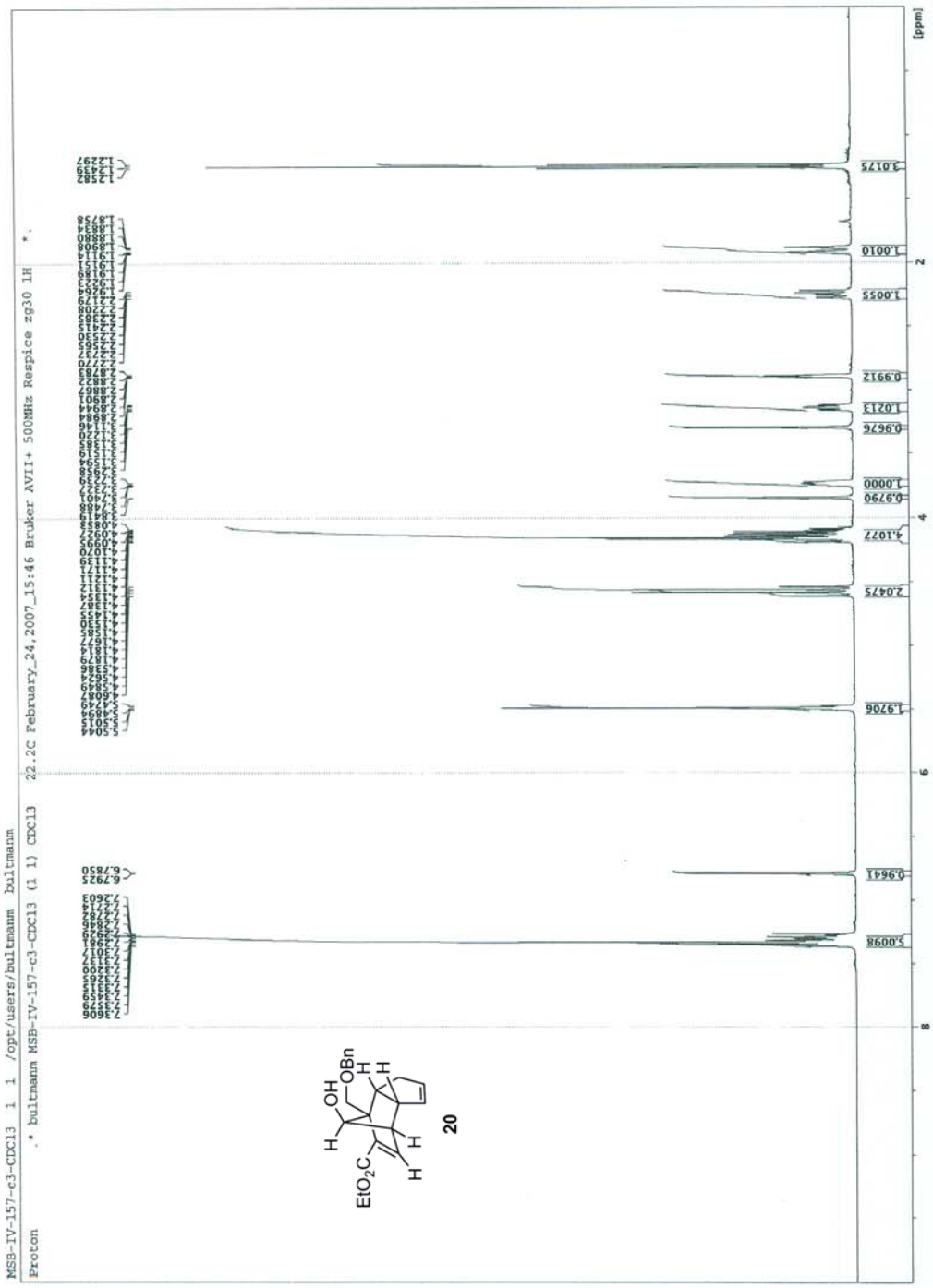

jm-I-275-crude 1 1 /opt/users/maj1 maj1
rel
120
100
80
60
40
20
0
2
4
6
8
[ppm]
OBn
H
H
Cl
H
N
HO
S5

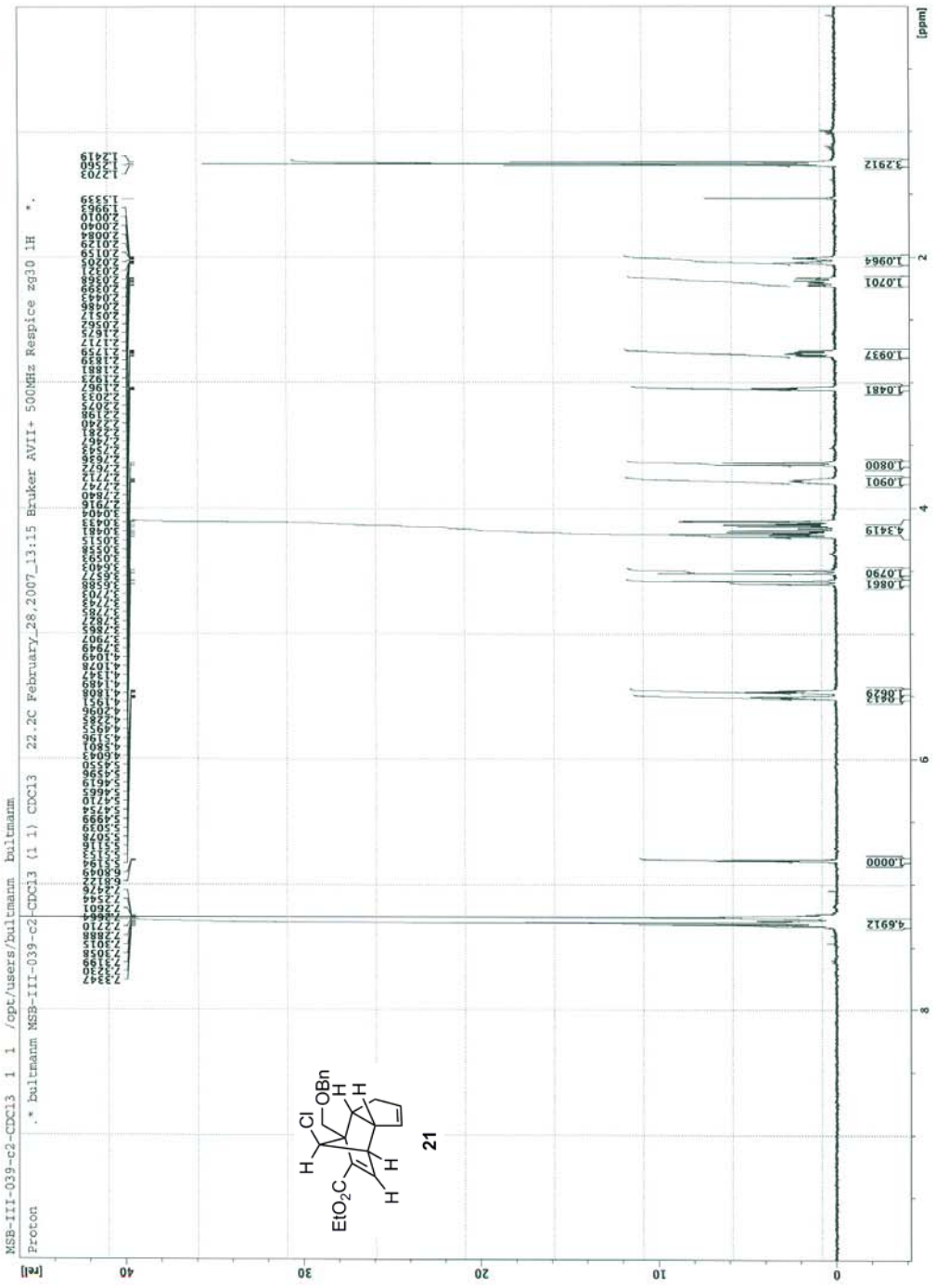

jm-I-276 1 1 /opt/users/maj1 maj1
[rel]
120
100
80
60
40
20
0
[ppm]
2
4
6
8
Cl
H
CH2OBn
H
H
N
H
H
O
16

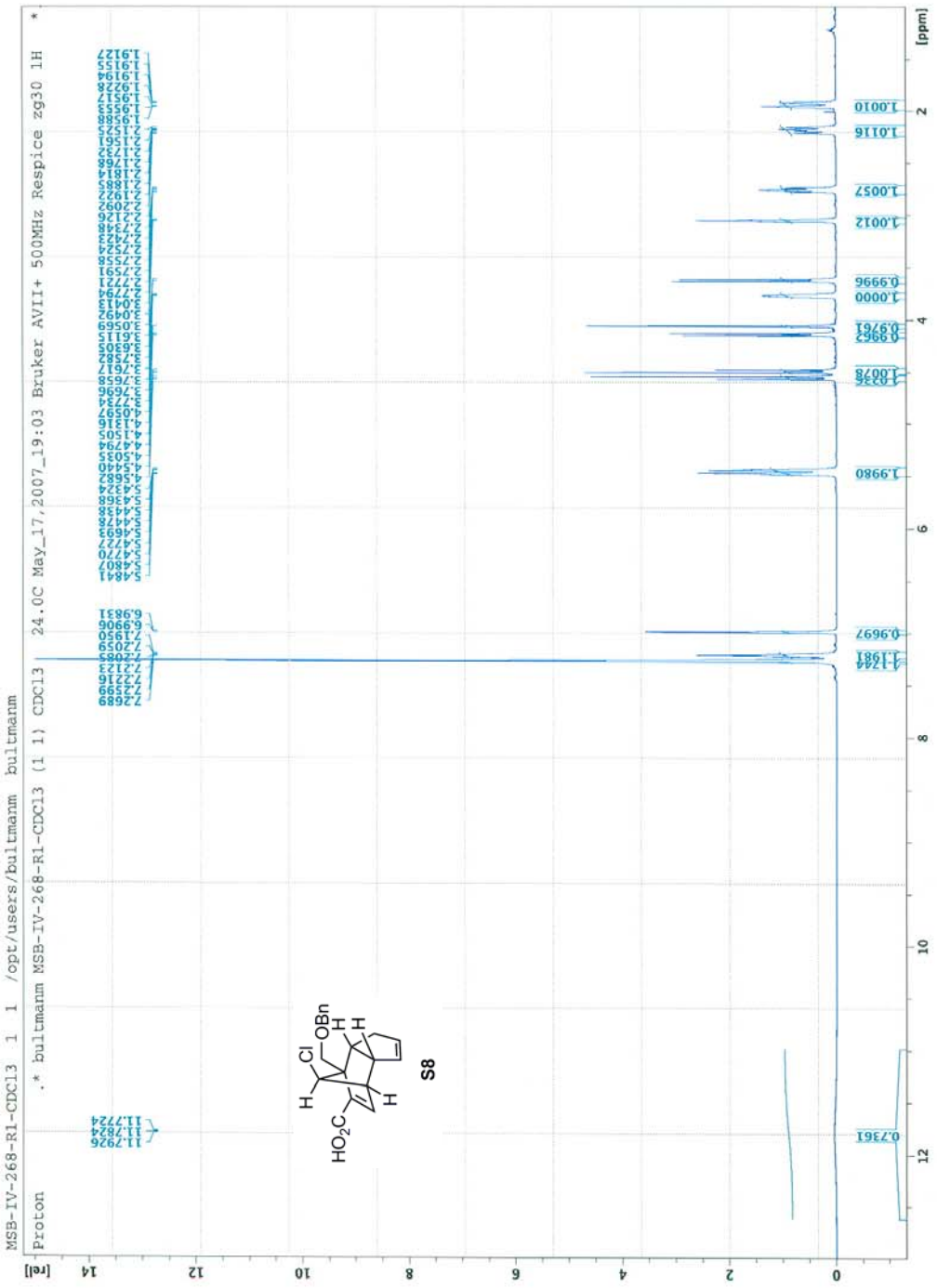

jm-III-26 1 1 /cpt/users/maj1 maj1
[rel]
0
20
40
60
80
100
120
140
[ppm]
2
4
6
8
Cl
H
OBn
H
H
N
H
OAc
OAc
O
S6

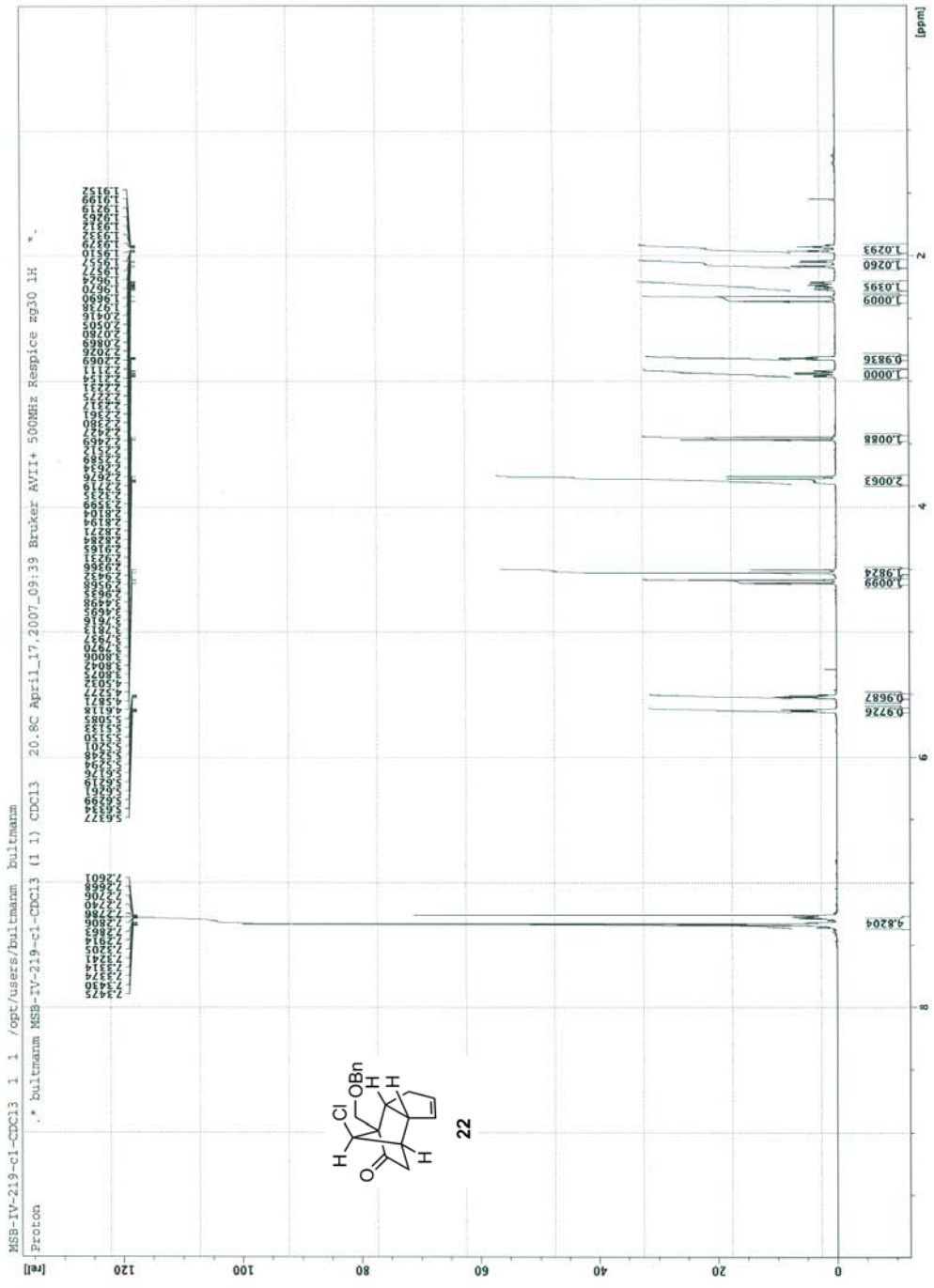

jm-III-27 1 1 /opt/users/maj1 maj1
[rel]
60
40
20
0
2
4
6
8
[ppm]
Cl
H
OBn
H
H
OAc
OAc
Boc-N
H
O
18

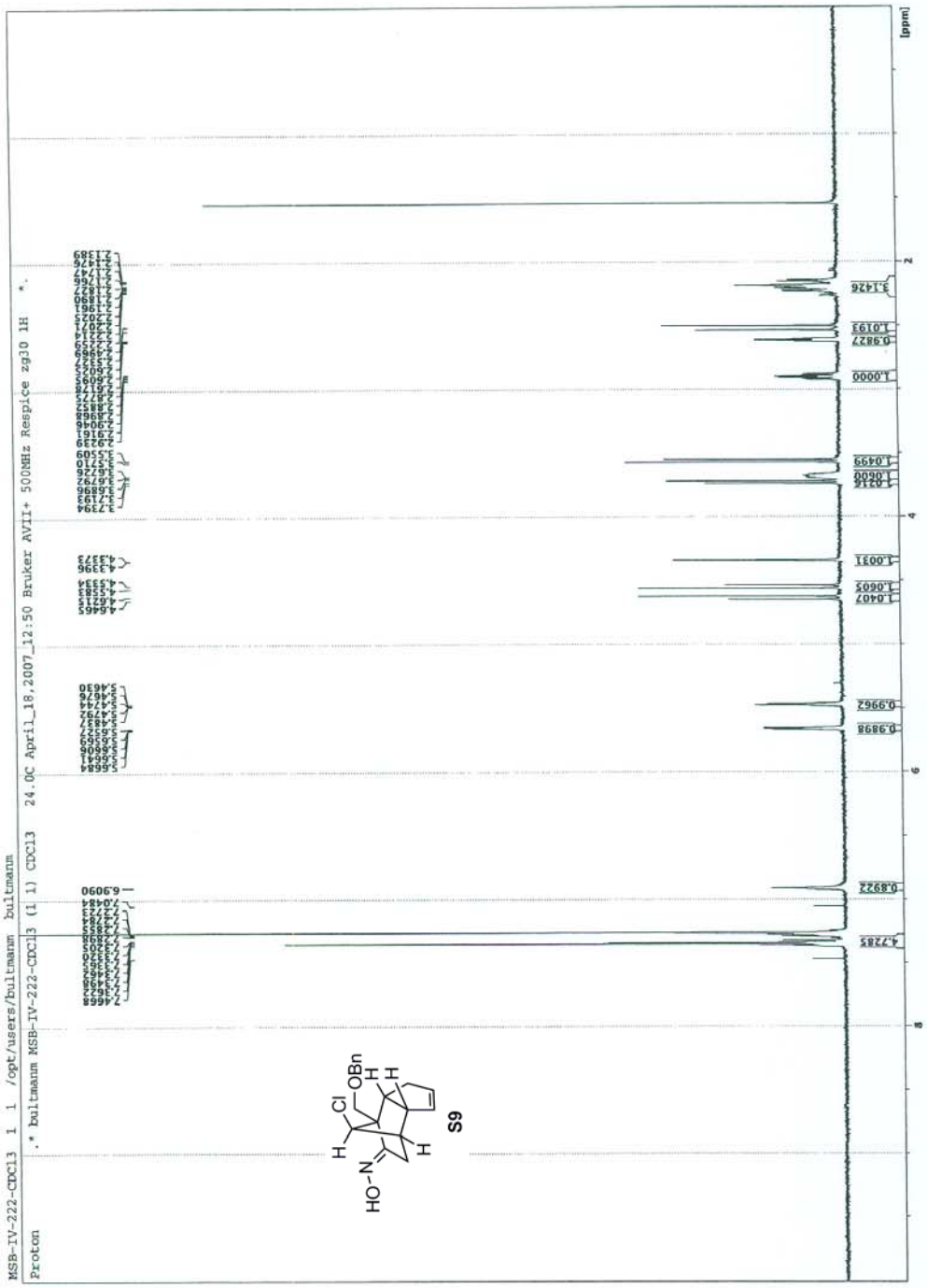

jm-III-31 1 1 /opt/users/maj1 maj1
[rel]
40
30
20
10
0
[ppm]
2
4
6
8
OBn
OH
BocHN
Cl
O
O
H
H
H
H
19

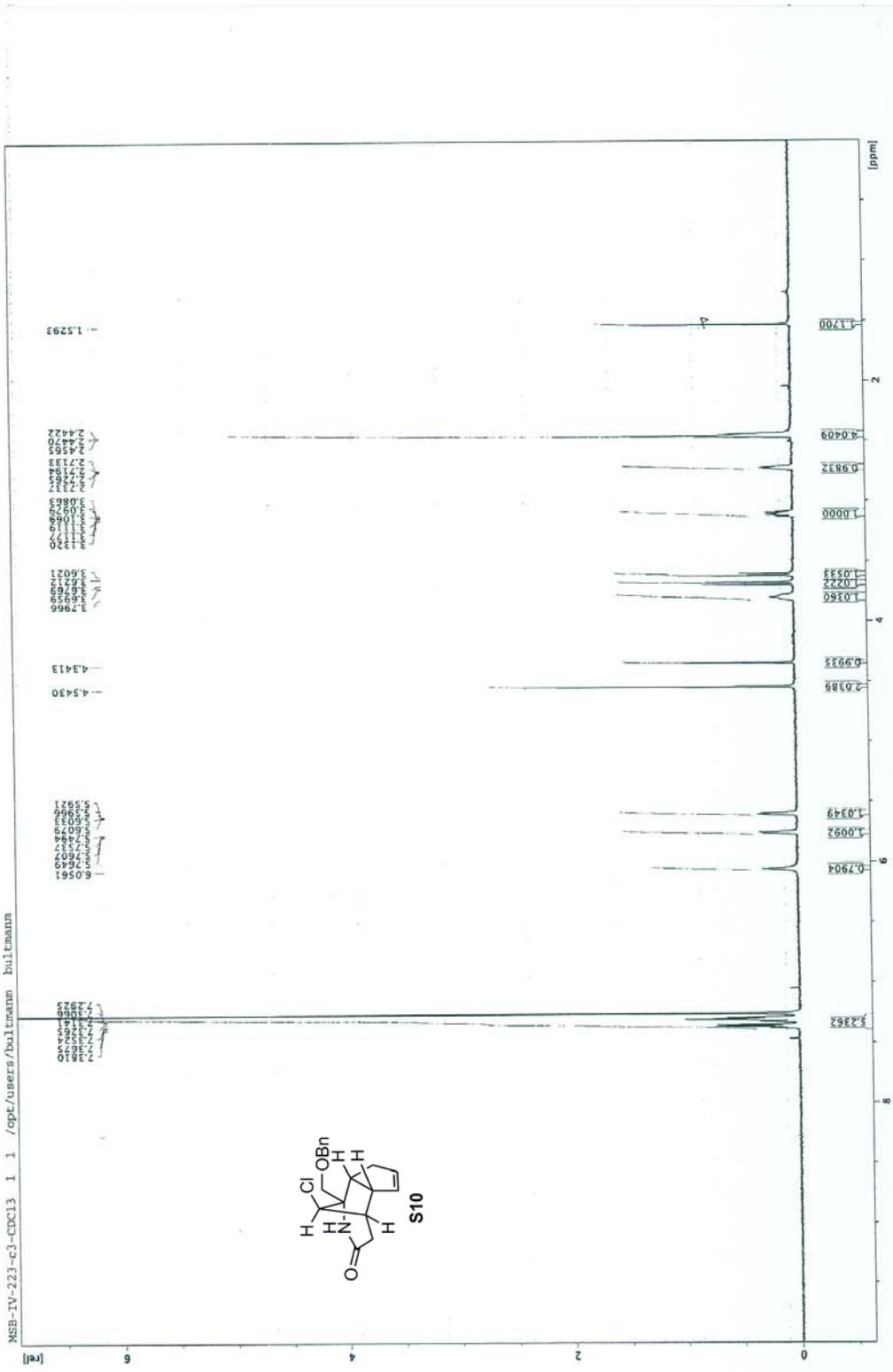

MSB-IV-157-c3-CDCl3 1 1 /opt/users/bultmann bultmann
Proton .* bultmann MSB-IV-157-c3-CDCl3 (1 1) CDCl3 22.2C February_24,2007_15:46 Bruker AVII+ 500MHz Respice zg30 1H *.
3.0175
1.0010
1.0055
0.9912
1.0213
0.9676
1.0000
0.9790
4.1077
2.0475
1.9706
0.9641
5.0098
[ppm]
OH
OBn
H
H
H
H
EtO2C
20

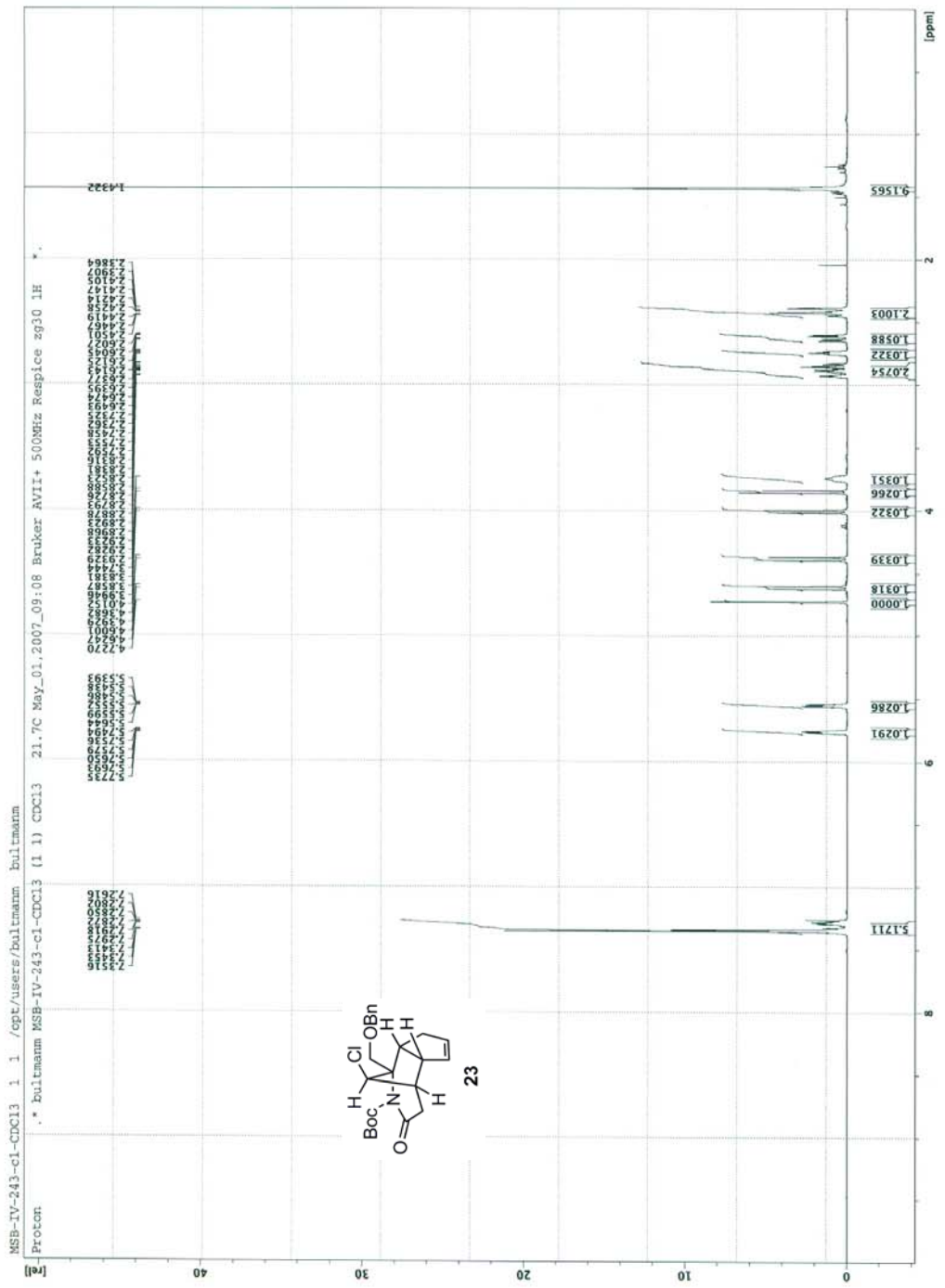

MSB-III-039-c2-CDCl3 1 1 /opt/users/bultmann bultmann
Proton .* bultmann MSB-III-039-c2 CDCl3 (1 1) CDCl3 22.2C February_28,2007_13:15 Bruker AVII+ 500MHz Respice zg30 1H *.
[rel]
[ppm]
3.2912
1.0964
1.0701
1.0937
1.0481
1.0800
1.0901
4.3419
1.0861
1.0790
1.0629
1.0000
4.6912
Cl
OBn
H
H
H
H
EtO2C
21

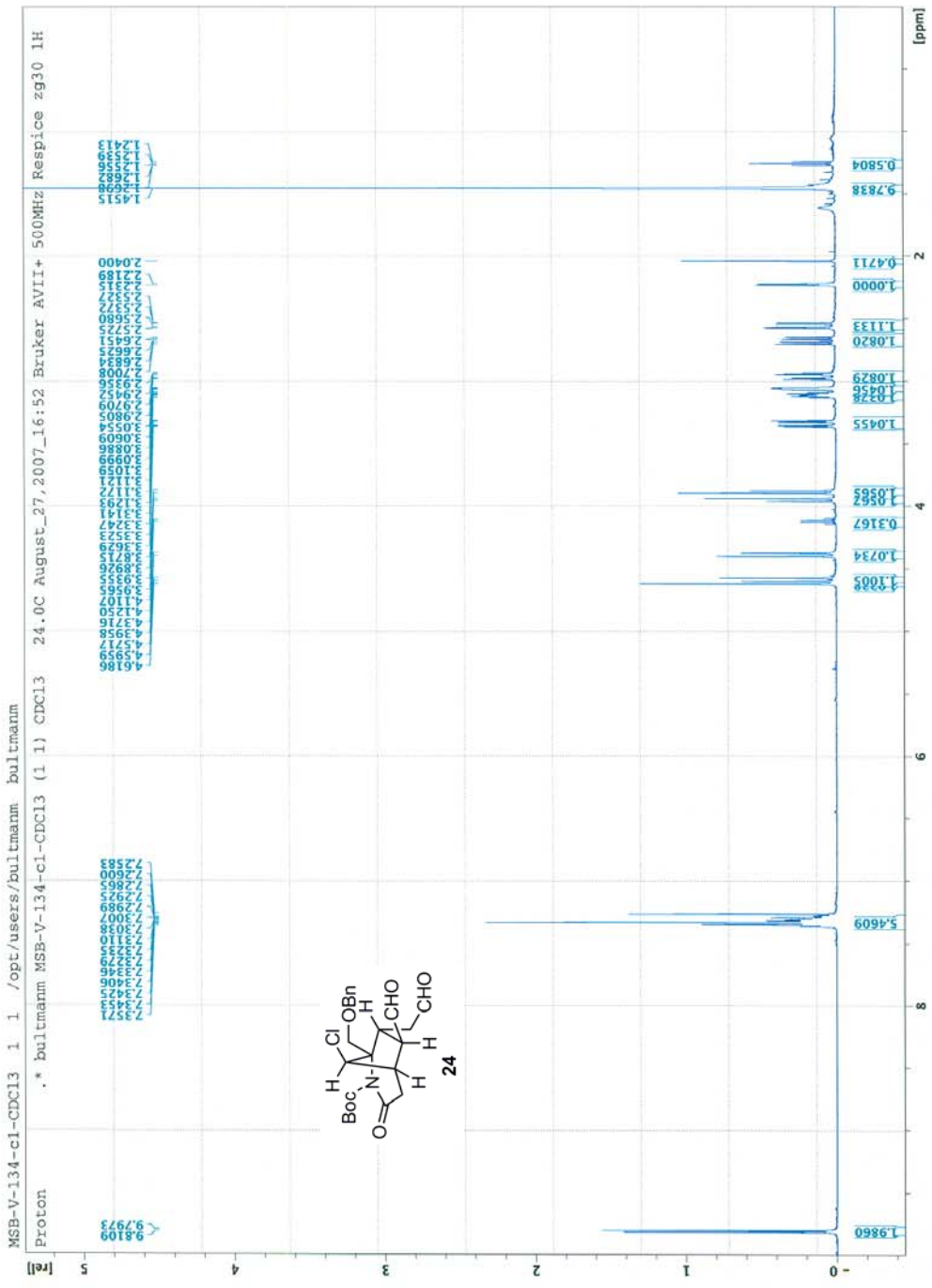

MSB-IV-268-R1-CDCl3 1 1 /opt/users/bultmanm bultmanm
Proton .* bultmanm MSB-IV-268-R1-CDCl3 (1 1) CDCl3 24.0C May_17_2007_19:03 Bruker AVII+ 500MHz Respice zg30 1H *
[rel]
[ppm]
S8

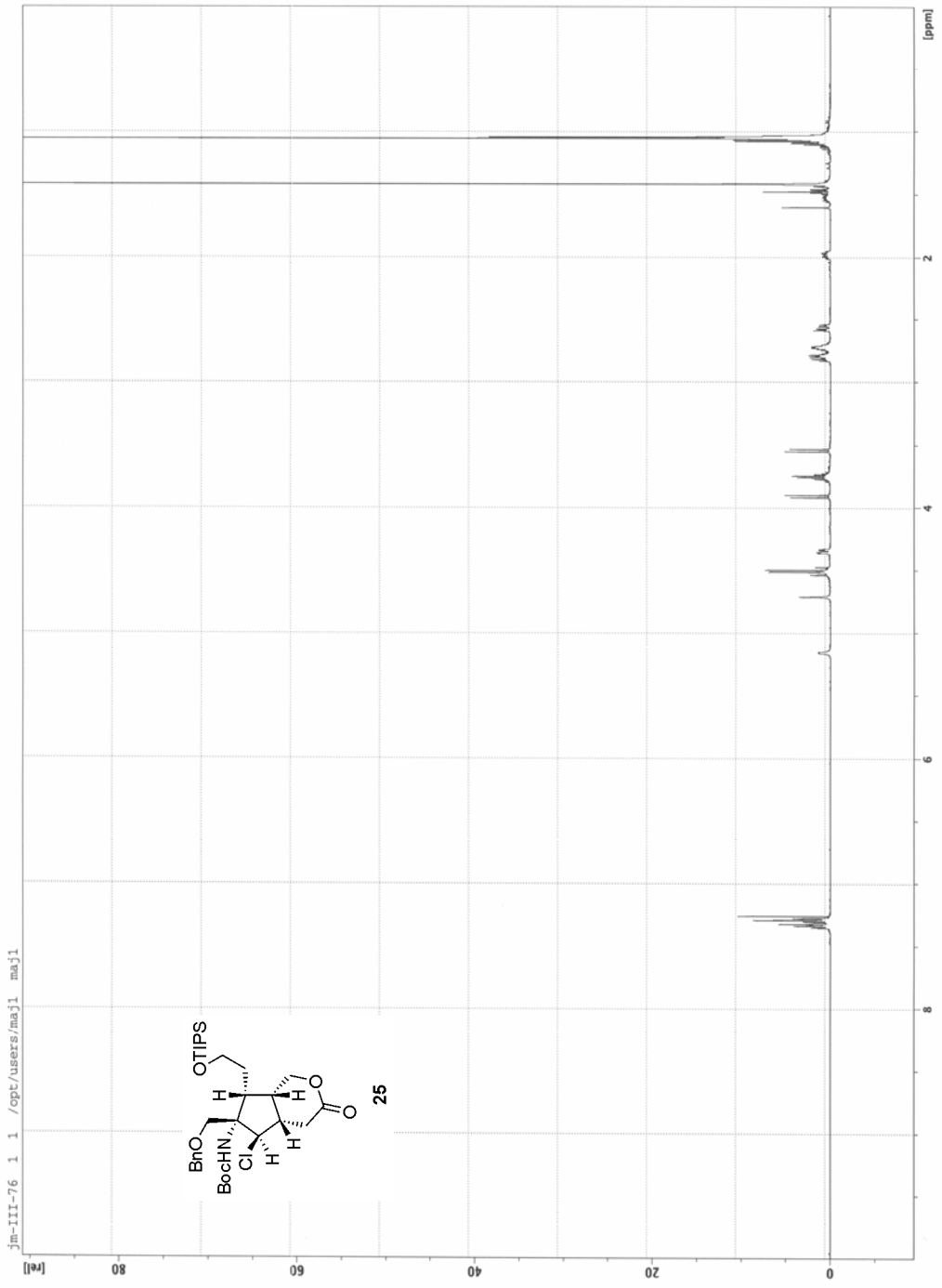

MSB-IV-219-c1-CDC13 1 1 /opt/users/bultmann bultmann
Proton .* bultmann MSB-IV-219-c1-CDC13 (1 1) CDC13 20.8C April_17_2007_09:39 Bruker AVII+ 500MHz Respice zg30 1H *.
[rel]
[ppm]
4.8204
0.9726
0.9687
1.0099
0.9824
2.0063
1.0088
1.0000
0.9836
1.0009
1.0395
1.0260
1.0293
Cl
OBn
H
H
H
O
22

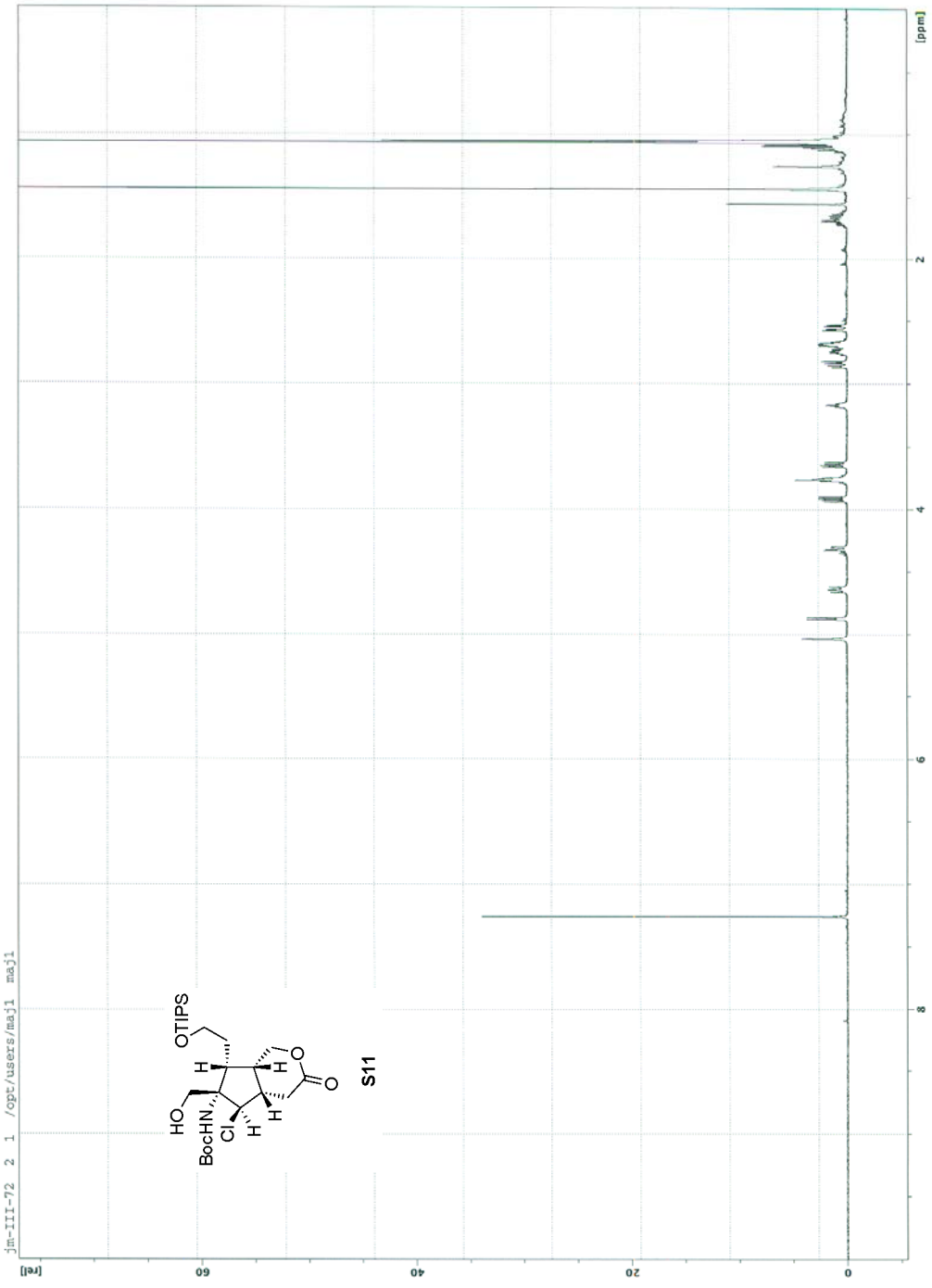

MSB-IV-222-CDCl3 1 1 /opt/users/bultmann bultmann
Proton
.* bultmann MSB-IV-222-CDCl3 (1 1) CDCl3 24.0C April_18.2007_12:50 Bruker AVII+ 500MHz Respice zg30 1H *.
[ppm]
3.1426
1.0193
0.9827
1.0000
0.0499
0.0216
0.0600
1.0031
0.0605
0.0407
0.9962
0.9898
0.8922
4.7285
Cl
OBn
H
H
H
HO-N
S9

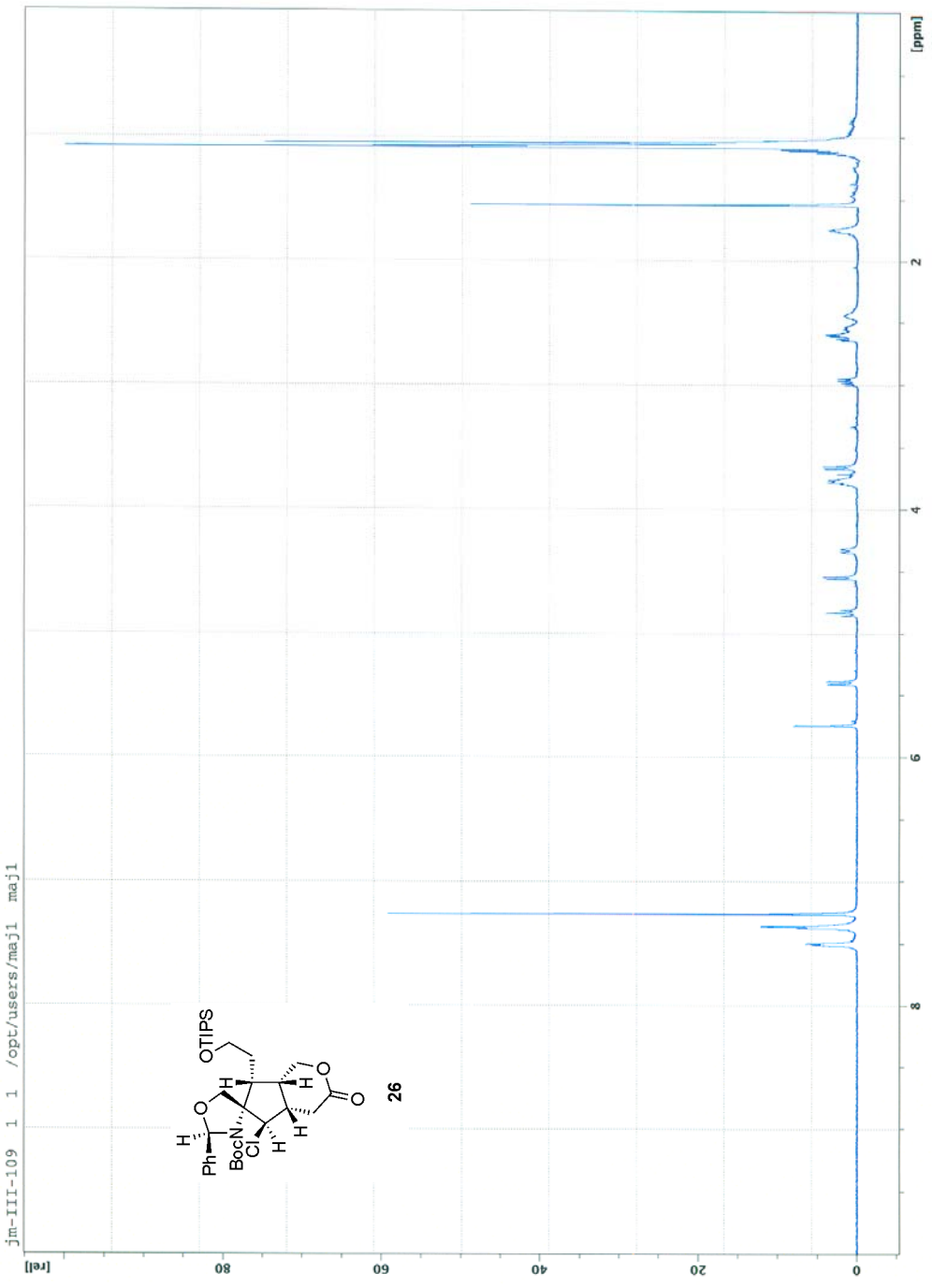

MSB-IV-223-c3-CDCl3 1 1 /opt/users/bultmann bultmann
[rel]
[ppm]
S10

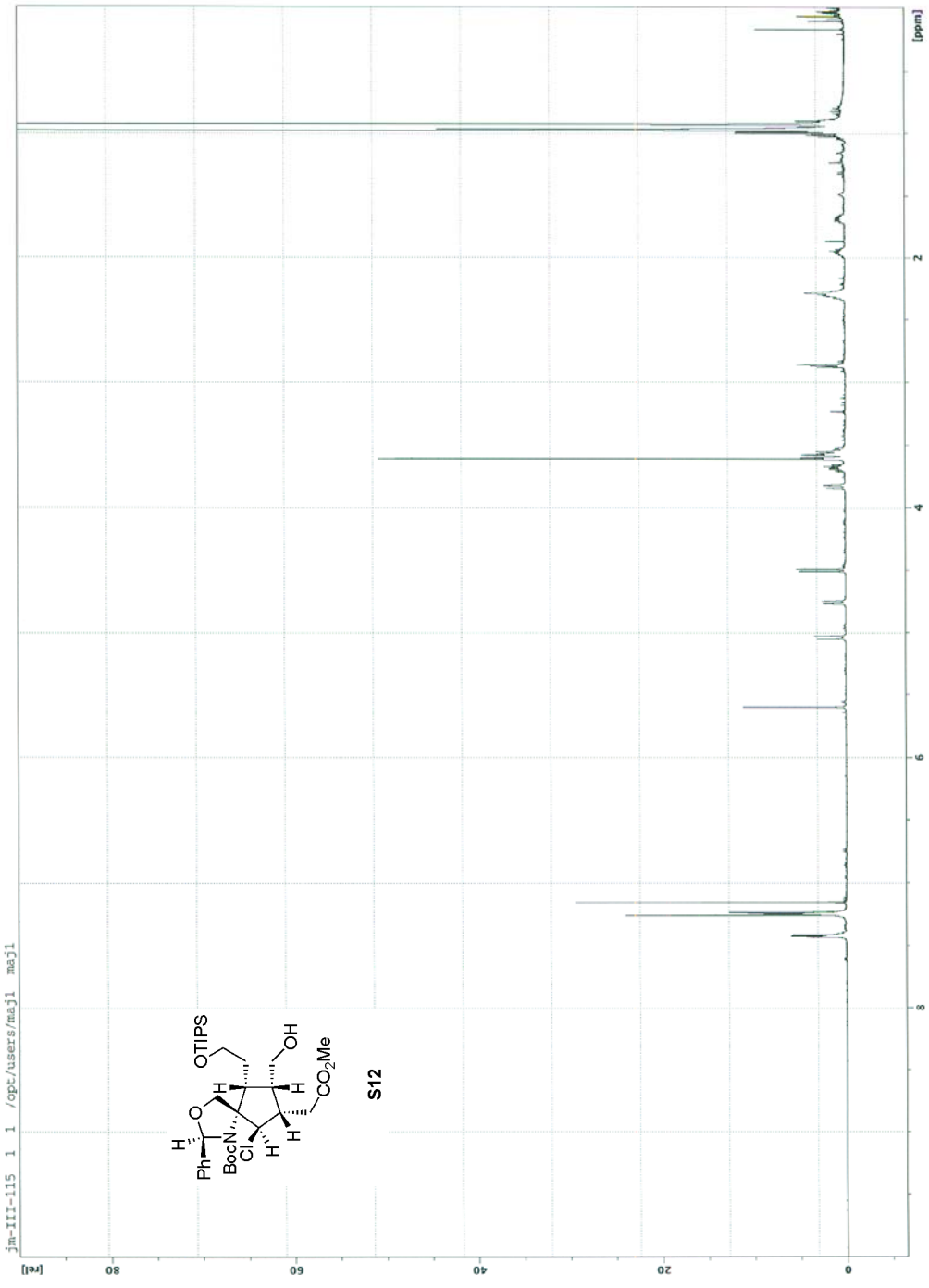

MSB-IV-243-c1-CDCl3 1 1 /opt/users/bultmann bultmann
Proton .* bultmann MSB-IV-243-c1-CDCl3 (1 1) CDCl3 21.7C May_01,2007_09:08 Bruker AVII+ 500Mhz Respice zg30 1H
[rel]
[ppm]
9.1565
2.1003
1.0588
1.0322
2.0754
1.0351
1.0266
1.0322
1.0339
1.0318
1.0000
1.0286
1.0291
5.1711
Cl
OBn
H
H
H
Boc
N
O
23

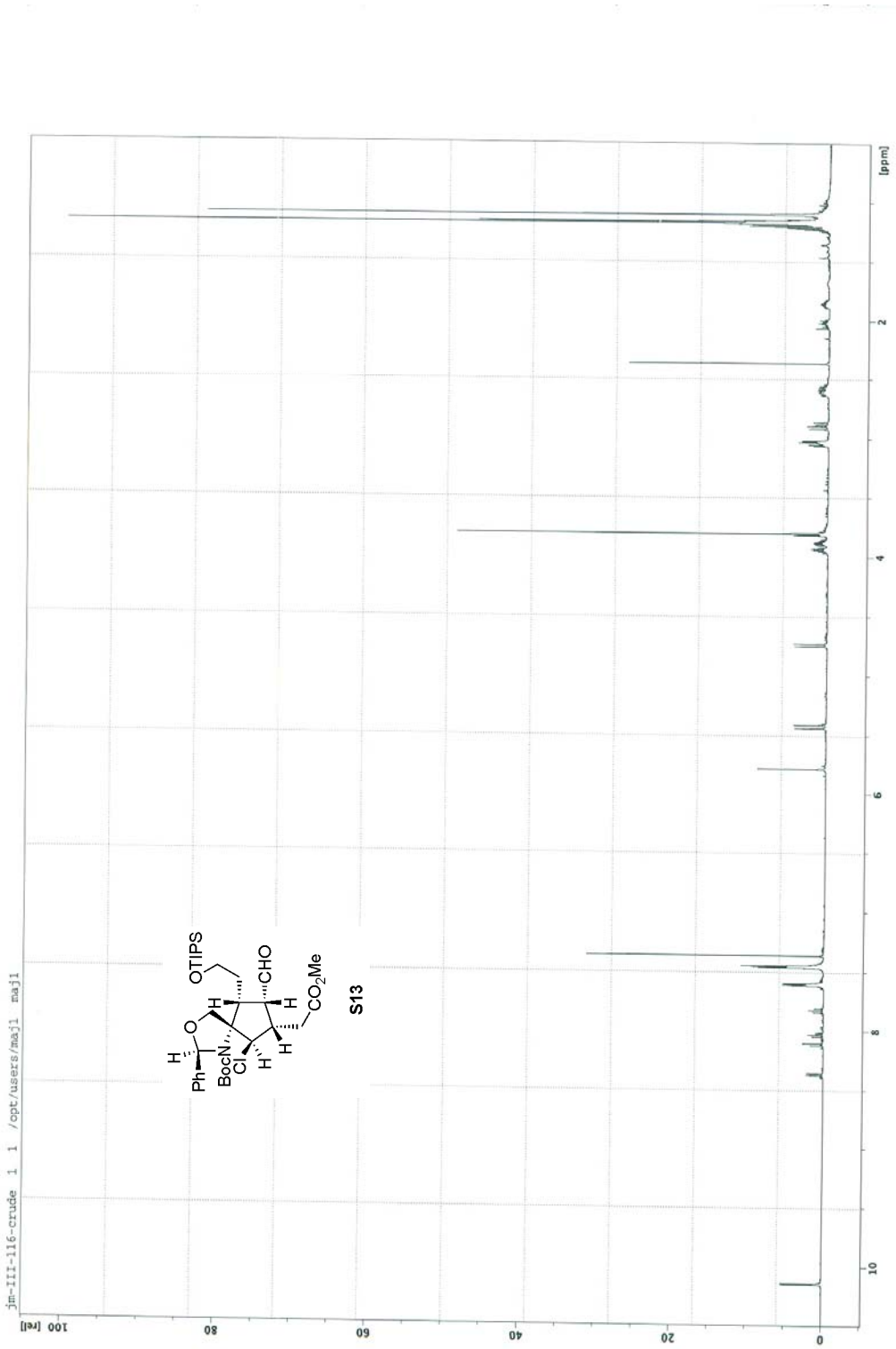

MSB-V-134-c1-CDC13 1 1 /opt/users/bultmanm bultmanm
Proton .* bultmanm MSB-V-134-c1-CDC13 (1 1) CDCl3 24.0C August_27,2007_16:52 Bruker AVII+ 500MHz Respice zg30 1H
[rel]
[ppm]
Cl
OBn
H
CHO
CHO
H
H
Boc
N
O
24


jm-III-76 1 1 /opt/users/maj1 maj1
[rel]
80
60
40
20
0
[ppm]
2
4
6
8
OTIPS
BnO
BocHN
Cl
H
H
H
O
O
25

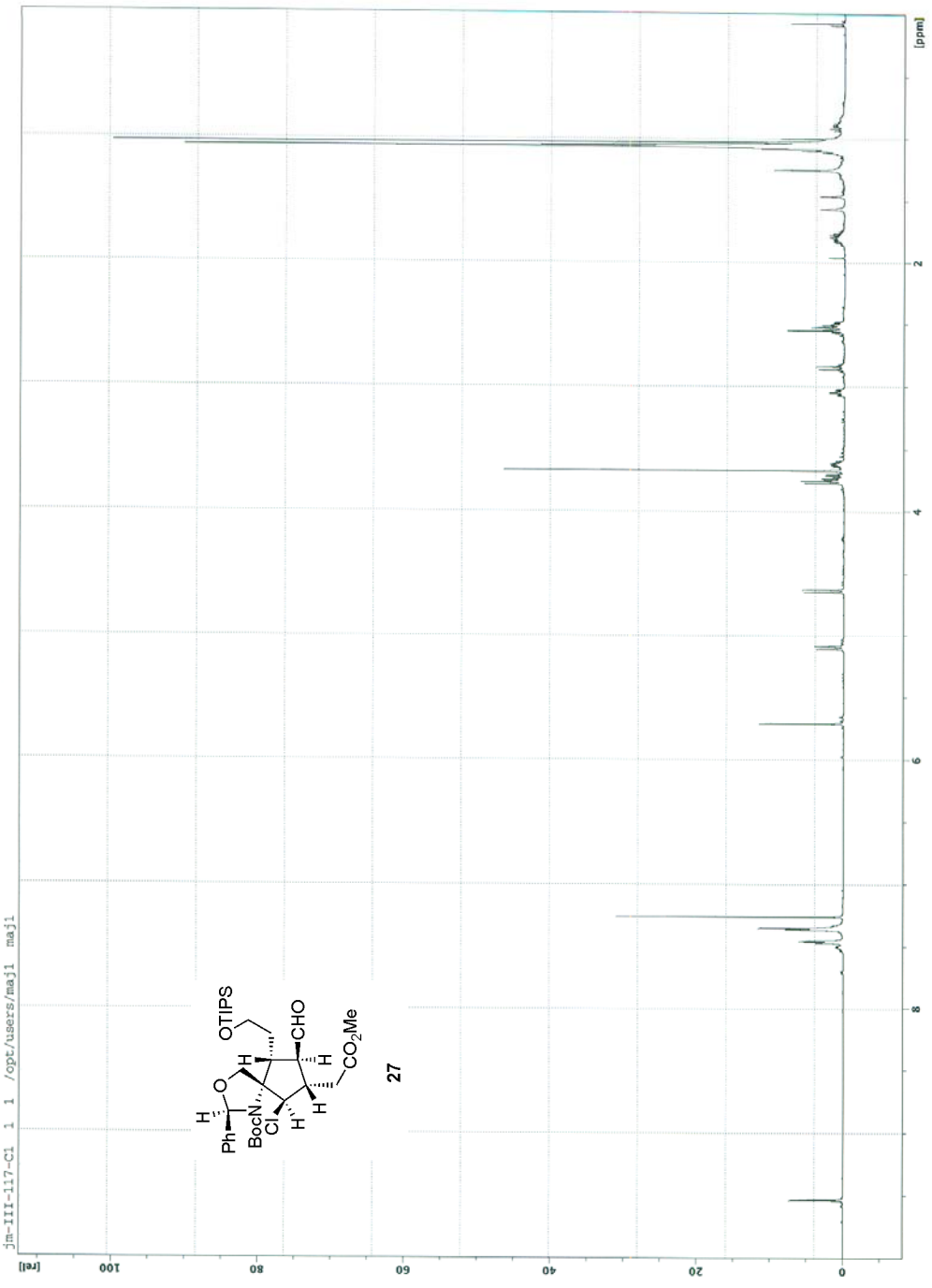

jm-III-72 2 1 /opt/users/maj1 maj1
[rel]
60
40
20
0
[ppm]
2
4
6
8
OTIPS
HO
BocHN
Cl
H
H
H
O
O
S11


jm-III-109 1 1 /opt/users/maj1 maj1
[rel]
[ppm]
0
20
40
60
80
2
4
6
8
OTIPS
H
O
Ph
BocN
Cl
H
H
H
O
O
26


jm-III-115 1 1 /opt/users/maj1 maj1
[rel]
80
60
40
20
0
[ppm]
2
4
6
8
OTIPS
OH
H
O
H
BocN
Cl
H
H
Ph
CO2Me
S12


jm-III-116-crude 1 1 /opt/users/maj1 maj1
[rel]
100
80
60
40
20
0
[ppm]
10
8
6
4
2
OTIPS
CHO
CO2Me
BocN
Cl
Ph
O
H

S13


jm-III-117-C1 1 1 /opt/users/maj1 maj1
[rel]
100
80
60
40
20
0
[ppm]
2
4
6
8
OTIPS
CHO
CO2Me
Ph
BocN
Cl
H
O

27