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General Procedures. Proton NMR spectra were collected on Bruker 400 or 500 MHz spectrometers at 25 °C. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0 ppm) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; CD_3OD, δ 3.31 ppm; D_2O, δ 4.79 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration, and *assignment*). Broad peaks are denoted by (br) before the chemical shift multiplicity. In some cases, heavily crowded chemical shifts precluded 1D assignment, and chemical shift, coupling and identity was determined by two dimensional methods. In these cases, the two dimensional method is indicated within the parenthesis. Compounds **6** and **21** were present as rotational isomers and phosphorous epimers, respectively, which complicated the coupling analysis. As such, apparent splitting patterns are noted.

Carbon NMR spectra were collected on Bruker 400 (101 MHz) or 500 (126 MHz) NMR spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with respective solvent resonances as the internal standard ($CDCl_3$, δ 77.0). Where indicated, carbon-phosphorous couplings are reported as: chemical shift, multiplicity, and coupling constant. Phosphorous NMR spectra were recorded on Bruker 400 (162 MHz) and 500 (202 MHz) NMR spectrometers with complete proton and carbon decoupling. Phosphorous chemical shifts are reported in ppm (δ) relative to 85% H_3PO_4 as an external standard.

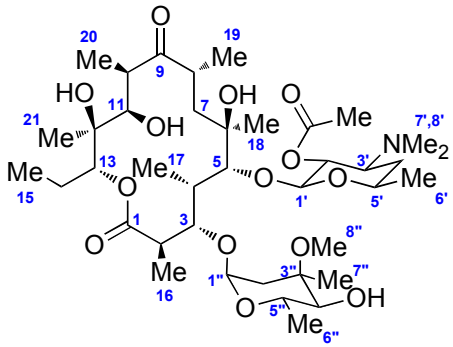
Infrared spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FT-IR instrument utilizing a ThermoScientific Small Orbit FT-IR ATR (Attenuated total reflectance) module. Thin-layer chromatography (TLC) was performed using silica gel 60 Å F254 precoated plates (0.25 mm thickness) and TLC R_f values are reported herein. Analytical TLC plates were developed utilizing cerium ammonium molybdate (CAM) or by UV absorbance. Flash chromatography was performed using Silica Gel 60Å (32-63 μM). Specific rotations were determined with a Perkin Elmer Polarimeter 341 at 20 °C on the sodium D line (path length 10.0 cm). High resolution mass spectra were obtained from institutional providers and the method of ionization reported herein.

Where noted, reactions were performed under inert atmosphere (N_2 or Ar) employing flame- or oven-dried glassware. All solvents were either distilled or taken from a solvent purification system (Glass Contour Solvent Sytems by SG Water USA). Dry pyridine was distilled fresh from calcium hydride, collected and stored under dry

nitrogen. Dry triethylamine was freshly distilled from calcium hydride, collected and stored under dry nitrogen. (-)-Erythromycin (98%) was purchased from Acros Organics and used without further purification. Methyl *N,N,N′,N′*-tetraisopropylphosphorodiamidite (CAS 92611-10-4) was purchased from Sigma-Aldrich and used without further purification. Diisopropylammonium tetrazolide was purchased from Chem-Impex International and used without further purification. Phenyltetazole was prepared according a procedure described by Sharpless and coworkers.[1]

*The proton and carbon NMR assignments for erythromycin A species are given in italics after integration values (for proton) and after chemical shift (carbon) and were validated based upon the literature.[2] For compounds **6** and **19** definitive assignments could not be made due to the existence of carbamate rotomers and phosphorous epimers, respectively.*

2′-Acetyl-Erythromycin A

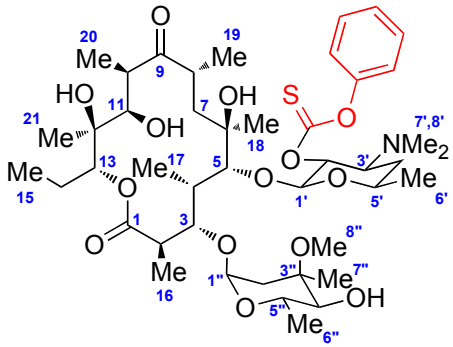


Procedure adapted from Lartey *et al.*[3]

A 100 mL round bottom flask was flame-dried and to it was added erythromycin A (1.43g, 1.95 mmol) followed by 50 mL of dichloromethane. The flask was charged with nitrogen. Upon complete dissolution, the flask was cooled to 0 ˚C and to it was added acetic anhydride (0.2 mL, 2.15 mmol). After 15 minutes at 0 ˚C, the bath was removed and the reaction was stirred at room temperature for 12 hours. The reaction was poured into a separatory funnel with saturated $NaHCO_3$. After separating the layers, the organic phase was washed three times with equal volumes of deionized water, dried with anhydrous sodium sulfate, filtered, and concentrated. The resulting white solid was dissolved in hot acetonitrile and allowed to cool over night to give crystals. The flask was transferred to a -20 ˚C freezer for several hours before filtration yielding 0.995 grams of pure 2′-acetyl-erythromycin A (1.28 mmol, 66% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.04 (dd, *J* = 10.9, 2.3 Hz, 1H, *13*), 4.89 (d, *J* = 4.5 Hz, 1H, *1″*), 4.76 (dd, *J* = 10.1, 8.1 Hz, 1H, *2′*), 4.55 (d, *J* = 7.5 Hz, 1H, *1′*), 3.99 (m, 1H, *5″*), 3.94 (m, 1H, *3*), 3.89 (s, 1H, *11-OH*), 3.79 (s, 1H, *11*), 3.50 (d, *J* = 7.3 Hz, 1H, *5*), 3.50 (m, *J* = 7.3 Hz, 1H, *5′*), 3.35 (s, 3H, *8″*), 3.10 (s, 1H, *12-OH*), 3.09 – 3.05 (m, 1H, *10*), 3.03 (t, 1H, *4″*), 2.85 (dq, *J* = 14.3, 7.1 Hz, 1H, *2*), 2.72 – 2.63 (m, 1H, *8*), 2.63 – 2.55 (m, 1H, *3′*), 2.36 (d, *J* = 15.2 Hz, 1H, $2''_{eq}$), 2.26 (s, 6H, *7′, 8′*), 2.17 (d, *J* = 10.1 Hz, 1H, *4″-OH*), 2.06 (s, 3H, *2′-Ac*), 1.95 – 1.87 (m, 2H, *4, 14*$_{eq}$), 1.81 – 1.59 (m, 4H, 7_{ax},7_{eq}, $2''_{ax}$,$4'_{eq}$), 1.50 (m, 1H, 14_{ax}), 1.45 (s, 3H, *18*), 1.31 – 1.28 (m, 1H, $4'_{ax}$), 1.27 (d, *J* = 6.2 Hz, 3H, *6″*), 1.26 (s, 3H, *7″*), 1.22 (d, *J* = 6.0 Hz, 3H, *6′*), 1.19 (d, *J* = 5.4 Hz, 3H, *16*), 1.17 (d, *J* = 5.4 Hz, 3H, *19*), 1.14 (d, *J* =

6.9 Hz, 3H, *20*), 1.13 (s, 3H, *21*), 0.94 (d, *J* = 7.5 Hz, 3H, *17*), 0.84 (t, *J* = 7.4 Hz, 3H, *15*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 222.5 (*9*), 175.7 (*1*), 170.1 (*2′Ac*), 101.0 (*1′*), 96.2 (*1″*), 83.5 (*5*), 79.9 (*3*), 78.0 (*4″*), 76.9 (*13*), 75.2 (*6*), 74.7 (*12*), 72.9 (*3″*), 71.8 (*2′*), 69.1 (*11*), 68.5 (*5′*), 65.8 (*5″*), 63.7 (3′), 49.5 (*8″*), 45.3 (*8*), 44.9 (*2*), 40.8 (*7′, 8′*), 39.3 (*4*), 38.2 (*7*), 37.9 (*10*), 35.1 (*2″*), 30.4 (*4′*), 27.2 (*18*), 21.7 (*2′Ac*), 21.6 (*6″*), 21.4 (*6′*), 21.2 (*14*), 18.8 (*7″*), 18.3 (*19*), 16.4 (*21*), 16.1 (*16*), 12.2 (*20*), 10.8 (*15*), 9.2 (*17*). **IR** (ATR, cm^{-1}) 3420, 2971, 2939, 2878, 2828, 2783, 2783, 1738, 1701, 1458, 1373, 1343, 1239, 1167, 1049, 997; **$[\alpha]_D$** = -74.2 (c = 0.5, $CDCl_3$); **TLC** (R_f = 0.23, 10 % 2-propanol, 1 % pyridine in DCM, CAM stain); **MS** (ESI): calculated for $[C_{39}H_{69}NO_{14}]H^+$ requires *m/z* 776.479, found 776.457.

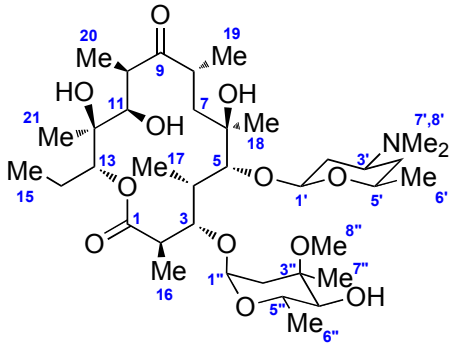
Erythromycin A-2′-Phenylthionoformate (Compound 5)



To an oven-dried 2 mL vial with stir bar was added 100 mg erythromycin A (0.136 mmol) followed by 1.4 mL dry dichloromethane. Upon complete dissolution, 1,2,2,6,6-pentamethylpiperidine (Sigma-Aldrich, 36.9 µL, 0.204 mmol) and *N*-methylimidazole (distilled, 1.1 µL, 0.014 mmol) were added, followed by *O*-phenyl chlorothionoformate (Sigma-Aldrich, 28.2 µL, 0.204 mmol). The reaction was allowed to stir at room temperature with a tightly sealed cap (no nitrogen gas flow) and monitored by TLC (R_f = 0.26, 5% 2-propanol, 1% pyridine in DCM, CAM stain). After 2 h, the reaction was deemed complete by the disappearance of starting material. The reaction mixture was quenched with 25 µL 2-propanol and was added directly to a silica gel column (eluted with 5 column volumes of 2.5% 2-propanol, 1% pyridine in DCM, then 3 each of 5% and 7.5% 2-propanol with 1% pyridine in DCM) to yield 89.6 mg of an off-white solid (0.103 mmol, 76% yield). Residual pyridine was removed by dissolving the product in toluene and removing *in vacuo*. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.9 Hz, 2H, *Ph, meta*), 7.28 (t, *J* = 7.4 Hz, 1H, *Ph, para*), 7.11 (d, *J* = 7.6 Hz, 2H, *Ph, ortho*), 5.34 (dd, *J* = 10.6, 7.4 Hz, 1H, *2'*), 5.08 (dd, *J* = 11.0, 2.0 Hz, 1H, *13*), 4.92 (d, *J* = 4.8 Hz, 1H, *1"*), 4.66 (d, *J* = 7.3 Hz, 1H, *1'*), 4.05 (s, 1H, *11-OH*), 3.99 – 3.90 (m, 2H, *5", 3*), 3.83 (s, 1H, *11*), 3.59 – 3.49 (m, 2H, *5', 5*), 3.26 (s, 1H, *12-OH*), 3.22 (s, 3H, *8"*), 3.07 (q, *J* = 6.5 Hz, 1H, *10*), 3.00 (t, *J* = 9.5 Hz, 1H, *4"*), 2.95 – 2.87 (m, 1H, *2*), 2.87 – 2.79 (m, 1H, *3'*), 2.70 – 2.60 (m, 1H, *8*), 2.42 – 2.31 (m, 7H, *7', 8', 2"$_{eq}$*), 2.28 (d, *J* = 10.0 Hz, 1H, *4"-OH*), 2.02 – 1.88 (m, 2H, *4, 14$_{eq}$*), 1.84 – 1.77 (m, 1H, *4'$_{eq}$*), 1.73 (m, 1H, *7$_{ax}$*), 1.67 (d, *J* = 13.8 Hz, 1H, *7$_{eq}$*), 1.59 – 1.53 (m, 1H, *2"$_{ax}$*), 1.50 (ddd, *J* = 10.8, 7.0, 2.8 Hz, 1H, *14$_{ax}$*), 1.44 (s, 3H, *18*), 1.43 – 1.36 (m, 1H, *4'$_{ax}$*), 1.27 (d, *J* = 6.2 Hz, 3H, *6'*), 1.25 (d, *J* = 6.1 Hz,

3H, *6"*), 1.24 (s, 3H, *7"*), 1.19 (d, *J* = 7.4 Hz, 3H, *16*), 1.18 (s, 3H, *21*), 1.14 (d, *J* = 6.8 Hz, 3H, *20*), 1.12 (d, *J* = 7.0 Hz, 3H, *19*), 1.05 (d, *J* = 7.5 Hz, 3H, *17*), 0.86 (t, *J* = 7.4 Hz, 3H, *15*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 221.7 *(9)*, 194.5 *(thiono)*, 175.6 *(1)*, 153.6 *(ph)*, 129.4 *(ph)*, 126.4 *(ph)*, 122.0 *(ph)*, 100.4 *(1')*, 96.0 *(1")*, 83.2 *(5)*, 82.0 *(2')*, 79.6 *(3)*, 78.1 *(4")*, 77.0 *(13)*, 74.9 *(6)*, 74.8 *(12)*, 72.7 *(3")*, 68.9 *(11)*, 68.5 *(5')*, 65.7 *(5")*, 63.2 *(3')*, 49.5 *(8")*, 45.2 *(8)*, 44.9 *(2)*, 41.2 *(7',8')*, 39.1 *(4)*, 38.4 *(7_{ax}, 7_{eq})*, 37.9 *(10)*, 35.1 *($2"_{ax}$, $2"_{eq}$)*, 31.3 *($4'_{ax}$, $4'_{eq}$)*, 26.9 *(18)*, 21.6 *(7")*, 21.3 *(6", 14_{eq}, 14_{ax})*, 18.9 *(6')*, 18.3 *(19)*, 16.4 *(21)*, 16.1 *(16)*, 12.1 *(20)*, 10.7 *(15)*, 9.1 *(17)*; **IR** (ATR, cm^{-1}) 3497, 2971, 2934, 2878, 1716, 1592, 1491, 1456, 1375, 1344, 1283, 1192, 1165, 1109, 1183, 1050, 998; **$[\alpha]_D$** = -71.3 (c = 1.0, $CDCl_3$); **TLC** (R_f = 0.26, 5% 2-propanol, 1% pyridine in DCM, CAM stain); **MS** (ESI): calculated for $[C_{44}H_{71}NO_{14}S]H^+$ requires *m/z* 870.467, found 870.462.

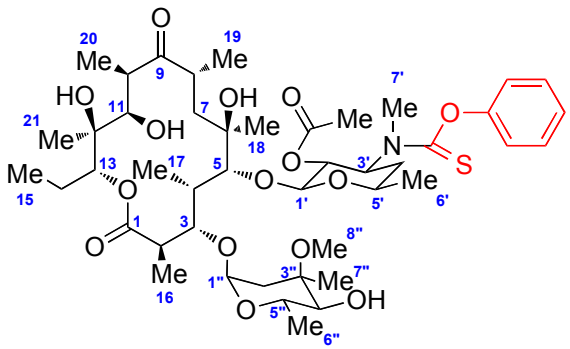
2′-Deoxyerythromycin A (Compound 23)



To a 15 mL screw top pressure tube, with magnetic stir bar, was added erythromycin A-2′-phenylthionoformate (**5**, 93 mg, 0.107 mmol), azoisobutyronitrile (AIBN, 5.4 mg, 0.032 mmol) and 4 mL anhydrous benzene. Upon complete dissolution, tributyltin hydride (89 µL, 0.320 mmol) was added, and the solution was stirred at room temperature and sparged for 10 minutes under a heavy stream of dry nitrogen with an outlet. The reaction tube was then sealed and place into an 80 ˚C oil bath. After 1.5 hours the reaction was cooled slightly, and examined by TLC (CAM stain), which indicated that the starting material had been completely consumed. The solution was allowed to cool completely to room temperature and then added directly to a silica gel column prepared with 1% pyridine in hexanes. The column was then washed with 1% pyridine in hexanes followed by 1% pyridine in DCM to remove residual tributyltin species. The product was eluted with a mobile phase consisting of 1% pyridine, 10% methanol in DCM. Fractions containing product were pooled, concentrated, azeotroped with toluene to remove any remaining pyridine, and yielded 56.9 mg (0.079 mmol, 74 % yield) of pure 2′-deoxyerythromycin A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.05 (dd, *J* = 11.0, 2.2 Hz, 1H, *13*), 4.87 (d, *J* = 4.7 Hz, 1H, *1"*), 4.51 (dd, *J* = 9.3, 1.8 Hz, 1H, *1'*), 3.97 – 3.89 (m, 3H, *5", 11-OH, 3*), 3.79 (s, 1H, *11*), 3.54 (d, *J* = 7.7 Hz, 1H, *5*), 3.45 – 3.34 (m, 1H, *5'*), 3.29 (s, 3H, *8"*), 3.12 (s, 1H, *12-OH*), 3.11 – 3.04 (m, 1H, *10*), 3.01 (d, *J* = 9.3 Hz, 1H, *4"*), 2.86 (dq, *J* = 14.2, 7.1 Hz, 1H, *2*), 2.73 – 2.62 (m, 1H, *8*), 2.47 (s, 1H, *3'*), 2.35 (d, *J* = 15.3 Hz, 1H, *$2"_{eq}$*), 2.32 (s, 6H, *7', 8'*), 2.07 (d, *J* = 12.8 Hz, 1H, *$2'_{eq}$*), 1.96 – 1.88 (m, 2H, *4, 14_{eq}*), 1.84 (dd, *J* = 14.7, 11.6 Hz, 1H, *7_{ax}*), 1.72 (d, *J* = 12.0 Hz, 1H, *$4'_{eq}$*), 1.69 – 1.60 (m, 1H, *7_{eq}*), 1.58 (dd, *J* = 15.2, 5.1 Hz, 1H, *$2"_{ax}$*), 1.48 (s, 3H, *18*), 1.48 – 1.45 (m, 1H, *14_{ax}*), 1.30 (m, 1H, *$2'_{ax}$*), 1.27 (d, *J* = 6.1 Hz, 3H, *6"*), 1.24 (s, 3H, *7"*), 1.23 (d, *J* = 6.3 Hz,

3H, *6′*), 1.18 (d, *J* = 5.7 Hz, 3H, *16*), 1.16 (d, *J* = 5.7 Hz, 3H, *19*), 1.14 (d, *J* = 6.9 Hz, 3H, *20*), 1.13 (s, 3H, *21*), 1.13-1.10 (m, 1H, $4'_{ax}$), 0.95 (d, *J* = 7.4 Hz, 3H, *17*), 0.84 (t, *J* = 7.4 Hz, 3H, *15*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 222.3 (*9*), 175.7 (*1*), 101.1 (*1′*), 96.6 (*1″*), 84.6 (*5*), 80.4 (*3*), 78.0 (*4″*), 77.0 (*13*), 75.0 (*6*), 74.7 (*12*), 72.9 (*3″*), 69.0 (*5′*), 68.9 (*11*), 65.8 (*5″*), 60.5 (*3′*), 49.6 (*8″*), 45.3 (*8*), 45.0 (*2*), 41.1 (*7′, 8′*), 39.1 (*4*), 38.4 (*7*), 37.8 (*10*), 35.1 (*2″*), 34.1 (*4′*), 33.9 (*2′*), 27.1 (*18*), 21.7 (*7″*), 21.6 (*6′*), 21.2 (*14*), 18.6 (*6″*), 18.4 (*19*), 16.4 (*21*), 16.1 (*16*), 12.2 (*20*), 10.8 (*15*), 9.3 (*17*). **IR** (ATR, cm^{-1}) 3498, 2964, 2936, 2874, 1738, 1715, 1459, 1400, 1376, 1285, 1263, 1244, 1165, 1123, 1091, 1065, 1000, 975, 958, 903; **[α]$_D$** = -67.9 (c = 0.5, $CDCl_3$); **TLC** (R_f = 0.30, 10% methanol, 1% NH_4OH ($14N_{aq}$) in DCM, CAM stain); **MS** (ESI): calculated for $[C_{37}H_{67}NO_{12}]H^+$ requires *m/z* 718.474, found 718.459.

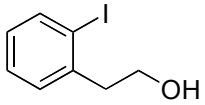
2′-Acetyl-3′-phenylthionoformyl-3′-*N*-desmethylerythromycin A (Compound 6)



To an oven-dried 2 mL vial with stir bar was added 2′-acetyl-erythromycin A (106 mg, 0.136 mmol) followed by 1.4 mL dichloromethane. Upon complete dissolution, 1,2,2,6,6-pentamethylpiperidine (37 µL, 0.204 mmol) and *N*-methylimidazole (1.1 µL, 0.014 mmol) were added followed by *O*-phenyl chlorothionoformate (28 µL, 0.204 mmol). The reaction was stirred with a tightly sealed cap (no nitrogen flow) and monitored by TLC (CAM stain) and deemed complete after 2 hours. The reaction was quenched with 25 µL of 2-propanol and added directly to a silica gel column (1% pyridine, 5% 2-propanol in DCM). The product was eluted with a two step mobile phase, first with 1% pyridine, 5% 2-propanol in DCM and then 1% pyridine, 7.5% 2-propanol in DCM. The fractions containing product were concentrated and azeotroped three times to remove residual pyridine then placed under vacuum over night to give 98.8 mg (0.107 mmol, 81% yield) of **6** as a mixture of two apparent thionocarbamate rotational isomers (~2:1 in $CDCl_3$, ~1:1 in acetone-d_6). *For a majority of chemical shifts a clear dispersion of isomers was not evident, however in obvious cases integrations may appear below as non-integer values reflective of the isomer ratio. Due to existence of isomers, ^{13}C chemical shifts were not assigned.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H, *meta-CH*), 7.30 – 7.21 (m, 1H, *para C-H*), 7.02 (d, *J* = 7.7 Hz, 0.63H, *ortho C-H, isomer 1*), 6.99 (d, *J* = 7.6 Hz, 1.43H, *ortho C-H, isomer 2*), 5.68 – 5.58 (m, 1H, *3′*), 5.06 (m, 1H, *13*), 4.94 – 4.79 (m, 3H, *1″, 2′, 1′*), 4.03 – 3.94 (m, 1H, *5″*), 3.92 (d, *J* = 9.6 Hz, 1H, *3*), 3.88 (s, 0.32H, *11-OH, isomer 1*), 3.87 (s, 0.62H, *11-OH, isomer 2*), 3.78 (s, 1H, *11*), 3.76 – 3.69 (m, 1H *5′*), 3.55 (d, *J* = 6.8 Hz, 0.68H, *5, isomer 2*), 3.53 (d, *J* = 7.0 Hz, 0.43H, *5, isomer 1*), 3.39 (s, 2H, *8″, isomer 2*), 3.25 (s, 1H, *8″, isomer 1*), 3.20 (s, 1H, *7′,*

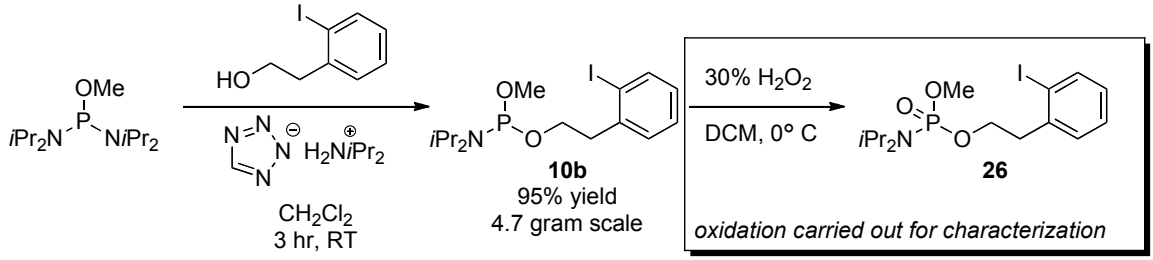
isomer 1), 3.15 (s, 2H, *7′, isomer 2*), 3.12 – 3.06 (m, 2H, *12-OH, 10*), 3.06 – 3.00 (m, 1H, *4″*), 2.91 – 2.83 (m, 1H, *2*), 2.73 – 2.63 (m, 1H, *8*), 2.35 (d, *J* = 15.1 Hz, 1H, $2''_{eq}$), 2.27 (d, *J* = 9.7 Hz, 1H, *4″-OH*), 2.11 (s, 1H, *Ac*, *isomer 1*), 2.07 (s, 2H, *Ac, isomer 2*), 1.99 – 1.87 (m, 3H, *4,* 14_{eq}, $4'_{eq}$), 1.83 – 1.73 (m, 1H, 7_{ax}), 1.66 – 1.57 (m, 3H, 7_{eq}, $2''_{ax}$, $4'_{ax}$), 1.53 – 1.42 (m, 4H, *18,* 14_{ax}), 1.31 – 1.12 (m, 21H, *21, 7″, 19, 16, 20, 6′, 6″*), 0.97 (d, *J* = 7.6 Hz, 2H, *17, isomer 2*), 0.95 (d, *J* = 7.6 Hz, 1H, *17 isomer 1*), 0.84 (t, *J* = 7.4 Hz, 3H, *15*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 222.2, 222.1, 189.7, 188.8, 175.6, 175.5, 170.3, 169.5, 154.0, 153.9, 129.4, 129.3, 126.2, 126.1, 122.8, 122.6, 100.2, 96.1, 96.0, 85.3, 84.3, 84.2, 79.6, 79.4, 78.0, 77.9, 75.5, 74.9, 74.8, 74.7, 74.7, 73.1, 73.0, 72.8, 71.5, 69.1, 69.0, 68.0, 66.0, 65.9, 60.7, 49.6, 49.3, 45.3, 45.3, 44.8, 44.8, 38.9, 38.1, 38.0, 37.9, 37.9, 36.4, 35.3, 35.1, 35.1, 31.7, 27.0, 21.7, 21.6, 21.3, 21.2, 21.1, 21.0, 18.7, 18.6, 18.4, 18.3, 16.4, 16.1, 12.2, 12.2, 10.7, 9.2, 9.2; **IR** (ATR, cm^{-1}) 3512, 2971, 2936, 1739, 1488, 1456, 1403, 1375, 1345, 1290, 1236, 1198, 1164, 1121, 1048, 997; **$[\alpha]_D$** = -110.4 (c = 0.5, $CDCl_3$); **TLC** (R_f = 0.47, 5% 2-propanol, 1% pyridine in DCM, CAM stain); **MS** (ESI): calculated for $[C_{45}H_{71}NO_{15}S]Na^+$ requires *m/z* 920.444, found 920.451.

2-(2-iodophenyl) ethanol



2-(2-iodophenyl) ethanol was prepared according to a procedure described by Buchwald and coworkers and the corresponding proton and carbon NMR spectra the literature.[4]

Phosphoramidite 10b

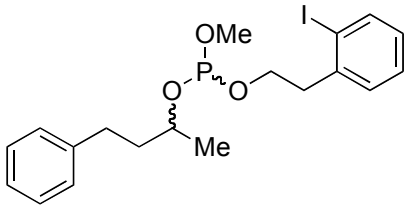


To a flame-dried 100 mL round bottom flask with stir bar was added 48 mL dry dichloromethane, methyl tetraisopropyl phosphorodiamidite (3.83 mL, 13.3 mmol) and diisopropyl ammonium tetrazolide (3.83 g, 6.05 mmol, *0.5 equivalents*). This was followed by the addition of 2-(2-iodophenyl) ethanol (3 g, 12.1 mmol). The solution was stirred under a stream of dry nitrogen at room temperature. After 3 hours, the solution was poured into a separatory funnel containing 200 mL saturated aqueous $NaHCO_3$ and extracted three times with 100 mL dichloromethane. The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography. A column was prepared with 75 : 25 : 5, hexanes to dichloromethane to triethylamine. The product was eluted at the solvent front with the same solvent system. Fractions containing product (bright orange by ninhydrin stain [no heating]) were combined to give 4.7 g (11.9 mmol, 95% yield) of **10b** as a viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 7.9, 0.8 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.89 (ddd, J = 7.8, 7.1, 2.1 Hz, 1H), 3.89 – 3.73 (m, 2H), 3.62 – 3.52 (m, 2H), 3.40 (d, $J_{H\text{-}P}$ = 13.2 Hz, 3H), 3.07 (t, J = 7.2 Hz, 2H), 1.17 (d, J = 6.8 Hz, 6H), 1.15 (d, J = 6.8 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.5, 139.6, 130.7, 128.3, 128.3, 100.9, 62.8 (d, $J_{C\text{-}P}$ = 18.4 Hz), 50.7 (d, $J_{C\text{-}P}$ = 17.7 Hz), 42.9 (d, $J_{C\text{-}P}$ = 12.3 Hz), 42.6 (d, $J_{C\text{-}P}$ = 7.3 Hz), 24.9, 24.8, 24.8; **^{31}P NMR** (202 MHz, $CDCl_3$) δ 147.5; **IR** (ATR, cm^{-1}) 2964, 2929, 2868, 2826, 1587, 1563, 1466, 1436, 1395, 1378, 1362, 1311, 1199, 1183, 1155, 1125, 930, 900; **Density** d = 1.314; **MS** (ESI): To prepare a sample suitable for mass spectrometry, 50 mg of **10b** was converted to **26** and submitted for analysis. **MS** (ESI): calculated for $[C_{15}H_{25}INO_3P]H^+$ requires *m/z* 426.069, found 426.071.

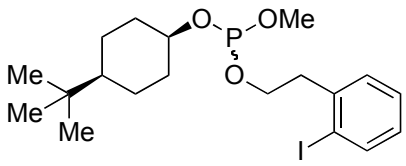
Reactions of compounds 13 and 14: Raw data for these experiments is highlighted in Supplemental Figure 1 and Supplemental Figure 2.

Compound 13



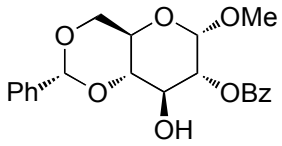
To a flame-dried 25 mL round bottom flask with magnetic stir bar was added 5-phenyl-1*H*-tetrazole (14.6 mg, 0.1 mmol), 10 mL dichloromethane, 4-phenyl-2-butanol (155 μL, 1.0 mmol), and then phosphoramidite **10b** (467 μL, 1.5 mmol). The reaction was allowed to stir under nitrogen for 10 minutes before the addition of phenylisocyanate (163 μL, 1.5 mmol). After 4 hours, the reaction was complete with >95% conversion of the starting material as indicated by ^{1}H-NMR (*see Supplemental Figure 1*). Water (20 μL) was added, and allowed to stir for 20 minutes to hydrolyze any remaining phosphoramidite, and then the entire reaction was added to a separatory funnel with saturated $NaHCO_3$. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were dried with anhydrous Na_2SO_4 filtered and concentrated. Various attempts to purify **13** were challenged by a propensity toward hydrolysis and oxidation on silica gel as well as difficulty to separate **13** from the *N,N*-diisopropyl-*N'*-phenylurea. Consequently, yields were highly variable, ranging from 39% - 73%. We found neutralization of the silica gel with 2% triethylamine in hexanes followed by elution with 5% ethyl acetate gave the best results with a 73 % yield of two diastereomers (both C- and P- stereogenic centers). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 1H), 7.23 – 7.14 (m, 4H), 7.13 – 7.07 (m, 3H), 6.85 – 6.78 (m, 1H), 4.19 – 4.09 (m, 1H), 3.99 – 3.89 (m, 2H), 3.41 (apparent dd, J = 12.4, 10.2 Hz, 3H), 3.00 (apparent q, J = 6.9 Hz, 2H), 2.70 – 2.60 (m, 1H), 2.59 – 2.50 (m, 1H), 1.89 – 1.79 (m, 1H), 1.75 – 1.65 (m, 1H), 1.19 (apparent dd, J = 8.0, 6.3 Hz, 3H); **^{31}P NMR** (202 MHz, $CDCl_3$) δ 139.5, 139.4; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.1, 142.0, 141.0, 141.0, 139.7, 130.6, 130.6, 128.6, 128.6, 128.5, 128.5, 128.4, 126.0, 100.8, 70.2, 70.2, 70.1, 70.1, 61.5, 61.4, 61.2, 61.1, 49.1, 49.1, 48.8, 48.8, 42.4, 42.4, 42.3, 40.1, 40.1, 40.1, 40.1, 32.0, 31.9, 22.8, 22.8, 22.8, 22.7.

Compound 14



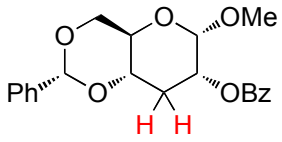
To a 25 mL flame-dried round bottom flask with magnetic stir bar was added *cis*-4-*tert*-butylcylcohexanol (TCI America, 156.3 mg, 1 mmol) followed by 5-phenyl-1*H*-tetrazole (14.6 mg, 0.1 mmol), dichloromethane (10 mL) and then phosphoramidite **10b** (467 μL, 1.5 mmol). The reaction was allowed to stir for 10 minutes under nitrogen before the addition of phenylisocyanate (163 μL, 1.5 mmol). After 4 hours, the reaction was complete with >95% conversion of the starting material as indicated by ^{1}H-NMR (100-200 μL sample of reaction added to 500 μL to $CDCl_3$, (*see Supplemental Figure 2*). To the reaction was added 30 μL water and allowed to stir for 20 minutes to consume remaining phosphoramidite. The entire reaction was then added to a separatory funnel with saturated $NaHCO_3$ and extracted 3 times with dichloromethane. The combined organics were dried with anhydrous Na_2SO_4, filtered and concentrated to give a crude mixture which was examined by ^{1}H-NMR (*see Supplemental Figure 2*). As observed previously with compound **13** a propensity toward hydrolysis and oxidation by column chromatrography as well as difficulty to separate **14** from the *N,N*-diisopropyl-*N'*-phenylurea led to varied yields. Purification on neutral alumina (5% ethyl acetate in hexanes) yielded 178.6 mg (0.385 mmol, 39%). Compound **14** was prepared previously by Koreeda and coworkers and was consistent with our characterization.[5]

Compound 15



Compound **13** was prepared according to a procedure described by Hung and coworkers and matched the characterization reported therein.[6]

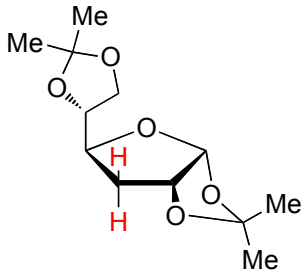
Compound 18



To a flame-dried 5 mL round bottom flask was added **15** (60 mg, 0.154 mmol), followed by 2 mL dry dichloromethane. The solution was placed under dry nitrogen, and phosphoramidite **10b** (71.9 µL, 0.23 mmol) was added followed by 5-phenyl-1*H*-tetrazole (2.3 mg, 0.015mmol). The solution was allowed to stir for 10 minutes under nitrogen before phenylisocyanate was added (27.5 µL, 0.23 mmol). The reaction was monitored by TLC (CAM stain) by adding an aliquot to a solution of 1% pyridine, 20% ethyl acetate in hexanes, and using the same solution for the mobile phase. After complete consumption of the starting material (R_f = 0.44, 3 hours) the reaction was poured into a flask containing saturated sodium bicarbonate, and extracted three times with dichloromethane. The combined organics were dried with anhydrous sodium sulfate, filtered and concentrated.

The crude material was then transferred to a 24 mL pressure tube, concentrated and place under high vacuum for at least 30 minutes. To this crude material was added azoisobutyronitrile (AIBN) (3.8 mg, 0.023 mmol) and 5.7 mL dry benzene. To this solution was added tributyltin hydride (90 µL, 0.32 mmol). The solution was sparged for 10 minutes with a heavy stream of nitrogen with an outlet before being sealed and placed in an 80 ˚C oil bath. After 2 hours the reaction was allowed to cool to room temperature, and to it was added DBU (48.3 µL, 0.32 mmol). A white precipitate immediately formed. The solution was allowed to stir for 20 minutes at room temperature before being filtered (solids washed 3x with anhydrous diethyl ether) and concentrated. The deoxygenated compound **18** was isolated in 77% yield (44.4 mg, 0.120 mmol) after silica gel chromatography (10% ethyl acetate in hexanes). A previous synthesis of C-3-d_1 **18** was reported by Liu and coworkers and was consistent with our characterization.[7]

Compound 17

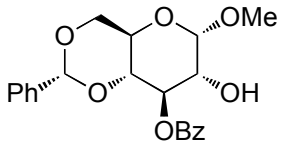


To a flame-dried 10 mL round bottom flask with stir bar was added 1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose (**16**, Sigma-Aldrich, 156 mg, 0.60 mmol) followed by 6 mL dry dichloromethane. The stirring solution was placed under dry nitrogen, and phosphoramidite **10b** (280 µL, 0.90 mmol) was added followed by phenyl tetrazole (9

mg, 0.06 mmol). The solution was allowed to stir for 10 minutes under nitrogen before phenylisocyanate was added (100 μL, 0.9 mmol). The reaction was monitored by TLC (CAM stain) by adding an aliquot to a solution of 1% pyridine, 50% ethyl acetate in hexanes, and using the same solution for the mobile phase. After complete consumption of the starting material (R_f = 0.57, 3 hours) the reaction was poured into a flask containing saturated sodium bicarbonate, and extracted three times with dichloromethane. The combined organics were dried with anhydrous Na_2SO_4, filtered and concentrated. The crude material was then transferred to a 24 mL pressure tube, concentrated *in vacuo*.

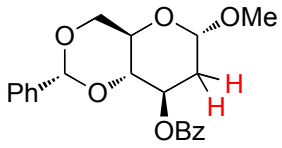
To this crude material was added AIBN (15 mg, 0.09 mmol) and 20 mL dry benzene. To this solution was added tributyltin hydride (350 μL, 1.26 mmol). The solution was sparged for 10 minutes with a heavy stream of nitrogen with an outlet before being sealed and placed in an 80 ˚C oil bath. After 2 hours the reaction was allowed to cool to room temperature, transferred to a round bottom flask and concentrated (product is too volatile for prolonged exposure to high vacuum!). The residue was redissolved in anhydrous ether (20 mL) and to it was added DBU (196 μL, 1.31 mmol). A white precipitate immediate formed. The solution was allowed to stir for 20 minutes at room temperature before being filtered (solids washed 3x with anhydrous diethyl ether then once with DCM) and concentrated. The deoxygenated compound **19** was isolated in 68% yield (100 mg, 0.409 mmol) after silica gel chromatography. Due to a very similar R_f for *N,N*-diisopropyl-*N'*-phenylurea, two silica gel columns were necessary for purification (5% diethyl ether in DCM). A previous synthesis of **19** was reported by Curran and coworkers and was consistent with our characterization.[8]

Compound 17



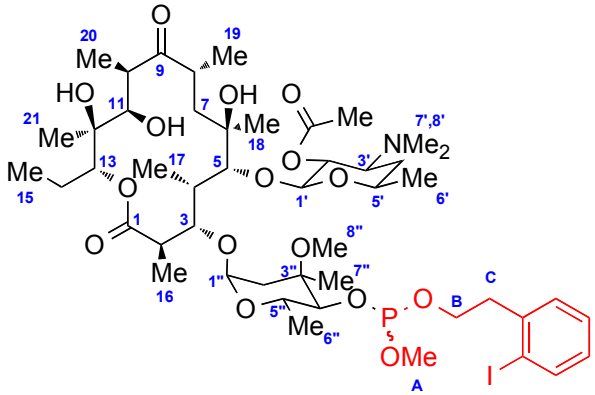
Compound **17** was prepared from the corresponding *bis*-benzoyl protected glucose via *mono*-deprotection as described by Nakazaki and coworkers using "condition B" as described therein.[9] The product isolated from various protected glucose species by silica gel chromatography (50% ethyl acetate in hexanes) followed by recrystallization from hot ethyl acetate. The characterization for compound **17** was consistent with what was previously reported by Ye and coworkers.[10]

Compound 20



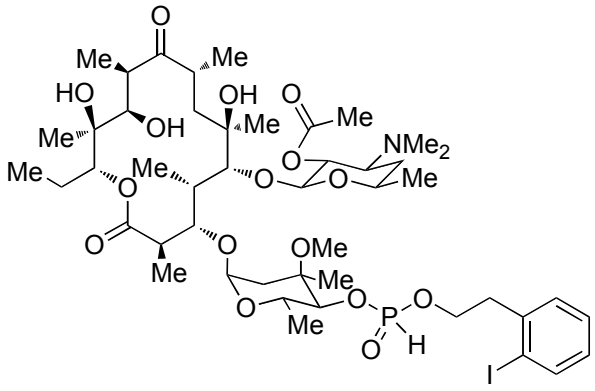
To a flame-dried 5 mL round bottom flask was added **17** (100 mg, 0.26 mmol), followed by 2.6 mL dry dichloromethane. The solution was placed under dry nitrogen, and phosphoramidite **10b** (113 µL, 0.36 mmol) was added followed by phenyl tetrazole (3.8 mg, 0.026 mmol). The solution was allowed to stir for 10 minutes under nitrogen before phenylisocyanate was added (39 µL, 0.36 mmol). The reaction was monitored by TLC by adding an aliquot to a solution of 1% pyridine, 50% ethyl acetate in hexanes, and using the same solution for the mobile phase. After complete consumption of the starting material (R_f = 0.59, 2.5 hours, CAM stain) the reaction was poured into a flask containing saturated sodium bicarbonate, and extracted three times with dichloromethane. The combined organics were dried with anhydrous sodium sulfate, filtered and concentrated. The crude material was then transferred to a 24 mL pressure tube, concentrated and placed under high vacuum for at least 30 minutes. To this crude material was added AIBN (6 mg, 0.036 mmol) and 11 mL dry benzene. To this solution was added tributyltin hydride (141 µL, 0.51 mmol). The solution was sparged for 10 minutes with a heavy stream of nitrogen with an outlet before being sealed and placed in an 80 ˚C oil bath. After 2 hours the reaction was allowed to cool to room temperature, transferred to a round bottom flask and concentrated. The residue was concentrated and added directly to a silica gel column (5%-10% ethyl acetate in hexanes). The deoxygenated compound **20** was coeluted with *N,N*-diisopropyl-*N'*-phenylurea as a 1:1 mixtures. Pure **20** was isolated by reverse phase chromatography (Biotage SP4 instrument C18 SNAP 30g, 30-100% acetonitrile in water) in 67% yield (64.4 mg, 0.174 mmol). A previous synthesis of **20** was reported by Thiem and coworkers and was consistent with our characterization.[11]

Compound 21

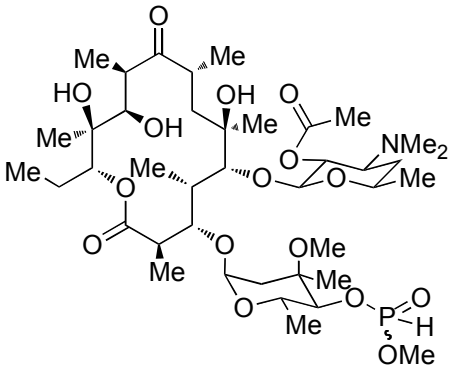


*Due to the apparent high rate of hydrolysis of **10b** in the presence of tetrazole catalysts, a stock solution of 2'-acetylerythromycin A was first dissolved in reaction solvent and dried with activated 4 Å molecular sieves (see below)*. To an oven-dried 4 mL vial was added 2′-acetylerythromycin A (151 mg, 0.195 mmol) followed by 2 mL anhydrous

dichloromethane. Upon complete dissolution, 5-10 pellets of activated 4 Å molecular sieves we added and the solution was allowed to stand for 10-15 minutes before 1.4 mL (106 mg 2′-acetylerythromycin A, 0.136 mmol) was transferred to another oven-dried 4 mL vial with magnetic stir bar. To this solution was added phenyl tetrazole (2 mg, 0.014 mmol) followed by **10b** (51 μL, 0.168 mmol). The solution was stirred for 10 minutes at room temperature before the addition of phenylisocyanate (17.7 μL, 0.168 mmol). The solution was stirred at room temperature for 22 hours before checking the reaction progress by ^{31}P-NMR (50 μL reaction in 600 μL $CDCl_3$), which indicated a complete absence of the phosphoramidite (δ 147.5 ppm) and the presence of two phosphorous chemical shifts indicative of an epimeric phosphite product (δ 144.0 and 143.2 ppm) as well as the chemical shift corresponding to the hydrolyzed phosphoramidite (9.0 ppm). The reaction was poured into a separatory funnel with dichloromethane and saturated $NaHCO_3$, extracted three times with dichloromethane, dried with Na_2SO_4 and concentrated. The crude material was purified by silica gel chromatography by first neutralizing the silica gel with a solution of 2% triethylamine in DCM, then equilibrating the column with a solution of 1% pyridine, 1% 2-propanol in DCM. The product was loaded and eluted with 1% pyridine, 1% 2-propanol in DCM. Fractions containing product were pooled, concentrated and then azeotroped with toluene to remove residual pyridine to give 123 mg (83% yield) of **21**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H, *arene*), 7.28 – 7.22 (m, 2H, *arene*), 6.94 – 6.86 (m, 1H, *arene*), 5.05 (apparent dt, J = 10.9, 1.9 Hz, 1H, *13*), 4.94 – 4.88 (m, 1H, *1″*), 4.78 – 4.64 (m, 2H, *2′, 1′*), 4.31 – 4.20 (m, 1H, *5″*), 4.10 – 3.83 (m, 2H, *B*), 3.92 – 3.87 (m, 2H, *3, 11-OH*), 3.78 (s, 1H, *11*), 3.77 – 3.68 (m, 1H, *5′*), 3.58 – 3.50 (m, 1H, *4″*), 3.50 – 3.40 (m, 4H, *5, A*), 3.33 (apparent d, 3H, *8″*), 3.10 (s, 1H, *12-OH*), 3.09 – 3.06 (m, 1H, *10*), 3.04 (t, J = 7.1 Hz, 2H, *C*), 2.92 – 2.81 (m, 1H, *2*), 2.72 – 2.59 (m, 2H, *3′, 8*), 2.40 – 2.32 (m, 1H, $2''_{eq}$), 2.23 (d, 6H, *7′, 8′*), 2.04 (s, 3H, *Ac*), 1.97 – 1.81 (m, 2H, $4, 14_{eq}$), 1.75 (m, 1H, 7_{ax}), 1.68 – 1.56 (m, 2H, 7_{eq}, $4'_{eq}$), 1.56 – 1.50 (m, 1H, $2''_{ax}$), 1.50 – 1.44 (m, 1H, 14_{ax}), 1.42 (apparent d, 3H, *18*), 1.29 – 1.22 (m, 1H, $4'_{ax}$), 1.23 – 1.10 (m, 21H, *6″, 16, 19, 6′, 20, 7″, 21*), 0.97 – 0.92 (m, 3H, *17*), 0.86 – 0.81 (m, 3H, *15*); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 222.2, 175.6, 170.1, 140.8, 140.6, 139.7, 139.6, 130.6, 130.4, 128.6, 128.5, 128.4, 128.4, 100.7, 100.4, 100.3, 96.1, 96.0, 83.5, 83.4, 81.8, 81.7, 81.7, 81.6, 79.4, 79.3, 76.8, 75.0, 75.0, 74.7, 73.1, 72.0, 69.1, 67.7, 67.6, 64.5, 64.5, 64.4, 63.4, 61.8, 61.7, 60.6, 60.5, 49.5, 49.4, 49.3, 48.2, 48.1, 45.3, 44.8, 42.5, 42.4, 42.2, 42.1, 40.8, 39.1, 38.0, 38.0, 35.8, 35.7, 30.8, 30.7, 27.0, 22.1, 22.1, 22.0, 22.0, 21.6, 21.6, 21.5, 21.3, 18.9, 18.3, 16.4, 16.1, 12.1, 10.7, 9.2; **^{31}P NMR** (202 MHz, $CDCl_3$) δ 143.9, 143.1; **IR** (ATR, cm^{-1}) 3518, 2971, 2940, 2881, 2833, 1737, 1455, 1369, 1346, 1240, 1168, 1047, 1001, 894; **TLC** (R_f = 0.19, 2.5% 2-propanol, 1% pyridine in DCM, CAM stain); **MS** (ESI): Due to the acid instability of phosphites under LCMS conditions, we did not observe intact **21** by LC-MS. We did observe the following expected phosphite hydrolysis products (see below); mass calculated for $[C_{45}H_{77}INO_{16}P]H^+$ requires *m/z* 1070.410, found 1070.407; mass calculated for $[C_{40}H_{72}NO_{16}P]H^+$ requires *m/z* 854.466, found 854.470.

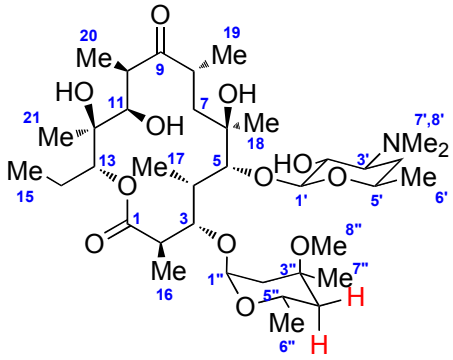


Chemical Formula: $C_{47}H_{77}INO_{16}P$



Chemical Formula: $C_{40}H_{72}NO_{16}P$

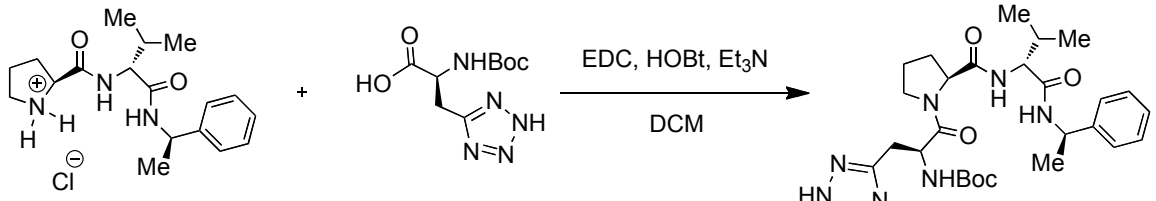
4′-Deoxyerythromycin A (Compound 22)



To a flame-dried pressure tube was added **21** (113 mg, 0.104 mmol), AIBN (1.7 mg, 0.010 mmol) and 3.8 mL dry benzene. Upon complete dissolution of the solids, tributyltin hydride was added (38.7 µL, 0.146 mmol) and the solution was sparged with a heavy stream of dry nitrogen with an outlet for ten minutes. The reaction tube was sealed and placed in an 80 ˚C oil bath for two hours. Upon cooling to room temperature the reaction was concentrated and loaded onto a silica gel column prepared with 1% NH_4OH (14 N_{aq}), 5% MeOH in DCM. The product (2′-acetyl-4″-deoxyerythromycin A) was eluted with 1% NH_4OH (14 N_{aq}), 5% MeOH in DCM. Fractions containing product were concentrated and then redissolved in 7 mL methanol and stirred at room temperature to remove the acetyl group. After three days the reaction was concentrated and loaded onto a silica gel column prepared with 1% NH_4OH (14 N_{aq}), 5% MeOH in DCM, and eluted with the same solvent mixture to give 63 mg (0.088 mmol, 84% yield) of 4″-deoxyerythromycin A. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.02 (dd, *J* = 10.9, 2.1 Hz, 1H, *13*), 4.98 (d, *J* = 4.7 Hz, 1H, *1″*), 4.50 (d, *J* = 7.3 Hz, 1H, *1′*), 4.30 – 4.22 (m, 1H, *5″*), 3.95 (d, *J* = 9.3 Hz, 1H, *3*), 3.94 – 3.89 (m, 1H, *11-OH*), 3.81 (s, 1H, *11*), 3.57 (d, *J* = 7.3 Hz, 1H, *5*), 3.54 – 3.45 (m, 1H, *5′*), 3.23 (s, 3H, *8″*), 3.18 (dd, *J* = 10.2, 7.3 Hz, 1H, *2′*), 3.11 (s, 1H, *12-OH*), 3.06 (dd, *J* = 13.8, 6.8 Hz, 1H, *10*), 2.86 (dq, *J* = 14.5, 7.1 Hz, 1H, *2*), 2.72 – 2.62 (m, 1H, *8*), 2.47 (td, *J* = 12.3, 3.7 Hz, 1H, *3′*), 2.26 (s, 6H, *7′, 8′*), 2.19 (d, *J* = 14.7 Hz, 1H $2''_{eq}$), 2.00 – 1.84 (m, 3H, *4, 14*$_{eq}$, 7_{ax}), 1.72 – 1.56 (m, 3H, $4'_{eq}$, 7_{eq}, $4''_{eq}$),

1.50 – 1.43 (m, 1H, *14$_{ax}$*), 1.42 (s, 3H, *18*), 1.39 (dd, *J* = 14.8, 5.1 Hz, 1H, *2″$_{ax}$*), 1.26 (dd, *J* = 13.4, 11.5 Hz, 1H, *4″$_{ax}$*), 1.19 (m, *J* = 3.5 Hz, 1H, *4′$_{ax}$*), 1.17 (d, COSY, 3H, *16*), 1.16 (d, COSY, 3H, *6′*), 1.14 (d, COSY, 3H, *6″*), 1.13 (d, COSY, 3H, *19*), 1.12 (d, COSY, 3H, *20*), 1.11 (s, HSQC, 3H, *7″*), 1.10 (d, COSY, 3H, *17*), 1.10 (s, COSY, 3H, *21*) 0.82 (t, *J* = 7.4 Hz, 3H, *15*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 221.8 (*9*), 176.0 (*1*), 102.7 (*1′*), 97.1 (*1″*), 83.2 (*5*), 79.3 (*3*), 76.9 (*13*), 74.9 (*6*), 74.8 (*12*), 71.1 (*2′*), 70.5 (*3″*), 69.0 (*11*), 68.6 (*5′*), 65.4 (*3′*), 61.5 (*5″*), 49.5 (*8″*), 45.6 (*4″*), 45.3 (*8*), 44.9 (*2*), 40.3 (*7′,8′*), 39.3 (*4*), 38.5 (*7*), 38.1 (*10*) 34.3 (*2″*), 28.8 (*4′*), 26.9 (*18*), 25.6 (*7″*), 22.0 (*6′*), 21.5 (*6″*), 21.3 (*14*), 18.4 (*19*), 16.3 (*21*), 16.0 (*16*), 12.1 (*20*), 10.8 (*15*), 9.3 (*17*). **IR** (ATR, cm^{-1}) 3494, 2970, 2936, 2878, 2828, 1734, 1715, 1458, 1377, 1349, 1334, 1276, 1162, 1108, 1032, 1009, 997, 975, 957, 913; **$[\alpha]_D$** = -65.6 (c = 0.5, $CDCl_3$); **TLC** (R_f = 0.36, 1% NH_4OH (14 N_{aq}), 10% methanol, in DCM); **MS** (ESI): calculated for $[C_{37}H_{67}NO_{12}]H^+$ requires *m/z* 718.474, found 718.456.

Synthesis of Peptide 24



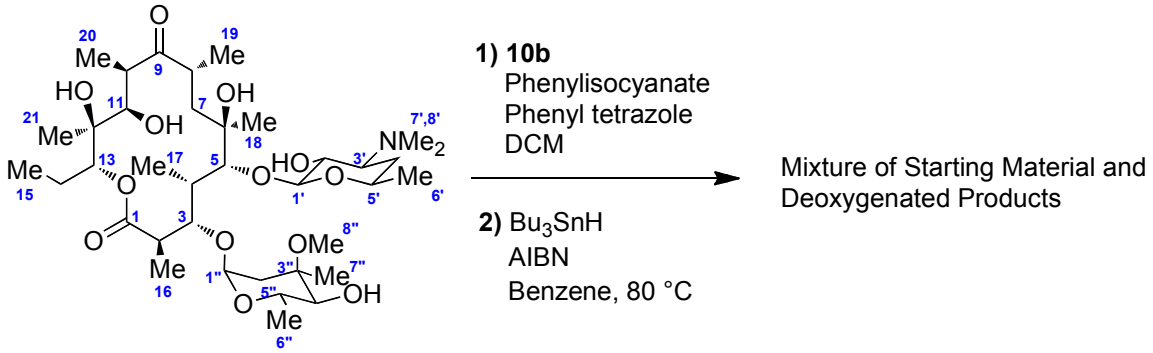
Pro-(D)Val-(R)Mba(HCl **Boc-Atz** **24**

The peptide dimer, H-Pro-(D)Val-(R)Mba•HCl, was synthesized using standard solution phase peptide chemistry with Boc amino acids. One equivalent of each coupling partner (e.g. Boc-(D)Val-OH and (R)-α-methyl benzylamine), 1.1 equivalents each of EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) and HOBt (hydroxybenzotriazole) and 1.2 equivalents of triethylamine (or Hünig's base) are combined with dichloromethane to make a 0.15 M solution that is stirred over night at room temperature. The following day the reaction is diluted with dichloromethane, washed with 10% aqueous citric acid, water, and saturated aqueous sodium bicarbonate. The organic layer is dried with anhydrous $MgSO_4$, filtered and concentrated. Prior to the next coupling step, the Boc protecting group is removed by stirring for 30 minutes with an excess (>10 equivalents) of 4 N HCl in dioxanes. The residual acid is then removed by a heavy stream of nitrogen and high vacuum.

To prepare peptide **24**, H-Pro-(D)Val-(R)Mba•HCl (0.425 g, 1.2 mmol) was stirred with Boc-Atz[12] (0.334 g, 1.3 mmol), EDC (0.299 g, 1.3 mmol), HOBt (0.239 g, 1.3 mmol) and triethylamine (0.435 mL, 3.12 mmol) in 6 mL dichloromethane overnight. The solution was concentrated and loaded onto a silica gel column and eluted with 1% acetic acid, 5% methanol in dichloromethane. Fractions containing peptide were collected, concentrated and further purified by reverse phase chromatrography (Biotage SP4 instrument (C18HS SNAP 30g, 10-100% acetonitrile in water with 0.1% TFA over) giving 0.280 g purified peptide (0.503 mmol, 42% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.06 (m, 5H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.36 (d, *J* = 7.9 Hz, 1H), 5.20 – 5.04 (m, 1H), 4.82 – 4.64 (m, 1H), 4.54 (br s, 1H), 4.23 (t, *J* = 7.6 Hz, 1H), 3.69 (dd, *J* = 15.9, 7.2 Hz, 1H), 3.39 – 3.14

(m, 2H), 3.06 (dd, J = 14.6, 6.4 Hz, 1H), 2.30 – 1.82 (m, 5H), 1.53 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 0.91 (d, J = 6.3 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 171.0, 170.6, 155.1, 142.8, 128.7, 127.6, 126.3, 80.8, 60.6, 59.7, 50.3, 49.6, 47.7, 30.7, 28.6, 28.4, 27.2, 25.3, 21.6, 19.4, 18.2; **IR** (ATR, cm^{-1}) 3293, 2973, 2934, 2876, 1699, 1632, 1522, 1496, 1446, 1391, 1367, 1245, 1160, 1052, 1018; **HPLC** t_R = 18.7 min (Phenomenex Luna 4.6x250 mm) on a gradient of 20 – 95% acetonitrile/water with 0.1% formic acid over 20 minutes; **$[\alpha]_D$** = -1.1 (c = 0.5, $CDCl_3$) **MS** (ESI+): calculated for $[C_{27}H_{40}N_8O_5 + H]+$ requires *m/z* 557.319, found 557.322.

Phenyl tetrazole catalyzed phosphitylation and deoxygenation of erythromycin A

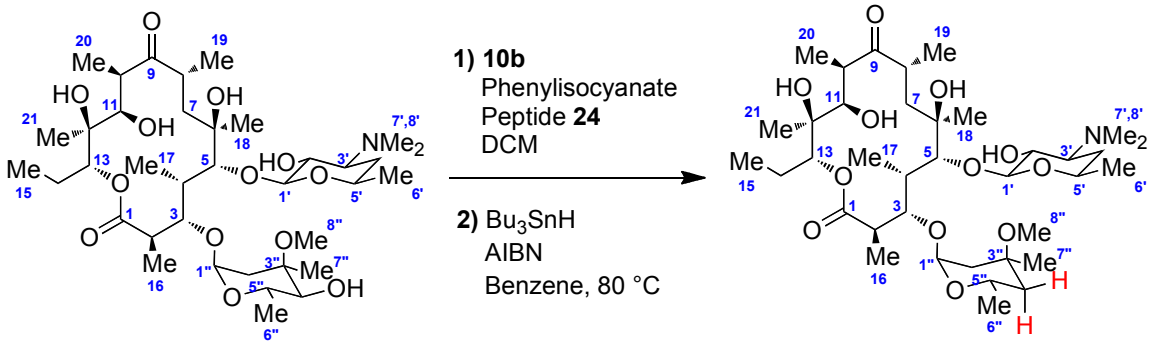


*Due to the apparent high rate of hydrolysis of **10b** in the presence of tetrazole catalysts, a stock solution of erythromycin A was first dissolved in reaction solvent and dried with activated 4 Å molecular sieves (see below).* To an oven-dried 4 mL vial was added 228.5 mg of erythromycin A followed by dry 4 mL dichloromethane and 5-10 pellets of activated 4 Å molecular sieves. This solution was allowed to stand for 10-15 minutes and then 3.5 mL (200 mg erythromycin A, 0.272 mmol) was transferred to another oven-dried 4 mL vial with stir bar. To this solution was added phenyl tetrazole (4 mg, 0.027 mmol) followed by **10b** (102 µL, 0.327 mmol). The solution was allowed to stir for 10 minutes at room temperature before the addition of phenylisocyanate (35.5 µL, 0.327 mmol). After 5 hours the reaction was checked by TLC (CAM stain, 10% methanol, 1% pyridine in DCM) by taking an aliquot of reaction and adding it to 1% pyridine, 5% 2-propanol in DCM). TLC indicated almost complete consumption of starting material. The solution was poured into a separatory funnel with saturated $NaHCO_3$ and extracted three times with dichloromethane. The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated. The crude mixture was examined by ^{31}P-NMR, which was characteristic of the unselective reaction seen previously (***see Supplemental Figure 3***).

The crude material was then transferred to a 15 mL pressure tube and concentrated. AIBN (5.4 mg, 0.033 mmol) and 10 mL anhydrous benzene was added. Upon complete dissolution, tributyltin hydride was added (127 µL, 0.458 mmol) and the solution was sparged with nitrogen for 10 minutes before being sealed and placed in an 80 ˚C oil bath for two hours. Upon cooling to room temperature, the reaction mixture was loaded directly onto a silica gel column (1% 14 N NH_4OH_{aq}, 2% MeOH in DCM) and eluted with a methanol gradient up to 5%. Due to the inseparable complex mixture of products, the fractions containing all the deoxygenated species and starting material were pooled (136 mg total) and analyzed by ^{1}H-NMR (***see Supplemental Figure 4***) which indicated that the 2′-deoxyerythromycin A was the dominant product and the 4″-

deoxyerythromycin A only a minor component of the mixture. By LCMS, three erythromycin A masses were present corresponding to the monodeoxygenatated (requires 718.374, found 718.461), bisdeoxygenated (requires 702.479, found 702.474) and erythromycin A (requires 734.469, found 734.462).

Peptide-catalyzed phosphitylation and deoxygenation of erythromycin A



*Due to the apparent high rate of hydrolysis of **10b** in the presence of tetrazole catalysts, a stock solution of erythromycin A was first dissolved in reaction solvent and dried with activated 4 Å molecular sieves (see below).* To an oven-dried 4 mL vial was added 228.5 mg of erythromycin A followed by 4 ml dry dichloromethane and 5-10 pellets of activated 4 Å molecular sieves. This solution was allowed to stand for 10-15 minutes and then 3.5 mL (200 mg erythromycin A, 0.272 mmol) was transferred to another oven-dried 4 mL vial with stir bar. To this solution was added peptide catalyst **24** (15 mg, 0.027 mmol) followed by **10b** (127 µL, 0.408 mmol). The solution was allowed to stir for 10 minutes at room temperature before the addition of phenylisocyanate (44.6 µL, 0.408 mmol). The reaction was monitored by TLC (CAM stain) by adding a few drops of reaction to a solution of 1% pyridine, 2.5% 2-propanol in DCM and running the TLC against starting material (1% pyridine, 10% methanol in DCM). After 6.5 hours the reaction was complete as indicated by the consumption of starting material, and to it was added 100 µL water to consume remaining phosphoramidite. The reaction was added to a separatory funnel containing saturated $NaHCO_3$ and extracted three times with dichloromethane. The organic phases were pooled, dried and concentrated and inspected by ^{31}P-NMR, which was characteristic of the 4"-selectivity observed previously (***see Supplemental Figure 3***). The crude material was then transferred (with benzene) to a 15 mL flame-dried sealed tube and enough benzene was added to make 10 mL of solvent. AIBN (6.7 mg, 0.041 mmol) and tributyltin hydride (151 µL, 0.571 mmol) were added and the solution was sparged with dry nitrogen at room temperature for 15 minutes. The tube was sealed and transferred to an 80 ˚C oil bath for two hours, cooled to room temperature and concentrated and loaded onto a column prepared with 1% NH_4OH (14 N_{aq}), 1% MeOH in dichloromethane. Product was eluted with a gradient of 1% NH_4OH (14 N_{aq}) and 1-5% MeOH in dichloromethane. Yields typically ranged between 50-60%, and the ^{1}H-NMR of purified 4″-deoxyerythromycin A was consistent with previously reported spectra (see above).

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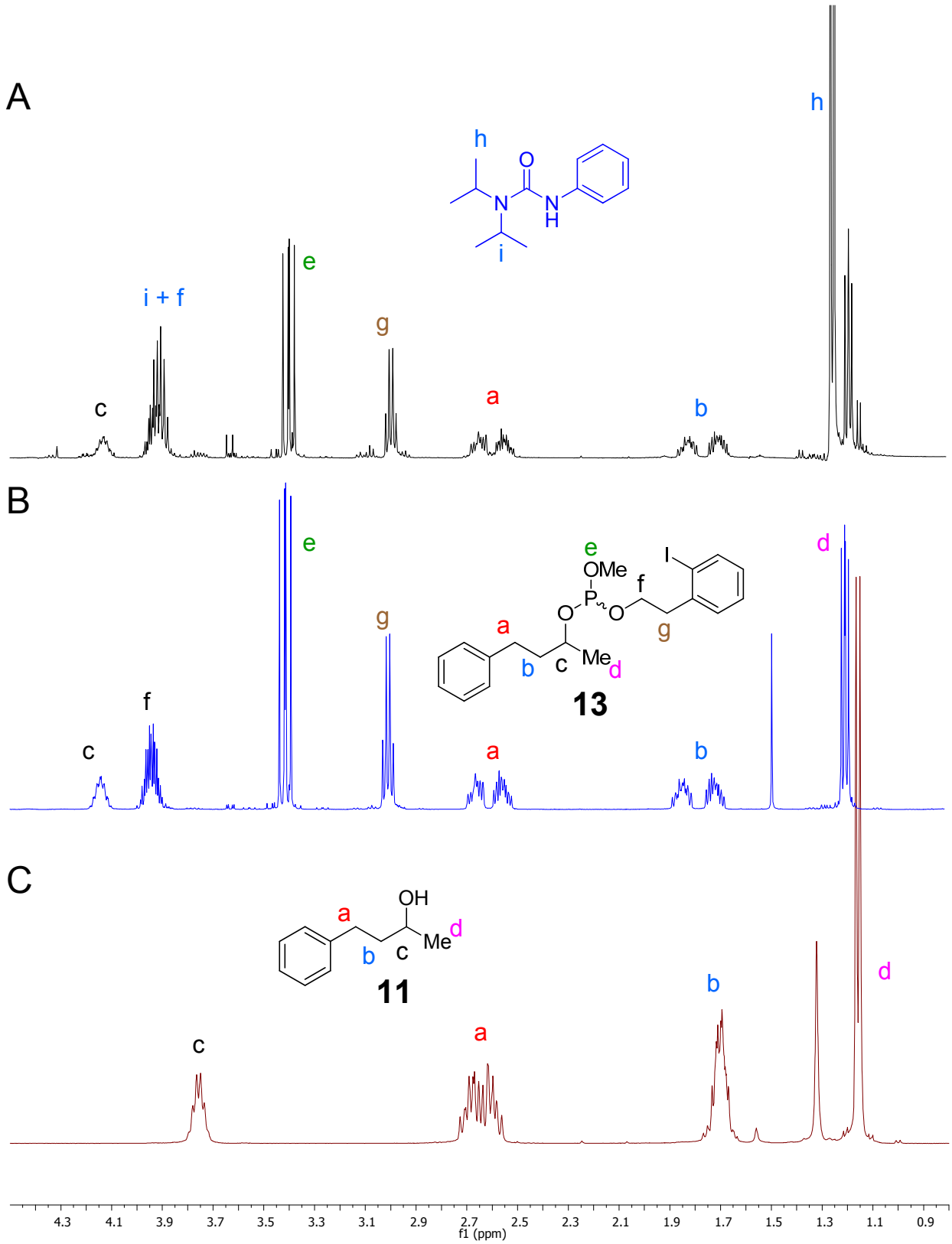
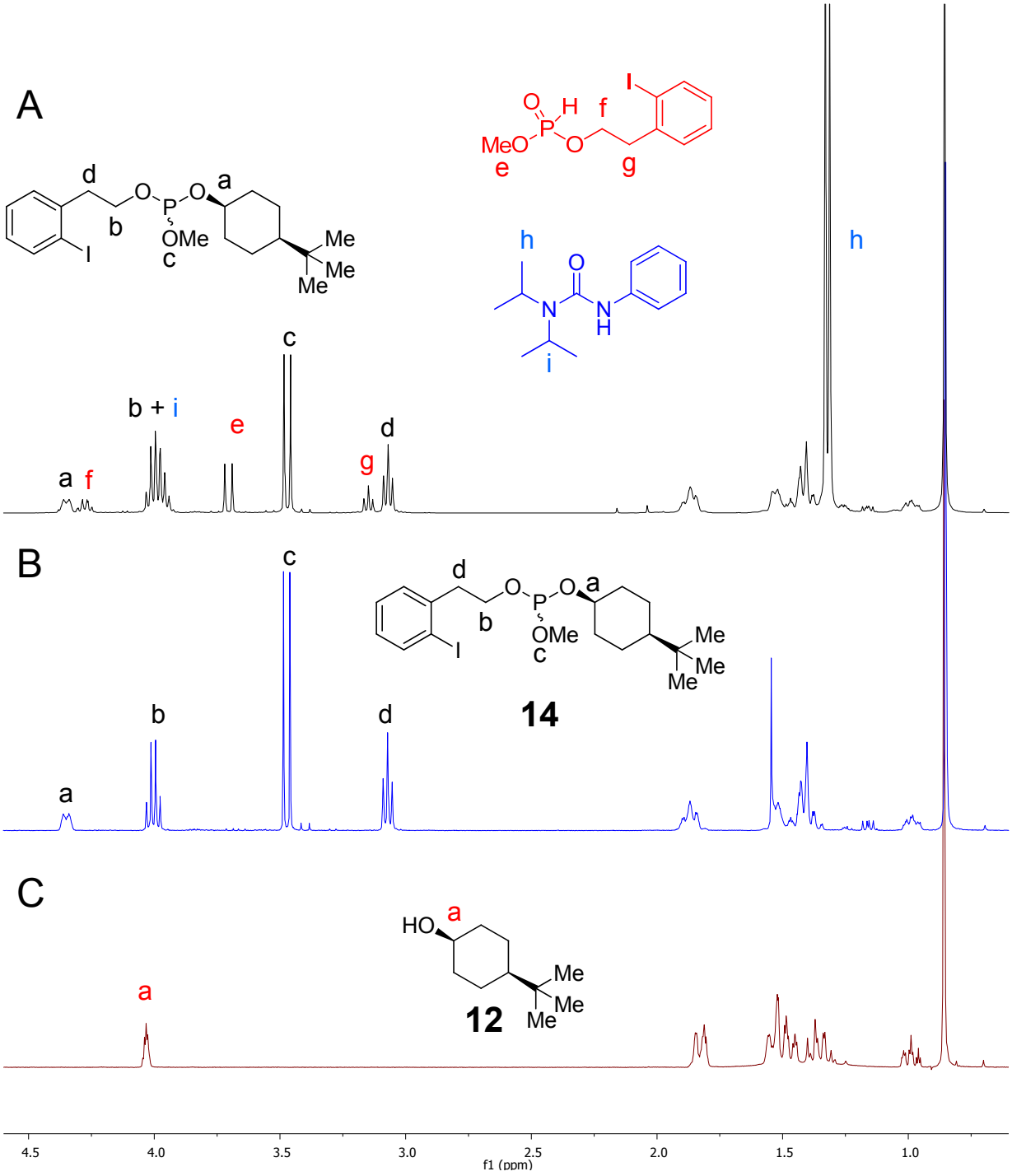
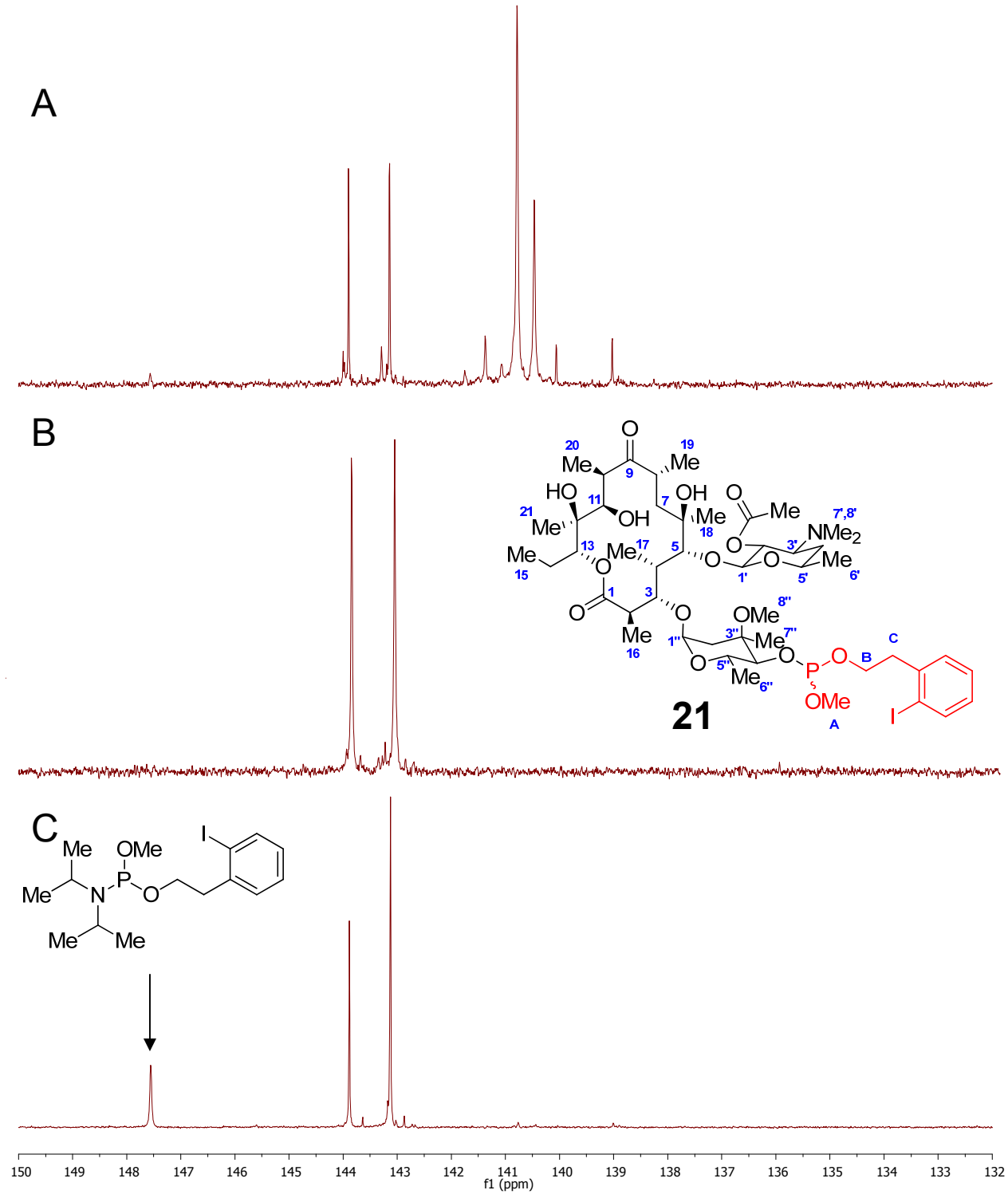


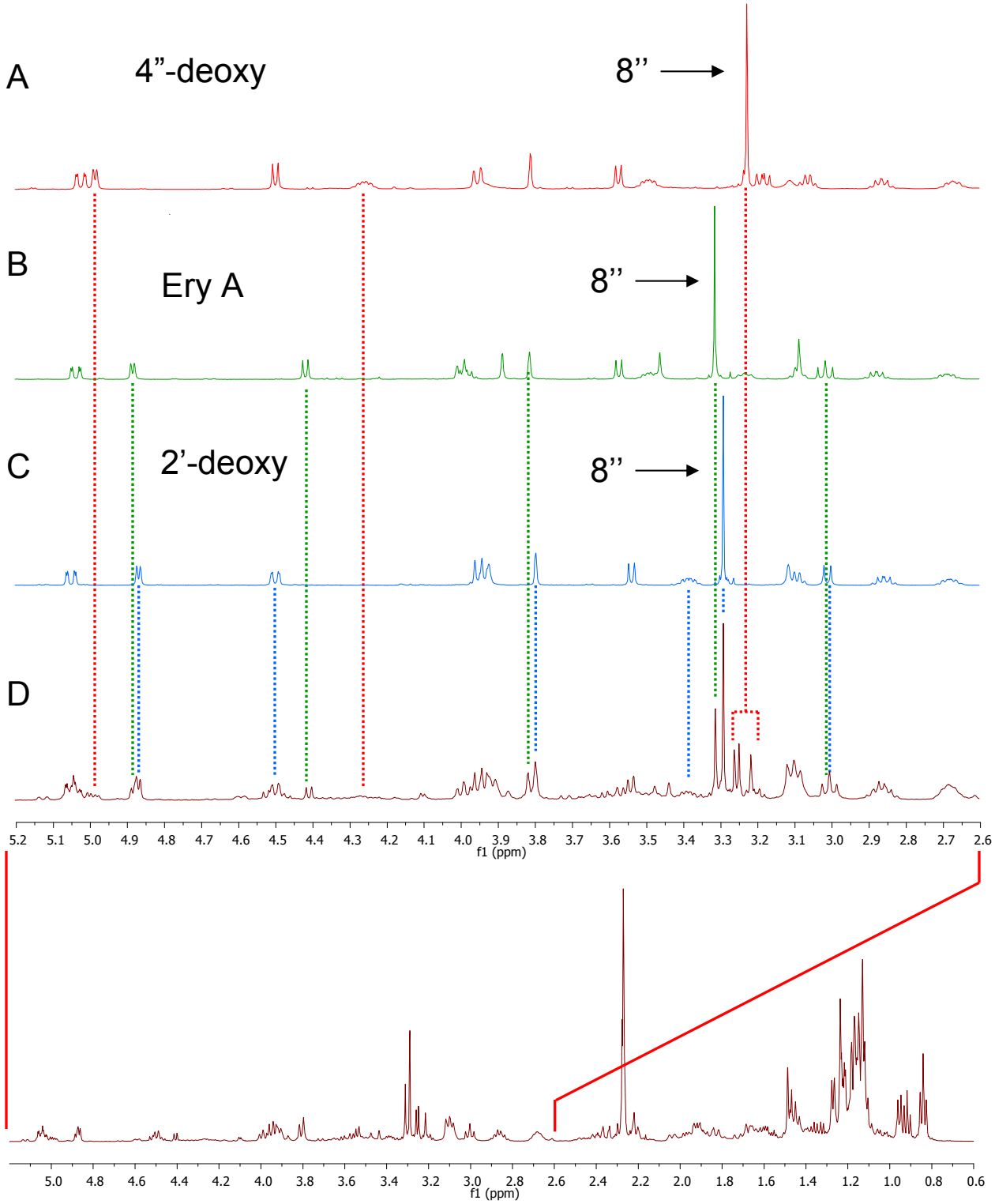
Supplemental Figure 1: Representative ^{1}H NMR ($CDCl_3$) of a crude reaction mixture after 4 hours where compound **11** undergoes the phenyl tetrazole catalyzed phosphitylation. A small sample of reaction mixture (100-200 µL) was added to 500 µL $CDCl_3$. Trace **A** represents the crude reaction mixture. Traces **B** and **C** represent the phosphite product **13** and starting material, respectively. A greater than 95% yield is estimated based upon the complete disappearance of characteristic peaks corresponding to starting material.



Supplemental Figure 2: Representative ^{1}H-NMR ($CDCl_3$) of a crude reaction mixture after 4 hours where compound **12** undergoes the phenyl tetrazole catalyzed phosphitylation. Trace **A** represents the crude reaction mixture which contains compound **14**, hydrolyzed phosphoramidite and diisopropyl phenyl urea (product of amine scavenging). Traces **B** and **C** represent the purified phosphite product **14** and starting material, respectively. A greater than 95% yield is estimated based upon the complete disappearance of characteristic peaks corresponding to starting material.

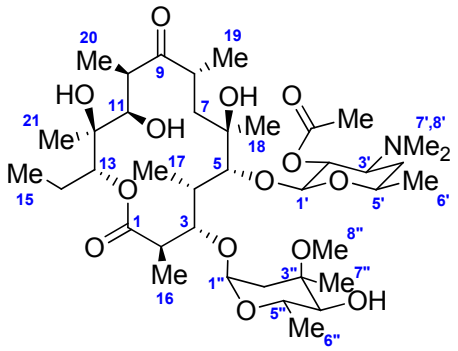


Supplemental Figure 3: Phosphorous NMR spectra of erythromycin A-phosphite products described in the text. Trace **A** is a representative example of the phosphite product distribution when phenyl tetrazole is employed as the catalyst. Two intense peaks between 140 and 141 ppm were proposed to be the 2'-regioisomer, as this is the major product upon deoxygenation (see Supplemental Figure 4). Trace **B** represents the phosphite chemical shift for compound **21**. Note that due to the phosphorous stereogenic center, each regioisomer produces two epimeric phosphorous signals. Trace **C** represents the typical regioselectivity when peptide catalyst **24** is employed.



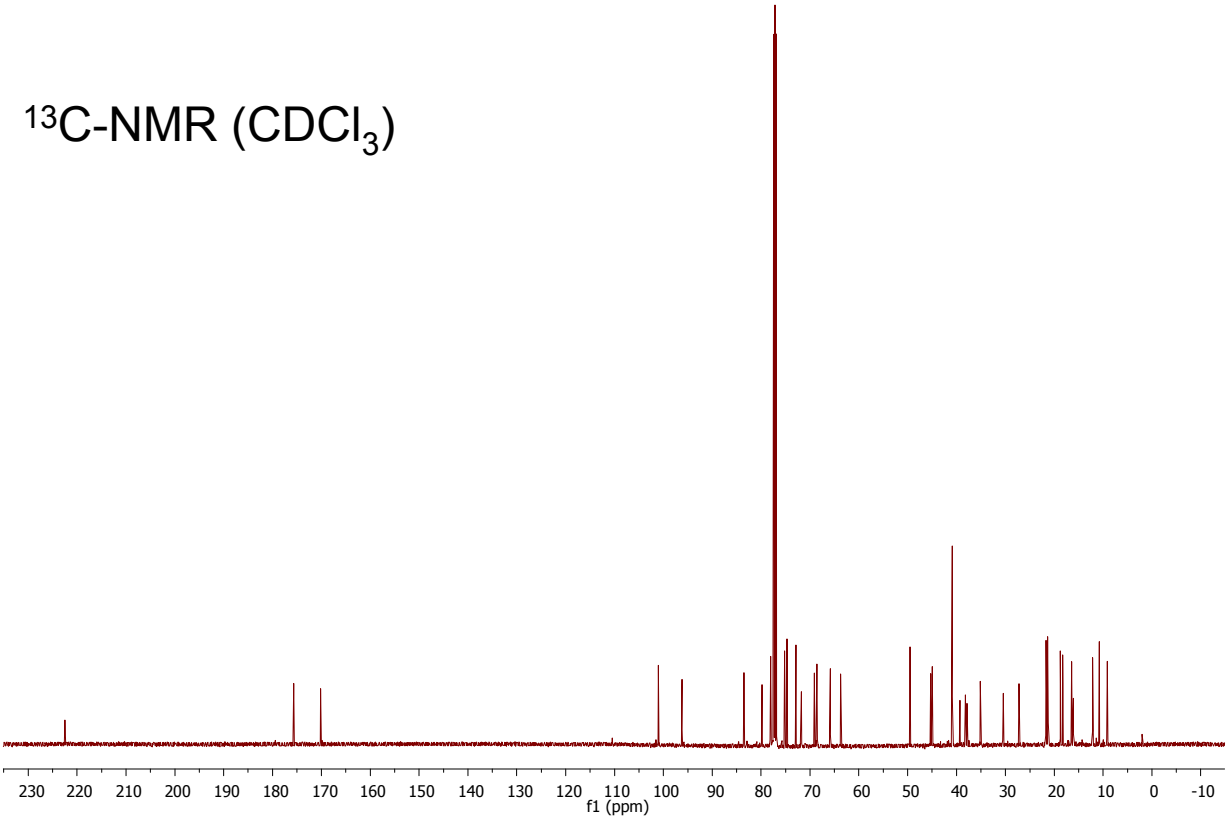
Supplemental Figure 4: Analysis of the crude mixture of deoxygenated products following the unselective phenyl tetrazole catalyzed phosphitylation of erythromycin A. Shown are 4’’-deoxyerythromycin A (**A**), erythromycin A (**B**), 2’-deoxyerythromycin A (**C**), and the crude mixture following unselective deoxygenation (**D**). Diagnostic features are traced with a colored dotted line from the parent spectrum to their corresponding location in the crude mixture. The methyl (-OMe) peak (8’’, cladinose) is the most informative of product distribution, showing 2’-deoxyerythromycin A to be the most abundant species followed by starting material. Little 4’’-deoxyerythromycin A appears to be present, and it could not be definitely identified in the crude mixture, presumably due to the existence of *bis*-deoxy products, as was observed by LCMS. A nominal product distribution of 3:1 can be inferred by assuming one of these three minor peaks between 3.20 and 3.27 ppm (each of equal area) represents 4’’-deoxyerythromycin A.

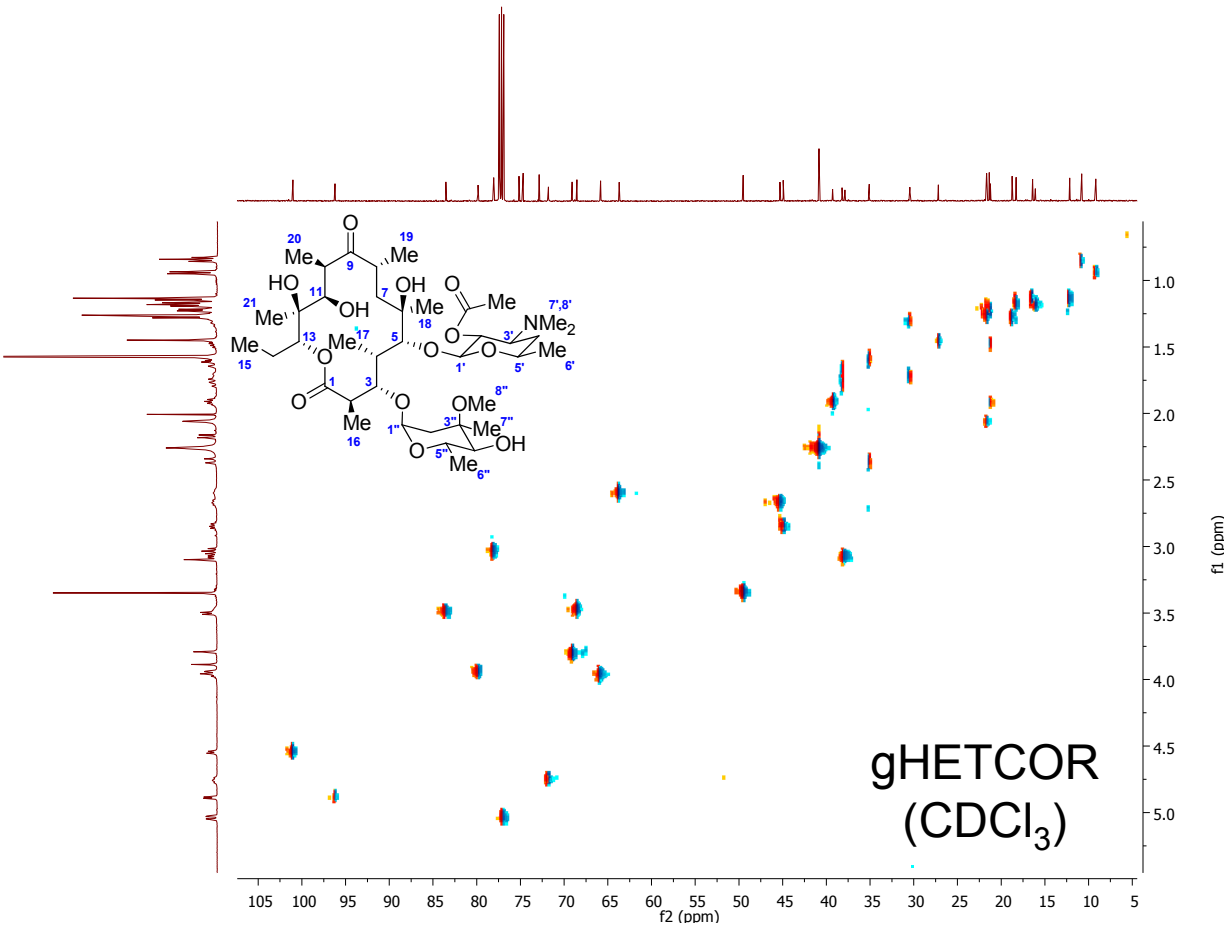
^{1}H-NMR ($CDCl_3$)



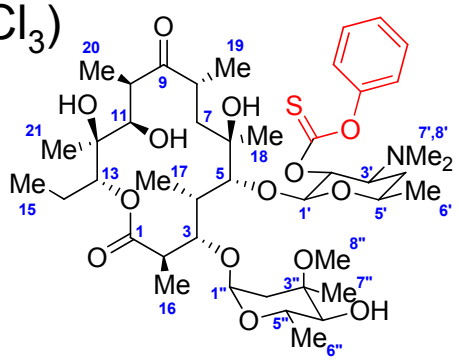
2‘-acetylerythromycin A

^{13}C-NMR ($CDCl_3$)



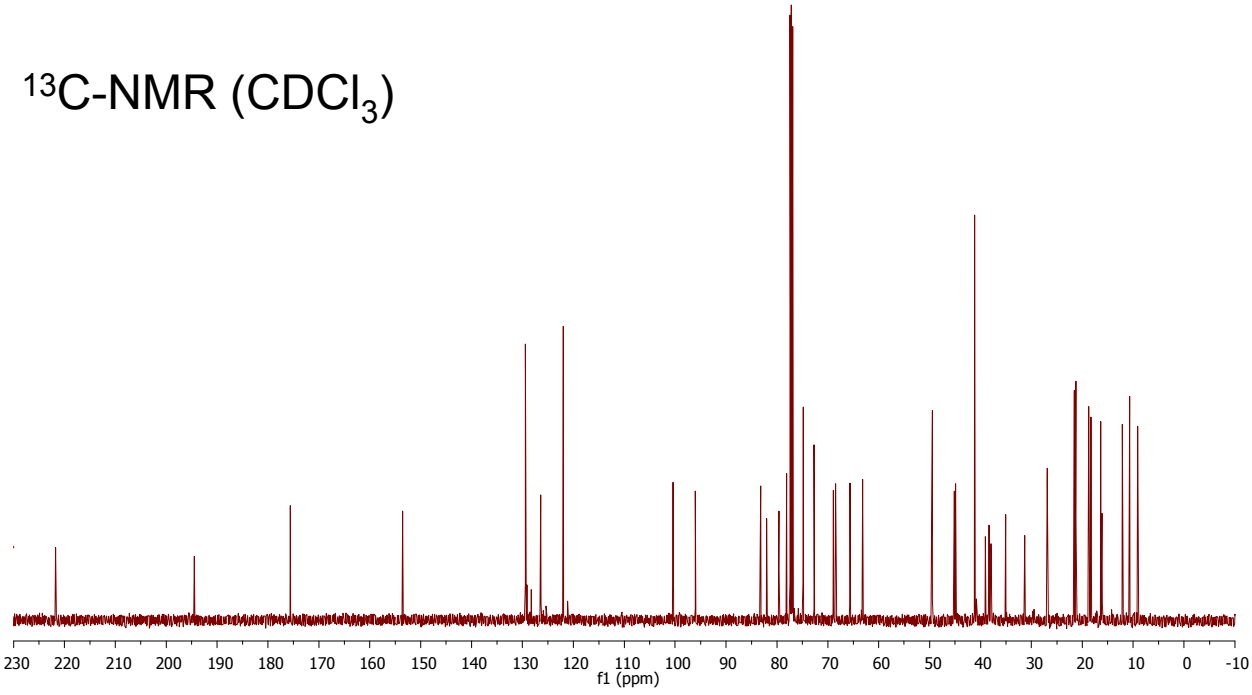

gHETCOR
(CDCl3)
f2 (ppm)
f1 (ppm)

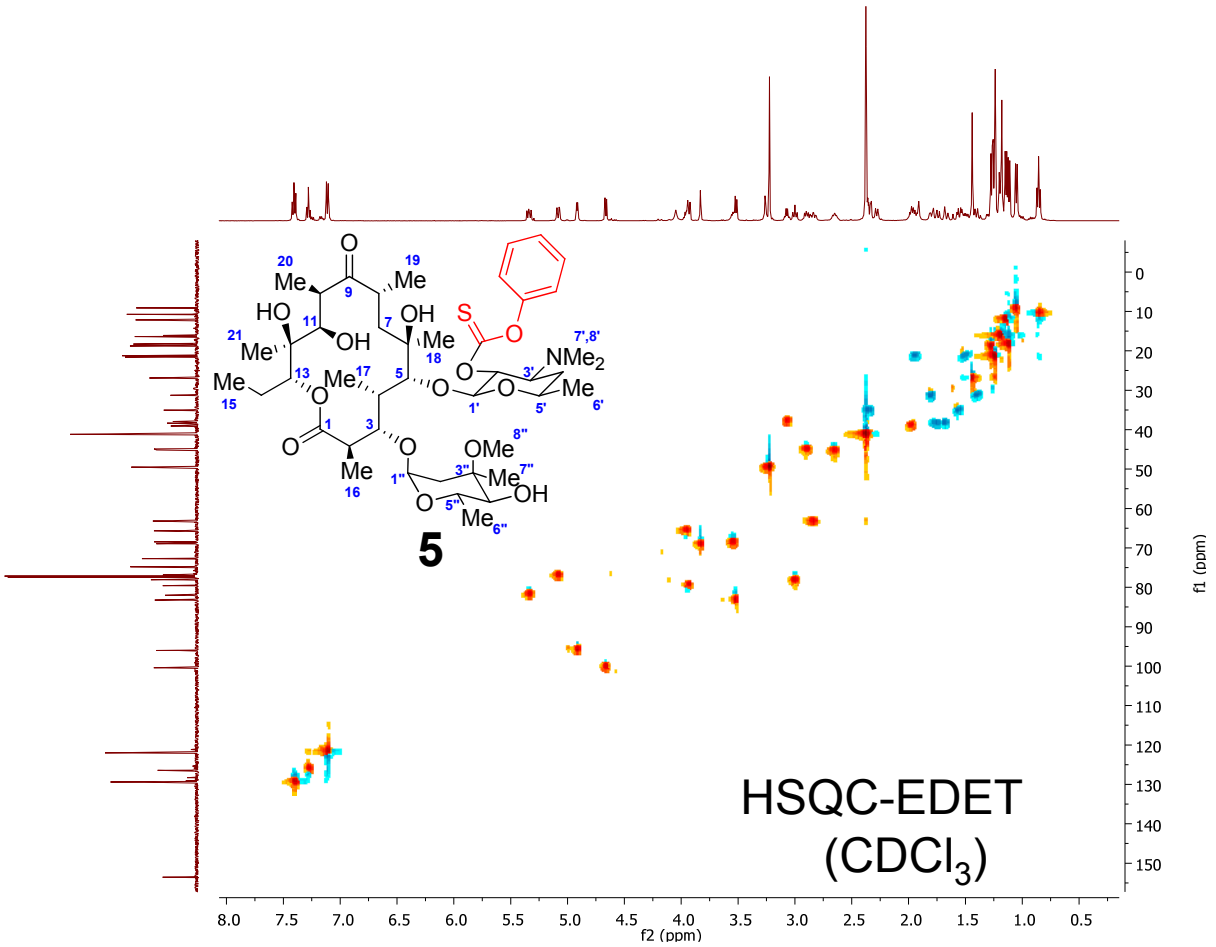
^{1}H-NMR ($CDCl_3$)



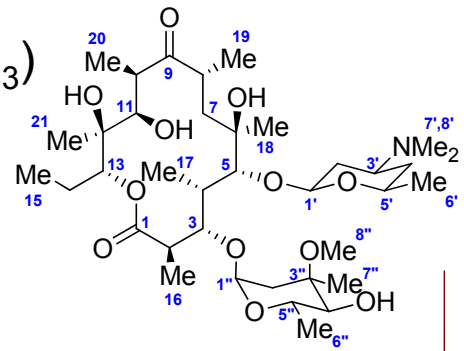
5

^{13}C-NMR ($CDCl_3$)



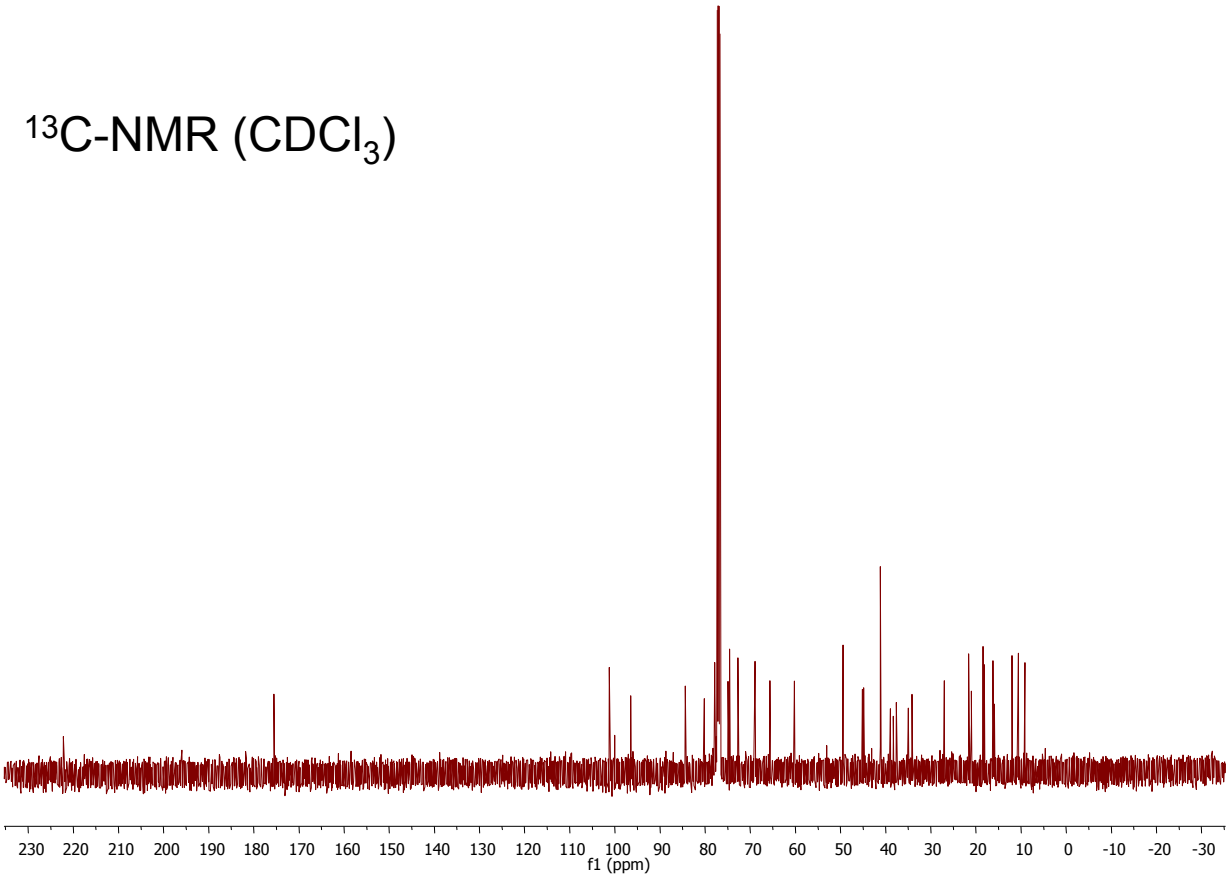

HSQC-EDET
(CDCl3)
5
f2 (ppm)
f1 (ppm)

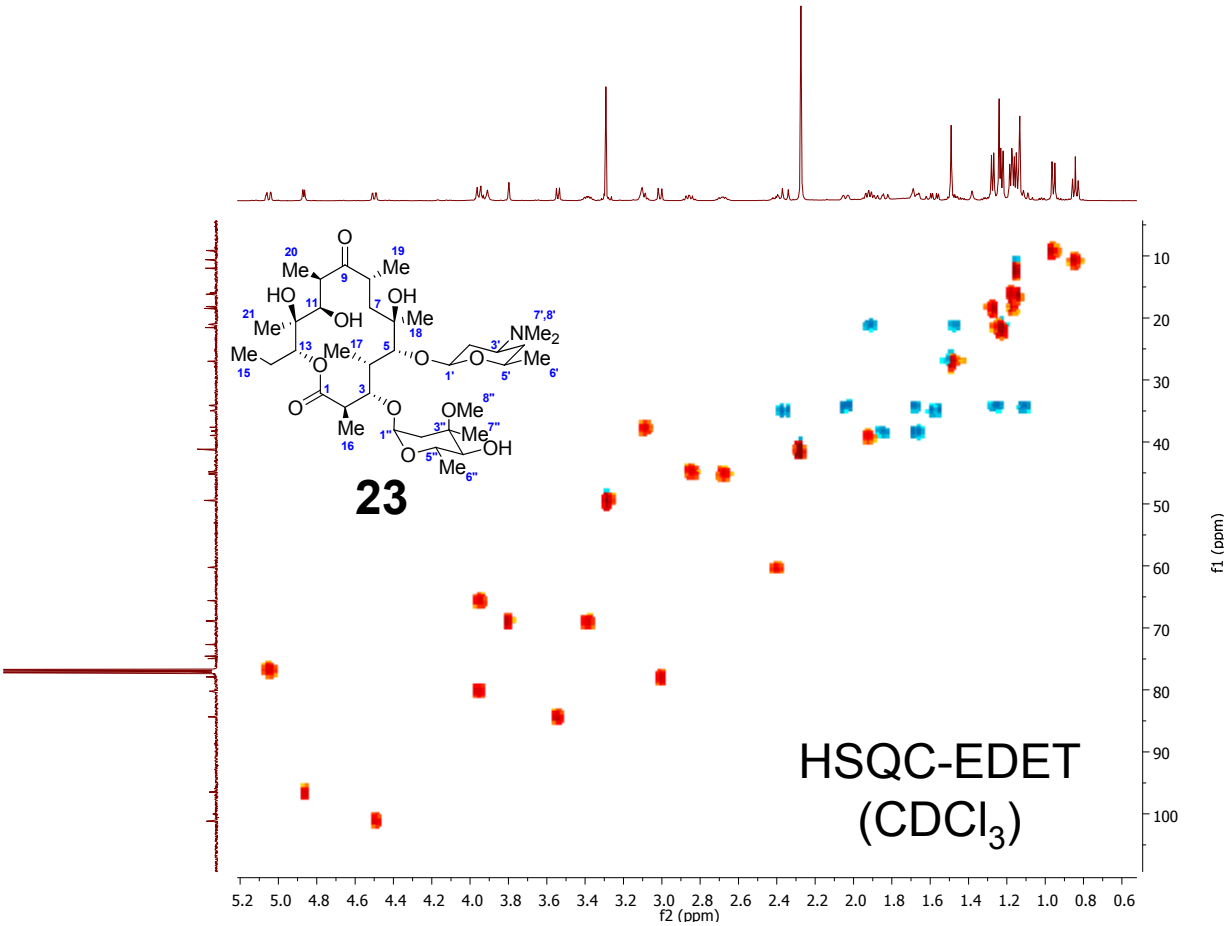
^{1}H-NMR ($CDCl_3$)



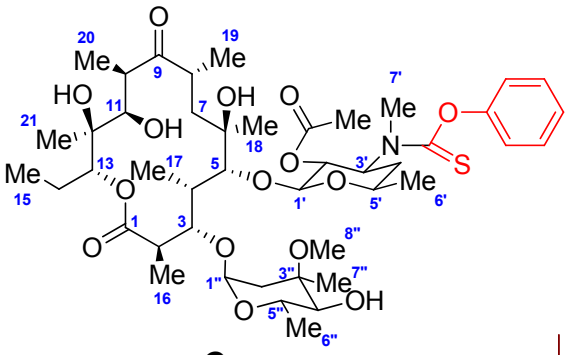
23

^{13}C-NMR ($CDCl_3$)



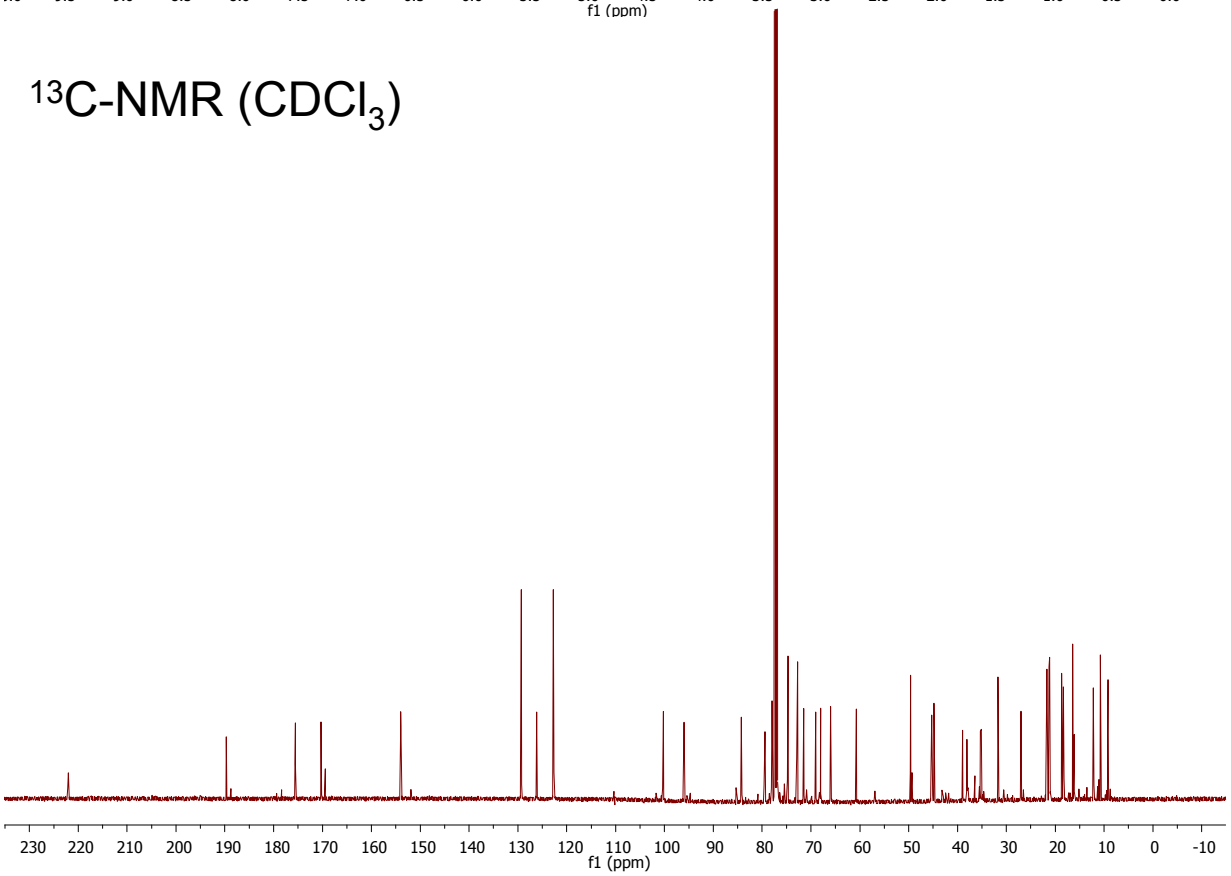

23
HSQC-EDET
(CDCl3)
f2 (ppm)
f1 (ppm)

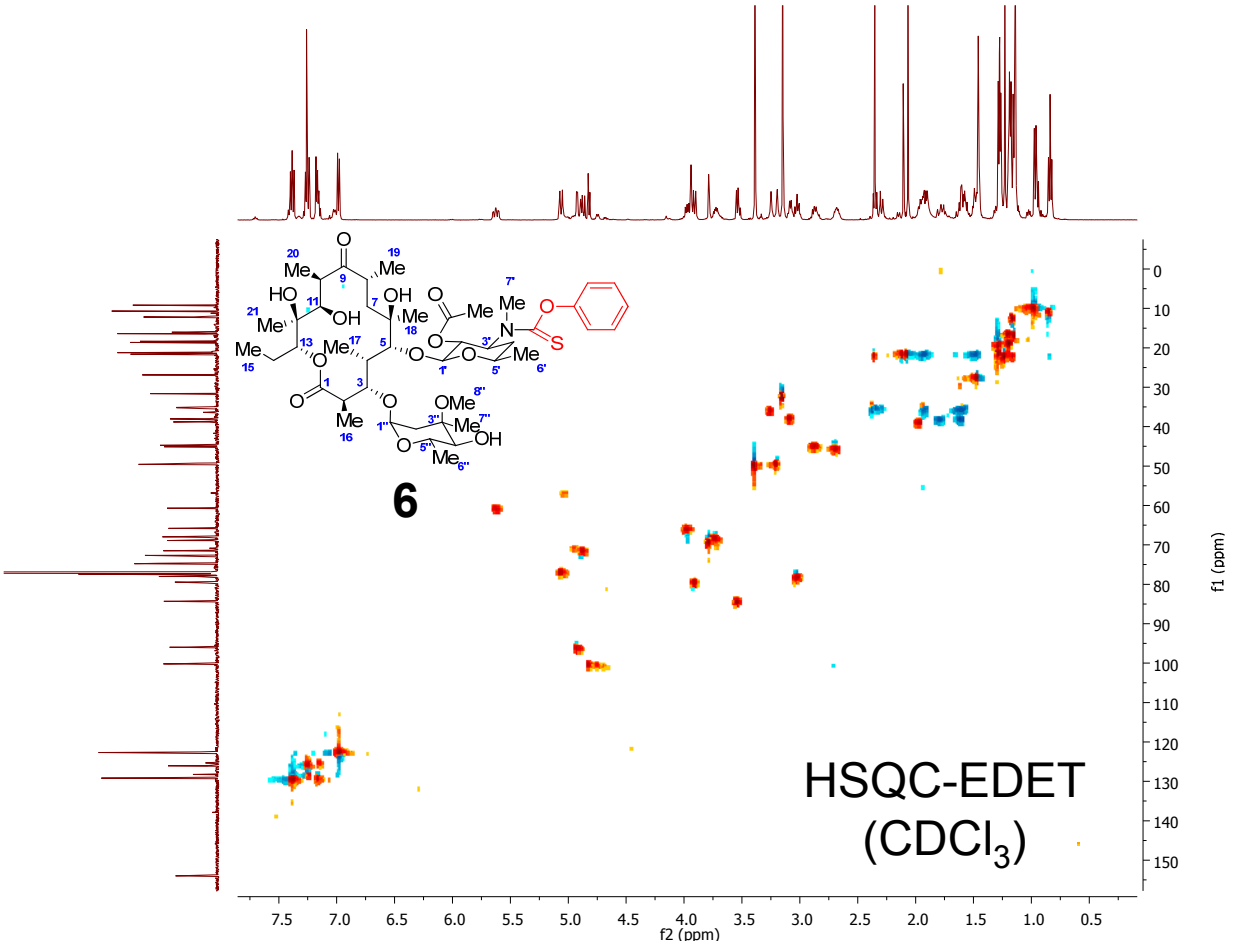
^{1}H-NMR ($CDCl_3$)



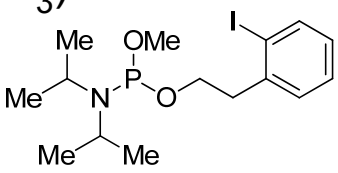
6

^{13}C-NMR ($CDCl_3$)



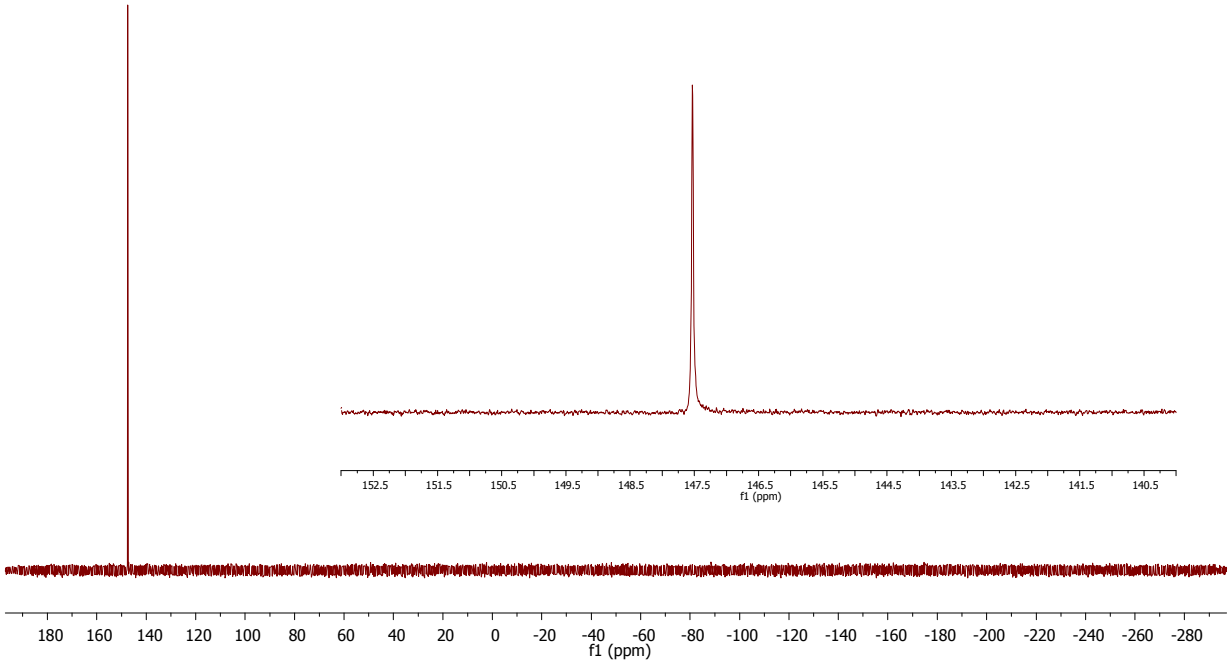

6
HSQC-EDET
(CDCl3)
f2 (ppm)
f1 (ppm)

^{1}H-NMR ($CDCl_3$)

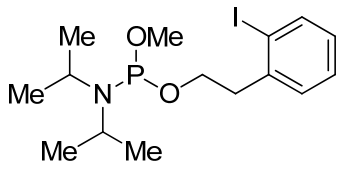


10b

^{31}P-NMR ($CDCl_3$)

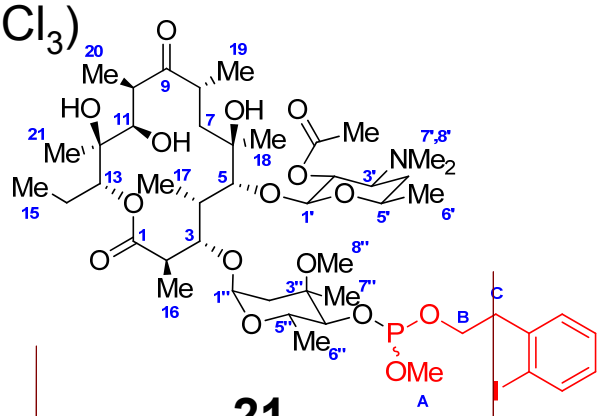


^{13}C-NMR ($CDCl_3$)



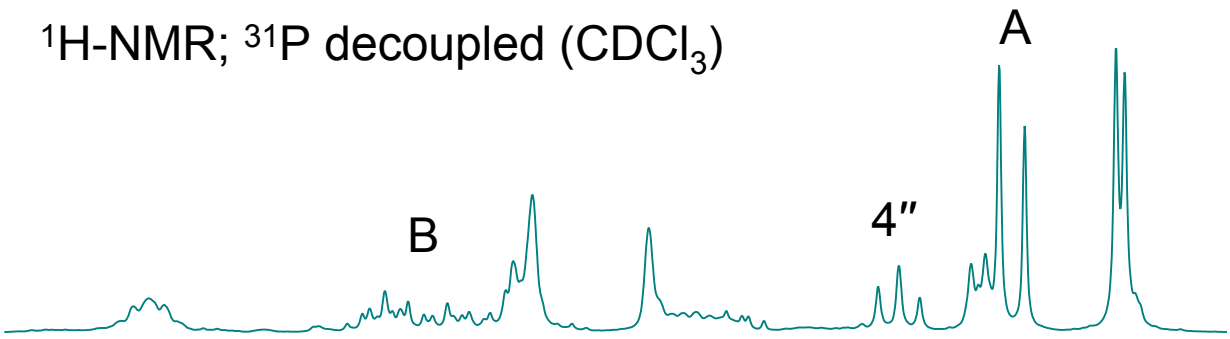
10b

^{1}H-NMR ($CDCl_3$)

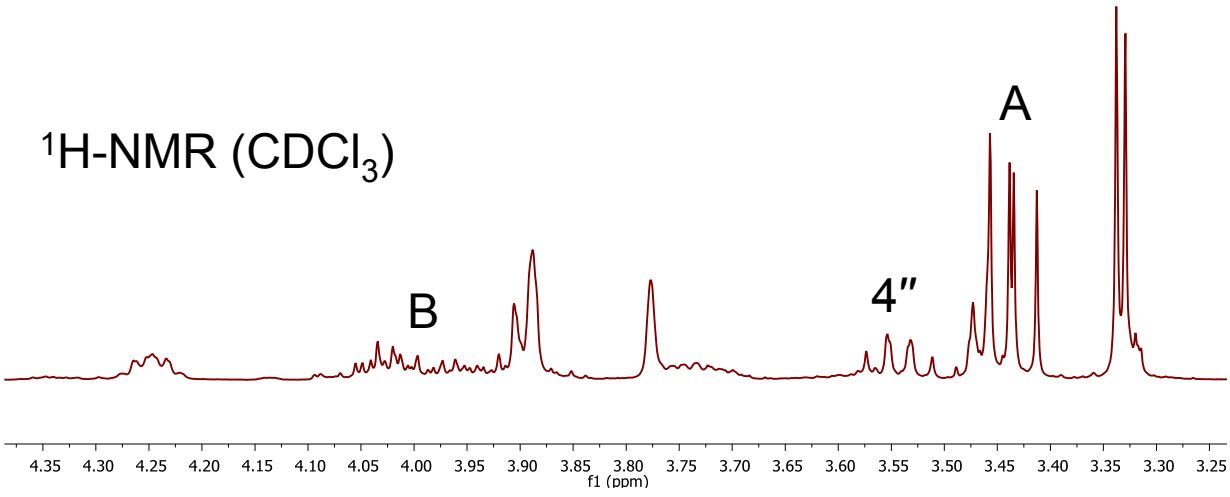


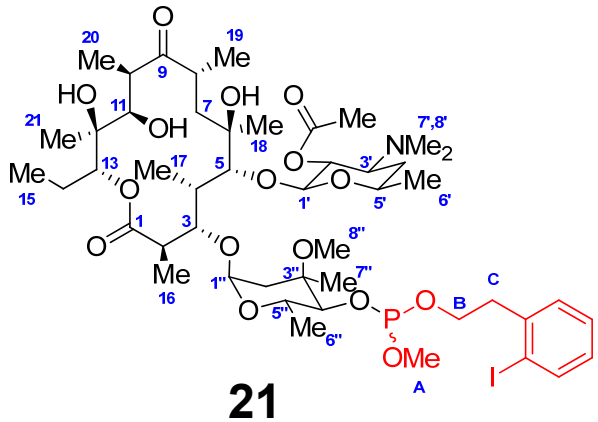
21

^{1}H-NMR; ^{31}P decoupled ($CDCl_3$)



^{1}H-NMR ($CDCl_3$)

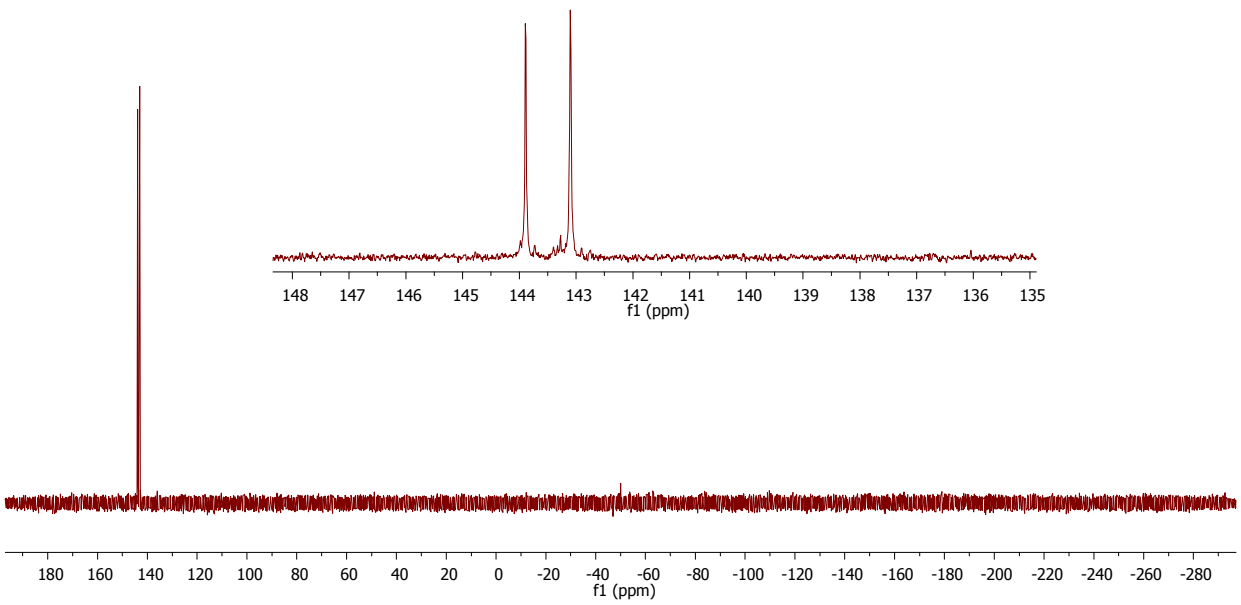


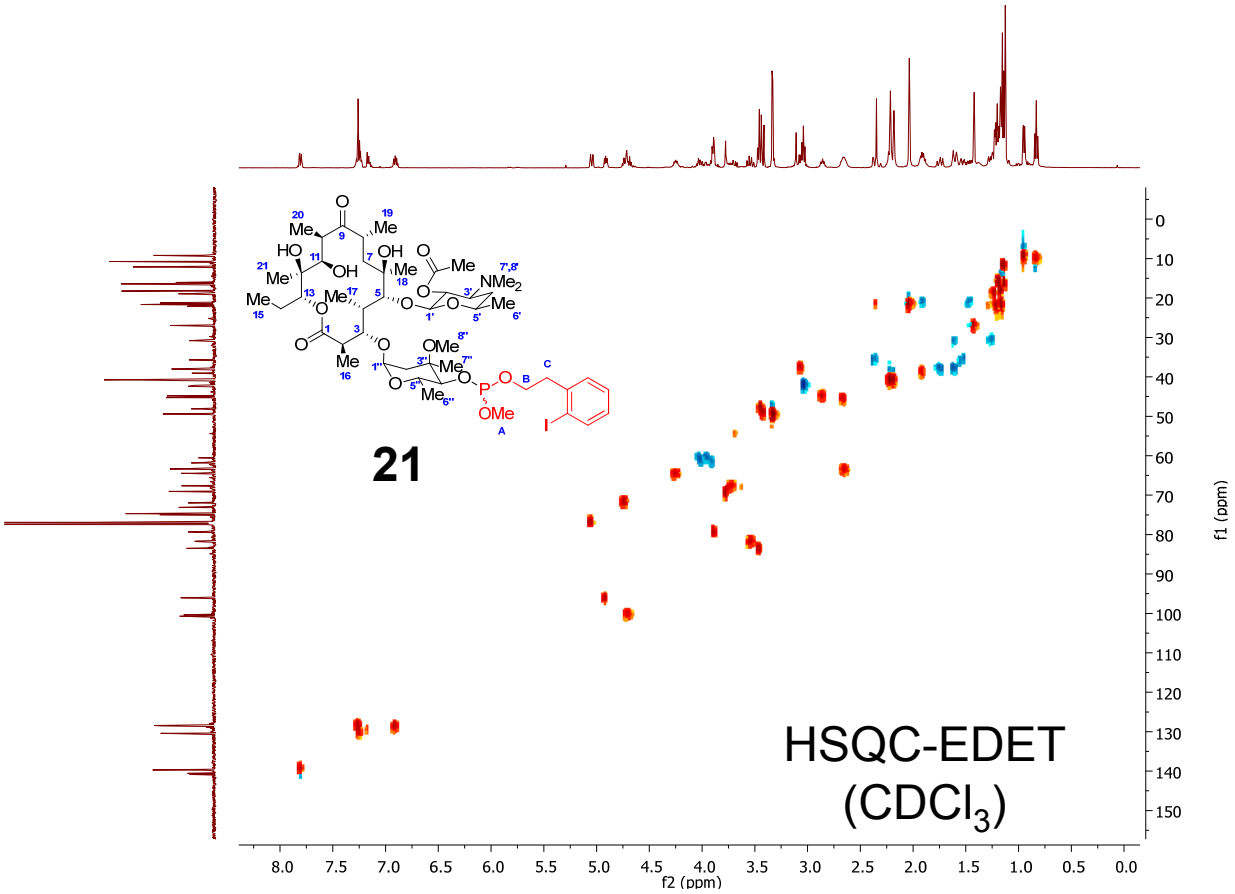


21

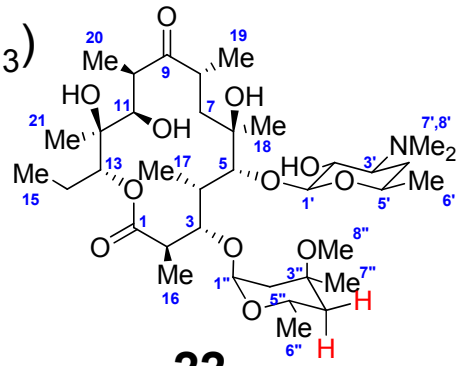
^{13}C-NMR ($CDCl_3$)

^{31}P-NMR ($CDCl_3$)



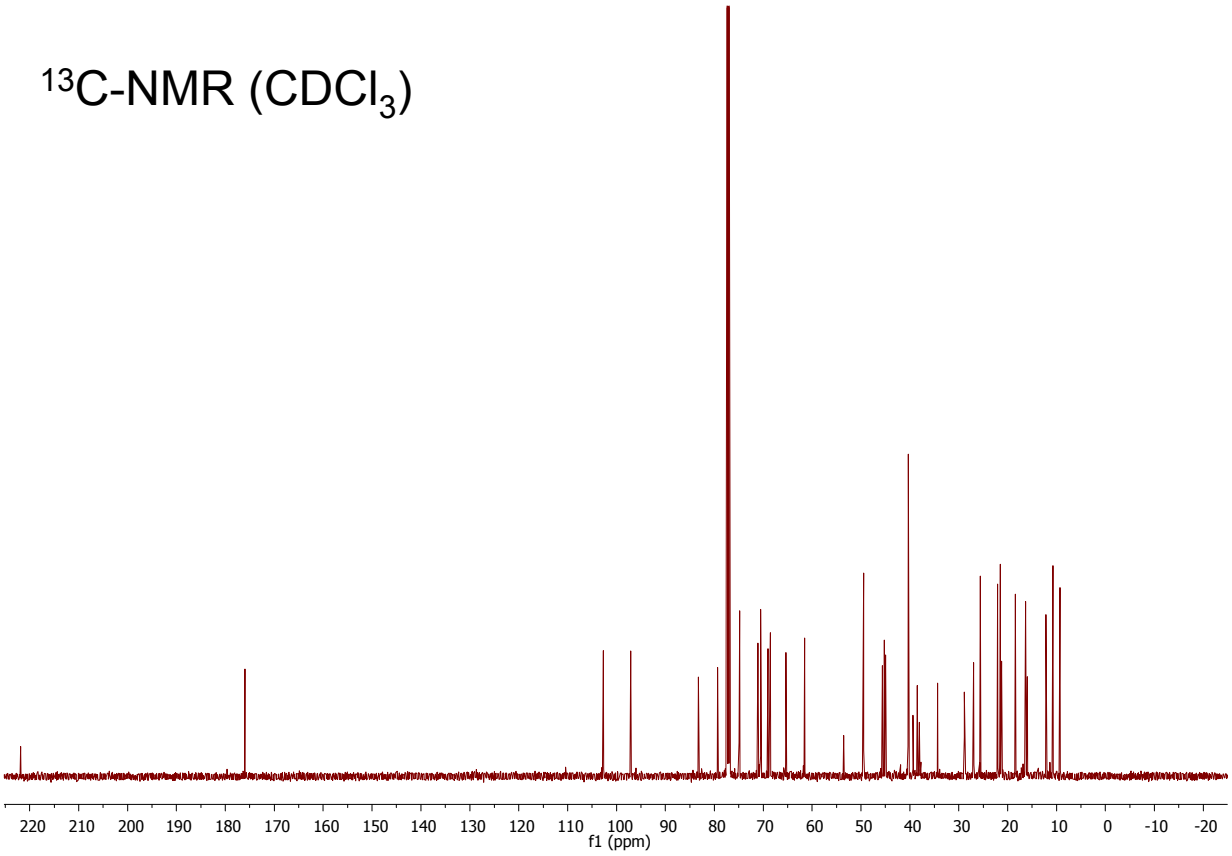

21
HSQC-EDET
(CDCl3)
f2 (ppm)
f1 (ppm)

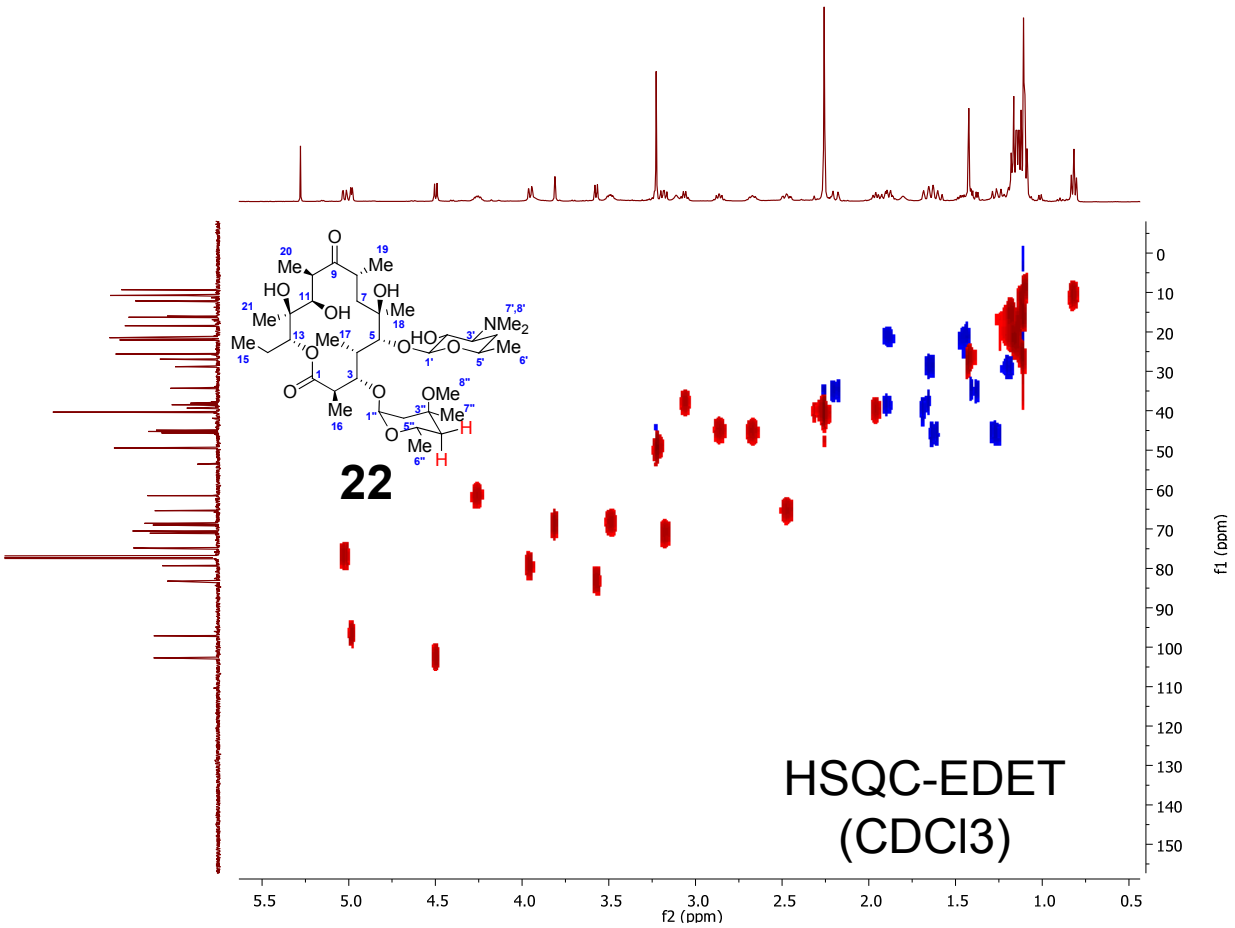
^{1}H-NMR ($CDCl_3$)



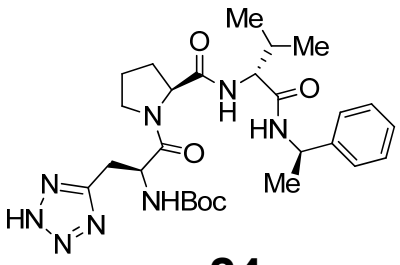
22

^{13}C-NMR ($CDCl_3$)




22
HSQC-EDET
(CDCl3)
f2 (ppm)
f1 (ppm)

^{1}H-NMR ($CDCl_3$)



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^{13}C-NMR ($CDCl_3$)