Component-Based Syntheses of Trioxacarcin A, DC-45-A1, and Structural Analogs

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Supplementary Information

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General Experimental Procedures

All reactions were performed in round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM), an acidic solution of *p*-anisaldehyde in ethanol (Anis), or an aqueous sodium hydroxide–potassium carbonate solution of potassium permanganate ($KMnO_4$) then briefly heated with a flameless heat gun. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å, 32–63 μM,

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

standard grade, Dynamic Adsorbents, Inc. and 60 Å, 40–60 μM, standard grade, Agela Technologies).

Materials

Commercial solvents and reagents were used as received with the following exceptions: Tetrahydrofuran, dichloromethane, benzene, and ether were purified by the method of Pangborn et al.[2]

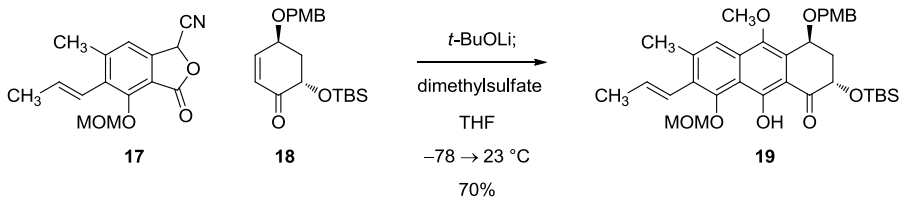
Instrumentation

Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Varian INOVA 500 (125 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]^{T[^\circ C]}_{\lambda}$ (c = g/100 mL, solvent). Circular dichroism spectra were obtained using a Jasco J-710 spectropolarimeter. High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. High performance liquid chromatography purifications were performed using an Agilent Technologies 1200 Series preparative HPLC system.

[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the Supporting Information beginning with **40**.)*

Large-Scale Synthesis of Synthetic Precursor 1

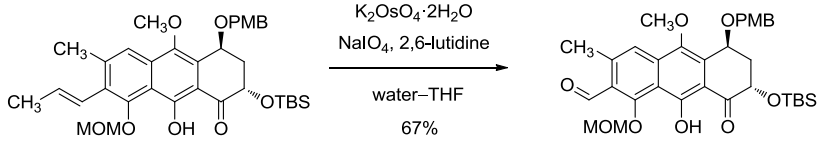


(*E*)-7-Propenyl-3,4-dihydroanthracen-1-one (19).[3]

Lithium *tert*-butoxide (1.0 M solution in tetrahydrofuran, 47.5 mL, 47.5 mmol, 3.0 equiv) was added to a solution of (*E*)-4-(methoxymethoxy)-6-methyl-3-oxo-5-(prop-1-enyl)-1,3-dihydroisobenzofuran-1-carbonitrile **17** (4.33 g, 15.8 mmol, 1 equiv) in tetrahydrofuran (86 mL) at –78 °C. After 5 min, a solution of (4*S*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)cyclohex-2-enone **18** (5.74 g, 15.83 mmol, 1.0 equiv) in tetrahydrofuran (86 mL) was added by cannula. The reaction flask was allowed to warm to –20 °C over 3 h, then dimethylsulfate (13.6 mL, 142 mmol, 9.0 equiv) was added. The reaction flask was allowed to warm to 23 °C over 2 h. After an additional 2 h, the reaction mixture was partitioned between saturated aqueous ammonium chloride solution (500 mL) and ethyl acetate (1 L). The layers were separated. The organic layer was washed sequentially with water (500 mL) then saturated aqueous sodium chloride solution (500 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (hexanes initially, grading to 5% ethyl acetate–hexanes) to provide the product, (*E*)-7-propenyl-3,4-dihydroanthracen-1-one (**19**), as an orange foam (6.87 g, 70%).[3] TLC: (17% ethyl acetate–hexanes) R_f = 0.36 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.89 (s, 1H), 7.63 (s, 1H), 7.28 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.2 Hz), 6.53 (d, 1H, *J* = 16.3 Hz), 6.11 (dq, 1H, *J* = 16.2, 6.4 Hz), 5.2 (m, 1H), 5.09 (d, 1H, *J* = 6.2 Hz), 5.04 (d, 1H, *J* = 6.2 Hz), 4.99 (dd, 1H, *J* = 12.6, 5.3 Hz), 5.78 (d, 1H, *J* = 11.0 Hz), 4.58 (d, 1H, *J* = 11.0 Hz), 3.85 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 2.72 (ddd, 1H, *J* = 13.3, 4.8, 3.2 Hz), 2.50 (s, 3H), 2.18 (m, 1H), 1.97 (d, 3H, *J* = 6.4 Hz), 0.98 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.7, 161.4, 159.2, 153.8, 144.8, 141.2,

[3] Švenda, J.; Hill, N.; Myers, A. G. *P. Natl. Acad. Sci. USA* **2011**, *108*, 6709–6714.

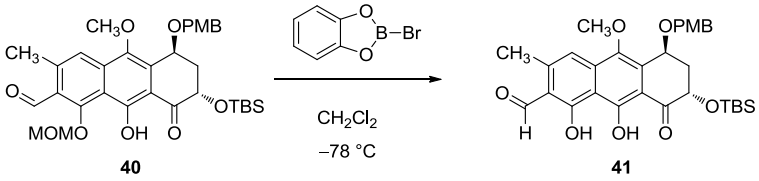
133.1, 132.4, 131.7, 130.2, 129.5, 125.4, 125.1, 119.1, 188.8, 113.8, 108.4, 101.3, 70.8, 69.4, 68.8, 62.8, 57.9, 55.3, 36.6, 25.9, 22.2, 19.3, 18.6, –4.4, –5.3; FTIR (neat), cm^{-1}: 2951 (w), 2930 (w), 1611 (m), 1514 (w), 1443 (w), 1381 (w), 1362 (m), 1248 (m), 1155 (m), 1124 (m), 1040 (s), 1003 (m), 928 (m), 872 (m), 835 (m), 779 (m); HRMS (ESI): Calcd for $(C_{35}H_{46}O_8Si+Na)^+$ 645.2854, found 645.2854.



19 **40**

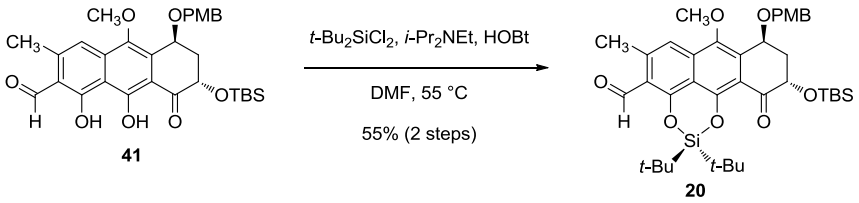
7-Formyl-3,4-dihydroanthracen-1-one (40)[3]

2,6-Lutidine (2.57 mL, 22.1 mmol, 2.0 equiv) was added to an ice-cooled solution of (*E*)-7-propenyl-3,4-dihydroanthracen-1-one **19** (6.87 g, 11.0 mmol, 1 equiv), potassium osmate dihydrate (203 mg, 0.552 mmol, 0.05 equiv), and sodium periodate (9.44 g, 44.1 mmol, 4.0 equiv) in a mixture of tetrahydrofuran (160 mL) and water (80 mL). After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 2.5 h, the reaction mixture was partitioned between water (600 mL), ethyl acetate (1.2 L), and hexanes (600 mL). The layers were separated. The organic layer was washed with water (600 mL) then saturated aqueous sodium chloride solution (600 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes) to provide the product, 7-formyl-3,4-dihydroanthracen-1-one (**40**), as an orange foam (4.52 g, 67%).[3] TLC: (10% ethyl acetate–hexanes) R_f = 0.18 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.96 (s, 1H), 9.64 (s, 1H), 7.64 (s, 3H), 7.28 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.5 Hz), 5.29–5.20 (m, 3H), 5.00 (dd, 1H, *J* = 12.2, 5.1 Hz), 4.70 (d, 1H, *J* = 11.0 Hz), 4.60 (d, 1H, *J* = 11.0 Hz), 3.86 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 2.74 (s, 3H), 2.73 (m, 1H), 2.19 (m, 1H), 0.98 (s, 9H), 0.26 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.2, 193.3, 163.2, 161.6, 159.4, 144.7, 141.8, 137.0, 129.9, 129.5, 127.6, 120.7, 118.1, 113.9, 109.2, 102.8, 71.1, 69.3, 68.6, 62.9, 58.4, 55.3, 36.3, 25.8, 22.3, 18.5, –4.5, –5.3; FTIR (neat), cm^{-1}: 2953 (w), 2930 (w), 2857 (w), 1686 (m), 1611 (s), 1514 (m), 1385 (m), 1364 (m), 1246 (s), 1153 (s), 1042 (s), 1011 (m), 930 (m), 872 (m), 837 (m), 779 (m); HRMS (ESI): Calcd for $(C_{33}H_{42}O_9Si+Na)^+$ 633.2490, found 633.2464.



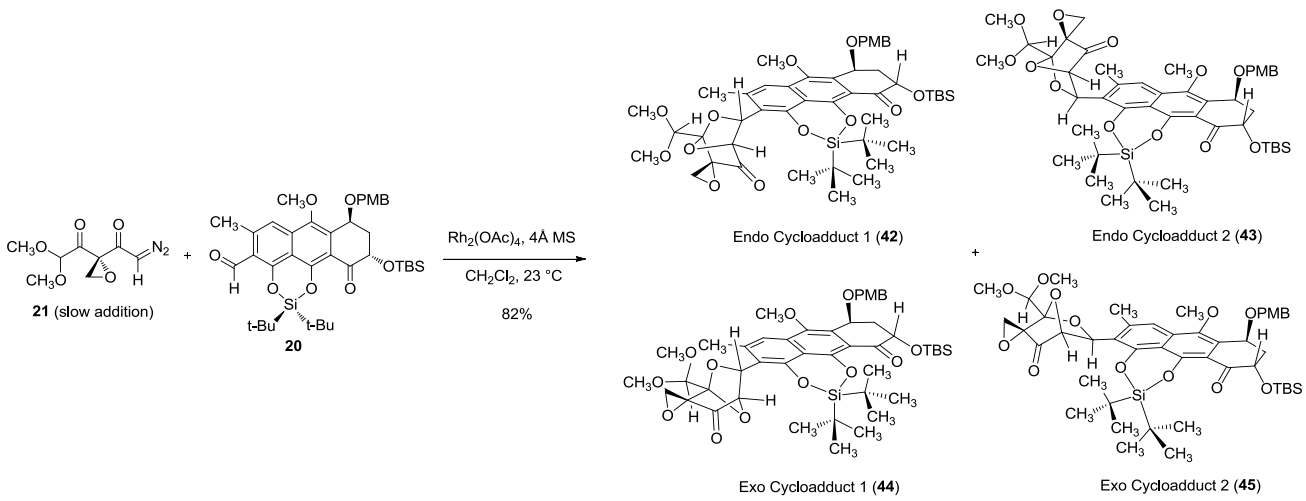
8,9-Dihydroxy-7-formyl-3,4-dihydroanthracen-1-one (41).[3]

A solution of *B*-bromocatecholborane (2.54 g, 12.8 mmol, 2.0 equiv) in dichloromethane (94 mL) was added to a solution of 7-formyl-3,4-dihydroanthracen-1-one **40** (3.90 g, 6.39 mmol, 1 equiv) in dichloromethane (94 mL) at –78 °C. After 50 min, the reaction mixture was diluted with saturated aqueous sodium bicarbonate solution (300 mL) and dichloromethane (500 mL). The cooling bath was removed, and the partially frozen mixture was allowed to warm to 23 °C. The biphasic mixture was diluted with 0.2 M aqueous sodium hydroxide solution (1.25 L). The layers were separated. The dark-purple aqueous layer was extracted with dichloromethane (2 × 1 L). The organic layers were combined. The combined solution was washed sequentially with 0.1 M aqueous hydrochloric acid solution (500 mL), water (3 × 500 mL), then saturated aqueous sodium chloride solution (500 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the product, 8,9-dihydroxy-7-formyl-3,4-dihydroanthracen-1-one (**41**), as a yellow foam.[3] Attempts to purify **41** by flash-column chromatography led to decomposition. TLC: (30% ethyl acetate–hexanes) R_f = 0.22 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 15.58 (br s, 1H), 10.51 (s, 1H), 7.28 (d, 2H, *J* = 8.7 Hz), 7.25 (s, 1H), 6.87 (d, 2H, *J* = 8.7 Hz), 5.16 (m, 1H), 4.99 (dd, 1H, *J* = 12.3, 5.2 Hz), 4.68 (d, 1H, *J* = 11.1 Hz), 4.59 (d, 1H, *J* = 10.7 Hz), 3.84 (s, 3H), 3.80 (s, 3H), 2.73 (s, 3H), 2.71 (m, 1H), 2.18 (m, 1H), 0.97 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.9, 192.7, 166.5, 163.6, 159.4, 144.8, 142.7, 137.7, 130.7, 129.9, 129.5, 114.8, 114.2, 113.9, 108.5, 71.1, 69.0, 68.6, 62.8, 55.3, 36.5, 25.8, 21.0, 18.5, –4.5, –5.3; FTIR (neat), cm^{-1}: 3329 (w, br), 2953 (m), 2930 (m), 2857 (m), 1682 (m), 1614 (s), 1514 (m) 1391 (m) 1246 (s), 1153 (s), 1049 (m), 1034 (m) 870 (m), 837 (s); HRMS (ESI): Calcd for $(C_{31}H_{38}O_8Si+H)^+$ 567.2409, found 567.2398.



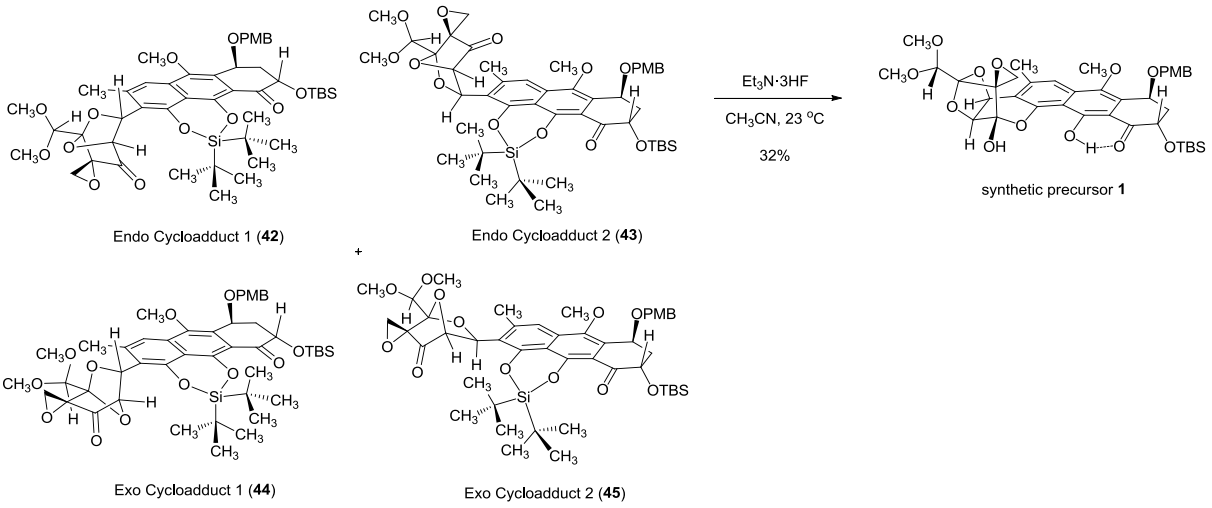
Differentially Protected Aldehyde 20.[3]

Di-*tert*-butyldichlorosilane (2.43 mL, 11.5 mmol, 1.8 equiv) was added to a solution of 8,9-dihydroxy-7-formyl-3,4-dihydroanthracen-1-one **41** (1 equiv, see paragraph above), *N*,*N*-diisopropylethylamine (5.58 mL, 31.9 mmol, 5.0 equiv), and anhydrous 1-hydroxybenzotriazole (432 mg, 3.19 mmol, 0.5 equiv) in dimethylformamide (128 mL) at 23 °C. The reaction flask was heated in an oil bath at 55 °C. After 80 min, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and ether (1.5 L). The layers were separated. The organic layer was washed with water (2 × 500 mL) then saturated aqueous sodium chloride solution (300 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes) to provide of the product **20** as a yellow foam (2.50 g, 55% over steps).[3] TLC: (40% ethyl acetate–hexanes) R_f = 0.87 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.8 (s, 1H), 7.34 (s, 1H), 7.31 (d, 2H, *J* = 6.5 Hz), 6.88 (d, 2H, *J* = 7.0 Hz), 5.20 (dd, 1H, *J* = 3.0, 3.0 Hz), 4.88 (dd, 1H, *J* = 12.5, 5.0 Hz), 4.73 (d, 1H, *J* = 11.0 Hz), 4.63 (d, 1H, *J* = 10.5 Hz), 3.90 (s, 3H), 3.79 (s, 3H), 2.77–2.72 (m, 1H), 2.72 (s, 3H), 2.19–2.13 (m, 1H), 1.15 (s, 9H), 1.12 (s, 9H), 0.96 (s, 9H), 0.24 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 194.2, 190.9, 160.4, 159.4, 150.2, 146.3, 140.3, 134.0, 133.2, 130.0, 129.8, 199.4, 116.5, 115.6, 115.3, 114.0, 71.4, 71.2, 69.8, 62.7, 55.3, 36.3, 26.1, 26.0, 26.0, 22.5, 21.4, 21.0, 18.7, –4.3, –5.4; FTIR (neat), cm^{-1}: 2936 (s), 1786 (s), 1684 (s), 1607 (s), 1373 (s), 1247 (s), 1157 (s), 1034 (s); HRMS (ESI): Calcd for $(C_{39}H_{54}O_8Si_2+H)^+$ 707.3430, found 707.3422.



Gram-Scale Endo-Selective Carbonyl Ylide–Aldehyde Cycloaddition:

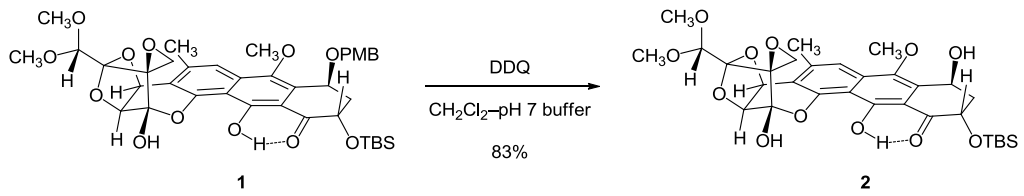
A solution of (*S*)-1-diazo-3-epoxy-5,5-dimethoxypenta-2,4-dione **21**[3] (2.27 g, 10.6 mmol, 3.0 equiv) in dichloromethane (3.9 mL) was added by a motor-driven syringe pump over 6 h to a suspension of differentially protected aldehyde **20** (2.50 g, 3.54 mmol, 1 equiv), rhodium(II) acetate (31 mg, 71 μmol, 0.02 equiv), and powdered 4-Å molecular sieves (500 mg) in dichloromethane (3.9 mL) at 23 °C. After 30 min, the reaction mixture was filtered through a short pad of silica gel (length: 10 cm; diameter: 1.5 cm), eluting with 40% ethyl acetate–hexanes to remove the rhodium(II) acetate and powdered 4-Å molecular sieves. The filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes) to provide, together, 2.59 g of a mixture of cycloadducts **42** (44%), **43** (37%), **44** (16%), and **45** (3%), as depicted above (82% yield).[3] In addition, 380 mg (15%) of the starting material, the differentially protected aldehyde **20**, was recovered.



Synthetic Precursor 1.

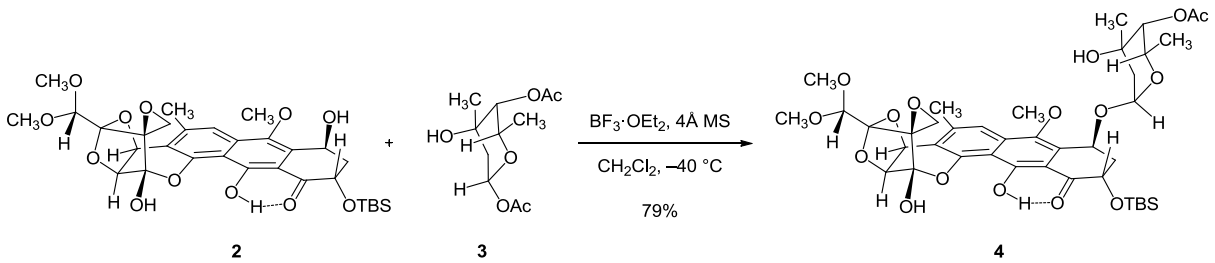
Triethylamine–trihydrofluoride (1.42 mL, 8.70 mmol, 3.0 equiv) was added to a solution of a mixture of cycloadducts **42**, **43**, **44**, and **45** (2.59 g, 2.90 mmol, 1 equiv, as described above) in acetonitrile (58 mL) at 23 °C. After 15 min, the bright yellow solution was diluted with dichloromethane (500 mL). The diluted solution was washed sequentially with pH 7 aqueous phosphate buffer solution (100 mL) then saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel deactivated with triethylamine (30% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes; two purifications) to provide synthetic precursor **1** as a yellow-green foam (690 mg, 32%).[3] TLC: (30% ethyl acetate–hexanes) R_f = 0.46 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (s, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 3.0 Hz, 1H), 5.48 (d, *J* = 3.5 Hz, 1H), 5.15 (dd, *J* = 2.5, 3.0 Hz, 1 H), 4.85 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.77 (s, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.63 (d, *J* = 6.0 Hz, 1H), 3.61 (s, 3H), 3.61 (s, 3H), 3.07 (d, *J* = 7.0 Hz, 1H), 2.75 (s, 3H), 2.73–2.69 (m, 1H), 2.17–2.11 (m, 1H), 1.19 (s, 9H), 1.07 (s, 9H), 0.95 (s, 9H), 0.23 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 201.0, 194.4, 159.3, 150.1, 149.1, 146.2, 139.6, 131.2, 130.3, 129.7, 129.4, 118.2, 116.8, 115.8, 114.5, 113.8, 107.0, 101.6, 83.4, 79.6, 71.3, 71.2, 69.6, 64.3, 62.6, 56.6, 55.9, 55.3, 50.9, 36.7, 26.4, 26.1, 26.0, 23.6, 21.2, 21.2, 18.7, –4.3, –5.3; FTIR (neat), cm^{-1}: 2928 (s), 2857 (s), 1784 (s), 1699 (s), 1611 (s), 1371 (s), 1250 (s); HRMS (ESI): Calcd for $(C_{47}H_{64}O_{13}Si_2+H)^+$ 893.3958, found 893.3932.

Synthesis of DC-45-A1 and Trioxacarcinose B Monoglycoside 9



Benzylic Alcohol 2.

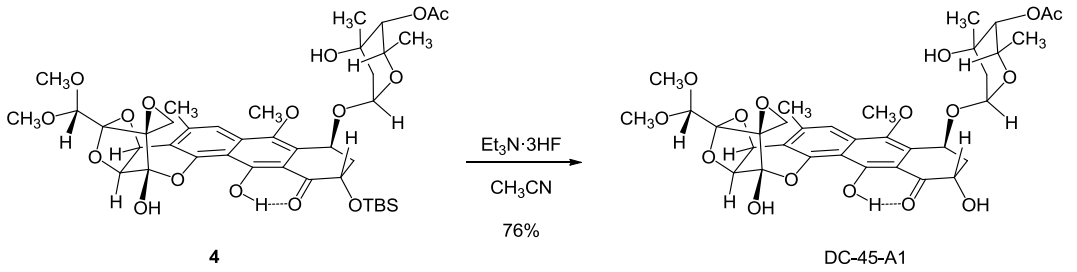
2,3-Dichloro-5,6-dicyanobenzoquinone (16 mg, 70 mmol, 1.1 equiv) was added to a vigorously stirring, biphasic solution of synthetic precursor **1** (48 mg, 64 mmol, 1 equiv) in dichloromethane (1.0 mL) and pH 7 aqueous phosphate buffer solution (100 μL) at 23 °C. The reaction flask was covered with aluminum foil to exclude light. Over the course of 2 h, the reaction mixture was observed to change from myrtle green to lemon yellow. The product solution was partitioned between water (5 mL) and dichloromethane (40 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure benzylic alcohol **2** as a yellow-green powder (33.6 mg, 83%). TLC: (60% ethyl acetate–hexanes) R_f = 0.39 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.62 (s, 1H), 7.40 (s, 1H), 5.41 (t, *J* = 3.4 Hz, 1H), 5.25 (d, *J* = 4.1 Hz, 1H), 4.88 (dd, *J* = 11.7, 4.8 Hz, 1H), 4.85 (d, *J* = 4.1 Hz, 1H), 4.70 (s, 1H), 4.55 (br, 1H), 3.90 (s, 3H), 3.61 (s, 3H), 3.46 (s, 3H), 3.10 (d, *J* = 5.5 Hz, 1H), 3.02 (d, *J* = 5.5 Hz, 1H), 2.58 (s, 3H), 2.52–2.46 (m, 1H), 2.36–2.30 (m, 1H), 0.94 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.9, 162.4, 151.5, 143.8, 142.0, 135.1, 129.5, 116.1, 114.7, 114.7, 107.9, 103.9, 100.1, 98.5, 73.2, 69.6, 69.4, 69.2, 62.6, 62.5, 57.0, 56.6, 50.4, 38.7, 25.8, 20.4, 18.5, –4.5, –5.3; FTIR (neat), cm^{-1}: 3466 (br), 2953 (w), 1622 (m), 1389 (m), 1123 (s), 1069 (s), 945 (s), 729 (s); HRMS (ESI): Calcd for $(C_{31}H_{41}O_{12}Si+H)^+$ 633.2362, found 633.2364.



α-Glycoside 4.

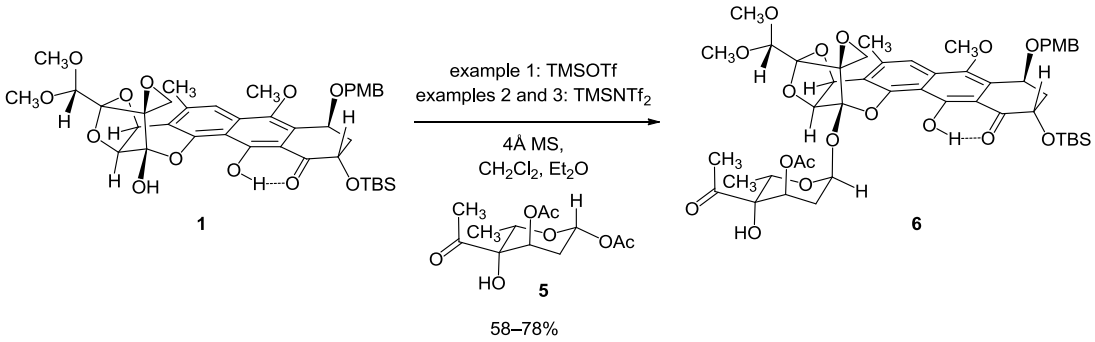
Boron trifluoride etherate (4.6 μL, 36 μmol, 1.0 equiv) was added to a suspension of benzylic alcohol **2** (23 mg, 36 μmol, 1 equiv), 1-*O*-acetyltrioxacarcinose A (**3**)[4] (18 mg, 73 μmol, 2.0 equiv, a 1:12 mixture of α- and β-anomers, respectively), and powdered 4-Å molecular sieves (~50 mg) in dichloromethane (720 μL) at –40 °C. After 5 min, saturated aqueous sodium bicarbonate solution (1 mL) was added rapidly, and the reaction flask was allowed to warm to 23 °C. The mixture was partitioned between dichloromethane (40 mL) and saturated aqueous sodium chloride solution (5 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide the pure α-glycoside **4** as a yellow-green powder (23.5 mg, 79%). TLC: (5% methanol–dichloromethane) R_f = 0.40 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.84 (s, 1H), 7.47 (s, 1H), 5.38 (d, *J* = 3.6 Hz, 1H), 5.35 (app s, 1H), 5.26 (d, *J* = 4.0 Hz, 1H), 4.84 (d, *J* = 4.0 Hz, 1H), 4.78 (dd, *J* = 12.3, 5.2 Hz, 1H), 4.75 (s, 1H), 4.71 (s, 1H), 4.52 (q, *J* = 6.6 Hz, 1H), 4.35 (s, 1H), 3.83 (s, 3H), 3.81 (s, 1H), 3.62 (s, 3H), 3.47 (s, 3H), 3.15 (d, *J* = 5.3 Hz, 1H), 3.05 (d, *J* = 5.3 Hz, 1H), 2.60 (s, 3H), 2.58 (m, 1H), 2.35 (dt, *J* = 12.5, 2.6 Hz, 1H), 2.14 (s, 3H), 1.96 (dd, *J* = 14.6, 4.1 Hz, 1H), 1.62 (d, *J* = 14.6 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 3H), 0.95 (s, 9H), 0.24 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.8, 170.5, 163.2, 151.8, 144.4, 142.4, 135.2, 126.6, 116.8, 115.2, 115.1, 108.3, 104.0, 100.3, 98.6, 98.3, 74.6, 73.4, 69.8, 69.5, 69.5, 68.9, 68.4, 62.9, 62.7, 57.2, 56.8, 50.7, 38.8, 36.8, 26.0, 25.9, 21.1, 20.6, 18.6, 17.0, –4.2, –5.3; FTIR (neat), cm^{-1}: 3516 (br), 2934 (w), 1749 (m), 1622 (m), 1391 (m), 1229 (s), 1121 (s), 995 (s), 943 (s), 868 (m), 837 (m); HRMS (ESI): Calcd for $(C_{40}H_{54}O_{16}Si+Na)^+$ 841.3073, found 841.3064.

[4] Smaltz, D. J.; Švenda, J.; Myers, A. G. *Org. Lett.* **2012,** *14,* 1812–1815.



DC-45-A1.

Triethylamine–trihydrofluoride (42 μL, 0.26 mmol, 30 equiv) was added to a solution of α-glycoside **4** (7.0 mg, 8.6 μmol, 1 equiv) in acetonitrile (290 μL) at 23 °C. The reaction flask was covered with aluminum foil to exclude light. After 15 h, the product solution was partitioned between dichloromethane (50 mL) and saturated aqueous sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration pure DC-45-A1 as a yellow-orange powder (4.6 mg, 76%). TLC: (5% methanol–dichloromethane) R_f = 0.30 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.23 (s, 1H), 7.49 (s, 1H), 5.40–5.37 (m, 2H), 5.26 (d, *J* = 4.0 Hz, 1H), 4.84 (d, *J* = 3.7 Hz, 1H), 4.78–4.73 (m, 2H), 4.71 (s, 1H), 4.54 (q, *J* = 6.2 Hz, 1H), 4.43 (br, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 3.58 (br, 1H), 3.47 (s, 3H), 3.16 (d, *J* = 5.1 Hz, 1H), 3.04 (d, *J* = 5.5 Hz, 1H), 2.83–2.77 (m, 1H), 2.62 (s, 3H), 2.22 (dt, *J* = 13.2, 2.6 Hz, 1H), 2.14 (s, 3H), 1.96 (dd, *J* = 14.3, 4.0 Hz, 1H), 1.61 (d, *J* = 14.3 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.8, 170.3, 163.1, 151.7, 144.8, 143, 135.5, 126.5, 116.8, 115.3, 114.8, 107.3, 103.9, 100.1, 98.6, 98.1, 74.4, 73.2, 69.5, 69.3, 68.8, 67.9, 67.7, 62.9, 62.7, 57.1, 56.6, 50.5, 36.7, 36.6, 25.7, 20.9, 20.5, 16.9; FTIR (neat), cm^{-1}: 3476 (br), 2934 (m), 1736 (s), 1622 (m), 1389 (s), 1229 (s), 1144 (s), 1082 (s), 997 (s); HRMS (ESI): Calcd for $(C_{34}H_{40}O_{16}+Na)^+$ 727.2209, found 727.2200.



α-Glycoside 6.

Example 1: (20 equiv TMSOTf, 30 equiv 5)

To a solution of the synthetic precursor **1** (30.0 mg, 0.040 mmol, 1 equiv) in benzene (3 mL) at 23 °C was added 1-*O*-β-acetyl glycoside **5**[5] (328 mg, 1.19 mmoL, 30.0 equiv). The bright yellow solution was concentrated and the residue was blanketed with argon. Dichloromethane (1.9 mL) and ether (0.27 mL) were added, followed by crushed 4-Å molecular sieves (600 mg). The bright yellow suspension was stirred for 90 min at 23 °C, then was cooled to –78 °C. Trimethylsilyl trifluoromethanesulfonate (72 μL, 0.399 mmol, 10.0 equiv) was added dropwise by syringe over 10 min. After 2 h, a second portion of trimethylsilyl trifluoromethanesulfonate (36 μL, 0.199 mmol, 5.0 equiv) was added over 10 min. After 1 h, a third portion of trimethylsilyl trifluoromethanesulfonate (36 μL, 0.199 mmol, 5.0 equiv) was added over 10 min and the internal temperature of the reaction mixture was maintained at –78 °C for 1 h. Triethylamine (111 μL, 0.747 mmol, 20.0 equiv) was added at –78 °C. The resulting yellow-orange solution was diluted with dichloromethane (50 mL) and the product mixture was filtered through a plug of Celite. The filtrate was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and dichloromethane (150 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. To remove the bulk of unreacted 1-*O*-β-acetyl glycoside **5**, the residue was passed through a short column of silica gel deactivated with triethylamine (20% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes). A colorless fraction containing unreacted 1-*O*-β-acetyl glycoside **5** was collected. A later-eluting, bright yellow fraction was concentrated. This residue was further purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **6** (30 mg, 78%, in fractions eluting at 44.8–47.0 min) as a bright yellow powder. TLC (50% ethyl acetate–hexanes): R_f = 0.30 (UV, CAM). $[\alpha]^{23}_D$ +47.3 (*c* 0.90, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.54 (s, OH), 7.46 (s, 1 H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.87

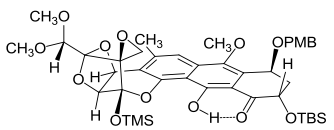
[5] Magauer, T.; Myers, A.G. *Org. Lett.* **2011,** *13*, 5584–5587.

(d, *J* = 8.4 Hz, 2 H), 5.83 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.30 (d, *J* = 4.2 Hz, 1H), 5.19 (d, *J* = 4.2 Hz, 1H), 5.19 (m, 1H), 5.00 (q, *J* = 6.0 Hz, 1H), 4.96 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.75 (t, *J* = 3.6 Hz, 1H), 4.74 (s, 1H), 4.70 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 3.86 (s, OH), 3.83 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 2.81 (d, *J* = 6.0 Hz, 1H), 2.73–2.68 (m, 1H), 2.70 (d, *J* = 6.0 Hz, 1H), 2.59 (s, 3H), 2.35 (s, 3H), 2.33–2.28 (m, 2H), 2.22 (s, 3H), 2.19–2.13 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.97 (s, 9H), 0.25 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 208.8, 203.4, 170.3, 162.9, 159.3, 151.7, 144.1, 141.8, 135.1, 130.1, 129.5, 127.7, 116.3, 114.9, 114.2, 113.9, 108.6, 104.5, 101.5, 99.4, 92.3, 78.1, 71.0, 70.6, 69.3, 69.1, 68.9, 68.2, 64.4, 62.7, 56.6, 55.8, 55.3, 47.3, 36.3, 29.7, 28.9, 26.6, 25.9, 21.3, 20.3, 18.6, 14.5, –4.4, –5.4; FTIR (neat), cm^{-1}: 3470 (w), 2928 (s), 1740 (s), 1719 (m), 1620 (s), 1514 (m), 1389 (s), 1248 (s), 1082 (m). HRMS (ESI): Calcd for $(C_{49}H_{62}O_{18}Si+H)^+$ 967.3778, found 967.3795; HRMS (ESI): Calcd for $(C_{49}H_{62}O_{18}Si+Na)^+$ 989.3598, found 989.3585.

Example 2: (5.7 equiv $TMSNTf_2$, 8.5 equiv 5)

To a solution of synthetic precursor **1** (160 mg, 0.213 mmol, 1 equiv) in benzene (10 mL) at 23 °C was added 1-*O*-β-acetyl glycoside **5**[5] (495 mg, 1.81 mmoL, 8.5 equiv). The bright yellow solution was concentrated and the residue was blanketed with argon. Dichloromethane (800 μL) and ether (250 μL) were added, followed by crushed 4-Å molecular sieves (250 mg). The bright yellow suspension was stirred for 60 min at 23 °C, then was cooled to –78 °C. A freshly prepared solution of *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide in dichloromethane (1.0 M, 1.21 mL, 1.21 mmol, 5.7 equiv) was added dropwise by syringe over 1.5 h. The internal temperature of the reaction mixture was maintained at –78 °C for 1 h. Triethylamine (296 μL, 2.13 mmol, 10 equiv) was added at –78 °C. The resulting yellow-orange solution was diluted with a 10:1 mixture of dichloromethane-methanol (50 mL), and the product mixture was filtered through a plug of Celite. The filtrate was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and dichloromethane (150 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **6** (120 mg, 58%, in fractions eluting at 44.8–47.0 min) as a bright yellow powder.[6]

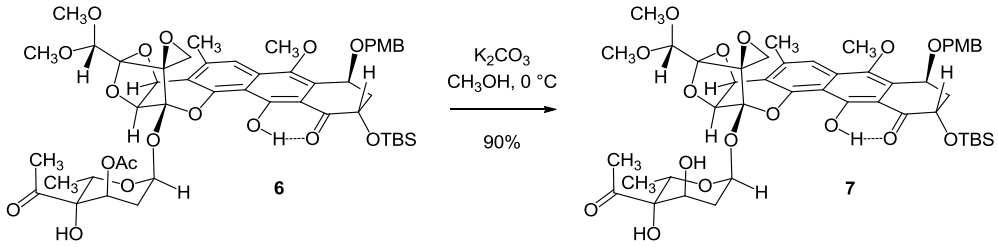
[6] In Example 2 only, 39 mg (22 %) of the trimethylsilylated hemiketal **46**, shown below, was isolated separately in fractions eluting at 72–76 min.



46

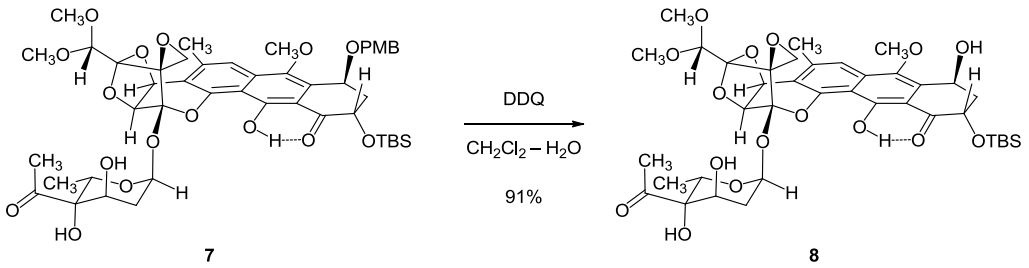
Example 3: (3.3 equiv $TMSNTf_2$, 5 equiv 5)

To a solution of synthetic precursor **1** (80.0 mg, 0.111 mmol, 1 equiv) in benzene (5 mL) at 23 °C was added 1-*O*-β-acetyl glycoside **5**[5] (146 mg, 0.531 mmoL, 5 equiv). The bright yellow solution was concentrated and the residue was blanketed with argon. Dichloromethane (800 μL) and ether (250 μL) were added, followed by crushed 4-Å molecular sieves (250 mg). The bright yellow suspension was stirred for 60 min at 23 °C, then was cooled to –78 °C. A freshly prepared solution of *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide in dichloromethane (1.0 M, 354 μL, 0.354 mmol, 3.3 equiv) was added dropwise by syringe over 2.5 h. The internal temperature of the reaction mixture was maintained at –78 °C for 1 h. Triethylamine (49.3 μL, 0.354 mmol, 3.3 equiv) was added at –78 °C. The resulting yellow-orange solution was diluted with a 10:1 mixture of dichloromethane-methanol (10 mL), and the product mixture was filtered through a plug of Celite. The filtrate was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **6** (65.0 mg, 63%, in fractions eluting at 44.8–47.0 min) as a bright yellow powder.



Alcohol 7.

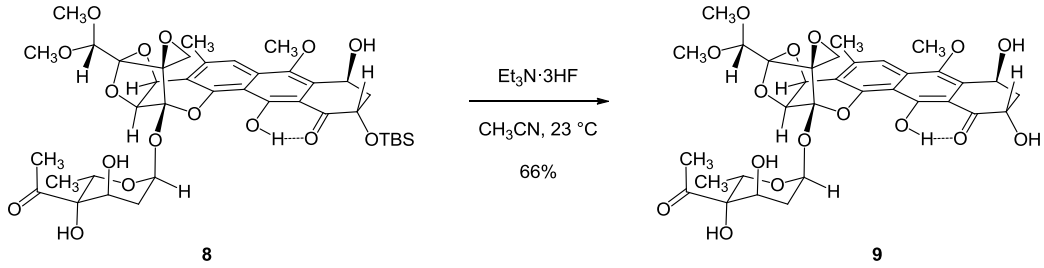
Potassium carbonate (2.6 mg, 0.5 equiv) was added to a solution of α-glycoside **6** (37 mg, 38 μmol, 1 equiv) in methanol (7.7 mL) at 0 °C. After 3 h, the mixture was partitioned between chloroform (100 mL) and saturated aqueous sodium chloride solution (20 mL). The layers were separated. The aqueous layer was extracted with chloroform (2 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the alcohol **7** (32 mg, 90%).



7 8

Benzylic Alcohol 8.

2,3-dichloro-5,6-dicyanobenzoquinone (4.7 mg, 21 μmol, 1.2 equiv) was added to a vigorously stirring, biphasic solution of alcohol **7** (16 mg, 17 μmol, 1 equiv) in dichloromethane (2.2 mL) and water (440 μL) at 23 °C. The reaction flask was covered with aluminum foil to exclude light. Over the course of 2.5 h, the color of the reaction mixture changed from myrtle green to yellow. The product solution was partitioned between water (10 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure benzylic alcohol **8** (12.7 mg, 91%) as a yellow-green oil.

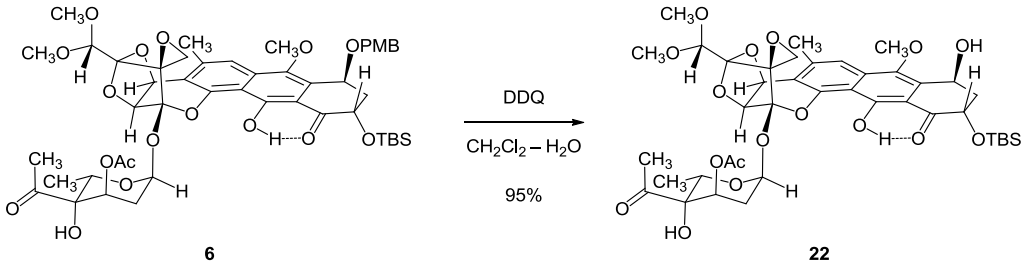


8 9

Trioxacarcinose B Monoglycoside 9.

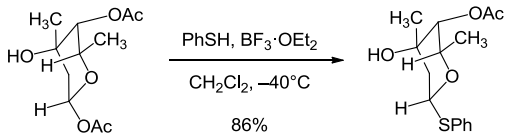
Triethylamine–trihydrofluoride (18 μL, 110 μmol, 30 equiv) was added to a solution of benzylic alcohol **8** (3.0 mg, 3.7 μmol, 1 equiv) in acetonitrile (0.5 mL) at 23 °C. The reaction flask was covered with aluminum foil to exclude light. After 21 h, the product solution was partitioned between dichloromethane (50 mL) and saturated aqueous sodium chloride solution (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→50% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure trioxacarcinose B monoglycoside **9** (1.7 mg, 66%). TLC: (ethyl acetate) R_f = 0.18 (UV, CAM); ^{1}H

NMR (500 MHz, $CDCl_3$) δ: 13.84 (br, 1H), 7.48 (s, 1H), 5.85 (d, 1H, *J* = 2.6 Hz), 5.46 (t, 1H, *J* = 2.9 Hz), 5.37 (d, 1H, *J* = 4.0 Hz), 5.24 (d, 1H, *J* = 4.0 Hz), 5.02 (q, 1H, *J* = 6.6 Hz), 4.93 (dd, 1H, *J* = 12.8, 5.5 Hz), 4.77 (s, 1H), 4.25 (d, 1H, *J* = 9.5 Hz), 4.16 (br, 1H), 3.92 (s, 3H), 3.71 (brd, 1H, *J* = 8.8 Hz), 3.63 (s, 3H), 3.49 (s, 3H), 3.00 (br, 1H), 2.98 (d, 1H, *J* = 5.9 Hz), 2.89 (d, 1H, *J* = 5.9 Hz), 2.74 (ddd, 1H, *J* = 13.2, 5.5, 2.9 Hz), 2.62 (s, 3H), 2.49 (s, 3H), 2.44 (dt, 1H, *J* = 14.7, 3.7 Hz), (dt, 1H, *J* = 13.2, 3.3 Hz), 2.11 (ddd, 1H, *J* = 14.7, 2.6, 1.5 Hz), 1.09 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.4, 203.3, 162.4, 151.8, 144.4, 142.6, 135.7, 129.6, 116.6, 114.6, 107.3, 104.7, 101.5, 99.7, 94.9, 79.6, 71.4, 70.2, 69.2, 68.3, 67.7, 63.8, 62.9, 61.9, 56.9, 56.1, 48.2, 45.7, 37.0, 31.6, 27.8, 20.4, 14.5; FTIR (neat), cm^{-1}: 3431 (br w), 2926 (m), 1713 (m), 1622 (s), 1256 (s), 1103 (s); HRMS (ESI): Calcd for $(C_{33}H_{38}O_{16} + Na)^+$: 713.2052. Found: 713.2029.



Benzylic Alcohol 22.

To a vigorously stirring, biphasic solution of α-glycoside **6** (120 mg, 0.124 mmol, 1 equiv) in dichloromethane (1.9 mL) and pH 7 phosphate buffer (380 μL) at 23 °C was added 2,3-dichloro-5,6-dicyanobenzoquinone (33.8 mg, 0.149 mmol, 1.1 equiv). The reaction flask was covered with aluminum foil to exclude light. Over the course of 2 h, the color of the reaction mixture changed from myrtle green to yellow. The product solution was partitioned between water (10 mL) and dichloromethane (60 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure benzylic alcohol **22** (100 mg, 95%, in fractions eluting at 32.6–36.5 min) as a bright yellow solid. TLC: (60% ethyl acetate–hexanes) R_f = 0.31 (UV, CAM); $[\alpha]^{23}_D$ +2.9 (*c* 0.614, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.40 (s, OH). 7.43 (s, 1 H), 5.82 (t, *J* = 2.4 Hz, 1H), 5.43 (app d, *J* = 1.8 Hz, 1H), 5.30 (d, *J* = 4.2 Hz, 1H), 5.30 (s, 1H), 5.19 (d, *J* = 3.6 Hz, 1H), 5.01 (q, *J* = 6.6 Hz, 1H), 4.90 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.75 (app t, *J* = 3.6 Hz, 1H), 4.74 (s, 1H), 3.90 (s, 3H), 3.89 (s, OH), 3.63 (s, 3H), 3.47 (s, 3H), 2.83 (d, *J* = 6.0 Hz, 1H), 2.74 (d, *J* = 5.4 Hz, 1H), 2.60 (s, 3H), 2.51–2.48 (m, 1H), 2.42 (br s, 1H), 2.36 (s, 3H), 2.35–2.30 (m, 2H), 2.23 (s, 3H), 1.08 (d, *J* = 6.6 Hz, 3H), 0.95 (s, 9H), 0.23 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7, 202.9, 170.3, 162.6, 151.8, 143.7, 142.1, 135.2, 129.6, 116.0, 114.8, 114.3, 107.9, 104.5, 101.6, 99.4, 92.4, 78.1, 72.10, 70.6, 69.3, 69.1, 68.2, 64.4, 62.7, 62.6, 56.6, 55.8, 47.4, 38.8, 28.9, 27.0, 25.8, 21.3, 20.4, 18.5, 14.5, –4.5, –5.4. FTIR (neat), cm^{-1}: 3475 (m), 2934 (s), 2857 (m), 1738 (s), 1721 (s), 1620 (s), 1570 (m), 1445 (m), 1389 (s), 1240 (s), 1082 (s). HRMS (ESI): Calcd for $(C_{41}H_{54}O_{17}Si + Na)^+$: 869.3023. Found: 869.2793.

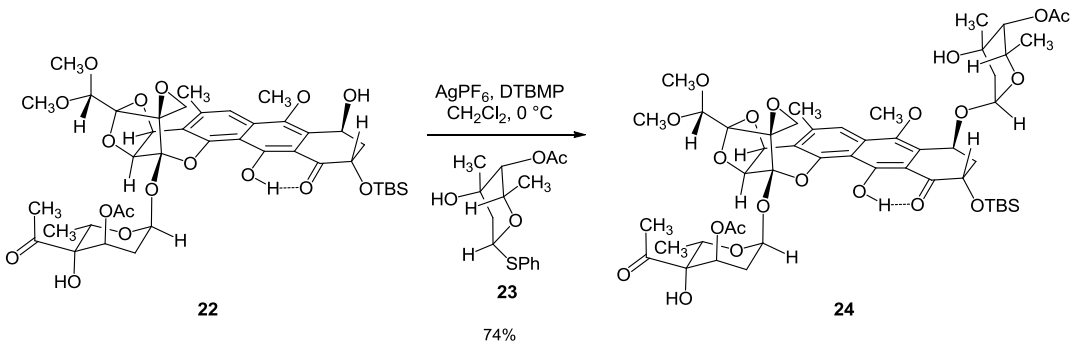


3
α:β ~ 1:12

23
α:β ~ 1:2.4

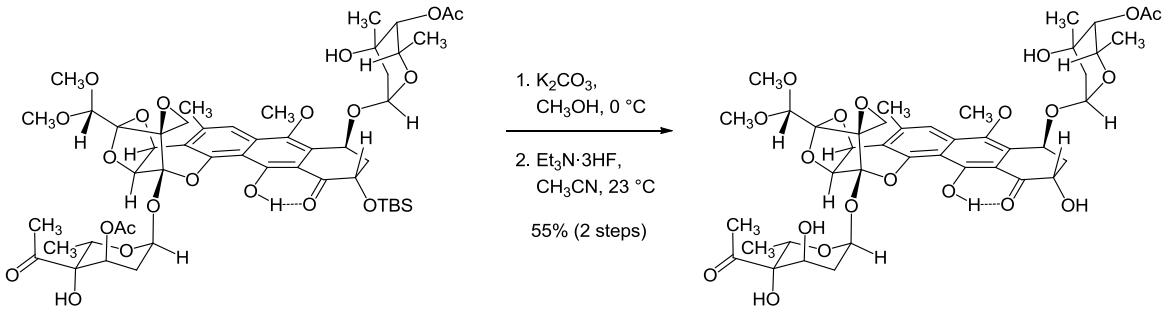
1-Phenylthiotrioxacarcinoside A (23).

Boron trifluoride etherate (72 μL, 0.57 mmol, 1.4 equiv) was added to a solution of 1-*O*-acetyltrioxacarcinoside A (**3**)[4] (100 mg, 0.41 mmol, 1 equiv, a 1:12 mixture of α- and β-anomers, respectively) and thiophenol (50 μL, 0.49 mmol, 1.2 equiv) in dichloromethane (8.1 mL) at –40 °C. After 5 min, saturated aqueous sodium bicarbonate solution (2 mL) was added rapidly. The cooling bath was removed and the reaction flask was allowed to warm to 23 °C. The mixture was partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (25% ethyl acetate–hexanes) to provide 1-phenylthiotrioxacarcinoside A (**23**), as a 2.4:1 mixture of β- and α-anomers, respectively (103 mg, 86%). TLC: (50% ethyl acetate–hexanes) R_f = 0.71 (CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: α-anomer (minor): 7.49 (d, *J* = 7.8 Hz, 2H), 7.31–7.22 (m, 3H), 5.64 (d, *J* = 6.4 Hz, 1H), 4.81 (q, *J* = 6.4 Hz, 1H), 4.74 (s, 1H), 2.58 (br, 1H), 2.35 (dd, *J* = 14.7, 6.4 Hz, 1H), 2.15 (s, 3H), 1.95 (m, 1H), 1.21 (s, 3H), 1.12 (d, *J* = 6.4 Hz, 3H); β-anomer (major): 7.51 (d, *J* = 7.8 Hz, 2H), 7.31–7.22 (m, 3H), 5.19 (d, *J* = 11.7 Hz, 1H), 4.62 (s, 1H), 4.21 (q, *J* = 6.4 Hz, 1H), 2.15 (s, 3H), 1.93 (m, 1H), 1.82 (d, *J* = 13.7 Hz, 1H), 1.20 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.8, 170.5, 136.4, 134.7, 130.7, 130.6, 128.8, 128.7, 126.9, 126.8, 83.4, 80.7, 74.4, 73.7, 70.6, 70.4, 69.1, 62.8, 39.5, 38.3, 27.0, 26.8, 20.8, 20.8, 17.0, 16.6; FTIR (neat), cm^{-1}: 3493 (br), 2980 (m), 1743 (s), 1373 (m), 1233 (s), 1067 (s), 1007 (s); HRMS (ESI): Calcd for $(C_{15}H_{20}O_4S+Na)^+$ 319.0975, found 319.0987.



3''-*O*-Acetyl-2-*O*-(*tert*-butyldimethylsilyl)-trioxacarcin A (24).

Silver hexafluorophosphate (116 mg, 0.460 mmol, 6.0 equiv) was added to a suspension of benzylic alcohol **22** (65.0 mg, 0.077 mmol, 1 equiv), 1-phenylthiotrioxacarcinoside A **23** (68 mg, 0.23 mmol, 3.0 equiv, a ~1:2.4 mixture of α and β anomers, respectively), 2,6-di-*tert*-butyl-4-methylpyridine (126 mg, 0.614 mmol, 8.0 equiv), and powdered 4-Å molecular sieves (~100 mg) in dichloromethane (3.8 mL) at 0 °C. After 1 h, pyridine (310 μL, 3.84 mmol, 50 equiv) was added, and the reaction flask was allowed to warm to 23 °C. After 30 min, the product mixture was filtered through a short pad of Celite, washing with dichloromethane (100 mL). The filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→100% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration pure 3''-*O*-acetyl-2-*O*-(*tert*-butyldimethylsilyl)-trioxacarcin A (**24**) as a yellow-green foam (58.3 mg, 74%). TLC (60% ethyl acetate–hexanes): R_f = 0.39 (UV, CAM); $[\alpha]^{23}_D$ –33.5 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.59 (s, 1H), 7.46 (s, 1H), 5.81 (t, *J* = 2.7 Hz, 1H), 5.37–5.35 (m, 2H), 5.31 (d, *J* = 4.4 Hz, 1H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.01 (q, *J* = 6.2 Hz, 1H), 4.78 (dd, *J* = 12.5, 5.1 Hz, 1H), 4.76–4.74 (m, 3H), 4.52 (q, 6.6 Hz, 1H), 3.89 (br, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 2.84 (d, *J* = 5.9 Hz, 1H), 2.76 (d, *J* = 5.9 Hz, 1H), 2.59 (s, 3H), 2.58–2.54 (m, 1H), 2.36 (s, 3H), 2.35–2.32 (m, 3H), 2.23 (s, 3H), 2.14 (s, 3H), 1.95 (dd, *J* = 14.7, 4.0 Hz, 1H), 1.63 (d, *J* = 14.7 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.09–1.07 (m, 3H), 1.08 (s, 3H), 0.96 (s, 9H), 0.25 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 208.6, 202.6, 170.3, 170.2, 163.1, 151.8, 144.1, 142.2, 134.8, 126.4, 116.4, 114.9, 114.6, 108.1, 104.4, 101.5, 99.3, 98.0, 92.3, 78.0, 74.3, 71.9, 70.5, 69.2, 68.9, 68.7, 68.1, 68.0, 64.4, 62.6, 62.5, 56.4, 55.8, 47.3, 38.7, 36.5, 29.6, 28.8, 26.8, 25.7, 21.2, 20.8, 20.2, 18.3, 16.8, 14.4, –4.4, –5.6; FTIR (neat), cm^{-1}: 3482 (br), 2934 (w), 1740 (m), 1620 (m), 1389 (m), 1227 (s), 1117 (s), 1082 (s), 995 (s), 943 (s); HRMS (ESI): Calcd for $(C_{50}H_{68}O_{21}Si+H)^+$ 1033.4095, found 1033.4008.

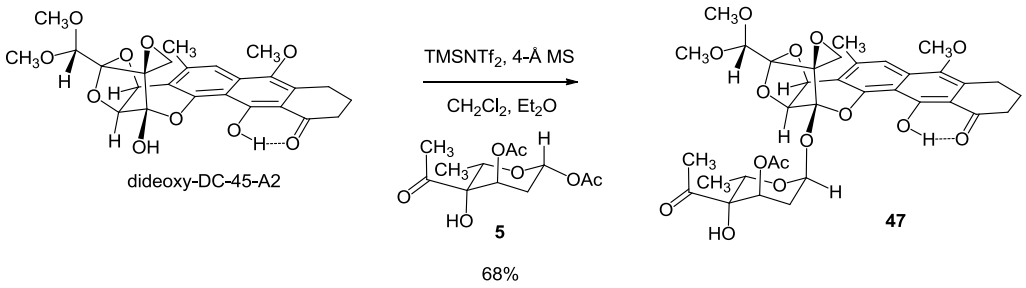


24 trioxacarcin A

Trioxacarcin A.

Potassium carbonate (13 mg, 95 μmol, 2.0 equiv) was added to a solution of 3''-*O*-acetyl-2-*O*-(*tert*-butyldimethylsilyl)-trioxacarcin A (**24**) (49 mg, 47 μmol, 1 equiv) in methanol (9.5 mL) at 0 °C. After 60 min, ammonium chloride (10 mg, 0.19 mmol, 4.0 equiv) was added. After 1 min, the mixture was filtered through a short pad of Celite, washing with methanol (50 mL). The filtrate was concentrated. Analysis of the residue by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$) established that the 3''-*O*-acetyl protecting group (δ 2.22, (s, 3H)) had been cleaved and that the 4'-*O*-acetyl group was retained (δ 2.13 (s, 3H)). The residue (1 equiv, see above) was dissolved in acetonitrile (1.6 mL), and triethylamine–trihydrofluoride (232 μL, 1.4 mmol, 30 equiv) was added at 23 °C. The reaction flask was covered with aluminum foil to exclude light. After 14 h, saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was extracted with dichloromethane (2 × 50 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→80% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration pure trioxacarcin A as an orange-red powder (23 mg, 55% yield over two steps). TLC (80% ethyl acetate–hexanes): R_f = 0.25 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.05 (s, 1H), 7.51 (s, 1H), 5.85 (d, *J* = 2.6 Hz, 1H), 5.39 (m, 1H), 5.37 (d, *J* = 4.0 Hz, 1H), 5.24 (d, *J* = 4.0 Hz, 1H), 5.02 (q, *J* = 6.6 Hz, 1H), 4.78 (m, 1H), 4.77 (s, 1H), 4.75 (app s), 4.54 (q, *J* = 6.6 Hz, 1H), 4.24 (d, *J* = 9.2 Hz, 1H), 4.16 (br, 1H), 3.84 (s, 3H), 3.72 (br d, *J* = 8.8 Hz, 1H), 3.63 (s, 3H), 3.56 (s, 1H), 3.49 (s, 3H), 2.99 (d, *J* = 5.9 Hz, 1H), 2.91 (d, *J* = 5.5 Hz, 1H), 2.81 (m, 1H), 2.62 (s, 3H), 2.50 (s, 3H), 2.45 (dt, *J* = 14.3, 3.3 Hz, 1H), 2.21 (dt, *J* = 13.2, 2.2 Hz, 1H), 2.14 (s, 3H), 2.11 (m, 1H), 1.97 (dd, *J* = 14.7, 4.0 Hz, 1H), 1.62 (d, *J* = 14.7 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ: 14.5, 16.8, 20.3, 20.9, 25.7, 27.8, 31.5, 36.6, 48.1, 56.2, 56.8, 62.7, 62.9, 63.8, 67.4, 67.9, 68.3, 68.8, 69.1, 70.2, 71.4, 74.4, 79.5, 94.8, 97.9, 99.7, 101.5, 104.6, 107.4, 114.8, 116.9, 126.6, 135.4, 142.8, 144.8, 151.7, 163.1, 170.3, 202.9, 210.3; FTIR (neat), cm^{-1}: 3514 (br), 2976 (w), 2940 (w), 1748 (m), 1620 (m), 1387 (m), 1225 (s), 1086 (s), 997 (s); HRMS (ESI): Calcd for $(C_{42}H_{52}O_{20}–H)^-$ 875.2979, found 875.2961.

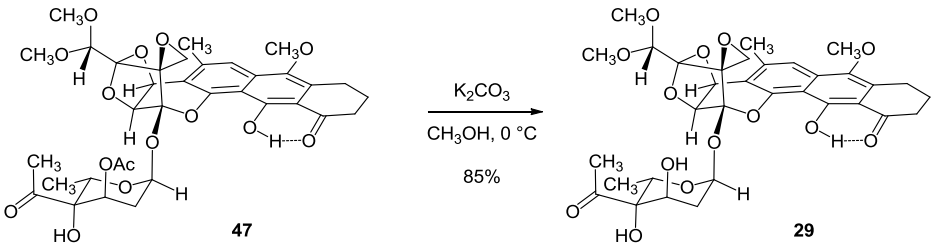
Preparation of Fully Synthetic Trioxacarcin Analogs



α-Glycoside 47.

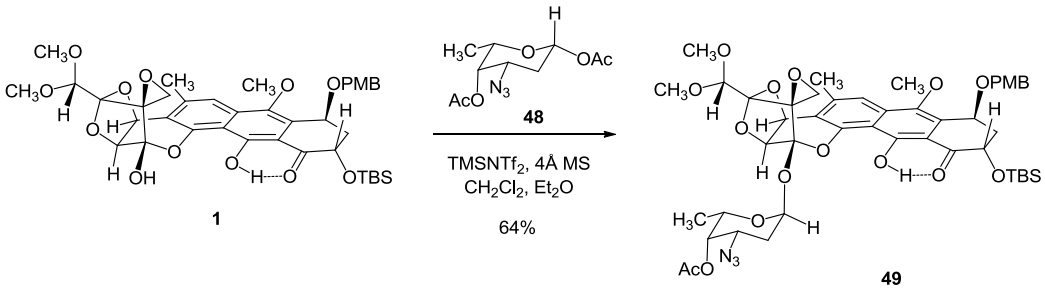
To a solution of dideoxy-DC-45-A2[3] (20.0 mg, 0.041 mmol, 1 equiv) in benzene (2.0 mL) at 23 °C was added 1-*O*-β-acetyl glycoside **5**[5] (56.4 mg, 0.206 mmol, 5.0 equiv). The bright yellow solution was concentrated and the residue was blanketed with argon. Dichloromethane (1.5 mL) and ether (500 μL) were added followed by crushed 4-Å molecular sieves (500 mg). The bright yellow suspension was stirred for 30 min at 23 °C, then was cooled to –78 °C. *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide (20.2 μL, 0.082 mmol, 2.0 equiv) was added dropwise by syringe over 10 min. After 20 min, a second portion of *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide (20.2 μL, 0.082 mmol, 2.0 equiv) was added over 10 min. After 2.5 h, the cold mixture was diluted with 15% methanol–dichloromethane (25 mL). Saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated. The aqueous layer was extracted with dichloromethane (25 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **47** (19.7 mg, 68%, in fractions eluting at 22.5–25.5 min) as a bright yellow solid. TLC: (50% ethyl acetate–hexane) R_f = 0.58 (UV, CAM). $[\alpha]^{23}_D$ +67.1 (*c* 0.23, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.65 (s, OH). 7.43 (s, 1 H), 5.84 (t, *J* = 3.6 Hz, 1H), 5.29 (d, *J* = 4.2 Hz, 1H), 5.19 (d, *J* = 4.2 Hz, 1H), 5.01 (q, *J* = 6.6 Hz, 1H), 4.75 (t, *J* = 3.6 Hz, 1H), 4.73 (s, 1H), 3.88 (s, OH), 3.77 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 3.03 (app q, *J* = 5.4 Hz, 2H), 2.84 (d, *J* = 6.0 Hz, 1H), 2.77 (d, *J* = 6.0 Hz, 1H), 2.72 (app t, *J* = 6.6 Hz, 2H), 2.58 (s, 3H), 2.36 (s, 3H), 2.33 (app t, *J* = 3.0 Hz, 2H), 2.23 (s, 3H), 2.11-2.06 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7, 204.3, 170.3, 162.9, 151.8, 142.3, 141.7, 135.2, 130.3, 115.6, 113.2, 113.1, 111.0, 104.5, 101.5, 99.5, 92.3, 78.2, 72.1, 70.7, 69.2, 68.3, 64.4, 60.9, 56.5, 55.8, 47.4, 38.8, 28.9, 27.0, 23.6, 22.1, 21.3, 20.3, 14.5. FTIR (neat), cm^{-1}: 3482 (w), 2928

(m), 2854 (w), 1740 (s), 1717 (s), 1622 (s), 1449 (m), 1389 (m), 1238 (s), 1096 (s). HRMS (ESI): Calcd for $(C_{35}H_{40}O_{15} + Na)^+$: 723.2259. Found: 723.2135.



Alcohol 29.

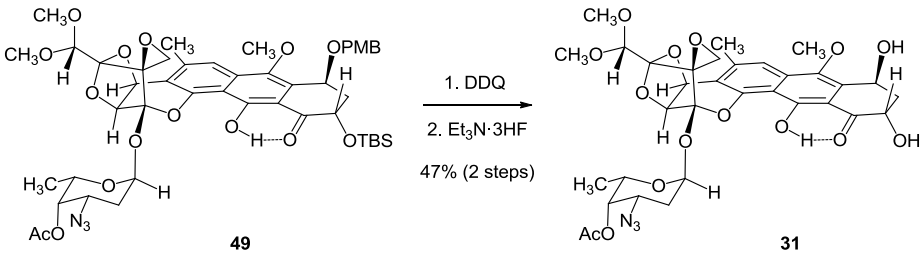
Potassium carbonate (1 mg, 7.24 μmol, 0.34 equiv) was added to a solution of the α-glycoside **47** (15 mg, 0.021 mmol, 1 equiv) in methanol (1 mL) at 0 °C. After 30 min, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. After 10 h, the reaction mixture was partitioned between saturated aqueous sodium chloride solution (20 mL) and chloroform (100 mL). The layers were separated. The aqueous layer was extracted with chloroform (3 × 30 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure alcohol **29** (12.0 mg, 85%, in fractions eluting at 18.0–24.1 min) as a yellow-orange solid. TLC: (50% ethyl acetate–hexane) R_f = 0.23 (UV, CAM); $[\alpha]^{23}_D$ +64.0 (*c* 0.60, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.69 (s, OH). 7.46 (s, 1 H), 5.86 (d, *J* = 2.4 Hz, 1H), 5.34 (d, *J* = 4.2 Hz, 1H), 5.24 (d, *J* = 3.6 Hz, 1H), 5.02 (q, *J* = 6.6 Hz, 1H), 4.77 (s, 1H), 4.29 (d, *J* = 9.6 Hz, OH), 4.15 (s, OH), 3.77 (s, 3H), 3.71 (dt, *J* = 9.6,3 Hz, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 3.04 (app q, *J* = 5.4 Hz, 2H), 2.98 (d, *J* = 5.4 Hz, 1H), 2.92 (d, *J* = 5.4 Hz, 1H), 2.73 (app t, *J* = 7.2 Hz, 2H), 2.59 (s, 3H), 2.50 (s, 3H), 2.43 (t, *J* = 14.4, 3.6 Hz, 2H), 2.11-2.08 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5, 204.5, 162.9, 151.6, 142.4, 141.6, 135.2, 130.5, 115.9, 113.1, 113.0, 111.1, 104.6, 101.4, 99.7, 94.8, 79.6, 77.2, 71.5, 70.3, 69.4, 68.4, 63.8, 60.9, 56.8, 56.1, 48.2, 38.8, 27.8, 23.6, 22.1, 20.3, 14.5. FTIR (neat), cm^{-1}: 3522 (w), 2930 (s), 2857 (m), 1746 (s), 1717 (s), 1622 (s), 1498 (s), 1456 (s), 1389 (s), 1256 (s), 1095 (s). HRMS (ESI): Calcd for $(C_{33}H_{38}O_{14} + Na)^+$: 681.2164. Found: 681.2110; HRMS (ESI): Calcd for $(C_{33}H_{38}O_{14} + NH_4)^+$: 676.2600. Found: 676.2530.



α-Glycoside 49

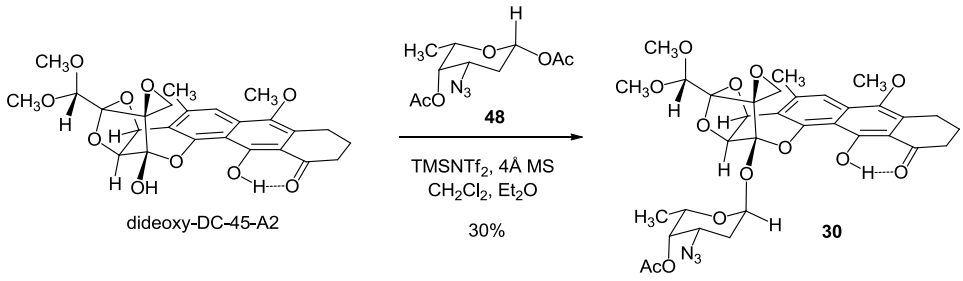
1-*O*-acetyl glycoside **48**[7] (27.3 mg, 0.106 mmol, 16.0 equiv) was added to a solution of synthetic precursor **1** (5.0 mg, 6.6 μmol, 1 equiv) in benzene (0.5 mL). The solution was concentrated and the residue was blanketed with argon. Dichloromethane (100 μL) and ether (30 μL) were added, followed by crushed 4-Å molecular sieves (20 mg). The suspension was stirred for 30 min at 23 °C then was cooled to –78 °C. A freshly prepared solution of *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide in dichloromethane (1.0 M, 70.4 μL, 0.070 mmol, 10.6 equiv) was added dropwise by syringe over 1.5 h. After 4 h, triethylamine (0.05 mL) was added. The mixture was diluted with 15% methanol–dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **49** (4.5 mg, 64%). TLC: (50% ethyl acetate–hexanes) R_f = 0.43 (UV, CAM); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.61 (br, 1H), 7.48 (s, 1H), 7.28 (d, 2H, *J* = 8.5 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 5.91 (t, 1H, *J* = 2.5 Hz), 5.23 (d, 1H, *J* = 2.3 Hz), 5.22 (d, 1H, *J* = 4.1 Hz), 5.19 (m, 2H), 4.97 (dd, 1H, *J* = 12.6, 5.3 Hz), 4.74 (s, 1H), 4.70 (d, 1H, *J* = 10.8 Hz), 4.60 (d, 1H, *J* = 11.0 Hz), 4.40 (q, 1H, *J* = 6.6 Hz), 4.09 (ddd, 1H, *J* = 11.2, 6.4, 3.0 Hz), 3.83 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.46 (s, 3H), 2.85 (d, 1H, *J* = 6.0 Hz), 2.74 (d, 1H, *J* = 6.0 Hz), 2.72 (m, 1H), 2.59 (s, 3H), 2.19 (s, 3H), 2.18–2.15 (m, 2H), 1.15 (d, 3H, *J* = 6.4 Hz), 0.98 (s, 9H), 0.25 (s, 3H), 0.17 (s, 3H); FTIR (neat), cm^{-1}: 2926 (s), 2854 (m), 2104 (m), 1746 (m), 1620 (s), 1516 (m), 1250 (s), 1107 (s); HRMS (ESI): Calcd for $(C_{47}H_{60}O_{16}N_3Si + H)^+$: 950.3737, Found: 950.3711.

[7] 1-*O*-Acetyl glycoside **48** was prepared from daunosamine hydrochloride by a two-step sequence which has been described previously: Zhang, G.; Fang, L.; Zhu, L.; Aimiuwu , J. E.; Shen, J.; Cheng, H.; Muller , M. T.; Lee, G. E.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2005**, *48*, 5269–5278.



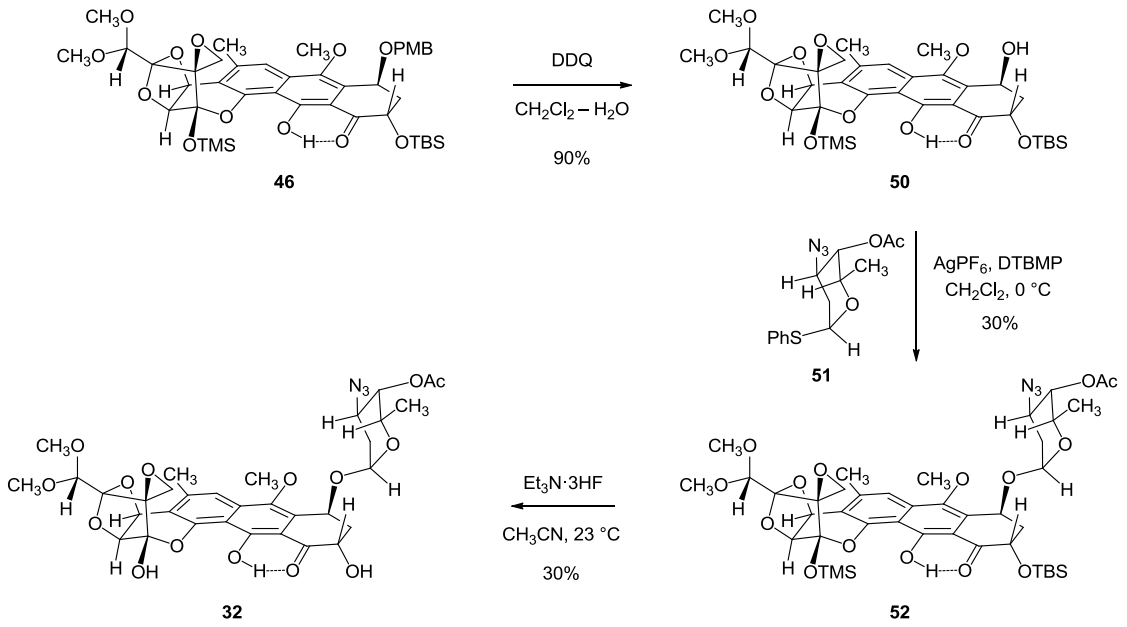
Azido Diol 31.

2,3-dichloro-5,6-dicyanobenzoquinone (1.1 mg, 4.7 μmol, 1.0 equiv) was added to a solution of α-glycoside **49** (4.5 mg, 4.7 μmol, 1 equiv) in a mixture of dichloromethane (833 μL) and water (167 μL) at 23 °C. The flask was covered with aluminum foil to exclude light. Over the course of 6.5 h, the color of the reaction mixture changed from myrtle green to yellow. The product solution was partitioned between water (10 mL) and dichloromethane (50 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was dissolved in acetonitrile (0.5 mL), and triethylamine–trihydrofluoride (23 μL, 0.14 mmol, 30 equiv) was added at 23 °C. The reaction flask was covered with aluminum foil to exclude light. After 14 h, saturated aqueous sodium bicarbonate solution (10 mL) was added. The mixture was extracted with dichloromethane (2 × 50 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→80% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure azido diol **31** (1.6 mg, 47% over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 13.86 (s, 1H), 7.47 (s, 1H), 5.88 (t, 1H, *J* = 2.5 Hz), 5.47 (br, 1H), 5.24 (app d, 2H, *J* = 4.1 Hz), 5.20 (d, 1H, *J* = 4.1 Hz), 4.94 (dd, 1H, *J* = 12.8, 5.5 Hz), 4.75 (s, 1H), 4.41 (q, 1H, *J* = 6.4 Hz), 4.11 (ddd, 1H, *J* = 11.7, 5.7, 3.0 Hz), 3.93 (s, 3H), 3.63 (s, 3H), 3.56 (br s, 1H), 3.47 (s, 3H), 2.89 (d, 1H, *J* = 6.0 Hz), 2.79 (d, 1H, *J* = 6.0 Hz), 2.75 (ddd, 1H, *J* = 13.3, 5.5, 2.8 Hz), 2.61 (s, 3H), 2.21 (br, 1H), 2.20–2.17 (m, 2H), 2.19 (s, 3H), 1.16 (d, 3H, *J* = 6.4 Hz); HRMS (ESI): Calcd for $(C_{33}H_{37}O_{15}N_3 + H)^+$: 716.2297, Found: 716.2278.



α-Glycoside 30.

1-*O*-acetyl glycoside **48**[7] (34.9 mg, 0.136 mmol, 6.0 equiv) was added to a solution of dideoxy-DC-45-A2[3] (11.0 mg, 0.023 mmol, 1 equiv) in benzene (2.0 mL). The solution was concentrated and the residue was blanketed with argon. Dichloromethane (850 μL) and ether (280 μL) were added, followed by crushed 4-Å molecular sieves (20 mg). The suspension was stirred for 20 min at 23 °C then was cooled to –78 °C. *N*-(trimethylsilyl)-bis(trifluoromethanesulfonyl)imide (22 μL, 0.090 mmol, 4.0 equiv) was added dropwise by syringe over 10 min. After 2 h, the mixture was diluted with 15% methanol–dichloromethane (50 mL). Saturated aqueous sodium bicarbonate solution (10 mL) was added. The layers were separated. The aqueous layer was extracted with dichloromethane (20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel deactivated with triethylamine (40% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes). The product was further purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **30** (4.6 mg, 30%). TLC: (80% ethyl acetate–hexanes) R_f = 0.77 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.72 (s, 1H), 7.44 (s, 1H), 5.91 (br t, 1H, *J* = 2.4 Hz), 5.24 (d, 1H, *J* = 2.3 Hz), 5.22 (d, 1H, *J* = 4.1 Hz), 5.19 (d, 1H, *J* = 4.1 Hz), 4.75 (s, 1H), 4.41 (q, 1H, *J* = 6.4 Hz), 4.11 (ddd, 1H, *J* = 11.9, 5.5, 2.8 Hz), 3.78 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 3.45 (s, 1H), 3.04 (m, 2H), 2.89 (d, 1H, *J* = 6.0 Hz), 2.82 (d, 1H, *J* = 6.0 Hz), 2.73 (s, 2H), 2.58 (s, 3H), 2.18 (s, 3H), 2.16 (m, 1H), 2.09 (m, 2H), 1.15 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.4, 170.5, 162.9, 151.6, 142.4, 141.8, 135.2, 130.4, 115.8, 113.2, 113.1, 111.1, 104.5, 101.6, 99.6, 93.3, 77.2, 71.9, 70.1, 69.2, 68.3, 66.4, 60.9, 56.9, 56.4, 54.2, 47.7, 38.8, 23.6, 22.1, 20.8, 20.3, 16.8; FTIR (neat), cm^{-1}: 2926 (m), 2102 (m), 1748 (m), 1662 (m), 1389 (m), 1233 (m), 1016 (s); HRMS (ESI): Calcd for $(C_{33}H_{37}O_{13}N_3 + H)^+$: 684.2399, Found: 684.2424.



Benzylic Alcohol 50.

2,3-dichloro-5,6-dicyanobenzoquinone (11 mg, 47 μmol, 1.0 equiv) was added to a solution of trimethylsilyl hemiketal **46** (39 mg, 47 μmol, 1.0 equiv) in a mixture of dichloromethane (1.7 mL) and water (330 μL) at 23 °C. The flask was covered with aluminum foil to exclude light. Over the course of 2 h, the color of the reaction mixture changed from myrtle green to yellow. The product solution was partitioned between water (10 mL) and dichloromethane (50 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure benzylic alcohol **50** (30 mg, 90%).

α-Glycoside 52.

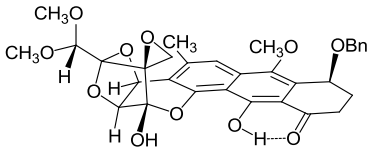
Thioglycoside **51**[8] (16 mg, 0.051 mmol, 6.0 equiv) was added to a solution of benzylic alcohol **50** (6 mg, 0.009 mmol, 1 equiv) in benzene (1.0 mL). The solution was concentrated and the residue was blanketed with argon. Dichloromethane (250 μL), crushed 4-Å molecular sieves (50 mg), and 2,6-di-*tert*-butyl-4-methylpyridine (7.0 mg, 0.034 mmol, 4 equiv) were added sequentially at 23 °C. After 10 min, the suspension was cooled to 0 °C. Silver hexafluorophosphate (4.3 mg,

[8] Thioglycoside **51** was prepared from daunosamine hydrochloride by a three-step sequence which has been described previously: Zhang, G.; Fang, L.; Zhu, L.; Aimiuwu , J. E.; Shen, J.; Cheng, H.; Muller , M. T.; Lee, G. E.; Sun, D.; Wang, P. G. *J. Med. Chem.* **2005**, *48*, 5269–5278.

0.017 mmol, 2.0 equiv) was added. After 15 min, an additional portion of silver hexafluorophosphate (4.3 mg, 0.017 mmol, 2.0 equiv) was added. After 12 h, additional portions of silver hexafluorophosphate (4.3 mg, 0.017 mmol, 2.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (3.5 mg, 0.017 mmol, 2 equiv) were added. After 20 min, dichloromethane (5 mL) was added and the mixture was filtered through short pad of Celite. The filtrate was partitioned between dichloromethane (30 mL) and water (5 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→100% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **52** (2.3 mg, 30%).

Alcohol 32.

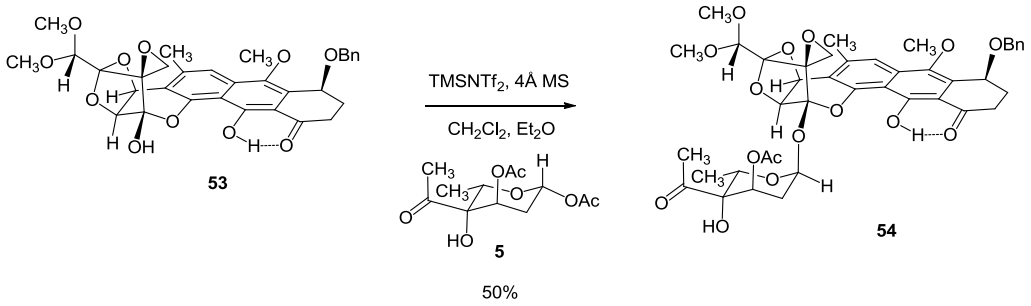
Triethylamine–trihydrofluoride (13 μL, 76 μmol, 30 equiv) was added to an ice-cooled solution of α-glycoside **52** (2.3 mg, 2.6 μmol, 1 equiv) in acetonitrile (0.5 mL). The flask was covered with aluminum foil to exclude light. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 23 h, the solution was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure alcohol **32** (0.55 mg, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.20 (s, 1H), 7.50 (s, 1H), 5.43 (d, 1H, *J* = 2.8 Hz), 5.35 (t, 1H, *J* = 2.8 Hz), 5.27 (d, 1H, *J* = 4.1 Hz), 5.19 (s, 1H), 4.86 (dd, 1H, *J* = 12.8, 5.5 Hz), 4.84 (d, 1H, *J* = 4.1 Hz), 4.71 (s, 1H), 4.39 (s, 1H), 4.17 (q, 1H, *J* = 6.4 Hz), 3.84 (s, 3H), 3.79 (ddd, 1H, *J* = 12.8, 4.6, 2.8 Hz), 3.62 (s, 3H), 3.59 (s, 1H), 3.47 (s, 3H), 3.16 (d, 1H, *J* = 5.5 Hz), 3.03 (d, 1H, *J* = 5.0 Hz), 2.72 (ddd, 1H, *J* = 13.3, 5.0, 3.2 Hz), 2.62 (s, 3H), 2.23–2.17 (m, 1H), 2.19 (s, 3H), 2.08 (dt, 1H, *J* = 12.8, 3.6 Hz), 1.78 (dd, 1H, *J* = 12.8, 4.6 Hz), 1.25 (d, 3H, *J* = 6.4 Hz); HRMS (ESI): Calcd for $(C_{33}H_{37}O_{15}N_3+Na)^+$: 738.2117, Found: 738.2084.



53

2-Deoxy Synthetic Precursor 53.[9]

2-Deoxy synthetic precursor **53** was assembled from the epoxy diazo diketone **21**, cyanophthalide **17**, and (*S*)-4-(benzyloxy)cyclohex-2-enone[10] by an analogous sequence as described in Figure 4 for the synthesis of synthetic precursor **1**. TLC: (67% ethyl acetate–hexanes) R_f = 0.34 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.98 (s, 1H), 7.43 (s, 1H), 7.35–7.27 (m, 5H), 5.24 (d, 1H, *J* = 4.0 Hz), 5.17 (br t, 1H, *J* = 2.8 Hz), 4.88 (d, 1H, *J* = 4.4 Hz), 4.70 (s, 1H), 4.69 (d, 1H, *J* = 12.3 Hz), 4.56 (d, 1H, *J* = 11.9 Hz), 4.54 (br s, 1H), 3.82 (s, 3H), 3.63 (s, 3H), 3.48 (s, 3H), 3.18 (ddd, 1H, *J* = 18.3, 13.6, 5.4 Hz), 3.10 (d, 1H, *J* = 5.2 Hz), 3.00 (d, 1H, *J* = 5.2 Hz), 2.62– 2.53 (m, 2H), 2.57 (s, 3H), 2.09 (tdd, 1H, *J* = 14.0, 4.6, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.2, 162.9, 151.4, 143.8, 141.8, 138.2, 135.1, 128.3, 128.1, 127.7, 127.6, 116.4, 114.6, 114.6, 109.5, 103.8, 100.1, 98.5, 73.2, 70.6, 69.6, 69.2, 67.7, 62.8, 57.0, 56.6, 50.4, 32.3, 26.3, 20.4; FTIR (neat), cm^{-1}: 2918 (s), 1740 (s), 1620 (s), 1389 (s), 1236 (s), 1084 (s); HRMS (ESI): Calcd for $(C_{32}H_{32}O_{11} + Na)^+$: 615.1837, Found: 615.1842.



53 → **5** (50%) → **54**

α-Glycoside 54.[11]

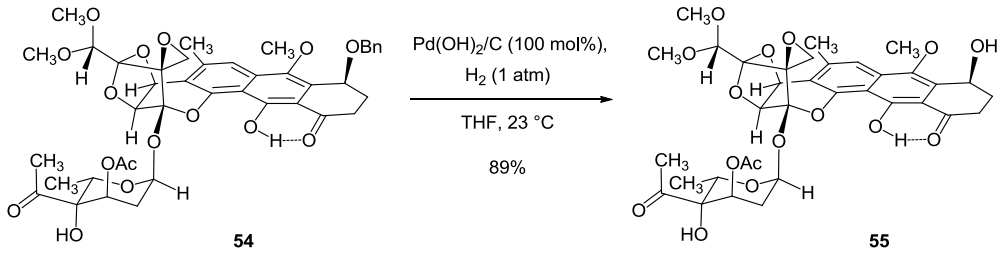
1-*O*-β-Acetyl glycoside **5**[5] (301 mg, 1.10 mmol, 5.0 equiv) was added to a solution of 2-deoxy synthetic precursor **53** (130 mg, 0.219 mmol, 1 equiv) in benzene (2.0 mL) at 23 °C. The bright yellow solution was concentrated and the residue was blanketed with argon. Dichloromethane (3 mL) and ether (600 μL) were added, followed by crushed 4-Å molecular sieves (1.2 g). The bright yellow suspension was stirred for 90 min at 23 °C, then was cooled to –78 °C. Trimethylsilyl

[9] Dr. Andreas Schumacher provided assistance in the large-scale synthesis of 2-deoxy synthetic precursor **53**, which we acknowledge with appreciation.

[10] (*S*)-4-(benzyloxy)cyclohex-2-enone was prepared by benzylation (silver(I) oxide, benzyl bromide, dichloromethane, 23 °C, 52% yield) of (*S*)-4-hydroxycyclohex-2-enone, which may be prepared from 1,4-cyclohexanedione monoethylene acetal by a four-step sequence: Matsuzawa, M; Kakeya, H; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. Asian J.* **2006**, *1*, 845–851.

[11] This procedure was conducted by Dr. Andreas Schumacher, whom we acknowledge with appreciation.

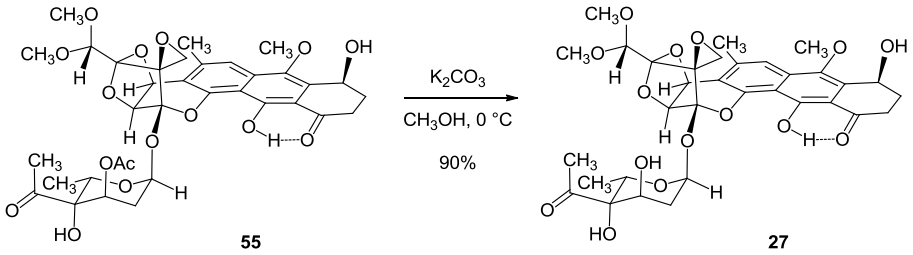
trifluoromethanesulfonate (120 μL, 0.659 mmol, 3.0 equiv) was added dropwise by syringe over 10 min. After 2 h, a second portion of trimethylsilyl trifluoromethanesulfonate (40 μL, 0.220 mmol, 1.0 equiv) was added dropwise by syringe over 10 min. After 3.5 h, triethylamine (122 μL, 0.878 mmol, 4.0 equiv) was added. The suspension was diluted with dichloromethane (50 mL) and filtered through a pad of Celite. Saturated aqueous sodium bicarbonate solution (10 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure α-glycoside **54** (88 mg, 50%, in fractions eluting at 22.5–25.5 min) as a bright yellow solid. TLC: (50% ethyl acetate–hexanes) R_f = 0.58 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.74 (s, 1H), 7.49 (s, 1H), 7.35–7.26 (m, 5H), 5.84 (t, 1H, *J* = 3 Hz), 5.31–5.29 (m, 2H), 5.2 (d, 1H, *J* = 4.0 Hz), 5.17 (app s, 1H), 5.02 (q, 1H, *J* = 6.4 Hz), 4.76 (t, 1H, *J* = 2.8 Hz), 4.75 (s, 1H), 4.7 (d, 1H, *J* = 11.5 Hz), 4.58 (d, 1H, *J* = 11.5 Hz), 3.94 (s, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.47 (s, 3H), 3.19 (ddd, 1H, *J* = 18.1, 13.5, 5.0 Hz), 2.83 (d, 1H, *J* = 6.0 Hz), 2.75 (d, 1H, *J* = 6.0 Hz), 2.61 (s, 3H), 2.56 (m, 1H), 2.36 (s, 3H), 2.36–2.33 (m, 2H), 2.23 (s, 3H), 2.06 (m, 1H), 1.09 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.6, 204.0, 170.1, 162.9, 151.7, 143.7, 141.8, 138.1, 135.0, 128.2, 128.1, 127.7, 127.5, 116.2, 114.6, 114.2, 109.4, 104.4, 101.4, 99.3, 92.2, 78.0, 71.9, 70.5, 69.0, 68.1, 67.6, 64.3, 62.7, 56.4, 55.8, 47.3, 32.3, 28.7, 26.9, 26.4, 21.2, 20.2, 14.4; FTIR (neat), cm^{-1}: 3404 (w), 2932 (m), 1717 (m), 1620 (s), 1389 (s), 1067 (s); HRMS (ESI): Calcd for $(C_{42}H_{46}O_{16} + Na)^+$: 829.2678, Found: 829.2680.



Benzylic alcohol 55.[11]

Palladium hydroxide on carbon (20 wt. %, 18 mg, 0.025 mmol, 1.0 equiv) was added to a solution of α-glycoside **54** (20 mg, 0.025 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a slow stream of pure hydrogen gas through a 22-gauge stainless steel needle. After 30 min, the mixture was diluted with ethyl acetate

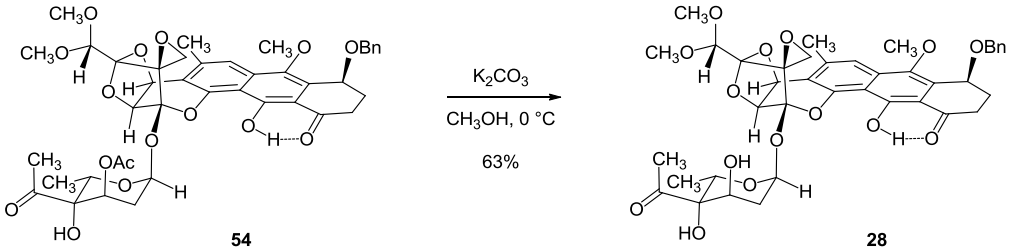
(20 mL) and filtered through a short pad of Celite. The filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→100% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure benzylic alcohol **55** (16 mg, 89%). TLC: (67% ethyl acetate–hexanes) R_f = 0.18 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.71 (s, 1H), 7.45 (s, 1H), 5.81 (t, 1H, *J* = 2.9 Hz), 5.39 (br s, 1H), 5.29 (d, 1H, *J* = 4.1 Hz), 5.19 (d, 1H, *J* = 4.1 Hz), 5.00 (q, 1H, *J* = 6.3 Hz), 4.74 (m, 2H), 3.90 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 3.10 (ddd, 1H, *J* = 17.3, 11.9, 5.2 Hz), 2.83 (d, 1H, *J* = 5.8 Hz), 2.75 (d, 1H, *J* = 5.8 Hz), 2.68 (d, 1H, *J* = 2.1 Hz), 2.63–2.60 (m, 1H), 2.60 (s, 3H), 2.35 (s, 3H), 2.33–2.27 (m, 3H), 2.24–2.22 (m, 1H), 2.22 (s, 3H), 1.07 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7, 203.7, 170.2, 163.0, 151.8, 143.4, 142.1, 135.2, 130.3, 116.0, 114.5, 114.3, 109.0, 104.5, 101.6, 99.4, 92.3, 78.2, 72.1, 70.7, 69.1, 68.3, 64.5, 62.7, 62.3, 56.5, 55.8, 47.4, 32.8, 29.2, 28.9, 27.0, 21.3, 20.3, 14.5; FTIR (neat), cm^{-1}: 3462 (w), 2926 (m), 1738 (m), 1618 (s), 1389 (s), 1236 (s), 1099 (s), 982 (s); HRMS (ESI): Calcd for $(C_{35}H_{40}O_{16} + H)^+$: 717.2389, Found: 717.2403.



Triol 27.[11]

Potassium carbonate (0.5 mg, 4 μmol, 0.3 equiv) was added to an ice-cooled solution of benzylic alcohol **55** (8.0 mg, 11 μmol, 1 equiv) in methanol (1.0 mL). After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 2.5 h, the mixture was partitioned between chloroform (40 mL) and saturated aqueous sodium chloride solution (10 mL). The layers were separated. The aqueous layer was extracted with chloroform (3 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure triol **27** (6.8 mg, 90%, in fractions eluting at 6–11 min) as a yellow solid. TLC: (75% ethyl acetate–hexanes) R_f = 0.22 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.75 (s, 1H), 7.48 (s, 1H), 5.85 (d, 1H, *J* = 2.5 Hz), 5.41 (t, 1H, *J* = 3.9 Hz), 5.35 (d, 1H, *J* = 4.1 Hz), 5.24 (d, 1H, *J* = 4.1 Hz),

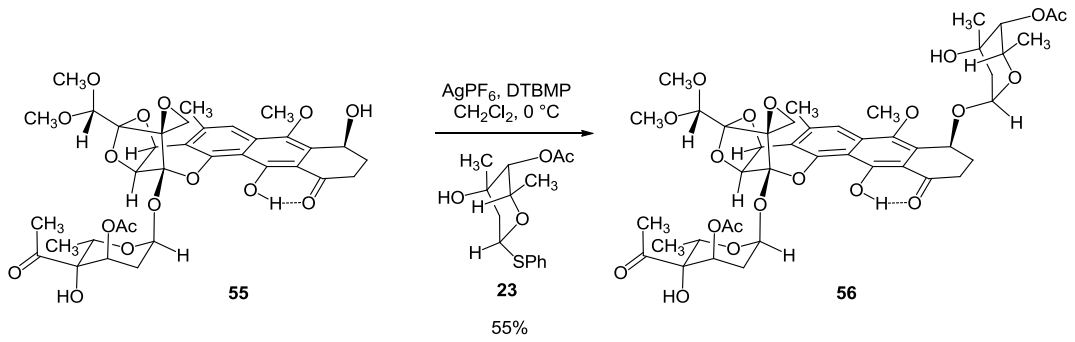
5.02 (q, 1H, J = 6.4 Hz), 4.77 (s, 1H), 4.16 (s, 1H), 3.92 (s, 3H), 3.71 (br s, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 3.13 (ddd, 1H, J = 17.3, 12.1, 5.2 Hz), 2.98 (d, 1H, J = 5.7 Hz), 2.91 (d, 1H, J = 5.7 Hz), 2.65–2.60 (m, 1H), 2.61 (s, 3H), 2.50 (s, 3H), 2.43 (dt, 1H, J = 14.5, 3.5 Hz), 2.32 (dq, 1H, J = 14.0, 4.7 Hz), 2.23 (m, 1H), 2.12 (ddd, 1H, J = 14.6, 2.5, 1.4 Hz), 1.09 (d, 3H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.4, 203.9, 162.9, 151.7, 143.5, 142.0, 135.3, 130.5, 116.3, 114.2, 110.7, 109.1, 104.6, 101.5, 99.7, 94.8, 79.6, 71.5, 70.2, 69.3, 68.3, 63.8, 62.7, 62.3, 56.8, 56.1, 48.2, 32.8, 31.5, 29.2, 27.8, 20.3, 14.5; FTIR (neat), cm^{-1}: 3514 (m), 2928 (m), 1620 (s), 1389 (s), 1105 (s), 984 (s); HRMS (ESI): Calcd for $(C_{38}H_{38}O_{15} + H)^+$: 675.2283, Found: 675.2279.



Diol 28.[11]

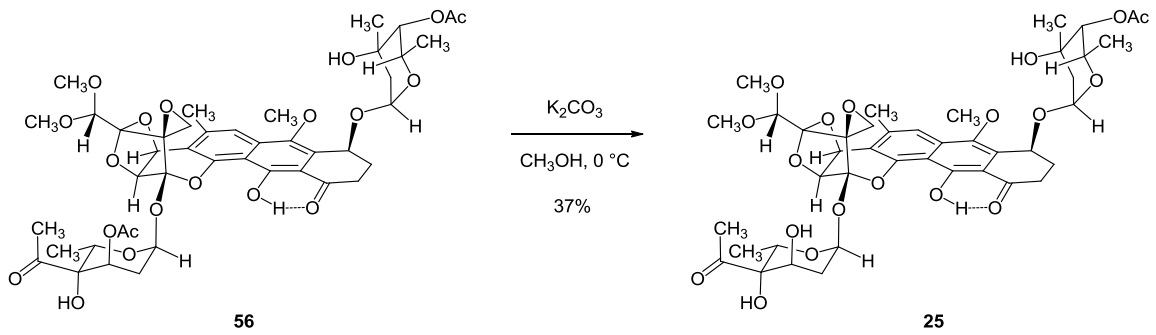
Potassium carbonate (0.3 mg, 2 μmol, 0.3 equiv) was added to an ice-cooled solution of α-glycoside **54** (5 mg, 6 μmol, 1 equiv) in methanol (1.0 mL). After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 2 h, the mixture was partitioned between chloroform (40 mL) and saturated aqueous sodium chloride solution (10 mL). The layers were separated. The aqueous layer was extracted with chloroform (3 × 20 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration the pure diol **28** (3 mg, 63%, in fractions eluting at 28–30 min) as a yellow solid. TLC: (67% ethyl acetate–hexanes) R_f = 0.32 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.76 (s, 1H), 7.52 (s, 1H), 7.36–7.28 (m, 5H), 5.86 (br d, 1H, J = 2.3 Hz), 5.34 (d, 1H, J = 4.4 Hz), 5.24 (d, 1H, J = 4.4 Hz), 5.17 (br s, 1H), 5.02 (q, 1H, J = 6.3 Hz), 4.76 (s, 1H), 4.7 (d, 1H, J = 11.5 Hz), 4.58 (d, 1H, J = 11.5 Hz), 4.26 (d, 1H, J = 9.5 Hz), 4.15 (s, 1H), 3.82 (s, 3H), 3.71 (d, 1H, J = 9.5 Hz), 3.63 (s, 3H), 3.49 (s, 3H), 3.2 (ddd, 1H, J = 18.1, 13.6, 5.2 Hz), 2.97 (d, 1H, J = 5.6 Hz), 2.9 (d, 1H, J = 5.9 Hz), 2.61 (s, 3H), 2.60–2.51 (m, 2H), 2.49 (s, 3H), 2.43 (dt, 1H, J = 14.5, 3.3 Hz), 2.12 (d, 1H, J = 14.7 Hz), 2.06 (tdd, 1H, J = 13.5, 4.0, 1.6 Hz), 1.09 (d, 3H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5, 204.3, 163.0, 151.6, 143.8, 141.8, 138.2, 135.2, 128.4, 128.3, 127.8, 127.7, 116.7, 114.7, 114.1, 109.7, 104.6, 101.4, 99.7, 94.8, 79.6, 71.5, 70.6, 70.3, 69.3, 68.3, 67.7, 63.8, 62.8, 56.8, 56.1, 48.2, 32.4, 31.5, 27.8, 26.5, 20.3,

14.5; FTIR (neat), cm^{-1}: 3512 (br w), 2926 (m), 1621 (s), 1389 (s), 1084 (s), 984 (s); HRMS (ESI): Calcd for $(C_{40}H_{44}O_{15} + Na)^+$: 787.2572, Found: 787.2571.



3''-*O*-Acetyl-2-deoxytrioxacarcin A (56).

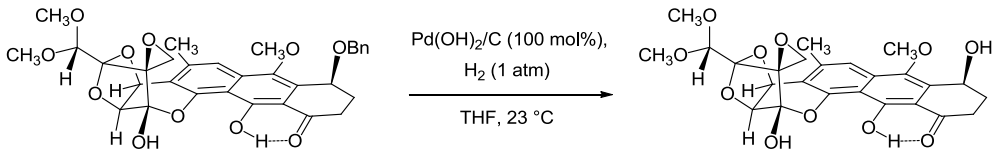
A suspension of benzylic alcohol **55** (9.0 mg, 13 μmol, 1 equiv), 1-phenylthiotrioxacarcinoside A **23** (11 mg, 38 μmol, 3.0 equiv, a 3:1 mixture of α and β anomers, respectively), 2,6-di-*tert*-butyl-4-methylpyridine (21 mg, 0.10 mmol, 8.0 equiv), and powdered 4-Å molecular sieves (~25 mg) in dichloromethane (0.6 mL) was stirred for 20 min at 23 °C. The mixture was cooled to 0 °C in an ice bath. Silver hexafluorophosphate (19 mg, 75 μmol, 6.0 equiv) was added in one portion. After 1 h, a solution of triethylamine (88 μL, 0.63 mmol, 50 equiv) in dichloromethane (10 mL) was added. The suspension was filtered through a pad of Celite, and the filtrate was concentrated. The residue was immediately purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→100% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration pure 3''-*O*-acetyl-2-deoxytrioxacarcin A (**56**) as a yellow-green foam (6.2 mg, 55%, in fractions eluting at 16–21 min). TLC: (5% methanol–dichloromethane) R_f = 0.47 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.75 (s, 1H), 7.48 (s, 1H), 5.81 (s, 1H), 5.37 (br, 1H), 5.29 (d, 1H, *J* = 4.1 Hz), 5.25 (m, 1H), 5.19 (d, 1H, *J* = 4.2 Hz), 5.00 (q, 1H, *J* = 6.4 Hz), 4.73 (m, 3H), 4.49 (q, 1H, *J* = 6.2 Hz), 4.07 (br, 1H), 3.90 (br, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 3.47 (s, 3H), 3.01 (ddd, 1H, *J* = 18.5, 13.8, 5.2 Hz), 2.85 (d, 1H, *J* = 5.5 Hz), 2.78 (d, 1H, *J* = 5.5 Hz), 2.66 (d, 1H, *J* = 18.2 Hz), 2.59 (s, 3H), 2.59–2.52 (m, 1H), 2.43 (m, 1H), 2.35 (s, 3H), 2.32 (m, 1H), 2.22 (s, 3H), 2.20 (m, 1H), 2.12 (s, 3H), 1.93 (dd, 1H, *J* = 14.4, 3.8 Hz), 1.60 (d, 1H, *J* = 14.4 Hz), 1.22 (d, 3H, *J* = 6.5 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.7, 203.1, 170.4, 170.2, 163.3, 151.9, 144.1, 142.3, 135.0, 126.7, 116.6, 114.9, 114.6, 109.2, 104.5, 101.6, 99.4, 96.9, 92.4, 78.2, 74.5, 72.0, 70.7, 69.1, 68.8, 68.3, 66.3, 64.5, 62.8, 62.7, 56.5, 55.9, 47.5, 36.5, 32.4, 28.9, 28.4, 27.0, 25.6, 21.3, 20.9, 20.3, 16.9, 14.5; FTIR (neat), cm^{-1}: 3480 (br, w), 2926 (m), 1740 (s), 1620 (m), 1373 (s), 1236 (s), 999 (s); HRMS (ESI): Calcd for $(C_{44}H_{54}O_{20}+H)^+$ 903.3281, found 903.3284.



56 25

2-deoxytrioxacarcin A (25).

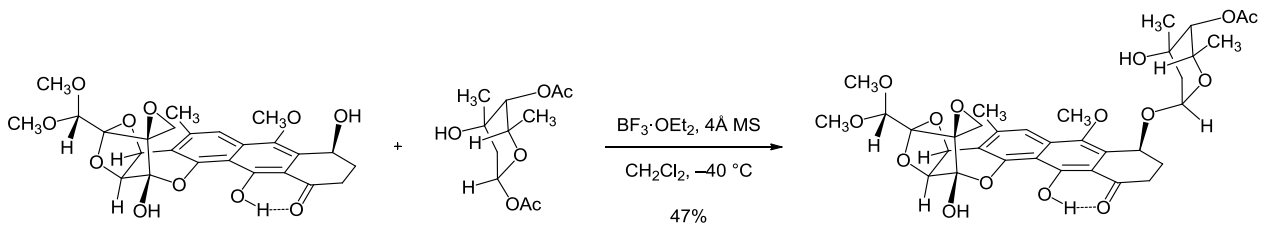
Potassium carbonate (1.8 mg, 13 μmol, 2.0 equiv) was added to an ice-cooled solution of 3"-*O*-Acetyl-2-deoxytrioxacarcin A **56** (6.0 mg, 6.7 μmol, 1 equiv) in methanol (1.3 mL). After 1 h, pH 7 aqueous phosphate buffer solution (10 mL) was added. The mixture was concentrated by rotary evaporation to remove methanol. The concentrated solution was extracted with dichloromethane (3 × 30 mL). The organic layers were combined and the combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 20→80% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration 2-deoxytrioxacarcin A (**25**) (2.1 mg, 37%). TLC: (5% methanol–dichloromethane) R_f = 0.41 (UV, CAM); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 14.80 (s, 1H), 7.51 (s, 1H), 5.84 (br s, 1H), 5.38 (br s, 1H), 5.35 (d, 1H, *J* = 4.2 Hz), 5.26 (m, 1H), 5.24 (d, 1H, *J* = 4.2 Hz), 5.02 (q, 1H, *J* = 6.4 Hz), 4.78 (s, 1H), 4.74 (s, 1H), 4.49 (q, 1H, *J* = 6.2 Hz), 4.25 (d, 1H, *J* = 9.9 Hz), 4.16 (s, 1H), 4.07 (s, 1H), 3.85 (s, 3H), 3.71 (d, 1H, *J* = 9.7 Hz), 3.63 (s, 3H), 3.49 (s, 3H), 3.03 (ddd, 1H, *J* = 19.3, 13.6, 5.1 Hz), 2.99 (d, 1H, *J* = 5.7 Hz), 2.94 (d, 1H, *J* = 5.7 Hz), 2.68 (dd, 1H, *J* = 18.2, 4.4 Hz), 2.61 (s, 3H), 2.50 (s, 3H), 2.46–2.41 (m, 1H), 2.25–2.18 (m, 1H), 2.15–2.11 (m, 1H), 2.13 (s, 3H), 1.94 (dd, 1H, *J* = 14.5, 4.0 Hz), 1.60 (d, 1H, *J* = 14.5 Hz), 1.22 (d, 3H, *J* = 6.6 Hz), 1.09 (d, 3H, *J* = 6.4 Hz), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.4, 203.3, 170.4, 163.3, 151.8, 144.1, 142.2, 135.1, 126.8, 116.9, 114.8, 114.5, 109.3, 104.7, 101.5, 99.7, 97.0, 94.8, 79.6, 74.5, 71.4, 70.2, 69.3, 68.8, 68.3, 66.2, 63.8, 62.8, 62.7, 56.8, 56.2, 48.2, 36.5, 32.4, 31.5, 28.4, 27.8, 25.6, 20.9, 20.3, 16.9, 14.5; FTIR (neat), cm^{-1}: 3509 (br m), 2928 (s), 1719 (s), 1622 (s), 1389 (s), 1234 (s), 1107 (s), 999 (s); HRMS (ESI): Calcd for $(C_{42}H_{52}O_{19}+Na)^+$ 883.2995, found 883.2974.



53 57

2-Deoxy-DC-45-A2 (57).

Palladium hydroxide on carbon (20 wt. %, 18 mg, 0.025 mmol, 1.0 equiv) was added to a solution of 2-deoxy synthetic precursor **53** (15 mg, 0.025 mmol, 1 equiv) in tetrahydrofuran (1.2 mL) at 23 °C. An atmosphere of hydrogen was maintained by sparging with a slow stream of pure hydrogen gas through a 22-gauge stainless steel needle. After 2 h, the mixture was diluted with ethyl acetate (20 mL) and filtered through a short pad of Celite. The filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide after concentration pure 2-deoxy-DC-45-A2 (**57**) (11.4 mg, 90%). TLC: (5% methanol–dichloromethane) R_f = 0.47 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.94 (s, 1H), 7.42 (s, 1H), 5.39 (t, 1H, *J* = 3.3 Hz), 5.24 (d, 1H, *J* = 4 Hz), 4.86 (d, 1H, *J* = 4 Hz), 4.74 (br s, 1H), 4.70 (s, 1H), 3.91 (s, 3H), 3.61 (s, 3H), 3.46 (s, 3H), 3.10 (ddd, 1H, *J* = 17.6, 12.1, 5.5 Hz), 3.09 (d, 1H, *J* = 5.1 Hz), 3.04 (d, 1H, *J* = 5.1 Hz), 2.75 (br s, 1H), 2.62 (t, 1H, *J* = 4.2 Hz), 2.58 (s, 3H), 2.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.9, 162.8, 151.5, 143.6, 142.1, 135.3, 130.2, 116.2, 114.7, 114.5, 109.0, 103.9, 100.1, 98.6, 73.2, 69.6, 69.2, 62.7, 62.2, 57.0, 56.6, 50.3, 32.7, 29.1, 20.4; FTIR (neat), cm^{-1}: 3437 (br w), 2926 (m), 1717 (m), 1620 (s), 1389 (s), 1065 (s), 978 (s); HRMS (ESI): Calcd for $(C_{25}H_{26}O_{11}+H)^+$ 503.1548, found 503.1555.

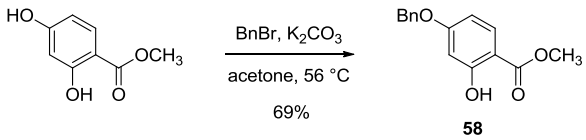


57 3 26

2-Deoxy-DC-45-A1 (26).

Boron trifluoride etherate (1.4 μL, 11 μmol, 1.0 equiv) was added to a suspension of 2-deoxy-DC-45-A2 (**57**) (5.7 mg, 11 μmol, 1 equiv), 1-*O*-acetyltrioxacarcinose A (**3**)[4] (5.6 mg, 23 μmol, 2.0 equiv, a ~1:12 mixture of α- and β-anomers, respectively), and powdered 4-Å molecular sieves (~30 mg) in dichloromethane (380 μL) at –40 °C. After 5 min, saturated aqueous sodium bicarbonate solution (1 mL) was added rapidly. The cooing bath was removed and the reaction flask was allowed to warm to 23 °C. The mixture was partitioned between dichloromethane (40 mL) and

saturated aqueous sodium bicarbonate solution (9 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory HPLC (Agilent Prep-C18 column, 10 μm, 30 × 150 mm, UV detection at 270 nm, gradient elution with 40→90% acetonitrile in water, flow rate: 15 mL/min) to provide pure 2-deoxy-DC-45-A1 (**26**) as a yellow-green powder (3.7 mg, 47%). TLC: (5% methanol–dichloromethane) R_f = 0.43 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 15.03 (s, 1H), 7.50 (s, 1H), 5.37 (app s, 1H), 5.26 (d, 2H, *J* = 4 Hz), 4.83 (d, 1H, *J* = 4 Hz), 4.73 (s, 1H), 4.71 (s, 1H), 4.49 (q, 1H, *J* = 6.5 Hz), 4.38 (s, 1H), 4.08 (s, 1H), 3.85 (s, 3H), 3.62 (s, 3H), 3.47 (s, 3H), 3.16 (d, 1H, *J* = 5.5 Hz), 3.08 (s, 1H), 3.01 (ddd, 1H, *J* = 18.7, 13.9, 5.1 Hz), 2.68 (dd, 1H, *J* = 18.3, 3.7 Hz), 2.61 (s, 3H), 2.46–2.40 (m, 1H), 2.27–2.19 (m, 1H), 2.13 (s, 3H), 1.93 (dd, 1H, *J* = 14.6, 3.7 Hz), 1.59 (d, 1H, *J* = 14.6 Hz), 1.22 (d, 3H, *J* = 6.2 Hz), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.2, 170.4, 163.3, 151.7, 144.1, 142.3, 135.1, 126.7, 116.8, 114.9, 114.9, 109.2, 103.9, 100.1, 98.5, 97.0, 74.5, 73.2, 69.6, 69.3, 68.8, 66.3, 62.8, 62.7, 57.1, 56.6, 50.6, 36.5, 32.4, 28.3, 25.6, 20.9, 20.4, 16.9; FTIR (neat), cm^{-1}: 3514 (br w), 2926 (m), 1746 (m), 1620 (m), 1391 (s), 1236 (s), 1084 (s), 997 (s); HRMS (ESI): Calcd for $(C_{34}H_{40}O_{15}+Na)^+$ 711.2259, found 711.2242.



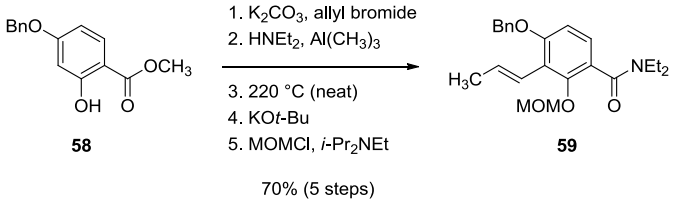
58

Methyl 4-(Benzyloxy)-2-hydroxybenzoate[12] (58).

Benzyl bromide (3.54 mL, 29.7 mmol, 1.00 equiv) was added dropwise to an ice-cooled suspension of methyl 2,4-dihydroxybenzoate (5.00 g, 29.7 mmol, 1 equiv) and potassium carbonate (5.75 g, 41.6 mmol, 1.4 equiv) in acetone (30 mL). The suspension was heated to reflux. After 18 h, the mixture was concentrated. The residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The layers were separated. The basic aqueous layer was neutralized (pH ~7) by addition of 1.0 M aqueous hydrochloric acid solution, and the neutralized solution was extracted with ethyl acetate (100 mL). The organic layers were combined. The combined solution was washed sequentially with water (50 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was recrystallized from methanol to provide methyl 4-(benzyloxy)-2-hydroxybenzoate (**58**) as a white solid (5.31 g, 69%).[12] ^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.96 (s, 1H), 7.75 (d, 1H, *J* = 8.8 Hz), 7.43–7.38 (m, 4H), 7.36–7.32 (m, 1H), 6.53 (d, 1H, *J* = 2.3 Hz), 6.51 (dd, 1H, *J* = 8.8, 2.4 Hz), 5.08 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.3, 164.6, 163.7,

[12] Tangdenpaisala, K.; Sualeka, S.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2009**, *65*, 4316–4325.

136.0, 131.2, 128.6, 128.2, 127.5, 108.0, 105.6, 101.6, 70.1, 51.9; FTIR (neat), cm^{-1}: 1667 (s), 1620 (s), 1439 (s), 1346 (s), 1252 (s), 1138 (s); HRMS (ESI): Calcd for $(C_{15}H_{14}O_4+H)^+$ 259.0965, found 259.0970.



58 **59**

70% (5 steps)

(*E*)-4-(benzyloxy)-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (59).

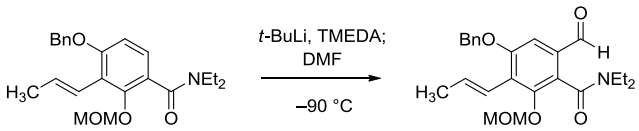
Allyl bromide (3.56 mL, 41.1 mmol, 2.0 equiv) was added to a vigorously stirred suspension of methyl 4-(benzyloxy)-2-hydroxybenzoate (**58**) (5.31 g, 20.6 mmol, 1 equiv) and potassium carbonate (5.68 g, 41.1 mmol, 2.0 equiv) in *N*,*N*-dimethylformamide (40 mL) at 23 °C. After 18 h, the mixture was partitioned between ethyl acetate (600 mL) and water (200 mL). The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide methyl 2-(allyloxy)-4-(benzyloxy)benzoate, which was used in the next step without purification.

Trimethylaluminum (1.8 M solution in toluene, 21.7 mL, 39.0 mmol, 1.9 equiv) was added to an ice-cooled solution of diethylamine (8.1 mL, 78 mol, 3.8 equiv) in benzene (10 mL). After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. A solution of methyl 2-(allyloxy)-4-(benzyloxy)benzoate (1 equiv, see paragraph above) in toluene (10 mL) was added to the reaction mixture over 5 min by cannula. The reaction mixture was heated at reflux in an oil bath at 120 °C (CAUTION: gas evolution). After 7 h, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was poured carefully into a mixture of ice water (100 mL) and 12 M aqueous hydrochloric acid solution (2 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined. The combined solution was washed sequentially with water (100 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide 2-(allyloxy)-4-(benzyloxy)-*N*,*N*-diethylbenzamide, which was used in the next step without purification.

2-(allyloxy)-4-(benzyloxy)-*N*,*N*-diethylbenzamide (see paragraph above) was heated neat in an oil bath at 220 °C. After 5 h, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. The product, 3-allyl-4-(benzyloxy)-*N*,*N*-diethyl-2-hydroxybenzamide, was used in the next step without purification.

Potassium *tert*-butoxide (11.52 g, 103 mmol, 5.0 equiv) was added to a solution of 3-allyl-4-(benzyloxy)-*N*,*N*-diethyl-2-hydroxybenzamide (1 equiv, see paragraph above) in dimethyl sulfoxide (21 mL) at 23 °C. The reaction flask was heated in an oil bath at 120 °C. After 70 min, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. The reaction mixture was diluted with water (40 mL). The diluted solution was acidified to pH ~2 with 6.0 M aqueous hydrochloric acid solution (~50 mL). The mixture was extracted with ethyl acetate (2 × 100 mL). The organic layers were combined. The combined solution was washed sequentially with water (5 × 100 mL) then saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide (*E*)-4-(benzyloxy)-*N*,*N*-diethyl-2-hydroxy-3-(prop-1-en-1-yl)benzamide, which was used in the next step without purification.

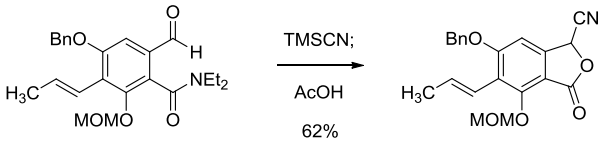
Chloromethyl methyl ether (2.34 mL, 30.7 mmol, 1.5 equiv) was added to a solution of (*E*)-4-(benzyloxy)-*N*,*N*-diethyl-2-hydroxy-3-(prop-1-en-1-yl)benzamide (1 equiv, see paragraph above) and *N*,*N*-diisopropylethylamine (7.17 mL, 41.0 mmol, 2.0 equiv) in dichloromethane (84 mL) at 0 °C. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 22 h, the reaction mixture was partitioned between water (200 mL) and dichloromethane (200 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (200 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes) to provide (*E*)-4-(benzyloxy)-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (**59**) as a yellow oil (5.50 g, 70% over 5 steps). TLC: (50% ethyl acetate–hexanes) R_f = 0.41 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.32 (m, 5H), 7.02 (d, 1H, *J* = 8.7 Hz), 6.75 (d, 1H, *J* = 8.2 Hz), 6.61 (m, 2H), 5.11 (s, 2H), 5.00 (br, 2H), 3.68 (br, 1H), 3.51 (s, 3H), 3.41 (br, 1H), 3.30–3.12 (br, 2H), 1.90 (d, 3H, *J* = 5.0 Hz), 1.24 (t, 3H, *J* = 6.9 Hz), 1.04 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 168.7, 157.3, 151.0, 136.4, 131.8, 128.2, 127.6, 126.9, 125.4, 124.8, 121.1, 120.9, 108.3, 99.4, 70.3, 57.3, 42.8, 38.8, 19.7, 13.6, 12.6; FTIR (neat), cm^{-1}: 2972 (w), 1626 (s), 1427 (m), 1265 (m), 1265 (m), 1055 (s), 926 (s), 733 (s); HRMS (ESI): Calcd for $(C_{23}H_{29}NO_4+Na)^+$ 406.1998, found 406.1989.



59 **60**

Aldehyde 60.

tert-Butyllithium (1.7 M solution in pentane, 1.84 mL, 3.13 mmol, 1.2 equiv) was added dropwise to a solution of *N*,*N*,*N*,*N*-tetramethylethylenediamine (472 μL, 3.13 mmol, 1.2 equiv) and (*E*)-4-(benzyloxy)-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (**59**) (1.00 g, 2.61 mmol, 1 equiv) in tetrahydrofuran (26 mL) at –90 °C in a liquid nitrogen–hexane bath. After 5 min, dimethylformamide (2.42 mL, 31.3 mmol, 12 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 40 min, the reaction mixture was diluted with water (10 mL), and the diluted solution was partially concentrated to remove the volatile organic solvents. The aqueous residue was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined. The combined solution was washed with water (2 × 50 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide aldehyde **60** as a pale yellow oil (1.07 g, >99%). TLC: (50% ethyl acetate–hexanes) R_f = 0.47 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.90 (s, 1H), 7.45–7.36 (m, 5H), 7.34 (s, 1H), 6.83 (dq, 1H, *J* = 16.0, 6.9 Hz), 6.64 (dd, 1H, *J* = 16.0, 1.8 Hz), 5.17 (s, 2H), 5.06 (d, 1H, *J* = 5.0 Hz), 5.01 (d, 1H, *J* = 5.0 Hz), 3.68–3.56 (m, 2H), 3.54 (s, 3H), 3.21–3.11 (m, 2H), 1.93 (dd, 3H, *J* = 6.9, 1.8 Hz), 1.30 (t, 3H, *J* = 7.3 Hz), 1.04 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.5, 165.9, 157.4, 151.3, 136.0, 135.6, 131.2, 128.6, 128.5, 128.1, 127.6, 127.4, 121.2, 107.0, 100.1, 70.9, 57.9, 43.3, 39.3, 20.2, 13.8, 12.8; FTIR (neat), cm^{-1}: 2936 (w), 1694 (m), 1628 (s), 1288 (m), 924 (m); HRMS (ESI): Calcd for $(C_{24}H_{29}NO_5+Na)^+$ 434.1938, found 434.1942.

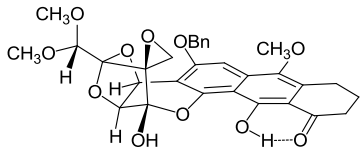


60 **61**

Cyanophthalide 61.

Cyanotrimethylsilane (524 μL, 3.91 mmol, 1.5 equiv) was added to an ice-cooled solution of aldehyde **60** (1.07 g, 2.61 mmol, 1 equiv) in dichloromethane (5.2 mL). After 5 min, potassium cyanide (1.7 mg, 0.026 mmol, 0.01 equiv) and 18-crown-6 (6.9 mg, 0.026 mmol, 1 equiv) were added. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 5 h, the solution was concentrated carefully. The residue was dissolved in glacial acetic

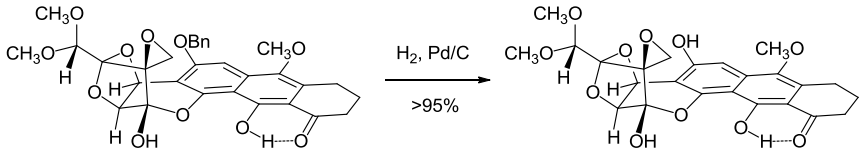
acid (5.2 mL) (CAUTION: the highly toxic gas hydrogen cyanide may be generated upon treatment of the residue with acetic acid: This operation should be conducted in a well-ventilated fume hood). The resulting solution was stirred at 23 °C. After 41 h, the solvent was removed by rotary evaporation. The residue was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (50 mL). The layers were separated. The organic layer was washed with water (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to provide cyanophthalide **61** as a white foam (588 mg, 62% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.33 (m, 5H), 6.89 (s, 1H), 6.64 (dq, 1H, J = 16.1, 6.2 Hz), 6.57 (d, 1H, J = 16.1 Hz), 5.90 (s, 1H), 5.34 (q, 2H, J = 6.5 Hz), 5.27 (d, 1H, J = 11.7 Hz), 5.20 (d, 1H, J = 11.7 Hz), 3.56 (s, 3H), 1.93 (d, 3H, J = 5.9 Hz).



35

Benzyl ether 35.

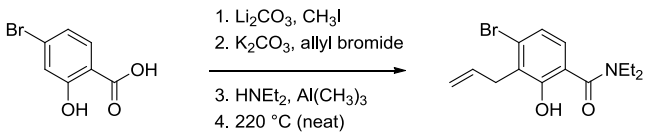
Benzyl ether **35** was assembled from the epoxy diazo diketone **21**, cyanophthalide **61**, and cyclohexenone by an analogous sequence as described in Figure 4 for the synthesis of synthetic precursor **1**. TLC: (40% ethyl acetate–hexanes) R_f = 0.13 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.97 (s, 1H), 7.48 (d, 2H, J = 7.0 Hz), 7.40–7.31 (m, 3H), 7.00 (s, 1H), 5.55 (d, 1H, J = 4.0 Hz), 5.30 (d, 1H, J = 12.1 Hz), 5.23 (d, 1H, J = 12.1 Hz), 4.78 (d, 1H, J = 4.0 Hz), 4.72 (s, 1H), 4.39 (br s, 1H), 3.66 (s, 3H), 3.60 (s, 3H), 3.48 (s, 3H), 3.20 (d, 1H, J = 5.5 Hz), 3.09 (d, 1H, J = 5.5 Hz), 3.01 (t, 2H, J = 6.2 Hz), 2.70 (m, 2H), 2.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.0, 163.0, 159.2, 152.8, 142.0, 136.5, 136.2, 130.7, 128.6, 128.1, 127.3, 110.1, 109.6, 106.2, 103.8, 100.0, 98.7, 95.3, 72.8, 70.4, 69.5, 67.2, 60.4, 56.7, 56.2, 50.6, 38.6, 23.6, 22.1; FTIR (neat), cm^{-1}: 3343 (br w), 2945 (w), 1616 (s), 13897 (m), 1080 (s); HRMS (ESI): Calcd for $(C_{31}H_{30}O_{11}+H)^+$ 579.1861, found 579.1856.



35 34

Phenol 34.

Palladium on activated charcoal (10 wt. %, 1.1 mg, 1.0 μmol, 0.1 equiv) was added to a solution of benzyl ether **35** (6 mg, 10 μmol, 1 equiv) in ethanol (200 μL) at 23 °C. The mixture was saturated with hydrogen by bubbling hydrogen gas below the liquid surface for 2 min through a 22-gague stainless steel needle, and the mixture was subsequently stirred under a hydrogen atmosphere at 23 °C. After 2 h, the mixture was diluted with ethyl acetate (20 mL) filtered through a short pad of Celite. The filtrate was concentrated to provide phenol **34** (5 mg, >95%) as a yellow-green oil. During attempts at purification by rp-HPLC and upon standing in chloroform, phenol **34** underwent decomposition, forming a complex mixture of products. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 16.62 (br s, 1H), 10.67 (s, 1H), 6.91 (s, 1H), 5.56 (d, 1H, *J* = 4.0 Hz), 4.79 (d, 1H, *J* = 3.7 Hz), 4.69 (s, 1H), 4.29 (br s, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.48 (s, 3H), 3.26 (d, 1H, *J* = 5.1 Hz), 3.05 (d, 1H, *J* = 5.1 Hz), 3.04–2.92 (m, 2H), 2.73 (t, 2H, *J* = 6.4 Hz), 2.09 (quin, 2H, *J* = 6.2 Hz); HRMS (ESI): Calcd for $(C_{24}H_{24}O_{11}+Na)^+$ 511.1211, found 511.1227.



62

3-allyl-4-bromo-*N*,*N*-diethyl-2-hydroxybenzamide (62).

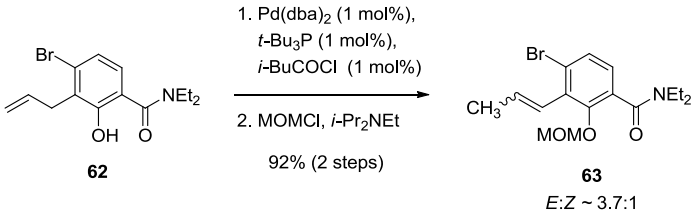
Iodomethane (1.66 mL, 26.6 mmol, 1.1 equiv) was added to a mixture of 4-bromo-2-hydroxybenzoic acid (5.24 g, 24.2 mmol, 1 equiv) and lithium carbonate (1.96 g, 26.6 mmol, 1.1 equiv) in dimethylformamide at 23 °C. The reaction flask was heated in an oil bath at 60 °C. After 3.5 h, the warm mixture was partitioned between ice water (50 mL) and ethyl acetate (80 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (80 mL). The organic layers were combined. The combined solution was washed sequentially with water (2 × 50 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the product, methyl 4-bromo-2-hydroxybenzoate, which was used in the next step without purification.

Methyl 4-bromo-2-hydroxybenzoate (1 equiv, see paragraph above) was added to an ice-cooled suspension of sodium hydride (60% dispersion in mineral oil, 1.16 g, 29.0 mmol, 1.2 equiv) and allyl bromide (4.18 mL, 48.3 mmol, 2.0 equiv) in dimethylformamide (40 mL). After 10 min,

the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 22 h, the mixture was partitioned carefully between ice water (50 mL) and ether (50 mL). The layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined. The combined solution was washed successively with water (3 × 40 mL) then saturated aqueous sodium chloride solution (40 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the product, methyl 2-(allyloxy)-4-bromobenzoate, which was used in the next step without purification.

Trimethylaluminum (2.0 M solution in toluene, 23.0 mL, 45.9 mmol, 1.9 equiv) was added to an ice-cooled solution of diethylamine (9.59 mL, 92.0 mmol, 3.8 equiv) in benzene (15 mL). After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. A solution of methyl 2-(allyloxy)-4-bromobenzoate (1 equiv, see paragraph above) in toluene (15 mL) was added. The reaction flask was heated in an oil bath at 120 °C (CAUTION: gas evolution). After 2.5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 °C. The solution was poured carefully into 0.2 M aqueous hydrochloric acid solution (100 mL). The mixture was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined. The combined solution was washed sequentially with water (100 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the product, 2-(allyloxy)-4-bromo-*N*,*N*-diethylbenzamide, which was used in the next step without purification.

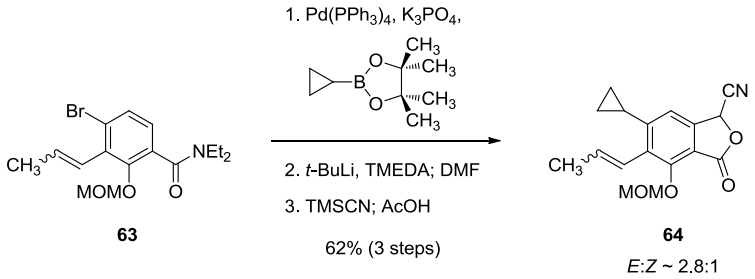
2-(allyloxy)-4-bromo-*N*,*N*-diethylbenzamide (see paragraph above) was heated neat in an oil bath at 220 °C. After 4 h, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. The product was purified by flash-column chromatography (5% ethyl acetate–hexanes initially, grading to 15% ethyl acetate–hexanes) to provide 3-allyl-4-bromo-*N*,*N*-diethyl-2-hydroxybenzamide (**62**) as a yellow oil (5.20 g, 69% yield over four steps). TLC: (20% ethyl acetate–hexanes) R_f = 0.49 (UV); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.4 (br s, 1H), 7.07 (d, 1H, *J* = 8.2 Hz), 7.01 (d, 1H, *J* = 8.8 Hz), 5.96 (dd, 1H, *J* = 17.0, 10.6 Hz), 5.10–5.04 (m, 2H), 3.62 (d, 2H, *J* = 6.5 Hz), 3.5 (q, 4H, *J* = 7.2 Hz), 1.27 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.2, 157.6, 134.3, 128.8, 128.4, 125.8, 122.3, 116.6, 115.5, 42.2, 33.8, 13.2; FTIR (neat), cm^{-1}: 2974 (m), 2932 (m), 1611 (s), 1587 (s), 1452 (s), 1275 (s); HRMS (ESI): Calcd for $(C_{14}H_{18}NO_2Br+H)^+$ 312.0594, found 312.0575.



4-bromo-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (63).

Bis(dibenzylideneacetone)palladium(0) (92 mg, 0.16 mmol, 0.01 equiv), tri-*tert*-butylphosphine (39 μL, 0.16 mmol, 0.01 equiv), and isobutyryl chloride (17 μL, 0.16 mmol, 0.01 equiv)[13] were added sequentially to a solution of 3-allyl-4-bromo-*N*,*N*-diethyl-2-hydroxybenzamide (**62**) (5.00 g, 16.0 mmol, 1 equiv) in toluene (40 mL) at 23 °C. The flask was heated in an oil bath at 80 °C. After 23 h, the solution was concentrated. The residue (1 equiv, see above) was dissolved in dichloromethane (80 mL). *N*,*N*-diisopropylethylamine (7.05 mL, 40.4 mmol, 2.5 equiv) and chloromethyl methyl ether (2.45 mL, 32.3 mmol, 2.0 equiv) were added at 23 °C. After 20 h, the mixture was partitioned between water (100 mL) and dichloromethane (150 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (150 mL). The organic layers were combined. The combined solution was washed sequentially with water (100 mL) the saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes) to provide the product, 4-bromo-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (**63**) as a ~3.7:1 mixture of *E*- and *Z*-isomers, respectively (the alkene stereochemistry is inconsequential) (5.25 g, 92% over two steps). TLC: (20% ethyl acetate–hexanes) R_f = 0.19, 0.13 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: *E*-isomer (major): 7.38 (d, 1H, *J* = 8.2 Hz), 6.94 (d, 1H, *J* = 8.2 Hz), 6.42–6.31 (m, 2H), 5.04–4.90 (m, 2H), 3.65 (br m, 1H), 3.47 (s, 3H), 3.44 (br m, 1H), 3.18 (br m, 2H), 1.93 (d, 3H, *J* = 6.0 Hz), 1.24 (t, 3H, *J* = 7.1 Hz), 1.06 (t, 3H, *J* = 7.1 Hz); *Z*-isomer (minor): 7.41 (d, 1H, *J* = 8.2 Hz), 7.03 (d, 1H, *J* = 8.2 Hz), 6.28 (dd, 1H, *J* = 11.2, 1.1 Hz), 5.95 (dq, 1H, *J* = 11.4, 6.9 Hz), 5.04–4.90 (m, 2H), 3.65 (br m, 1H), 3.46 (s, 3H), 3.44 (br m, 1H), 3.18 (br m, 2H), 1.58 (d, 3H, *J* = 6.9, 1.8 Hz), 1.20 (t, 3H, *J* = 7.1 Hz), 1.06 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 167.9, 167.8, 151.2, 151.1, 134.0, 133.9, 132.9, 131.7, 130.2, 129.0, 128.4, 127.1, 126.1, 125.4, 125.2, 125.1, 124.5, 99.6, 99.5, 98.1, 57.6, 57.4, 43.0, 42.9, 39.0, 39.0, 19.1, 19.1, 15.1, 14.9, 13.8, 12.8; FTIR (neat), cm^{-1}: 2976 (w), 1632 (s), 1429 (s), 1159 (s), 949 (s); HRMS (ESI): Calcd for $(C_{16}H_{22}NO_3Br+H)^+$ 356.0856, found 356.0863.

[13] Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.

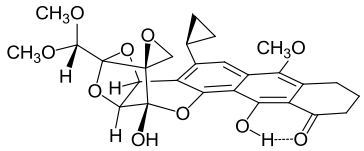


Cyanophthalide 64.

In a 150-mL heavy-walled glass pressure vessel, a suspension of 4-bromo-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (**63**) (940 mg, 2.64 mmol, 1 equiv, a ~3.7:1 mixture of *E*- and *Z*-isomers, respectively), cyclopropylboronic acid pinacol ester (893 μL, 5.28 mmol, 2.0 equiv), and tripotassium phosphate (1.68 g, 7.92 mmol, 3.0 equiv) in a mixture of tetrahydrofuran (17 mL) and water (17 mL) was degassed by sparging for 30 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tetrakis(triphenylphosphine)palladium(0) (152 mg, 0.132 mmol, 0.05 equiv) was added. The flask was sealed and heated in an oil bath at 120 °C. After 90 min, the heating bath was removed and the reaction flask was allowed to cool to 23 °C. Dichloromethane (250 mL) and saturated aqueous ammonium chloride solution (100 mL) were added. The layers were separated. The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes) to provide the product, 4-cyclopropyl-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide.

tert-Butyllithium (1.6 M solution in pentane, 3.30 mL, 5.28 mmol, 2.0 equiv) was added dropwise to a solution of *N*,*N*,*N*,*N*-tetramethylethylenediamine (797 μL, 5.28 mmol, 2.0 equiv) and 4-cyclopropyl-*N*,*N*-diethyl-2-(methoxymethoxy)-3-(prop-1-en-1-yl)benzamide (1 equiv, see paragraph above) in tetrahydrofuran (26 mL) at –78 °C. After 10 min, dimethylformamide (2.42 mL, 31.3 mmol, 12 equiv) was added. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 °C. After 30 min, the reaction mixture was diluted with water (10 mL), and the diluted solution was partially concentrated to remove the volatile organic solvents. The aqueous residue was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined. The combined solution was washed with water (2 × 50 mL) then saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue (1 equiv, see above) was dissolved in dichloromethane (5.3 mL). Cyanotrimethylsilane (531 μL, 3.96 mmol, 1.5 equiv) was added at 23 °C. After 5 min, potassium cyanide (1.7 mg, 0.026 mmol, 0.01 equiv) and 18-crown-6 (7 mg, 0.03 mmol, 1 equiv) were added. After 5 min, the cooling bath was removed and the reaction flask was

allowed to warm to 23 °C. After 3 h, the solution was concentrated carefully. The residue was dissolved in glacial acetic acid (5.3 mL) (CAUTION: the highly toxic gas hydrogen cyanide may be generated upon treatment of the residue with acetic acid: This operation should be conducted in a well-ventilated fume hood). The resulting solution was stirred at 23 °C. After 71 h, the solvent was removed by rotary evaporation. The residue was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (100 mL). The layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (50 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes) to provide cyanophthalide **64** as a colorless oil (490 mg, 62% over three steps, a ~2.8:1 mixture of *E*- and *Z*-isomers, respectively). TLC: (30% ethyl acetate–hexanes) R_f = 0.53 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: *E*-isomer (major): 6.88 (s, 1H), 6.54 (dd, 1H, *J* = 16.1, 1.5 Hz), 6.22 (dq, 1H, *J* = 16.1, 6.5 Hz), 5.91 (s, 1H), 5.33–5.28 (m, 2H), 3.55 (s, 3H), 2.20–2.13 (m, 1H), 1.98 (dd, 3H, *J* = 6.6, 1.7 Hz), 1.17–1.10 (m, 2H), 0.86–0.75 (m, 2H); *Z*-isomer (minor): 6.80 (s, 1H), 6.40 (d, 1H, *J* = 6.4 Hz), 6.08 (dq, 1H, *J* = 11.2, 6.8 Hz), 5.92 (s, 1H), 5.33–5.28 (m, 2H), 3.55 (s, 3H), 2.20–2.13 (m, 1H), 1.58 (dd, 3H, *J* = 6.8, 1.5 Hz), 1.17–1.10 (m, 2H), 0.86–0.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.7, 165.6, 154.5, 154.2, 154.1, 153.2, 142.2, 141.3, 135.4, 134.4, 134.1, 131.2, 123.1, 123.0, 114.2, 114.1, 113.5, 112.6, 112.3, 112.1, 100.8, 100.4, 64.7, 64.7, 57.8, 57.6, 19.3, 15.1, 15.0, 14.2, 10.6, 10.6, 10.1, 10.0; FTIR (neat), cm^{-1}: 2934 (w), 1778 (s), 1605 (m), 1157 (m), 991 (s), 912 (s); HRMS (ESI): Calcd for $(C_{17}H_{17}NO_4+Na)^+$ 322.1050, found 322.1053.



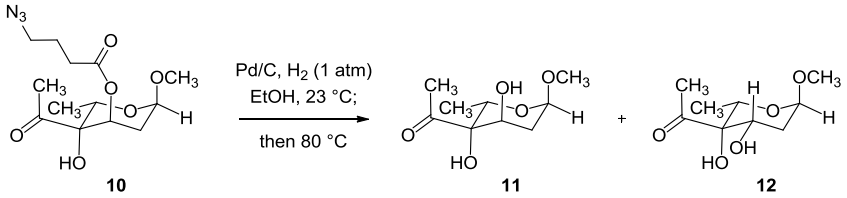
33

Cyclopropyl Analog 33.

Cyclopropyl analog **33** was assembled from the epoxy diazo diketone **21**, cyanophthalide **64**, and cyclohexenone by an analogous sequence as described in Figure 4 for the synthesis of synthetic precursor **1**. TLC: (60% ethyl acetate–hexanes) R_f = 0.39 (UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 14.92 (br s, 1H), 7.25 (s, 1H), 5.64 (d, 1H, *J* = 4.0 Hz), 4.84 (d, 1H, *J* = 4.0 Hz), 4.72 (s, 1H), 4.38 (br s, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.47 (s, 3H), 3.17 (d, 1H, *J* = 5.5 Hz), 3.07 (d, 1H, *J* = 5.1 Hz), 3.03 (td, 2H, *J* = 6.0, 2.9 Hz), 2.74–2.70 (m, 2H), 2.27–2.21 (m, 1H), 2.08 (quin, 2H, *J* = 6.3 Hz), 1.20–1.11 (m, 2H), 1.06–1.01 (m, 1H), 0.57–0.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 204.4,

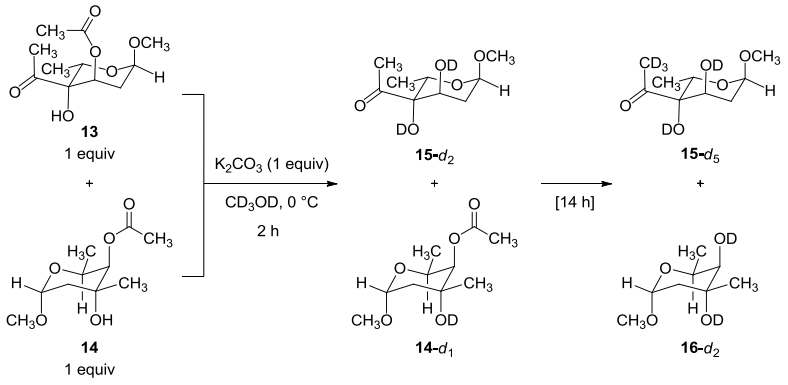
162.7, 151.3, 146.7, 142.5, 135.3, 130.1, 114.2, 112.9, 111.2, 111.0, 103.9, 100.1, 98.4, 73.3, 69.4, 69.3, 60.8, 57.0, 56.4, 50.4, 38.7, 23.5, 22.0, 13.5, 9.9, 6.2; FTIR (neat), cm^{-1}: 3420 (br w), 2928 (s), 1717 (m), 1618 (s), 1520 (s), 1366 (s), 1107 (s); HRMS (ESI): Calcd for $(C_{27}H_{28}O_{10}+Na)^{+}$ 535.1575, found 535.1573.

Additional Experiments



Diols 11 and 12[5]

Palladium on carbon (10 wt. %, wet, 1.8 mg) was added to a solution of **10** (18.0 mg, 0.057 mmol, 1 equiv) in ethanol (2 mL). The mixture was saturated with hydrogen by bubbling hydrogen gas below the liquid surface for 10 min using a 19-gauge stainless steel needle. Stirring was continued for 3.5 h under a hydrogen atmosphere. The black suspension was filtered through a pad of Celite, eluting with ethanol (10 mL). The filtrate was concentrated to a volume of ~7 mL and the concentrated solution was heated to reflux. After 3 h, heating was discontinued and the solution was concentrated. The residue was purified via flash-column chromatography (40% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes). Fractions 5–6 contained **11** together with several unidentified byproducts. Concentration of the later fractions (8–15) and ^{1}H NMR analysis of the residue revealed that the *cis*-diol **12** had formed.



Competition Experiment: Diols 15 and 16.

Potassium carbonate (5.7 mg, 0.040 mol, 1.0 equiv) was added to a solution of methyl α-3-*O*-acetyltrioxacarcinoside B (**13**)[5] (9.0 mg, 0.040 mmol, 1 equiv) and methyl α-trioxacarcinoside A (**14**)[4] (10.2 mg, 0.040 mmol, 1 equiv) in methanol-d_4 (3 mL) at 0 °C. After 2 h, analysis of the solution by ^{1}H NMR spectroscopy (500 MHz, CD_3OD) established that the 3-*O*-acetyl protecting group of **13** had been cleaved to afford methyl α-trioxacarcinoside B (diol **15**-d_2) and that the 4-*O*-acetyl group of **14** was retained. After 16 h, ^{1}H NMR analysis showed that the 4-*O*-acetyl group of

14 had been cleaved to give diol **16-**d_2 as the major product; additionally, complete proton-deuterium exchange of the methyl ketone of **15-**d_2 had occurred to give **15-**d_5.

Measurement of GI_{50} Values

Cell Culture.

All cell-culture work was conducted in a class II biological safety cabinet. H460 cells (P2–P4, American Type Culture Collection) were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS).

Cell Proliferation Assay.

H460 cells were grown to approximately 80% confluence, and then were trpysinized, collected, and pelleted by centrifugation (10 min at 183 × *g*, 4 °C). The supernatant was discarded and the cell pellet was resuspended in 10 mL of fresh medium. A sample was diluted 10-fold in fresh medium, and the concentration of cells was determined using a hemacytometer. The cell suspension was diluted to a concentration of 3000 cells/100 μL. The wells of a pre-sterilized 96-well plate were charged with 100 μL per well of the diluted cellular suspension. The plate was incubated for 24 h at 37 °C (5% CO_2).

Stock solutions of each compound in DMSO were diluted serially with RPMI-1640 medium (supplemented with FBS), and 100-μL aliquots of the resulting solutions were added to the wells containing adhered cells to achieve final concentrations of 0.11 nM to 250 nM (trioxacarcin A) or 1.1 nM to 2500 nM (all other compounds). After incubating at 37 ºC for 72 h (5% CO_2), 20 μL of resazurin solution (Promega CellTiter-Blue® Cell Viability Assay) was added to each well. After incubating at 37 °C for 2.0 h (5% CO_2), the fluorescence (544 nm excitation/590 nm emission) was recorded using a microplate reader (SpectraMax PLUS^{384}) as a measure of viable cells.

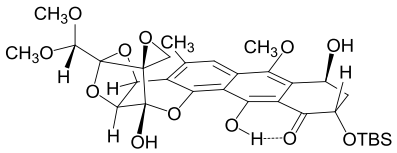
Percent growth inhibition was calculated for each well, based upon the following formula:

$$\text{Percent growth inhibition} = 100 \times (S - B_0) / (B_t - B_0)$$

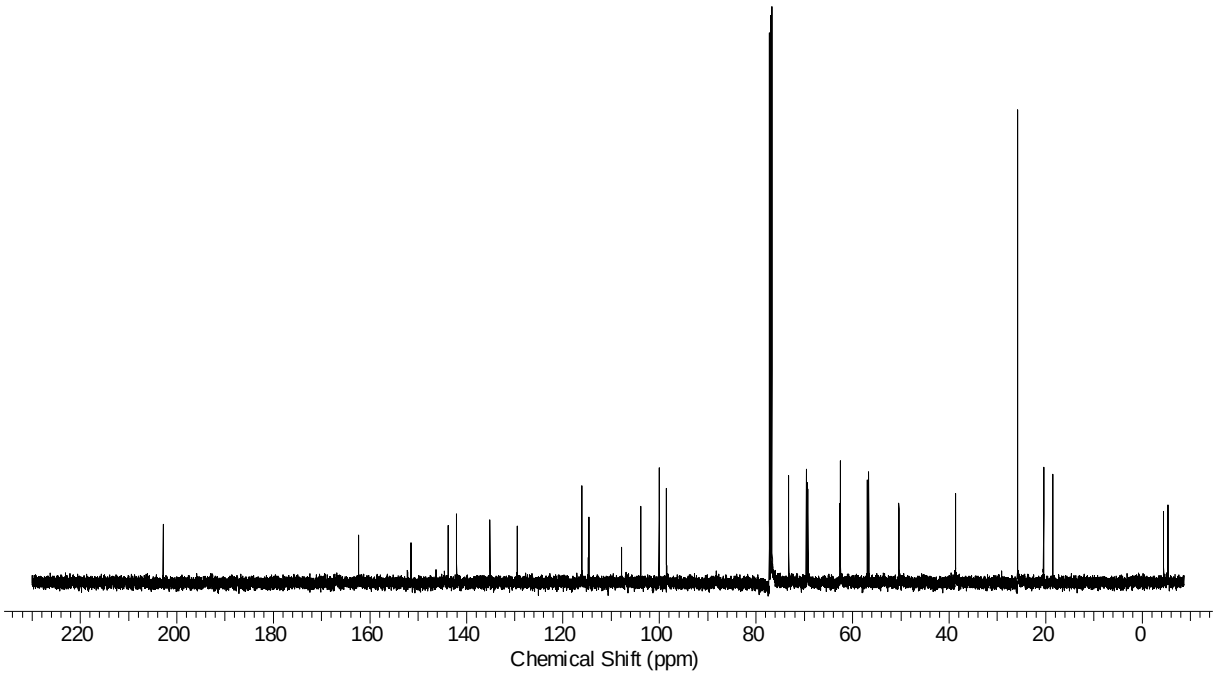
where S is the sample fluorescence, B_t is the average fluorescence of an untreated population of cells at the completion of the assay, and B_0 is the average fluorescence of an untreated population of cells at the beginning of the assay.

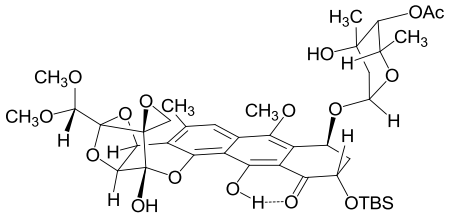
Each compound was assayed at eight separate concentrations per experiment. The percent inhibition at each concentration was plotted against log(concentration), and a curve fit was generated using the XLfit4 plugin (IDBS Software) running in Excel (Microsoft). GI_{50} values were computed to reflect the concentrations at which the resulting curves pass through 50% inhibition. GI_{50} values for each compound are reported as the average of at least six experiments, with standard deviation.

^{1}H and ^{13}C NMR Spectra



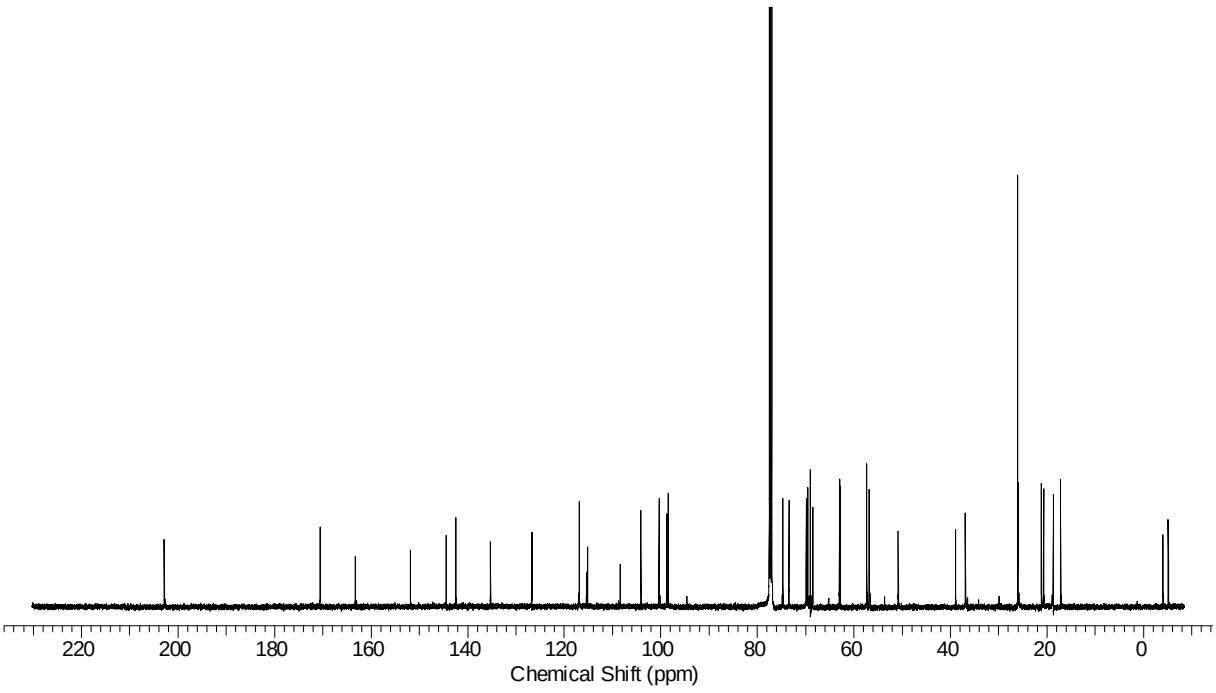
2

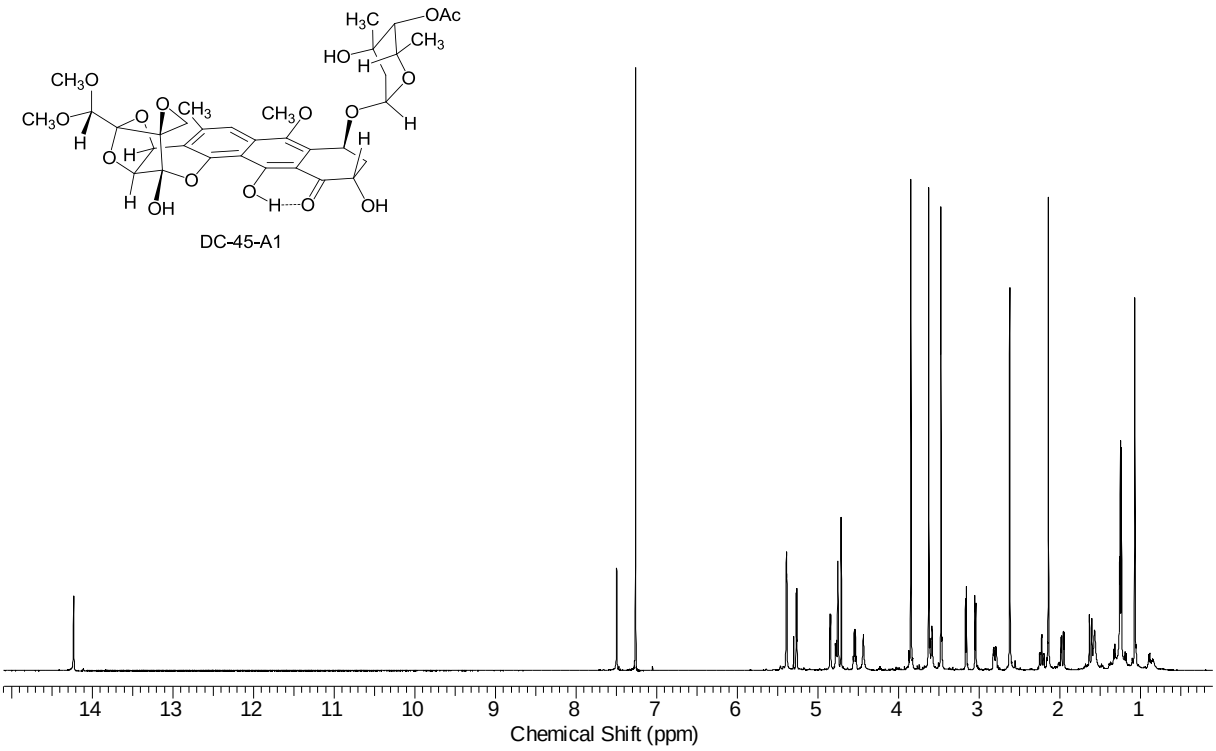


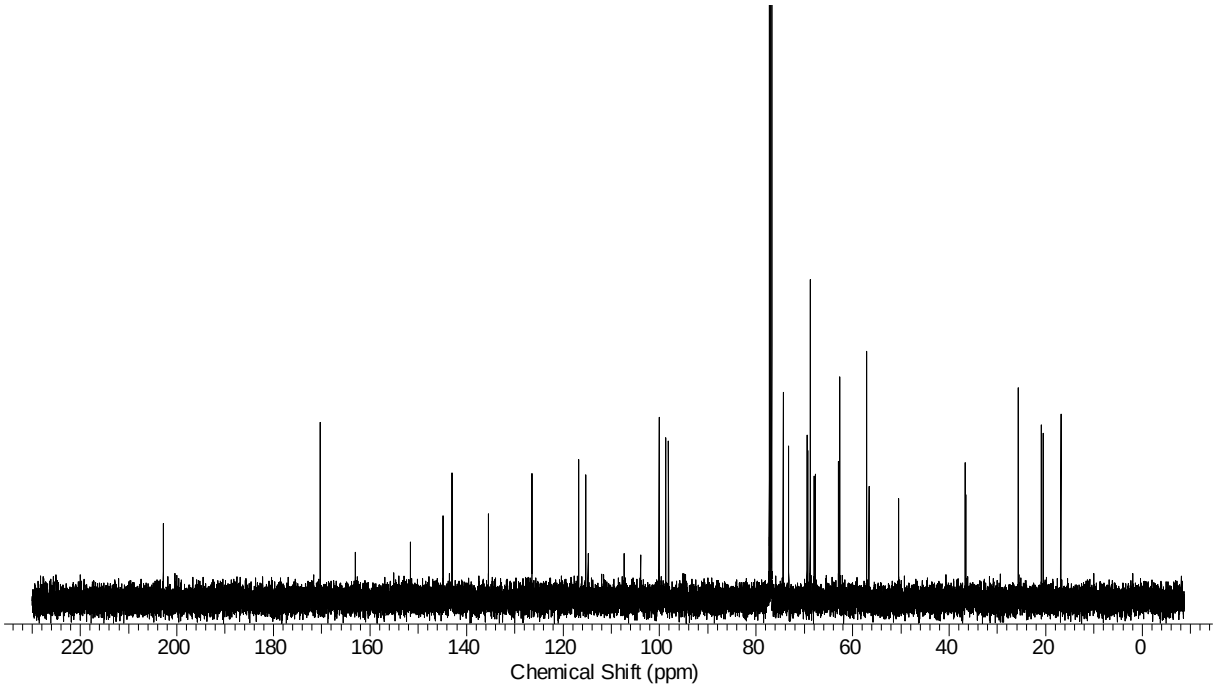

H3C
OAc
CH3
HO
H
O
CH3O
CH3O
H
O
O
CH3
CH3O
O
H
H
O
O
H
H
OH
O
H
O
OTBS

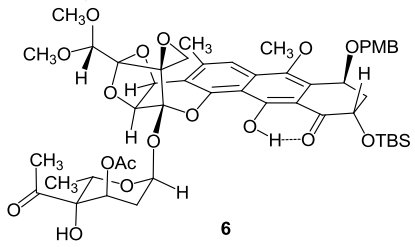
4

14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

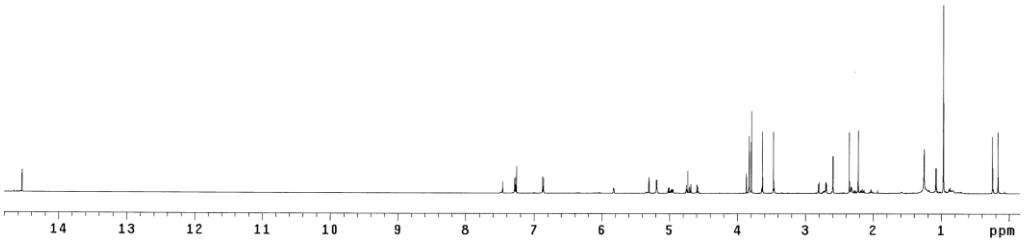

220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

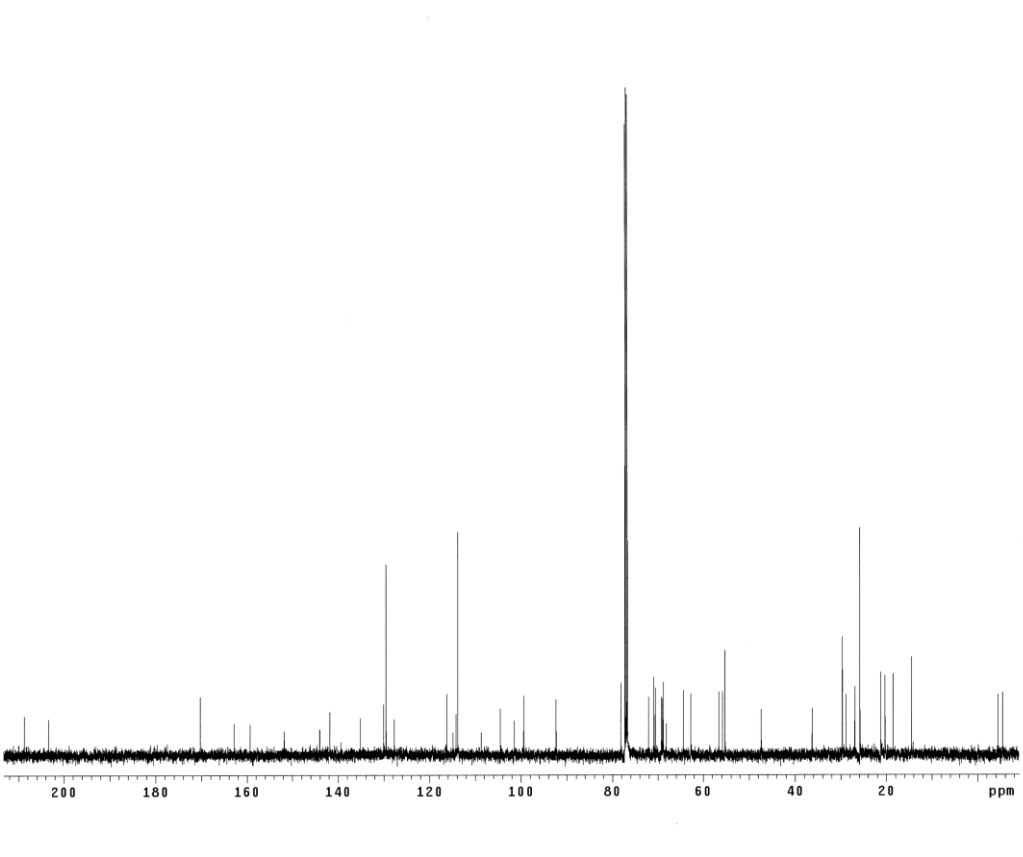

DC-45-A1
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

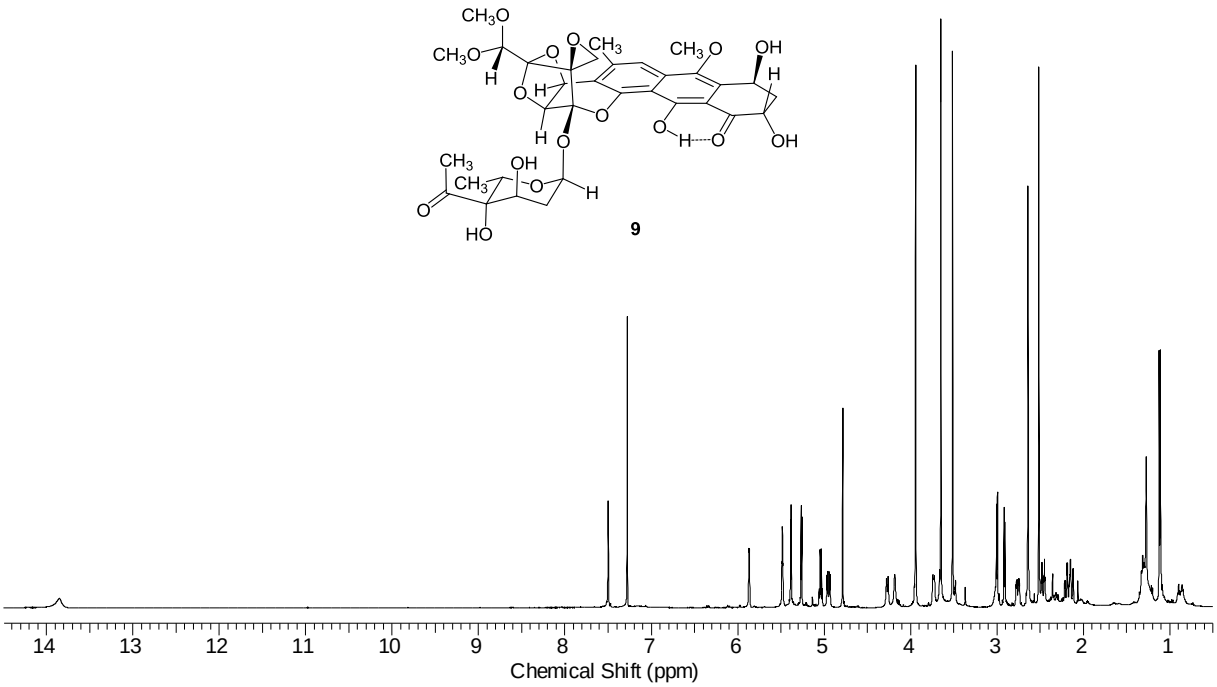

220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CH3O
CH3O
H
O
O
CH3
CH3O
OPMB
H
O
H
H
O
O
H
O
OTBS
CH3
OAc
CH3
O
H
O
HO

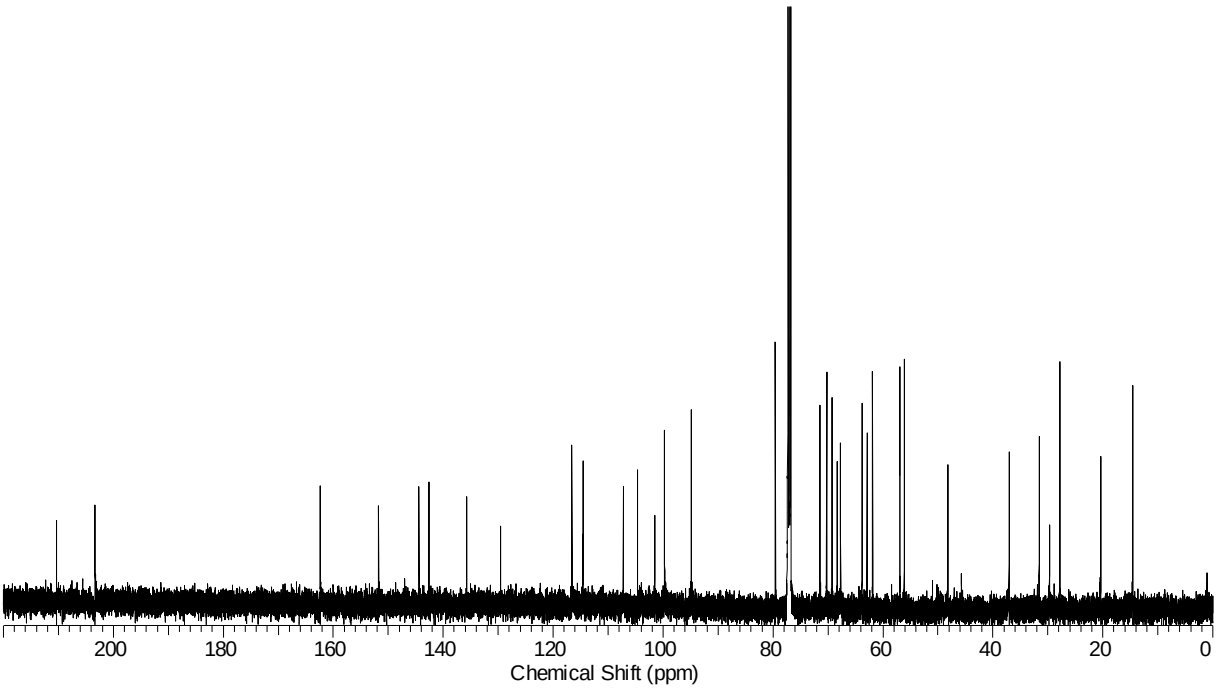
6

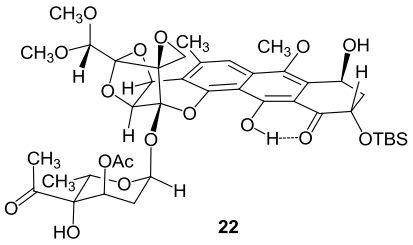

14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

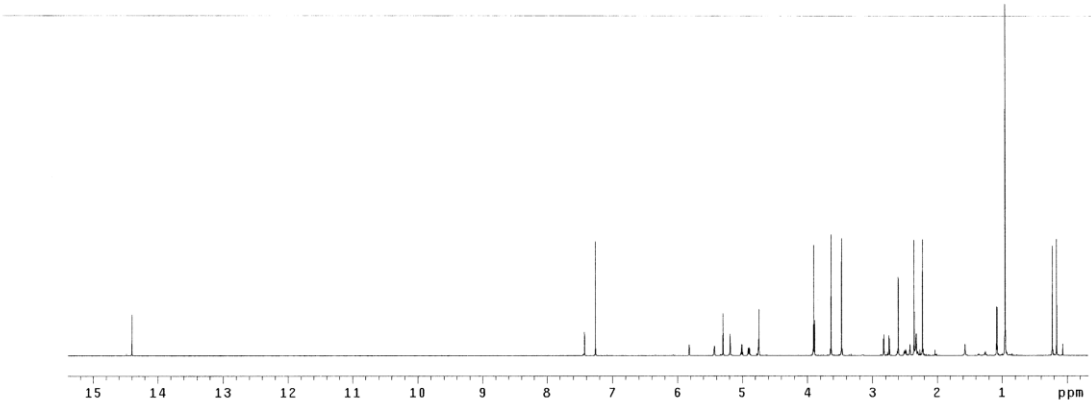


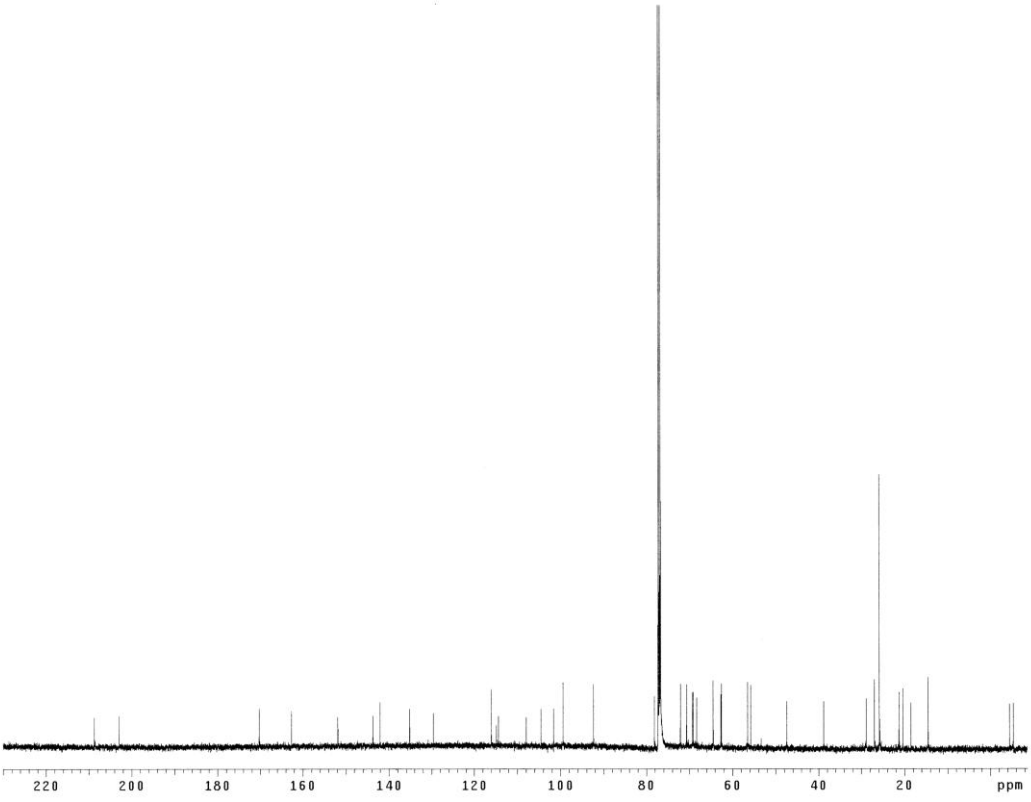
9

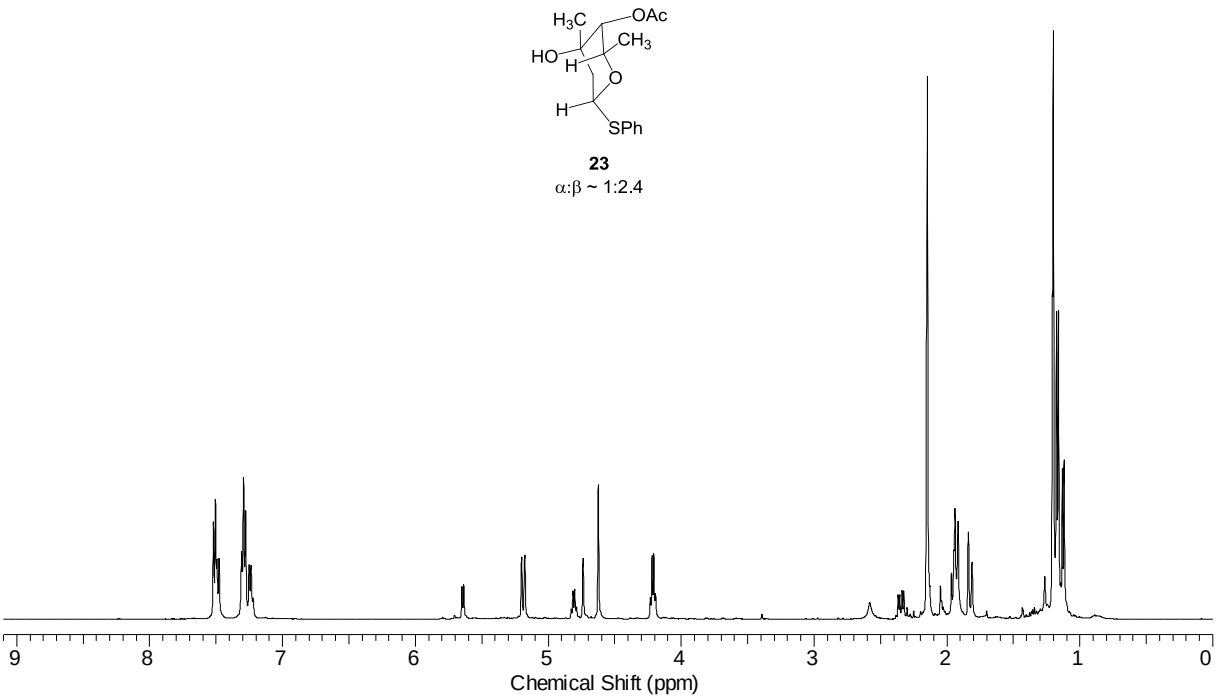



CH3O
CH3O
H
O
CH3
CH3O
OH
H
O
H
O
O
H
O
H
O
H···O
OTBS
CH3
OAc
CH3
O
O
H
O
HO

22

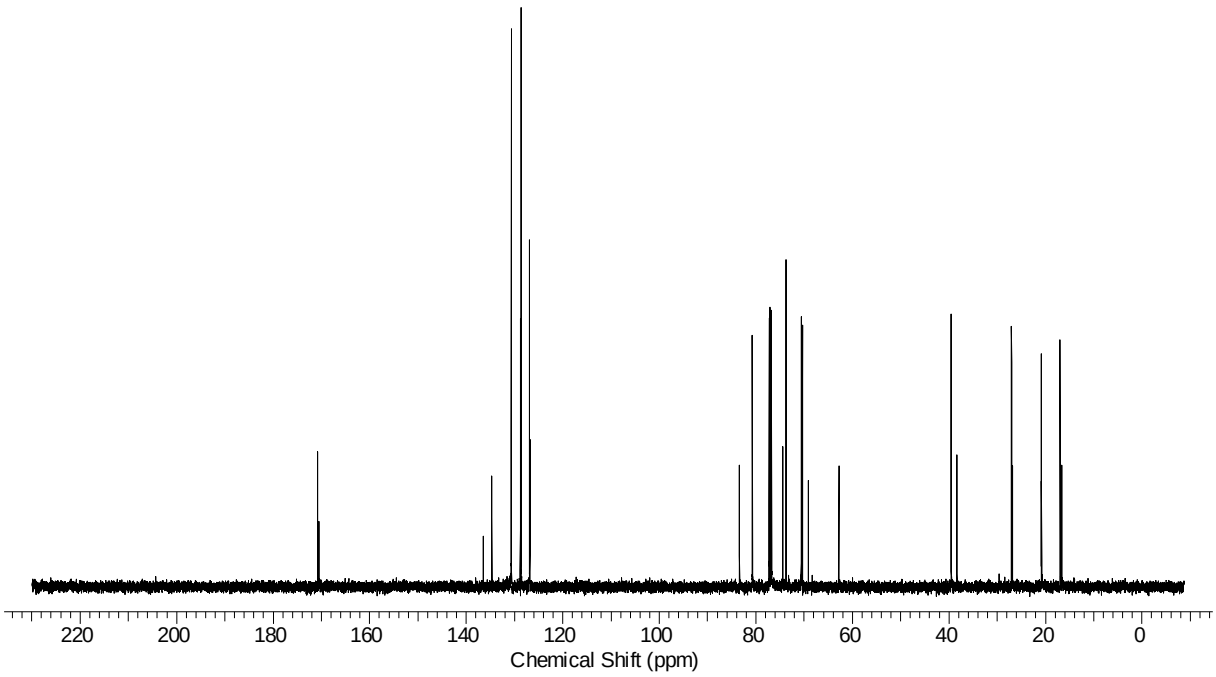

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

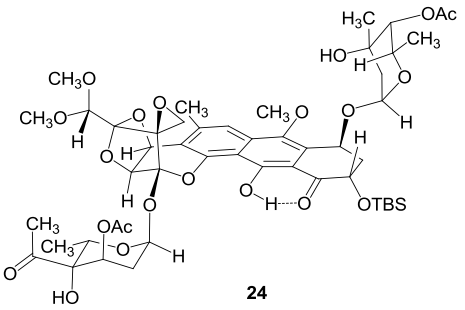

220
200
180
160
140
120
100
80
60
40
20
ppm


H3C
OAc
CH3
HO
H
O
H
SPh
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

23

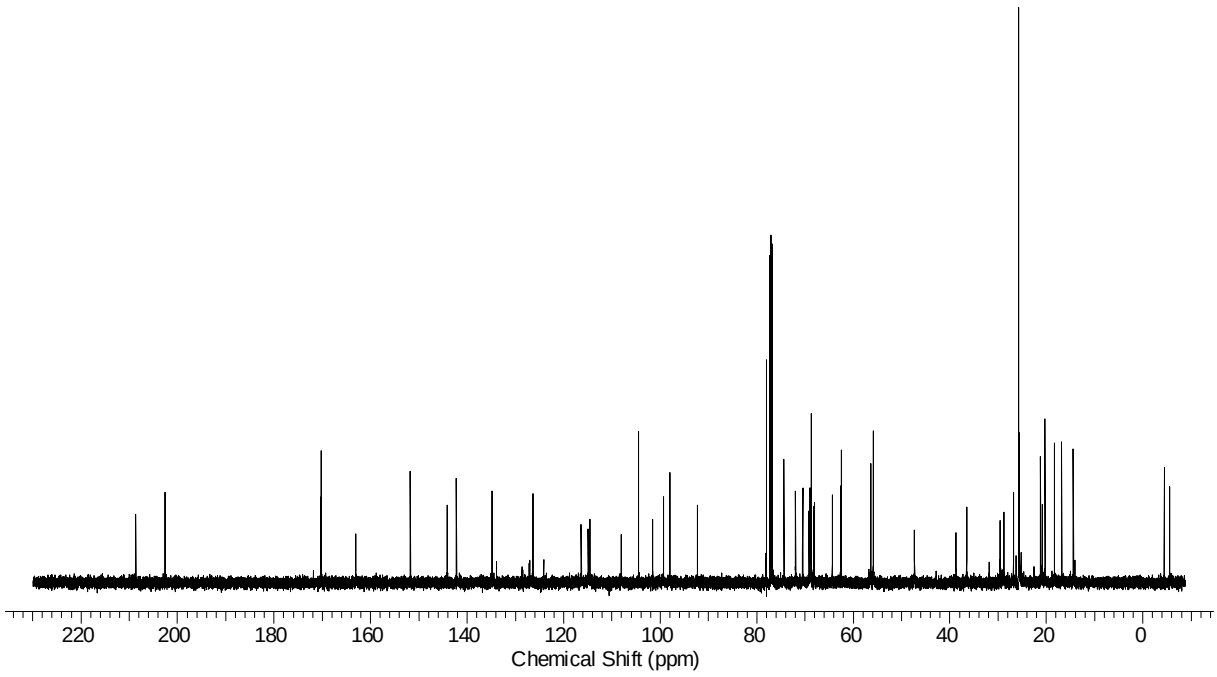
α:β ~ 1:2.4

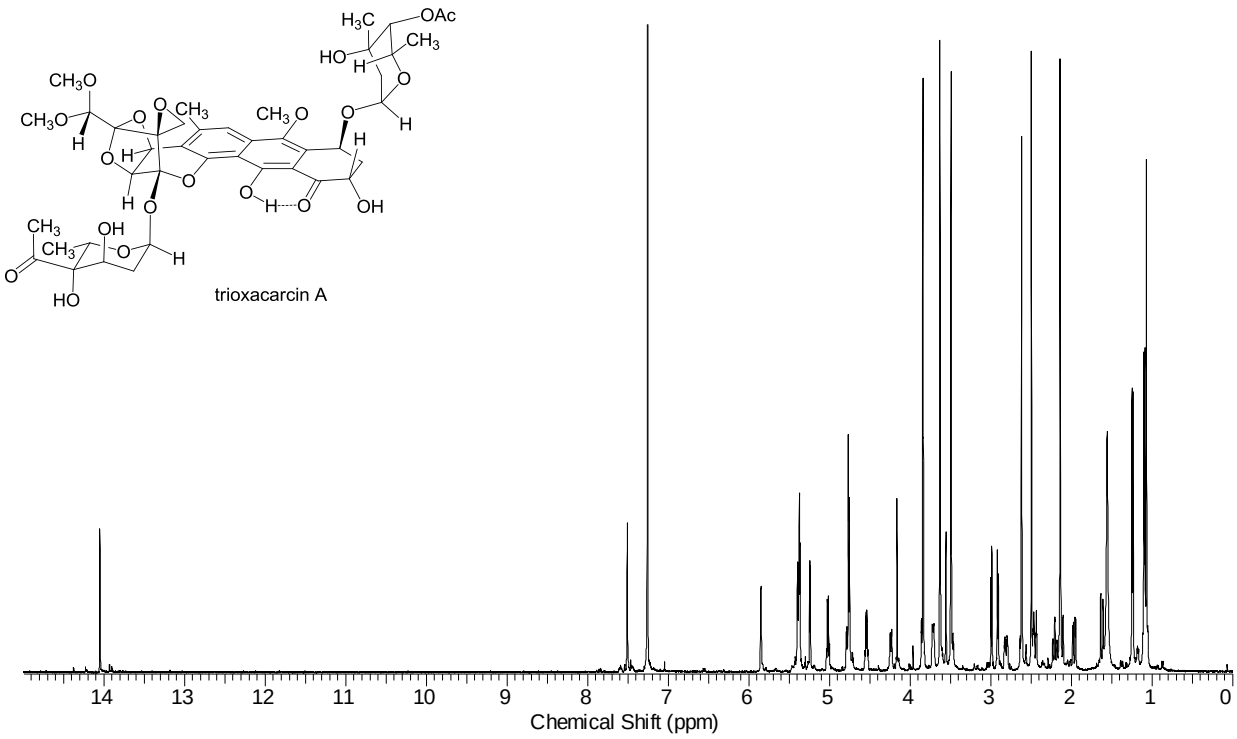

220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

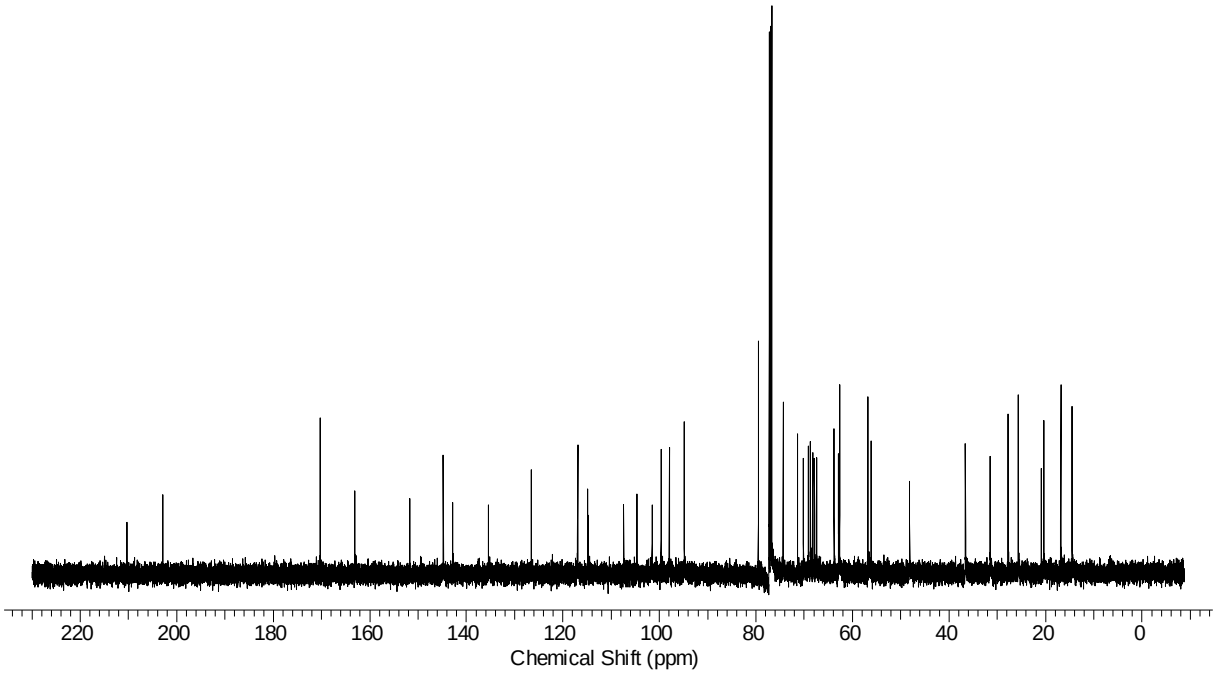

H3C
OAc
CH3
HO
H
O
CH3O
CH3O
H
O
O
CH3
CH3O
O
H
O
H
O
H
H
O
O
H
O
OTBS
CH3
OAc
CH3
O
O
H
O
HO

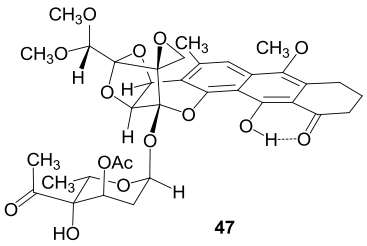
24

14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

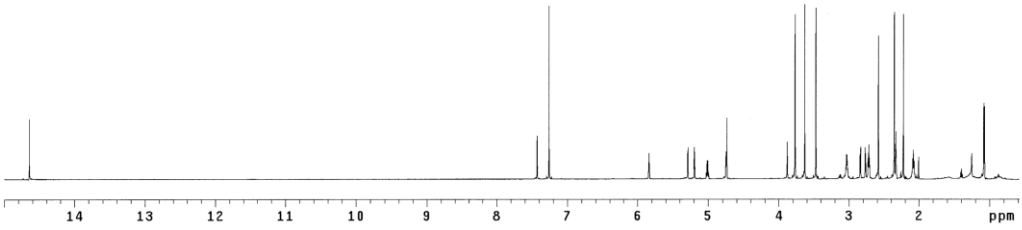

220
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

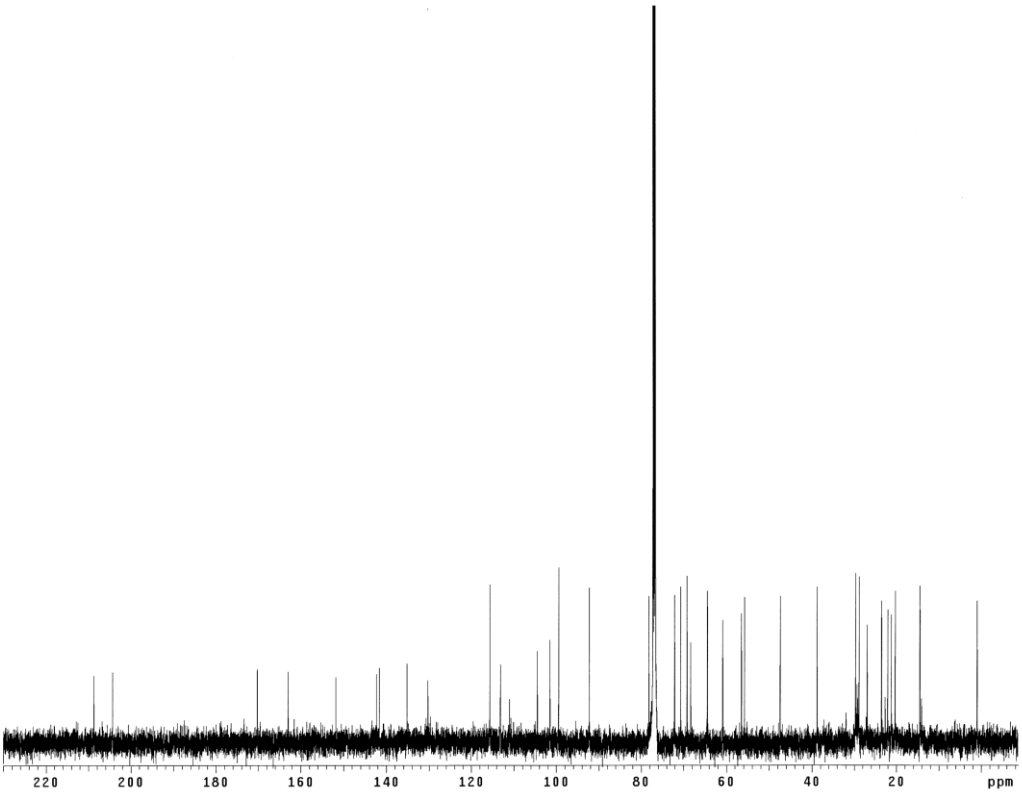

trioxacarcin A
Chemical Shift (ppm)

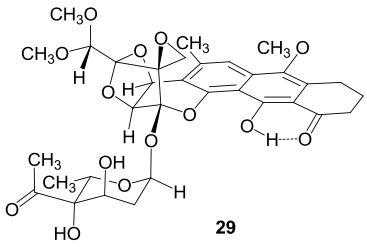

Chemical Shift (ppm)



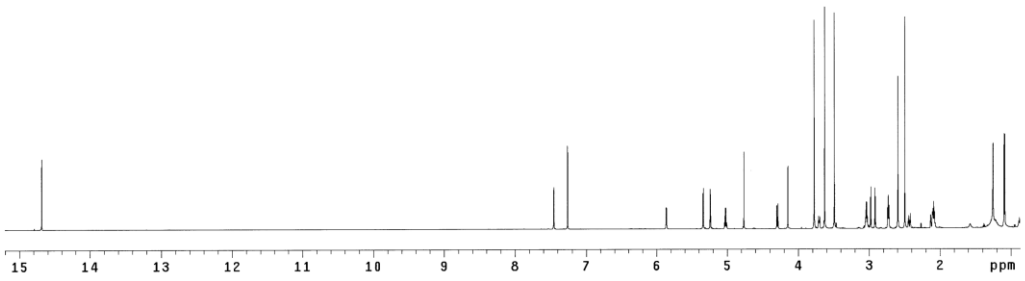
47

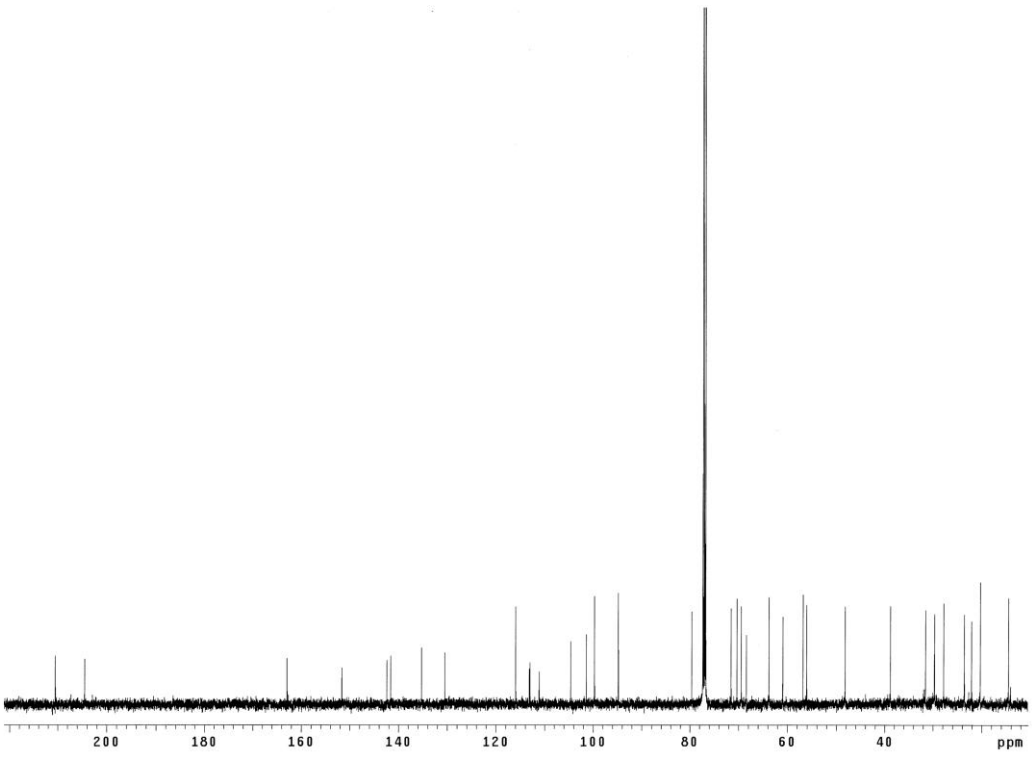

14
13
12
11
10
9
8
7
6
5
4
3
2
ppm

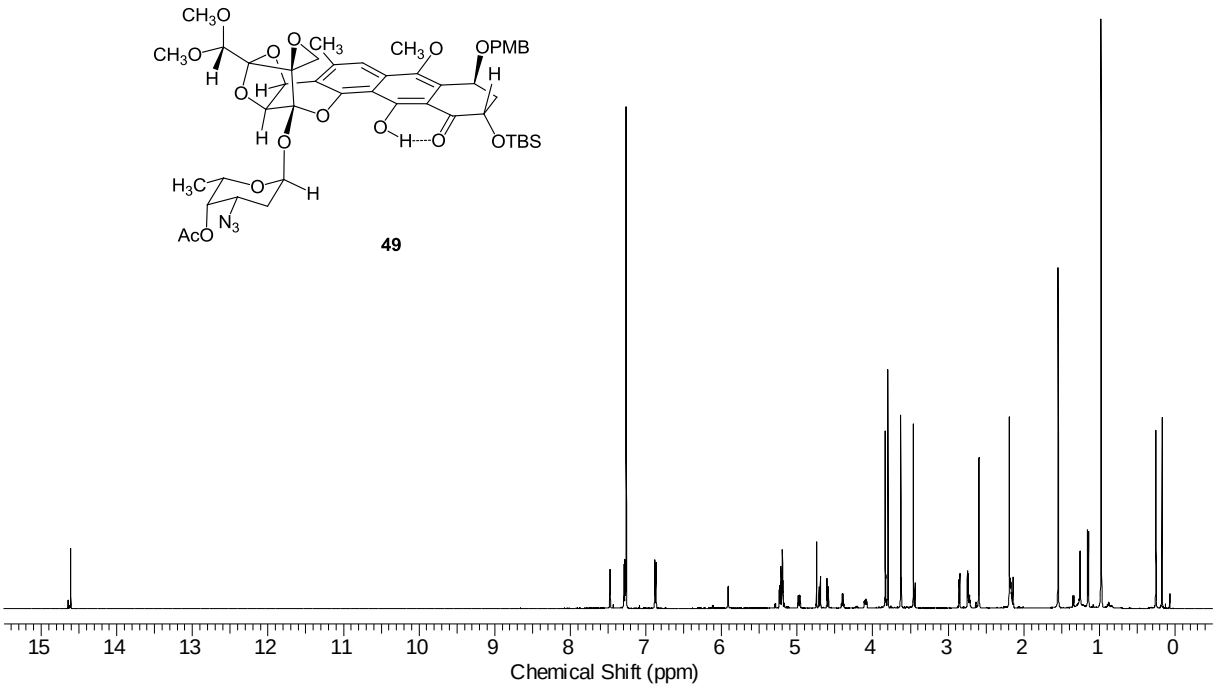

220
200
180
160
140
120
100
80
60
40
20
ppm

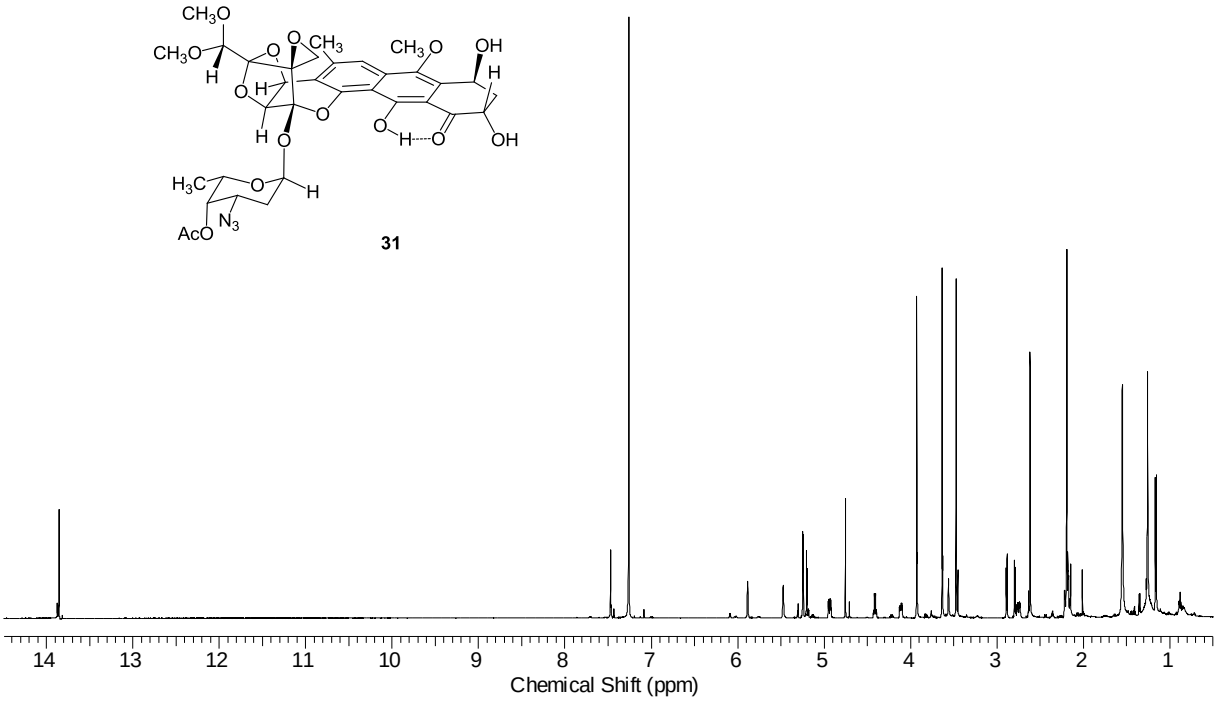


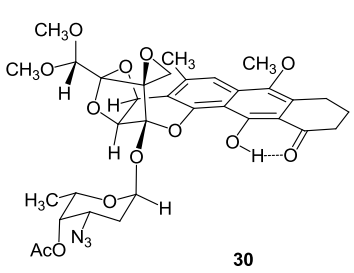
29


15
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm


200
180
160
140
120
100
80
60
40
ppm

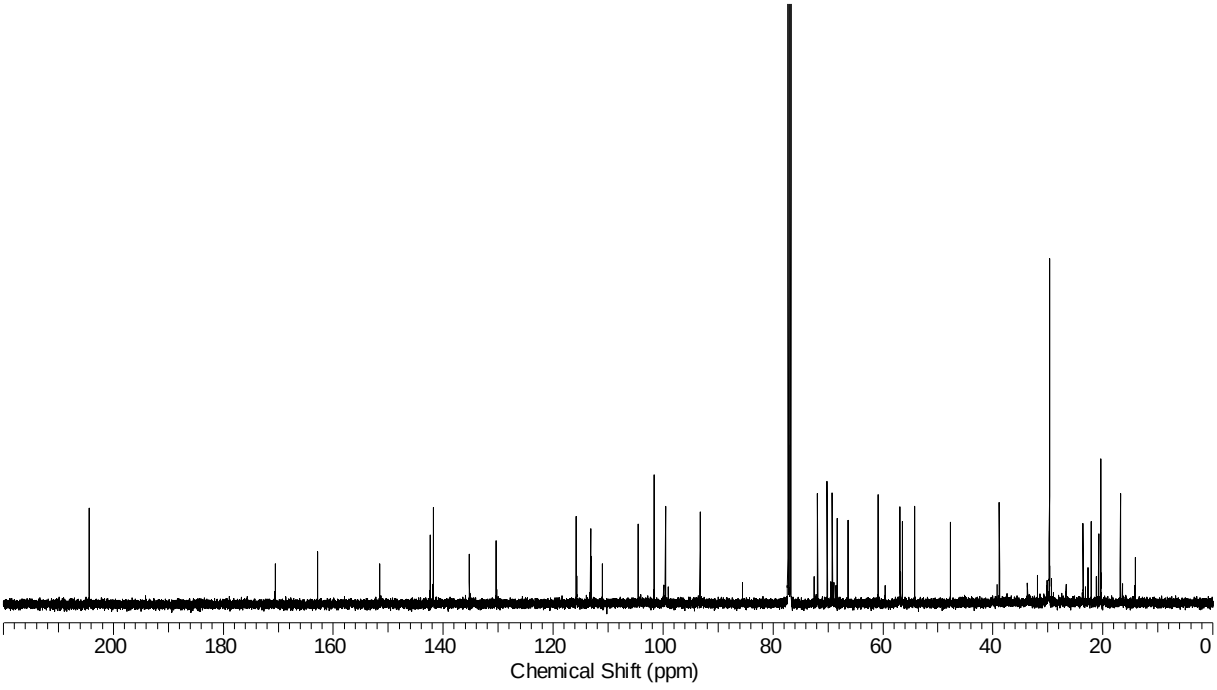

CH3O
CH3O
O
O
CH3
CH3O
OPMB
H
H
O
H
O
O
H
O
O
H
O
H
OTBS
H3C
O
H
N3
AcO
49
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

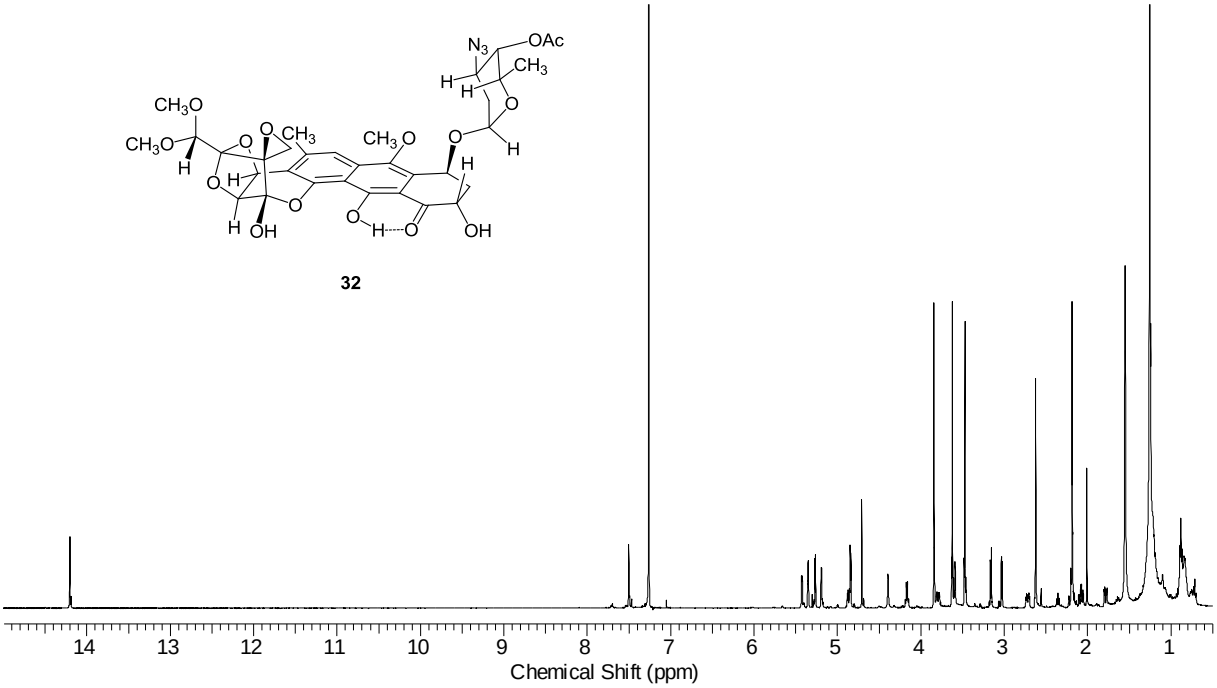

CH3O
CH3O
O
O
CH3
CH3O
OH
H
H
O
H
O
O
H
O
O
H
O
H
OH
H3C
O
H
N3
AcO
31
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)



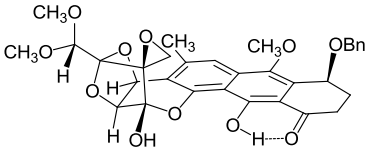
30

14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

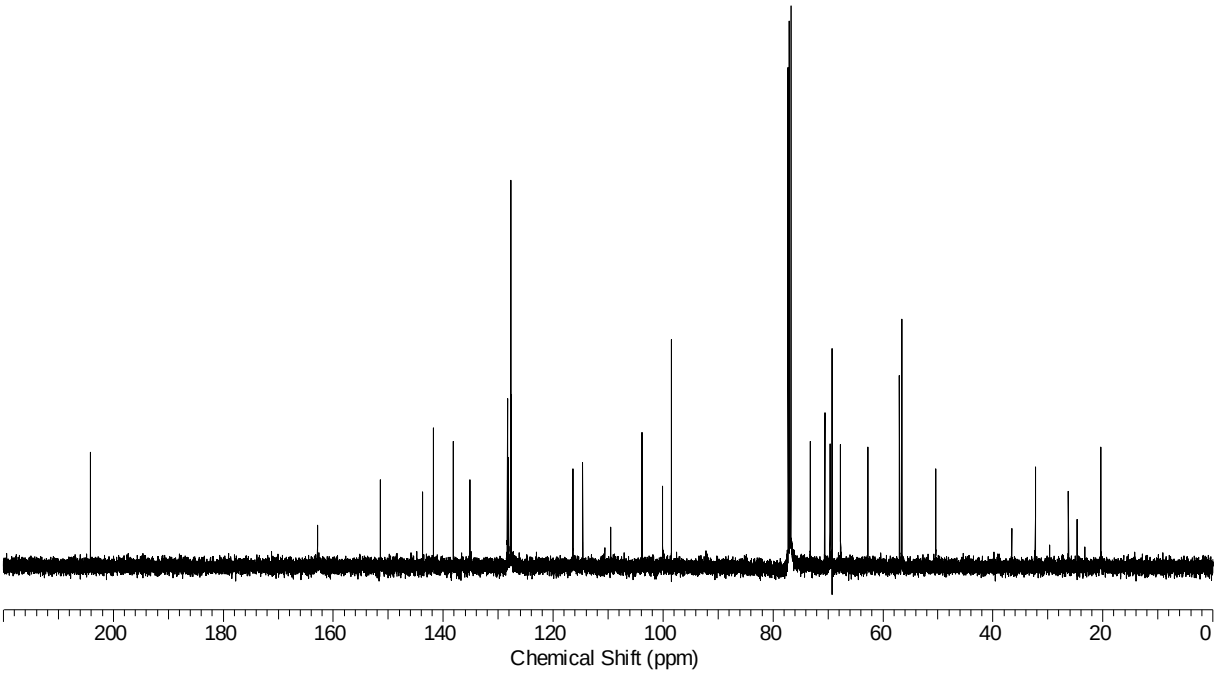

N3
OAc
CH3
H
H
O
CH3O
CH3O
H
O
O
CH3
CH3O
O
H
O
H
H
O
H
OH
O
H
O
OH
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

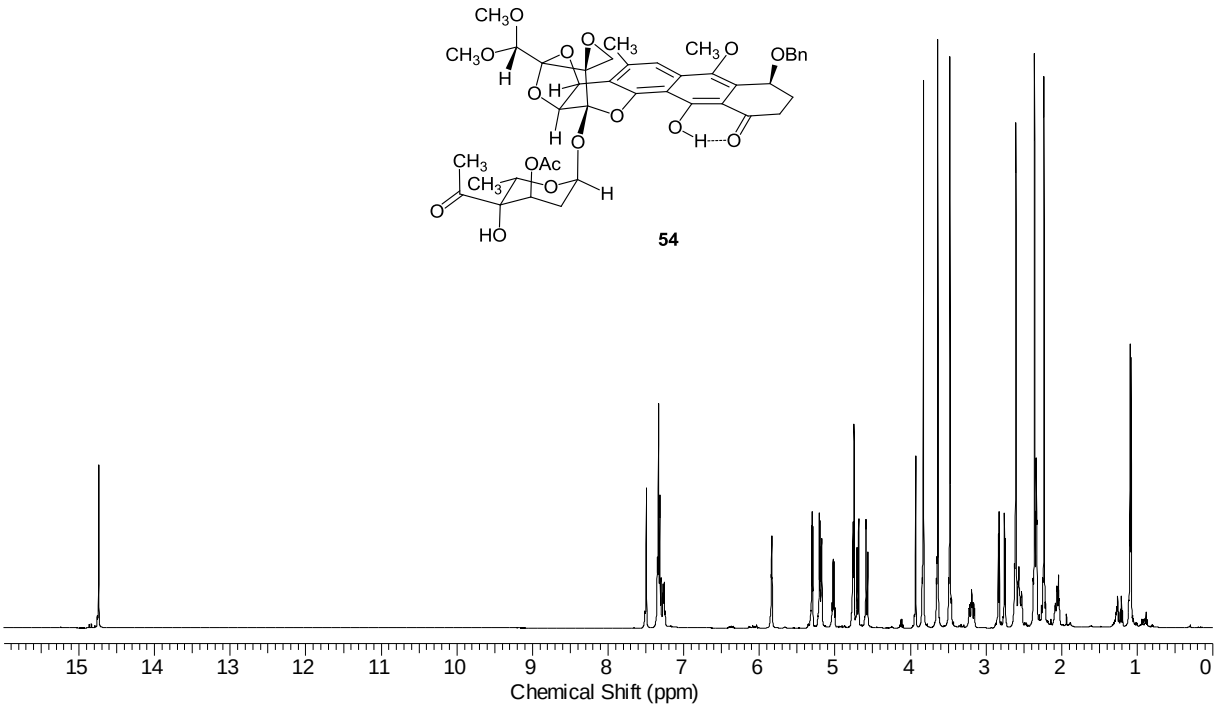
32



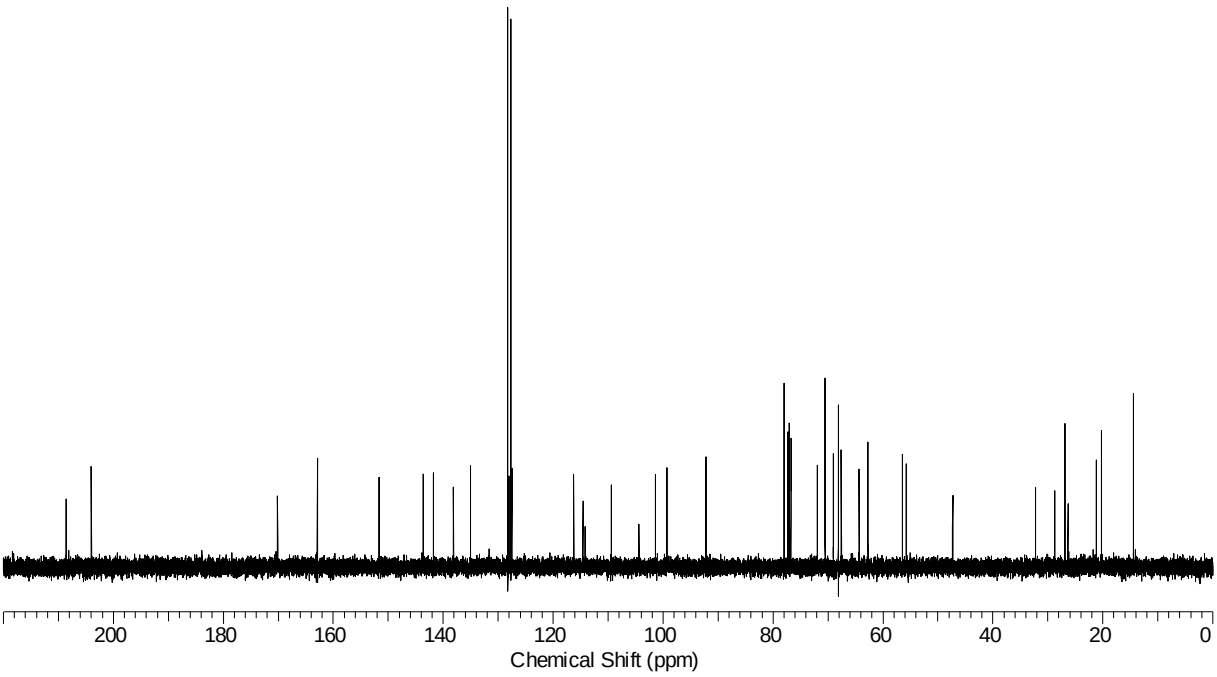
53

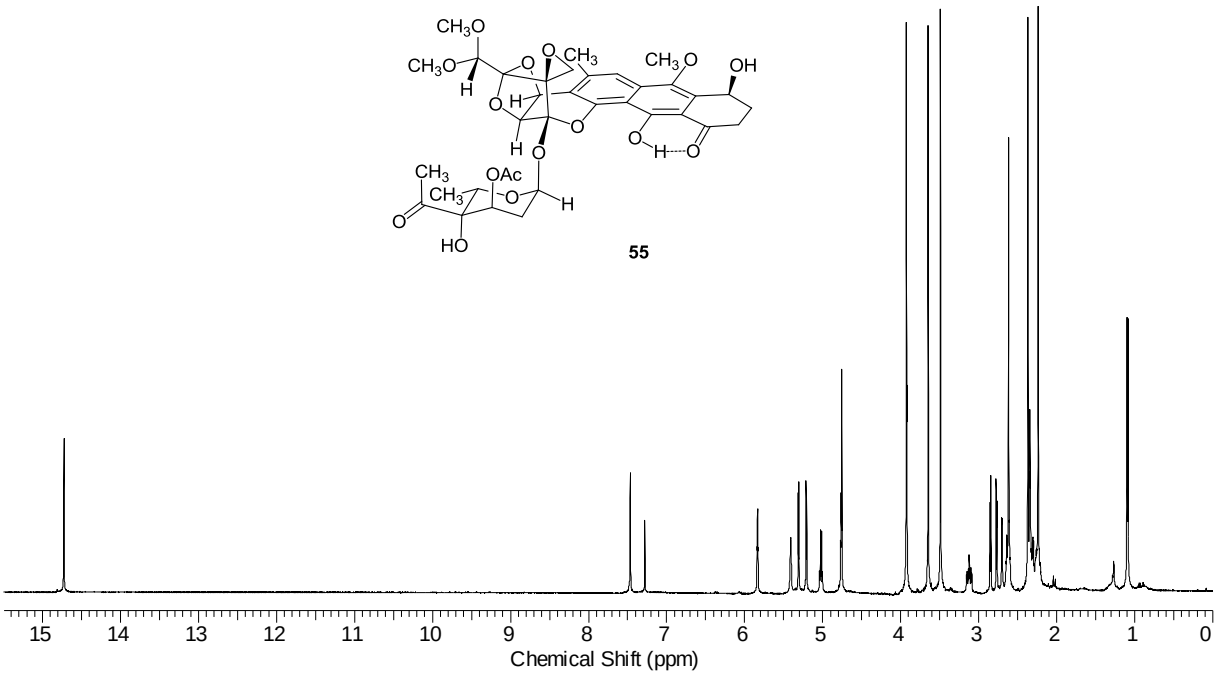
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

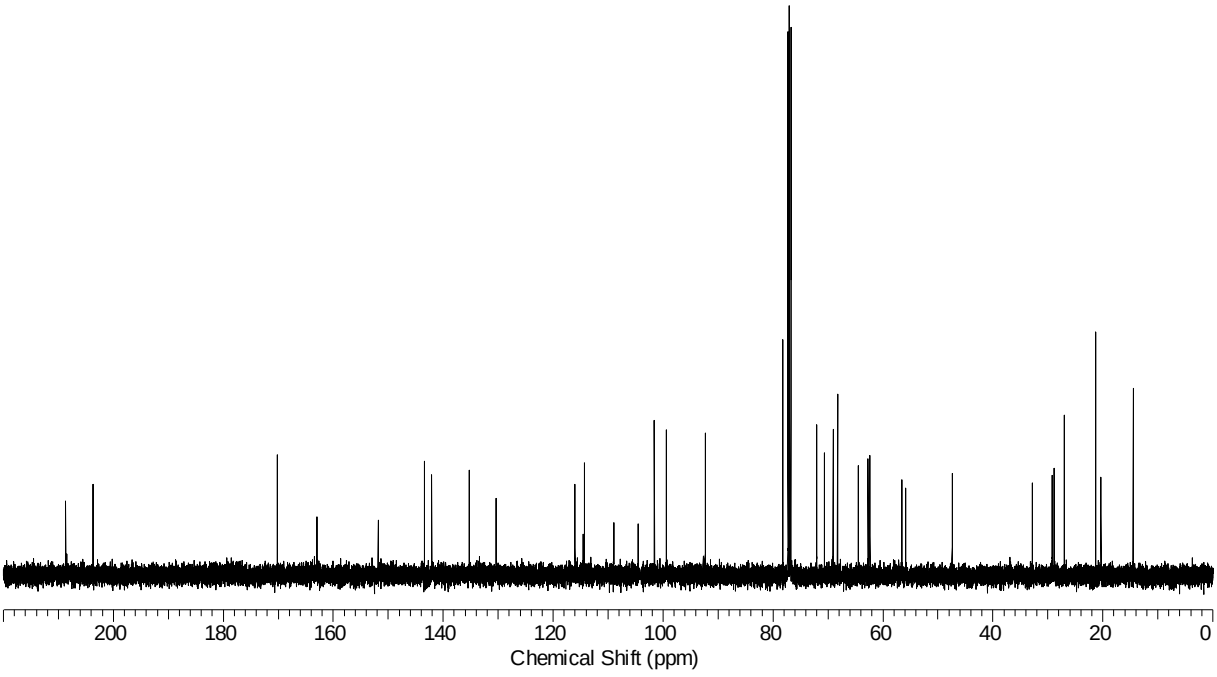

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

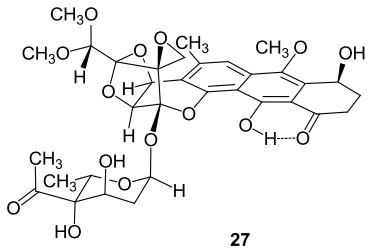
54


200 180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)


15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

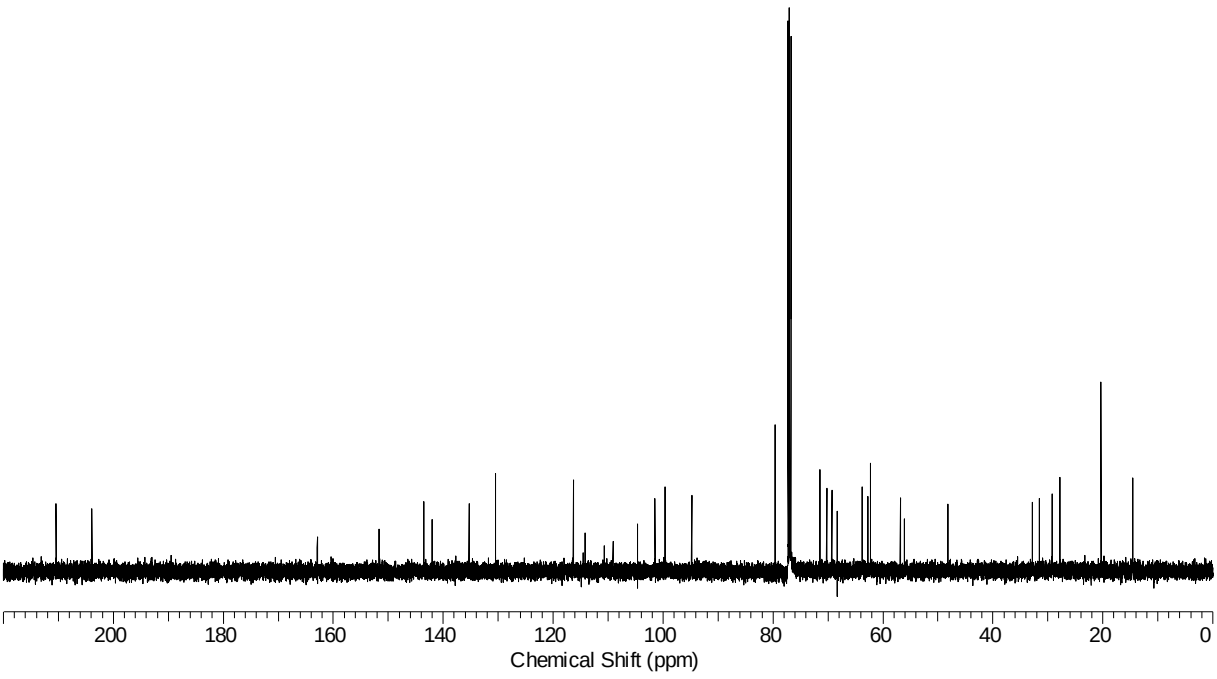
55

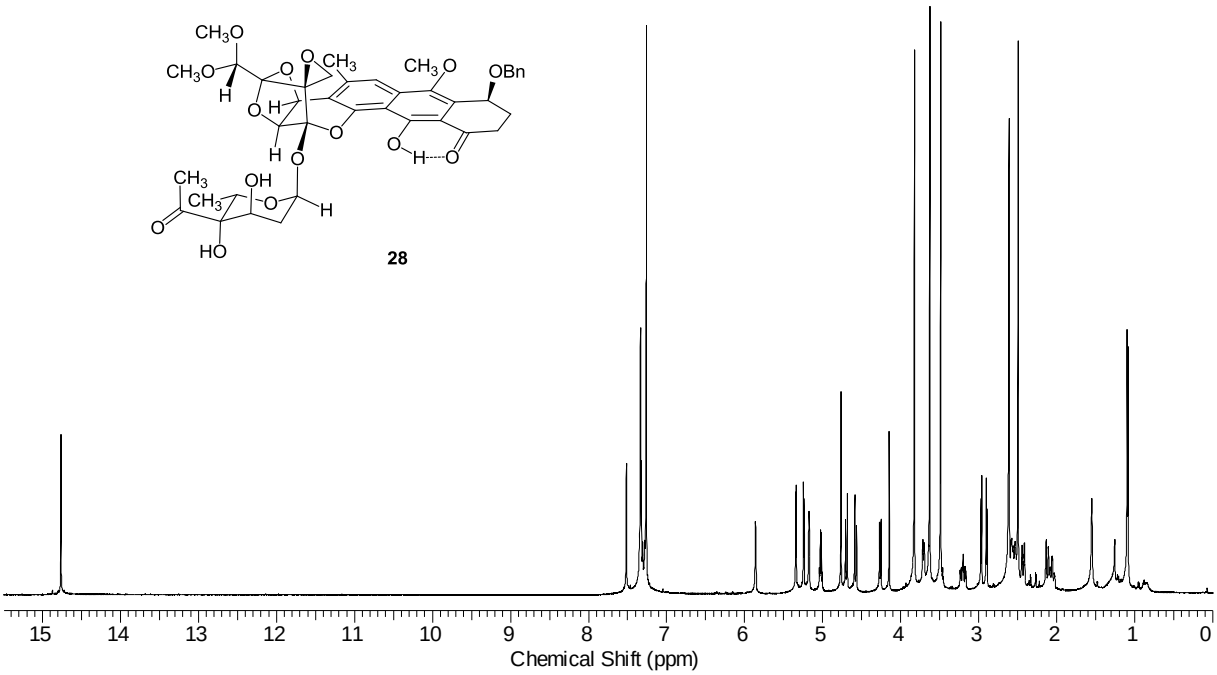

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



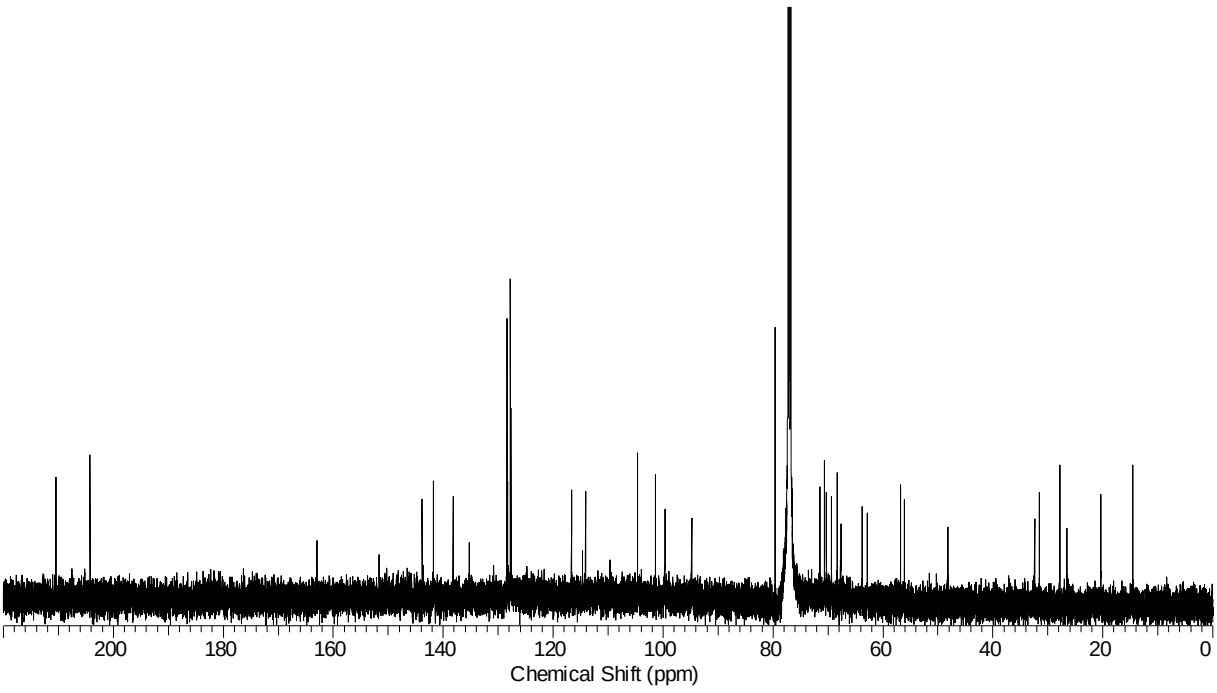
27

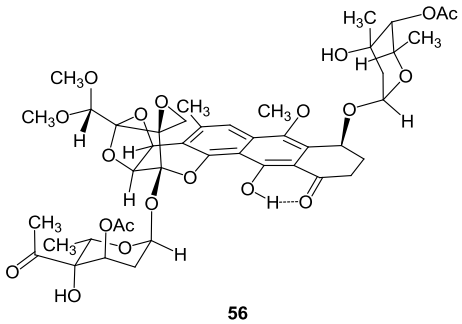
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CH3O
CH3O
H
O
CH3
CH3O
OBn
O
H
O
H
O
O
H
O
CH3
CH3
OH
O
H
O
HO
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

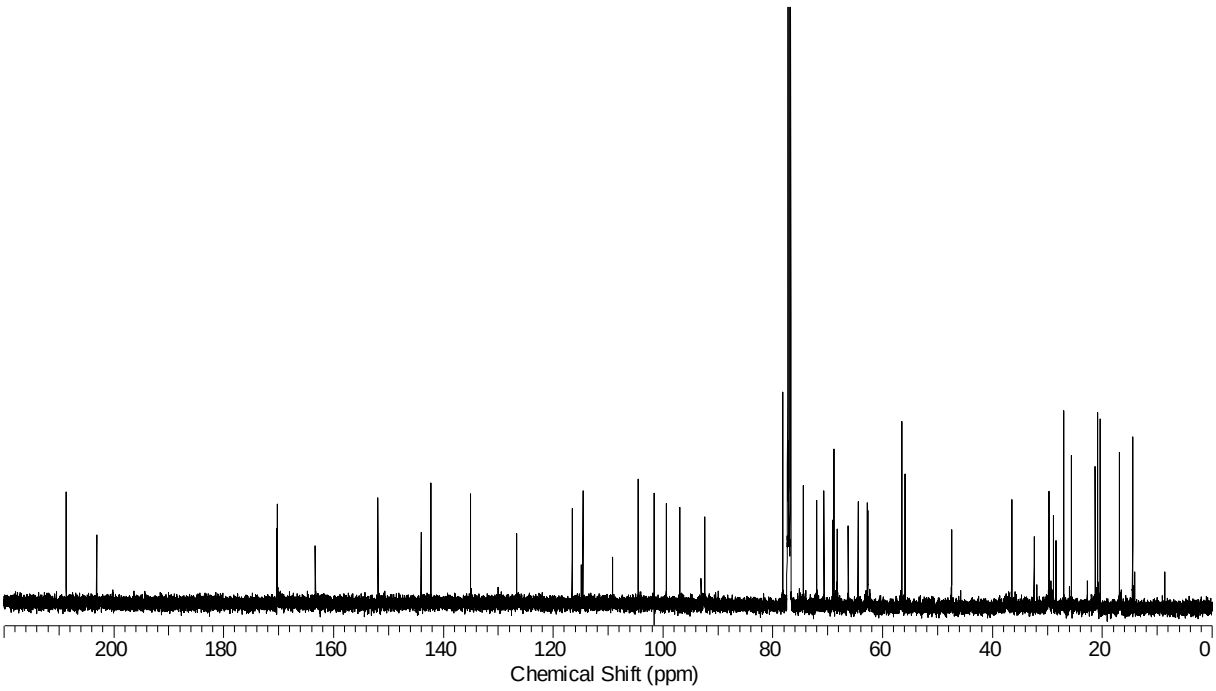
28

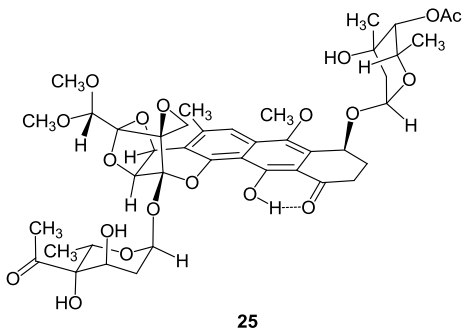

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



56

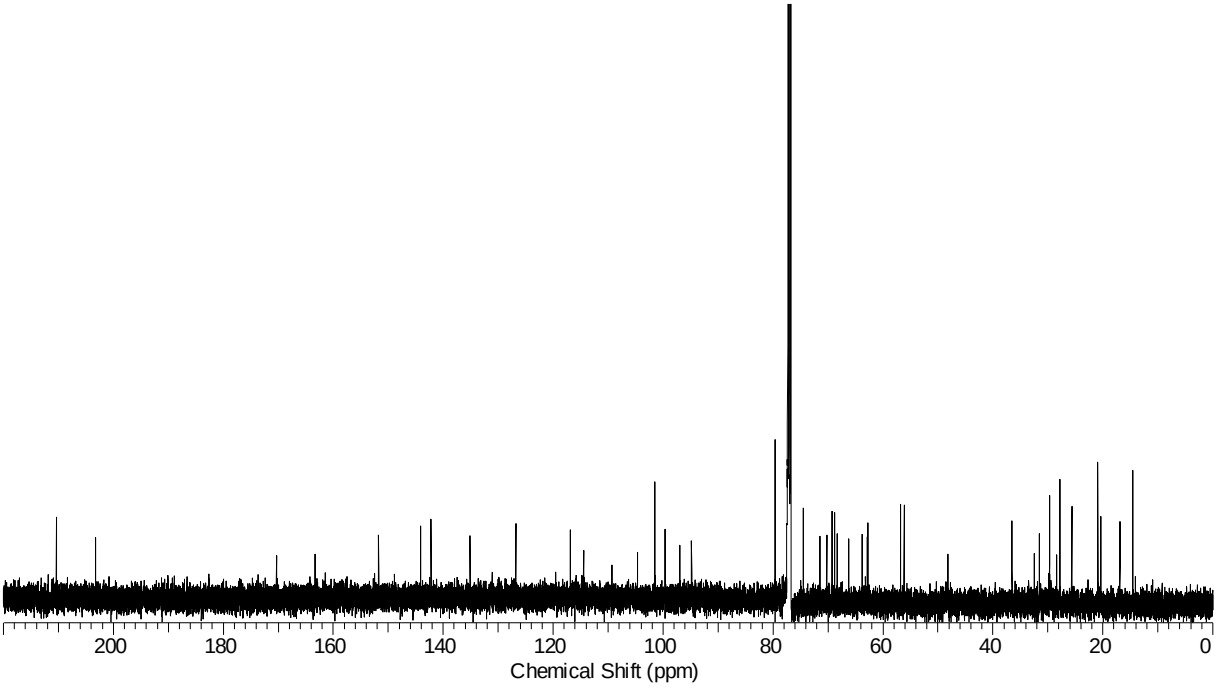
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

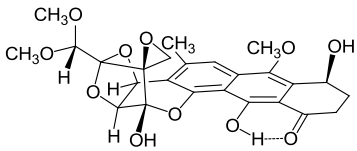

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



25

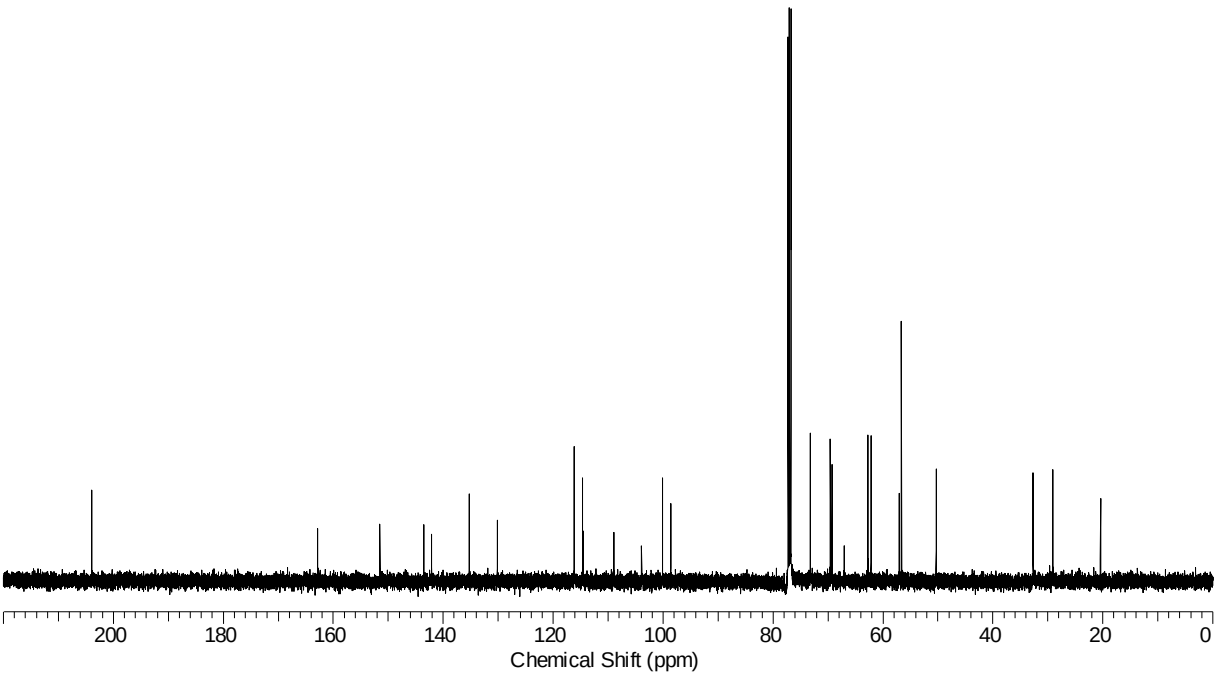
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

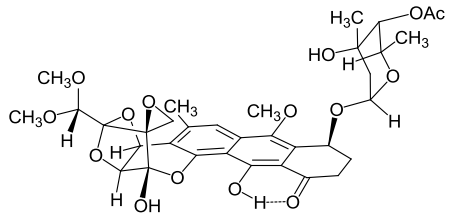

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CH3O
CH3O
H
O
O
CH3
H
O
H
O
H
OH
CH3O
OH
O
H
O

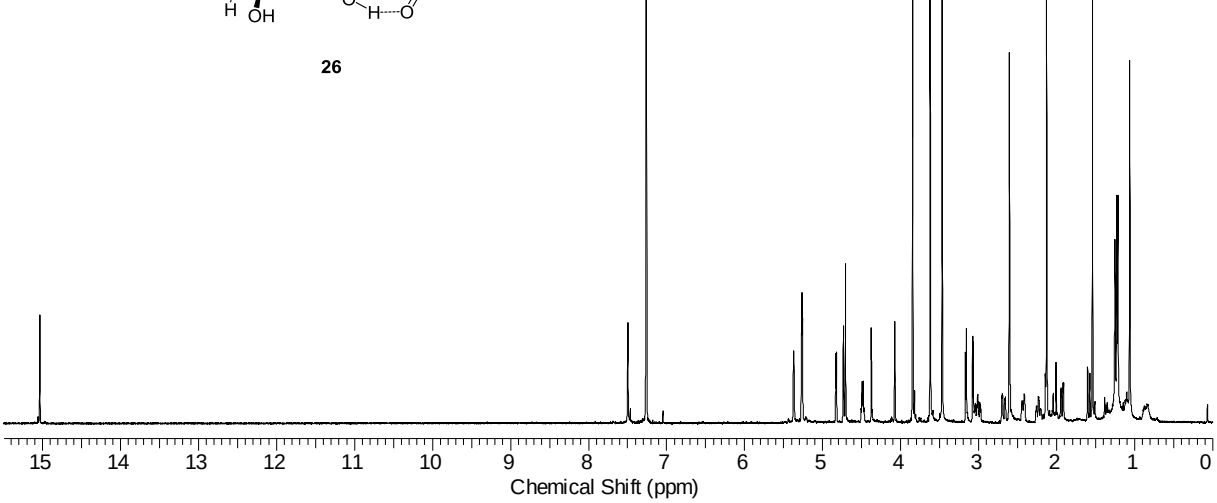
57

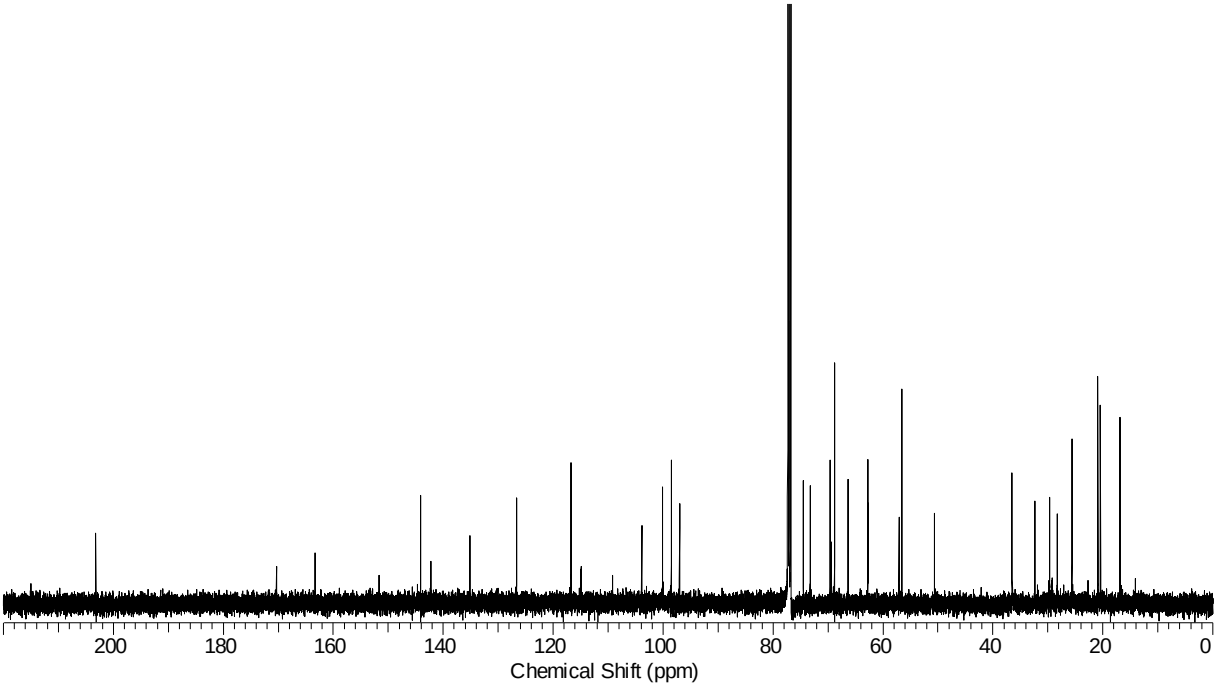
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

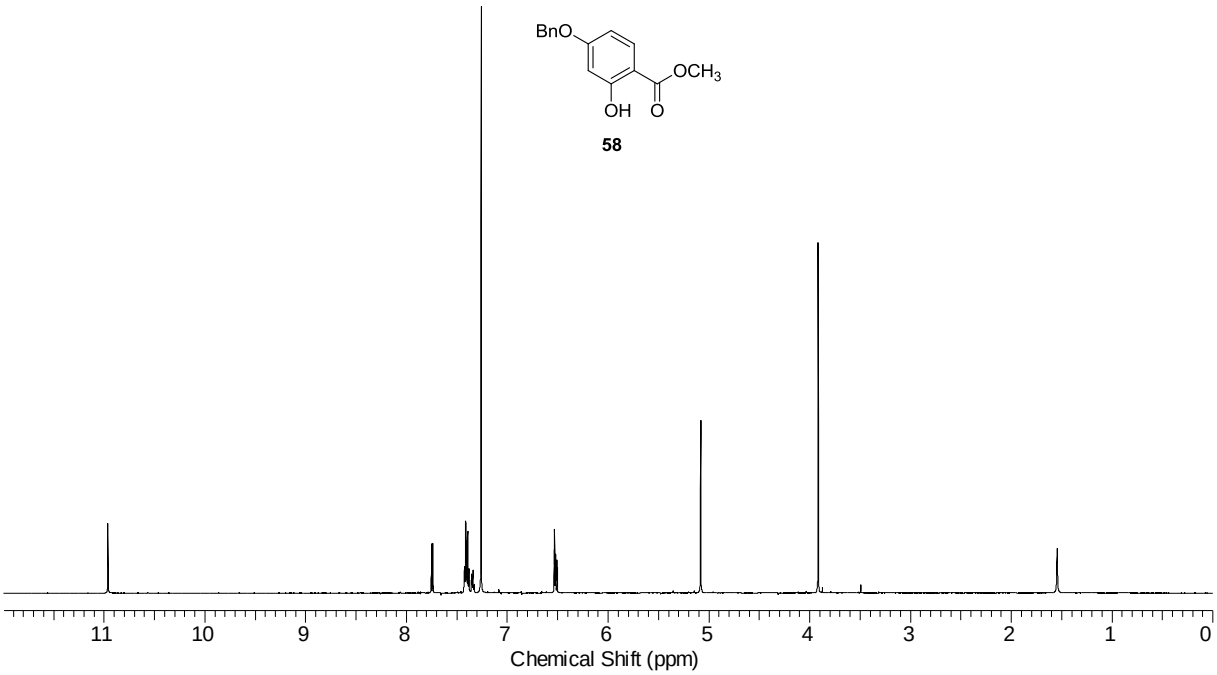

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

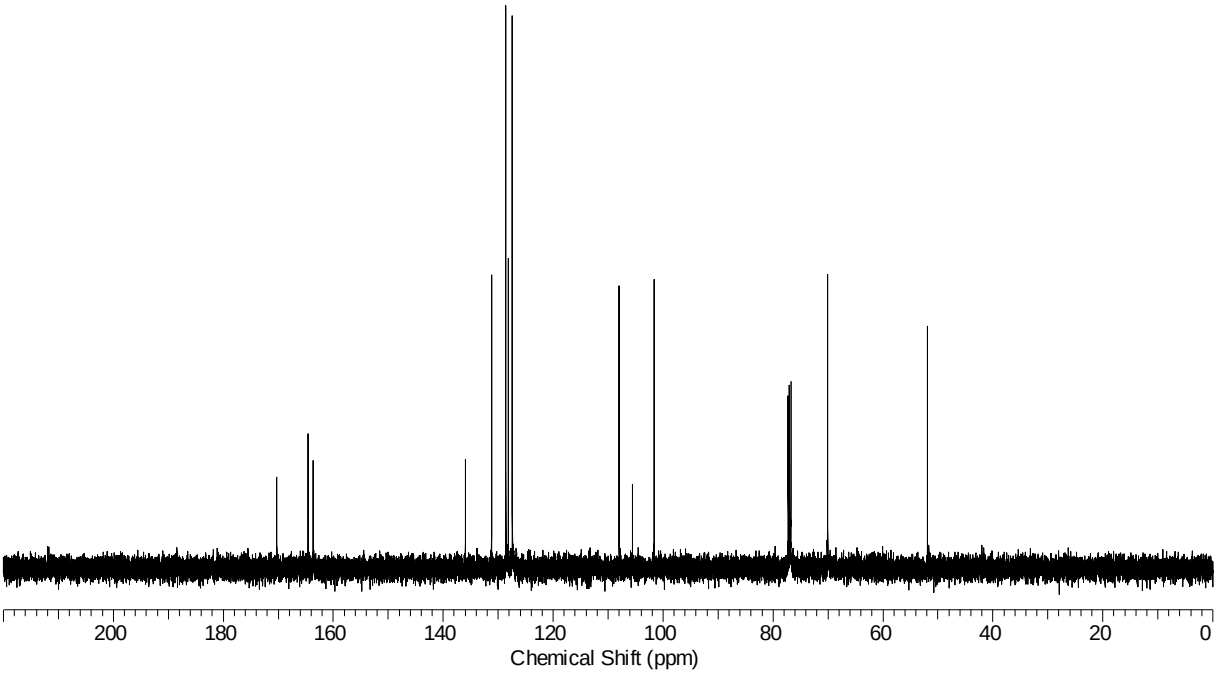

H3C
OAc
CH3
HO
H
O
CH3O
CH3O
O
CH3
CH3O
O
H
O
H
O
H
OH
O
H
O

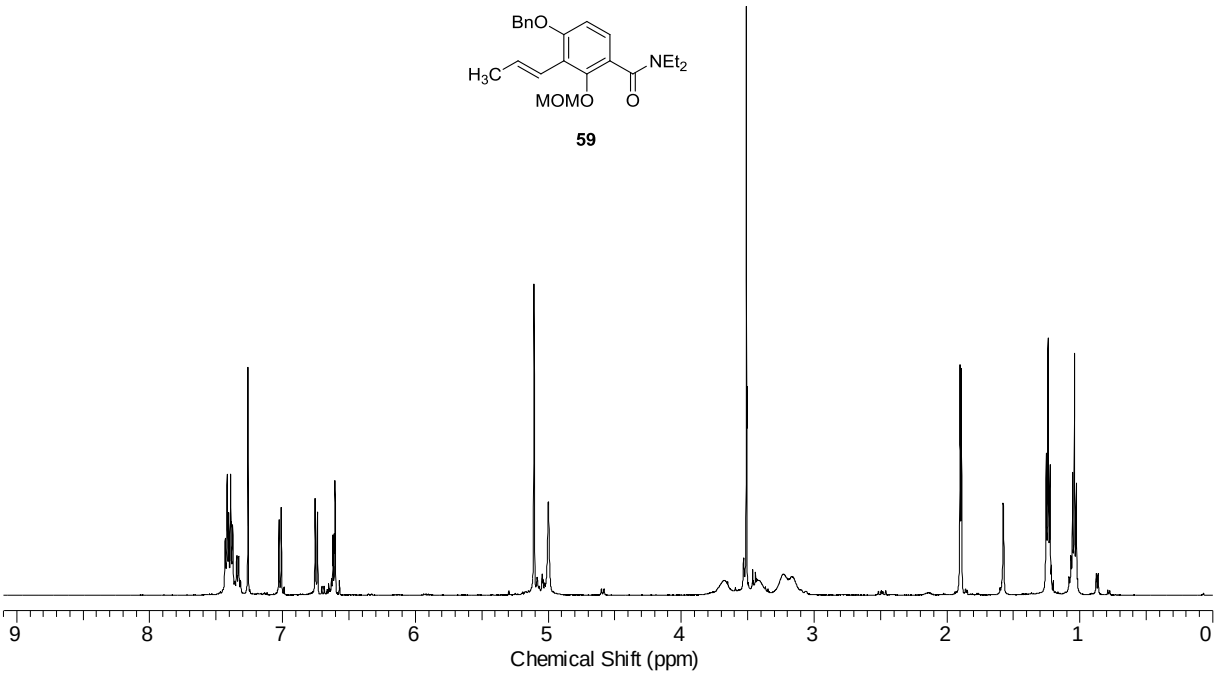
26


15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

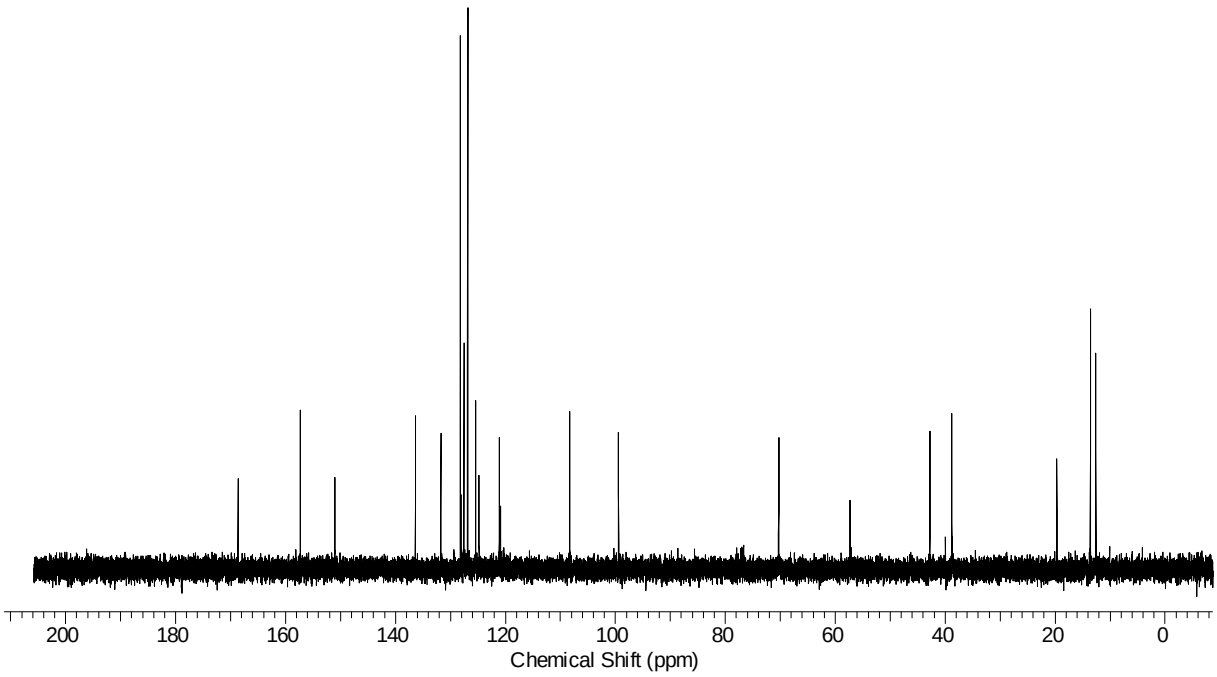

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

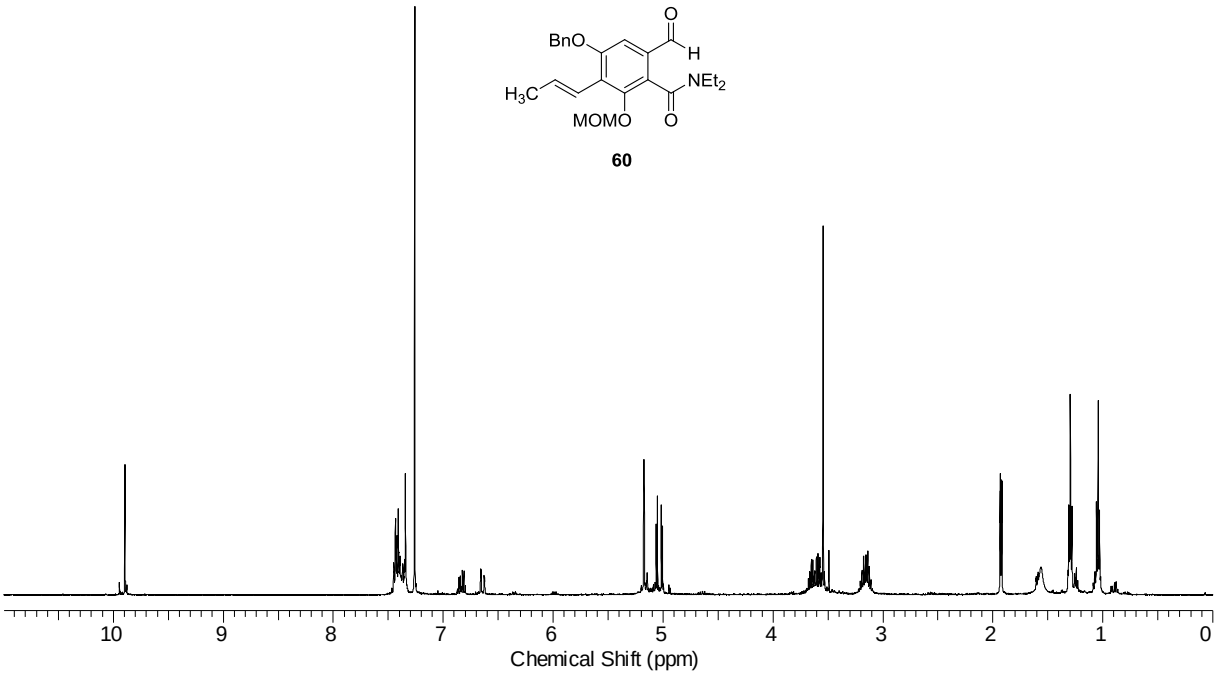

BnO
OCH3
OH
O
58
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

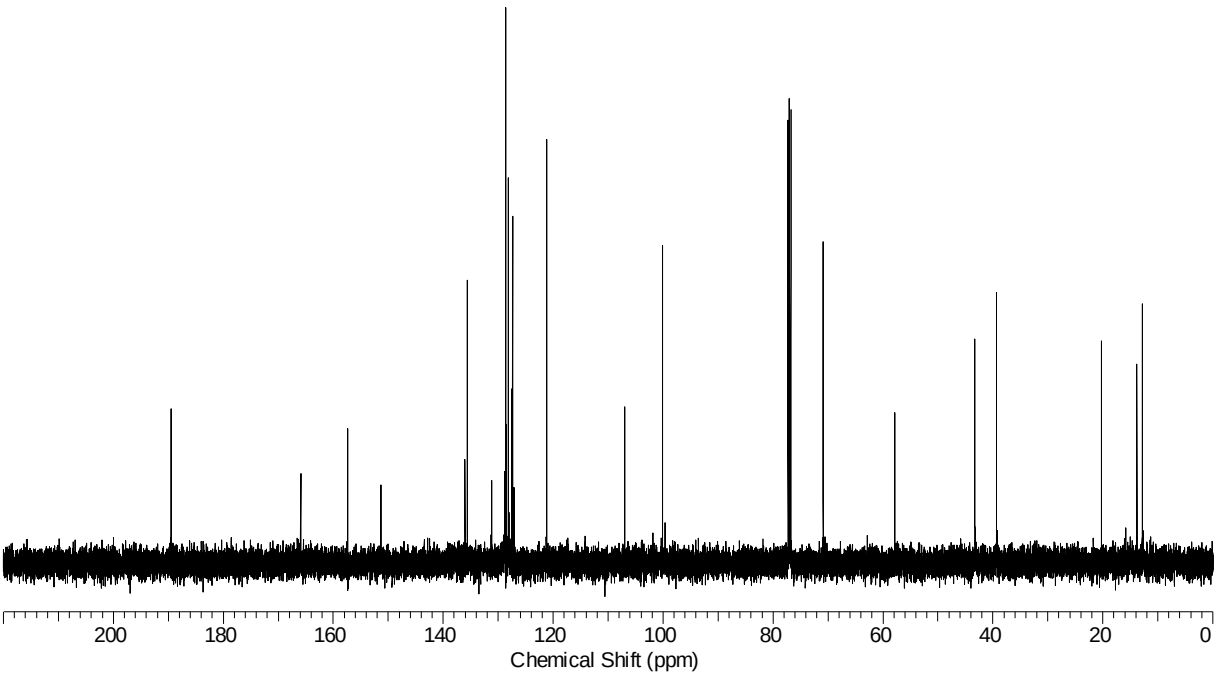

BnO
NEt2
H3C
MOMO
O
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

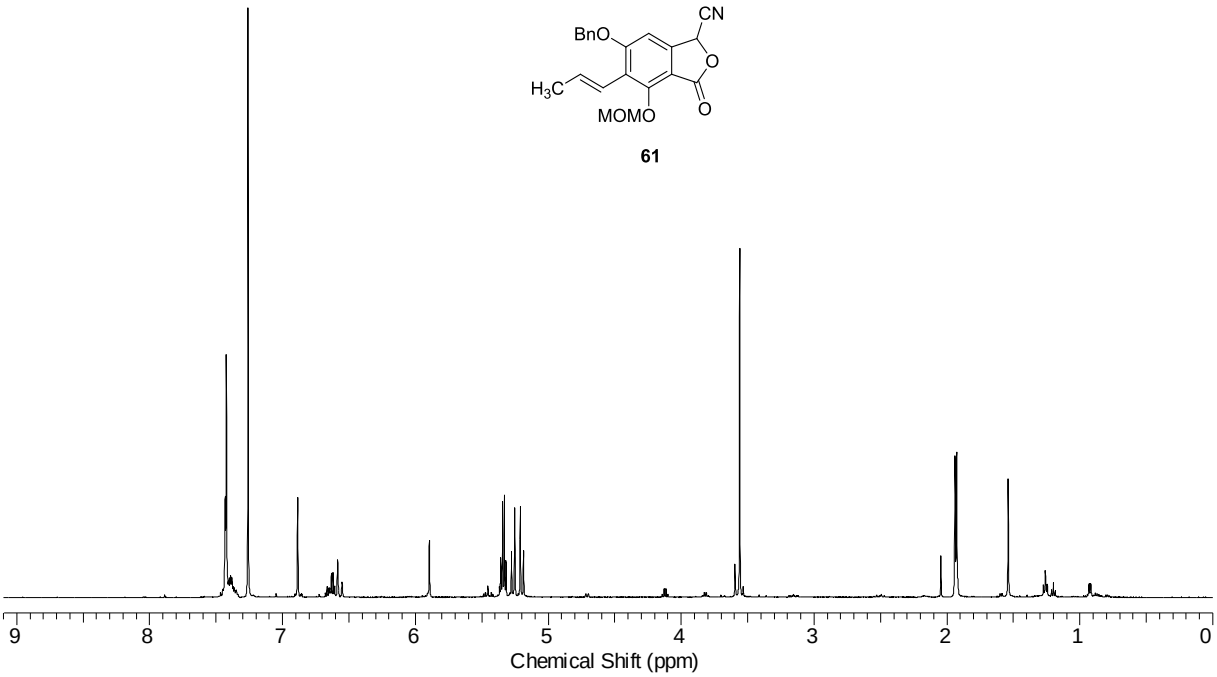
59


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

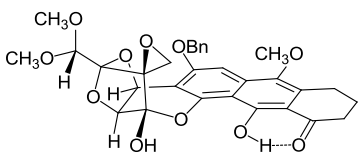

BnO
O
H
NEt2
H3C
MOMO
O
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

60


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

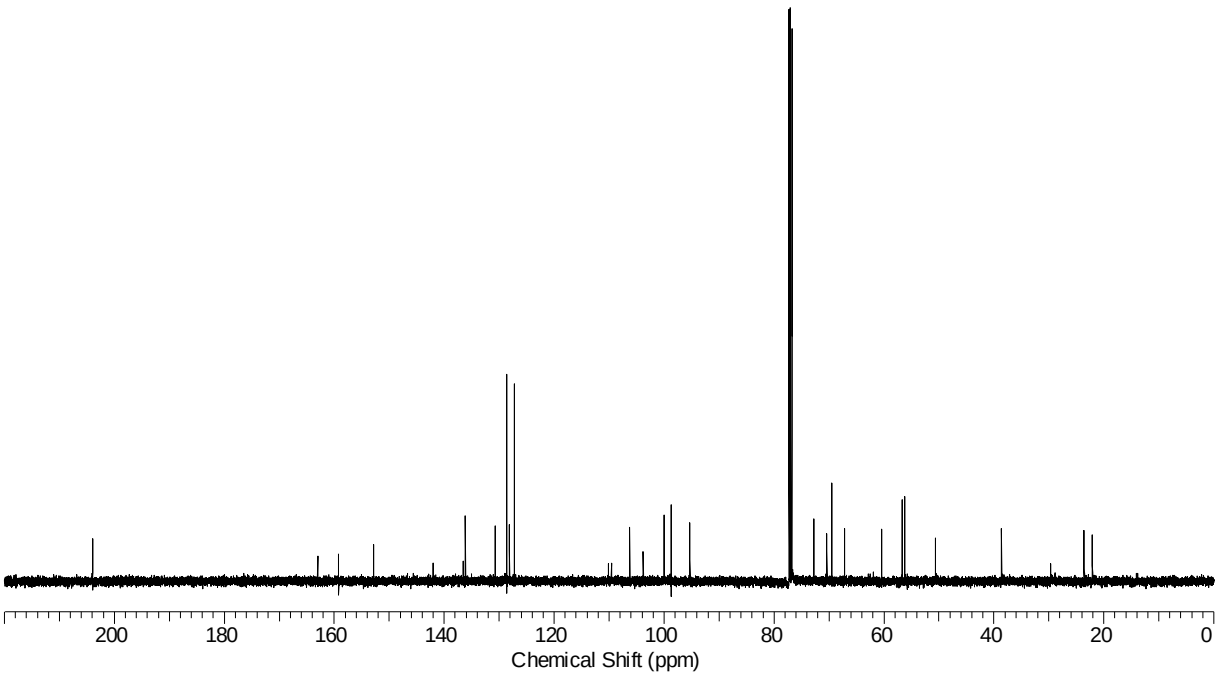


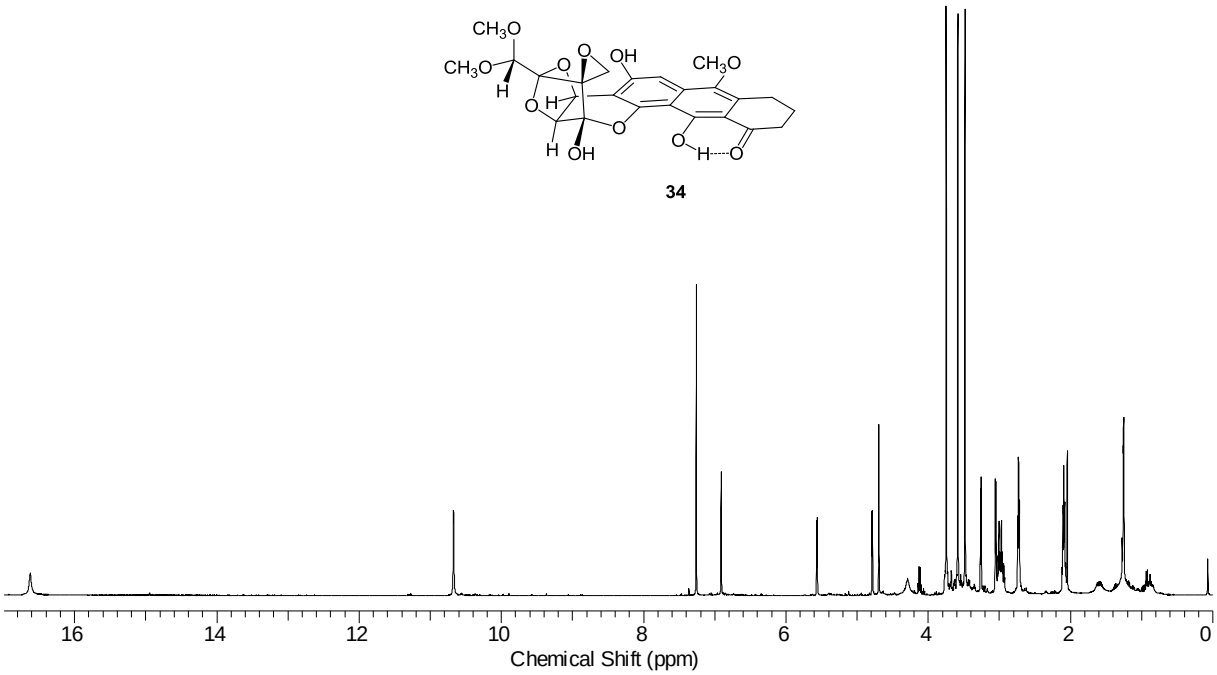
61


CH3O
CH3O
H
O
O
OBn
CH3O
O
H
H
O
H
OH
O
H
O

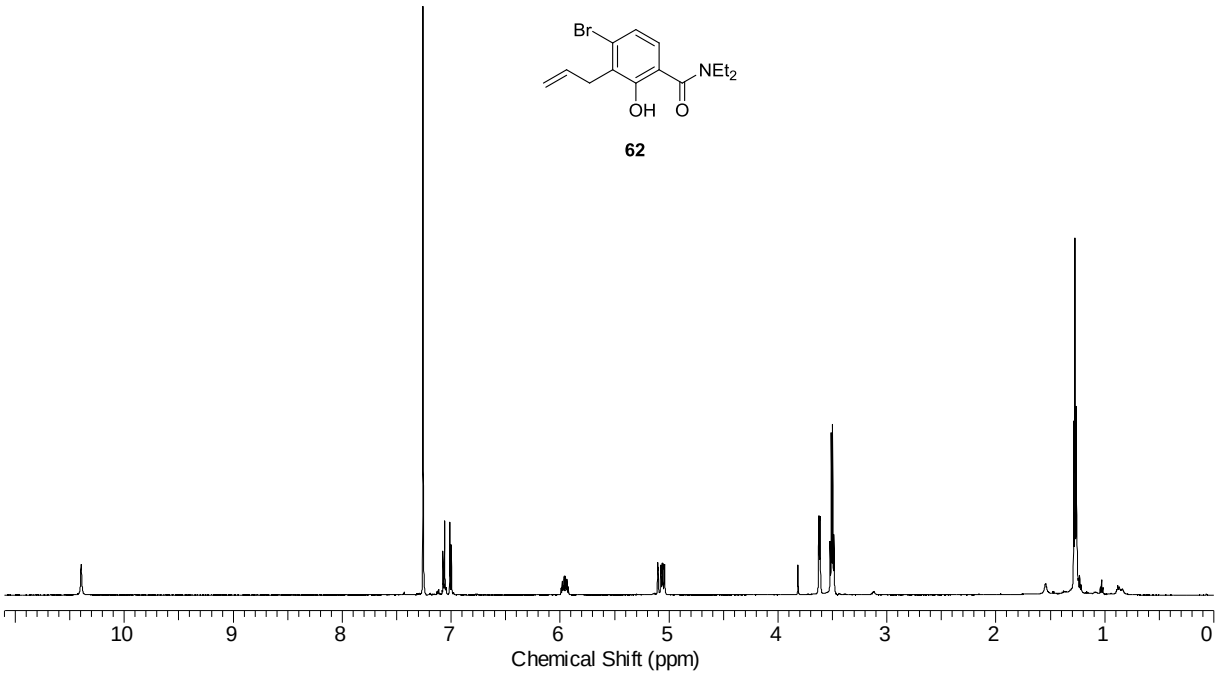
35

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

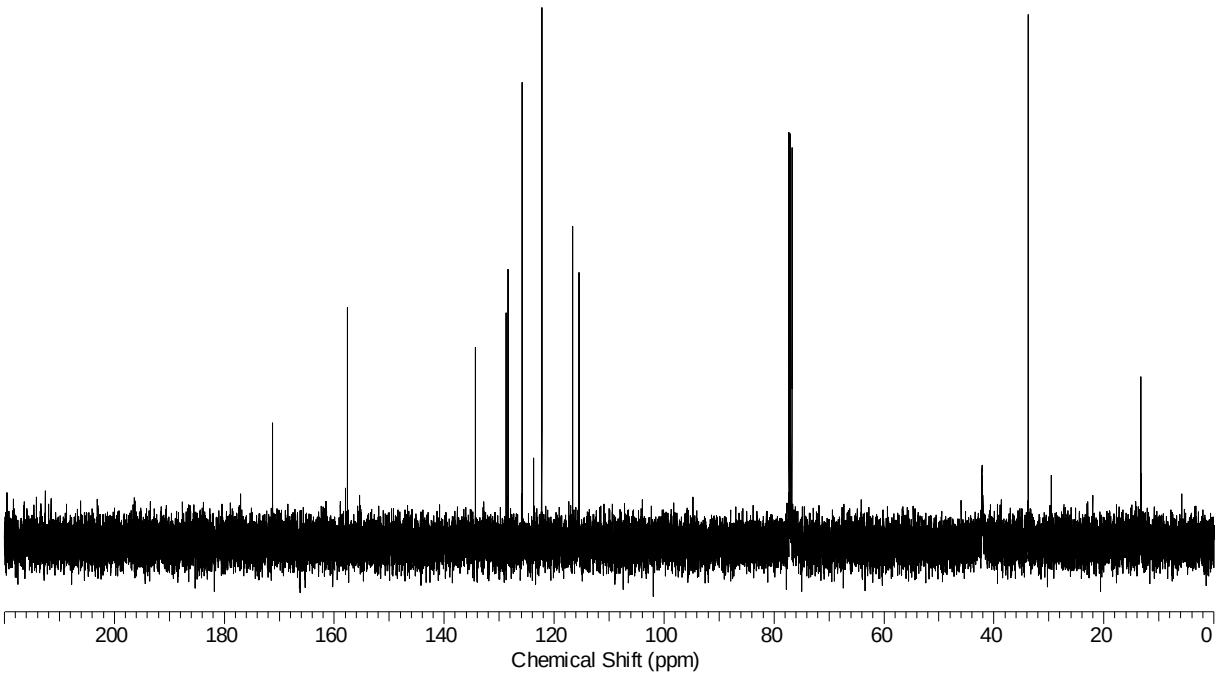

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

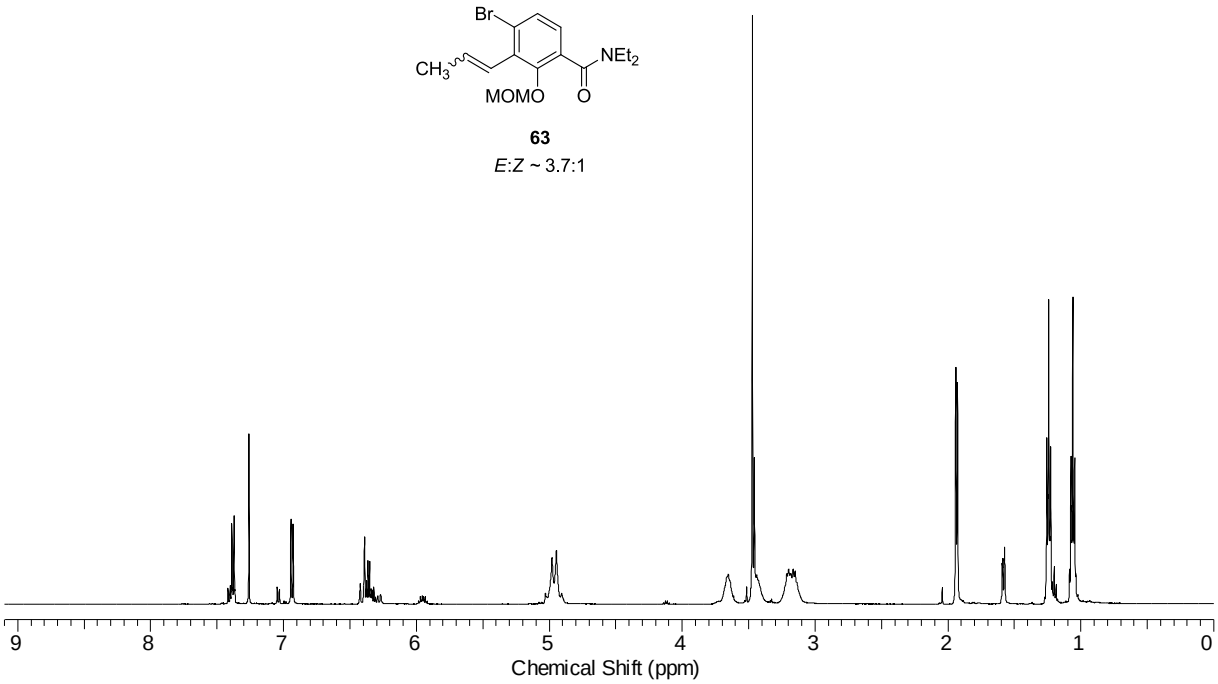

CH3O
CH3O
H
O
O
OH
CH3O
O
H
O
H
OH
O
O
H
O
16
14
12
10
8
6
4
2
0
Chemical Shift (ppm)

34


Br
NEt2
OH
O
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

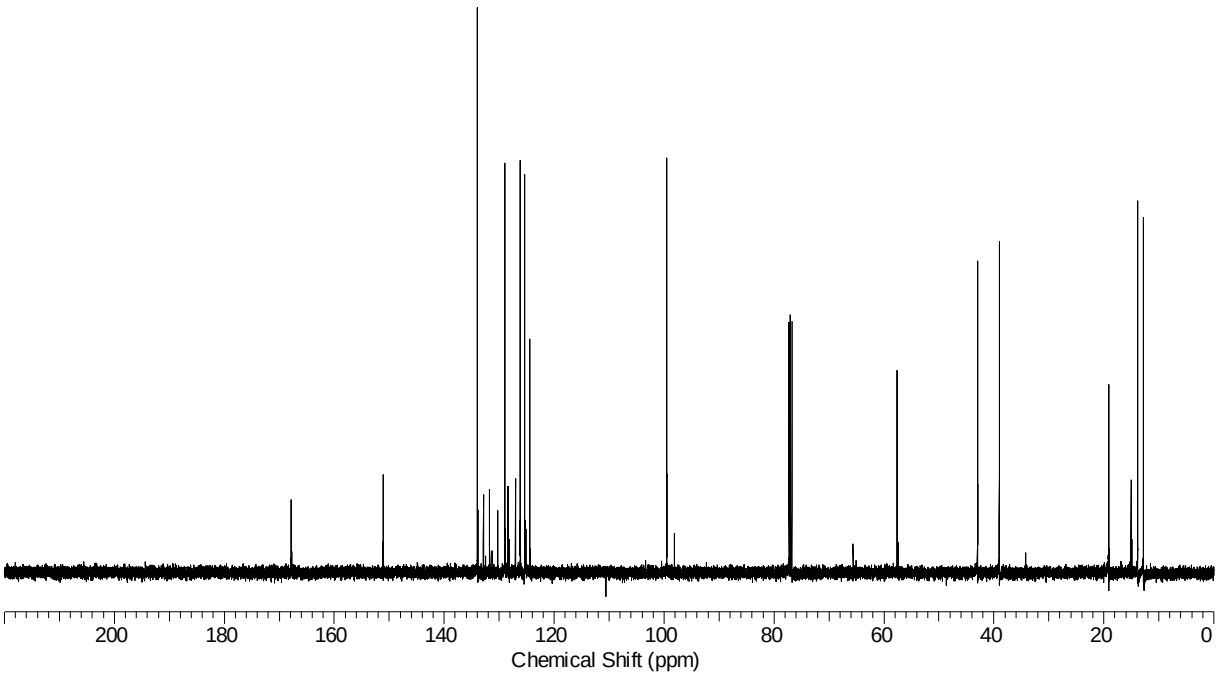
62

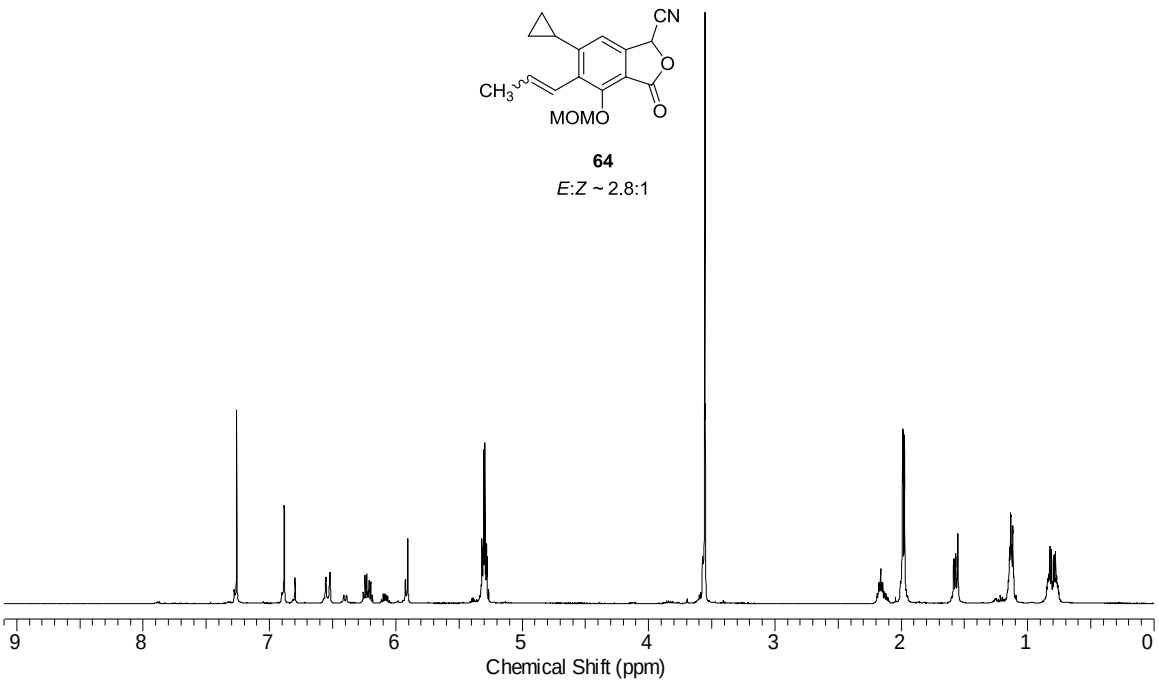

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


Br
CH3
NEt2
MOMO
O
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

63

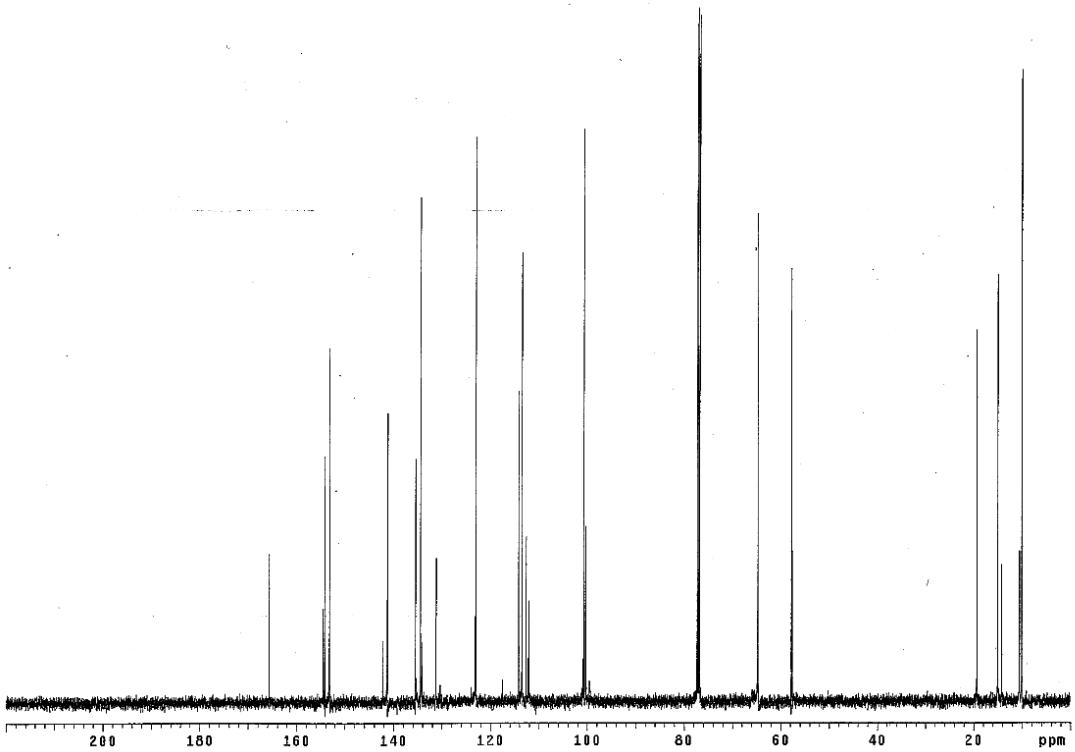
E:*Z* ~ 3.7:1

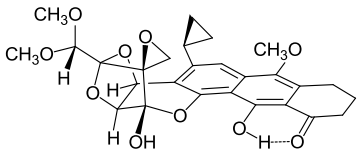

200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CN
O
O
CH3
MOMO
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

64

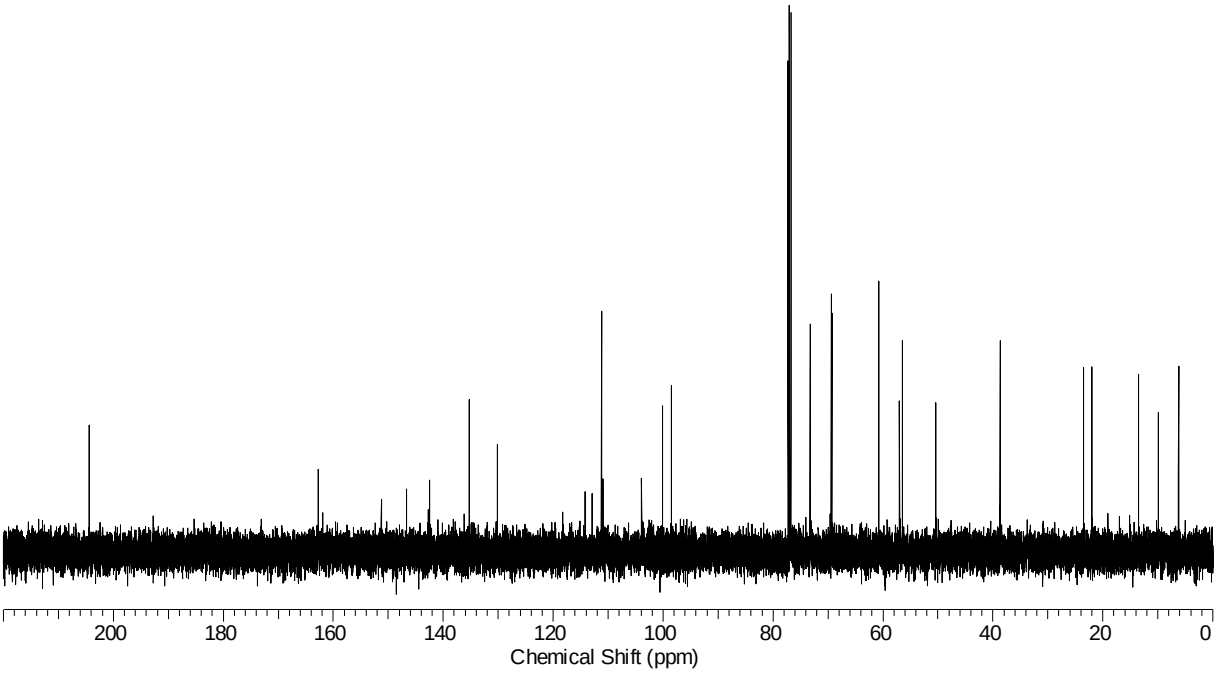
E:*Z* ~ 2.8:1


200
180
160
140
120
100
80
60
40
20
ppm

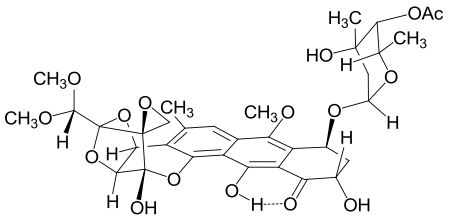

CH3O
CH3O
H
O
O
H
O
H
OH
CH3O
O
H
O

33

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

Comparison of Natural and Synthetic DC-45-A1



DC-45-A1

Comparison of ^{1}H NMR Spectral Data of Natural and Synthetic DC-45-A1

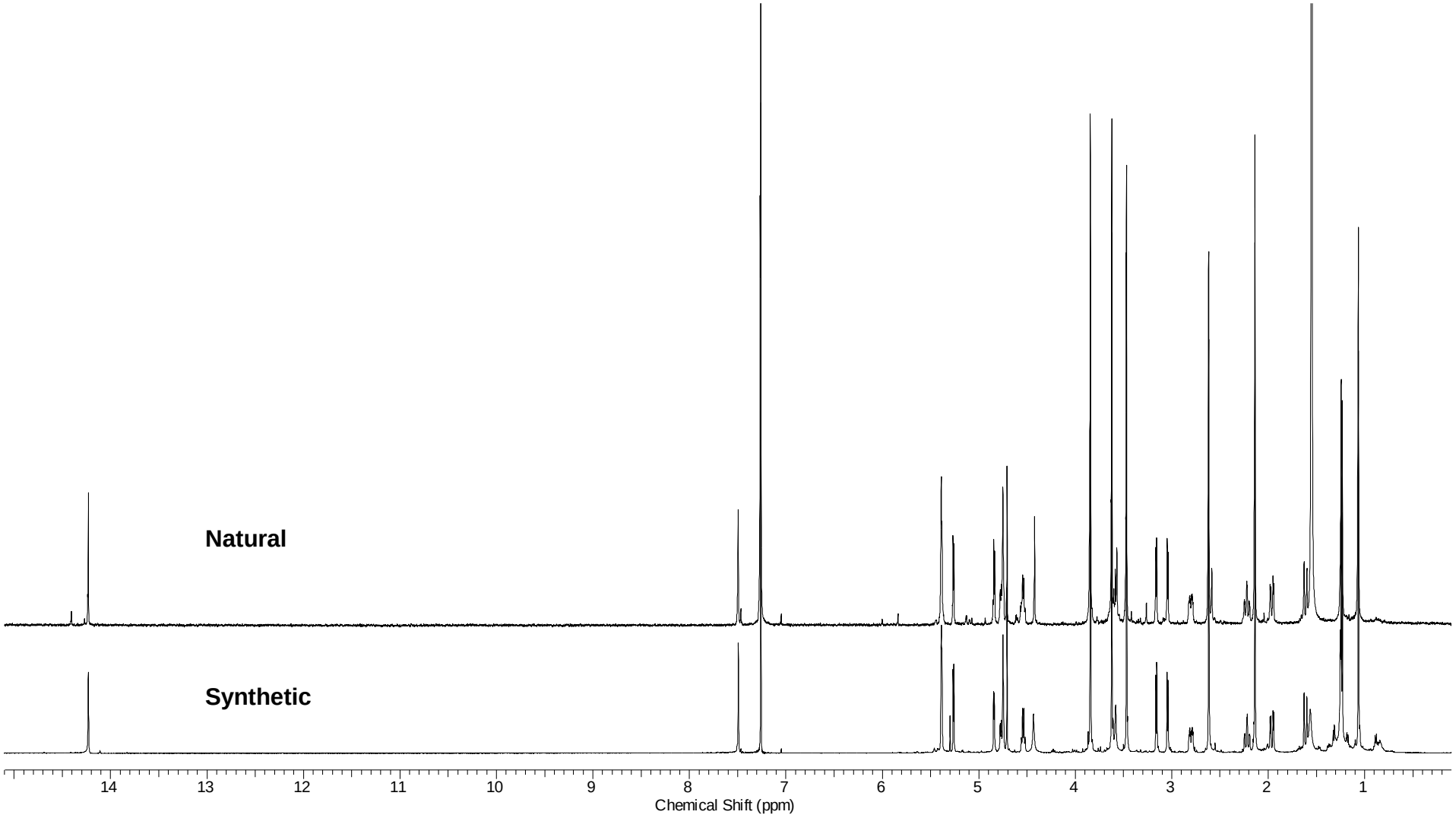
Natural[14] ($CDCl_3$)	**Synthetic** 500 MHz ($CDCl_3$)
1.07 (s, 3H)	1.07 (s, 3H)
1.24 (d, *J* = 6.4 Hz, 2H)	1.24 (d, *J* = 6.2 Hz, 3H)
1.50–2.50	1.61 (d, *J* = 14.3 Hz, 1H)
–	1.96 (dd, *J* = 14.3, 4.0 Hz, 1H)
2.14 (s, 3H)	2.14 (s, 3H)
–	2.22 (dt, , *J* = 13.2, 2.6 Hz, 1H)
2.60 (s, 3H)	2.62 (s, 3H)
–	2.83–2.77 (m, 1H)
3.02 (d, *J* = 5.4 Hz, 1H)	3.04 (d, *J* = 5.5 Hz, 1H)
3.13 (d, *J* = 5.4 Hz, 1H)	3.16 (d, *J* = 5.1 Hz, 1H)
3.46 (s, 3H)	3.47 (s, 3H)
–	3.58 (br, 1H)
3.63 (s, 3H)	3.62 (s, 3H)
3.84 (s, 3H)	3.84 (s, 3H)
4.50–5.50	4.43 (br, 1H)
–	4.54 (q, *J* = 6.2 Hz, 1H)
–	4.71 (s, 1H)
–	4.78–4.73 (m, 2H)
–	4.84 (d, *J* = 3.7 Hz, 1H)
–	5.26 (d, *J* = 4.0 Hz, 1H)
–	5.40–5.37 (m, 2H)
7.43 (s, 1H)	7.49 (s, 1H)
14.3 (s, 1H)	14.2 (s, 1H)

[14] Shirahata, K.; Iida, T. Compounds Having Antibiotic Activity, Processes for Their Preparation, Pharmaceutical Compositions Containing Them and Their Use as Medicaments. *U.S. Patent* 4,459,291, **1984**.

Comparison of ^{13}C NMR Spectral Data of Natural and Synthetic DC-45-A1

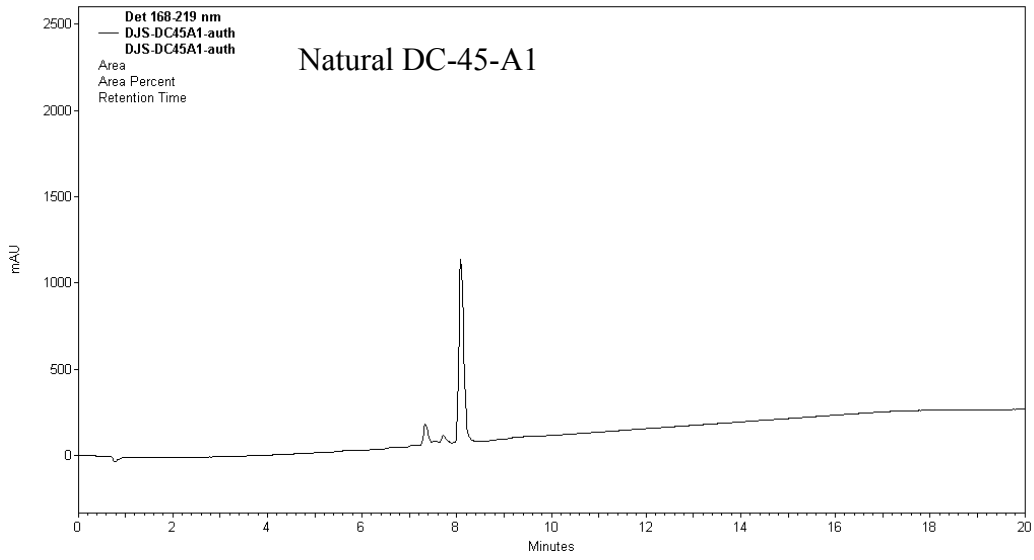
Natural[14] ($CDCl_3$)	**Synthetic** 125 MHz ($CDCl_3$)
16.9	16.9
20.5	20.5
20.9	20.9
25.7	25.7
36.7	36.6
36.7	36.7
50.2	50.5
56.6	56.6
57	57.1
62.7	62.7
63	62.9
68	67.7
68	67.9
68.9	68.8
69.2	69.3
69.4	69.5
73.3	73.2
74.4	74.4
98.3	98.1
99	98.6
100.1	100.1
104.1	103.9
107.1	107.3
114.8	114.8
115.4	115.3
116.7	116.8
126.5	126.5
135.4	135.5
143	143
144.9	144.8
151.6	151.7
163	163.1
170.4	170.3
203.1	202.8

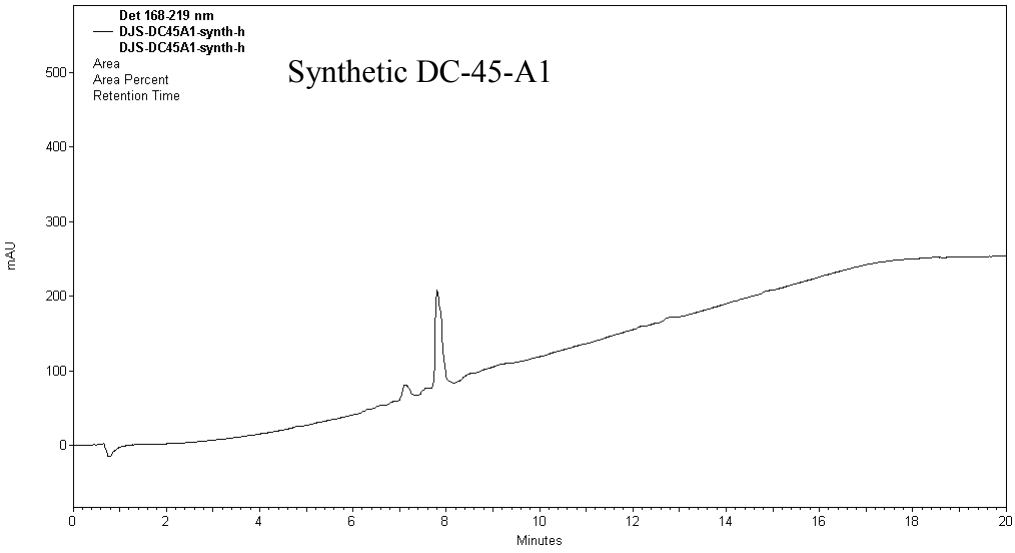
Comparison of Natural and Synthetic DC-45-A1 (^{1}H NMR, $CDCl_3$, 500 MHz). Natural sample obtained from Pfizer, Inc.

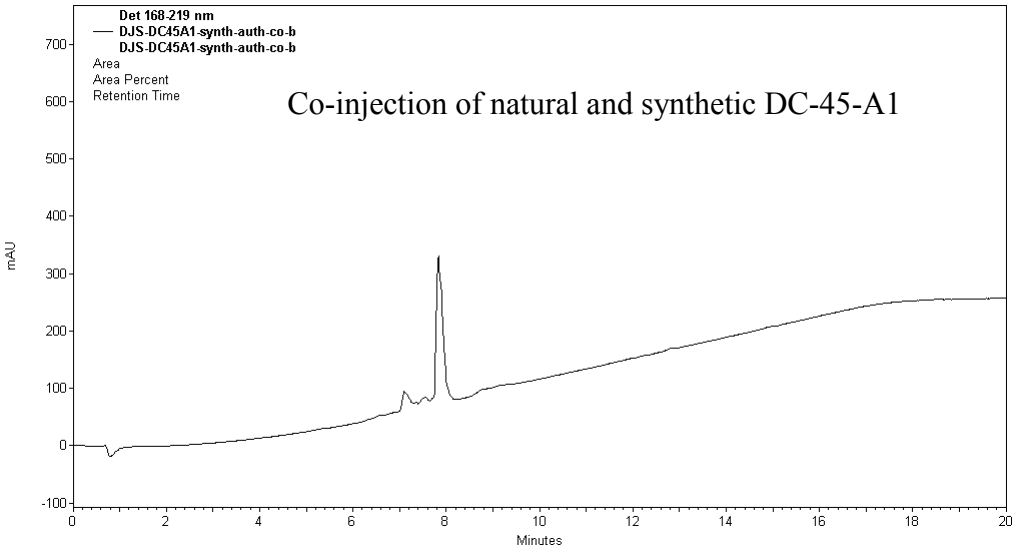


Comparison of Natural and Synthetic DC-45-A1

(reversed-phase HPLC, 10–90% acetonitrile–water containing 0.1% trifluoroacetic acid)

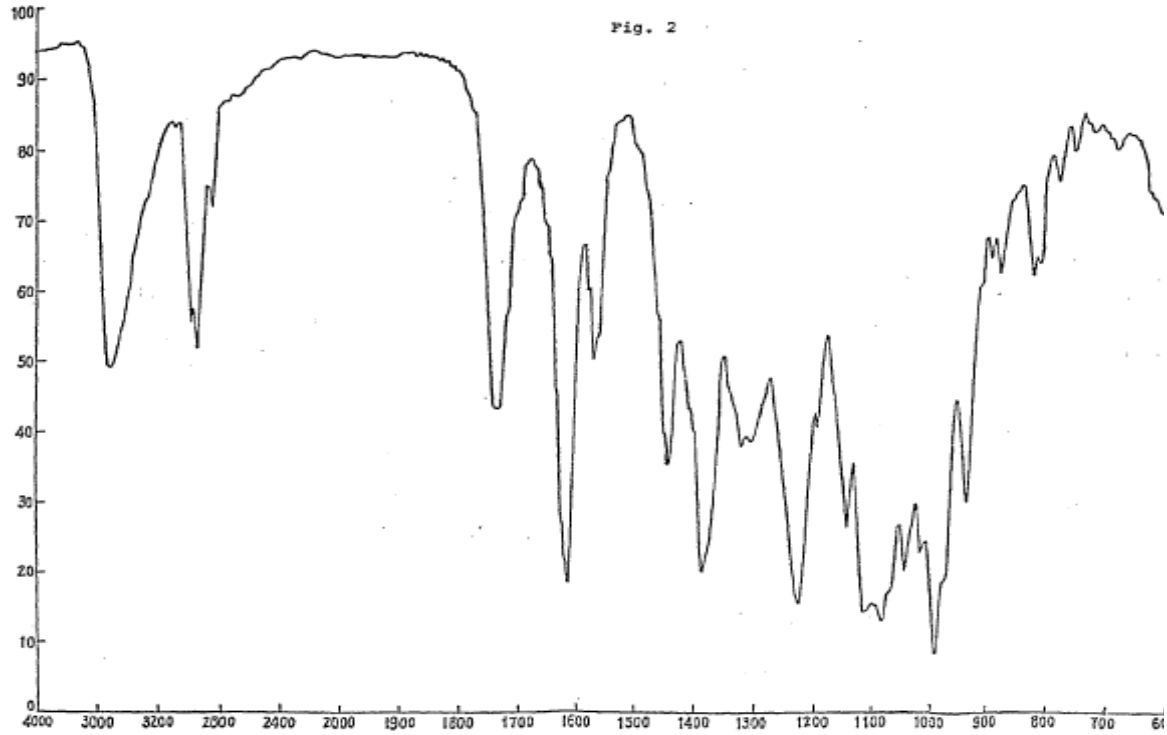




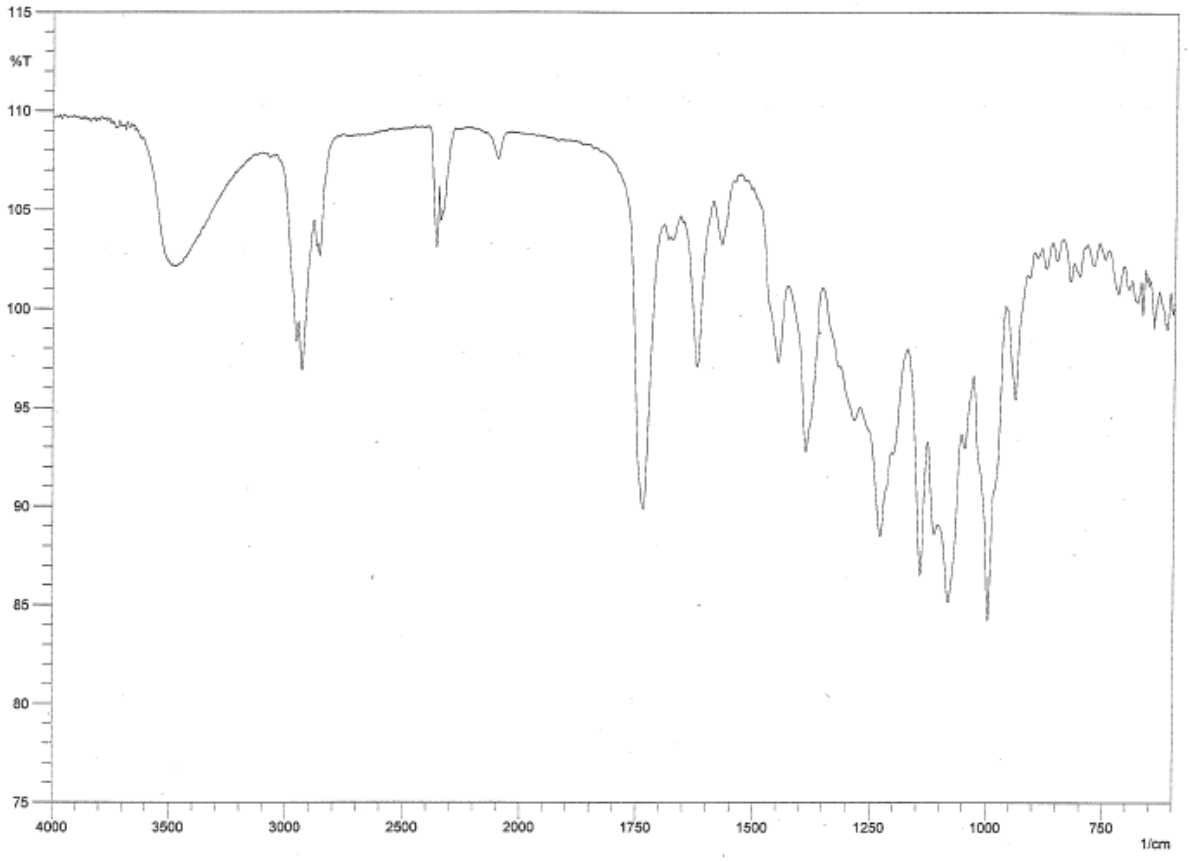


Comparison of Natural and Synthetic DC-45-A1 (FT-IR)

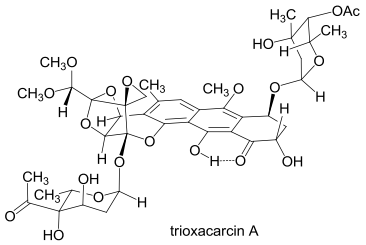
Natural DC-45-A1 (Scanned Image from Ref. 14):



Synthetic DC-45-A1



Comparison of Natural and Synthetic Trioxacarcin A



Comparison of ^{1}H NMR Spectral Data of Natural and Synthetic Trioxacarcin A

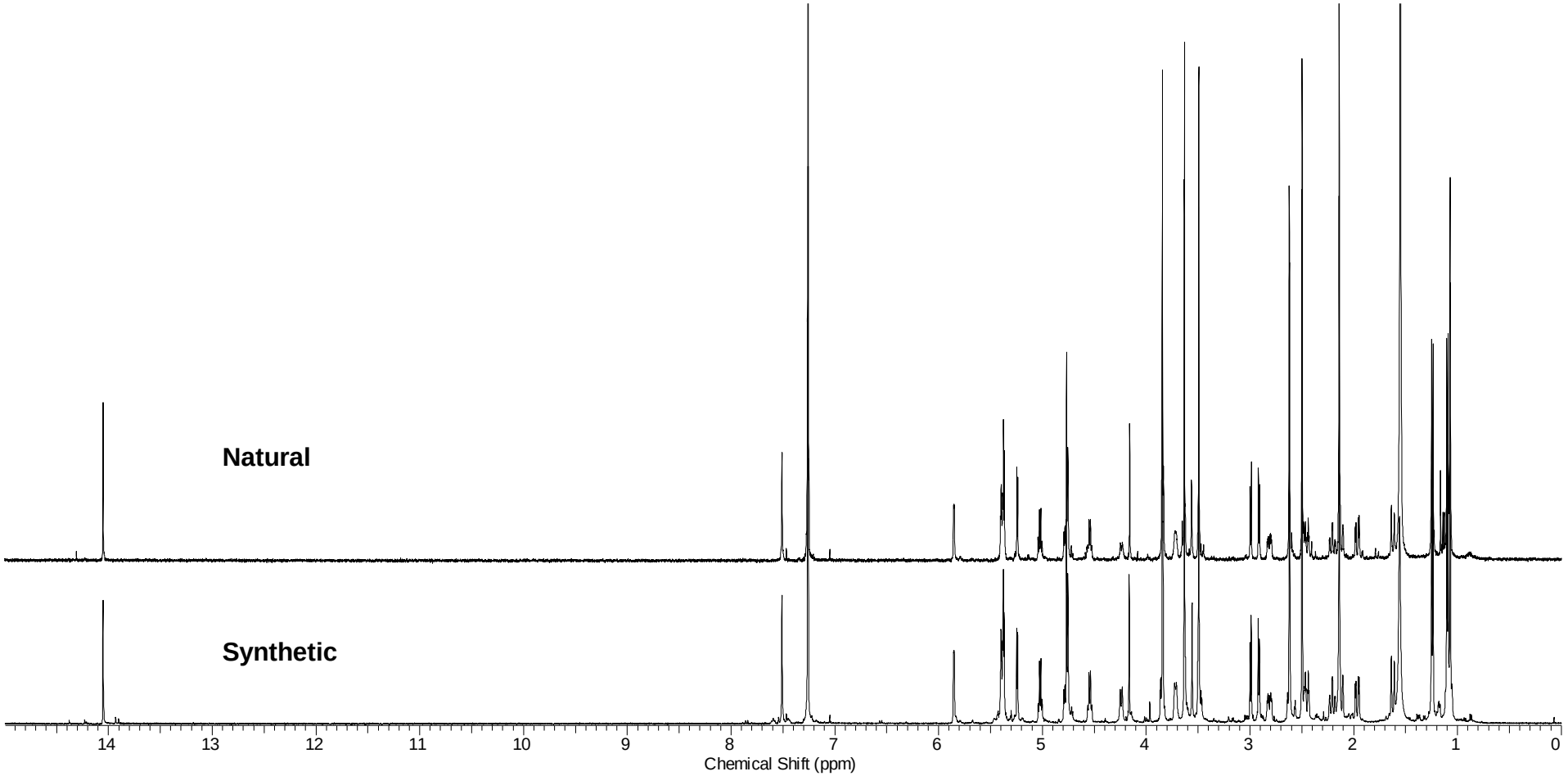
Natural[15]	**Natural**[16]	**Synthetic**
100 MHz ($CDCl_3$)	100 MHz ($CDCl_3$)	500 MHz ($CDCl_3$)
1.07 (s, 3H)	1.07 (s)	1.07 (s, 3H)
1.10 (d, *J* = 6.8 Hz, 3H)	1.10 (d)	1.10 (d, *J* = 6.2 Hz, 3H)
1.24 (d, *J* = 6.5 Hz, 3H)	1.24 (d)	1.24 (d, *J* = 6.6 Hz, 3H)
1.40–2.30	–	1.62 (d, *J* = 14.7 Hz, 1H)
–	–	1.97 (dd, *J* = 14.7, 4.0 Hz, 1H)
–	–	2.11 (m, 1H)
2.14 (s, 3H)	2.14 (s)	2.14 (s, 3H)
–	–	2.21 (dt, *J* = 13.2, 2.2 Hz, 1H)
–	–	2.45 (dt, *J* = 14.3, 3.3 Hz, 1H)
2.49 (s, 3H)	2.50 (s)	2.50 (s, 3H)
2.63 (s, 3H)	2.62 (s)	2.62 (s, 3H)
2.30–2.81	–	2.81 (m, 1H)
2.91 (d, *J* = 5.6 Hz, 1H)	2.90 (d)	2.91 (d, *J* = 5.5 Hz, 1H)
3.00 (d, *J* = 5.6 Hz, 1H)	3.00 (d)	2.99 (d, *J* = 5.9 Hz, 1H)
3.49 (s, 3H)	3.49 (s)	3.49 (s, 3H)
–	–	3.56 (s, 1H)
3.63 (s, 3H)	3.63 (s)	3.63 (s, 3H)
3.60–4.00	–	3.72 (br d, *J* = 8.8 Hz, 1H)
3.85 (s, 3H)	3.85 (s)	3.84 (s, 3H)
4.18 (s, OH)	4.16 (s)	4.16 (s, OH)
–	–	4.24 (d, *J* = 9.2 Hz, 1H)
4.55 (q, *J* = 6.8 Hz, 1H)	4.55 (q)	4.54 (q, *J* = 6.6 Hz, 1H)
4.70–4.90	4.77 (s)	4.75 (app s)
–	–	4.77 (s, 1H)
–	–	4.78 (m, 1H)
5.03 (q, *J* = 6.5 Hz, 1H)	5.02 (q)	5.02 (q, *J* = 6.6 Hz, 1H)
5.25 (d, *J* = 4.0 Hz, 1H)	5.24 (d)	5.24 (d, *J* = 4.0 Hz, 1H)
5.39 (d, *J* = 4.0 Hz, 1H)	5.38 (d)	5.37 (d, *J* = 4.0 Hz, 1H)
–	–	5.39 (m, 1H)
5.87 (m, 1H)	5.87 (d)	5.85 (d, *J* = 2.6 Hz, 1H)
7.52 (s, 1H)	7.51 (s)	7.51 (s, 1H)
14.10 (s, 1H)	14.1 (s)	14.05 (s, 1H)

[15] Tomita, F.; Tamaoki, T.; Shirahata, K.; Iida, T.; Morimoto, M.; Fujimoto, K. Antibiotic Substances DC-45, and Their Use as Medicaments. U.S. Patent 4,511,560, **1985**.
[16] Shirahata, K.; Iida, T.; Hirayama, N. *Symposium on the Chemistry of Natural Products* **1981**, *24*, 199–206.

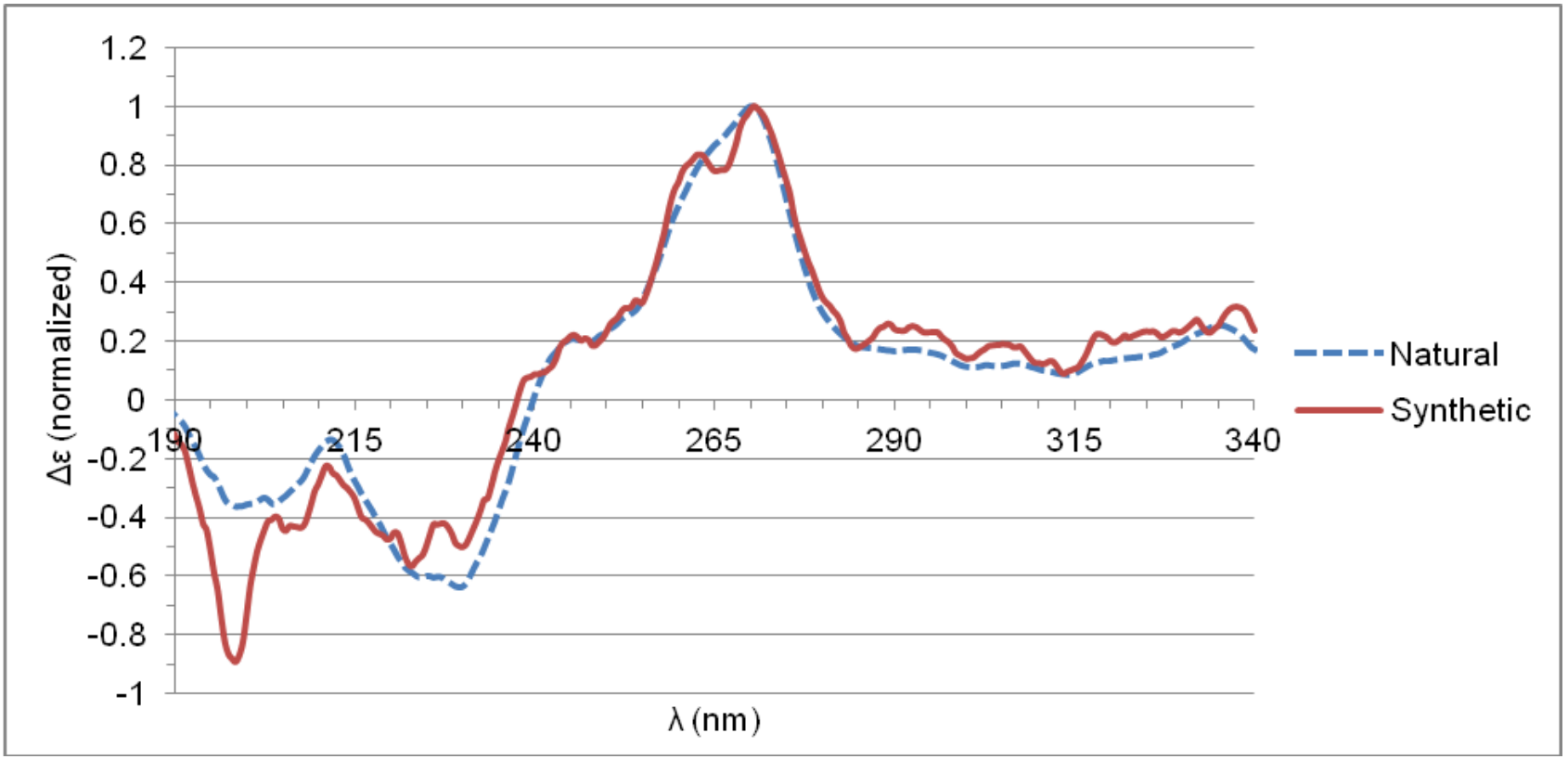
Comparison of ^{13}C NMR Spectral Data of Natural and Synthetic Trioxacarcin A

Natural[15]	**Natural**[16]	**Synthetic**
25 MHz ($CDCl_3$)	25 MHz ($CDCl_3$)	125 MHz ($CDCl_3$)
14.5	14.7	14.5
16.8	17.0	16.8
20.3	20.2	20.3
20.8	20.9	20.9
25.7	25.7	25.7
27.7	28.0	27.8
31.5	32.2	31.5
36.7 ($2 \times CH_2$)	36.5	36.6
48.1	–	48.1
56.2	55.9	56.2
56.7	57.3	56.8
62.7	–	62.7
62.9	62.8	62.9
63.8	64.0	63.8
67.6	66.3	67.4
67.9	67.9	67.9
68.3	68.8	68.3
68.8	69.3	68.8
69.1	69.6	69.1
70.2	–	70.2
71.5	71.1	71.4
74.4	74.6	74.4
79.5	79.0	79.5
94.8	85.1	94.8
98.0	93.7	97.9
99.7	97.2	99.7
101.5	99.7	101.5
104.6	105.3	104.6
107.5	108.3	107.4
114.8 ($2 \times C_q$)	114.2	114.8
116.9	117.0	116.9
126.6	126.7	126.6
135.4	135.3	135.4
142.8	142.3	142.8
144.7	145.2	144.8
151.7	152.5	151.7
163.1	162.1	163.1
170.2	170.3	170.3
203.0	203.8	202.9
210.3	210.9	210.3

Comparison of Natural and Synthetic Trioxacarcin A (^{1}H NMR, $CDCl_3$, 500 MHz). Natural sample obtained from Pfizer, Inc.

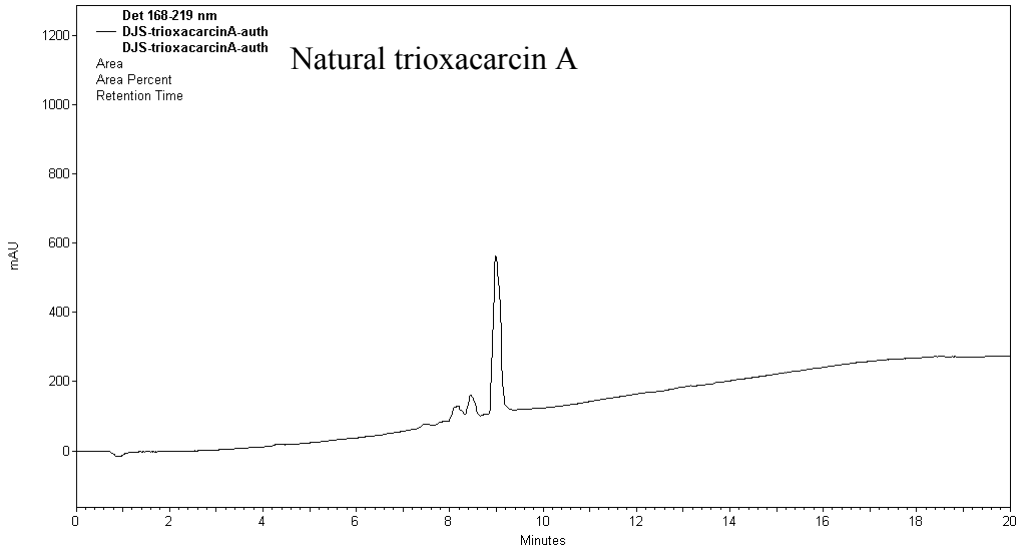


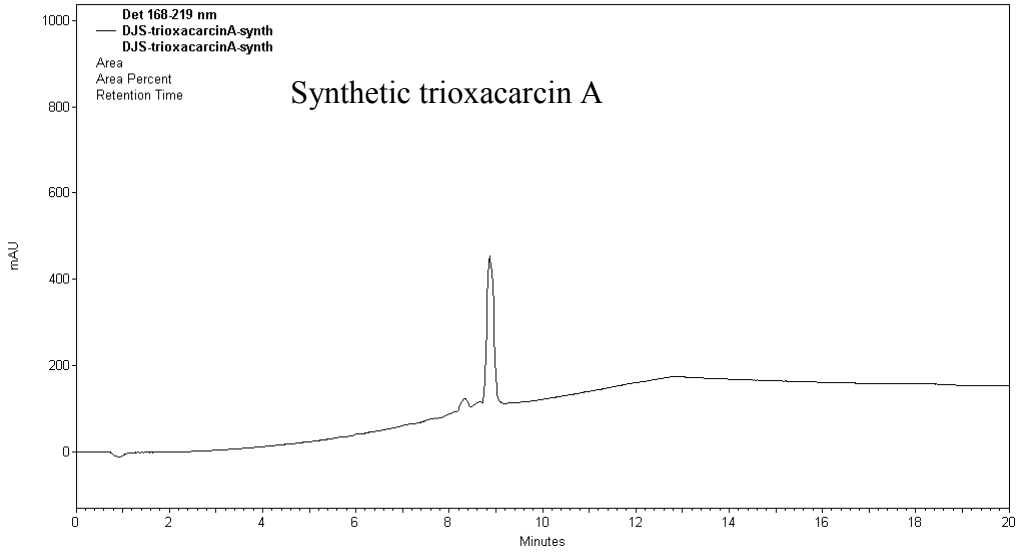
Comparison of Natural and Synthetic Trioxacarcin A (Circular Dichroism). Natural sample obtained from Pfizer, Inc. Ellipticity (Δε) values are normalized such that the maximum for each sample (at 270 nm) equals 1.

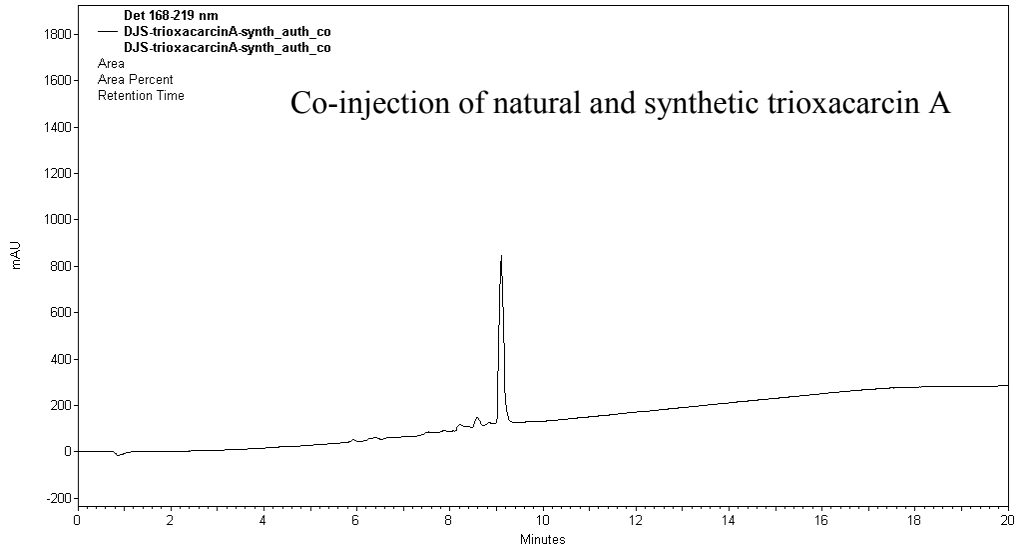


Comparison of Natural and Synthetic Trioxacarcin A

(reversed-phase HPLC, 10–90% acetonitrile–water containing 0.1% trifluoroacetic acid)

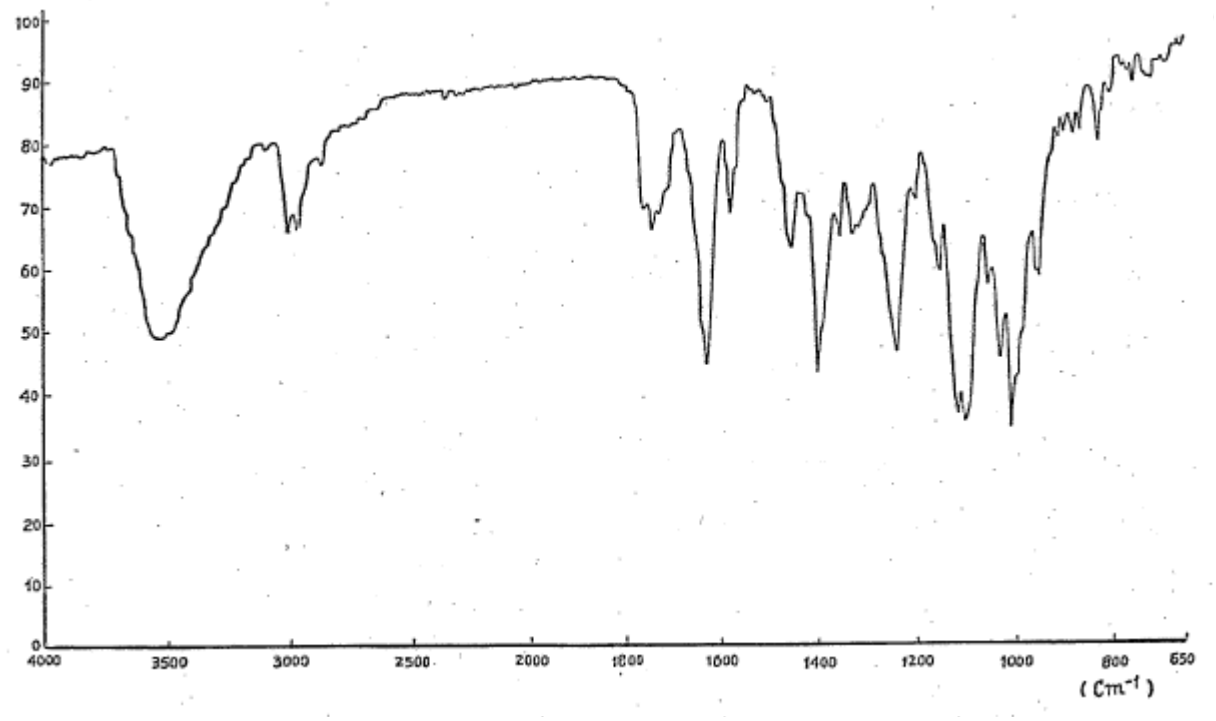






Comparison of Natural and Synthetic Trioxacarcin A (FT-IR)

Natural Trioxacarcin A (Scanned Image from Ref. 15):



Synthetic Trioxacarcin A