Understanding Anthracyclines: Synthesis of a Focused Library of Doxorubicin/Aclarubicin - Inspired Structures

Wander, D.P.A.

Citation

Wander, D. P. A. (2019, November 19). *Understanding Anthracyclines: Synthesis of a Focused Library of Doxorubicin/Aclarubicin - Inspired Structures*. Retrieved from https://hdl.handle.net/1887/80757

Author: Wander, D.P.A.
Title: Understanding Anthracyclines: Synthesis of a Focused Library of Doxorubicin/Aclarubicin - Inspired Structures
Issue Date: 2019-11-19

Chapter 5

Synthesis of glycosyl regio- and stereoisomers of doxorubicin

Introduction

In the search for more potent anthracyclines with fewer side-effects, several thousands of analogs of doxorubicin (**1**) have been isolated from natural sources and prepared by synthetic and chemo-enzymatic approaches.[1,2] In contrast to most doxorubicin analogs, its 4’-epimer epirubicin (**3**, Figure 1) is a clinically approved anthracycline. Compared to doxorubicin, the amine in epirubicin has a lower pK_{aH}, likely because of hydrogen bonding of the resultant ammonium salt with the *cis* 4’-hydroxyl function.[3] Additionally, Pedersen *et al.* have described the orientation of hydroxyl groups on a sugar ring to be of influence on the pK_a of amine groups on aminosugars.

The first reported[4] synthesis of epirubicin was based on glycosylation of a protected acosamine donor to the daunorubicin aglycone (**14a**, Chapter 2), followed by 14-hydroxylation and deprotection.[5] Later efforts involved the direct conversion of doxorubicin to 4-*epi*-doxorubicin (**3**) through a sequence of protection group manipulations, oxidation of the 4’-hydroxyl to the corresponding ketone and stereoselective reduction to provide the epimeric 4’-alcohol followed by final deprotection.[6] Today, clinical grade epirubicin is produced by means of a mutated *Streptomyces peucetius* in a biotechnological process.[7] In the treatment of certain cancers (breast/ovarian cancer, gastric cancer, lung cancer and lymphomas), epirubicin is preferred over doxorubicin as it exhibits higher efficacy and lower cardiotoxicity.

Chapter 3 presented a coherent set of compounds featuring structural elements of doxorubicin (**1**) and aclarubicin (**4**) in which the aglycone, amine/dimethylamine and nature of the sugar chain were varied. In all presented examples, the stereochemistry and substitution pattern (amine at the 3’-position and hydroxyl at the 4’-position) were kept the same as in the two natural products, that is, 2,3-dideoxy-3-amino-ʟ-fucopyranose or daunosamine. This Chapter focuses on the construction of a focused library of anthracyclines that feature regio- and stereoisomeric deoxyfucose analogues. All compounds contain the doxorubicin aglycone and are in line with the strategy presented in Chapter 3, compounds featuring a non-methylated amine are prepared together with their *N,N*-dimethyl substituted counterparts.

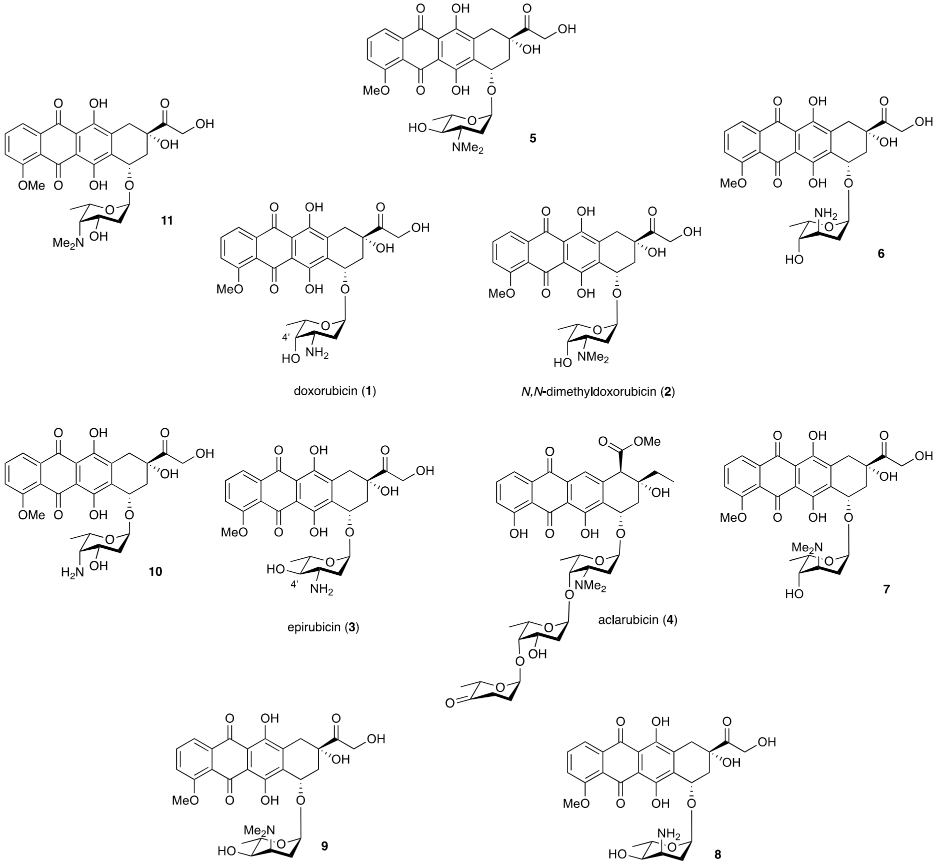
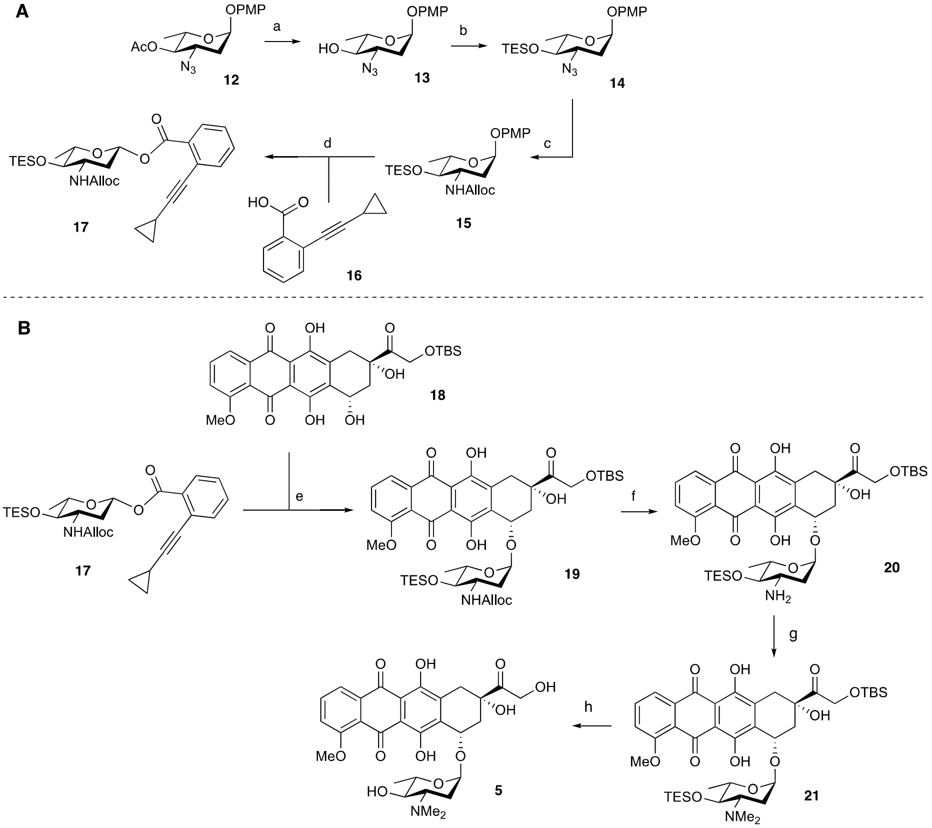


Figure 1. Chemical structures of the doxorubicin derivatives **5**-**11** prepared in this Chapter, differing in stereo- and regiochemistry on the sugar.

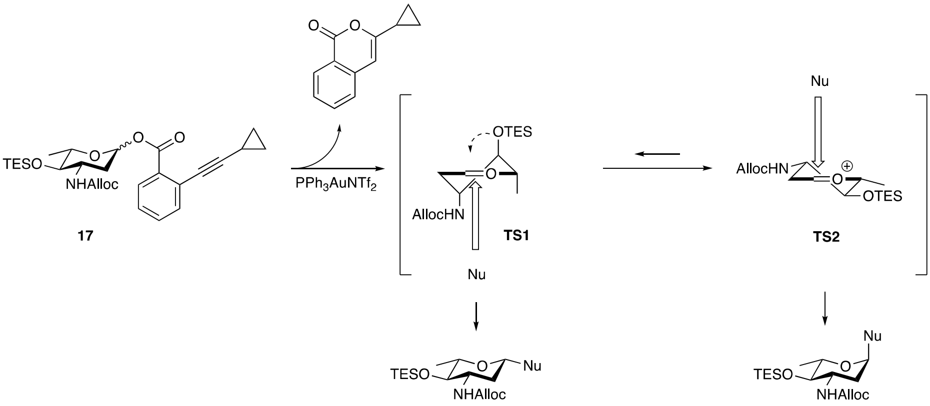
Results and discussion

The synthesis of *N,N*-dimethylepirubicin (**5**), the 4'-epimer of *N,N*-dimethyldoxorubicin (**2**) commenced with orthogonally protected acosamine[8] **12** (Scheme 1A), the synthesis of which is described in Chapter 2. Deprotection of the 4-acetate was followed by triethylsilylation to give **14**. At this stage, the azide was reduced and ensuing carbamoylation with allyl chloroformate provided Alloc-protected amine **15**. Oxidative hydrolysis of the anomeric *p*-methoxyphenolate (using Ag(DPAH)$_2$), followed by Steglich esterification to carboxylic acid **16** provided donor glycoside **17**. Treatment of tetracycle **18** with donor **17** in the presence of catalytic gold(I) yielded anthracycline glycoside **19** in excellent yield (Scheme 1B) and good stereoselectivity (8:1 α:β).



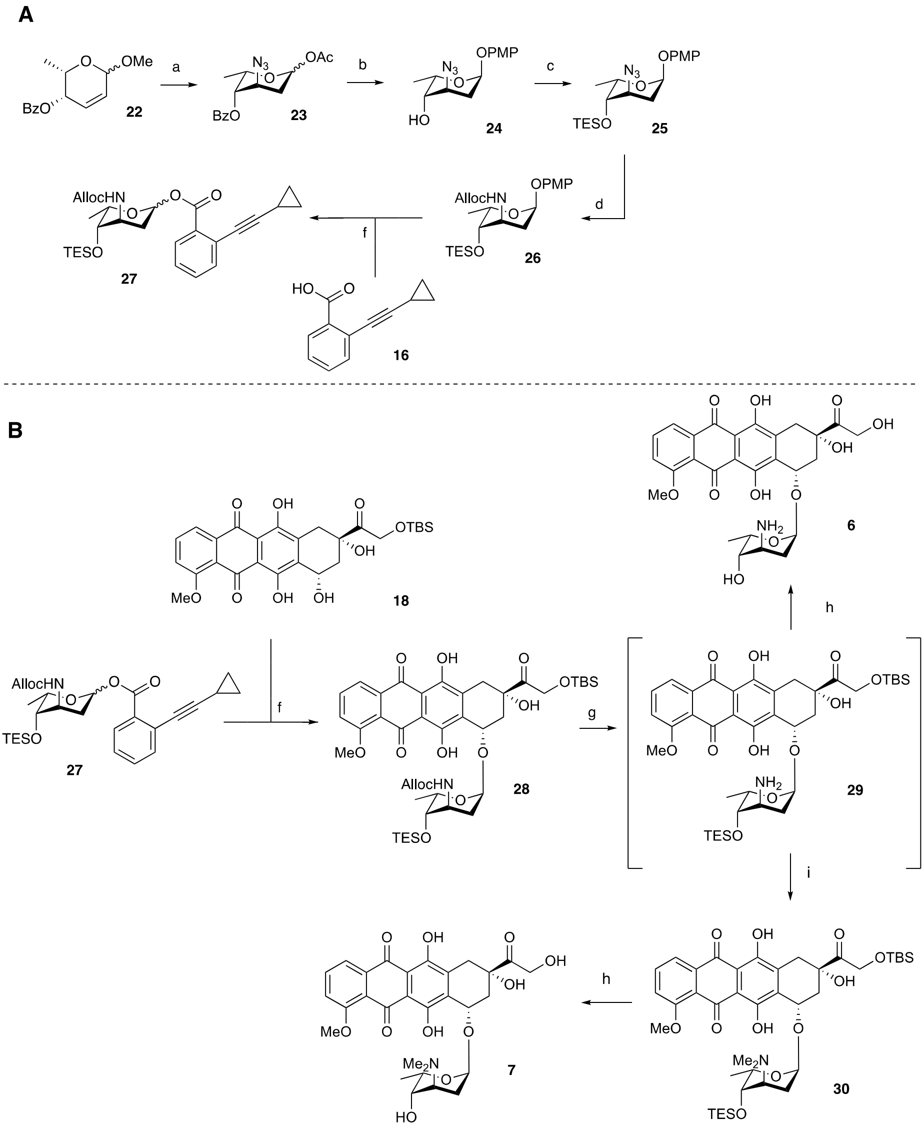
Scheme 1. Synthesis of *N,N*-dimethylepirubicin (**5**). *Reagents and conditions:* (a) NaOMe, MeOH, quant.; (b) TESOTf, pyr., DCM, 95% over 2 steps; (c) *i.* polymer-bound PPh$_3$, THF, H$_2$O; *ii.* allyl chloroformate, pyr., DCM, quant. over 2 steps; (d) *i.* Ag(DPAH)$_2$·H$_2$O, NaOAc, MeCN, H$_2$O, 0 °C; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 49% over 2 steps (β-adduct only); (e) PPh$_3$AuNTf$_2$, DCM, 91% (8:1 α:β); (f) Pd(PPh$_3$)$_4$, DMBA, DCM, 82%; (g) NaBH(OAc$_3$), aq. CH$_2$O, EtOH, 82%; (h) HF·pyr., pyr., 83%.

A mechanistic rationale for the observed selectivity is shown in Scheme 2. Although the 4-silyl ether in TS1 is able to stabilize the positive charge on the oxocarbenium ion, approach of the nucleophile from the bottom face of the ring is hindered by 1,3-diaxial interaction with the 6-methyl group, and the bulky Alloc group on the backside of the ring. The 4-silyl ether in TS2 is unable to stabilize the $^3H_4$ conformation of the reactive intermediate, but approach from the top face can proceed with little hindrance. Long-range participation[9] by the allyloxycarbonyl group can also account for the observed stereoselectivity, but in light of the stereoselectivity observed in the assembly of 3'-epidoxorubicin, *vide infra*, less likely. The desired α-anomer of **19** could be separated by means of column chromatography. Following Pd-mediated removal of the Alloc group to give **20**, reductive dimethylation of the liberated amine took place uneventfully to yield **21**. A final desilylation gave *N,N*-dimethylepirubicin (**5**) in good yield.



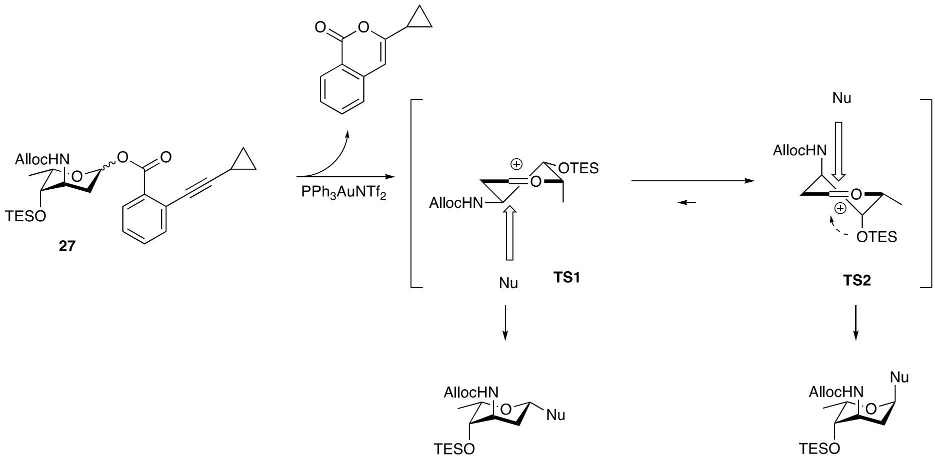
Scheme 2. Mechanistic rationale for the stereoselectivity found in the formation of **19**.

The synthesis of 3'-epi-doxorubicins **6** and **7** commenced with *eno*-pyranoside **22** (Scheme 3A), the construction of which was discussed in Chapter 3. Following the protocol as reported by Renneberg *et al.*[8], exposure of **22** to acidic hydrolysis was followed by 1,4-addition of the azide anion (ca. 2:1 axial:equatorial) to the resulting enal function. Anomeric acetylation gave a mixture from which the desired C3-axial isomer **23** could be isolated. Subjection of this compound together with *p*-methoxyphenol to $BF_3{\cdot}OEt_2$ from -60 °C to -40 °C followed by debenzoylation under Zemplén conditions gave α-glycoside **24**. Silylation of the free alcohol in **24** gave **25** and conversion of the azide in **25** to the corresponding *N*-allyloxycarbamate by means of Staudinger reduction and carbamoylation with allylchloroformate gave **26**.



Scheme 3. Synthesis of 3'-epidoxorubicins (**6**) and (**7**). *Reagents and conditions:* (a) *i.* HCl, THF, H_2O; *ii.* NaN_3, AcOH, THF, H_2O; *iii.* Ac_2O, pyr., DCM, 55% over 3 steps (10:1 α:β); (b) *i. p*-methoxyphenol, $BF_3\cdot OEt_2$, DCM, -60 °C to -40 °C; *ii.* NaOMe, MeOH, 77% over 2 steps; (c) TESOTf, pyr., quant.; (d) *i.* PPh_3, THF, H_2O; *ii.* allyl chloroformate, pyr., DCM, -20 °C, quant. over 2 steps; (e) *i.* $Ag(DPAH)_2\cdot H_2O$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 79% over 2 steps (1:3 α:β); (f) PPh_3AuNTf_2, DCM, 58% (α only); (g) $Pd(PPh_3)_4$, DMBA, DCM; (h) HF·pyr., pyr., 72% over 2 steps for **5**, 66% for **6**; (i) $NaBH(OAc)_3$, aq. CH_2O, EtOH, 72% over 2 steps.

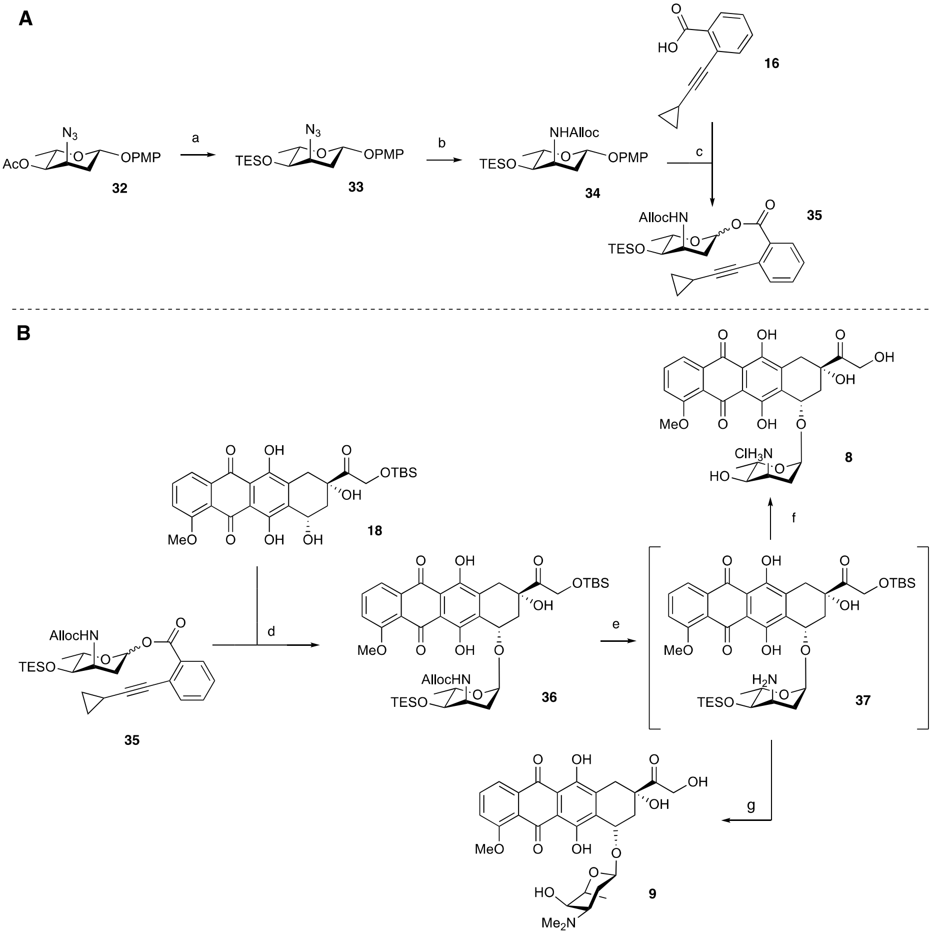
Silver(II)-mediated oxidation of the anomeric *p*-methoxyphenolate was followed by esterification with *o*-cyclopropylethynylbenzoic acid **16** to give 3-epidaunosamine donor **27**. Gold-mediated glycosylation of acceptor **18** with donor **27** proceeded in excellent stereoselectivity to give α-glycoside **28**. Scheme 4 provides a mechanistic rationale for the observed stereoselectivity. In the $^3H_4$ conformation, the incoming nucleophile would encounter 1,3-diaxial interaction with the 6-methyl group. Meanwhile, in the $^4H_3$ half-chair, the silyl ether is able to stabilize the oxocarbenium ion. Since solely α-product is observed, participating properties of the carbamate that would guide formation of the 1,3-*trans* product appear to be insignificant.



Scheme 4. Mechanistic rationale for the 1,3-*cis* stereoselectivity found in the formation of **28**.

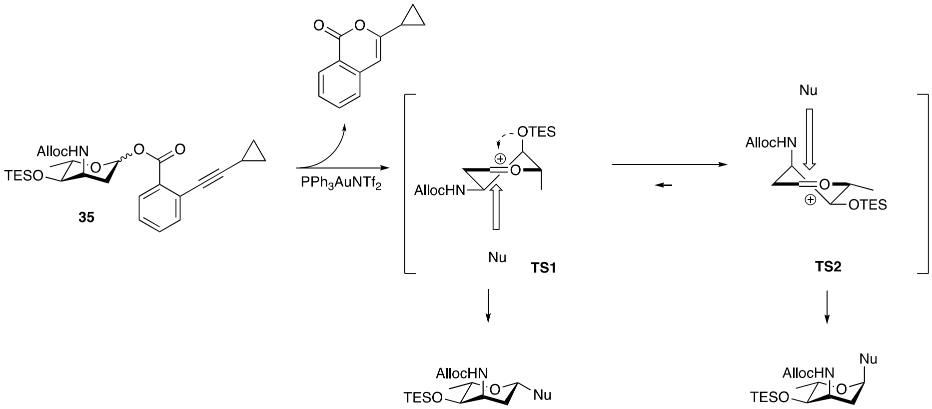
Pd-mediated deblocking of the carbamate in **28** gave free amine **29**. Global desilylation gave 3-epidoxorubicin (**6**) in good yield over the two steps. Subjection of amine **29** to reductive amination (CH_2O, $NaBH(OAc)_3$) finished the nogalamine[10] moiety in **30** and a final desilylation yielded *N,N*-dimethyl-3-epidoxorubicin (**7**).

The synthesis of 3’-epi-4’-epidoxorubicins **8** and **9** (Scheme 5A) starts from orthogonally protected β-ristosamine[4] **31**, the construction of which was discussed in Chapter 2. Following procedures similar to those described before in this Chapter, protecting group manipulations yielded orthogonally protected **34**. Liberation of the anomeric *p*-methoxyphenolate and subsequent esterification to **16** gave rise to ristosaminyl glycosyl donor **35**. The envisaged glycosylation to **18** under gold(I)-mediated conditions took place in a non-stereoselective manner and with modest yield. The desired α-configured **36** could be obtained in sufficient quantities and purity nonetheless after by silica gel column chromatography.



Scheme 5. Synthesis of ristosaminyl doxorubicins **8** and **9**. *Reagents and conditions:* (a) *i.* NaOMe, MeOH, quant.; *ii.* TESOTf, pyr., quant.; (b) *i.* PPh_3, THF/H_2O; *ii.* allyl chloroformate, pyr., DCM, -20 °C, 95% over 2 steps; (c) *i.* $Ag(DPAH)_2H_2O$, NaOAc, MeCN, H_2O; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 57% over 2 steps; (d) PPh_3AuNTf_2, DCM, 50% (1.5:1 α:β); (e) *i.* $Pd(PPh_3)_4$, DMBA, DCM; (f) *i.* HF·pyr., pyr., 0 °C; *ii.* lyophilization from aq. HCl, 54% over 3 steps; (g) *i.* $NaBH(OAc)_3$, aq. CH_2O, EtOH; *ii.* HF·pyr., pyr., 0 °C, 35% over 3 steps.

The poor stereoselectivity of the glycosylation is in line with results reported by as Zeng *et al.* who reported that glycosylations of ristosaminyl alkynylbenzoate donors to various glycosyl acceptors proceeded with variable (2.8:1 – 1:4 α:β) selectivity.[11] As depicted in Scheme 6, the 3-Alloc disfavors α-attack because of unfavorable 1,3-diaxial interactions of this substituent in the $^3H_4$ conformation and the incoming nucleophile. At the same time, the 4-silyl ether is unable to stabilize the oxocarbenium ion in this conformation. Conversely, β-face attack is on the alternative half chair oxocarbenium ion conformer is hampered by the axial methyl group, although the oxocarbenium can benefit from stabilization of the silyl ether in this constellation.



Scheme 6. Mechanistic rationale for the stereoselectivity found in the formation of **36**.

α-Configured glycoside **36** was subjected to Pd-mediated removal of the Alloc group to obtain free amine **37**. Desilylation followed by lyophilization from aqueous HCl (10 µM, 2 eq) yielded 3,4-epidoxorubicin (or ristosaminyl-doxorubicinone) (**8**). Converting amines **8** and **10** to their hydrochloride salts facilitated in obtaining clear NMR spectra of this compound and did not lead to degradation. Reductive amination onto amine **37** followed by final desilylation yielded the megosaminyl-doxorubicinone (**9**).

Rather than the $^{1}C_{4}$ conformation observed for **36** and **8**, it was found that **9** takes up the $^{4}C_{1}$ chair conformation instead. Figure 2 depicts the ^{1}H-spectra of compounds **9** and **36**, annotated with the peak multiplicity and coupling constants of the glycosidic protons. Most notable are the coupling constants found for the anomeric proton in **8**. Whereas in $^{1}C_{4}$-conformed 2-deoxy fucosides, the anomeric proton typically shows as a doublet (d) with $J_{(H1\text{-}H2ax)}$ = 1-5 Hz, the anomeric proton in **9** instead shows a dd ($J_{(H1\text{-}H2ax)}$ = 8.8 Hz; $J_{(H1\text{-}H2eq)}$ = 4.8 Hz), indicating a trans-diaxial relationship between H1 and H2$_{ax}$. Furthermore, whereas H4 in **36** shows as a dd ($J_{(H4\text{-}H5)}$ = 8.6 Hz; $J_{(H4\text{-}H3)}$ = 4.1 Hz) indicative of a diaxial relationship, H4 in **9** appears as an apparent triplet with a small coupling constant (4.6 Hz), also indicating a $^{4}C_{1}$-conformer. Finally, the large *J*-value expected for H5 as in **36** is absent in **9**, as H5 shows as a dq ($J_{(H5\text{-}H6)}$ = 6.3 Hz; $J_{(H5\text{-}H4)}$ = 1.2 Hz). The observed conformation of the L-megosamine moiety in **9** is consistent with that found in the macrolide megalomycin.[12] As a result, the tertiary amine in **9** now points away from the aglycone, rather than towards it, which could have major implications for its biological activity.

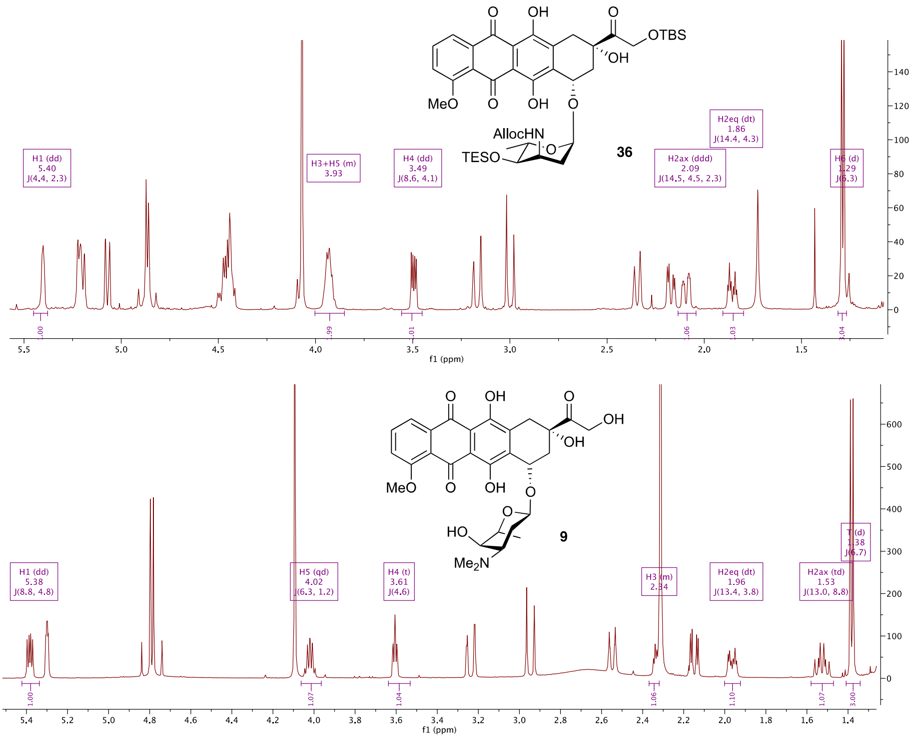
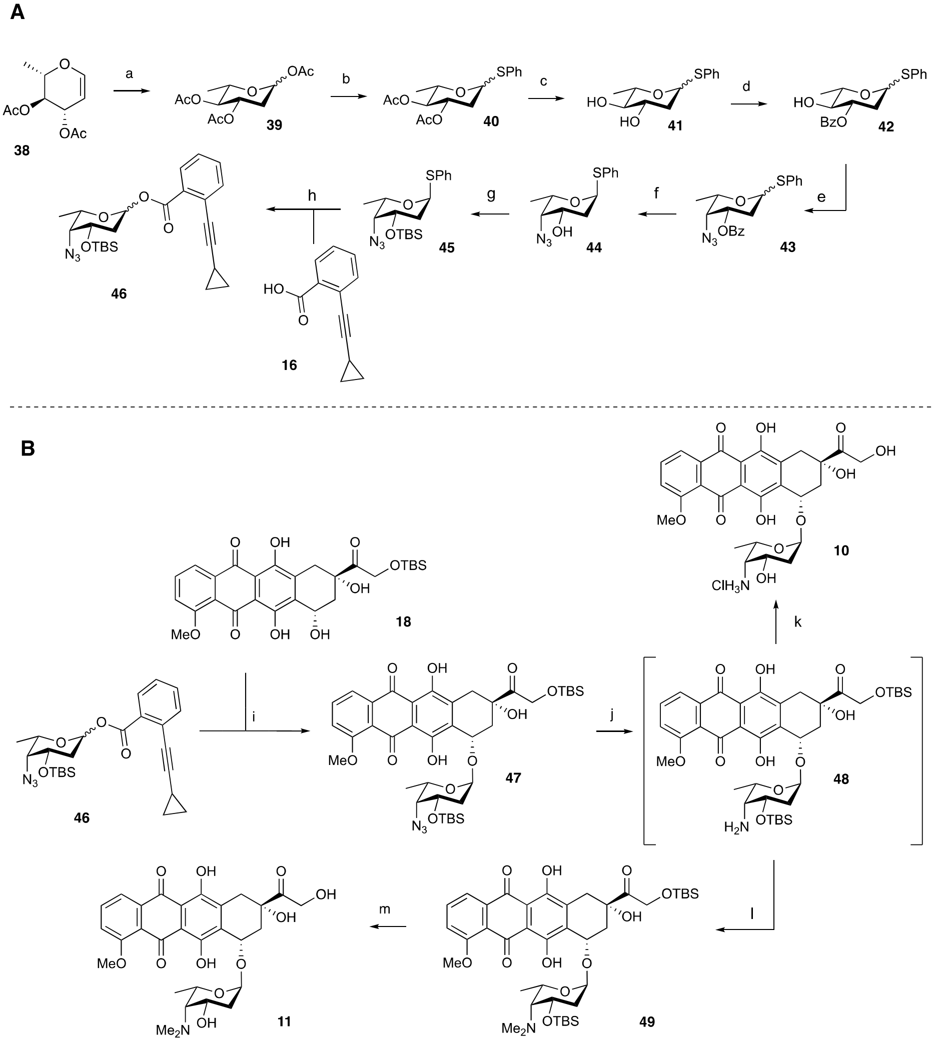


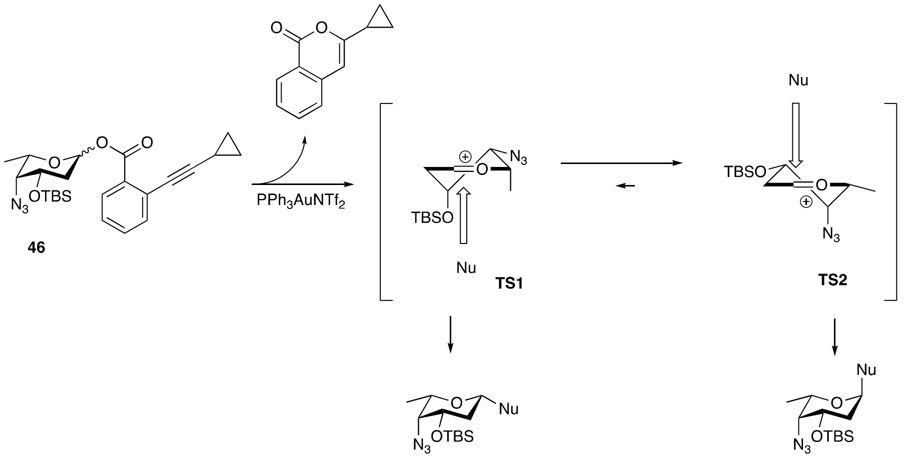
Figure 2. ^{1}H-NMR spectra of $^1C_4$-conformed **34a** and $^4C_1$-conformed **9**, zoomed in to the glycosidic protons and annotated with the chemical shift, peak splitting pattern and J-couplings.

The synthesis of kedarosamine[13,14] donor **46** is depicted in Scheme 6A. Treatment of 3,4-di-*O*-acetyl-L-rhamnal **38** (Chapter 2) with catalytic $PPh_3{\cdot}HBr$ yielded 2-deoxyrhamnoside **39**, following the procedure reported by Oberthur *et al.*[15] Installation of an anomeric thiophenyl group was followed by Zemplén deacetylation to give diol **41**. A 3-benzoyl group was regioselectively introduced using catalytic dibutyltin dichloride[16] to yield **42**. Triflation of the C-4-OH followed by substitution with sodium azide yielded protected **43** in 68% over 2 steps. Crucial in the latter procedure was the (co-)evaporation at 0 °C at the end of the workup of the triflation reaction to prevent decomposition of the intermediate triflate. Debenzoylation was followed by installation of a TBS group on the 3-position to yield thioglycoside **45**. Subjection to hydrolysis of the anomeric group using the $AgNO_3$/lutidine system described in Chapter 4 afforded the corresponding hemiacetal. Final Steglich-esterification gave alkynylbenzoate **46**.



Scheme 6. Synthesis of 3,4-*iso*-doxorubicins **10** and **11**. *Reagents and conditions:* (a) AcOH, $PPh_3·HBr$, DCM, 51% (5:1 α:β); (b) PhSH, $BF_3·Et_2O$, DCM, quant.; (c) NaOMe, MeOH, 88%; (d) benzoyl chloride, Bu_2SnCl_2, DIPEA, THF, 84%; (e) *i.* triflic anhydride, pyr., 0 °C, *ii.* NaN_3, DMF, 68% over 2 steps; (f) NaOMe, MeOH, 86%; (g) TBS-Cl, imidazole, DMF, 94%; (h) *i.* $AgNO_3$, 2,6-lutidine, THF/H_2O; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 65% over 2 steps (1:3 α:β); (i) PPh_3AuNTf_2, DCM, 91% (>20:1 α:β); (j) PPh_3, THF, H_2O, 50 °C; (k) *i.* HF·pyr., pyr., 0 °C; *ii.* lyophilization from aq. HCl, 36% over 3 steps for **9**; (l) $NaBH(OAc_3)$, aq. CH_2O, EtOH, 43% over 2 steps; (m) HF·pyr., pyr., 0 °C, 72%.

Subjection of donor **46** and doxorubicinone acceptor **18** to catalytic gold(I) as depicted in Scheme 6B proceeded uneventfully to give the resulting glycoside **47** in excellent yield and stereoselectivity. As depicted in Scheme 7, the oxocarbenium ion that takes up a $^3H_4$ conformation in TS2 is strongly favored over the alternative $^3H_4$ conformation, as it is able to put the large silyl ether in an equatorial position, with the incoming nucleophile suffering no steric hindrance. Additionally, the axial azide should be able to stabilize the oxocarbenium ion in this conformation. Conversely, β-face attack in TS1 is hindered by 1,3-diaxial hindrance induced by the TBS group and the 6-methyl substituent.



Scheme 7. Mechanistic rationale for the stereoselectivity found in the formation of **47**.

Staudinger reduction of azide **47** provided the corresponding amine **48**, after which global desilylation gave **10**. Reductive amination on amine **48** gave rise to dimethylamine **49**. Final desilylation yielded the envisaged regio-isomer of *N,N*-dimethyldoxorubicin (**2**), kedarosamino-doxorubicinone **11**.

Conclusions

Despite decades of use in the clinic and severe side effects, the structure-activity profile of doxorubicin remains poorly understood. The discovery of histone eviction as a cytotoxic property of anthracyclines comprises a new incentive for the synthesis of doxorubicin analogs. This Chapter describes the synthesis of stereo- and regio-isomers within the aminosugar moiety of doxorubicin using Yu's gold(I)-catalyzed glycosylation method. Additionally, the corresponding dimethylamines were prepared to be able to directly compare these compounds with doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**2**, Chapter 2). In all, the research described in this Chapter led to the synthesis of a set of known and unprecedented anthracyclines, specifically *N,N*-dimethyl-4-epidoxorubicin (**5**[17]), (*N,N*-dimethyl)-3-epidoxorubicin (**6**[18]) and (**7**), (*N,N*-dimethyl)-3,4-diepidoxorubicin (**8**[2,19]) and (**9**) and (*N,N*-dimethyl)-3',4'-isodoxorubicin (**10**[14]) and (**11**). The in literature obtained biological data on the known anthracyclines in this Chapter (**5**, **6**, **8** and **10**) is fragmented and incomplete. The now-available fully coherent set allows for side-by-side biological evaluation of these doxorubicin stereo- and regioisomers, and aid in understanding the structure-activity relationship of doxorubicin (**1**) and possibly assist in the identification of a better anti-cancer anthracycline.

Experimental procedures and characterization data

All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamedried 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63µm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-d5 or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150ºC overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a “lock mass”, or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as “lock mass”. Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

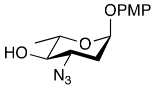
General procedure A: Oxidative hydrolysis of *p*-methoxyphenyl glycosides: To a solution of the glycoside in MeCN/H_2O (0.03 M, 1:1 v/v) were added NaOAc (10 eq) and $Ag(DPAH)_2\cdot H_2O$ (2.5 eq). The reaction mixture was stirred for 1h, diluted with sat. aq. $NaHCO_3$ and extracted thrice with DCM. Combined organics were dried over $MgSO_4$ and solvent was removed *in vacuo*. Column chromatography gave the crude hemiacetals.

General procedure B: Steglich esterification with *ortho*-cyclopropylbenzoic acid: To a solution of the hemiacetal in DCM (0.1 M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3.5 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **16** (Chapter 2) (3 eq). After disappearance of the starting hemiacetal, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography gave the corresponding anomeric benzoates.

General procedure C: Glycosylation of of alkynylbenzoate donors: To a solution of the alkynylbenzoate donor and 14-*O*-tert-butyldimethylsilyl-doxorubicinone **18** (Chapter 2) (1.5 eq) in DCM (0.05M), were added activated molecular sieves (4Å) and the mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise. After stirring 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography gave the desired anthracyclines.

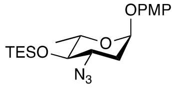
General procedure D: Global desilylation: A solution of the amine in pyridine (0.01-0.05 M) was cooled to 0 ºC. HF·pyridine (70 wt% HF) was added and the reaction mixture was stirred for 1-5h at this temperature. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. Salts were then filtered off and the filtrate was diluted with DCM (10 volumes), washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography gave the deprotected anthracyclines.

***p*-Methoxyphenyl-3-azido-2,3-dideoxy-α-L-rhamnopyranoside (13)**



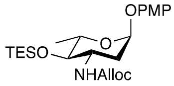
Acetate **11** (Chapter 2) (11.8 g, 3.72 mmol) was dissolved in MeOH (200 mL) and DCM (50 mL), NaOMe (400 mg, 37.4 mmol, 0.2 eq) was added and the reaction was stirred for 2 days. Dry ice was added to quench and the reaction mixture was concentrated in vacuo. Column chromatography (25:75 EtOAc:pentane) afforded the title compound as a white solid (10.38 g, 3.72 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.07 – 6.97 (m, 2H), 6.91 – 6.82 (m, 2H), 5.50 (d, J = 2.2 Hz, 1H), 3.99 (ddd, J = 12.1, 9.4, 4.9 Hz, 1H), 3.86 (dq, J = 9.4, 5.9 Hz, 1H), 3.81 (s, 3H), 3.25 (t, J = 9.4 Hz, 1H), 2.40 (ddd, J = 13.1, 4.9, 1.4 Hz, 1H), 2.24 (s, 1H), 1.89 (ddd, J = 13.2, 12.2, 3.5 Hz, 1H), 1.29 (d, J = 6.2 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-d) δ 154.8, 150.4, 117.6, 114.6, 95.6, 76.0, 68.3, 60.3, 55.7, 35.2, 17.8. HRMS: [M + H]$^+$ calculated for $C_{13}H_{18}N_3O_4$: 280.1297; found 280.1292.

***p*-Methoxyphenyl-3-azido-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside (14)**



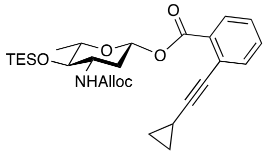
Alcohol **13** (370 mg, 1.32 mmol) was dissolved in DMF (2.23 mL) and pyridine (320 µL, 3.96 mmol, 3 eq) and cooled to 0 °C. TESOTf (0.51 mL, 2.38 mmol, 1.8 eq) was added and the reaction mixture was stirred for 1.5 h at the same temperature. Et_2O (80 mL) was added and the reaction mixture was washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 EtOAc:pentane) afforded the title compound as a colourless oil (494 mg, 1.26 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.04 – 6.98 (m, 2H), 6.89 – 6.82 (m, 2H), 5.47 (d, *J* = 2.3 Hz, 1H), 3.89 (ddd, *J* = 12.2, 9.2, 4.9 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.80 (s, 3H), 3.19 (t, *J* = 9.2 Hz, 1H), 2.41 (ddd, *J* = 13.3, 4.9, 1.4 Hz, 1H), 1.88 (ddd, *J* = 13.2, 12.2, 3.5 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.73 (qd, *J* = 7.9, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 150.5, 117.6, 114.6, 95.5, 76.4, 69.2, 61.4, 55.6, 35.7, 18.2, 6.9, 5.2. HRMS: [M + Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.1976; found 416.2671.

***p*-Methoxyphenyl-3-allyl-*N*-carbamate-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside (15)**



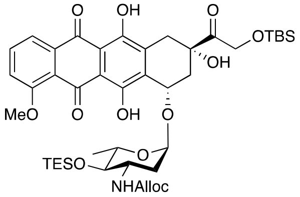
To a solution of azide **14** (1.57 g, 4.00 mmol) in THF/H_2O (40 mL, 10:1 v/v) was added PPh_3 (3.15 g, 20.0 mmol, 5 eq) and the reaction mixture was stirred for 2 days at 50^{o}C. Solvent was removed *in vacuo* and the residue was co-evaporated with toluene twice. The crude amine was dissolved in DCM (30 mL) and pyridine (1.0 mL, 12.9 mmol, 3.2 eq). Allyl chloroformate (0.64 mL, 24.0 mmol, 6 eq) was added at -20 ^{o}C and the resulting mixture was stirred for 2h at that temperature. It was then poured into H_2O and extracted with DCM thrice, combined organics were dried over $MgSO_4$ and solvent was removed *in vacuo*. Purification by column chromatography (0:100 – 5:95 EtOAc:pentane) afforded the title compound as a colourless oil (1.85 g, 4.0 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.93 (m, 2H), 6.89 – 6.76 (m, 2H), 5.94 (ddt, *J* = 16.5, 11.0, 5.7 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.33 (d, *J* = 16.5 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.59 (d, *J* = 5.7 Hz, 3H), 4.08 (dtd, *J* = 12.1, 9.2, 4.6 Hz, 1H), 3.83 (dq, *J* = 9.0, 6.3 Hz, 1H), 3.77 (s, 3H), 3.28 (t, *J* = 9.1 Hz, 1H), 2.32 (ddd, *J* = 13.3, 4.7, 1.5 Hz, 1H), 1.88 (t, *J* = 12.8 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 154.7, 150.9, 133.0, 118.0, 117.7, 114.6, 95.8, 76.6, 69.7, 65.7, 55.8, 51.0, 36.7, 18.6, 7.1, 5.5. HRMS: [M + Na]$^+$ calculated for $C_{22}H_{24}NO_5Na$ 474.2282; found 474.2289.

***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-4-*O*-triethylsilyl-β-L-rhamnopyranoside (17)**



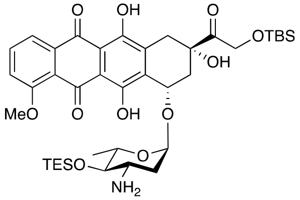
Glycoside **15** (903 mg, 2.00 mmol) was hydrolysed according to general procedure A. Column chromatography (30:70 – 50:50 EtOAc:pentane) afforded the hemiacetal. The hemiacetal in was esterified to according to general procedure B. Column chromatography (0:100 – 15:85 Et_2O:pentane) afforded the title compound as an off-white solid (498 mg, 0.97 mmol, 49%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.40 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.33 – 7.23 (m, 1H), 6.00 (dd, *J* = 9.6, 2.3 Hz, 1H), 5.93 (ddt, *J* = 16.5, 10.9, 5.7 Hz, 1H), 5.39 – 5.26 (m, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 3.76 (dtd, *J* = 12.1, 9.1, 4.7 Hz, 1H), 3.55 (dq, *J* = 8.6, 6.2 Hz, 1H), 3.33 – 3.22 (m, 1H), 2.40 (ddd, *J* = 12.7, 4.8, 2.4 Hz, 1H), 1.85 (q, *J* = 11.6 Hz, 1H), 1.51 (tt, *J* = 8.2, 6.1 Hz, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.93 – 0.84 (m, 4H), 0.63 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 155.5, 134.3, 134.1, 132.8, 132.1, 131.5, 131.1, 130.9, 127.4, 127.0, 125.2, 118.0, 99.8, 92.6, 75.7, 75.0, 74.5, 65.8, 53.3, 36.6, 18.6, 9.1, 8.9, 7.0, 5.4, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2444; found 536.2437.

7-[3-*N*-allyloxycarbonyl-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (19)



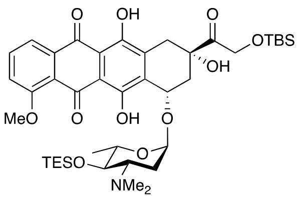
According to general procedure C, glycosyl donor **17** (411 mg, 0.800 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (555 mg, 1.05 mmol 1.5 eq). Column chromatography (3:97 – 10:90 EtOAc:toluene) afforded the title compound as a red solid (545 mg, 0.64 mmol, 91%, 8:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.96 (d, *J* = 2.6 Hz, 1H), 13.26 (d, *J* = 2.8 Hz, 1H), 8.03 (d, *J* = 6.4 Hz, 1H), 7.78 (td, *J* = 8.2, 2.2 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 5.99 – 5.78 (m, 1H), 5.47 – 5.40 (m, 1H), 5.27 (d, *J* = 15.3 Hz, 2H), 5.18 (d, *J* = 10.6 Hz, 1H), 5.03 – 4.86 (m, 2H), 4.57 (s, 1H), 4.08 (d, *J* = 2.1 Hz, 3H), 3.82 (d, *J* = 7.5 Hz, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.29 (s, 1H), 3.21 (d, *J* = 18.7 Hz, 1H), 2.98 (dd, *J* = 19.3, 2.8 Hz, 1H), 2.34 (d, *J* = 14.8 Hz, 1H), 2.16 (d, *J* = 15.1 Hz, 1H), 2.10 (d, *J* = 13.4 Hz, 1H), 1.81 (s, 1H), 1.30 (dd, *J* = 6.3, 2.1 Hz, 3H), 1.04 – 0.91 (m, 19H), 0.62 (qd, *J* = 7.9, 2.1 Hz, 6H), 0.14 (d, *J* = 2.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 187.3, 186.9, 161.2, 156.6, 156.1, 135.8, 134.5, 134.0, 121.1, 111.6, 111.5, 90.0, 77.6, 77.3, 77.2, 76.9, 66.9, 36.0, 34.2, 18.8, 5.5. HRMS: $[M + Na]^+$ calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.3574; found 878.3599.

7-[3-Amino-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (20)



To a solution of **19** (135 mg, 0.158 mmol) and 1,3-dimethylbarbituric acid (74 mg, 0.47 mmol, 3 eq) in DCM (15 mL) was portionwise added $Pd(PPh_3)_4$ (18.5 mg, 0.016 mmol, 0.1 eq). The reaction mixture was stirred overnight and solvent was removed *in vacuo*. The residue was submitted to column chromatography (3:97 – 15:85 acetone:toluene) to afford the title compound as a red solid (95 mg, 0.13 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.43 (d, *J* = 3.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.03 – 4.82 (m, 2H), 4.73 (s, 1H), 4.08 (s, 3H), 3.73 (dq, *J* = 8.9, 6.2 Hz, 1H), 3.16 (dd, *J* = 19.0, 2.0 Hz, 1H), 3.06 (t, *J* = 8.9 Hz, 1H), 2.92 (d, *J* = 18.9 Hz, 1H), 2.87 (dt, *J* = 8.7, 4.1 Hz, 1H), 2.34 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.95 (dd, *J* = 13.4, 4.4 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.05 – 0.93 (m, 18H), 0.69 (q, *J* = 8.1 Hz, 6H), 0.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7, 187.1, 186.7, 161.1, 156.5, 155.9, 135.8, 135.6, 134.4, 134.1, 120.9, 119.9, 118.5, 111.5, 111.3, 100.7, 80.4, 70.0, 69.6, 66.8, 56.8, 50.3, 37.9, 35.8, 34.0, 26.0, 18.7, 18.4, 7.1, 5.7, -5.2. HRMS: $[M+H]^+$ calculated for $C_{39}H_{59}NO_{11}Si_2$ 772.3543; found 772.3568.

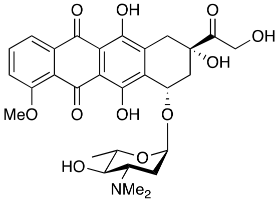
7-[3-Dimethylamino-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (21)



To a solution of **20** (97 mg, 0.13 mmol) in EtOH (10 mL) were added formaldehyde solution (aqueous 37% w/v, 0.31 mL, 3.9 mmol, 30 eq) and sodium trisacetoxyborohydride (52 mg, 0.24 mmol, 1.95 eq). After stirring for 1.5 h, the reaction mixture was partitioned between DCM and sat. aq. $NaHCO_3$ and extracted thrice with DCM. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:200 - 10:90 acetone:toluene) afforded the title compound as a red solid (77 mg, 96 µmol, 77%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.97 (s, 1H), 13.26 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 3.9 Hz, 1H), 5.25 (d, *J* = 3.1 Hz, 1H), 5.06 – 4.85 (m, 2H), 4.79 (s, 1H), 4.09 (s, 3H), 3.82 – 3.68 (m, 1H), 3.32 – 3.12 (m, 2H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.51 (d, *J* = 13.4 Hz, 1H), 2.37 (d, *J* = 14.7 Hz, 1H), 2.14 (d, *J* = 4.6 Hz, 6H), 1.89 – 1.79 (m, 1H), 1.60 (td, *J* = 12.9, 4.2 Hz, 1H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.02

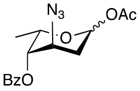
– 0.91 (m, 18H), 0.60 (qd, *J* = 7.6, 3.4 Hz, 6H), 0.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8, 187.3, 186.8, 161.1, 156.6, 156.1, 135.8, 135.7, 134.6, 134.3, 121.1, 119.9, 118.5, 111.5, 111.4, 101.5, 73.6, 71.2, 69.8, 66.8, 61.8, 56.8, 40.7, 35.8, 34.0, 26.2, 26.0, 18.8, 18.7, 7.2, 5.6, -5.3. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$: 800.3856; found 800.3888.

***N,N*-dimethyl-4'-*epi*-doxorubicin (5)**



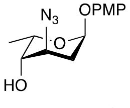
According to general procedure D, **21** (33 mg, 41 µmol) was subjected to HF·pyridine (70 wt% HF, 190 µL). Column chromatography on neutral silica (0:100 - 20:80 MeOH:DCM) afforded the title compound as a red solid (24 mg, 41 µmol, quant.). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.16 (s, 1H), 7.99 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.56 (d, *J* = 3.9 Hz, 1H), 5.29 (s, 1H), 5.26 (dd, *J* = 4.2, 2.1 Hz, 1H), 4.88 – 4.71 (m, 2H), 4.08 (s, 3H), 3.80 (dq, *J* = 9.0, 6.2 Hz, 1H), 3.23 – 3.12 (m, 2H), 2.90 (d, *J* = 18.7 Hz, 1H), 2.63 (ddd, *J* = 13.3, 9.9, 3.8 Hz, 1H), 2.38 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.20 (s, 6H), 2.17 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.84 (ddd, *J* = 13.2, 4.0, 1.3 Hz, 1H), 1.63 (td, *J* = 13.0, 4.2 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 187.2, 186.7, 161.1, 156.4, 155.8, 135.9, 135.5, 133.9, 133.9, 120.9, 120.0, 118.6, 111.6, 111.4, 101.5, 76.8, 71.5, 70.8, 69.8, 65.7, 61.9, 56.8, 40.0, 35.7, 34.0, 25.9, 18.4. HRMS: $[M+H]^+$ calculated for $C_{29}H_{35}NO_{11}$ 572.2126; found 572.2134.

Acetyl-3-*epi*-azido-4-*O*-benzoyl-3-deoxy-L-daunosamine (23)



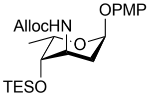
A solution of **22** (Chapter 3)[8] (18.1 g, 45.0 mmol) in THF (360 mL) and 1M aq. HCl (360 mL) was stirred for 1 h at 50ºC. It was then poured into sat. aq. $NaHCO_3$, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the crude enal thus obtained in H_2O (64 mL) and THF (72 mL) were added acetic acid (9.6 mL, 167.7 mmol, 3.7 eq) and NaN_3 (5.12 g, 81.5 mmol, 1.8 eq). The reaction mixture was stirred for 2 days, poured into sat. aq. $NaHCO_3$, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was submitted to column chromatography (10:90 - 30:70 Et_2O:pentane) to yield the crude 3-azide hemiacetal. To a solution of the hemiacetal thus obtained in DCM (113 mL) and pyridine (34 mL) were added Ac_2O (34.0 mL, 360 mmol, 9.5 eq). The reaction mixture was stirred for 5 h, concentrated *in vacuo*, and partitioned between H_2O and EtOAc, washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* to obtain the product title product (7.92 g, 24.8 mmol, 55% over 3 steps, 1:5 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.25 (d, *J* = 4.3 Hz, 1H), 4.87 (s, 1H), 4.19 (d, *J* = 3.9 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.19 – 2.16 (m, 1H), 2.15 (d, *J* = 1.3 Hz, 3H), 2.13 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3 H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.2, 165.8, 133.8, 130.0, 129.3, 128.7, 90.2, 69.8, 63.6, 54.0, 26.5, 21.3, 14.1. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.02 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.89 (s, 1H), 4.29 (q, *J* = 6.6 Hz, 1H), 4.19 (d, *J* = 3.9 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.19 – 2.16 (m, 1H), 2.15 (d, *J* = 1.3 Hz, 3H), 2.13 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.2. 165.8, 133.8, 130.0, 128.7, 90.6, 69.3, 57.7, 30.5, 21.3, 16.7. HRMS: $[M + Na]^+$ calculated for $C_{13}H_{15}N_3O_4Na$ 342.10604; found 342.10607.

***p*-Methoxyphenyl-3-*epi*-azido-α-L-daunosamine (24)**



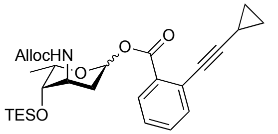
Anomeric acetate **23** (7.92 g, 24.8 mmol) and *p*-methoxyphenol (4.62 g, 37.2 mmol, 1.5 eq) were coevaporated with toluene. DCM (880 mL) and activated molecular sieves (4Å) were added and the reaction was stirred for 30 minutes at room temperature. $BF_3 \cdot OEt_2$ (7.65 mL, 62 mmol, 2.5 eq) was added at -60 ºC and the reaction mixture gradually allowed to warm up from -60 ºC to -40 ºC over 2.5h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, extracted with DCM, washed twice with NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (42 ml), to which NaOMe (284 mg, 5.0 mmol, 0.2 eq) was added after which the reaction mixture was stirred for 4 days. Dry ice was added and the reaction mixture was concentrated *in vacuo*. Column chromatography (8:92 – 40:60 EtOAc:pentane) afforded the title compound as a white solid (4.38 g, 17.3 mmol, 77%, 10:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 6.94 (m, 2H), 6.94 – 6.73 (m, 2H), 5.46 (dd, *J* = 4.3, 1.4 Hz, 1H), 4.43 (qd, *J* = 6.7, 1.4 Hz, 1H), 4.00 (dt, *J* = 4.2, 3.1 Hz, 1H), 3.80 (s, 3H), 3.43 (s, 1H), 2.35 (dt, *J* = 15.3, 4.4 Hz, 1H), 2.26 – 2.05 (m, 2H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.8, 151.0, 117.8, 114.6, 95.3, 69.0, 62.7, 57.1, 55.7, 29.7, 27.0, 16.3. HRMS: [M + H]$^+$ calculated for $C_{13}H_{18}N_3O_4$ 280.1297; found 280.1292.

***p*-Methoxyphenyl-3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-α-L-daunosamine (26)**



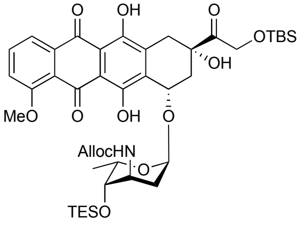
To a solution of **25** (1.22 mg, 4.38 mmol) in DMF (7.4 mL) and pyridine (1.06 mL, 13.1 mmol, 3 eq) was added TESOTf (1.08 mL, 1.8 mmol, 1.8 eq) at 0^{o}C and the reaction mixture was stirred for 1 hour. It was subsequently poured into EtOAc, washed with H$_2$O, dried over MgSO$_4$ and concentrated *in vacuo.* The residue was dissolved in THF/H$_2$O (165 mL, 10:1 v/v), PPh$_3$ (2.30 g, 8.76 mmol, 2 eq) was added and the reaction mixture was stirred for 3 days after which it was concentrated *in vacuo*. The amine thus obtained was co-evaporated with toluene thrice and dissolved in DCM (31.4 mL) and pyridine (1.1 mL, 14 mmol, 3.2 eq). Allyl choroformate (0.70 mL, 6.6 mmol, 1.5 eq) was added at -25 ^{o}C and the reaction mixture was stirred at that temperature for 1h. The mixture was left to warm to room temperature and diluted with DCM, washed with H$_2$O, dried over MgSO$_4$ and concentrated *in vacuo.* Purification by column chromatography (2:98:1 – 40:60:1 Et$_2$O:pentane:Et$_3$N) afforded the title compound as a colourless oil (1.98 g, 4.38 mmol, quant. over 3 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 6.98 (m, 2H), 6.91 – 6.77 (m, 2H), 6.29 (d, *J* = 7.8 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 5.41 – 5.16 (m, 2H), 4.72 – 4.50 (m, 2H), 4.26 – 4.13 (m, 1H), 3.90 (ddt, *J* = 7.9, 5.4, 2.7 Hz, 1H), 3.78 (s, 3H), 3.53 (d, *J* = 3.4 Hz, 1H), 2.52 – 2.32 (m, 1H), 1.79 (ddt, *J* = 14.4, 2.4, 1.2 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.06 – 0.95 (m, 9H), 0.80 – 0.64 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.7, 155.1, 150.7, 133.1, 118.0, 117.9, 114.7, 97.6, 69.4, 65.7, 63.4, 55.8, 49.1, 27.9, 17.2, 7.0, 4.9. HRMS: [M + Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 474.2282; found 474.2289.

***o*-Cyclopropylethynylbenzoyl-3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-L-daunosamine (27)**



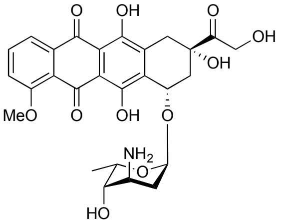
Glycoside **26** (990 mg, 2.19 mmol) was hydrolyzed according to general procedure A. The hemiacetal thus obtained was esterified according to general procedure B. Column chromatography (0:100 – 15:85 Et$_2$O) in pentane afforded the title compound as a pale-yellow oil (879 mg, 1.71 mmol, 79%, 3:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.96 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H, NH), 7.47 (dt, *J* = 7.5, 1.9 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.34 – 7.27 (m, 1H), 6.09 (dd, *J* = 9.2, 2.5 Hz, 1H), 5.93 (ddd, *J* = 16.2, 10.8, 5.4 Hz, 1H), 5.37 – 5.22 (m, 2H), 4.59 (s, 2H), 4.00 (dt, *J* = 6.5, 2.9 Hz, 2H), 3.57 (s, 1H), 2.42 – 2.34 (m, 1H), 1.88 – 1.78 (m, 1H), 1.31 – 1.27 (m, 3H), 1.27 – 1.23 (m, 1H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.91 – 0.88 (m, 4H), 0.73 – 0.65 (m, 8H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.7, 155.6, 134.9, 134.3, 132.1, 130.8, 127.2, 99.9, 91.8, 74.6, 71.5, 69.3, 65.9, 50.7, 30.6, 17.0, 9.0, 7.1, 4.85, 0.8. HRMS: [M + Na]$^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.24389; found 536.24362.

7-[3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-α-L-daunosamino]-14-*O*-tert-butyldimethylsilyldoxorubicinone (28)



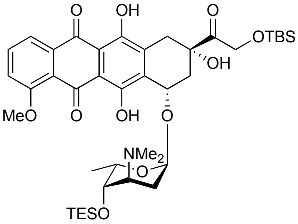
According to general procedure C glycosyl donor **27** (384 mg, 0.769 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (593 mg, 0.2 mmol 1.5 eq). Column chromatography (2:98 – 10:90 acetone:toluene) and size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) afforded the title compound as a red solid (368 mg, 0.43 mmol, 57%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.24 (s, 1H), 7.99 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.00 – 5.80 (m, 1H), 5.50 (d, *J* = 3.7 Hz, 1H), 5.40 – 5.01 (m, 3H), 4.74 (s, 2H), 4.51 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.20 – 4.13 (m, 1H), 4.11 (s, 1H), 4.08 (s, 3H), 3.81 – 3.71 (m, 1H), 3.49 (d, *J* = 3.6 Hz, 1H), 3.19 (d, *J* = 18.8 Hz, 1H), 3.02 (d, *J* = 18.8 Hz, 1H), 2.39 – 2.09 (m, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 24.0 Hz, 19H), 0.70 (q, *J* = 7.7 Hz, 6H), 0.15 (d, *J* = 1.3 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 210.9, 187.1, 186.7, 161.1, 156.8, 155.8, 135.8, 135.6, 135.1, 133.7, 133.3, 121.0, 119.8, 118.5, 117.3, 111.5, 111.2, 99.4, 76.1, 69.5, 67.0, 66.9, 65.3, 63.6, 56.8, 48.7, 35.2, 33.5, 27.4, 25.9, 18.5, 17.2, 7.1, 4.9, -5.3. HRMS: [M + Na]$^+$ calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.35740; found 878.35817.

3’-*epi*-Doxorubicin (6)



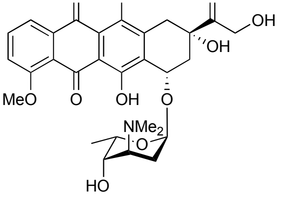
To a solution of **28** (46 mg, 54 µmol) in DCM (5 mL) were added 1,3-dimethylbarbituric acid (25 mg, 0.16 mmol, 3 eq) and Pd(PPh$_3$)$_4$ (27 mg, 5.4 µmol, 0.05 eq). The reaction mixture was stirred for 1.5 h after which solvent was removed *in vacuo*. The residue was submitted to column chromatography (0:100 – 10:90 acetone:toluene) to afford the crude amine **29**. The crude amine was desilylated using HF·pyridine (70 wt% HF, 0.2 mL) according to general procedure D. Column chromatography on neutral silica (0:100 - 50:50 MeOH:DCM) afforded the title compound as a red solid (18 mg, 33 µmol, 62% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 8.04 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.46 – 5.37 (m, 1H), 5.25 (dd, *J* = 3.7, 2.4 Hz, 1H), 4.79 (s, 2H), 4.59 – 4.42 (m, 1H), 4.09 (s, 3H), 3.79 – 3.66 (m, 1H), 3.08 (d, *J* = 18.9 Hz, 1H), 2.39 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.21 – 2.04 (m, 2H), 1.94 – 1.80 (m, 2H), 1.46 (d, *J* = 12.1 Hz, 2H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 214.8, 187.2, 186.8, 161.2, 156.3, 156.0, 135.8, 135.7, 134.6, 134.0, 121.1, 119.9, 118.5, 111.6, 111.3, 100.0, 76.4, 72.0, 68.3, 65.7, 62.9, 48.7, 35.5, 34.1, 31.2, 16.4. HRMS: $[M+H^+]$ calculated for $C_{27}H_{30}NO_{11}$: 544.1813; found 544.1812.

7-[3-*epi*-Dimethylamino-4-*O*-triethylsilyl-α-L-daunosamine]-14-*O*-tert-butyldimethylsilyldoxorubicinone (30)



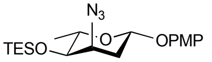
To a solution of **28** (34 mg, 40 µmol) in DCM (4.0 mL) was added 1,3-dimethylbarbituric acid (19 mg, 119 µmol, 3 eq). Pd(PPh$_3$)$_4$ (5 mg, 4 µmol, 0.1 eq) was added and the reaction mixture was stirred for 1h, after which it was concentrated *in vacuo*. The residue was submitted to column chromatography (0:100 – 15:85 acetone:toluene) to give the crude amine. To a solution of this amine in EtOH (2.5 mL) was added formaldehyde (aqueous 37% w/v solution, 0.1 mL, mmol, 30 eq) and sodium trisacetoxy borohydride (14 mg, 66 µmol, 1.95 eq). The reaction mixture was stirred for 2h and partitioned between DCM and sat. aq. NaHCO$_3$. The aqueous layer was extracted with DCM, combined organics were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 10:90 acetone in toluene) afforded the title compound as a red solid (23 mg, 29 µmol, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.85 (s, 1H), 13.31 (s, 1H), 8.02 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.2 Hz, 1H), 5.34 (d, *J* = 3.7 Hz, 1H), 5.18 (dd, *J* = 3.6, 2.3 Hz, 1H), 5.00 – 4.90 (m, 2H), 4.24 (h, *J* = 5.7 Hz, 1H), 4.08 (s, 3H), 3.77 – 3.71 (m, 1H), 3.44 – 3.26 (m, 1H), 3.22 – 2.98 (m, 2H), 2.39 – 2.26 (m, 1H), 2.15 (s, 6H), 2.12 – 1.98 (m, 3H), 1.82 – 1.70 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.03 – 0.93 (m, 19H), 0.71 – 0.56 (m, 6H), 0.14 (d, *J* = 3.7 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 213.0, 187.2, 186.8, 161.1, 156.5, 156.3, 135.8, 135.7, 135.4, 134.7, 121.2, 119.8, 118.4, 111.3, 111.1, 99.9, 76.8, 68.9, 67.7, 66.8, 64.7, 64.0, 56.8, 44.0, 35.7, 34.0, 26.0, 25.6, 18.8, 17.5, 7.1, 5.1, -5.1, -5.3. HRMS: $[M+H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.3856; found 800.3880.

***N,N*-dimethyl-3’-epidoxorubicin (7)**



According to general procedure D, **30** (19 mg, 24 µmol) was desilylated using HF·pyridine (70 wt% HF, 0.2 mL). Column chromatography on neutral silica (0:100 - 20:80 MeOH:DCM) afforded the title compound as a red solid (9.0 mg, 16 µmol, 66%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.27 (s, 1H), 8.04 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.80 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.36 (dd, *J* = 5.5, 3.9 Hz, 1H), 5.28 (dd, *J* = 3.7, 2.3 Hz, 1H), 4.80 (s, 2H), 4.38 (qd, *J* = 6.8, 3.4 Hz, 1H), 4.10 (s, 3H), 3.74 (dd, *J* = 6.6, 3.4 Hz, 1H), 3.23 (dd, *J* = 18.9, 2.0 Hz, 1H), 3.04 (d, *J* = 18.8 Hz, 1H), 2.52 – 2.41 (m, 2H), 2.23 (s, 6H), 2.11 (dd, *J* = 14.7, 3.8 Hz, 1H), 1.98 (dt, *J* = 14.0, 3.8 Hz, 1H), 1.60 (ddd, *J* = 13.7, 8.0, 5.5 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 215.0, 187.2, 186.8, 161.1, 156.3, 156.0, 135.7, 134.3, 134.3, 121.0, 119.9, 111.5, 111.3, 99.7, 77.4, 77.1, 76.9, 76.4, 76.4, 68.5, 68.2, 66.9, 65.7, 62.6, 56.8, 35.6, 34.0, 26.4, 26.4, 15.1. HRMS: $[M+H]^+$ calculated $C_{29}H_{35}NO_{11}$ for 572.2126; found 572.2131.

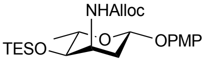
p-Methoxyphenyl-3-azido-4-O-triethylsilyl-2,3,6-trideoxy-β-L-ribohexapyranoside (32)



To a solution of **31** (Chapter 2) (2.26 g, 7.03 mmol) in MeOH (120 ml) was added sodium methoxide (76 mg, 1.41 mmol, 0.2 eq). After stirring for two days the reaction mixture was quenched by addition of dry ice. Solvent was removed in vacuo and coevaporated thrice with toluene. The residue was purified by column chromatography (10:90 – 50:50 Et_2O:pentane) to afford the alcohol as a pale-yellow oil (1.96 mg, 7.03 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 – 6.89 (m, 2H), 6.90 – 6.76 (m, 2H), 5.27 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.11 (q, *J* = 3.7 Hz, 1H), 3.80 (dt, *J* = 8.7, 6.3 Hz, 1H), 3.76 (s, 3H), 3.48 (td, *J* = 8.3, 3.6 Hz, 1H), 2.28 (ddd, *J* = 13.8, 4.2, 2.3 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 151.1, 117.7, 114.6, 96.3, 72.4, 70.8, 60.7, 55.7, 35.1, 18.2. HRMS: [M+Na]$^+$ calculated for $C_{13}H_{17}N_3O_4Na$ 302.1111; found 302.1118.

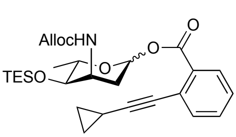
To a solution of the above alcohol (1.12 g, 4.00 mmol) in pyridine (20 mL) was added TESOTf (1.29 mL, 1.59 g, 6.00 mmol, 1.5 eq). The reaction mixture was stirred for 30 minutes and then diluted with DCM, washed twice with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 7:93 Et_2O:pentane) afforded the title compound as a colorless oil (1.57 g, 4.0 mmol quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.97 – 6.90 (m, 2H), 6.86 – 6.75 (m, 2H), 5.25 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.98 (q, *J* = 3.5 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 8.7, 3.3 Hz, 1H), 2.17 (ddd, *J* = 13.6, 4.0, 2.3 Hz, 1H), 1.96 (ddd, *J* = 13.6, 9.0, 3.4 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.68 (qd, *J* = 8.3, 7.9, 1.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 151.2, 117.8, 114.6, 96.5, 74.8, 70.8, 60.8, 55.8, 35.8, 18.5, 7.0, 5.0. HRMS: [M+Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.1976; found 416.1983.

p-Methoxyphenyl-3-N-allyloxycarbonyl-4-O-triethylsilyl-2,3,6-trideoxy-3-azido-β-L-ribohexapyranoside (34)



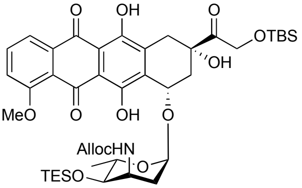
To a solution of **33** (1.57 mg, 4.00 mmol) in THF/H_2O (40 ml, 10:1 v/v) was added PPh_3 (3.15 g, 2.00 mmol, 2 eq) and the reaction mixture was stirred overnight at 50°C. Solvent was removed *in vacuo* and the residue was co-evaporated with toluene twice. The crude amine was dissolved in DCM (30 ml) and pyridine (1 mL) to which allyl chloroformate (0.64 ml, 0.72 g, 6 eq) was added at -20°C. This mixture was stirred for 1 hour at this temperature. It was then poured into H_2O and extracted with DCM thrice, organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:200 Et_3N:pentane) afforded the title compound as a colorless oil (1.81 mg, 4.00 mmol quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 – 6.91 (m, 2H), 6.87 – 6.70 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.43 – 5.25 (m, 2H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.04 (s, 1H), 4.65 – 4.45 (m, 2H), 4.11 (q, *J* = 4.9, 4.2 Hz, 1H), 3.77 (s, 4H), 3.63 (dd, *J* = 6.7, 4.0 Hz, 1H), 2.51 (dd, *J* = 14.0, 6.3 Hz, 1H), 1.90 (ddd, *J* = 13.5, 7.0, 3.7 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 154.8, 151.4, 132.9, 117.9, 117.6, 114.6, 97.0, 72.6, 71.9, 65.7, 55.8, 48.4, 19.2, 6.9, 5.0. HRMS: [M+Na]$^+$ calculated for $C_{23}H_{37}NO_6SiNa$ 474.2282; found 474.2290.

o-Cyclopropylethynylbenzoyl-3-N-allyloxycarbonyl-4-O-triethylsilyl-2,3,6-trideoxy-L-ribohexapyranoside (35)



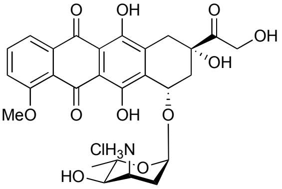
Glycoside **34** (1.71 g, 3.80 mmol) was hydrolyzed according to general procedure A. Column chromatography (90:10 EtOAc:pentane) afforded the hemiacetal. The resulting hemiacetal was esterified according to general procedure B. Column chromatography (0:100 -10:90 Et_2O:pentane) afforded the title compound as a pale yellow oil (1.11 g, 2.20 mmol, 57% over 2 steps, 1:3 α:β). Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.41 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.27 (dd, *J* = 6.6, 2.8 Hz, 1H), 5.93 (dddd, *J* = 18.0, 10.5, 6.1, 5.2 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.3 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.06 (s, 1H), 4.59 (q, *J* = 6.8, 6.2 Hz, 2H), 4.15 (tq, *J* = 6.6, 3.7 Hz, 1H), 3.91 (p, *J* = 6.5 Hz, 1H), 3.67 (dd, *J* = 6.1, 3.9 Hz, 1H), 2.55 – 2.39 (m, 1H), 1.93 (ddd, *J* = 13.5, 6.6, 3.8 Hz, 1H), 1.53 (tt, *J* = 8.1, 5.6 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 0.97 (dd, *J* = 8.3, 7.5 Hz, 9H), 0.92 – 0.83 (m, 4H), 0.63 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 156.2, 134.4, 132.9, 131.9, 131.2, 130.6, 127.1, 125.2, 117.9, 99.8, 92.1, 74.6, 73.6, 71.5, 65.8, 47.6, 32.2, 19.3, 9.0, 6.9, 5.0, 0.8. HRMS: [M+Na]$^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2434; found 536.2450.

7-[3-Allyl-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-2,3,6-trideoxy-L-ribohexapyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (36)



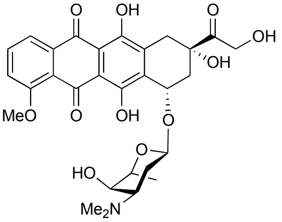
According to general procedure C, glycosyl donor **35** (128 mg, 0.240 mmol) was coupled to 14-O-*tert*-butyldimethylsilyldoxorubicinone **18** (198 mg, 0.37 mmol, 1.5 eq). Column chromatography (0:100 – 5:95 EtOAc:pentane - 1:99 - 3:97 acetone:toluene) gave the title compound as a red solid (103 mg, 0.120 mmol, 50%, 1.5:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.22 (s, 1H), 7.98 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 5.82 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.71 (d, *J* = 6.7 Hz, 1H), 5.40 (dd, *J* = 4.4, 2.3 Hz, 1H), 5.26 – 5.17 (m, 2H), 5.07 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.95 – 4.78 (m, 2H), 4.54 – 4.37 (m, 3H), 4.07 (s, 3H), 3.93 (dq, *J* = 12.5, 6.5 Hz, 2H), 3.49 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.17 (dd, *J* = 18.9, 1.8 Hz, 1H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.34 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.17 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.09 (ddd, *J* = 14.5, 4.5, 2.3 Hz, 1H), 1.86 (dt, *J* = 14.4, 4.3 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.99 – 0.93 (m, 18H), 0.71 – 0.59 (m, 6H), 0.15 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 186.9, 186.6, 161.0, 156.4, 156.3, 155.7, 135.6, 135.5, 134.5, 134.0, 133.1, 120.9, 119.7, 118.4, 116.9, 111.4, 111.2, 98.9, 72.5, 66.8, 66.4, 65.1, 56.7, 48.4, 35.6, 33.7, 33.4, 25.8, 18.5, 18.1, 6.8, 4.8, -5.5. HRMS: [M+Na$^+$] calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.3574; found 878.3602.

3'-4'-Di-*epi*-dimethyldoxorubicin hydrochloride (8)



To a solution of **36** (45mg, 53 µmol) in DCM (5 mL) were added 1,3-dimethylbarbituric acid (25 mg, 0.16 mmol, 3 eq) and Pd(PPh$_3$)$_4$ (6.0 mg, 5.3 mmol, 0.1 eq). The reaction mixture was stirred overnight and solvent was removed in vacuo. The residue was submitted to column chromatography (1:99 – 15:85 acetone in toluene) to give the crude amine **37**. The crude amine thus obtained was desilylated according to general procedure D using HF·pyridine (70 wt% HF, 0.2 mL). Column chromatography on neutral silica (0:100 - 50:50 MeOH:DCM) and lyophilization from aqueous 10 µM HCl (1 mL/µmol, 2 eq) afforded the title compound as a dark red solid (17 mg, 29 µmol, 54% over 2 steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.98 (s, 1H), 13.22 (s, 1H), 7.92 (q, *J* = 4.4, 3.8 Hz, 2H), 7.80 – 7.55 (m, 4H), 6.29 (s, 1H), 6.18 (d, *J* = 4.8 Hz, 1H), 5.30 (d, *J* = 3.3 Hz, 1H), 5.04 – 4.89 (m, 2H), 4.73 – 4.43 (m, 2H), 3.99 (s, 3H), 3.98 – 3.91 (m, 1H), 3.46 (dt, *J* = 9.3, 4.5 Hz, 3H), 3.17 (d, *J* = 18.8 Hz, 1H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.24 (d, *J* = 14.8 Hz, 1H), 2.11 – 1.81 (m, 3H), 1.28 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 214.0, 187.2, 187.1, 161.4, 156.1, 155.1, 136.9, 135.3, 135.1, 134.6, 120.5, 120.4, 119.6, 111.4, 111.3, 98.7, 75.7, 68.9, 68.6, 65.0, 64.4, 57.2, 49.7, 40.4, 35.6, 32.1, 31.7, 18.0. HRMS: [M+H$^+$] calculated for $C_{27}H_{31}NO_{11}$:544.1813; found 544.1814.

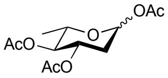
3'-4'-Di-*epi*-dimethyldoxorubicin (9)



To a solution of **36** (73 mg, 85 µmol) in DCM (6 mL) was added 1,3-dimethylbarbituric acid (40 mg, 0.26 mmol, 3 eq). Pd(PPh$_3$)$_4$ (9.0 mg, 8.5 µmol, 0.1 eq) was added and the reaction mixture was stirred overnight. After concentrating *in vacuo,* the residue was submitted to silica gel column chromatography (0:100 - 15:85 acetone in toluene) to give the crude amine **37**. To a solution of the crude amine in EtOH (4 mL) was added formaldehyde (aqueous 37% w/v solution, 0.13 mL) and sodium trisacetoxyborohydride (22.5 mg, 106 µmol, 1.95 eq). The reaction mixture was stirred for 2h, partitioned between DCM and sat. aq. $NaHCO_3$ and the aqueous layer was extracted thrice with DCM. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*, followed by purification through column chromatography (0:100 – 20:80 acetone in toluene) to give the crude dimethylamine. This was then desilylated using HF·pyridine (70 wt% HF, 0.3 mL) according to general procedure D. Column chromatography on neutral silica (0:100 - 7:93 MeOH:DCM) afforded the title compound as a red solid (17 mg, 30 µmol, 35% over 3 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.99 (s, 1H), 13.22 (s, 1H), 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.40 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.38 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.30 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.85 – 4.71 (m, 2H), 4.09 (s, 3H), 4.02

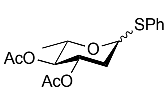
(dd, *J* = 6.8, 5.3 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.24 (dd, *J* = 18.8, 2.1 Hz, 1H), 2.95 (d, *J* = 18.7 Hz, 1H), 2.55 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.37 – 2.31 (m, 6H), 2.31 (s, 6H), 2.15 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.53 (td, *J* = 13.0, 8.8 Hz, 1H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 214.9, 187.3, 186.7, 161.2, 156.5, 156.0, 135.9, 135.7, 134.4, 133.9, 121.0, 120.0, 118.5, 111.6, 111.4, 100.3, 76.6, 71.4, 69.0, 68.3, 65.8, 60.1, 56.8, 43.0, 36.0, 33.9, 29.0, 18.7. HRMS: [M+H$^+$] calculated $C_{29}H_{35}NO_{11}$ 572.2126; found 572.2131. ^{13}C-GATED NMR (Chloroform-*d*, 126 MHz) δ 100.31 ($J_{C1', H1'}$= 169 Hz, C-1).

1,3,4-Tri-*O*-acetyl-2-deoxy-L-rhamnopyranoside (39)[15]



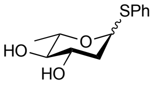
To a solution of 3,4-di-*O*-acetyl-L-rhamnal **38** (Chapter 2) (9.37 g, 54.0 mmol) in DCM (300 mL) were added acetic acid (5.10 mL, 5.39 g, 86.0 mmol, 1.6 eq) and PPh$_3$·HBr (2.20 g, 3.26 mmol, 0.1 eq). The reaction mixture was stirred for two days and concentrated *in vacuo.* Column chromatography (25:75 – 30:70 Et$_2$O:pentane) afforded the title compound as a white solid (7.63 g, 26.6 mmol, 51%, 5:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

Phenyl-3,4-di-*O*-acetyl-2-deoxy-1-thio-L-rhamnopyranoside (40)[15]



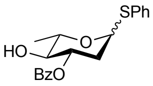
To a solution of **39** (7.6 g, 28 mmol) in DCM (200 mL) were added thiophenol (3.7 mL, 33 mmol, 1.2 eq) and BF$_3$·OEt$_2$ (4.9 mL, 33 mmol, 1.2 eq). The reaction mixture was stirred for 1 h, diluted with DCM and washed with sat. aq. NaHCO$_3$, 1M NaOH and brine. The organic layer was dried over Na$_2$SO$_4$ and concentrated *in vacuo* to obtain the title compound as a colorless oil (8.9 g, 28 mmol, quant., 1:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.

Phenyl-2-deoxy-1-thio-L-rhamnopyranoside (41)[15]



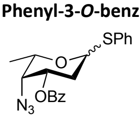
To a solution of **40** (9.9 g, 30 mmol) in MeOH (250 mL) was added sodium methoxide (330 mg, 6.11 mmol, 0.2 eq). After stirring for 2h, the reaction mixture was quenched by addition of dry ice. Solvent was removed *in vacuo* and the residue was coevaporated thrice with toluene. Column chromatography (50:50 – 100:0 Et$_2$O:pentane) afforded the title compound as a sticky pale yellow syrup (6.30 g, 26.3 mmol, 88%, 1:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

Phenyl-3-*O*-benzoyl-2-deoxy-1-thio-L-rhamnopyranoside (42)[15]



Diol **41** (5.89 g, 24.5 mmol) and dibutyltin dichloride (365 mg, 1.20 mmol, 0.05 eq) were dissolved in THF (125 mL). Benzoyl chloride (3.4 mL, 29 mmol, 1.2 eq) was added and the reaction mixture was stirred overnight. The reaction mixture was quenched by addition of 1M HCl and was subsequently partitioned between EtOAc and 1M HCl. The organic layer was washed with sat. aq. NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$ and solvent was removed *in vacuo*. Purification by column chromatography (30:70 Et$_2$O:pentane) afforded the title compound as a sticky syrup (7.10 g, 20.5 mmol, 84%, 3:2 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

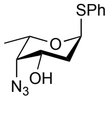
Phenyl-3-*O*-benzoyl-4-azido-2,4-deoxy-1-thio-L-fucopyranoside (43)



To a solution of **42** (5.20 g, 15.3 mmol) in DCM (150 mL) were added pyridine (15 mL) and triflic anhydride (2.3 mL, 18 mmol, 1.2 eq) at 0˚C. After stirring at that temperature for 15 minutes, the reaction was diluted with DCM and washed successively with 1M aq. CuSO$_4$ and brine, dried over MgSO$_4$, filtered, and concentrated *in vacuo* at 0ºC. The colorless oil thus obtained was dissolved in DMF (5 mL), to which NaN$_3$ (15.3 g, 37.5 mmol, 5 eq) was added, and the mixture was stirred overnight. The reaction mixture was then partitioned between H$_2$O and Et$_2$O, and the organic layer was washed with H$_2$O and brine and dried over MgSO$_4$. Solvent was removed *in vacuo* and purification by column chromatography (5:95 – 30:70 Et$_2$O:pentane) gave the title compound as a white solid (4.09 g, 11.1 mmol, 68%, 1:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 – 8.05 (m, 2H), 7.64 – 7.54 (m, 1H), 7.51 – 7.41 (m, 4H), 7.35 – 7.20 (m, 3H), 5.72 (d, *J* = 5.8 Hz, 1H), 5.60 (ddd, *J* = 12.3, 4.7, 3.2 Hz, 1H), 4.58 (qd, *J* = 6.4, 1.5 Hz, 1H), 3.94 (dt, *J* = 3.0, 1.3

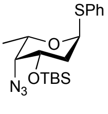
Hz, 1H), 2.63 (td, *J* = 12.8, 5.9 Hz, 1H), 2.25 (ddt, *J* = 13.2, 4.8, 1.2 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 134.7, 133.7, 133.6, 131.1, 130.0, 129.3, 129.1, 128.7, 127.3, 83.7, 70.3, 66.1, 63.7, 30.9, 17.8. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.04 (m, 2H), 7.65 – 7.49 (m, 3H), 7.49 – 7.38 (m, 2H), 7.38 – 7.19 (m, 3H), 5.33 (ddd, *J* = 11.3, 5.4, 3.4 Hz, 1H), 4.81 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.80 (dt, *J* = 3.5, 1.1 Hz, 1H), 3.71 (qd, *J* = 6.3, 1.3 Hz, 1H), 2.49 – 2.09 (m, 2H), 1.39 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 133.7, 133.5, 132.0, 130.0, 129.2, 129.0, 128.6, 127.7, 82.4, 73.6, 72.8, 62.5, 31.5, 18.3. HRMS: $[M+Na]^+$ calculated for $C_{19}H_{20}O_4SNa$ 392.1039; found 392.1044.

Phenyl-4-azido-2,4-deoxy-1-thio-α-L-fucopyranoside (44)



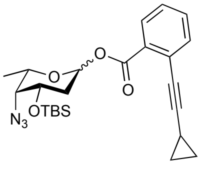
To a solution of **43α** (1.94 g, 5.25 mmol) in MeOH (200 mL) was added NaOMe until pH >10. After stirring overnight, the reaction mixture was quenched by addition of dry ice and solvent was removed *in vacuo*. Purification by column chromatography (10:90 - 50:50 Et_2O:pentane) afforded the title compound as a white solid (1.20 g, 4.52 mmol, 86%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.36 (m, 2H), 7.36 – 7.16 (m, 5H), 5.65 (d, *J* = 5.4 Hz, 1H), 4.48 (qdd, *J* = 6.5, 1.6, 0.6 Hz, 1H), 4.32 – 4.13 (m, 1H), 3.67 (dt, *J* = 3.1, 1.3 Hz, 1H), 2.27 (ddd, *J* = 13.4, 12.0, 5.8 Hz, 1H), 2.11 (ddt, *J* = 13.3, 4.9, 1.1 Hz, 1H), 1.92 (d, *J* = 7.8 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9, 131.1, 129.1, 127.3, 84.0, 67.2, 66.6, 66.6, 34.4, 17.9. HRMS: $[M\text{-}N_2 +H]^+$ calculated for $C_{19}H_{20}NO_3S$ 238.0896; found 238.0903.

Phenyl-3-*O*-*tert*-butyldimethylsilyl-4-azido-2,4-deoxy-1-thio-L-fucopyranoside (45)



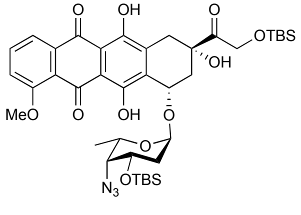
To a solution of **44** (318 mg, 1.20 mmol) in DMF (7.5mL), imidazole (204 mg, 1.80 mmol, 1.5 eq) and TBS-Cl (50 wt% in toluene, 0.20 mL, 2.4 mmol, 2 eq) were added and the reaction mixture was stirred for 3h. The reaction mixture was diluted with Et_2O, washed 4x with H_2O and once with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. Purification by column chromatography (5:95 Et_2O:pentane) afforded the title compound as a white solid (429 mg, 1.13 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.37 (m, 2H), 7.33 – 7.20 (m, 3H), 5.64 (d, *J* = 5.7 Hz, 1H), 4.38 (qd, *J* = 6.3, 1.5 Hz, 1H), 4.28 (ddd, *J* = 11.8, 4.7, 3.3 Hz, 1H), 3.56 (dt, *J* = 2.9, 1.3 Hz, 1H), 2.43 (ddd, *J* = 13.5, 11.9, 5.8 Hz, 1H), 1.96 (ddt, *J* = 13.4, 4.7, 1.2 Hz, 1H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.15 (d, *J* = 2.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.8, 129.1, 127.1, 84.2, 68.9, 66.4, 66.0, 34.8, 25.9, 18.0, -4.4. HRMS: $[M\text{-}N_2 +H]^+$ calculated for $C_{24}H_{34}NO_4Si$ 352.1761; found 352.1772.

***o*-Cyclopropylethynylbenzoyl-3-*O*-*tert*-butyldimethylsilyl-4-azido-2,4-deoxy-L-fucopyranoside (46)**



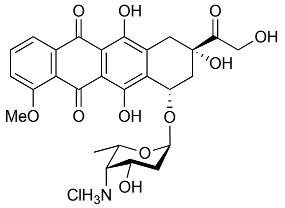
Thioglycoside **45** (410 mg, 1.09 mmol, 1 eq) was dissolved in THF/H_2O (6 mL, 9:1 v/v), to which $AgNO_3$ (648 mg, 3.82 mmol, 3.5 eq) was added. After stirring in the dark overnight under regular atmosphere, ethyl acetate (60 mL) and Na_2SO_4 were added and the reaction mixture was stirred for 1h, filtered over Celite and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane) afforded the crude hemiacetal. This was esterified according to general procedure B. Column chromatography (0:100 - 5:95 Et_2O:pentane) afforded the title compound as a colourless oil (297 mg, 0.598 mmol, 65%, 1:3 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (ddd, *J* = 8.0, 1.4, 0.6 Hz, 1H), 7.48 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 – 7.26 (m, 2H), 5.88 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.10 (ddd, *J* = 11.6, 4.8, 3.4 Hz, 1H), 3.69 (qd, *J* = 6.3, 1.4 Hz, 1H), 3.49 (dt, *J* = 3.4, 1.2 Hz, 1H), 2.16 (td, *J* = 11.9, 10.1 Hz, 1H), 2.01 (dddd, *J* = 12.3, 4.8, 2.5, 1.1 Hz, 1H), 1.57 – 1.45 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.91 – 0.88 (m, 4H), 0.14 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 134.4, 132.2, 131.0, 130.7, 127.1, 125.3, 99.9, 92.6, 74.6, 71.0, 70.3, 65.1, 34.5, 25.8, 17.9, 9.0, 0.8, -4.4, -4.6. HRMS: $[M +Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133; found 478.2141.

7-[3-*O*-*tert*-butylsilyldimethylsilyl-4-azido-2,4-deoxy-α-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (47)



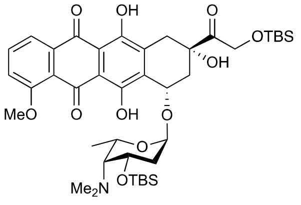
According to general procedure B, glycosyl donor **46** (266 mg, 0.585 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (464 mg, 0.877 mmol, 1.5 eq). Column chromatography (15:85 Et_2O:pentane and then 1:99 - 10:90 acetone:toluene) of the residue gave the title compound as a red solid (440 mg, 0.551 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.84 (s, 1H), 13.07 (s, 1H), 7.91 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.73 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.47 (d, *J* = 4.0 Hz, 1H), 5.18 (dd, *J* = 4.0, 2.1 Hz, 1H), 4.96 – 4.77 (m, 2H), 4.50 (s, 1H), 4.07 (s, 3H), 4.05 – 3.94 (m, 2H), 3.54 (d, *J* = 3.1 Hz, 1H), 3.09 (dd, *J* = 18.9, 1.8 Hz, 1H), 2.80 (d, *J* = 18.9 Hz, 1H), 2.25 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.03 (ddd, *J* = 13.4, 11.8, 4.2 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.85 (s, 9H), 0.14 (d, *J* = 1.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 186.8, 186.5, 161.0, 156.3, 155.6, 135.7, 135.3, 134.0, 133.8, 120.7, 119.8, 118.5, 111.3, 111.3, 101.3, 77.5, 77.3, 77.2, 76.8, 69.6, 67.9, 66.6, 66.1, 56.7, 35.5, 34.0, 33.8, 25.9, 25.7, 18.7, 18.1, 18.0, -4.4, -4.7, -5.2, -5.3. HRMS: [M +Na]$^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.3267; found 820.3287.

3'-Desamino-3'-hydroxy-4'-deoxy-4'-aminodoxorubicin hydrochloride (isodoxorubicin hydrochloride) (10)



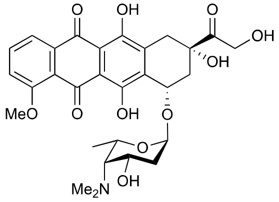
To a solution of **47** (110 mg, 0.138 mmol, 1 eq) in THF/H_2O (20 mL, 10:1 v/v) was added triphenylphosphine (108 mg, 0.412 mmol, 3 eq) and the reaction mixture was stirred for a week at 50 °C. Solvent was removed *in vacuo* and the residue was subjected to column chromatography (30:70 EtOAc:pentane, then 10:90 – 20:80 acetone:toluene) to give the crude amine **48**. The amine thus obtained was desilylated using HF·pyridine (70 wt% HF, 0.24 mL) according to general procedure C. Column chromatography on neutral silica (0:100 – 10:90 MeOH:DCM) afforded the title compound as a red solid (27 mg, 49.7 µmol, 36% over 2 steps). The corresponding HCl salt was prepared by lyophilization from aqueous 10 µM HCl (1 mL/µmol, 2 eq). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 14.06 (s, 1H), 13.26 (s, 1H), 7.92 (q, *J* = 4.0, 3.2 Hz, 2H), 7.87 – 7.75 (m, 3H), 7.71 – 7.62 (m, 1H), 5.69 (d, *J* = 26.2 Hz, 1H), 5.51 (s, 1H), 5.29 (d, *J* = 3.9 Hz, 1H), 4.95 (t, *J* = 4.5 Hz, 1H), 4.58 (s, 2H), 4.37 (q, *J* = 6.5 Hz, 1H), 3.99 (s, 5H), 3.19 (d, *J* = 27.2 Hz, 2H), 3.05 – 2.88 (m, 2H), 2.12 (d, *J* = 4.4 Hz, 2H), 1.75 (dd, *J* = 13.5, 5.4 Hz, 1H), 1.65 (td, *J* = 13.1, 4.0 Hz, 1H), 1.21 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 213.9, 186.6, 186.6, 160.8, 156.0, 154.4, 136.3, 135.1, 134.7, 134.2, 120.0, 119.8, 119.1, 110.8, 100.2, 74.8, 70.2, 63.7, 63.0, 61.5, 56.6, 54.1, 36.5, 32.4, 32.0, 16.9. HRMS: [M+H]$^+$ calculated for $C_{27}H_{30}NO_{11}$ 544.1813; found 544.1816.

7-[3-*O*-*tert*-butyldimethylsilyl-4-dimethylamino-2,4-deoxy-α-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (49)



To a solution of **47** (130 mg, 0.160 mmol, 1 eq) in THF/H_2O (26 mL, 10:1 v/v) was added triphenylphosphine (129 mg, 49 mmol, 3 eq) and the reaction mixture was stirred for four days at 50 °C. Solvent was removed *in vacuo* and the red residue was subjected to column chromatography (1:99 – 15:85 acetone:toluene). To the amine **48** thus obtained (65 mg, 83 µmol) in EtOH (6.8 mL) were added aq. CH_2O (aq. 37% w/v, 0.20 mL, 30 eq) and NaBH$(OAc)_3$ (34.6 mg, 16.4 mmol, 1.95 eq). The reaction mixture was stirred for two hours and partitioned between DCM and sat. aq. $NaHCO_3$. The aqueous layer was extracted thrice with DCM and combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:199 - 5:95 acetone:toluene) afforded the title compound as a red solid (55 mg, 69 µmol, 43% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.23 (s, 1H), 8.00 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.2 Hz, 1H), 5.51 (t, *J* = 4.0 Hz, 1H), 5.26 (dd, *J* = 3.9, 2.2 Hz, 1H), 5.02 – 4.83 (m, 2H), 4.78 (s, 1H), 4.20 (ddq, *J* = 18.2, 9.1, 4.5, 4.1 Hz, 2H), 4.09 (s, 3H), 3.17 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.97 (d, *J* = 18.9 Hz, 1H), 2.53 (s, 6H), 2.47 (t, *J* = 2.1 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.16 – 2.04 (m, 2H), 1.96 (s, 1H), 1.69 (dt, *J* = 13.7, 4.5 Hz, 1H), 1.40 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.90 (s, 9H), 0.14 (d, *J* = 2.8 Hz, 6H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 187.1, 186.7, 161.1, 156.5, 156.0, 135.7, 135.6, 134.6, 134.1, 121.1, 119.9, 118.5, 111.5, 111.4, 99.6, 77.3, 70.1, 69.7, 69.2, 66.8, 65.4, 56.8, 44.9, 37.7, 35.4, 34.0, 26.0, 18.7, 18.1, 17.1, -4.3, -4.6, -5.1, -5.2. HRMS: $[M+H^+]$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.3861; found 800.3852.

***N,N*-dimethylisodoxorubicin (11)**



49 (29 mg, 36 µmol) was desilylated using HF·pyridine (70 wt% HF, 0.14 mL) according to general procedure C. Column chromatography on neutral silica (0:100 – 95:5 MeOH:DCM) afforded the title compound as a red solid (15 mg, 26 µmol, 72%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.22 (s, 1H), 8.01 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.55 (t, *J* = 4.2 Hz, 1H), 5.30 (dd, *J* = 3.9, 2.2 Hz, 1H), 4.81 (s, 1H), 4.77 (d, *J* = 1.3 Hz, 2H), 4.29 (qd, *J* = 7.0, 3.8 Hz, 1H), 4.08 (s, 3H), 3.94 (dt, *J* = 9.0, 4.8 Hz, 1H), 3.24 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.99 (d, *J* = 18.8 Hz, 1H), 2.54 (s, 6H), 2.49 – 2.43 (m, 2H), 2.12 (dd, *J* = 14.7, 3.9 Hz, 1H), 1.91 (ddd, *J* = 14.0, 8.5, 3.8 Hz, 1H), 1.78 (dt, *J* = 14.0, 4.8 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 187.1, 186.8, 161.2, 156.4, 155.8, 135.8, 135.6, 134.0, 133.8, 121.1, 119.9, 118.6, 111.7, 111.6, 99.1, 70.0, 69.4, 65.7, 64.4, 64.0, 56.8, 44.7, 35.9, 35.4, 34.1, 17.4. HRMS: $[M+H]^+$ calculated $C_{29}H_{35}NO_{11}$ for 572.2126; found 572.2142.

References

1 K. Krohn, *Anthracycline Chemistry and Biology I Biological Occurence and Biosynthesis, Synthesis and Chemistry*, Springer Verlag, 2008.
2 D. J. Booser and G. N. Hortobagyi, *Drugs*, 1994, **47**, 223–258.
3 A. P. Launchbury and N. Habboubi, *Cancer Treat. Rev.*, 1993, **19**, 197–228.
4 F. Arcamone, *Doxorubicin: Anticancer Antibiotics*, ACADEMIC PRESS, INC, 1981.
5 F. M. M. Arcamone, *Biochimie*, 1998, **80**, 201–206.
6 A. Suarato, S. Penco, A. Vigevani and F. Arcamone, *Carbohydr. Res.*, 1981, **98**, C1–C3.
7 K. Madduri, J. Kennedy, G. Rivola, A. Inventi-Solari, S. Filippini, G. Zanuso, A. L. Colombo, K. M. Gewain, J. L. Occi, D. J. MacNeil and C. R. Hutchinson, *Nat. Biotechnol.*, 1998, **16**, 69–74.
8 B. Renneberg, Y.-M. Li, H. Laatsch and H.-H. Fiebig, *Carbohydr. Res.*, 2000, **329**, 861–872.
9 L. Bohé and D. Crich, *Carbohydr. Res.*, 2015, **403**, 48–59.
10 V. Siitonen, M. Claesson, P. Patrikainen, M. Aromaa, P. Mäntsälä, G. Schneider and M. Metsä-Ketelä, *ChemBioChem*, 2012, **13**, 120–128.
11 J. Zeng, G. Sun, W. Yao, Y. Zhu, R. Wang, L. Cai, K. Liu, Q. Zhang, X.-W. Liu and Q. Wan, *Angew. Chemie Int. Ed.*, 2017, **56**, 5227–5231.
12 P. Bartner, D. L. Boxler, R. Brambilla, A. K. Mallams, J. B. Morton, P. Reichert, F. D. Sancilio, H. Surprenant, G. Tomalesky, G. Lukacs, A. Olesker, T. T. Thang, L. Valente and S. Omura, *J. Chem. Soc., Perkin Trans. 1*, 1979, **0**, 1600–1624.
13 T. Vuljank, J. Kihlberg and P. Somfai, *Tetrahedron Lett.*, 1994, **35**, 6937–6940.
14 S. I. Elshahawi, K. A. Shaaban, M. K. Kharel and J. S. Thorson, *Chem. Soc. Rev.*, 2015, **44**, 7591–7697.
15 M. Oberthür, C. Leimkuhler, R. G. Kruger, W. Lu, C. T. Walsh and D. Kahne, *J. Am. Chem. Soc.*, 2005, **127**, 10747–10752.
16 S. R. Sanapala and S. S. Kulkarni, *J. Am. Chem. Soc.*, 2016, **138**, 4938–4947.
17 WO 2007/075094 A1, 2006.
18 J. Boivin, A. Montagnac, C. Monneret and M. Pais, *Carbohydr. Res.*, 1980, **85**, 223–242.
19 B. Hagen, S. Ali, H. S. Overkleeft, G. A. van der Marel and J. D. C. Codée, *J. Org. Chem.*, 2017, **82**, 848–868.