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Synthetic Diversification of Natural Products: Semi-Synthesis and Evaluation of Triazole Jadomycins

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Electronic Supporting Information

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Experimental section

Synthetic Techniques and Instrumentation:

All reagents used were purchased from commercial sources and used without further purification. With the exception of amino acid synthesis and formation of non-jadomycin triazoles, all solvents used were HPLC grade. Thin layer chromatography (TLC) plates used to monitor reactions, assess purity, and run preparative TLC were all glass-backed normal phase silica gel plates, 250 μm (SiliCycle®). Preparative TLC plates were 20 x 20 cm and 1000 μm in thickness. No visualization was required for jadomycins (**2**, **11-18**), as the bands are highly coloured. For all other compounds, plates were visualized with potassium permanganate dip (1.5 g $KMNO_4$, 10 g K_2CO_3, 125 mg NaOH, 200 mL water) and heat. Flash chromatography was performed on a Biotage SP1™ unit using pre-packaged columns (Biotage®, SiliCycle®).

All purified compounds were characterized by mass spectrometry and NMR spectroscopy. Low resolution mass spectra were recorded using electrospray ionization (ESI) on a 2000Qtrap linear ion trap instrument (Applied Biosystems™). Samples were scanned in positive mode over a range of 300-700 m/z (Q1) and then in MS/MS mode. High resolution mass spectra were recorded using electrospray ionization (ESI) on a Bruker Daltonics® MicroTOF instrument in positive mode from 50-1500 m/z. With the exception of jadomycin *O*PS (**2**) and all triazole jadomycins (**11-18**), NMR spectra were recorded using a Bruker Avance 500 instrument (^{1}H at 500 MHz, ^{13}C at 125 MHz) with broadband observe (BBO) probe at the Nuclear Magnetic Resonance Research Resource (NMR-3), Dalhousie University. NMR spectra of jadomycin *O*PS (**2**) and **11-18** were recorded using a 700 MHz Bruker Avance III instrument (^{1}H at 700 MHz, ^{13}C at 150 MHz) with cryoprobe at the National Research Council Canada Institute for Marine Biosciences (NRC-IMB), Halifax. Spectra were recorded in $CDCl_3$, MeOD, or D_2O. Chemical shift values (δ in ppm) were calibrated to residual solvent peak (MeOH at 3.31 ppm in MeOD, $CHCl_3$ at 7.24 ppm in $CDCl_3$, H_2O at 4.71 ppm in D_2O). Peak assignment was achieved using chemical shifts and peak multiplicities from the proton spectra as well as through the use of ^{1}H-^{1}H COSY, and where noted, 1D TOCSY and 1D nOe experiments. Assignment of the ^{13}C spectra was achieved through HSQC, and where noted, HMBC experiments. Not all ^{13}C resonances could be assigned, despite varying the J value for the HMBC experiments. Stereochemistry at the anomeric centers of all carbohydrates synthesized was determined by measuring $^1J_{C1,H1}$ using an HETCOR (^{13}C-^{1}H heteronuclear correlation) experiment.

HPLC method

HPLC of jadomycin analogues was performed on a Hewlett Packard Series 1050 instrument with an Agilent Zorbax 5 μm Rx-C18 column (4.6 x 150 mm). Elution of the compounds was monitored at an absorbance of 254 nm using an isocratic gradient of 9:1 (A:B) over 0.5 min followed by an increasing linear gradient from 9:1 (A:B) to 4:6 (A:B) over 7.5 min, followed by an isocratic gradient of 4:6 (A:B) for an additional 2 min. This was then followed by a decreasing linear gradient from 4:6 (A:B) to 9:1 (A:B) over 1 min, ending with an isocratic

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gradient of 9:1 (A:B) over 4 min (total time 15 min; flow rate of 1 ml/min). Buffer A was an aqueous buffer comprised of 12 mM Bu4NBr, 10 mM KH2PO4, and 5% HPLC grade MeCN (pH 4.0) and B was HPLC grade MeCN.

Synthesis

***N*-Boc-*O*-Propargyl-L-Serine.** *N*-Boc-L-Serine (4.10 g, 20 mmol) was dissolved in anhydrous DMF (180 mL) under a nitrogen atmosphere and cooled in an ice bath to 0°C. NaH (1.6 g, 66 mmol) was added portionwise. After effervescence ceased (15 min), propargyl bromide solution (1.2 mL, 20 mmol; 80% in toluene) was added dropwise over 15 min. The solution was stirred on ice for 1-2 hours until the reaction was determined complete by TLC analysis. The reaction was quenched with dH_2O (50 mL) and evaporated to dryness under vacuo. The crude material was dissolved in dH_2O (100 mL) and washed with diethyl ether (50 mL x 5). The aqueous solution was adjusted to pH 2-3 using $KHSO_4$ (0.5 M), and the product was extracted with DCM (100 mL x 3). The organic layer was washed with $KHSO_4$ solution at pH 2-3 (50 mL x 3), dried with Na_2SO_4, and evaporated to dryness to yield an orange oil (4.18 g, 86% yield). R_f = 0.22 (95:3:1 $CHCl_3$:MeOH:AcOH). $^{\delta}$H ($CDCl_3$, 500 MHz): 1.39 (9H, s, C(C**H**$_3$)$_3$); 2.42 (1H, t, J = 2.4 Hz, $CH_2C{\equiv}C$**H**); 3.75 (1H, dd, J = 9.1 & 2.1 Hz, αCHC**H**$_{2\ a}$); 3.91 (1H, d, J = 8.5 Hz, αCHC**H**$_{2\ b}$); 4.11 (2H, d, J = 2.6 Hz, C**H**$_2$C≡CH); 4.41 (1H, m, αC**H**); 5.48 (1H, d, J = 8.3 Hz, N**H**); 10.97 (1H, bs, COO**H**). $^{\delta}$C ($CDCl_3$, 125 MHz): 28.2 (3C, s, C(**C**H$_3$)$_3$); 53.6 (1C, s, α**C**H); 58.4 (1C, s, **C**H$_2$C≡CH); 69.6 (1C, s, αCH**C**H$_2$); 75.1 (1C, s, CH$_2$C≡**C**H); 78.9 (1C, s, CH$_2$**C**≡CH); 79.9 (1C, s, **C**(CH$_3$)$_3$); 155.6 (1C, s, **C**OC(CH$_3$)$_3$); 173.1 (1C, s, **C**OOH). HRMS (ESI^+) for $C_{11}H_{17}N_1O_5Na$ $[M+Na]^+$: calcd = 266.0999; found = 266.0990. These data are consistent with literature values.[1]

***O*-Propargyl-L-serine hydrochloride Salt (1).** *N*-Boc-*O*-Propargyl-L-Serine (4.18 g, 17.2 mmol) was dissolved in EtOAc (8 mL), HCl (12 mL, 10 M) was added, and the reaction was stirred at room temperature. After 10 minutes, all starting material was consumed by TLC analysis, and white crystals had precipitated out of solution. The reaction mixture was evaporated to dryness and volatiles were removed *in vacuo* overnight. The resulting white crystals were triturated and washed with DCM (30 mL x 3) followed by diethyl ether (30 mL x 3) to yield a white powder (2.65 g, 89% yield). $^{\delta}$H (D_2O, 500 MHz): 2.81 (1H, t, J = 2.4 Hz, $CH_2C{\equiv}C$**H**); 3.88 (1H, dd, J = 10.9 & 3.2 Hz, αCHC**H**$_{2\ a}$); 3.99 (1H, dd, J = 10.9 & 4.9 Hz, αCHC**H**$_{2\ b}$); 4.15 (2H, d, J = 2.4 Hz, C**H**$_2$C≡CH); 4.18 (1H, dd, J = 4.8 & 3.3 Hz, α**CH**). $^{\delta}$C (D_2O, 125 MHz): 53.1 (1C, s, α**C**H); 58.4 (1C, s, **C**H$_2$C≡CH); 66.7 (1C, s, αCH**C**H$_2$); 76.4 (1C, s, CH$_2$C≡**C**H); 78.7 (1C, s, CH$_2$**C**≡CH); 170.0 (1C, s, **C**OOH). HRMS (ESI^+) for $C_6H_{10}N_1O_3Na$ $[M+Na]^+$: calcd = 144.0655; found = 144.0651.

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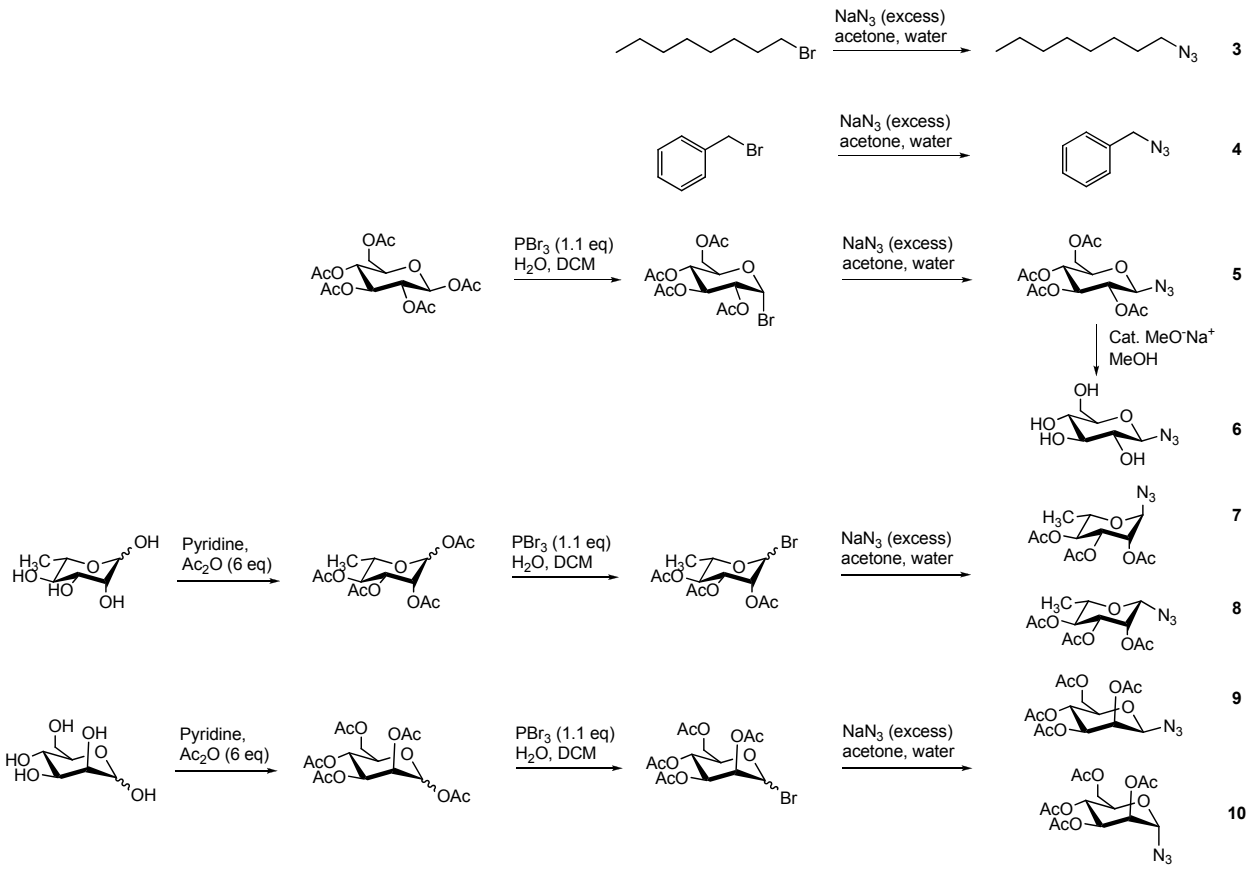

Scheme S1. Synthesis of eight azides.

Octyl azide (3). Octyl bromide (10.0 mL, 56.7 mmol) was dissolved in acetone (100 mL) and added to a solution of sodium azide (17 g, 262 mmol) in dH_2O (100 mL). The reaction mixture was stirred vigorously at room temperature for 48 hours. The reaction mixture was extracted with DCM (3 x 150 mL), and the combined organic layers were washed with dH_2O (2 x 150 mL) and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness yielding a yellow oil (6.79 g, 77% yield). $^{\delta}$H ($CDCl_3$, 500 MHz): 0.92 (3H, t, J = 6.9Hz, C**H$_3$**); 1.27-1.42 (10H, m, -(C**H$_2$**)$_5$); 1.63 (2H, p, J = 6.9Hz, C**H$_2$**CH_2N_3); 3.29 (2H, t, J = 6.9Hz, CH_2C**H$_2$**N_3). $^{\delta}$C ($CDCl_3$, 125 MHz): 14.2 (1C, s, **C**8H_3); 22.8 (1C, s, **C**7); 26.9 (1C, s, **C**6); 29.0 (1C, s, **C**2); 29.2 (1C, s, **C**4); 29.3 (1C, s, **C**3); 31.9 (1C, s, **C**5); 51.7 (1C, s, **C**1N_3). These data are consistent with literature values.[2]

Benzyl azide (4). Benzyl bromide (10.0 mL, 85.0 mmol) was dissolved in acetone (100 mL) and added to a solution of sodium azide (25 g, 385 mmol) in dH_2O (100 mL). The reaction mixture was stirred vigorously at room temperature for 48 hours until the reaction was determined complete by TLC analysis. The reaction mixture was extracted with DCM (3 x 150 mL), and the combined organic layers were washed with dH_2O (2 x 150 mL) and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness yielding a pale yellow oil (9.50 g, 84% yield). R_f = 0.89 (toluene). $^{\delta}$H ($CDCl_3$, 500 MHz): 4.40 (2H, s, C**H$_2$**); 7.40-7.49 (5H, m, Ar-C**H**). $^{\delta}$C ($CDCl_3$, 125

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MHz): 54.9 (2C, s, **C**H_2); 128.3 (2C, s, ortho-**C**H); 128.4 (1C, s, para-**C**H); 128.9 (2C, s, meta-**C**H); 135.5 (1C, s, 4°**C**). These data are consistent with literature values.[3]

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide. 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranoside (19.5 g, 50.0 mmol) was dissolved in DCM (160 mL) and cooled in an ice bath to 0°C. Phosphorus tribromide (8.0 mL, 84.8 mmol) and dH_2O (5.45 mL, 303 mmol) were added dropwise, and the reaction was allowed to warm to room temperature. The solution was stirred for 3 hours until the reaction was determined complete by TLC analysis. The reaction mixture was diluted with DCM (250 mL) and washed with dH_2O (2 x 400 mL), saturated aqueous sodium bicarbonate (400 mL), and brine (400 mL). The organic layer was dried with Na_2SO_4 and evaporated to dryness to yield a pale yellow oil (19.5 g). This product was impure by TLC but was used in the next synthetic step without further purification due to its instability. R_f = 0.88 (50:50 EtOAc:Hexanes).

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (5). Compound **47** (19.5 g, ≤50.0 mmol) was dissolved in acetone (100 mL) and added to a solution of sodium azide (15 g, 231 mmol) in dH_2O (100 mL). The reaction mixture was stirred vigorously at room temperature for 18 hours until the reaction was determined complete by TLC analysis. The reaction mixture was extracted with DCM (3 x 150 mL), and the combined organic layers were washed with dH_2O (2 x 150 mL) and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness yielding an off-white powder (17.0 g). The crude material was purified by flash column chromatography using a normal phase silica column (18 cm x 6.5 cm, 75 mLmin^{-1}) and an isocratic solvent system (20:80 EtOAc:Hexanes). The purified product took the form of a bright white powder (8.24 g, 44% yield). R_f = 0.75 (50:50 EtOAc:Hexanes). $^{\delta}$H ($CDCl_3$, 500 MHz): 2.04, 2.06, 2.11, 2.13 (12H, s x 4, OCOC**H$_3$** x 4); 3.83 (1H, ddd, J = 9.6 & 4.7 & 2.0 Hz, C5**H**); 4.20 (1H, dd, J = 12.4 & 2.0 Hz, C6**H$_{2b}$**); 4.30 (1H, dd, J = 12.4 & 4.7 Hz, C6**H$_{2a}$**); 4.68 (1H, d, J = 8.8 Hz, C1**H**); 4.99 (1H, t, J = 9.2 Hz, C2**H**); 5.13 (1H, t, J = 9.6 Hz, C4**H**); 5.25 (1H, t, J = 9.6 Hz, C3**H**). $^{\delta}$C ($CDCl_3$, 125 MHz): 20.7, 20.7, 20.8, 20.9 (4C, s x 4, OCO**C**H_3 x 4); 61.8 (1C, s, **C**6); 68.0 (1C, s, **C**4); 70.8 (1C, s, **C**2); 72.8 (1C, s, **C**3); 74.2 (1C, s, **C**5); 88.1 (1C, s, **C**1); 169.4, 169.5, 170.3, 170.8 (4C, s x 4, O**C**OCH_3 x 4). $^1J_{C1,H1}$ = 160 Hz. These data are consistent with literature values.[4]

β-D-Glucopyranosyl azide (6). Compound 48 (335 mg, 0.90 mmol) was stirred at room temperature in a solution of elemental sodium (7.5 mg) in methanol (15 mL). After 30 minutes, complete dissolution had occurred and the starting material had disappeared by TLC analysis. The reaction mixture was evaporated to dryness, and volatiles were removed in vacuo overnight, affording shiny white crystals (180 mg, 98% yield). $^{\delta}$H (D_2O, 500 MHz): 3.15 (1H, t, J = 8.9 Hz, C2H); 3.30 (1H, t, J = 8.9 Hz, C4H); 3.40 (1H, t, J = 8.9 Hz, C3H); 3.42 (1H, ddd, J = 9.8 & 5.5 & 2.3 Hz, C5H); 3.15 (1H, t, J = 8.9 Hz, C2H); 3.63 (1H, dd, J = 12.5 & 5.5 Hz, C6H2a); 3.80 (1H, dd, J = 12.5 & 2.3 Hz, C6H2b); 4.63 (1H, d, J = 8.8 Hz, C1H). $^{\delta}$C (D_2O, 125 MHz): 60.5 (1C, s, C6); 69.1 (1C, s, C4); 72.8 (1C, s, C2); 75.7 (1C, s, C3); 77.8 (1C, s, C5); 90.1 (1C, s, C1). LRMS (ESI+): Q1 found 228 m/z [M+Na]+, 433 m/z [2M+Na]$^+$; MS/MS (433) found 228

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m/z $[M+Na]^+$.HRMS (ESI+) for $C_6H_{11}N_3O_5Na$ $[M+Na]^+$: calcd = 228.0591; found = 228.0579. These data are consistent with literature values.[5]

1,2,3,4,-Tetra-*O*-acetyl-α/β-L-rhamnopyranoside. α/β-L-Rhamnose monohydrate (10.0 g, 54.9 mmol) was dissolved in pyridine (75 mL) and cooled in an ice bath to 0°C. Acetic anhydride (26 mL, 276 mmol) was added dropwise, and the reaction was allowed to warm to room temperature. The solution was stirred for 16 hours until the reaction was determined complete by TLC analysis. The reaction was quenched with dH_2O (25 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were washed with water (2 x 150 mL), 1 M HCl (5 x 200 mL), and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness to yield a yellow syrup (16.90 g, 93% yield), as a mixture of α/β anomers. R_f = 0.73 (75:25 EtOAc:Hexanes). $^{\delta}$H ($CDCl_3$, 500 MHz): α/β = 3/1; α-anomer = 1.26 (3H, d, J = 6.2 Hz, C6**H$_3$**); 2.03, 2.09, 2.18, 2.20 (12H, s x 4, OCOC**H$_3$** x 4); 3.96 (1H, dq, J = 10.1 & 6.2 Hz, C5**H**); 5.15 (1H, t, J = 10.1 Hz, C4**H**); 5.28 (1H, dd, J = 3.5 & 1.9 Hz, C2**H**); 5.33 (1H, dd, J = 10.1 & 3.5 Hz, C3**H**); 6.04 (1H, d, J = 1.9 Hz, C1**H**); β-anomer = 1.32 (3H, d, J = 6.2 Hz, C6**H$_3$**); 2.03, 2.09, 2.13, 2.24 (12H, s x 4, OCOC**H$_3$** x 4); 3.69 (1H, dq, J = 9.5 & 6.2 Hz, C5**H**); 5.09-5.13 (1H, m, C3**H**); 5.10-5.14 (1H, m, C4**H**); 5.50 (1H, dd, J = 2.6 & 1.1 Hz, C2**H**); 5.86 (1H, d, J = 1.1 Hz, C1**H**). $^{\delta}$C ($CDCl_3$, 125 MHz): α-anomer = 17.5 (1C, s, **C**6); 20.7, 20.7, 20.8, 20.9 (4C, s x 4, OCO**C**H_3 x 4); 68.6 (1C, s, **C**3); 68.7 (1C, s, **C**2); 68.8 (1C, s, **C**5); 70.5 (1C, s, **C**4); 90.6 (1C, s, **C**1); 168.4, 169.9, 169.9, 170.1 (4C, s x 4, O**C**OCH_3 x 4); β-anomer = 17.4 (1C, s, **C**6); 20.6, 20.8, 20.8, 20.9 (4C, s x 4, OCO**C**H_3 x 4); 68.5 (1C, s, **C**2); 70.2 (1C, s, **C**3); 70.7 (1C, s, **C**4); 71.5 (1C, s, **C**5); 90.3 (1C, s, **C**1); 168.5, 169.9, 170.3, 170.4 (4C, s x 4, O**C**OCH_3 x 4). These data are consistent with literature values.[6]

2,3,4-Tri-*O*-acetyl-α/β-L-rhamnopyranosyl bromide. 1,2,3,4,-Tetra-*O*-*a*cetyl-α/β-L-rhamnopyranoside (16.9 g, 50.9 mmol) was dissolved in DCM (160 mL) and cooled in an ice bath to 0°C. Phosphorus tribromide (8.0 mL, 84.8 mmol) and dH_2O (5.45 mL, 303 mmol) were added dropwise, and the reaction was allowed to warm to room temperature. The solution was stirred for 3 hours until the reaction was determined complete by TLC analysis. The reaction mixture was diluted with DCM (250 mL) and washed with dH_2O (2 x 400 mL), saturated aqueous sodium bicarbonate (400 mL), and brine (400 mL). The organic layer was dried with Na_2SO_4 and evaporated to dryness to yield a pale yellow oil (16.8 g). This product was impure by TLC but was used in the next synthetic step without further purification due to its instability. R_f = 0.85 (50:50 EtOAc:Hexanes).

2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl azide (7) & 2,3,4-tri-*O*-acetyl-β-L-rhamnopyranosyl azide (8). 2,3,4-Tri-*O*-acetyl-α/β-L-rhamnopyranosyl bromide (16.8 g, ≤50.9 mmol) was dissolved in acetone (100 mL) and added to a solution of sodium azide (15 g, 231 mmol) in dH_2O (100 mL). The reaction mixture was stirred vigorously at room temperature for 18 hours until the reaction was determined complete by TLC analysis. The reaction mixture was extracted with DCM (3 x 150 mL), and the combined organic layers were washed with dH_2O (2 x 150 mL) and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness yielding a yellow

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syrup (15.5 g). The crude material was purified by flash column chromatography using a normal phase silica column (18 cm x 6.5 cm, 75 $mLmin^{-1}$) and EtOAc:Hexanes (20:80). This yielded a mixture of **7** and **8** (3.79 g, 24% yield over 2 steps), which were then separated by a further chromatic step using a second normal phase silica column (8.0 cm x 4.0 cm, 40 $mLmin^{-1}$) and EtOAc:Hexanes (10:90). This afforded **7** as a yellow oil (45.2 mg) and **8** as a white powder (952 mg). R_f: **7** = 0.76, **8** = 0.70 (50:50 EtOAc:Hexanes). $^{\delta}$H ($CDCl_3$, 500MHz): **7** = 1.30 (1H, d, J = 6.2Hz, C6**H**); 2.02, 2.09, 2.19 (9H, s x 3, OCOC**H**$_3$ x 3); 4.06 (1H, dq, J = 9.7 & 6.2Hz, C5**H**); 5.11 (1H, t, J = 10.1Hz, C4**H**); 5.17 (1H, dd, J = 3.3 & 1.9Hz, C2**H**); 5.23 (1H, dd, J = 10.1 & 3.3Hz, C3**H**); 5.34 (1H, d, J = 1.9Hz, C1**H**); **8** = 1.35 (1H, d, J = 6.2Hz, C6**H**); 2.02, 2.09, 2.23 (9H, s x 3, OCOC**H**$_3$ x 3); 3.65 (1H, dq, J = 9.6 & 6.2Hz, C5**H**); 4.72 (1H, d, J = 1.2Hz, C1**H**); 5.02 (1H, dd, J = 10.2 & 3.2Hz, C3**H**); 5.11 (1H, t, J = 10.1Hz, C4**H**); 5.46 (1H, dd, J = 3.2 & 1.2Hz, C2**H**). $^{\delta}$C ($CDCl_3$, 125MHz): **7** = 17.5 (1C, s, **C**6); 20.7, 20.8, 20.9 (3C, s x 3, OCO**C**H_3); 68.3 (1C, s, **C**3); 68.6 (1C, s, **C**5); 69.5 (1C, s, **C**2); 70.5 (1C, s, **C**4); 87.5 (1C, s, **C**1); 169.9, 169.9, 170.0 (3C, s x 3, O**C**OCH_3); **8** = 17.4 (1C, s, **C**6); 20.6, 20.8, 20.8 (3C, s x 3, OCO**C**H_3); 69.6 (1C, s, **C**2); 70.0 (1C, s, **C**4); 71.0 (1C, s, **C**3); 73.0 (1C, s, **C**5); 85.0 (1C, s, **C**1); 169.8, 170.1, 170.1 (3C, s x 3, O**C**OCH_3). $^{1}J_{C1,H1}$: **7** = 170 Hz, **8** = 158 Hz. LRMS (ESI^+): **7** = Q1 found 338 m/z $[M+Na]^+$, 653 m/z $[2M+Na]^+$; MS/MS (653) found 338 m/z $[M+Na]^+$; **8** = Q1 found 338 m/z $[M+Na]^+$, 653 m/z $[2M+Na]^+$; MS/MS (653) found 338 m/z $[M+Na]^+$. HRMS (ESI^+) for $C_{14}H_{17}N_3O_7Na$ $[M+Na]^+$: calcd = 338.0959; **7** found 338.0970; **8** found 338.0953. These data are consistent with literature values.[7]

1,2,3,4,6-Penta-*O*-acetyl-α/β-D-mannopyranoside. α/β-D-Mannose (10.0 g, 55.5 mmol) was dissolved in pyridine (75 mL) and cooled in an ice bath to 0°C. Acetic anhydride (31.5 mL, 334 mmol) was added dropwise, and the reaction was allowed to warm to room temperature. The solution was stirred for 16 hours until the reaction was determined complete by TLC analysis. The reaction was quenched with dH_2O (25 mL) and extracted with DCM (3 x 150 mL). The combined organic layers were washed with water (2 x 150 mL), 1 M HCl (5 x 200 mL), and brine (150 mL), dried with Na_2SO_4, and evaporated to dryness to yield a yellow syrup (19.32 g, 89% yield), as a mixture of α/β anomers. R_f = 0.72 (75:25 EtOAc:Hexanes). $^{\delta}$H ($CDCl_3$, 500 MHz): α/β = 4/1; α-anomer = 2.02, 2.06, 2.10, 2.18, 2.19 (15H, s x 5, OCOC**H**$_3$ x 5); 4.06 (1H, ddd, J = 9.4 & 4.7 & 2.4 Hz, C5**H**); 4.10 (1H, dd, J = 12.5 & 2.4 Hz, C6**H**$_{2b}$); 4.29 (1H, dd, J = 12.5 & 4.7 Hz, C6**H**$_{2a}$); 5.27 (1H, dd, J = 2.4 & 1.8 Hz, C2**H**); 5.34-5.37 (1H, m, C3**H**); 5.34-5.37 (1H, m, C4**H**); 6.09 (1H, d, J = 1.8 Hz, C1**H**); β-anomer = 2.01, 2.06, 2.11, 2.19, 2.22 (15H, s x 5, OCOC**H**$_3$ x 5); 3.82 (1H, ddd, J = 9.9 & 5.3 & 2.3 Hz, C5**H**); 4.15 (1H, dd, J = 12.4 & 2.3 Hz, C6**H**$_{2b}$); 4.32 (1H, dd, J = 12.4 & 5.3 Hz, C6**H**$_{2a}$); 5.15 (1H, dd, J = 10.0 & 3.3 Hz, C3**H**); 5.34-5.38 (1H, m, C4**H**); 5.49 (1H, dd, J = 3.3 & 1.1 Hz, C2**H**); 5.88 (1H, d, J = 1.1 Hz, C1**H**). $^{\delta}$C ($CDCl_3$, 125 MHz): α-anomer = 20.6, 20.6, 20.7, 20.8, 20.9 (5C, s x 5, OCO**C**H_3 x 5); 62.1 (1C, s, **C**6); 65.5 (1C, s, **C**3); 68.3 (1C, s, **C**2); 68.7 (1C, s, **C**4); 70.6 (1C, s, **C**5); 90.6 (1C, s, **C**1); 168.1, 169.5, 169.7, 170.0, 170.7 (5C, s x 5, O**C**OCH_3 x 5); β-anomer = 20.5, 20.6, 20.7, 20.8, 20.8 (5C, s x 5, OCO**C**H_3 x 5); 62.0 (1C, s, **C**6); 65.4 (1C, s, **C**4); 68.2 (1C, s, **C**2); 70.6

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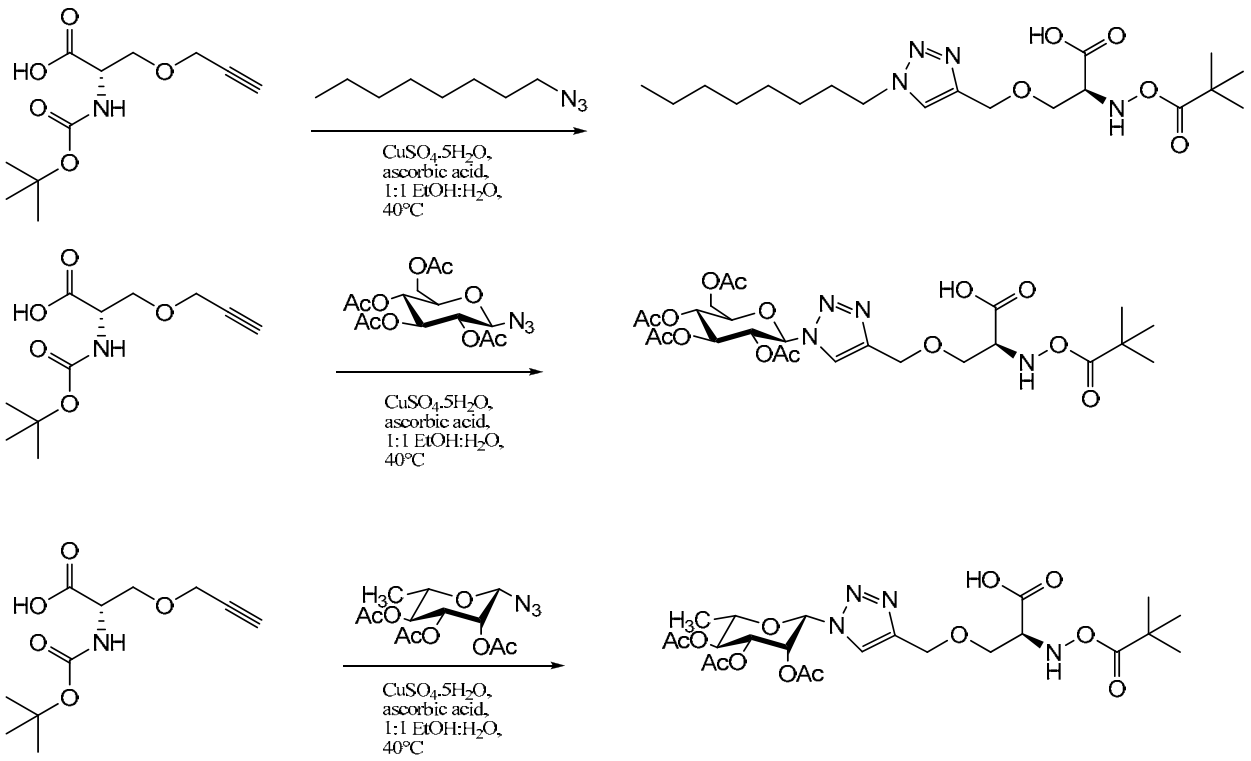
(1C, s, **C**3); 73.3 (1C, s, **C**5); 90.4 (1C, s, **C**1); 168.4, 169.6, 169.8, 170.2, 170.6 (5C, s x 5, O**C**OCH$_3$ x 5). These data are consistent with literature values.[55]

2,3,4,6-Tetra-*O*-acetyl-α/β-D-mannopyranosyl bromide. 1,2,3,4,6-Penta-*O*-*a*cetyl-α/β-D-mannopyranoside (19.32 g, 49.5 mmol) was dissolved in DCM (160 mL) and cooled in an ice bath to 0°C. Phosphorus tribromide (8.0 mL, 84.8 mmol) and dH$_2$O (5.45 mL, 303 mmol) were added dropwise, and the reaction was allowed to warm to room temperature. The solution was stirred for 3 hours until the reaction was determined complete by TLC analysis. The reaction mixture was diluted with DCM (250 mL) and washed with dH$_2$O (2 x 400 mL), saturated aqueous sodium bicarbonate (400 mL), and brine (400 mL). The organic layer was dried with Na$_2$SO$_4$ and evaporated to dryness to yield a pale yellow oil (20.8 g). This product was impure by TLC but was used in the next synthetic step without further purification due to its instability. R_f = 0.74 (50:50 EtOAc:Hexanes).

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl azide (10) & 2,3,4,6-tetra-*O*-*a*cetyl-β-D-mannopyranosyl azide (9). 2,3,4,6-Tetra-*O*-acetyl-α/β-D-mannopyranosyl bromide (20.8 g, ≤49.5 mmol) was dissolved in acetone (100 mL) and added to a solution of sodium azide (15 g, 231 mmol) in dH$_2$O (100 mL). The reaction mixture was stirred vigorously at room temperature for 18 hours until the reaction was determined complete by TLC analysis. The reaction mixture was extracted with DCM (3 x 150 mL), and the combined organic layers were washed with dH$_2$O (2 x 150 mL) and brine (150 mL), dried with Na$_2$SO$_4$, and evaporated to dryness yielding a yellow syrup (17.0 g). The crude material was purified by flash column chromatography using a normal phase silica column (18 cm x 6.5 cm, 75 mLmin^{-1}) and EtOAc:Hexanes (30:70). This yielded a mixture of **10** and **9** (1.61 g, 10% yield over 2 steps), which were then separated by a further chromatic step using a second normal phase silica column (8.0 cm x 4.0 cm, 40 mLmin^{-1}) and EtOAc:Hexanes (10:90). This afforded **10** as a yellow oil (626 mg) and **9** as a white powder (377 mg). R_f: **10** = 0.65, **9** = 0.60 (50:50 EtOAc:Hexanes). $^{\delta}$H (CDCl$_3$, 500 MHz): **10** = 2.03, 2.09, 2.15, 2.20 (12H, s x 4, OCOC**H$_3$** x 4); 4.16-4.20 (1H, m, C5**H**); 4.20 (1H, dd, J = 12.4 & 2.3 Hz, C6**H$_{2b}$**); 4.34 (1H, dd, J = 12.4 & 5.5 Hz, C6**H$_{2a}$**); 5.19 (1H, dd, J = 3.0 & 1.8 Hz, C2**H**); 5.28 (1H, dd, J = 10.0 & 3.0 Hz, C3**H**); 5.32 (1H, t, J = 10.0 Hz, C4**H**); 5.42 (1H, d, J = 1.8 Hz, C1**H**); **9** = 2.03, 2.09, 2.15, 2.25 (12H, s x 4, OCOC**H$_3$** x 4); 3.80 (1H, ddd, J = 10.1 & 5.7 & 2.5Hz, C5**H**); 4.24 (1H, dd, J = 12.3 & 2.5Hz, C6**H$_{2b}$**); 4.32 (1H, dd, J = 12.3 & 5.7Hz, C6**H$_{2a}$**); 4.77 (1H, d, J = 1.1Hz, C1**H**); 5.08 (1H, dd, J = 10.1 & 3.3Hz, C3**H**); 5.30 (1H, t, J = 10.1Hz, C4**H**); 5.49 (1H, dd, J = 3.3 & 1.1Hz, C2**H**). $^{\delta}$C (CDCl$_3$, 125MHz): **10** = 20.6, 20.7, 20.8, 20.9 (4C, s x 4, OCO**C**H$_3$ x 4); 62.2 (1C, s, **C**6); 65.6 (1C, s, **C**4); 68.3 (1C, s, **C**3); 69.2 (1C, s, **C**2); 70.6 (1C, s, **C**5); 87.5 (1C, s, **C**1); 169.7, 169.8, 169.9, 170.7 (4C, s x 4, O**C**OCH$_3$ x 4); **53** = 20.6, 20.7, 20.8, 20.8 (4C, s x 4, OCO**C**H$_3$ x 4); 62.3 (1C, s, **C**6); 65.3 (1C, s, **C**4); 69.2 (1C, s, **C**3); 71.0 (1C, s, **C**2); 74.7 (1C, s, **C**5); 85.1 (1C, s, **C**1); 170.0, 170.0, 170.0, 169.6 (4C, s x 4, O**C**OCH$_3$ x 4). $^1J_{C1,H1}$: **10** = 170 Hz, **9** = 158 Hz. LRMS (ESI$^+$): **10** = Q1 found 396 m/z [M+Na]$^+$, 769 m/z [2M+Na]$^+$; MS/MS (769) found 396 m/z [M+Na]$^+$; **9** = Q1 found 396 m/z [M+Na]$^+$, 769 m/z [2M+Na]$^+$; MS/MS (769) found 396 m/z [M+Na]$^+$. HRMS (ESI$^+$) for

$C_{14}H_{19}N_3O_9Na$ $[M+Na]^+$: calcd = 396.1014; **10** found 396.1011; **9** found 396.1006. These data are consistent with literature values.[8]



Scheme S2. Control CuAAC reactions carried out using alkyne **1** and azides **3**, **5** and **8**.

***N*-Boc-*O*-(1-octyl-1H-1,2,3-triazol-4-yl)methyl-L-serine.** Compound **1** (107 mg, 0.44 mmol) was dissolved in ethanol (3 mL). Compound **3** (150 mg, 0.97 mmol) was added, and the mixture was stirred vigorously. To this mixture was added a solution of $CuSO_4 \cdot 5H_2O$ (22 mg, 88 µmol) and L-ascorbic acid (30.5 mg, 0.17 mmol) in dH_2O (3 mL), and the suspension was warmed to 35°C. After 1 hour, complete dissolution had occurred and the reaction was complete by TLC analysis. The reaction was removed from heat and diluted with dH_2O (10 mL), then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with dH_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and evaporated to dryness. Volatiles were removed *in vacuo* overnight, affording a clear oil (174 mg, 99% yield). R_f = 0.29 (75:25 EtOAc:Hexanes). $^{\delta}$H ($CDCl_3$, 500 MHz): 0.89 (3H, t, J = 7.0 Hz, octyl C8**H$_3$**); 1.25-1.36 (10H, m, octyl C3**H$_2$**,C4**H$_2$**,C5**H$_2$**,C6**H$_2$**,C7**H$_2$**); 1.45 (9H, s, C(C**H$_3$**)$_3$); 1.91 (2H, q, J = 7.3 Hz, octyl C2**H$_2$**); 3.80 (1H, d, J = 8.0 Hz, αCHC**H$_{2a}$**); 4.0 (1H, d, J = 8.0 Hz, αCHC**H$_{2b}$**); 4.35 (2H, t, J = 7.3 Hz, octyl C1**H$_2$**); 4.43-4.49 (1H, m, αC**H**); 4.69 (2H, bs, αCHCH$_2$OC**H$_2$**); 5.63 (1H, d, J = 6.4 Hz, N**H**); 7.60 (1H, s, C=C**H**NC$_8$H$_{17}$); 8.33 (1H, bs, COO**H**). $^{\delta}$C ($CDCl_3$, 125 MHz): 14.1 (1C, s, octyl **C8**H$_3$); 23.3 (3C, s, C(**C**H$_3$)$_3$); 30.3 (1C, s, **C2**H$_2$); 31.7, 29.0, 29.1, 26.5, 22.6 (5C, s x 5, octyl **C3**H$_2$**C4**H$_2$**C5**H$_2$**C6**H$_2$**C7**H$_2$); 50.6 (1C, s, octyl **C1**H$_2$); 50.6 (1C, s, **α**CH); 64.6 (1C, s, αCHCH$_2$O**C**H$_2$); 70.5 (1C, s, αCH**C**H$_2$); 80.2 (1C, s, **C**(CH$_3$)$_3$); 122.8 (1C, s, C=**C**HNC$_8$H$_{17}$); 144.5 (1C, s, **C**=CHNC$_8$H$_{17}$); 156.0 (1C, s, **C**OC(CH$_3$)$_3$); 173.9 (1C, s, **C**OOH). LRMS (ESI^+):

Q1 found 421 m/z $[M+Na]^+$, 399 m/z $[M+H]^+$. HRMS (ESI^+) for $C_{19}H_{34}N_4O_5Na$ $[M+Na]^+$: calcd = 421.2421; found = 421.2412.

***N*-Boc-*O*-(1-(2,3,4,6-tetra-*O*-*a*cetyl-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl)methyl-L-serine.** Compound **1** (107 mg, 0.44 mmol) was dissolved in ethanol (3 mL). Compound **5** (164 mg, 0.44 mmol) was added, and the mixture was stirred vigorously. To this mixture was added a solution of $CuSO_4 \cdot 5H_2O$ (22 mg, 88 μmol) and L-ascorbic acid (30.5 mg, 0.17 mmol) in dH_2O (3 mL), and the suspension was warmed to 35°C. After 1 hour, complete dissolution had occurred and both starting materials had disappeared by TLC analysis. The reaction was removed from heat and diluted with dH_2O (10 mL), then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with dH_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and evaporated to dryness yielding a white solid (264 mg, 97% yield). R_f = 0.25 (75:25 EtOAc:Hexanes). $^{\delta}H$ ($CDCl_3$, 500 MHz): 1.42 (9H, s, C(C**H**$_3$)$_3$); 1.91, 2.06, 2.11, 2.14 (12H, s x 4, OCOC**H**$_3$ x 4); 3.74 (1H, d, J = 8.5 Hz, αCHC**H**$_{2a}$); 3.89 (1H, d, J = 8.5 Hz, αCHC**H**$_{2b}$); 4.04-4.10 (1H, m, Glc-C5**H**); 4.19 (1H, d, J = 12.5 Hz, Glc-C6**H**$_{2a}$); 4.30 (1H, dd, J = 12.5 & 4.7 Hz, Glc-C6**H**$_{2b}$); 4.42-4.48 (1H, m, αC**H**); 4.60 (1H, d, J = 12.5 Hz, αCHCH$_2$OC**H**$_{2a}$); 4.69 (1H, d, J = 12.5 Hz, αCHCH$_2$OC**H**$_{2b}$); 5.27 (1H, t, J = 9.6 Hz, Glc-C4**H**); 5.42-5.50 (1H, m, Glc-C3**H**); 5.42-5.50 (1H, m, Glc-C4**H**); 5.66 (1H, d, J = 7.3 Hz, N**H**); 5.95 (1H, d, J = 8.7 Hz, Glc-C1**H**); 7.42 (1H, bs, COO**H**); 7.88 (1H, s, C=C**H**N-tetraAcGlc). $^{\delta}C$ ($CDCl_3$, 125 MHz): 20.4, 20.7, 20.8, 20.9 (12C, s x 4, OCO**C**H$_3$ x 4); 28.5 (3C, s, C(**C**H$_3$)$_3$); 53.9 (1C, s, **α**CH); 61.6 (1C, s, Glc-**C6**H$_2$); 64.4 (1C, s, αCHCH$_2$O**C**H$_2$); 67.9 (1C, s, Glc-**C4**H); 70.4 (1C, s, Glc-**C3**H); 70.6 (1C, s, αCH**C**H$_2$); 72.7 (1C, s, Glc-**C2**H); 75.4 (1C, s, Glc-**C5**H); 85.9 (1C, s, Glc-**C1**H); 80.4 (1C, s, **C**(CH$_3$)$_3$); 121.5 (C=**C**HN-tetraAcGlc); 145.6 (1C, s, **C**=CHN-tetraAcGlc); 156.1 (1C, s, **C**OC(CH$_3$)$_3$); 169.5, 169.6, 169.9, 170.2 (4C, s x 4, O**C**OCH$_3$ x 4); 171.4 (1C, s, **C**OOH). LRMS (ESI^+): Q1 found 639 m/z $[M+Na]^+$, 617 m/z $[M+H]^+$. HRMS (ESI^+) for $C_{25}H_{36}N_4O_{14}Na$ $[M+Na]^+$: calcd = 639.2120; found = 639.2101.

***N*-Boc-*O*-(1-(2,3,4-tri-*O*-acetyl-β-L-rhamnopyranosyl)-1H-1,2,3-triazol-4-yl)methyl-L-serine.** Compound **1** (107 mg, 0.44 mmol) was dissolved in ethanol (3 mL). Compound **8** (139 mg, 0.44 mmol) was added, and the mixture was stirred vigorously. To this mixture was added a solution of $CuSO_4 \cdot 5H_2O$ (22 mg, 88 μmol) and L-ascorbic acid (30.5 mg, 0.17 mmol) in dH_2O (3 mL), and the suspension was warmed to 35°C. After 1 hour, complete dissolution had occurred and both starting materials had disappeared by TLC analysis. The reaction was removed from heat and diluted with dH_2O (10 mL), then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with dH_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, and evaporated to dryness yielding a white solid (244 mg, 99% yield). R_f = 0.25 (75:25 EtOAc:Hexanes). $^{\delta}H$ ($CDCl_3$, 500 MHz): 1.37 (3H, d, J = 6.2 Hz, Rha-6**H**$_3$); 1.45 (9H, s, C(C**H**$_3$)$_3$); 2.01, 2.11, 2.12 (9H, s x 3, OCOC**H**$_3$ x 3); 3.77 (1H, d, J = 8.5 Hz, αCHC**H**$_{2a}$); 3.88 (1H, dq, J = 9.7 & 6.2 Hz, Rha-C5**H**); 3.96 (1H, d, J = 8.5 Hz, αCHC**H**$_{2b}$); 4.39-4.46 (1H, m, αC**H**); 4.62 (1H, d, J = 12.5 Hz, αCHCH$_2$OC**H**$_{2a}$); 4.70 (1H, d, J = 12.5 Hz, αCHCH$_2$OC**H**$_{2b}$); 5.20 (1H, t, J = 10.0 Hz, Rha-C4**H**); 5.29 (1H, dd, J = 10.2 & 3.1 Hz, Rha-C3**H**); 5.60 (1H, d, J =

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7.3 Hz, N**H**); 5.74 (1H, dd, J = 3.0 & 0.6 Hz, Rha-C2**H**); 6.19 (1H, s, Rha-C1**H**); 7.37 (1H, bs, COO**H**); 7.81 (1H, s, C=C**H**N-triAcRha). $^{\delta}$C ($CDCl_3$, 125 MHz): 17.5 (1C, s, Rha-**C6**H_3); 20.6, 20.6, 20.8 (9C, s x 3, OCO**C**H_3 x 3); 23.3 (3C, s, C(**C**H_3)$_3$); 54.0 (1C, s, **α**CH); 64.3 (1C, s, αCHCH_2O**C**H_2); 69.2 (1C, s, Rha-**C2**H); 69.7 (1C, s, Rha-**C4**H); 70.4 (1C, s, αCH**C**H_2); 70.8 (1C, s, Rha-**C3**H); 73.9 (1C, s, Rha-**C5**H); 80.2 (1C, s, **C**(CH$_3$)$_3$); 84.7 (1C, s, Rha-**C1**H); 121.7 (C=**C**HN-triAcRha); 144.5 (1C, s, **C**=CHN-triAcRha); 156.0 (1C, s, **C**OC(CH$_3$)$_3$); 179.8, 169.9, 170.0 (3C, s x 3, O**C**OCH$_3$ x 3); 176.9 (1C, s, **C**OOH). LRMS (ESI$^+$): Q1 found 581 m/z [M+Na]$^+$, 559 m/z [M+H]$^+$. HRMS (ESI$^+$) for $C_{23}H_{34}N_4O_{12}Na$ [M+Na]$^+$: calcd = 581.2065; found = 581.2042.

Jadomycin *O*-propargyl serine (OPS) (2). *Streptomyces venezuelae* ISP5230 VS1099[9] colonies were grown on MYM-agar plates [maltose (0.4% w/v), yeast extract (0.4% w/v), malt extract (1% w/v), and agar (1.5% w/v)] for two to four weeks. Single colonies were used to inoculate MYM media [4 x 250 mL in 4-1 L flasks; maltose (0.4% w/v), yeast extract (0.4% w/v), malt extract (1% w/v); pH 7.0] which was then stirred at 30 °C for 20 h. The resulting broth was centrifuged at 3750 rpm for 15 min, and the pellet was washed with MSM medium. MSM medium consisted of the following, per litre: $MgSO_4$ (0.4 g), MOPS (1.9 g), salt solution (9 mL of 1% w/v NaCl and 1% w/v $CaCl_2$), $FeSO_4 \cdot 7H_2O$ (4.5 mL of 0.2% w/v), and trace mineral solution (4.5 mL). The trace mineral solution contained, per litre: $ZnSO_4 \cdot 7H_2O$ (880 mg), $CuSO_4 \cdot 5H_2O$ (39 mg), $MnSO_4 \cdot 4H_2O$ (6.1 mg), H_3BO_3 (5.7 mg), and $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (3.7 mg).

Culture media were prepared by dissolving **1** in 2 L MSM media to a final concentration of 30 mM, adjusting the pH to 7.5 with 5 M NaOH, and autoclaving the solution (8 x 250 mL in 8-1 L flasks). Subsequently, glucose (33 mM) and phosphate (50 μM) were added aseptically, and the *S. venezuelae* pellet slurry was added until the OD_{600} reached 0.6. The culture medium was ethanol shocked using 100% ethanol (3% v/v in the medium) and stirred at 30 °C for 48 h until the A_{526} measured between 0.5 and 1.0. Aliquots were taken and read as described previously.[10] The cellular debris was removed from production media by suction filtration through No. 5 filter paper, then 0.45 μm and 0.22 μm MF filtration disks. The filtered media was passed through a reversed-phase capture C18 column (6 x 6 cm; Biotage®) which had been preconditioned with HPLC grade methanol. Water-soluble compounds and other metabolites were eluted using distilled water (until flow-through was colourless, 10-20 L), followed by increasing amounts of methanol in water: 10%, 20%, 30%, and 40% (approx. 250 mL each). The desired secondary metabolite was eluted as a deep purple solution at 60% methanol. Solvent was removed *in vacuo* to yield crude secondary metabolite (120 mg). Thin layer chromatography using normal phase silica gel plates (10:90 MeOH:DCM as eluant) confirmed the presence of a jadomycin derivative.

The crude material was used without further purification for reaction with azides. For the purposes of characterization and biological testing, the crude material was purified by preparative TLC (5:95 MeOH:DCM), affording the pure secondary metabolite as a deep purple

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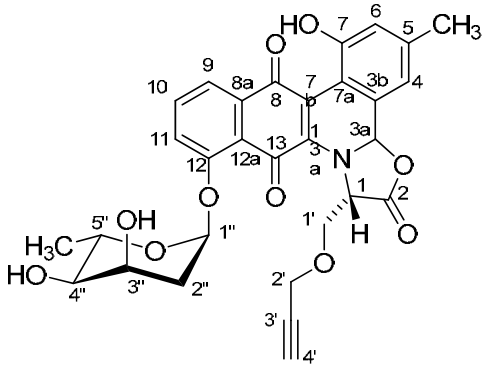
powder (6.0 mg from 30 mg crude, 12 mg/L), as a mixture of diastereomers (3a*S*/3a*R* = 64/20). R_f = 0.54 (10:90 MeOH:DCM). NMR data follows. For labeling of various protons, see Figure S1. UV-Vis (1.78 x 10^{-5} M, MeOH): λ_{max} (ε) = 278 (19710), 376 (7525), 447 (3257), 528 (1516), 634 (898), 755 (337). LRMS (ESI^+): Q1 found 562 m/z $[M+H]^+$; MS/MS (562) found 432 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{30}H_{27}N_1O_{10}Na$ $[M+Na]^+$: calcd = 584.1527; found = 584.1539.



Jadomycin *O*PS (**2**) 3a*S* NMR data.

Position	δ ^{1}H (ppm)	Multiplicity (J(Hz))	δ ^{13}C (ppm)	COSY
1	5.41	t (2.1)	59.4	1'
2	-	-	170.1	-
3a	6.51	s	88.8	-
3b	-	-		-
4	6.88	s	115.2	-
5	-	-	143.6	-
5-CH_3	2.39	s	21.3	-
6	6.93	s	120.8	-
7	-	-	155.3	-
7-OH	10.62	s	-	-
7a	-	-	111.5	-
7b	-	-	136.5	-
8	-	-	183.3	-
8a	-	-		-
9	7.99	d (7.6)	120.3	10
10	7.75	t (7.6)	136.6	9, 11
11	7.50	d (7.6)	119.2	10
12	-	-	156.1	-
12a	-	-	119.0	-
13	-	-		-
13a	-	-		-
1' CH_{2a}	4.26	dd (10.5, 2.1)	68.9	1
1' CH_{2b}	4.13-4.16	m	68.9	1

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2' CH_{2a}	4.21	dd (16.3, 2.4)	58.6	4'
2' CH_{2b}	4.10	dd (16.3, 2.4)	58.6	4'
3'	-	-	79.6	-
4'	2.20	t (2.4)	74.8	2'
1''	5.90	d (3.1)	94.6	2''ax, 2''eq
2''ax	2.25-2.27	m	35.1	2''eq, 1'', 3''
2''eq	2.46-2.49	m	35.0	2''ax, 3'', 1''
3''	4.10-4.14	m	66.0	2''ax, 2''eq, 4', 3''OH
3''OH	4.91	d (10.5)	-	3''
4''	3.30-3.34	m	72.2	5'', 3''
5''	3.70-3.74	m	66.0	5''-CH_3, 4''
5''-CH_3	1.28	d (6.3)	17.8	5''
$CDCl_3$	7.24	s	77.2	-

Jadomycin *O*PS (**2**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.45	t (2.1)	65.0	1'
2	-	-	170.1	-
3a	6.29	s	87.8	-
3b	-	-		-
4	6.84	s	114.2	-
5	-	-	143.6	-
5-CH3	2.39	s	21.3	-
6	6.91	s	120.8	-
7	-	-	155.3	-
7-OH	10.04	s	-	-
7a	-	-	111.5	-
7b	-	-		-
8	-	-	183.0	-
8a	-	-	136.4	-
9	8.02	d (7.6)	118.4	10
10	7.77	t (7.6)	136.6	9, 11
11	7.54	d (7.6)	126.8	10
12	-	-	156.6	-
12a	-	-	118.9	-
13	-	-		-
13a	-	-		-
1' CH2a	4.04	dd (10.5, 2.1)	57.9	1
1' CH2b	3.84-3.87	m	57.9	1
2' CH2a	3.78-3.81	m	68.0	4'
2' CH2b	3.75-3.78	m	68.0	4'
3'	-	-	79.6	-

4'	2.18	t (2.4)	76.7	2'
1"	5.94	d (3.1)	98.1	2"ax, 2"eq
2"ax	2.23-2.25	m	35.1	2"eq, 1", 3"
2"eq	2.49-2.51	m	35.0	2"ax, 3", 1"
3"	4.11-4.15	m	66.0	2"ax, 2"eq, 4', 3"OH
3"OH	5.08	d (10.5)	-	3"
4"	3.28-3.32	m	73.6	5", 3"
5"	3.74-3.79	m	66.0	5"-CH3, 4"
5"-CH3	1.29	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

CuAAC Reactions using Jadomycin *O*PS (2)

General synthetic protocol

Crude **2** (30 mg, <53 µmol) was dissolved in ethanol (1 mL). The azide (~ 60 mmol) was added, and the mixture was stirred vigorously. To this mixture was added a solution of $CuSO_4 \cdot 5H_2O$ (7 mg, 28 µmol) and L-ascorbic acid (10 mg, 57 µmol) in dH_2O (1 mL). At ten minutes, the reaction was determined complete by TLC analysis (Figure 2). The reaction was diluted with dH_2O (5 mL), then extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with dH_2O (25 mL) and brine (25 mL), dried with Na_2SO_4, and evaporated to dryness. Volatiles were removed *in vacuo* overnight, affording a purple solid.

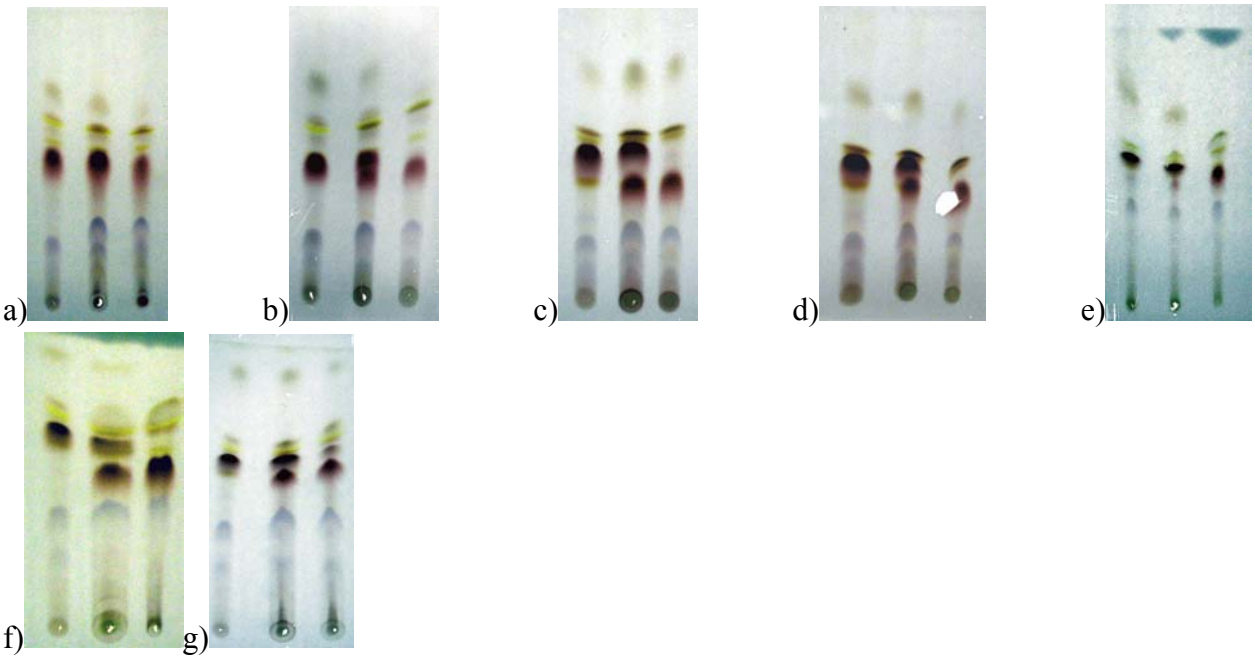

Figure S1. TLC images from CuAAC reactions with crude **28** and azides **10** (a), **9** (b), **7** (c), **8** (d), **3** (e), **4** (f), and **5** (g): lane A = crude **2**; lane B = cospot; lane C = reaction mixture at ten minutes. The plates show complete conversion of **2** to triazole products.

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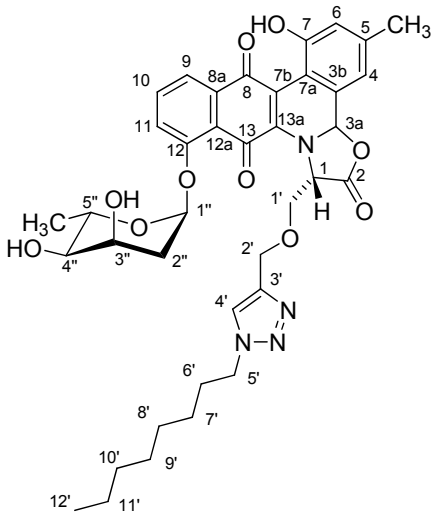
Jadomycin octyl triazole (11). The crude product (28 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (3.5 mg, >10% yield), as a mixture of diastereomers (3a*S*/3a*R* = 55/35). R_f = 0.43 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.39 x 10^{-5} M, MeOH): λ_{max} (ε) = 280 (29602), 378 (21091), 442 (6142), 529 (1480), 669 (1184), 759 (444). LRMS (ESI^+): Q1 found 718 m/z $[M+H]^+$; MS/MS (718) found 588 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{38}H_{44}N_4O_{10}Na$ $[M+Na]^+$: calcd = 739.2950; found = 739.2886.



Jadomycin octyl triazole (**11**) 3a*S* NMR data.

Position	δ ^{1}H (ppm)	Multiplicity (J(Hz))	δ ^{13}C (ppm)	COSY
1	5.38-5.41	m	59.7	1'
2	-	-	171.1	-
3a	6.40	s	87.4	-
3b	-	-		-
4	6.84	s	115.1	-
5	-	-	143.9	-
5-CH_3	2.37	s	21.2	-
6	6.91	s	120.9	-
7	-	-	155.2	-
7-OH	10.66	s	-	-
7a	-	-	111.8	-
7b	-	-		-
8	-	-	183.4	-
8a	-	-	136.4	-
9	7.97	d (7.6)	121.1	10
10	7.75	t (7.6)	136.5	9, 11
11	7.53	d (7.6)	119.3	10
12	-	-	156.5	-

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12a	-	-	119.0	-
13	-	-		-
13a	-	-		-
1' CH_{2a}	4.13-4.17	m	69.4	1
1' CH_{2b}	4.01-4.05	m	69.4	1
2' CH_{2a}	4.65	d (12.4)	64.4	-
2' CH_{2b}	4.62	d (12.4)	64.4	-
3'	-	-	145.2	-
4'	7.43	s	122.0	-
5'	3.74-3.80	m	50.2	6'
6'	1.68-1.74	m	30.0	5', 7'
7'	1.60-1.65	m	30.4	6', 8'
8'	1.52-1.59	m	24.5	7', 9'
9'	1.11-1.24	m	22.5-25.9	8', 10'
10'	1.11-1.24	m	22.5-25.9	9', 11'
11'	1.11-1.24	m	22.5-25.9	10', 12'
12'	0.87-0.91	m	14.1	11'
1''	5.92-5.94	m	94.9	2''ax, 2''eq
2''ax	2.25-2.27	m	34.9	2''eq, 1'', 3''
2''eq	2.56-2.58	m	34.9	2''ax, 3'', 1''
3''	4.11-4.17	m	66.0	2''ax, 2''eq, 4', 3''OH
3''OH	4.87	d (10.5)	-	3''
4''	3.27-3.31	m	72.2	5'', 3''
5''	3.64-3.68	m	66.0	5''-CH_3, 4''
5''-CH_3	1.11-1.24	m	17.8	5''
$CDCl_3$	7.24	s	77.2	-

Jadomycin octyl triazole (**11**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.43-5.45	m	60.3	1'
2	-	-	171.1	-
3a	6.29	s	88.8	-
3b	-	-		-
4	6.88	s	114.9	-
5	-	-	143.5	-
5-CH3	2.41	s	21.2	-
6	6.93	s	120.6	-
7	-	-	155.0	-
7-OH	10.19	s	-	-
7a	-	-	111.8	-
7b	-	-		-
8	-	-	184.8	-

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8a	-	-	136.4	-
9	8.00	d (7.6)	121.4	10
10	7.77	t (7.6)	136.5	9, 11
11	7.55	d (7.6)	120.0	10
12	-	-	157.1	-
12a	-	-	118.5	-
13	-	-		-
13a	-	-		-
1' CH2a	3.95-3.99	m	68.5	1
1' CH2b	3.90	dd (10.4, 2.7)	68.5	1
2' CH2a	4.37	d (12.4)	64.3	-
2' CH2b	4.27	d (12.4)	64.3	-
3'	-	-	145.2	-
4'	6.50	s	121.3	-
5'	3.74-3.80	m	50.2	6’
6'	1.68-1.74	m	30.0	5’, 7’
7'	1.60-1.65	m	30.4	6’, 8’
8'	1.52-1.59	m	24.5	7’, 9’
9'	1.11-1.24	m	22.5-25.9	8’, 10’
10'	1.11-1.24	m	22.5-25.9	9’, 11’
11'	1.11-1.24	m	22.5-25.9	10’, 12’
12'	0.87-0.91	m	14.1	11’
1"	5.92-5.94	m	94.9	2"ax, 2"eq
2"ax	2.22-2.25	m	34.9	2"eq, 1", 3"
2"eq	2.59-2.61	m	34.9	2"ax, 3", 1"
3"	4.07-4.12	m	66.0	2"ax, 2"eq, 4', 3"OH
3"OH	5.04	d (10.5)	-	3"
4"	3.27-3.31	m	72.2	5", 3"
5"	3.67-3.72	m	66.0	5"-CH3, 4"
5"-CH3	1.11-1.24	m	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin benzyl triazole (12). The crude product (31 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (3.7 mg, >11% yield), as a mixture of diastereomers (3a*S*/3a*R* = 60/36). R_f = 0.46 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.44 x 10^{-5} M, MeOH): λ_{max} (ε) = 280 (31122), 378 (23133), 443 (6322), 529 (1459), 665 (1181), 756 (417). LRMS (ESI^+): Q1 found 717 m/z $[M+Na]^+$, 695 m/z $[M+H]^+$; MS/MS (665) found 565 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{37}H_{35}N_4O_{10}$ $[M+H]^+$: calcd = 695.2348; found = 695.2328.

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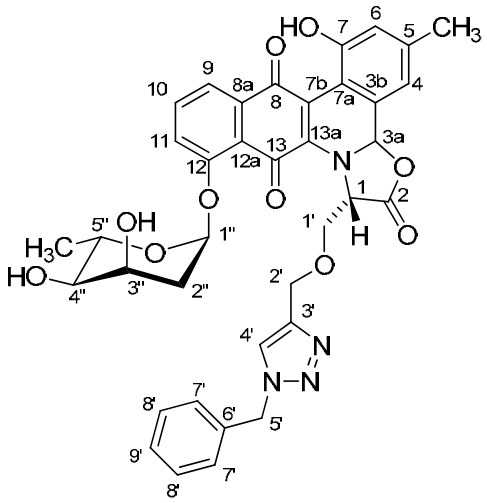

Jadomycin benzyl triazole (**12**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.29-5.31	m	61.0	1'
2	-	-	172.2	-
3a	6.24	s	89.1	-
3b	-	-		-
4	6.73	s	113.9	-
5	-	-	143.2	-
5-CH3	2.29	s	21.4	-
6	6.82	s	120.8	-
7	-	-	155.3	-
7-OH	10.57	s	-	-
7a	-	-	111.0	-
7b	-	-		-
8	-	-	183.4	-
8a	-	-	136.5	-
9	7.89	d (7.6)	119.2	10
10	7.67	t (7.6)	136.7	9, 11
11	7.45	d (7.6)	124.2	10
12	-	-	156.5	-
12a	-	-	119.1	-
13	-	-		-
13a	-	-		-
1' CH2a	4.16	dd (10.4, 2.2)	69.7	1
1' CH2b	4.05	dd (10.4, 2.2)	69.7	1
2' CH2a	4.52	d (12.4)	64.4	-
2' CH2b	4.49	d (12.4)	64.4	-
3'	-	-	145.9	-
4'	7.24	s	124.3	-

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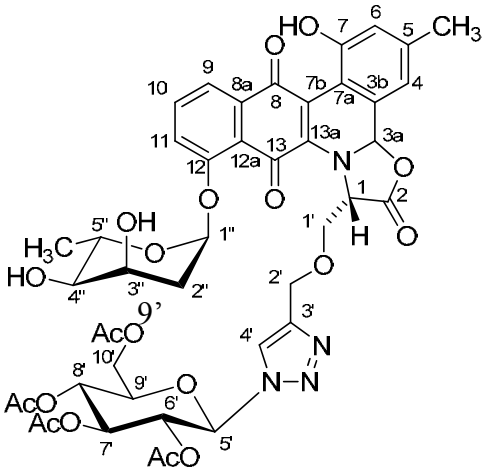
5'	5.22	s	53.5	-
6'	-	-	115.8	-
7'	7.20-7.27	m	127.5	8', 9'
8'	7.07-7.10	m	132.7	7', 9'
9'	7.20-7.27	m	128.1	7', 8'
1"	5.84	d (3.1)	95.5	2"ax, 2"eq
2"ax	2.15-2.17	m	35.3	2"eq, 1", 3"
2"eq	2.49-2.52	m	35.3	2"ax, 3", 1"
3"	4.03-4.07	m	65.8	2"ax, 2"eq, 4', 3"OH
3"OH	4.78	d (10.5)	-	3"
4"	3.20-3.22	m	72.3	5", 3"
5"	3.56-3.63	m	63.9	5"-CH3, 4"
5"-CH3	1.19	d (6.3)	17.9	5"
CDCl3	7.24	s	77.2	-

Jadomycin benzyl triazole (**12**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.34	t (2.2)	60.2	1'
2	-	-	172.2	-
3a	6.18	s	87.1	-
3b	-	-		-
4	6.74	s	114.8	-
5	-	-	143.9	-
5-CH3	2.22	s	21.1	-
6	6.78	s	120.8	-
7	-	-	155.4	-
7-OH	10.14	s	-	-
7a	-	-	111.4	-
7b	-	-		-
8	-	-	183.9	-
8a	-	-	136.8	-
9	7.92	d (7.6)	123.9	10
10	7.69	t (7.6)	138.1	9, 11
11	7.47	d (7.6)	126.2	10
12	-	-	156.2	-
12a	-	-	118.5	-
13	-	-		-
13a	-	-		-
1' CH2a	3.99	dd (10.4, 2.2)	69.7	1
1' CH2b	3.84	dd (10.4, 2.2)	69.7	1
2' CH2a	4.24	d (12.4)	64.1	-
2' CH2b	4.15	d (12.4)	64.1	-

3'	-	-	146.4	-
4'	6.47	s	124.3	-
5'	5.28	s	53.6	
6'	-	-	116.0	-
7'	7.20-7.27	m	127.9	8', 9'
8'	7.04-7.06	m	132.7	7', 9'
9'	7.20-7.27	m	128.4	7', 8'
1"	5.84	d (3.1)	94.5	2"ax, 2"eq
2"ax	2.13-2.15	m	35.0	2"eq, 1", 3"
2"eq	2.47-2.49	m	35.0	2"ax, 3", 1"
3"	4.03-4.07	m	66.1	2"ax, 2"eq, 4', 3"OH
3"OH	4.95	d (10.5)	-	3"
4"	3.18-3.20	m	72.6	5", 3"
5"	3.63-3.70	m	63.6	5"-CH3, 4"
5"-CH3	1.20	d (6.3)	17.9	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylglucosyl triazole (**13**). The crude product (59 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (9.0 mg, >16% yield), as a mixture of diastereomers (3a*S*/3a*R* = 60/31). R_f = 0.50 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.07 x 10^{-5} M, MeOH): λ_{max} (ε) = 285 (31785), 371 (11031), 442 (5235), 529 (2898), 670 (935), 758 (374). LRMS (ESI^+): Q1 found 957 m/z $[M+Na]^+$, 935 m/z $[M+H]^+$; MS/MS (935) found 805 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{44}H_{46}N_4O_{19}Na$ $[M+Na]^+$: calcd = 957.2648; found = 957.2651.



Jadomycin β-tetraacetylglucosyl triazole (**13**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.33	t (2.2)	59.8	1'

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2	-	-	171.5	-
3a	6.37	s	88.9	-
3b	-	-		-
4	6.78	s	115.3	-
5	-	-	143.5	-
5-CH3	2.28	s	21.2	-
6	6.81	s	120.9	-
7	-	-	155.1	-
7-OH	10.53	s	-	-
7a	-	-	111.9	-
7b	-	-		-
8	-	-	183.5	-
8a	-	-	136.4	-
9	7.88	d (7.6)	121.2	10
10	7.66	t (7.6)	136.4	9, 11
11	7.42	d (7.6)	119.3	10
12	-	-	156.4	-
12a	-	-	119.4	-
13	-	-		-
13a	-	-		-
1' CH2a	4.15-4.18	m	70.0	1
1' CH2b	4.03-4.06	m	70.0	1
2' CH2a	4.59	d (12.4)	64.7	-
2' CH2b	4.54	d (12.4)	64.7	-
3'	-	-	145.9	-
4'	7.65	s	120.9	-
5'	5.69	d (8.9)	85.6	6'
6'	5.28-5.31	m	70.0	5', 7'
7'	5.30-5.33	m	72.4	6', 8'
8'	5.16	t (9.5)	67.5	7', 9'
9'	3.90	ddd (10.1, 5.0, 2.1)	75.0	8', 10' CH2a, 10' CH2b
10' CH2a	4.20	dd (12.7, 4.9)	61.4	9', 10' CH2b
10' CH2b	4.29	dd (12.7, 4.9)	61.4	9', 10' CH2a
4 (OAc CH3)	1.66, 1.95, 2.00, 2.01	s x 4	20.6	-
4 (OAc C=O)	-	-	171.1	-
1"	5.82-5.85	m	94.6	2"ax, 2"eq
2"ax	2.15-2.17	m	35.0	2"eq, 1", 3"
2"eq	2.39-2.42	m	35.0	2"ax, 3", 1"
3"	4.03-4.07	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.83	d (10.5)	-	3"

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4"	3.18-3.20	m	72.2	5", 3"
5"	3.56-3.62	m	66.0	5"-CH3, 4"
5"-CH3	1.18	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylglucosyl triazole (**13**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.39	t (2.2)	60.2	1'
2	-	-	171.3	-
3a	6.17	s	87.5	-
3b	-	-		-
4	6.90	s	114.8	-
5	-	-	144.1	-
5-CH3	2.33	s	21.2	-
6	6.81	s	120.5	-
7	-	-	154.8	-
7-OH	10.16	s	-	-
7a	-	-	111.9	-
7b	-	-		-
8	-	-	184.7	-
8a	-	-	136.4	-
9	7.88	d (7.6)	121.2	10
10	7.65	t (7.6)	136.4	9, 11
11	7.42	d (7.6)	119.3	10
12	-	-	157.1	-
12a	-	-	118.5	-
13	-	-		-
13a	-	-		-
1' CH2a	3.92	dd (10.6, 2.3)	69.3	1
1' CH2b	3.67	dd (10.6, 2.3)	69.3	1
2' CH2a	4.33	d (12.4)	64.4	-
2' CH2b	4.19	d (12.4)	64.4	-
3'	-	-	146.3	-
4'	6.65	s	121.0	-
5'	5.53	d (8.9)	85.4	6'
6'	5.25	-	70.2	5', 7'
7'	5.24-5.28	m	72.5	6', 8'
8'	5.26-5.30	m	67.5	7', 9'
9'	3.91	dd (10.1, 5.0, 2.1)	75.0	8', 10' CH2a, 10' CH2b
10' CH2a	4.20	dd (12.7, 4.9)	61.4	9', 10' CH2b

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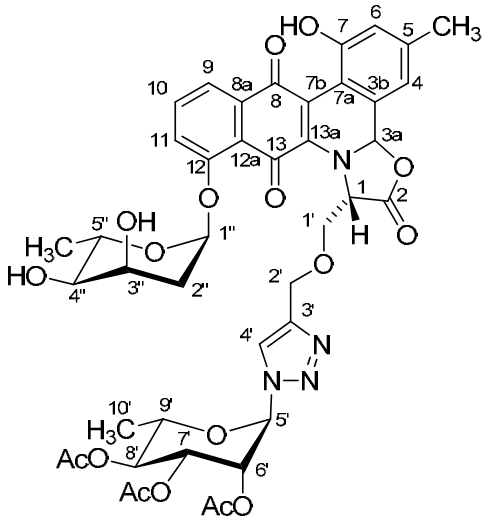
10' CH2b	4.29	dd (12.7, 4.9)	61.4	9', 10' CH2a
4 (OAc CH3)	1.59, 1.96, 2.01, 2.05	s x 4	20.6	-
4 (OAc C=O)	-	-	171.1	-
1"	5.80-5.82	m	94.6	2"ax, 2"eq
2"ax	2.12-2.15	m	35.0	2"eq, 1", 3"
2"eq	2.41-2.45	m	35.0	2"ax, 3", 1"
3"	4.04-4.08	m	65.9	2"ax, 2"eq, 4', 3"OH'
3"OH	4.95	d (10.5)	-	3"
4"	3.19-3.22	m	72.2	5", 3"
5"	3.65-3.70	m	65.9	5"-CH3, 4"
5"-CH3	1.20	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin α-triacetylrhamnosyl triazole (15). The crude product (60 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (7.1 mg, >15% yield), as a mixture of diastereomers (3a*S*/3a*R* = 52/30). R_f = 0.45 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.14 x 10^{-5} M, MeOH): λ_{max} (ε) = 280 (29421), 369 (10311), 438 (5025), 528 (2826), 666 (1214), 768 (614). LRMS (ESI^+): Q1 found 899 m/z $[M+Na]^+$, 877 m/z $[M+H]^+$; MS/MS (877) found 747 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{42}H_{45}N_4O_{17}$ $[M+H]^+$: calcd = 877.2774; found = 877.2770.



Jadomycin α-triacetylrhamnosyl triazole (**15**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.34	t (2.2)	59.8	1'
2	-	-	171.4	-
3a	6.33	s	88.6	-

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3b	-	-		-
4	6.76	s	114.9	-
5	-	-	143.7	-
5-CH3	2.28	s	21.1	-
6	6.82	s	120.8	-
7	-	-	155.3	-
7-OH	10.63	s	-	-
7a	-	-	111.7	-
7b	-	-		-
8	-	-	183.5	-
8a	-	-	136.3	-
9	7.88	d (7.6)	121.1	10
10	7.65	t (7.6)	136.8	9, 11
11	7.44	d (7.6)	119.5	10
12	-	-	155.9	-
12a	-	-	119.1	-
13	-	-		-
13a	-	-		-
1' CH2a	4.19	dd (12.4, 2.2)	70.1	1
1' CH2b	4.14	dd (12.4, 2.2)	70.1	1
2' CH2a	4.59	d (12.9)	64.7	-
2' CH2b	4.61	d (12.9)	64.7	-
3'	-	-	145.7	-
4'	7.58	s	121.3	-
5'	5.77	d (1.9)	83.6	-
6'	5.78	dd (3.3, 1.9)	68.4	7'
7'	5.62	dd (9.3, 3.3)	68.6	6', 8'
8'	5.07	t (9.3)	69.3	7', 9'
9'	3.48	dq (9.1, 6.3)	69.8	8', 10'
10'	1.10	d (6.3)	17.9	9'
3 (OAc CH3)	1.97, 2.02, 2.09	s x 3	20.8	-
3 (OAc C=O)	-	-	171.3	-
1"	5.86-5.88	m	94.6	2"ax, 2"eq
2"ax	2.16-2.18	m	35.1	2"eq, 1", 3"
2"eq	2.39-2.42	m	35.1	2"ax, 3", 1"
3"	4.03-4.09	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.82	d (10.5)	-	3"
4"	3.18-3.23	m	72.1	5", 3"
5"	3.66-3.73	m	66.0	5"-CH3, 4"
5"-CH3	1.18-1.20	m	17.6	5"
CDCl3	7.24	s	77.2	-

Jadomycin α-triacetylrhamnosyl triazole (**15**) 3a*R* NMR data.

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Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.37	t (2.2)	60.3	1'
2	-	-	171.4	-
3a	6.20	s	87.5	-
3b	-	-		-
4	6.74	s	114.9	-
5	-	-	144.3	-
5-CH3	2.28	s	21.0	-
6	6.80	s	120.8	-
7	-	-	155.2	-
7-OH	10.00	s	-	-
7a	-	-	111.7	-
7b	-	-		-
8	-	-	183.5	-
8a	-	-	136.1	-
9	7.93	d (7.6)	121.1	10
10	7.68	t (7.6)	136.8	9, 11
11	7.49	d (7.6)	120.6	10
12	-	-	155.8	-
12a	-	-	118.5	-
13	-	-		-
13a	-	-		-
1' CH2a	3.98	dd (11.5, 2.2)	69.3	1
1' CH2b	3.80	dd (11.5, 2.2)	69.3	1
2' CH2a	4.37	d (12.9)	64.9	-
2' CH2b	4.23	d (12.9)	64.9	-
3'	-	-	146.2	-
4'	6.65	s	121.6	-
5'	5.70	d (1.9)	83.4	-
6'	5.80	dd (3.3, 1.9)	68.8	7'
7'	5.70	dd (9.3, 3.3)	69.0	6', 8'
8'	5.05	t (10.3)	69.3	7', 9'
9'	3.53	dq (9.1, 6.3)	69.8	8', 10'
10'	1.04	d (6.3)	17.9	9'
3 (OAc CH3)	1.96, 2.03, 2.15	s x 3	20.8	-
3 (OAc C=O)	-	-	171.0	-
1"	5.84-5.86	m	94.5	2"ax, 2"eq
2"ax	2.14-2.16	m	34.9	2"eq, 1", 3"
2"eq	2.45-2.48	m	34.9	2"ax, 3", 1"
3"	4.03-4.09	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.95	d (10.5)	-	3"
4"	3.18-3.23	m	73.5	5", 3"
5"	3.59-3.64	m	66.0	5"-CH3, 4"

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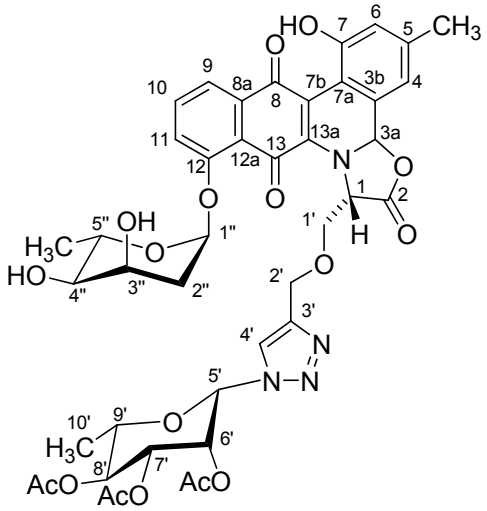
5"-CH3	1.18-1.20	m	17.6	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-triacetylrhamnosyl triazole (16). The crude product (52 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (5.8 mg, >14% yield), as a mixture of diastereomers (3a*S*/3a*R* = 63/20). R_f = 0.43 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.14 x 10^{-5} M, MeOH): λ_{max} (ε) = 282 (27883), 369 (9294), 438 (4823), 529 (2630), 667 (1228), 771 (701). LRMS (ESI^+): Q1 found 899 m/z $[M+Na]^+$, 877 m/z $[M+H]^+$; MS/MS (877) found 747 $[M+H\text{-digitoxose}]^+$, 305 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{42}H_{44}N_4O_{17}Na$ $[M+Na]^+$: calcd = 899.2594; found = 899.2540.



Jadomycin β-triacetylrhamnosyl triazole (**16**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.25	t (2.2)	59.6	1'
2	-	-	171.1	-
3a	6.20	s	88.8	-
3b	-	-		-
4	6.74	s	114.9	-
5	-	-	143.4	-
5-CH3	2.27	s	21.1	-
6	6.80	s	120.8	-
7	-	-	155.2	-
7-OH	10.50	s	-	-
7a	-	-	111.7	-
7b	-	-		-
8	-	-	183.4	-
8a	-	-	136.4	-
9	7.86	d (7.6)	120.7	10

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10	7.72	t (7.6)	136.5	9, 11
11	7.49	d (7.6)	119.7	10
12	-	-	156.8	-
12a	-	-	119.1	-
13	-	-		-
13a	-	-		-
1' CH2a	4.23	dd (12.1, 2.2)	68.9	1
1' CH2b	4.11	dd (12.1, 2.2)	68.9	1
2' CH2a	4.55	d (12.9)	63.6	-
2' CH2b	4.45	d (12.9)	63.6	-
3'	-	-	145.2	-
4'	7.57	s	121.2	-
5'	5.44	d (1.1)	84.5	-
6'	5.50	dd (3.3, 1.9)	68.5	7'
7'	5.03-5.04	m	70.6	6', 8'
8'	5.00-5.04	m	69.3	7', 9'
9'	3.70-3.75	m	73.9	8', 10'
10'	1.16	d (6.3)	17.8	9'
3 (OAc CH3)	1.92, 1.95, 2.03	s x 3	20.7	-
3 (OAc C=O)	-	-	170.9	-
1"	5.86-5.88	m	95.3	2"ax, 2"eq
2"ax	2.15-2.17	m	35.0	2"eq, 1", 3"
2"eq	2.56-2.59	m	35.0	2"ax, 3", 1"
3"	4.05-4.08	m	66.0	2"ax, 2"eq, 4', 3"OH
3"OH	4.76	d (10.5)	-	3"
4"	3.20-3.23	m	72.2	5", 3"
5"	3.70	dq (9.9, 6.2)	66.0	5"-CH3, 4"
5"-CH3	1.22	d (6.2)	17.5	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-triacetylrhamnosyl triazole (**16**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.32	t (2.2)	60.2	1'
2	-	-	171.1	-
3a	6.17	s	87.5	-
3b	-	-		-
4	6.74	s	114.2	-
5	-	-	144.0	-
5-CH3	2.31	s	21.1	-
6	6.79	s	122.0	-
7	-	-	155.0	-
7-OH	9.97	s	-	-

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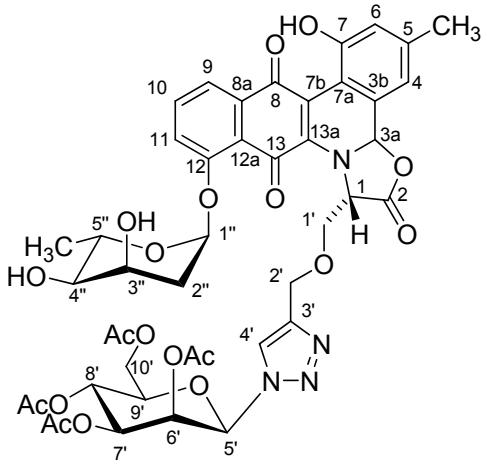
7a	-	-	111.7	-
7b	-	-		-
8	-	-	183.4	-
8a	-	-	136.4	-
9	7.91	d (7.6)	121.1	10
10	7.71	t (7.6)	136.5	9, 11
11	7.49	d (7.6)	119.7	10
12	-	-	156.8	-
12a	-	-	118.6	-
13	-	-		-
13a	-	-		-
1' CH2a	3.98	dd (12.1, 2.2)	68.2	1
1' CH2b	3.86	dd (12.1, 2.2)	68.2	1
2' CH2a	4.16	d (12.9)	63.2	-
2' CH2b	4.13	d (12.9)	63.2	-
3'	-	-	145.1	-
4'	7.08	s	121.6	-
5'	5.55	d (1.1)	84.4	-
6'	5.48	dd (3.3, 1.9)	68.5	7'
7'	5.06-5.07	m	70.6	6', 8'
8'	5.04-5.07	m	69.6	7', 9'
9'	3.62	dq (9.6, 6.3)	73.9	8', 10'
10'	1.19	d (6.3)	17.8	9'
3 (OAc CH3)	1.89, 1.92, 2.04	s x 3	20.7	-
3 (OAc C=O)	-	-	170.9	-
1"	5.84-5.86	m	94.5	2"ax, 2"eq
2"ax	2.13-2.15	m	35.0	2"eq, 1", 3"
2"eq	2.54-2.56	m	35.0	2"ax, 3", 1"
3"	4.05-4.08	m	66.0	2"ax, 2"eq, 4', 3"OH
3"OH	4.94	d (10.5)	-	3"
4"	3.18-3.21	m	72.2	5", 3"
5"	3.62	dq (9.6, 6.2)	66.0	5"-CH3, 4"
5"-CH3	1.33	d (6.2)	17.5	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylmannosyl triazole (17). The crude product (66 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (4.8 mg, >9.1% yield), as a mixture of diastereomers (3a*S*/3a*R* = 65/22). R_f = 0.49 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.07×10^{-5} M, MeOH): λ_{max} (ε) = 280 (36459), 371 (10751), 442 (5422), 528 (3459), 669 (1589), 758 (841). LRMS (ESI^+): Q1 found 957 m/z $[M+Na]^+$, 935 m/z $[M+H]^+$; MS/MS (935) found 805 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{44}H_{46}N_4O_{19}Na$ $[M+Na]^+$: calcd = 957.2648; found = 957.2641.



Jadomycin β-tetraacetylmannosyl triazole (**17**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.34	t (2.2)	59.9	1'
2	-	-	171.4	-
3a	6.34	s	88.8	-
3b	-	-		-
4	6.73	s	115.1	-
5	-	-	143.7	-
5-CH3	2.28	s	21.2	-
6	6.82	s	120.9	-
7	-	-	155.3	-
7-OH	10.60	s	-	-
7a	-	-	112.1	-
7b	-	-		-
8	-	-	183.0	-
8a	-	-	136.3	-
9	7.87	d (7.6)	121.2	10
10	7.66	t (7.6)	136.7	9, 11
11	7.43	d (7.6)	119.3	10
12	-	-	156.3	-
12a	-	-	119.2	-
13	-	-		-
13a	-	-		-
1' CH2a	4.17	dd (12.4, 2.2)	70.1	1
1' CH2b	4.03	dd (12.4, 2.2)	70.1	1
2' CH2a	4.61	d (12.7)	64.8	-
2' CH2b	4.51	d (12.7)	64.8	-
3'	-	-	145.2	-
4'	7.66	s	121.2	-

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5'	5.98	d (1.1)	84.6	6'
6'	5.54	dd (3.3, 1.1)	68.6	5', 7'
7'	5.17	dd (10.3, 3.3)	70.7	6', 8'
8'	5.28	t (10.3)	64.7	7', 9'
9'	3.87	dd (10.1, 5.0, 2.1)	75.7	8', 10' CH2a, 10' CH2b
10' CH2a	4.13-4.27	m	61.9	9', 10' CH2b
10' CH2b	4.13-4.27	m	61.9	9', 10' CH2a
4 (OAc CH3)	1.93, 1.99, 2.03, 2.04	s x 4	20.6	-
4 (OAc C=O)	-	-	170.9	-
1"	5.82-5.85	m	94.7	2"ax, 2"eq
2"ax	2.15-2.17	m	35.0	2"eq, 1", 3"
2"eq	2.41-2.45	m	35.0	2"ax, 3", 1"
3"	4.03-4.08	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.80	d (10.5)	-	3"
4"	3.18-3.23	m	72.2	5", 3"
5"	3.67	dq (9.8, 6.2)	66.0	5"-CH3, 4"
5"-CH3	1.19	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylmannosyl triazole (**17**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.36	t (2.2)	60.3	1'
2	-	-	171.0	-
3a	6.18	s	87.5	-
3b	-	-		-
4	6.71	s	115.1	-
5	-	-	143.7	-
5-CH3	2.28	s	21.2	-
6	6.84	s	120.9	-
7	-	-	155.1	-
7-OH	10.07	s	-	-
7a	-	-	112.1	-
7b	-	-		-
8	-	-	183.4	-
8a	-	-	136.5	-
9	7.92	d (7.6)	121.5	10
10	7.68	t (7.6)	136.7	9, 11
11	7.46	d (7.6)	119.7	10

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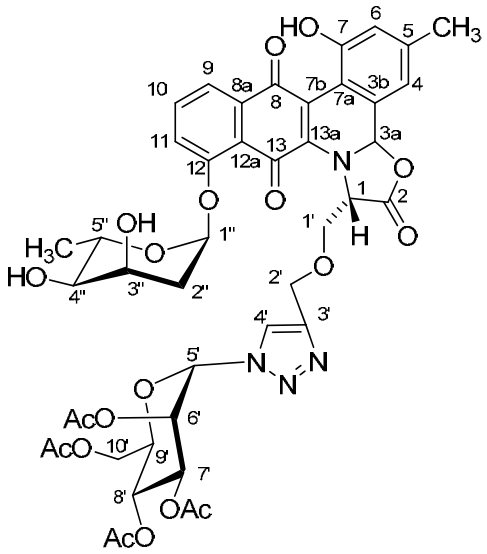
12	-	-	156.3	-
12a	-	-	118.5	-
13	-	-		-
13a	-	-		-
1' CH2a	3.99	dd (12.4, 2.2)	69.4	1
1' CH2b	3.73	dd (12.4, 2.2)	69.4	1
2' CH2a	4.22	d (12.7)	64.5	-
2' CH2b	4.17	d (12.7)	64.5	-
3'	-	-	145.5	-
4'	7.11	s	118.3	-
5'	5.90	d (1.1)	84.4	6'
6'	5.59	dd (3.3, 1.1)	68.3	5', 7'
7'	5.18	dd (10.3, 3.3)	70.5	6', 8'
8'	5.30	t (10.3)	64.7	7', 9'
9'	3.89	dd (10.1, 5.0, 2.1)	75.7	8', 10' CH2a, 10' CH2b
10' CH2a	4.13-4.27	m	61.9	9', 10' CH2b
10' CH2b	4.13-4.27	m	61.9	9', 10' CH2a
4 (OAc CH3)	1.93, 1.98, 2.03, 2.04	s x 4	20.6	-
4 (OAc C=O)	-	-	170.9	-
1"	5.82-5.85	m	94.7	2"ax, 2"eq
2"ax	2.13-2.15	m	35.0	2"eq, 1", 3"
2"eq	2.45-2.48	m	35.0	2"ax, 3", 1"
3"	4.03-4.08	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.94	d (10.5)	-	3"
4"	3.18-3.23	m	72.2	5", 3"
5"	3.61	dq (9.8, 6.2)	65.9	5"-CH3, 4"
5"-CH3	1.20	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylmannosyl triazole (18). The crude product (67 mg) was purified by preparative TLC (5:95 MeOH:DCM), affording a shiny purple solid (5.0 mg, >9.0% yield), as a mixture of diastereomers (3a*S*/3a*R* = 41/35). R_f = 0.54 (10:90 MeOH:DCM). NMR data follows in tables. UV-Vis (1.07 x 10^{-5} M, MeOH): λ_{max} (ε) = 282 (26830), 371 (10844), 442 (4394), 528 (2337), 667 (935), 756 (374). LRMS (ESI^+): Q1 found 957 m/z $[M+Na]^+$, 935 m/z $[M+H]^+$; MS/MS (935) found 805 $[M+H\text{-digitoxose}]^+$, 306 $[M+H\text{-}C_6H_{10}O_2]^+$. HRMS ($ESI^+$) for $C_{44}H_{46}N_4O_{19}Na$ $[M+Na]^+$: calcd = 957.2648; found = 957.2632.



Jadomycin β-tetraacetylmannosyl triazole (**18**) 3a*S* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.30-5.32	m	59.6	1'
2	-	-	171.2	-
3a	6.19	s	87.4	-
3b	-	-		-
4	6.75	s	115.9	-
5	-	-	143.6	-
5-CH3	2.28	s	21.2	-
6	6.81	s	120.8	-
7	-	-	155.4	-
7-OH	10.57	s	-	-
7a	-	-	111.8	-
7b	-	-		-
8	-	-	183.3	-
8a	-	-	136.3	-
9	7.84	d (7.6)	121.0	10
10	7.65	t (7.6)	136.7	9, 11
11	7.63	d (7.6)	119.9	10
12	-	-	156.5	-
12a	-	-	119.2	-
13	-	-		-
13a	-	-		-
1' CH2a	4.15	dd (10.4, 2.2)	69.6	1
1' CH2b	4.04	dd (10.4, 2.2)	69.6	1
2' CH2a	4.61	d (12.9)	64.2	-
2' CH2b	4.57	d (12.9)	64.2	-

3'	-	-	146.0	-
4'	7.60	s	122.8	-
5'	5.79	d (1.9)	83.9	-
6'	5.30-5.31	m	67.8	7'
7'	5.66	dd (10.1, 3.7)	68.8	6', 8'
8'	5.28	t (10.1)	65.6	7', 9'
9'	3.61	dd (10.1, 5.0, 2.1)	71.7	8', 10' CH2a, 10' CH2b
10' CH2a	4.28	dd (12.6, 4.9)	61.5	9', 10' CH2b
10' CH2b	4.16	dd (12.6, 4.9)	61.5	9', 10' CH2a
4 (OAc CH3)	1.98, 1.98, 2.03, 2.13	s x 4	20.7	-
4 (OAc C=O)	-	-	171.2	-
1"	5.86-5.88	m	94.8	2"ax, 2"eq
2"ax	2.14-2.16	m	34.9	2"eq, 1", 3"
2"eq	2.48-2.51	m	34.9	2"ax, 3", 1"
3"	4.05-4.10	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	4.83	d (10.5)	-	3"
4"	3.19-3.22	m	72.1	5", 3"
5"	3.54-3.59	m	66.0	5"-CH3, 4"
5"-CH3	1.19	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

Jadomycin β-tetraacetylmannosyl triazole (**18**) 3a*R* NMR data.

Position	δ 1H (ppm)	Multiplicity (J(Hz))	δ 13C (ppm)	COSY
1	5.37	t (2.2)	60.2	1'
2	-	-	169.4	-
3a	6.33	s	88.7	-
3b	-	-		-
4	6.78	s	115.9	-
5	-	-	144.2	-
5-CH3	2.31	s	21.2	-
6	6.81	s	120.8	-
7	-	-	155.0	-
7-OH	9.90	s	-	-
7a	-	-	111.8	-
7b	-	-		-
8	-	-	185.3	-
8a	-	-	136.3	-
9	7.91	d (7.6)	121.6	10

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10	7.63	t (7.6)	136.7	9, 11
11	7.44	d (7.6)	119.9	10
12	-	-	157.0	-
12a	-	-	118.4	-
13	-	-		-
13a	-	-		-
1' CH2a	4.00	dd (12.4, 2.2)	69.0	1
1' CH2b	3.91	dd (12.4, 2.2)	69.0	1
2' CH2a	4.33	d (12.9)	63.9	-
2' CH2b	4.21	d (12.9)	63.9	-
3'	-	-	146.3	-
4'	6.55	s	122.2	-
5'	5.77	d (1.9)	83.9	-
6'	5.25-5.26	m	67.8	7'
7'	5.71	dd (10.1, 3.3)	68.8	6', 8'
8'	5.24	t (10.1)	65.5	7', 9'
9'	3.47	dd (10.1, 5.0, 2.1)	71.3	8', 10' CH2a, 10' CH2b
10' CH2a	3.99	dd (12.6, 4.9)	61.4	9', 10' CH2b
10' CH2b	3.91	dd (12.6, 4.9)	61.4	9', 10' CH2a
4 (OAc CH3)	1.93, 1.94, 2.01, 2.18	s x 4	20.7	-
4 (OAc C=O)	-	-	170.8	-
1"	5.88-5.91	m	94.8	2"ax, 2"eq
2"ax	2.12-2.14	m	34.9	2"eq, 1", 3"
2"eq	2.50-2.53	m	34.9	2"ax, 3", 1"
3"	4.05-4.10	m	65.9	2"ax, 2"eq, 4', 3"OH
3"OH	5.02	d (10.5)	-	3"
4"	3.20-3.23	m	72.1	5", 3"
5"	3.65-3.71	m	66.0	5"-CH3, 4"
5"-CH3	1.21	d (6.3)	17.8	5"
CDCl3	7.24	s	77.2	-

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DNA cleavage and binding

Materials and methods

Supercoiled pUC19 plasmid (Form I) was prepared by transformation of NovaBlue cells (Novagen) followed by purification using the QIAprep Spin Miniprep Kit (Qiagen) to yield approximately 30 μg of plasmid DNA per 20-mL culture.

All jadomycins were dissolved initially in 95% EtOH and subsequent dilutions were made with water (distilled, deionized from a Milli-Q system) where the final assay tubes contained <1% EtOH.

UV-vis measurements were recorded using a Jasco V530 spectrophotometer (JASCO Corp).

DNA binding

UV-vis titration experiments were performed at 25°C with calf thymus DNA (Sigma). The DNA concentration was determined by UV absorption at 260 nm (ε = 6600 $M^{-1}cm^{-1}$, where concentration units refer to bases). Samples of jadomycin compounds (20 μM) were prepared in 5 mM Tris (pH 7.4) and 50 μM NaCl. UV-vis spectra were collected for jadomycins alone and the jadomycins with the addition of calf thymus DNA (200 μM bases).

Copper-mediated DNA cleavage assays

Reaction mixtures (20 μL total volume) were prepared in 0.5 mL sterile microfuge tubes. Transformed pUC19 plasmid (final concentration 130 ng, or 20 μM bases, >95% Form I) was delivered to the assay tubes as a solution in 10 mM Tris-Cl (pH 8.5) and diluted with Tris (pH 7.4, final concentration 5 mM) and NaCl (final concentration 50 mM). Solutions of the jadomycins, pre-mixed with $Cu(OAc)_2$ where appropriate, were added to give the desired concentrations, and the reaction mixtures were diluted to a final volume of 20 μL with ultra-pure water. Reaction mixtures were incubated at 37°C for 2 or 4 hr. All samples were quenched by the addition of gel loading buffer (4 μL), loaded onto 1% agarose gels containing ethidium bromide (0.75 μg mL^{-1}) and electrophoresed for 30 min at 8 V cm^{-1} in 1X TAE (40 mM Tris-acetate, 1 mM EDTA, pH 8.2). The bands were visualized with UV-transillumination (UVP transilluminator) and quantified using the Gel-Doc-It Imaging system (UVP) or GNU Image Manipulation Program (GIMP).

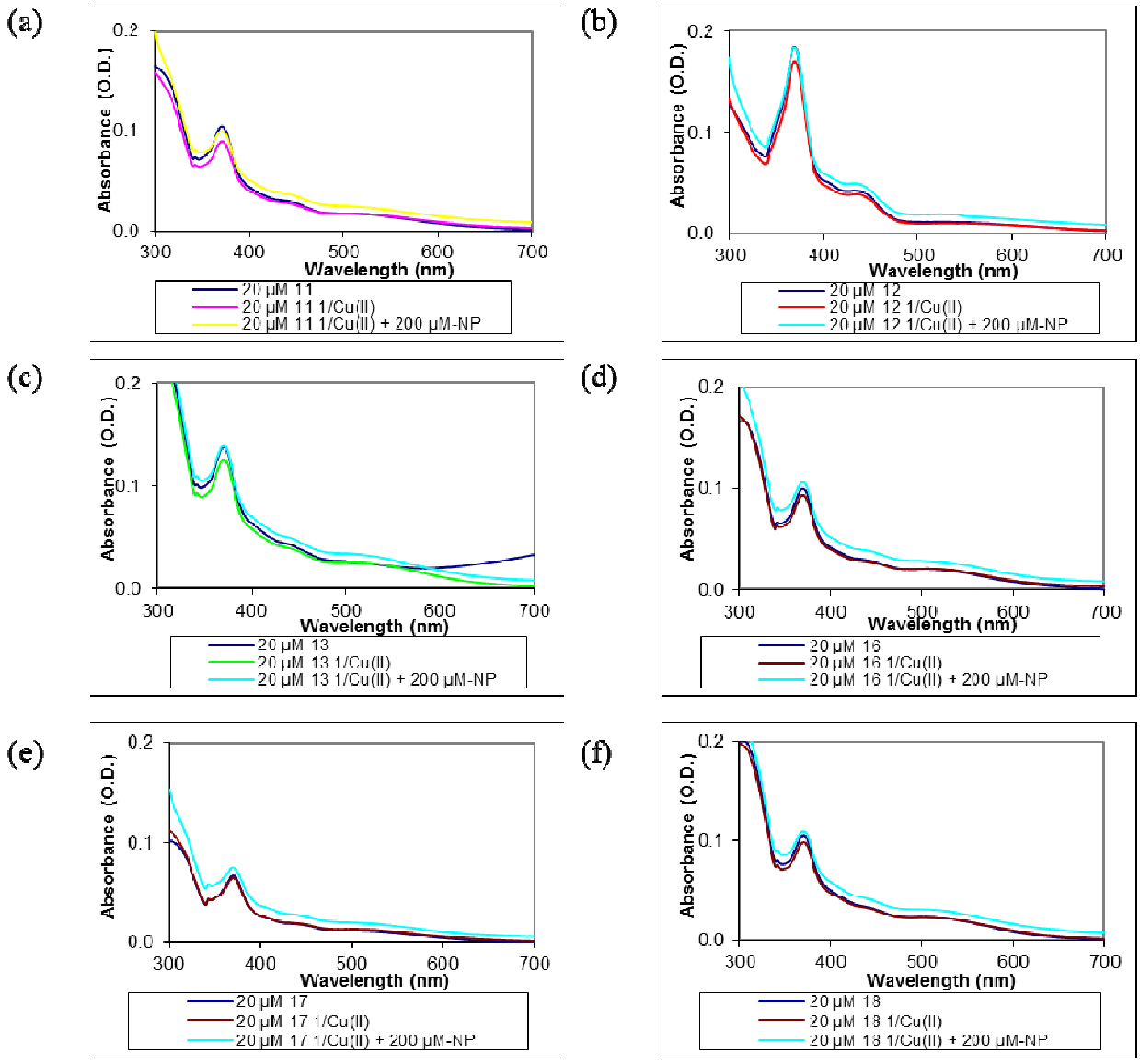

Figure S2. UV-vis titrations of jadomycins (20 μM) with 20 μM $Cu(OAc)_2$ and 200 μM-NP calf thymus DNA in 5 mM Tris, 50 mM NaCl, pH 7.4: (a) jadomycin **11**; (b) jadomycin **12**; (c) jadomycin **13**; (d) jadomycin **16**; (e) jadomycin **17**; (f) jadomycin **18**.

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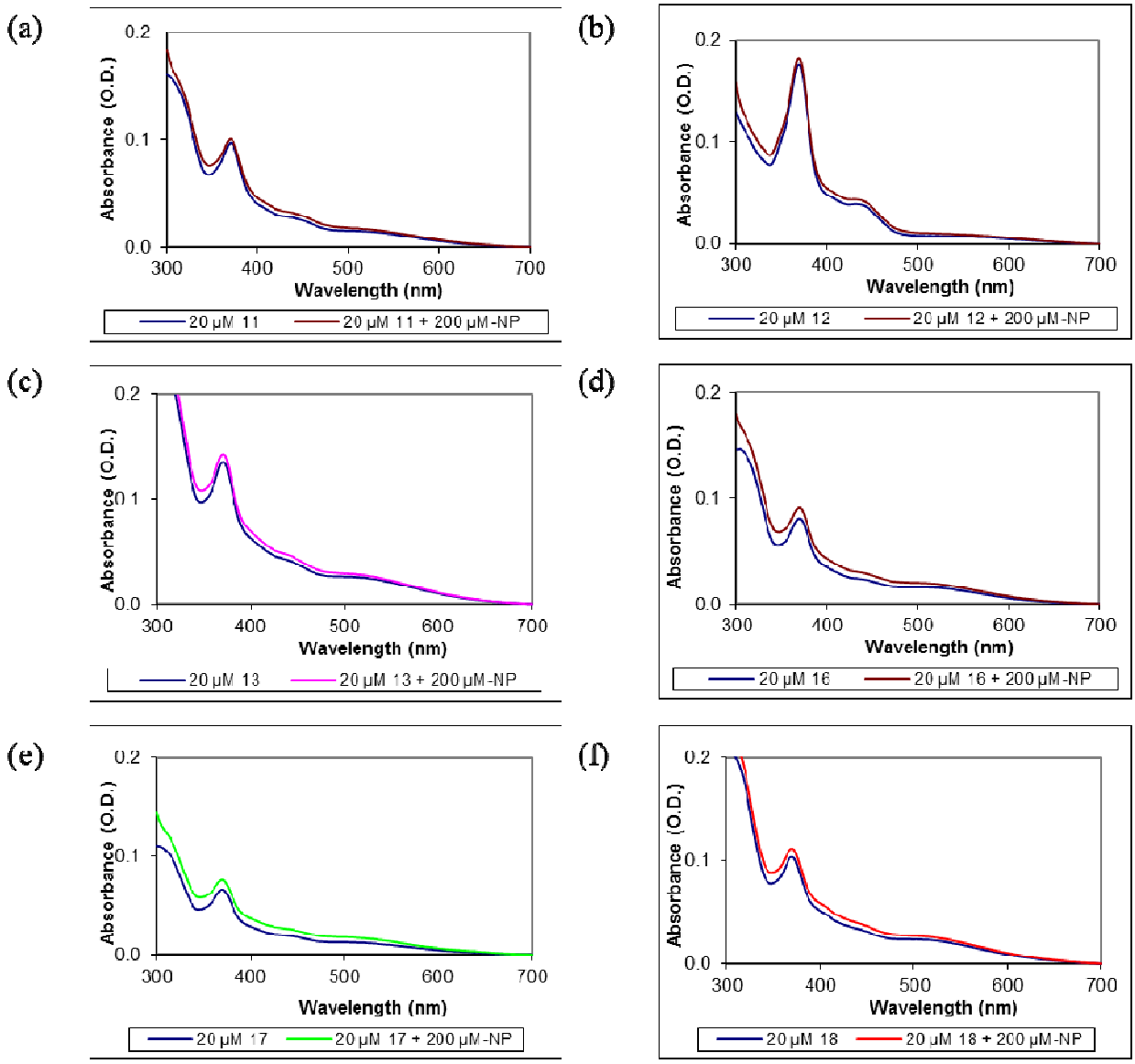

Figure S3. UV-vis titrations of jadomycins (20 μM) with calf thymus DNA (200 μM-NP) in 5 mM Tris, 50 mM NaCl, pH 7.4: (a) jadomycin **11;** (b) jadomycin **12;** (c) jadomycin **13;** (d) jadomycin **16;** (e) jadomycin **17;** (f) jadomycin **18.**

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Cytotoxicity study data

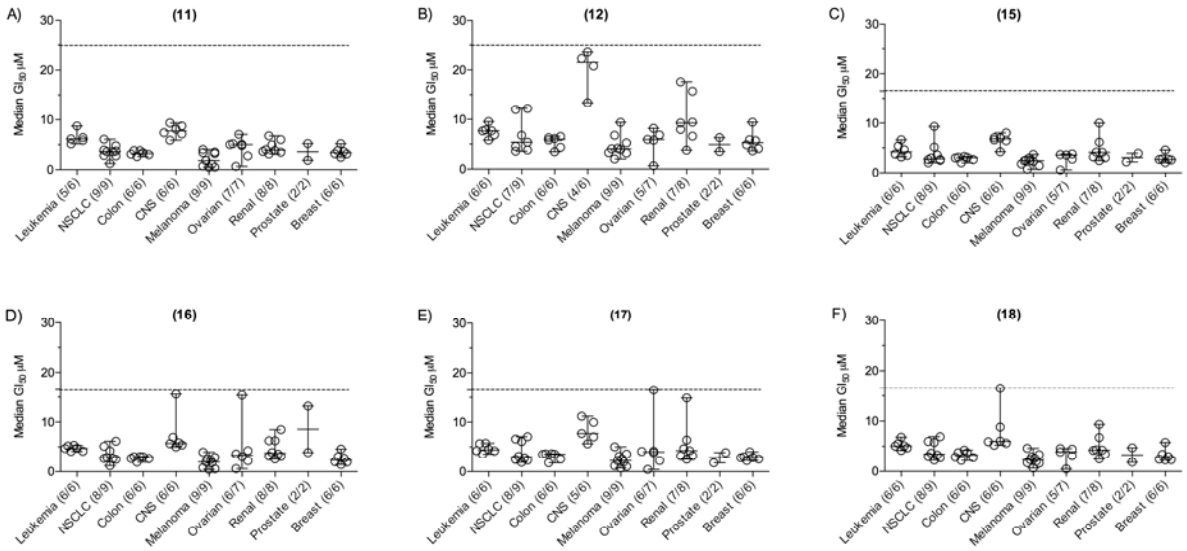

Figure legend S4. GI_{50} values (µM) for jadomycins 11 (A), **12** (B), **15** (C), **16** (D), **17** (E) and **18** (F) grouped according to cancer cell type. Each open circle represents the GI_{50} value against an individual cancer cell line. The solid horizontal lines represent the median and range values for each group of cancer cells. The numbers in brackets below the x-axis indicate the number of cell lines out of the total number of cell lines tested per cancer cell group in which GI_{50} values were quantifiable below the maximal jadomycin concentrations used in the cytotoxicity assay (dotted line).

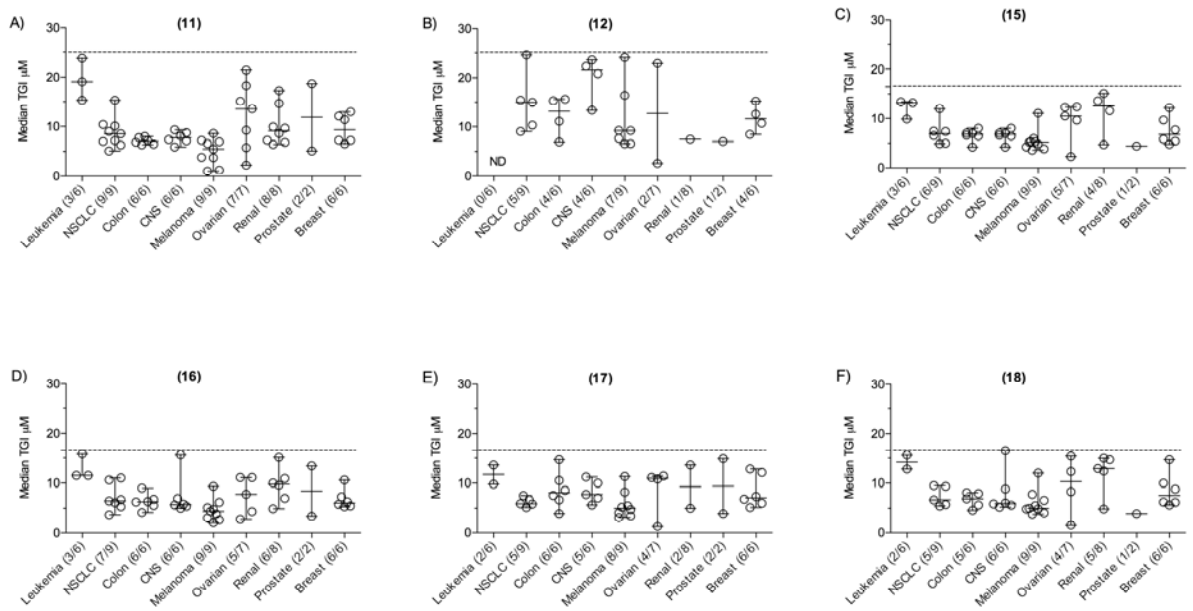

Figure legend S5. TGI values (µM) for jadomycins **11** (A), **12** (B), **15** (C), **16** (D), **17** (E) and **18** (F) grouped according to cancer cell type. Each open circle represents the TGI value against an individual cancer cell line. The solid horizontal lines represent the median and range values for each group of cancer cells. The numbers in brackets below the x-axis indicate the number of cell lines out of the total number of cell lines tested per cancer cell group in which TGI values were quantifiable below the maximal jadomycin concentrations used in the cytotoxicity assay (dotted line).

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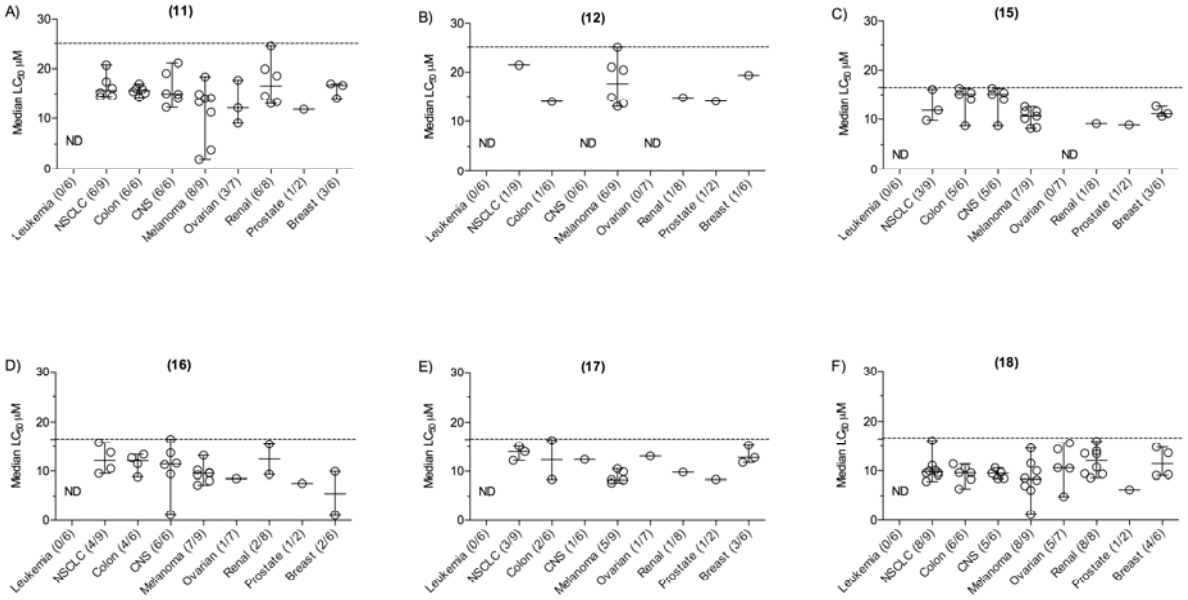

Figure legend S6. LC_{50} values (µM) for jadomycins **11** (A), **12** (B), **15** (C), **16** (D), **17** (E) and **18** (F) grouped according to cancer cell type. Each open circle represents the LC_{50} value against an individual cancer cell line. The solid horizontal lines represent the median and range values for each group of cancer cells. The numbers in brackets below the x-axis indicate the number of cell lines out of the total number of cell lines tested per cancer cell group in which LC_{50} values were quantifiable below the maximal jadomycin concentrations used in the cytotoxicity assay (dotted line).

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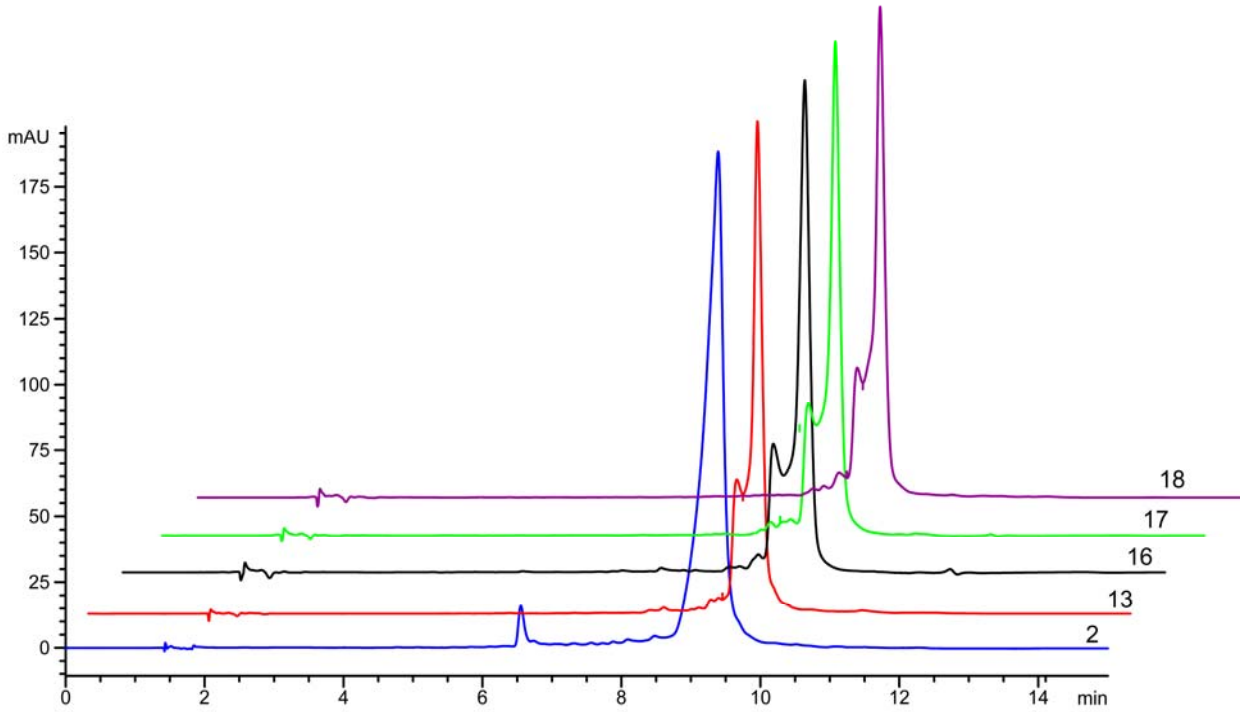
Representative HPLC data, 254 nm

Compound	Retention times*
2	9.33, 9.39
13	9.33, 9.63
16	9.36, 9.82
17	9.27, 9.66
18	9.49, 9.82

* The two HPLC peaks correspond to the two diastereomers at 3a. The proportions are equivalent to the integration in the 1H NMR spectrum for each diastereomer. The minor diastereomer is the first retention time. The trace of **2** was not sufficiently resolved to observe two distinct peaks by HPLC. See HPLC spectra below.



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NMR spectra, 700 MHz in $CDCl_3$

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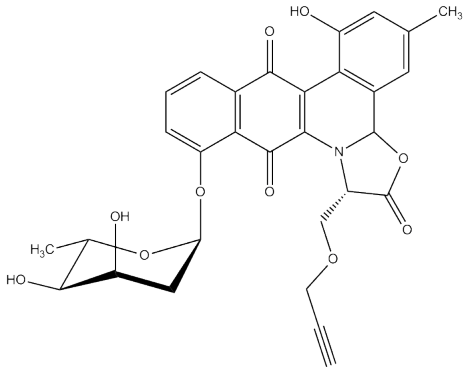

Jadomycin *O*-propargyl-L-serine (**2**) in $CDCl_3$

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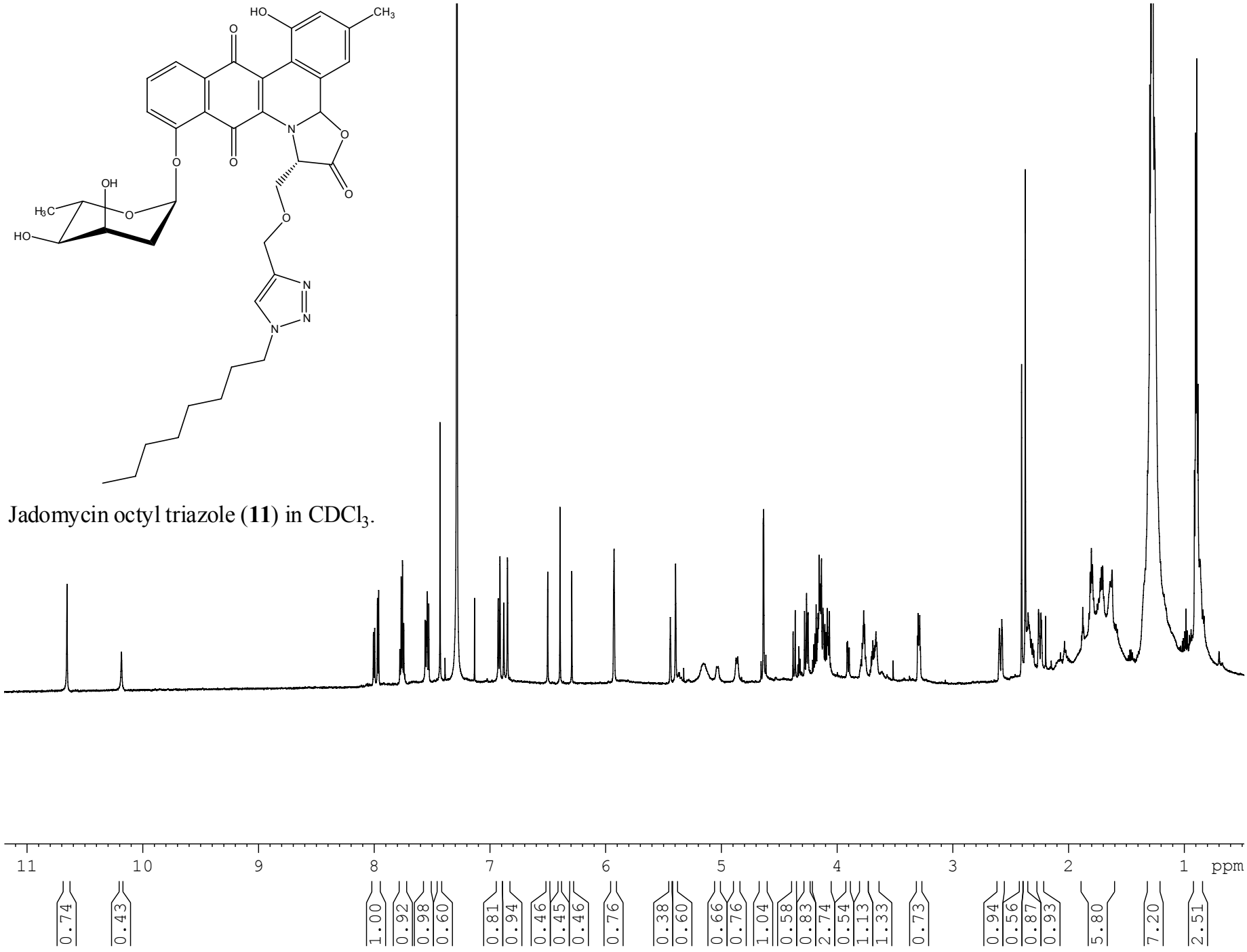

Jadomycin octyl triazole (**11**) in $CDCl_3$.

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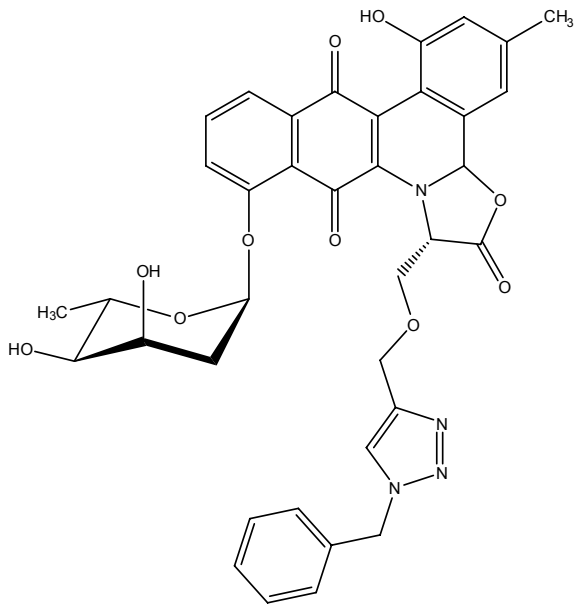

Jadomycin benzyl triazole (**12**) in $CDCl_3$.

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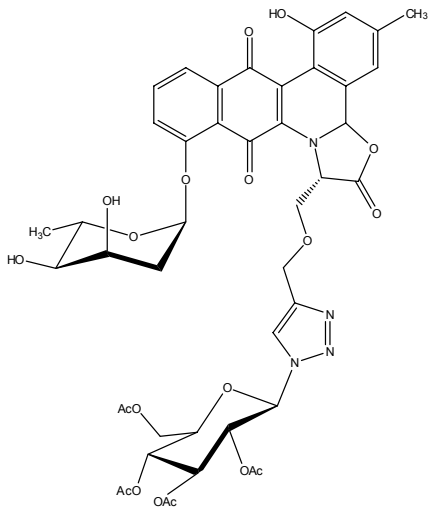

Jadomycin β-tetraacetylglucosyl triazole (**13**) in $CDCl_3$.

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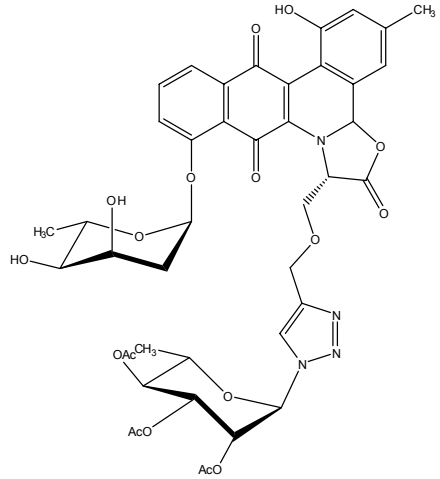

Jadomycin α-triacetylrhamnosyl triazole (**15**) in $CDCl_3$

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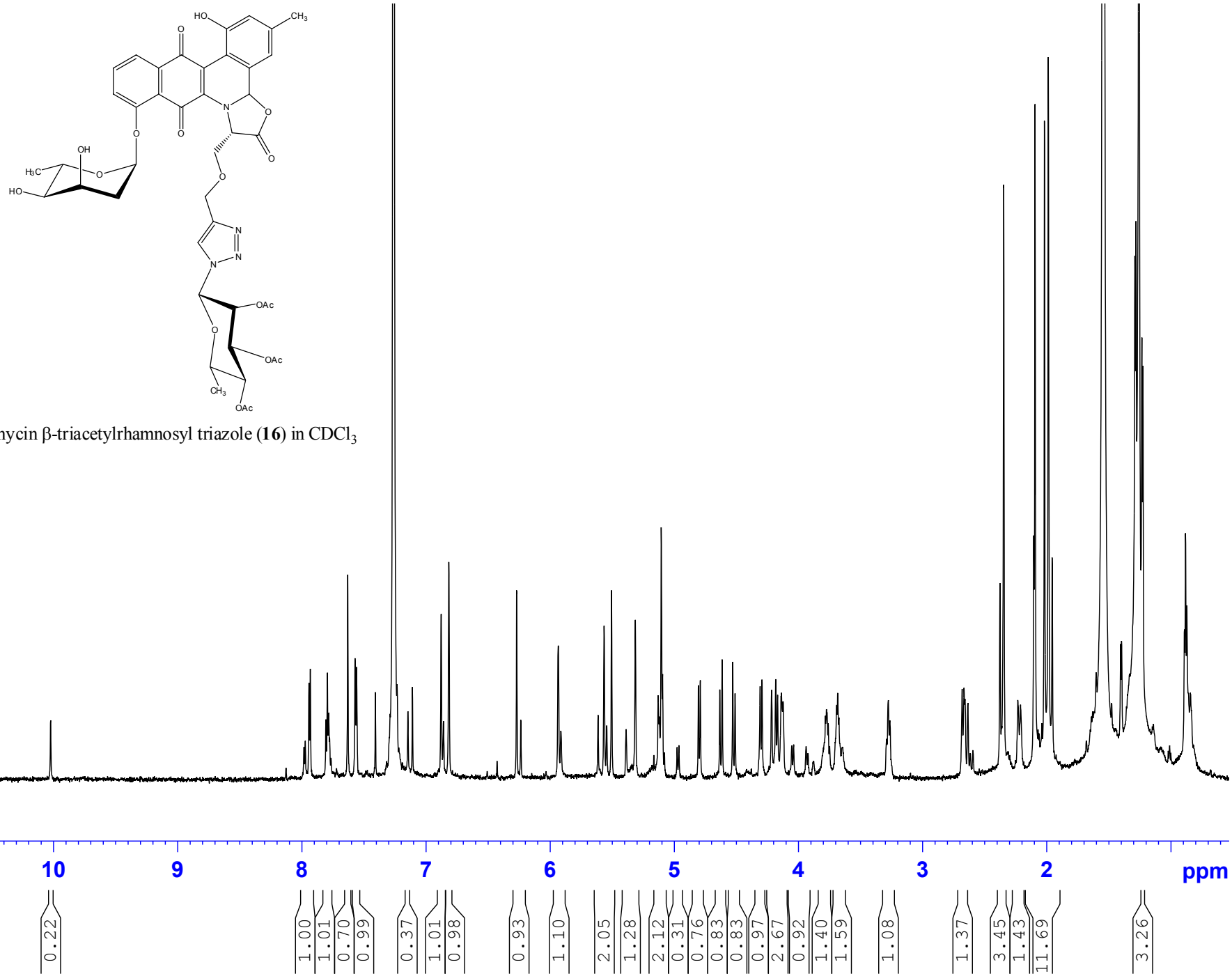

Jadomycin β-triacetylrhamnosyl triazole (**16**) in $CDCl_3$

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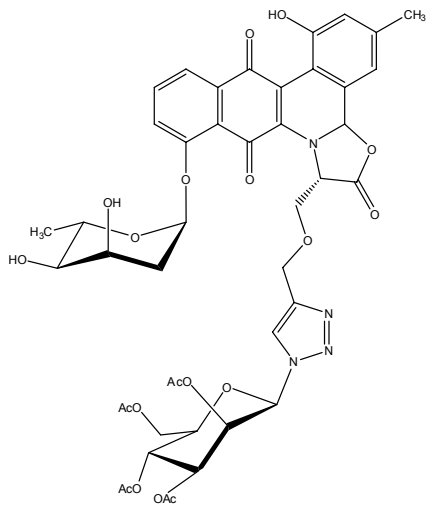

Jadomycin β-tetraacetylmannosyl triazole (**17**) in $CDCl_3$

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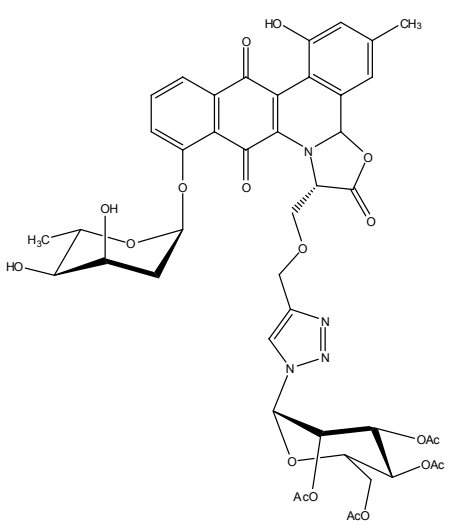

Jadomycin α-tetraacetylmannosyl triazole (**18**) in $CDCl_3$