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

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Chapter 4

Changing the 3'-substitution pattern on doxorubicin

Introduction

Since the discovery of doxorubicin in 1969,[1] it has become one of the most used anti-cancer drugs, with an annual market of over $800 million.[2] In spite of its efficacy against (amongst others) leukemia and non-Hodgkin's lymphoma,[3] the use of this drug is limited by its cardiotoxic side effect.[4] In the search for more potent anthracyclines with fewer side-effects, several thousands of analogs of daunorubicin and doxorubicin have been isolated from natural source, produced by mutant enzymes or prepared by organic synthesis.[5,6] Disappointingly, only a handful of these made it to a clinical setting (see Chapter 1) as these were not significantly more potent or less cardiotoxic enough, and doxorubicin itself remains the most used anti-cancer anthracycline. Chapter 1 discussed the recently uncovered mechanism of action of anthracyclines, namely histone eviction.[7] It was shown that doxorubicin is both able to induce both DNA DSBs and histone eviction, whereas the much less cardiotoxic aclarubicin only possesses the latter ability, prompting the hypothesis that histone eviction may be the most important mechanism of action by which anthracyclines cause cancer cell death.

In order to understand what structural elements in doxorubicin and aclarubicin result in this differential activity profile, Chapter 3 presented a coherent set of hybrid structures between these two drugs in which the aglycone, amine/dimethylamine and sugar chain were varied. This Chapter focuses more deeply on further varying the 3'-amine by synthesizing 11 doxorubicin analogs that differ in this position. These include neutral 3'-analogs (lacking the basic amine), 3'-methyl analogs that introduce steric bulk onto the daunosamine ring, singly *N*-methylated and doubly *N*-ethylated doxorubicin and finally *N*-heterocyclic doxorubicins.

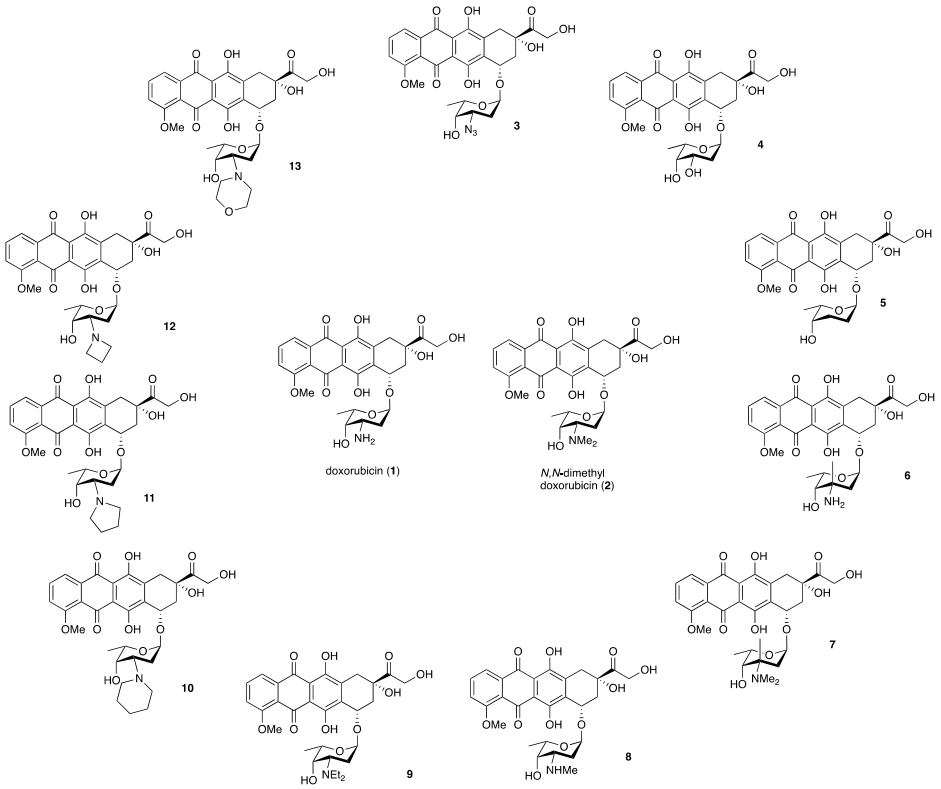


Figure 1. Chemical structures of the doxorubicin derivatives **3**-**13** subject of this Chapter, differing in substitution pattern on the 3-position of the sugar moiety.

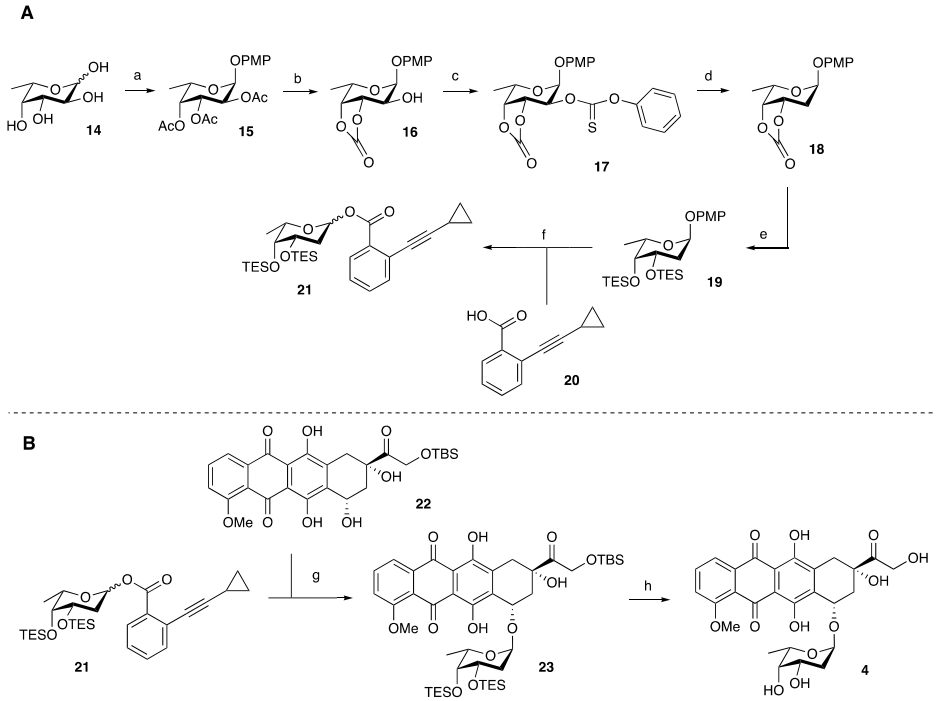
Depicted in the middle of the circle in Figure 1 are doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**2**) (see also Chapter 2). Compounds **3**, **4** and **5** represent non-basic analogs of doxorubicin, all lacking the amine that would be protonated at physiological pH. The absence of a basic amine may have implications for the intracellular processing of the compound,[8] for example by altering interactions with negatively charged DNA backbones[9] and by abolishing P-glycoprotein recognition.[10] In known azidodoxorubicin (**3**),[10,11] the amine is masked as an azide. Second, in 3'-desamino-3'-hydroxydoxorubicin (**4**), the amine function in doxorubicin is replaced with a hydroxyl instead, keeping the hydrogen bonding ability of the 3-position. This compound was earlier prepared by means of modified Koenigs-Knorr glycosylation in the group of Varela in 1984 in their search for an improved doxorubicin analogue.[12] *In vivo* evaluation in the P388 lymphocytic leukemia system in mice showed decreased cytotoxicity when compared to doxorubicin (**1**), with later evaluation by Capranico *et al.*[13] showing that hydroxyrubicin (**4**) is no less potent than doxorubicin with respect to the induction of DNA breaks. A difference in their respective histone evicting abilities

might be able to explain the difference in cytotoxicity instead. Third, 3'-desaminodoxorubicin (**5**) was designed, lacking any substituent on the 3-position of the sugar moiety.

Vancosaminyl doxorubicinone (**6**) and its *N,N*-dimethylated analog (**7**) were envisaged to introduce steric bulk on the ring, with the introduction of a 3'-Me substituent. Its sugar moiety, L-vancosamine, can be prepared *de novo,*[14–16] from sugars/amino acids,[17–19] or it can be cleaved off of its parent drug vancomycin.[20,21] This Chapter shows the application of the latter strategy in the assembly of these two doxorubicin-vancomycin hybrids. *N*-methyldoxorubicin (**8**) fills the chemical space in between doxorubicin (**1**) and its *N,N*-dimethyldoxorubicin (**2**). Elaborating further on this theme, *N,N*-diethyldoxorubicin (**9**) was designed, a compound previously prepared by Tong *et al*.,[22] bearing a sterically less accessible amine compared to **2**. *N*-cyclic doxorubicins (**10**-**13**) were designed in the same vein, offering cyclic structures as a means of sterically constraining the tertiary amine. Compound **10-12** contain a piperidino, pyrrolidino and azetidino moiety, respectively. Morpholino-doxorubicin (also known as KRN8602(MX2)) (**13**) has already been evaluated in phase II trials but has not yet been probed within the context of histone eviction.[23] This compound introduces an oxygen in the ring versus **10**, giving rise to intramolecular hydrogen bonding with the amine, lowering its basicity.[24]

Although many of these compounds have been previously reported in the literature, their biological evaluation was often incomplete (e.g. not tested for histone evicting property). The availability of these compounds will aid in establishing an in-depth structure-activity relationship to explain the different biological activities of doxorubicin and provide insight how to manipulate these.

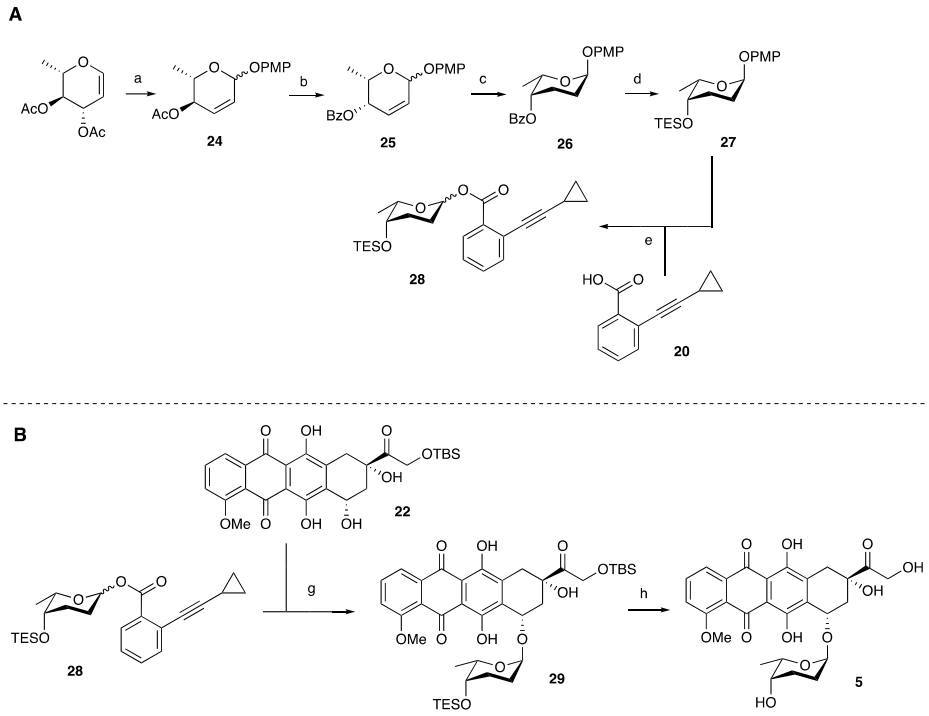
Results and discussion



Scheme 1. Synthesis of 3'-desamino-3'-hydroxydoxorubicin (**4**). *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii. p*-methoxyphenol, $BF_3{\cdot}OEt_2$, DCM, 0 °C to RT, 76% over 2 steps; (b) *i.* NaOMe, MeOH; *ii.* carbonyldiimidazole, DMF, 85 °C, quant. over 2 steps; (c) *O*-phenyl thionochloroformate, pyr., DCM, 92%; (d) Bu_3SnH, AIBN, toluene, 80 °C, 85%; (e) *i.* NaOMe, MeOH; *ii.* triethylsilyl triflate, pyr., DMF, 64% over 2 steps; (f) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, ACN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 61% over 2 steps (1:9 α:β); (g) PPh_3AuNTf_2, DCM, 63% (α-only); (h) HF·pyridine, THF/pyr., 78%.

Azidodoxorubicin (**3**) was prepared in Chapter 2 by means of copper-catalysed diazotransfer on doxorubicin (**1**).[11] Key step the synthesis of hydroxydoxorubicin (**4**) in Scheme 1 is the glycosylation of anomeric *ortho*-alkynylbenzoate **21** to doxorubicinone-acceptor **22** by means of catalytic gold(I) activation, according to the method developed by Yu's group and discussed in more detail in Chapter 2 and 3.[25] Peracetylation of L-fucose **14** was followed by treatment with $BF_3{\cdot}OEt_2$ in the presence of *p*-methoxyphenol to give α-fucoside **15** in good yield according to literature procedure.[26] Subjection to global deacetylation was followed by installation of a 3,4-carbonate function as a temporary protecting group using carbonyldiimidazole to furnish **16** quantitatively. Then, the 2-hydroxyl was transformed to its corresponding *O*-phenyl-thiono-carbonate **17**.[27] Treatment of **17** with excess tributyltin hydride and a catalytic amount of AIBN cleanly afforded 2-deoxy fucoside **18**. The carbonate was then subjected to Zemplén conditions and the resulting diol disilylated to yield **19**. This was converted into the

corresponding *ortho*-alkynylbenzoate donor **21** by means of silver(II)-mediated oxidation of the anomeric *p*-methoxyphenolate, followed by Steglich esterification of the resultant hemiacetal to carboxylic acid **20**. Treatment of a mixture of this donor **21** and 14-*O*-TBS-doxorubicinone **22** with catalytic PPh_3AuNTf_2 gave the desired anthraquinone glycoside **23** with good α-selectivity. Desilylation (using HF·pyridine) afforded hydroxyrubicin **4**, whose spectral data were in agreement with those reported in the literature.[12]

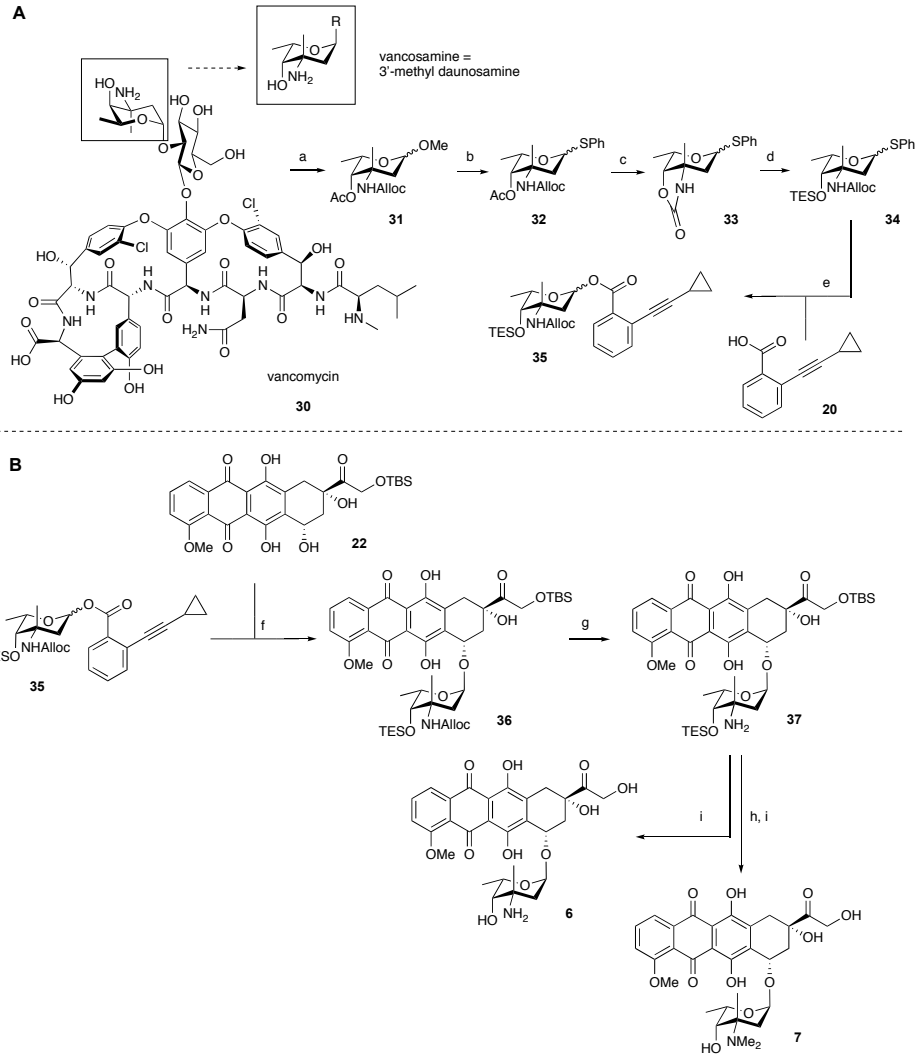


Scheme 2. Synthesis of 3'-desaminodoxorubicin (**5**). *Reagents and conditions:* (a) *p*-methoxyphenol, $BF_3{\cdot}OEt_2$, toluene, -10 °C, 41%, (12.5:1 α:β); (b) *i.* NaOMe, MeOH; *ii.* benzoic acid, PPh_3, diethylazodicarboxylate, THF, 0 °C to RT, 80% over 2 steps; (c) Rh/Al_2O_3, H_2, toluene, EtOAc, 0 °C, quant.; (d) *i.* NaOMe, MeOH; *ii.* triethylsilyl triflate, pyr., DMF, 73% over 2 steps; (e) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, ACN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 61% over 2 steps (1:9 α:β); (g) PPh_3AuNTf_2, DCM, 39% (α-only); (h) HF·pyridine, THF/pyr., 93%.

The synthesis of 3'-desaminodoxorubicin (**5**) commenced with L-rhamnal (Chapter 2), as depicted in Scheme 2A. Treatment hereof with *p*-methoxyphenol in toluene at -10 °C in the presence of 5 mol% $BF_3{\cdot}OEt_2$ afforded enopyranoside **24**, according to literature procedure.[28] The Lewis acid was used in low amount to suppress the amount of rearrangement of the phenolic O-glycoside to the aryl-C-glycoside.[29] Under these conditions, the reported[28] yield of 91% could not be reproduced: instead only 41% of

the product could be isolated from a complex mixture. The 4-acetate in **24** was then subjected to deacetylation under Zemplén conditions and ensuing Mitsunobu inversion of the resulting allylic alcohol to give 4-benzoate **25**. Rhodium-catalysed hydrogenation of the double bond yielded rhodinoside **26**. Debenzoylation and silylation yielded **27**, which was subjected to oxidative cleavage of the anomeric *p*-methoxyphenolate, followed by esterification to **20** to give *ortho*-alkynylbenzoate **28** in good yield. Treatment of this donor with PPh_3AuNTf_2 in the presence of acceptor **22** delivered **29** α-selectively (Scheme 2B), but in only 39% yield, likely due to instability of the reactive intermediates of this highly deoxygenated donor. A final HF·pyridine-mediated desilylation afforded desaminodoxorubicin (**5**).

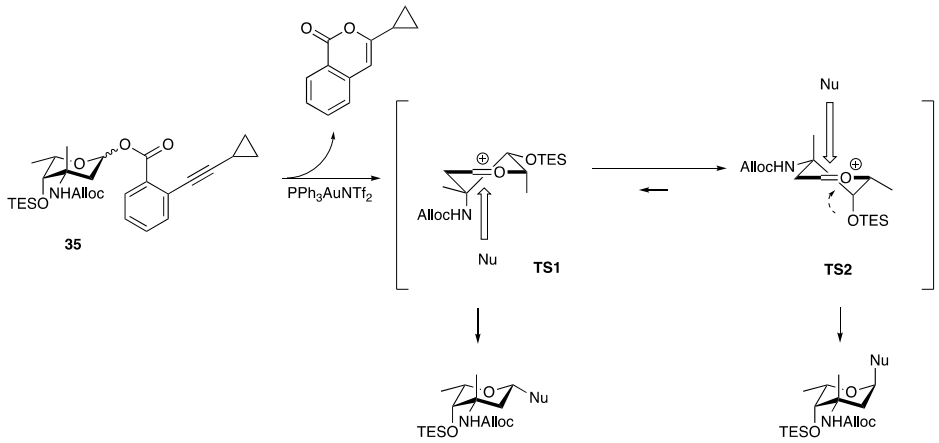
The synthesis of (*N,N*-dimethyl)-vancosaminyl doxorubicinones **6** and **7** is depicted in Scheme 3. Vancomycin (**30**), commercially available and relatively inexpensive ($350/50g at Carbosynth[30]) has been shown to be suitable for obtaining vancosamine-related glycosyl donors by the groups of Kahne and Bennett.[20,21] Combining lessons learned from their procedures, both amines found in vancomycin **30** were protected as their Alloc-carbamates using Alloc-succinimide, after which acidic methanolysis liberated the vancosamine synthon from its aglycone (Scheme 3A). After acetylation of its 4-hydroxyl function, protected vancosamine **31** was obtained in 57% over the three steps. Installation of a thiophenyl group on the anomeric position gave **32** as an anomeric mixture. 4-Deacylation under Zemplén conditions was accompanied by intramolecular attack onto the neighboring carbamate to give 3,4-carbamate **33**, with concomitant release of allyl alcohol. Hydrolysis of the carbamate in refluxing aqueous sodium hydroxide gave the free amine, and re-installation of the *N*-Alloc-group and 4-silylation to afford fully protected **34** in 90% yield over the three steps. Treatment of thioglycoside **34** with silver nitrate and lutidine afforded the corresponding hemiacetal.[31,32] Presumably, a silver-dilutidinium complex[33] is formed which is able to effect hydrolysis of the thioether. Ensuing Steglich esterification of this hemiacetal yielded *ortho*-alkynylbenzoate **35**. Activation of alkynylbenzoate **35** (Scheme 3B) by means of PPh_3AuNTf_2 in the presence of doxorubicinone-acceptor **22** afforded **36** as a 6:1 α:β mixture with respect to the newly formed anomeric center, for which a mechanistic rationale is shown in Scheme 4. In line with the stereoselective additions reported in Chapter 2 and 3, it is proposed that oxocarbenium ion-like intermediates are at the basis of the observed stereoselectivity. The oxocarbenium ion in TS1 is stabilized by the axial allyloxycarbamate. However, the most favorable trajectory for the incoming nucleophile is blocked by this same group. The alternative TS2 features an oxocarbenium ion, that places the C4-*O*-TBS group in an optimal orientation to provide electronic stabilization of the electron depleted anomeric center.



Scheme 3. Synthesis of (*N,N*-dimethyl)-vancosaminyl doxorubicinones **6** and **7**. *Reagents and conditions:* (a) *i.* Alloc-OSu, $NaHCO_3$, THF, H_2O; *ii.* HCl, MeOH; *iii.* Ac_2O, DMAP, pyr., 57% over 3 steps; (b) PhSH, $BF_3{\cdot}OEt_2$, DCM, 0 °C to RT, 83%; (c) NaOMe, MeOH, 88%; (d) *i.* aq. NaOH, 110°C; *ii.* Alloc-OSu, $NaHCO_3$, THF, H_2O (1:1, v/v); *iii.* triethylsilyl triflate, pyr., DCM, 90% over 3 steps; (e) *i.* $AgNO_3$, 2,6-lutidine, THF, H_2O; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 45% over 2 steps (1:10 α:β); (f) PPh_3AuNTf_2, DCM, 68% (6:1 α:β); (g) $Pd(PPh_3)_4$, NDMBA, DCM, 77%; (h) aq. CH_2O, $NaBH(OAc)_3$, EtOH; then Alloc-OSu, DCM, 52% over 2 steps; (i) HF·pyridine, pyr., 89% for **6**, 88% for **7**.

It also positions the C5-methyl group in a sterically favorable *pseudo*-equatorial position. Attack on this half chair oxocarbenium ion preferentially occurs on the top (*i.e.* α)-face to lead to the product through a chair-like transition state. Additionally,

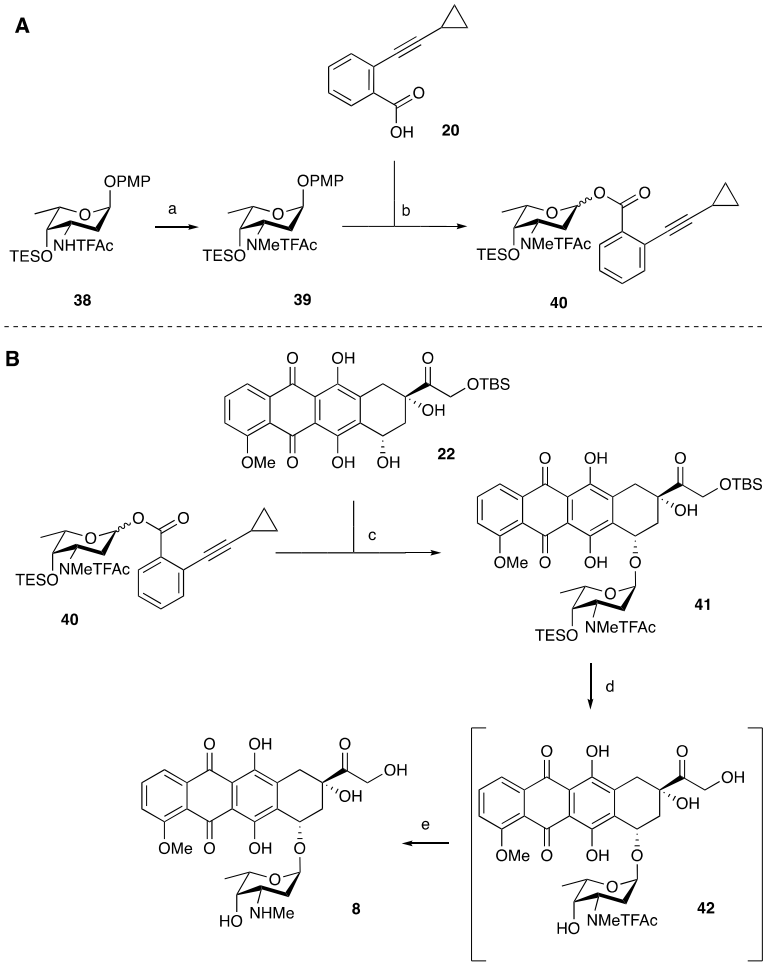
neighboring-group participation of the 3-Alloc group would also yield the α-product, which cannot be excluded at this stage.[34]



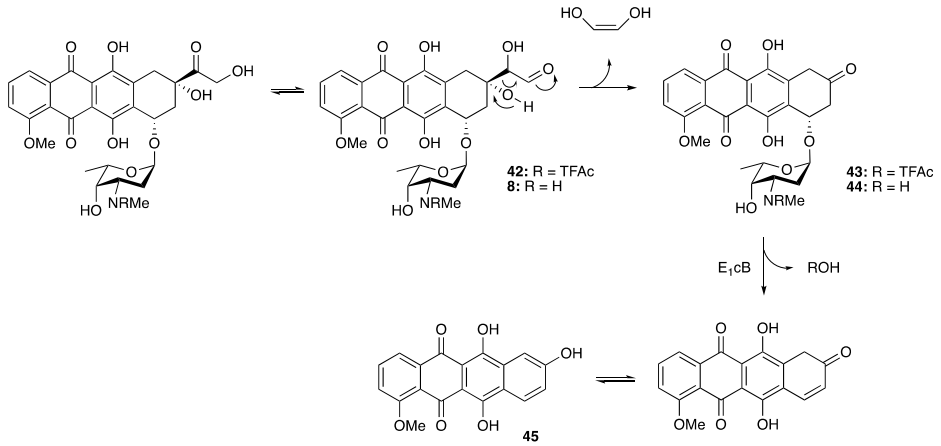
Scheme 4. Mechanistic rationale for the observed stereoselectivity of the glycosylation of donor **19** to acceptor **22**.

The desired, pure α-glycoside **36** could be isolated from the mixture by silica gel column chromatography. Alloc-removal with $Pd(PPh_3)_4$/NDMBA cleanly afforded the free amine in **37**. Desilylation thereof gave 3'-Me-doxorubicin (**6**) in good yield. Reductive amination (CH_2O, $NaBH(OAc)_3$) afforded a mixture of the starting amine and its mono- and dimethylated products, which could not be separated at this stage. Treatment of the mixture with a large excess of Alloc-OSu capped the undesired (*N*-methyl)-amine to facilitate isolation of the pure dimethylated amine in modest yield over these two steps, whose sugar moiety is known as brasiliose.[35] A final desilylation gave 3'-Me-dimethyldoxorubicin **7**.

The synthesis of *N*-monomethyldoxorubicin **8** is depicted in Scheme 5. Acetamide **38** (Chapter 2) was alkylated using iodomethane in acetone, using potassium carbonate as the base. The anomeric *p*-methoxyphenolate in **39** was then converted into its anomeric *ortho*-alkynylbenzoate **40** as described earlier in this Chapter. A mixture of this donor **40** and 14-*O*-TBS-doxorubicinone **22** was treated with PPh_3AuNTf_2 to give **41** α-selectively. After global desilylation hereof using triethylamine trihydrofluoride, the removal of the trifluoroacetamide (excess NaOMe, MeOH[36]) proceeded alongside extensive degradation towards the 9-ketone and fully aromatized **47**. A putative mechanism for this process is shown in Scheme 6.



Scheme 5. Synthesis of *N*-monomethyldoxorubicin **8**. *Reagents and conditions:* (a) MeI, K_2CO_3, acetone, 50 °C, quant.; (b) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 70% over 2 steps (1:5 α:β); (c) PPh_3AuNTf_2, DCM, 71%; (d) triethylamine·3HF, THF/pyr.; (e) NaOMe, MeOH, 23% over 2 steps.

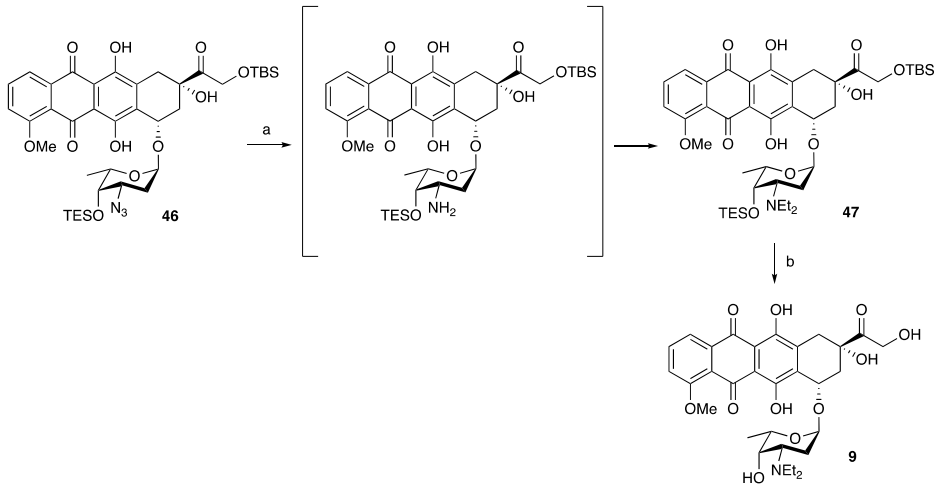


Scheme 6. Degradation of **8** and **42** *via* the bis-(hydroxy)ketone moiety.

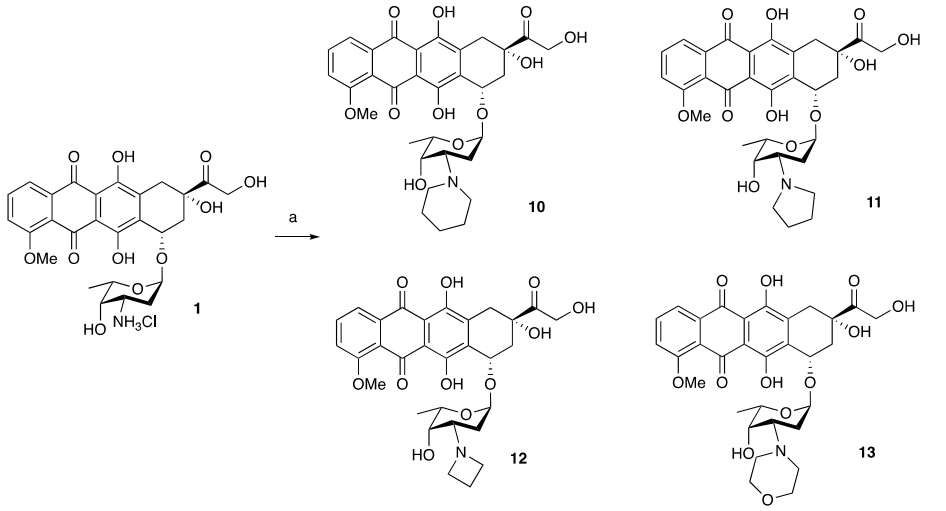
Tautomerisation of the exocyclic hydroxyketone can give rise to base-induced release of ethene-1,2-diol in a *retro*-aldol fashion to give **43**/**44**. This delivers a good substrate for E_1cB elimination, releasing the glycan and giving an enone that tautomerizes to give the phenol in **45**. This type of degradation was also observed by Tong *et al*.[37] during regular silica gel column chromatography of *N,N*-dialkyl doxorubicins and daunorubicins, and by Penco *et al.*[38] upon acid treatment of doxorubicin derivatives. Nevertheless, *N*-monomethylated **8** was obtained in 23% yield over the two steps after extensive purification. Glycosylation of the *N*-Me-Alloc alkynylbenzoate to acceptor **22** proceeded in poor yield (22%) and degraded during attempted removal of the Alloc group.

For the synthesis of *N,N*-diethyldoxorubicin **9**, protected doxorubicin **46** (Chapter 2) was subjected to Staudinger reduction conditions, followed by reductive amination using ethanolic acetaldehyde to afford the dialkylated product **47** in modest yield over both steps. A similar drop in yield upon reductive diethylation when compared to dimethylation was observed by Tong *et al.*,[22] who also prepared **9**. Final desilylation gave *N,N*-diethyldoxorubicin (**9**) near quantitatively.

N-cyclic doxorubicins **10-13** could be prepared in a single step by means of dialkylation of the amine in doxorubicin (**1**) to form the heterocycle, according to a previously reported procedure.[39] Treatment of doxorubicin with diiodopentane, diiodobutane, diiodopropane or bis(2-iodo)ethyl ether in the presence of triethylamine afforded **10**-**13** respectively, in modest yields but good final purity.



Scheme 7. Synthesis of *N,N*-diethyldoxorubicin **9**. *Reagents and conditions:* (a) *i.* polymer-bound PPh_3, THF, H_2O, 50 °C; *ii.* ethanolic acetaldehyde, $NaBH(OAc)_3$, EtOH, 30% over 2 steps; (b) HF·pyr., pyr., 98%.



Scheme 8. Synthesis of *N*-cyclic doxorubicins **10**-**13**. *Reagents and conditions:* (a) corresponding diiodoalkane, Et_3N, DMF, 25% for **10**, 53% for **11**, 34% for **12**, 60% for **13**.

Conclusions

Despite doxorubicin (**1**) having been used in a clinical setting for several decades, its structure-activity relationship is still not fully understood. Its use is still plagued by cumulative cardiotoxicity, severely limiting treatment. Histone eviction having been recently uncovered to be a previously unknown mode of action of anthracyclines brings renewed interest and incentive to make doxorubicin analogs. The synthesis and biological evaluation of coherent sets of analogs should aid in understanding the structure-activity relationship of this oft-used anti-cancer drug. To this end, this Chapter describes the synthesis of 11 derivatives of doxorubicin (**1**), differing in substitution pattern on the 3'-position of the sugar. Hydroxyrubicin (**4**) and desaminodoxorubicin (**5**), *N*-monomethyl- and *N,N*-diethyldoxorubicin (**8**) and (**9**) were prepared through the appropriate multiply deoxygenated *ortho*-alkynylbenzoate glycosyl donors from either L-rhamnose or L-fucose, followed by gold(I)-catalysed glycosylation.

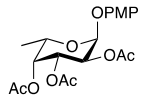
As Chapter 2 and 3 demonstrated the hydrolysis of natural glycosides doxorubicin and aclarubicin to obtain their respective aglycons, in this Chapter the methanolysis of vancomycin facilitated the isolation of its sugar moiety vancosamine which was used for the synthesis of **6** and **7**. This strategy of cleaving rare sugars off of natural products and appending them onto anthracycline aglycones can be expanded to other (bacterial) secondary metabolites to yield additional doxorubicin analogs.

N-cyclic doxorubicins **10**-**13** and azidodoxorubicin **3** could be prepared in a single reaction from the parent compound doxorubicin (**1**). The focused library of doxorubicin analogs **4**-**13** together with the ones described in Chapters 3 and 5 can now be evaluated for their ability to induce DNA breaks, cardiotoxic effects and chromatin damage as well as the regio-selectivity thereof within the genome, to aid in establishing a proper structure-activity relationship to explain the biological activities of anthracyclines.

Experimental procedures and characterization data

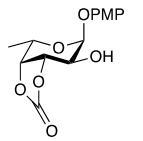
All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 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). ^{1}H 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 (^{1}H 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 150°C 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).

_p_-Methoxyphenyl-2,3,4-O-acetyl-α-L-fucopyranoside (15)[26]



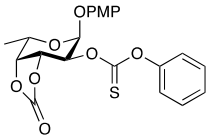
Commercially available L-fucose (6.53 g, 39.8 mmol) was suspended in pyridine (155 mL) and acetic anhydride (77 mL), to which DMAP (690 mg, 5.65 mmol, 0.14 eq) was added. After stirring overnight, the mixture was concentrated *in vacuo*. It was then partitioned between EtOAc and 1M HCl, and the organic layer was successively washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude peracetylated fucose. This was then together with *p*-methoxyphenol (7.41 g, 59.7 mmol, 1.5 eq) coevaporated from toluene and dissolved in DCM (320 mL). Then at 0°C, $BF_3\cdot OEt_2$ (8.42 mL, 79.6 mmol, 2 eq) was added and the mixture was allowed to warm up to RT overnight. It was then poured into sat. aq. $NaHCO_3$, and the organic layer was washed with 1M NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (9:1:1 pentane:EtOAc:DCM) gave the title compound as a colourless syrup (12.5g, 31.6 mmol, 79% over 3 steps). Spectral data was in accordance with that of literary precedence.[26]

_p_-Methoxyphenyl-3,4-O-carbonate-α-L-fucopyranoside (16)



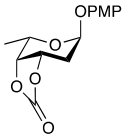
To a solution of **15** (10.38 g, 26.2 mmol) in MeOH (180 mL) was added NaOMe until pH>10 and the mixture was stirred for 3.5 hours. It was then neutralized by addition of AcOH and concentrated *in vacuo* to yield the corresponding triol. This crude triol was then dissolved in DMF (100 mL) and added dropwise to a solution of carbonyl diimidazole (4.25 g, 26.2 mmol, 1 eq) in DMF (130 mL) by syringe pump over 1 hour at 85 °C. Thereafter, 1M HCl (200 mL) was added and the mixture was stirred for a further 15 minutes at the same temperature. It was then diluted with EtOAc and washed with H_2O thrice and sat. aq. $NaHCO_3$. Drying over $MgSO_4$ and concentration *in vacuo* gave the title compound as a white solid (7.76 g, 26.2 mmol, quant. over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 – 6.91 (m, 2H), 6.91 – 6.79 (m, 2H), 5.40 (d, *J* = 4.0 Hz, 1H), 4.97 (dd, *J* = 7.5, 5.7 Hz, 1H), 4.68 (dd, *J* = 7.6, 2.1 Hz, 1H), 4.37 (qd, *J* = 6.6, 2.1 Hz, 1H), 4.18 (dt, *J* = 6.1, 3.0 Hz, 1H), 3.77 (s, 3H), 3.49 (d, *J* = 4.0 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 154.3, 150.1, 118.2, 114.8, 95.9, 77.0, 76.0, 66.6, 63.8, 55.7, 15.6. HRMS: $(M + Na)^+$ calculated for $C_{14}H_{16}O_7Na$ 319.0794; found 319.0788.

***p*-Methoxyphenyl-3,4-O-carbonate-2-*O*-(phenoxy)thiocarbonyl-α-L-fucopyranoside (17)**



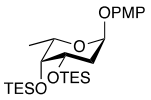
To a solution of **16** (6.70 g, 22.6 mmol) in DCM/pyr (220 mL, 1:1 v/v), after which *O*-phenyl chlorothionoformate (4.84 mL, 1.55 eq) was added at 0°C. After stirring overnight, MeOH (6 mL) was added to quench and the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, then the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5-20% EtOAc in pentane) gave the title compound as an orange foam (9.00g, 20.8 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.36 (m, 2H), 7.36 – 7.29 (m, 1H), 7.16 – 7.08 (m, 2H), 7.09 – 6.95 (m, 2H), 6.91 – 6.80 (m, 2H), 5.85 (d, *J* = 3.7 Hz, 1H), 5.63 (dd, *J* = 7.6, 3.7 Hz, 1H), 5.24 (dd, *J* = 7.6, 6.9 Hz, 1H), 4.79 (dd, *J* = 6.9, 2.6 Hz, 1H), 4.33 (qd, *J* = 6.7, 2.6 Hz, 1H), 3.79 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 155.8, 153.5, 153.4, 150.2, 129.8, 127.1, 121.8, 117.7, 114.9, 93.8, 78.0, 77.7, 74.5, 63.2, 55.8, 15.8. HRMS: $(M + Na)^+$ calculated for $C_{21}H_{20}O_8SNa$ 455.0777; found 455.0778.

***p*-Methoxyphenyl-2-deoxy-3,4-*O*-carbonate-α-L-fucopyranoside (18)**



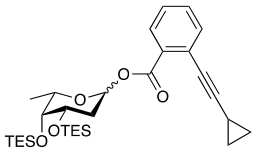
A solution of **17** (2.12 g, 4.90 mmol), tributyltin hydride (3.95 mL, 14.7 mmol, 3 eq) and AIBN (0.2M in toluene, 0.98 mmol, 0.2 eq) in toluene (160 mL) was heated at 100°C for 10 minutes. It was then allowed to cool to room temperature, washed with 1M NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (20:80 – 40:60 Et_2O:pentane) gave the title compound as a colourless oil (1.16 g, 4.14 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.89 (m, 2H), 6.89 – 6.74 (m, 2H), 5.53 (t, *J* = 6.3 Hz, 1H), 5.08 (dt, *J* = 8.3, 3.6 Hz, 1H), 4.60 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.18 (qd, *J* = 6.6, 1.8 Hz, 1H), 3.77 (s, 3H), 2.62 (ddd, *J* = 15.7, 5.9, 4.0 Hz, 1H), 2.11 (ddd, *J* = 15.8, 6.8, 3.4 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.4, 150.7, 118.3, 114.7, 95.0, 76.0, 72.5, 64.1, 55.8, 29.1, 15.5. HRMS: $(M + Na)^+$ calculated for $C_{14}H_{16}O_6Na$ 303.0845; found 303.0847.

***p*-Methoxyphenyl-2-deoxy-3,4-*O*-triethylsilyl -α-L-fucopyranoside (19)**



To a solution of **18** (420 mg, 1.5 mmol) in MeOH (3.8 mL) was added NaOMe (16 mg, 0.30 mmol, 0.2 eq) and the mixture was allowed to stir overnight. It was quenched by addition of dry ice and concentrated *in vacuo* to yield the corresponding diol. This was then dissolved in DMF (7.6 mL), to which pyridine (0.70 mL, 8.7 mmol, 5.8 eq) and triethylsilyl triflate (1.2 mL, 5.1 mmol, 3.4 eq) were added at 0°C. The resulting mixture was allowed to stir overnight, after which another portion of both reagents was added at 0°C, and the mixture was allowed to stir overnight once again. It was then poured into EtOAc, washed with H_2O 5x, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (100:1 pentane:Et_3N – 90:10:1 pentane:Et_2O:Et_3N) gave the title compound as a clear oil (460 mg, 0.95 mmol, 64% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.90 (m, 2H), 6.90 – 6.72 (m, 2H), 5.50 (d, *J* = 3.2 Hz, 1H), 4.18 (ddd, *J* = 11.7, 4.5, 2.5 Hz, 1H), 3.92 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.64 (d, *J* = 2.5 Hz, 1H), 2.20 (td, *J* = 12.3, 3.6 Hz, 1H), 1.78 (ddt, *J* = 12.7, 4.6, 1.3 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.99 (dt, *J* = 8.9, 8.0 Hz, 18H), 0.78 – 0.44 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.7, 118.0, 114.9, 97.8, 73.9, 68.7, 67.9, 56.1, 33.6, 17.8, 7.5, 7.3, 5.7, 5.3. HRMS: $(M + Na)^+$ calculated for $C_{25}H_{46}O_5Si_2Na$ 505.2782; found 505.2777.

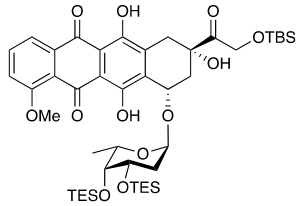
***o*-Cyclopropylethynylbenzoyl-2-deoxy-3,4-*O*-triethylsilyl-L-fucopyranoside (21)**



To a solution of **19** (450 mg, 0.93 mmol) in MeCN:H_2O (50 mL, 1:1 v/v) were added NaOAc (808 mg, 9.3 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$ (1.76 g, 3.72 mmol, 4 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 3.5 hours; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude lactol. To a solution of this in DCM were added DIPEA (0.75 mL, 4.2 mmol, 4.5 eq), DMAP (119 mg, 0.93 mmol, 1 eq), EDCI·HCl (581 mg, 2.93 mmol, 3.2 eq) and freshly saponified cyclopropylethynylbenzoic acid **20** (559 mg, 2.79 mmol, 3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (2:98 – 4:96 EtOAc:pentane) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the

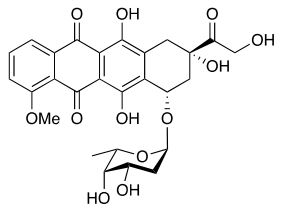
title compound as a white solid (312 mg, 0.57 mmol, 1:9 α:β, 62% over 2 steps). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.54 – 7.34 (m, 2H), 7.29 (qd, *J* = 7.3, 1.4 Hz, 1H), 5.90 (dd, *J* = 10.2, 2.3 Hz, 1H), 3.77 (ddd, *J* = 11.9, 4.3, 2.6 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.20 (td, *J* = 11.8, 10.1 Hz, 1H), 1.82 (dddd, *J* = 11.6, 4.3, 2.3, 1.0 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.98 (tt, *J* = 7.5, 3.8 Hz, 18H), 0.92 – 0.85 (m, 4H), 0.76 – 0.54 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 134.2, 132.0, 131.0, 131.0, 127.0, 125.1, 99.8, 93.2, 74.7, 72.7, 72.5, 70.8, 33.8, 17.3, 9.0, 7.2, 6.9, 5.3, 4.9, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{30}H_{48}O_5Si_2Na$ 567.2938; found 567.2946.

7-[2-Deoxy-3,4-*O*-triethylsilyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (23)



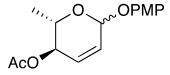
To a solution of glycosyl donor **21** (207 mg, 0.38 mmol) and the glycosyl acceptor **22** (301 mg, 0.57 mmol, 1.5 eq) in DCM (7.6 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes at room temperature andthen a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.38 mL, 0.1 eq) in DCM was added dropwise. After 15 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane and then 1:99 – 2:98 acetone:toluene) of the residue gave the title compound as a red solid (211 mg, 0.24 mmol, 63%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.12 (s, 1H), 7.93 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.50 (d, *J* = 3.8 Hz, 1H), 5.23 (dd, *J* = 4.0, 2.2 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.79 (s, 1H), 4.08 (s, 3H), 3.91 (q, *J* = 6.4 Hz, 1H), 3.77 (ddd, *J* = 12.0, 4.6, 2.4 Hz, 1H), 3.69 – 3.56 (m, 1H), 3.11 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.86 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.58 (dd, *J* = 12.9, 4.5 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 4H), 1.04 – 0.92 (m, 18H), 0.87 (t, *J* = 7.9 Hz, 9H), 0.67 (qd, *J* = 8.3, 7.9, 3.7 Hz, 6H), 0.53 (qd, *J* = 8.3, 7.9, 1.9 Hz, 6H), 0.15 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 186.8, 186.5, 161.0, 156.4, 155.7, 135.6, 135.4, 134.1, 120.8, 119.7, 118.4, 111.2, 101.6, 73.4, 69.0, 68.9, 67.5, 66.7, 56.7, 35.4, 34.0, 32.9, 26.0, 18.7, 17.5, 7.1, 6.8, 5.3, 4.8, -5.2. HRMS: (M + Na)$^+$ calculated for $C_{45}H_{70}O_{12}Si_3Na$ 909.4073; found 909.4107.

7-[2-Deoxy-α-L-fucopyranoside]-doxorubicinone (4)



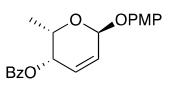
23 (105 mg, 0.118 mmol) was dissolved in THF:pyr (12.3 mL, 2:1 v/v), to which HF·pyr complex (743 µL) was added at 0°C. After stirring for 3 hours, the same amount of HF·pyr complex was added and the mixture was stirred a further 1.5 hours. It was then poured into sat. aq. $NaHCO_3$, extracted with DCM twice, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (33:66 – 50:50 acetone:toluene) gave a solid, which was triturated with $CHCl_3$ and filtered. Evaporation of the filtrate gave the title compound as a red solid (50 mg, 92 µmol, 78%). Analytical data were in agreement with literature precedence.[12] ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 3.8 Hz, 1H), 5.50 – 5.37 (m, 3H), 4.68 (q, *J* = 6.4 Hz, 1H), 4.52 (ddd, *J* = 12.1, 4.9, 2.9 Hz, 1H), 4.06 (s, 4H), 3.53 (q, *J* = 18.4 Hz, 2H), 2.92 – 2.83 (m, 1H), 2.65 (td, *J* = 12.5, 4.0 Hz, 1H), 2.54 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.38 (dd, *J* = 12.7, 4.9 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, Pyr) δ 215.5, 187.8, 162.1, 136.9, 135.2, 124.7, 121.7, 120.2, 112.5, 112.1, 103.2, 77.3, 72.5, 71.4, 68.8, 67.0, 66.1, 57.4, 38.0, 34.5, 34.2, 18.2. HRMS: (M + H)$^+$ calculated for $C_{27}H_{29}O_{12}$ 545.1659; found 545.2017.

***p*-Methoxyphenyl-4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hexopyranoside (24)**[28,40]



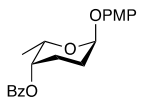
3,4-di-*O*-acetyl-L-rhamnal (Chapter 2) (3.96 g, 18.5 mmol) and *p*-methoxyphenol (2.48 g, 20.0 mmol, 1.08 eq) were jointly coevaporated from toluene, after which they were dissolved in toluene (150 mL). To this solution at -10 °C was added $BF_3{\cdot}OEt_2$ (0.11 mL, 0.93 mmol, 0.05 eq) and the mixture was stirred at this temperature for 2 h. It was then poured into sat. aq. $NaHCO_3$ and extracted with DCM. The resulting organic layer was washed with 1M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a white solid (2.13 g, 7.65 mmol, 41%, 12.5:1 α:β). Spectral data was in accordance with that of literary precedence.[28,40]

***p*-Methoxyphenyl-4-*O*-benzoyl-2,3,6-trideoxy-L-*threo*-hexopyranoside (25)**



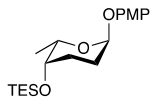
To a solution of **24** (2.13 g, 7.65 mmol, 12.5:1 α:β) in MeOH (77 mL) was added NaOMe (83 mg, 1.54 mmol, 0.2 eq) and the mixture was stirred for 1.5 hours. It was then quenched by addition of dry ice and concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting allylic alcohol was then dissolved in THF (17 mL), together with benzoic acid (1.96 g, 16.1 mmol, 2.1 eq) and triphenylphosphine (4.21 g, 16.1 mmol, 2.1 eq). To this, diethyl azodicarboxylate (4.6 mL, 14.9 mmol, 1.95 eq) was added dropwise at 0°C. After stirring overnight, the reaction mixture was concentrated *in vacuo*. Then, Et_2O was added to the residue and this was filtered off. The filtrate was washed with sat. aq. $NaHCO_3$ twice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as an orange oil (2.07 g, 6.08 mmol, 80% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 8.08 (m, 2H), 7.58 (ddt, *J* = 7.8, 6.9, 1.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.10 – 7.06 (m, 2H), 6.93 – 6.83 (m, 2H), 6.33 (ddd, *J* = 9.9, 5.5, 1.1 Hz, 1H), 6.21 (ddd, *J* = 9.9, 3.2, 0.6 Hz, 1H), 5.71 – 5.64 (m, 1H), 5.23 (ddd, *J* = 5.5, 2.5, 0.6 Hz, 1H), 4.51 (qd, *J* = 6.6, 2.5 Hz, 1H), 3.79 (s, 3H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.1, 151.5, 133.4, 129.9, 128.6, 126.8, 118.4, 114.7, 94.1, 65.9, 65.5, 55.8, 16.3. HRMS: $(M + Na)^+$ calculated for $C_{20}H_{20}O_5Na$ 363.1208; found 363.1214.

***p*-Methoxyphenol-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranoside (26)**



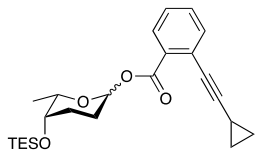
To a solution of **25** (2.07 g, 6.08 mmol) in toluene:EtOAc (9:1 v/v, 125 mL) was added rhodium on alumina (5% rhodium, 250 mg) at 0°C. The reaction was then placed under hydrogen atmosphere and stirred overnight. It was then filtered off over Celite and concentrated *in vacuo* to give the title compound as a light-yellow solid (2.08 g, 6.08 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.12 (m, 2H), 7.59 (ddt, *J* = 8.7, 7.0, 1.3 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.10 – 6.99 (m, 2H), 6.88 – 6.79 (m, 2H), 5.57 (d, *J* = 2.6 Hz, 1H), 5.12 (s, 1H), 4.25 (qd, *J* = 6.6, 1.5 Hz, 1H), 3.78 (s, 3H), 2.37 (tdd, *J* = 14.0, 4.6, 2.8 Hz, 1H), 2.21 – 2.10 (m, 1H), 2.10 – 1.96 (m, 1H), 1.83 (ddt, *J* = 13.5, 4.0, 1.8 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.7, 151.2, 133.2, 130.4, 129.8, 128.6, 117.7, 114.7, 96.4, 70.0, 66.2, 55.8, 24.6, 23.1, 17.4. HRMS: $(M + Na)^+$ calculated for $C_{20}H_{22}O_5Na$ 365.1365; found 365.1362.

***p*-Methoxyphenol-2,3-dideoxy-1-thio-α-L-fucopyranoside (27)**



A solution of **26** (2.08 g, 6.08 mmol) in dioxane (40 mL), MeOH (40 mL) and 1M NaOH (20 mL) was stirred at 60 °C for 2.5 hours, after which it was concentrated *in vacuo*. The residue was partitioned between EtOAc and sat. aq. NH_4Cl, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol was then redissolved in DMF (10 mL), after which pyridine (1.47 mL, 18.2 mmol, 3 eq) and triethylsilyl triflate (2.47 mL, 10.9 mmol, 1.8 eq) were added at 0°C and allowed to stir overnight. The reaction mixture was then partitioned between EtOAc and sat. aq. $NaHCO_3$, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:98:1 – 5:95:1 Et_2O:pentane:Et_3N) gave the title compound as a light yellow oil (1.57 g, 4.45 mmol, 73% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.91 (m, 2H), 6.89 – 6.70 (m, 2H), 5.46 (t, *J* = 2.0 Hz, 1H), 4.05 – 3.89 (m, 1H), 3.77 (s, 3H), 3.67 – 3.62 (m, 1H), 2.23 – 2.15 (m, 2H), 1.75 – 1.63 (m, 2H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.73 – 0.55 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 151.5, 117.6, 114.6, 96.4, 67.8, 55.8, 26.5, 23.9, 17.6, 7.1, 5.0. HRMS: $(M + Na)^+$ calculated for $C_{19}H_{32}O_4SiNa$ 375.1968; found 375.197.

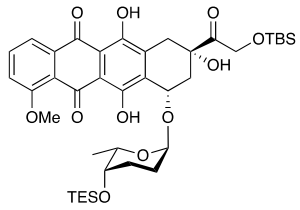
***o*-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-*O*-triethylsilyl-L-fucopyranoside (28)**



To a solution of **27** (386 mg, 0.93 mmol) in MeCN:H_2O (50 mL, 1:1 v/v) were added NaOAc (808 mg, 9.3 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$ (1.76 g, 3.72 mmol, 4 eq) at 0°C. The mixture was stirred for 30 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 – 50:50 Et_2O:pentane) gave the lactol. To a solution of this in DCM were added DIPEA (0.75 mL, 4.2 mmol, 4.5 eq), DMAP (119 mg, 0.93 mmol, 1 eq), EDCI·HCl (581 mg, 2.93 mmol, 3.2 eq) and freshly saponified cyclopropylethynylbenzoic acid **20** (559 mg, 2.79 mmol, 3 eq). After stirring overnight, the mixture was diluted with

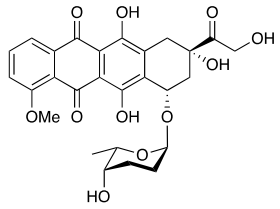
DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (5:95 EtOAc:pentane) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the title compound as a white solid (236 mg, 0.803 mmol, 82% over 2 steps, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 – 7.97 (m, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.35 – 7.27 (m, 1H), 5.96 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.79 (qd, *J* = 6.5, 1.9 Hz, 1H), 3.63 (p, *J* = 2.2 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.98 (dq, *J* = 13.4, 5.3, 4.6 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.51 (ddd, *J* = 8.2, 5.2, 2.8 Hz, 1H), 1.26 (d, *J* = 6.5 Hz, 3H), 0.99 (td, *J* = 7.9, 3.7 Hz, 9H), 0.93 – 0.82 (m, 4H), 0.64 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 134.3, 131.8, 131.4, 130.9, 127.0, 125.1, 99.7, 95.2, 75.5, 67.0, 29.8, 25.1, 17.4, 9.0, 7.0, 5.0, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{24}H_{34}O_4SiNa$ 437.2124; found 437.2126.

7-[2,3-Dideoxy-4-*O*-triethylsilyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (29)



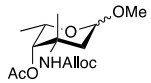
To a solution of glycosyl donor **28** (61 mg, 0.183 mmol) and the glycosyl acceptor **22** (109 mg, 0.27 mmol, 1.5 eq) in DCM (3.7 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes at room temperature andthen a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.19 mL, 0.1 eq) in DCM was added dropwise. After 15 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane and then 1:99 acetone:toluene) of the residue gave the title compound as a red solid (43 mg, 0.057 mmol, 39%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.89 (s, 1H), 13.24 (s, 1H), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.43 (d, *J* = 3.5 Hz, 1H), 5.29 (dd, *J* = 4.1, 2.2 Hz, 1H), 5.03 – 4.81 (m, 3H), 4.08 (s, 3H), 3.98 (tt, *J* = 6.5, 3.6 Hz, 1H), 3.67 (s, 1H), 3.19 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.99 (d, *J* = 18.9 Hz, 1H), 2.38 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.22 – 1.96 (m, 2H), 1.75 (tt, *J* = 13.4, 3.6 Hz, 1H), 1.61 (dd, *J* = 13.7, 3.9 Hz, 1H), 1.56 – 1.40 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 18H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.14 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 187.1, 186.7, 161.1, 156.5, 156.0, 135.7, 135.6, 134.5, 134.2, 121.0, 119.9, 118.5, 111.5, 111.3, 101.0, 69.3, 68.4, 67.6, 66.8, 56.8, 35.6, 34.1, 26.4, 26.0, 23.5, 18.7, 17.6, 7.1, 5.0, -5.3. HRMS: (M + Na)$^+$ calculated for $C_{39}H_{56}O_{11}Si_2Na$ 779.3259; found 779.3276.

3'-Desaminodoxorubicin (5)



29 (21 mg, 28 µmol) was dissolved in THF/pyr (3 mL, 2:1 v/v), to which HF·pyr complex (356 µL) was added at 0°C. After stirring for 1 hour, it was poured into sat. aq. $NaHCO_3$, extracted with DCM twice, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (20:80 acetone:toluene) gave the title compound as a red solid (14 mg, 26 µmol, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.23 (s, 1H), 8.02 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.88 – 7.71 (m, 1H), 7.40 (dd, *J* = 8.5, 1.2 Hz, 1H), 5.45 (d, *J* = 3.8 Hz, 1H), 5.34 (dd, *J* = 3.9, 2.2 Hz, 1H), 4.97 (s, 1H), 4.77 (s, 2H), 4.19 – 4.02 (m, 4H), 3.67 (s, 1H), 3.32 – 3.17 (m, 1H), 3.10 – 2.93 (m, 2H), 2.38 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.16 (dd, *J* = 14.6, 4.0 Hz, 1H), 2.01 (tdd, *J* = 11.4, 8.5, 5.0 Hz, 1H), 1.78 (dq, *J* = 10.3, 3.4 Hz, 2H), 1.55 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.1, 133.8, 121.0, 119.9, 118.6, 111.6, 111.5, 100.8, 69.2, 67.7, 67.1, 65.6, 56.8, 35.6, 34.2, 25.7, 23.2, 17.3. HRMS: (M + Na)$^+$ calculated for $C_{27}H_{28}O_{11}Na$ 551.1529; found 551.1533.

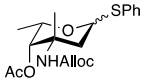
Methyl 3-*N*-allyloxycarbonyl-4-*O*-acetyl-L-vancosamine (31)[20,21]



A suspension of vancomycin hydrochloride **30** (22.0 g, 14.8 mmol) and $NaHCO_3$ (4.0 g, 47.4 mmol, 3.2 eq) in dioxane/H_2O (400 mL, 1:1 v/v) was stirred for 30 minutes. To the resulting pink solution was added allyloxycarbonyl succinimide (12.0 g, 59.2 mol, 4 eq) in dioxane (10 mL) and the resulting mixture was stirred for 3 hours, after which it was then poured into acetone (3 L) and stirred vigorously for 1h. It was then filtered, the residue was collected and the filter was thoroughly rinsed with MeOH. This wash and the residue were jointly concentrated *in vacuo*, coevaporated with toluene and

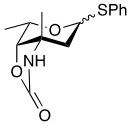
dried under high vacuum overnight to yield crude bis-*N*-Alloc-vancomycin (23.7 g, max. 14.8 mmol) as a light pink solid. This was redissolved in MeOH (250 mL), to which 4M methanolic HCl (prepared by adding acetyl chloride to MeOH, 40 mL) was added. After 3 hours, $NaHCO_3$ (15 g) was portionwise added to the resulting light-yellow suspension until neutral pH. The tan suspension was then filtered and the filter was thoroughly rinsed with MeOH. This wash and the residue were concentrated *in vacuo* until precipitation, after which acetone (1L) was added. The resulting suspension was stirred for 10 minutes and filtered over a paper funnel, and the filtrate was concentrated *in vacuo* to yield a brown sludge. This was dissolved in a minimal amount of MeOH, after which it was loaded onto a silica gel column equilibrated to 80:20 pentane:EtOAc. This was eluted with 80:20 – 100:0 pentane:EtOAc, and all fractions containing the desired product were filtered and the filtrate was concentrated *in vacuo*. The residue was absorbed onto Celite from MeOH, after which column chromatography (30:70 – 50:50 EtOAc:pentane) yielded the crude methyl 3-*N*-allyloxycarbonyl-L-vancosamine as a green oil (3.61 g, max. 13.9 mmol). This was then suspended in pyridine (60 mL), after which Ac_2O (10 mL) and a catalytic amount of DMAP were added. After stirring overnight, the reaction was quenched by addition of MeOH (12 mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc and 1M HCl, after which the organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 EtOAc:pentane) gave the title compound as a clear thick oil (2.53 g, 8.40 mmol, 57% over 3 steps from vancomycin hydrochloride **30**). Spectral data was in accordance with that of literary precedence.[20,21]

Phenyl 3-*N*-allyloxycarbonyl-4-*O*-acetyl-1-thio-L-vancosamine (32)[20]



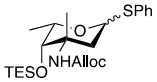
31 (2.53 g, 8.4 mmol) was coevaporated from toluene, after which it was dissolved in DCM (100 mL). Activated molecular sieves (4Å) were added and the mixture was allowed to stir for 30 minutes. It was then cooled down to 0°C, after which thiophenol (0.90 mL, 8.8 mmol, 1.05 eq) and $BF_3{\cdot}OEt_2$ (1.14 mL, 9.24 mmol, 1.1 eq) were added dropwise and the mixture was allowed to warm up to RT. Over the course of 5 hours, an additional such portion of $BF_3{\cdot}OEt_2$ was added. The mixture was then filtered and poured onto sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM, and the combined organic layers were washed with 1M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 EtOAc:pentane) gave the title compound as a white solid (2.64 g, 6.96 mmol, 83%). Spectral data was in accordance with that of literary precedence.[20]

Phenyl 3,4-carbamoyl-1-thio-L-vancosamine (33)



To a solution of **32** (2.64 g, 6.96 mmol) in MeOH (55 mL) was added NaOMe until pH>10. The reaction was stirred for 2.5 hours, after which it was quenched by addition of dry ice and concentrated *in vacuo*. Column chromatography (15:85 – 100:0 EtOAc:pentane) gave the title compound as a colourless oil (1.70 g, 6.09 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (ddt, *J* = 8.1, 5.0, 1.1 Hz, 3H), 7.40 – 7.17 (m, 7H), 6.14 (s, 1H), 6.00 (s, 1H), 5.50 (dd, *J* = 10.3, 6.2 Hz, 1H), 4.63 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.23 – 4.02 (m, 2H), 3.85 (d, *J* = 2.0 Hz, 1H), 3.77 (qd, *J* = 6.5, 2.1 Hz, 1H), 2.25 (dd, *J* = 15.2, 6.2 Hz, 1H), 2.11 (dd, *J* = 13.5, 2.2 Hz, 1H), 1.95 (dd, *J* = 13.5, 11.4 Hz, 1H), 1.75 (dd, *J* = 15.2, 10.4 Hz, 1H), 1.49 – 1.37 (m, 9H), 1.30 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 158.6, 134.2, 133.5, 132.2, 132.0, 129.1, 127.9, 127.7, 82.8, 81.3, 81.1, 80.7, 70.7, 64.8, 56.6, 55.5, 41.6, 35.8, 29.0, 23.3, 17.1, 15.8. HRMS: $(M + H)^+$ calculated for $C_{14}H_{18}NO_3S$ 280.1007; found 280.1000.

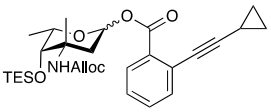
Phenyl 3-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-1-thio-L-vancosamine (34)



A solution of **33** (852 mg, 3.05 mmol) in 1M NaOH (61 mL) was refluxed for 6 hours, after which it was extracted thrice with DCM. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude amine was redissolved in THF/H_2O (1:1 v/v, 30 mL) after which $NaHCO_3$ (513 mg, 6.1 mmol, 2 eq) and allyloxycarbonyl succinimide (975 mg, 4.88 mmol, 1.6 eq) was added. After stirring for 3 days, it was partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol was redissolved in DCM (33 mL), after which pyridine (0.8 mL, 11.9 mmol, 3.9 eq) and triethylsilyl triflate (1.34 mL, 6.1 mmol, 2 eq) were added at 0°C. After stirring at that temperature for 15 minutes, the reaction mixture was diluted

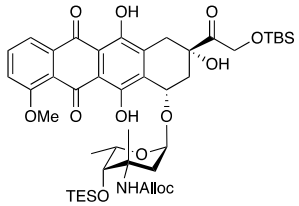
with EtOAc. It was then washed with aq. sat. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:96 – 10:90 Et_2O:pentane) gave the title compound as a colourless oil (1.24 g, 2.75 mmol, 90% over 3 steps). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.43 (m, 4H), 7.43 – 7.16 (m, 6H), 6.03 – 5.77 (m, 2H), 5.38 – 5.15 (m, 6H), 4.96 – 4.82 (m, 2H), 4.59 – 4.45 (m, 4H), 4.27 – 4.13 (m, 1H), 3.85 – 3.74 (m, 1H), 3.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 3.54 (s, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.66 (dd, *J* = 14.2, 9.3 Hz, 1H), 1.45 (s, 3H), 1.29 (dd, *J* = 6.9, 1.2 Hz, 3H), 1.27 (dd, *J* = 6.4, 1.2 Hz, 3H), 0.98 (tdd, *J* = 7.9, 4.2, 1.5 Hz, 27H), 0.70 – 0.50 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0, 133.0, 131.7, 131.2, 128.9, 128.8, 127.2, 127.1, 117.6, 80.5, 75.1, 74.0, 72.4, 65.2, 55.5, 37.5, 18.7, 14.8, 7.2, 7.0, 6.7, 5.9, 5.5, 5.2. HRMS: $(M + Na)^+$ calculated for $C_{23}H_{37}NO_4SSiNa$ 474.2110; found 474.2105.

_o_-Cyclopropylethynylbenzoyl-3-_N_-allyloxycarbonyl-4-_O_-triethylsilyl-L-vancosamine (35)



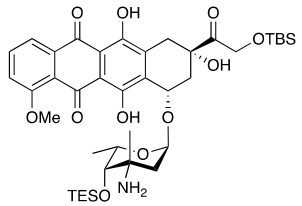
To a solution of **34** (635 mg, 1.41 mmol) in THF/H_2O (10:1 v/v, 24 mL) were added 2,6-lutidine (0.49 mL, 4.23 mmol, 3 eq) and $AgNO_3$ (838 mg, 4.94 mmol, 3.5 eq) and the mixture was stirred in the dark overnight. It was then diluted with EtOAc (200 mL), Na_2SO_4 was added and the mixture was allowed to stir for 40 minutes. This was filtered and concentrated *in vacuo*. Column chromatography (30:70 EtOAc:pentane) gave the crude lactol. To a solution this in DCM (33 mL) were then added DMAP (177 mg, 1.41 mmol, 1 eq), DIPEA (2.3 mL, 12.7 mmol, 9 eq), EDCI.HCl (883 mg, 4.61 mmol, 3.3 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (847 mg, 4.23 mmol, 3 eq) and the mixture was stirred overnight. The reaction mixture was partitioned between sat. aq. $NaHCO_3$ and DCM, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (6:94 – 20:80 Et_2O:pentane) gave the title compound as a colourless oil (340 mg, 0.644 mmol, 45% over 2 steps, α:β 1:11). Spectral data for the β-anomer: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 7.33 – 7.19 (m, 1H), 6.11 (dd, *J* = 8.6, 2.8 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.35 – 5.13 (m, 2H), 5.07 (s, 1H), 4.50 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.99 (qd, *J* = 6.5, 2.0 Hz, 1H), 3.59 (d, *J* = 2.0 Hz, 1H), 2.25 (dd, *J* = 12.7, 8.6 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.60 (s, 3H), 1.51 (tt, *J* = 7.6, 6.4 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.9 Hz, 9H), 0.91 – 0.85 (m, 4H), 0.70 (qd, *J* = 7.9, 1.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 134.4, 131.9, 131.2, 130.8, 127.0, 125.2, 117.6, 99.8, 91.9, 74.7, 74.1, 70.8, 65.2, 54.9, 36.2, 18.0, 9.0, 9.0, 7.2, 5.4, 0.8. HRMS: $(M + Na)^+$ calculated for $C_{29}H_{41}NO_6SiNa$ 550.2601; found 550.2593.

7-[3-_N_-allyloxycarbonyl-4-_O_-triethylsilyl-α-L-vancosamino]-14-O-tert-butyldimethylsilyl-doxorubicinone (36)



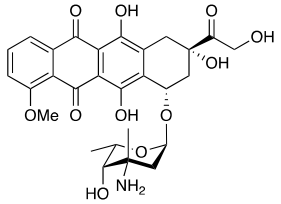
To a solution of donor **35** (330 mg, 0.625 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **22** (496 mg, 0.938 mmol, 1.5 eq) in DCM (12.5 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.63 mL, 0.1 eq) in DCM was added dropwise. After stirring at room temperature for 80 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (10:90 Et_2O:pentane – 1:99 - 10:90 acetone:toluene) of the residue gave the title compound (262 mg, 0.301 mmol, 48%), in addition to an α/β mixture (100 mg, 0.115 mmol, 20%). Total yield as a red solid (362 mg, 0.446 mmol, 68%, α:β 6:1). ^1H NMR (500 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.14 (s, 1H), 7.94 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.72 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.36 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.44 (t, *J* = 4.6 Hz, 1H), 5.34 – 5.21 (m, 2H), 5.20 (td, *J* = 2.5, 1.2 Hz, 2H), 5.11 (s, 1H), 4.99 – 4.84 (m, 2H), 4.60 (s, 1H), 4.54 – 4.51 (m, 2H), 4.12 (qd, *J* = 6.6, 2.6 Hz, 1H), 4.07 (s, 3H), 3.66 (d, *J* = 2.6 Hz, 1H), 3.19 – 2.77 (m, 2H), 2.48 – 2.36 (m, 2H), 2.14 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.65 (dd, *J* = 14.0, 4.4 Hz, 1H), 1.46 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.96 (s, 9H), 0.70 (q, *J* = 7.6 Hz, 6H), 0.15 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 186.8, 186.6, 161.1, 156.5, 155.8, 135.7, 135.5, 134.2, 134.0, 133.2, 120.9, 119.8, 118.6, 117.5, 111.4, 111.3, 100.0, 75.1, 69.4, 66.9, 66.8, 65.1, 56.8, 53.5, 36.0, 33.9, 26.0, 18.7, 17.0, 7.1, 5.4, -5.2. HRMS: $(M + Na)^+$ calculated for $C_{44}H_{63}NO_{13}Si_2Na$ 892.3736; found 892.3729.

7-[4-*O*-triethylsilyl-α-L-vancosamino]-14-O-tert-butyldimethylsilyl-doxorubicinone (37)



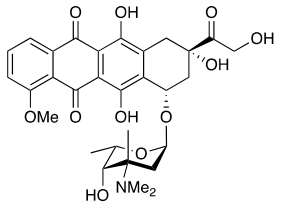
A solution of **36** (252 mg, 0.290 mmol) and *N,N*-dimethylbarbituric acid (202 mg, 1.31 mmol, 4.5 eq) in DCM (29 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (17 mg, 0.073 mmol, 0.025 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 20:80 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, eluent DCM:MeOH, 1:1) gave the title compound as a red solid (175 mg, 0.223 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.38 – 7.33 (m, 1H), 5.48 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.15 (dd, *J* = 4.3, 2.1 Hz, 1H), 4.95 – 4.79 (m, 2H), 4.52 (s, 1H), 4.18 – 3.94 (m, 4H), 3.34 (s, 1H), 3.19 – 2.70 (m, 3H), 2.33 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.14 (dd, *J* = 14.7, 4.2 Hz, 1H), 1.89 (dd, *J* = 14.0, 5.0 Hz, 1H), 1.60 (d, *J* = 13.9 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.20 (s, 3H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.96 (s, 9H), 0.72 (q, *J* = 7.8 Hz, 6H), 0.15 (d, *J* = 4.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5, 186.7, 186.4, 161.0, 156.5, 155.6, 135.6, 135.3, 134.1, 134.0, 120.7, 119.7, 118.5, 111.2, 111.2, 100.9, 69.5, 66.6, 66.1, 56.7, 35.8, 33.8, 25.9, 18.7, 17.9, 7.2, 5.6, -5.2, -5.3. HRMS: $(M + H)^+$ calculated for $C_{40}H_{60}NO_{11}Si_2$ 786.3705 found 786.3695.

7-[α-L-Vancosamino]-doxorubicinone (6)



To a solution of **37** (35.0 mg, 44.6 µmol) in pyridine (4.5 mL) in a PTFE tube, was added HF·pyr complex (70 wt% HF, 350 µL) at 0°C. After 45 minutes of stirring at room temperature, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) gave the title compound as a red solid (22.2 mg, 39.8 µmol, 89%). ^{1}H NMR (500 MHz, Pyridine-d_5) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 5.80 (d, *J* = 4.7 Hz, 1H), 5.43 (s, 2H), 5.34 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.76 (q, *J* = 6.5 Hz, 1H), 3.96 (s, 3H), 3.66 – 3.29 (m, 3H), 2.87 (dt, *J* = 14.3, 2.2 Hz, 1H), 2.46 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.38 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.08 (d, *J* = 13.7 Hz, 1H), 1.68 (s, 3H), 1.53 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Pyr) δ 215.6, 187.4, 187.3, 161.9, 157.7, 156.2, 121.5, 120.0, 119.8, 112.2, 111.7, 102.3, 76.8, 75.6, 70.8, 66.2, 66.1, 57.1, 51.7, 39.4, 37.9, 33.9, 27.0, 18.5. HRMS: $(M + H)^+$ calculated for $C_{28}H_{32}NO_{11}$ 558.1975; found 558.1971.

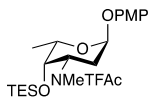
7-[3-Dimethylamino-α-L-vancosamino]-doxorubicinone (7)



A solution of **37** (72.0 mg, 91.6 µmol) in EtOH (23.2 mL) and 37% aq. CH_2O (204 µL, 30 eq) was stirred for 3 hours, before addition of $NaBH(OAc)_3$ (37.9 mg, 0.179 mmol, 1.95 eq). The mixture was stirred for a further 2.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (10:90 – 30:70 acetone:toluene) gave a crude product which was redissolved in DCM (5.5 mL), to which allyloxycarbonylsuccinimide (90 mg, 0.46 mmol, 5 eq) was added. After stirring overnight, the mixture was concentrated *in vacuo*. Column chromatography (5:95 – 20:80 acetone:toluene) gave the dimethylated amine as a red solid (37 mg, 0.045 mmol, 50%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.88 (s, 1H), 13.16 (s, 1H), 7.96 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 5.52 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.15 (dd, *J* = 4.2, 2.0 Hz, 1H), 4.99 – 4.83 (m, 2H), 4.59 (s, 1H), 4.08 (s, 3H), 3.97 (q, *J* = 6.5 Hz, 1H), 3.48 (s, 1H), 3.10 (dd, *J* = 18.7, 2.0 Hz, 1H), 2.84 (d, *J* = 18.7 Hz, 1H), 2.44 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.12 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.06 (s, 6H), 2.00 (dd, *J* = 13.6, 5.0 Hz, 1H), 1.55 (d, *J* = 13.6 Hz, 1H), 1.35 – 1.22 (m, 6H), 0.98 (d, *J* = 16.4 Hz, 18H), 0.65 (qd, *J* = 7.9, 1.7 Hz, 6H), 0.15 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.8, 187.0, 186.6, 161.1, 156.8, 155.9, 135.8, 135.6, 134.5, 134.3, 121.0, 119.9, 118.5, 111.4, 111.3, 101.7, 73.7, 70.1, 67.3, 66.8, 56.8, 37.7, 36.0, 33.8, 26.1, 18.8, 18.2, 13.4, 7.4, 5.9, -5.2. HRMS: $(M + H)^+$ calculated for $C_{42}H_{64}NO_{11}Si_2$ 814.4018; found 814.4011.

To a solution of the above compound (33.3 mg, 40.9 µmol) in pyridine (4.1 mL) in a PTFE tube, was added HF·pyr complex (70 wt% HF, 320 µL) at 0°C. After 70 minutes of stirring at room temperature, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and partitioned between DCM and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 50:50 MeOH:DCM) gave the title compound as a red solid (21.1 mg, 36 µmol, 88%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.20 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 5.57 (d, *J* = 5.2 Hz, 1H), 5.22 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.76 (s, 2H), 4.59 (s, 1H), 4.09 (s, 3H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.55 – 3.13 (m, 3H), 2.95 (d, *J* = 18.7 Hz, 1H), 2.49 – 2.33 (m, 1H), 2.13 (s, 7H), 1.83 (dd, *J* = 14.0, 5.3 Hz, 1H), 1.67 (d, *J* = 13.8 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 0.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 187.2, 186.8, 161.2, 156.6, 155.8, 135.9, 135.6, 134.1, 133.8, 121.0, 119.9, 118.6, 111.6, 111.5, 101.2, 70.0, 69.7, 65.5, 64.6, 56.8, 56.3, 36.4, 35.9, 35.4, 34.0, 17.9, 12.8. HRMS: $(M + H)^+$ calculated for $C_{30}H_{36}NO_{11}$ 586.228; found 586.2282.

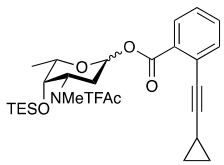
***p*-Methoxyphenyl-3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (39)**



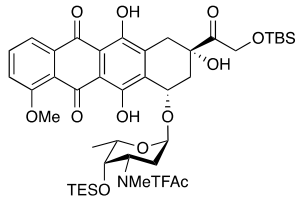
A suspension of **38** (Chapter 3) (638 mg, 1.38 mmol) and K_2CO_3 (3.82 g, 13.8 mmol, 20 eq) in acetone:iodomethane (5:1 v/v, 90 mL) was stirred in a sealed vessel at 50 °C over 3 days. It was then concentrated *in vacuo* and partitioned between DCM and H_2O. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 – 10:90 Et_2O:pentane) gave the title compound as a white solid (659 mg, 1.38 mmol, quant.). Spectral data for the major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.4 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 2H), 5.61 (s, 1H), 4.91 (d, *J* = 13.0 Hz, 1H), 4.11 (d, *J* = 6.3 Hz, 1H), 4.04 (s, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 2.54 (t, *J* = 12.8 Hz, 1H), 1.85 (d, *J* = 11.8 Hz, 1H), 1.49 (m, 1H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 157.8, 157.5, 157.1, 154.8, 150.9, 117.5, 114.7, 96.1, 71.1, 68.0, 55.7, 53.0, 27.6, 17.6, 7.1, 5.5. HRMS: $[M + H]^+$ calculated for $C_{22}H_{35}F_3NO_5Si$ 478.22311; found 478.22287.

***o*-Cyclopropylethynylbenzoyl-3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (40)**

To a solution of **39** (80 mg, 0.17 mmol) in MeCN:H_2O (1:1 v/v, 4.4 mL) were added NaOAc (140 mg, 1.71 mmol, 10 eq) and $Ag(DPAH)_2.H_2O$ (312 mg, 0.681 mmol, 4 eq) consecutively at 0°C. After stirring for 2 hours at that temperature, the reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with DCM twice. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude hemiacetal as a yellow solid. To a solution of the above hemiacetal in DCM (1.7 mL) were then added DMAP (21 mg, 0.17 mmol, 1 eq), DIPEA (0.13 mL, 0.77 mmol, 4.5 eq), EDCI·HCl (104 mg, 0.543 mmol, 3.2 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (96 mg, 0.51 mmol, 3 eq) and the mixture was stirred overnight. Thereafter, an equal portion of all reagents mentioned above was added again. After stirring another night, the reaction mixture was partitioned between sat. aq. $NaHCO_3$ and DCM, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a white solid (64 mg, 0.12 mmol, 70%, 1:5 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.4, 6.9, 5.2 Hz, 1H), 6.01 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.46 (dt, *J* = 13.7, 3.4 Hz, 1H), 3.98 (s, 1H), 3.80 (q, *J* = 6.3 Hz, 1H), 3.16 (s, 3H), 2.43 (ddd, *J* = 13.7, 11.1, 9.7 Hz, 1H), 1.95 (dt, *J* = 11.2, 2.6 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.92 – 0.88 (m, 4H), 0.68 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 158.1, 157.8, 157.4, 157.1, 134.4, 132.2, 130.9, 130.7, 127.1, 125.2, 118.0, 115.1, 99.9, 94.0, 74.6, 73.7, 70.0, 56.2, 32.3, 28.4, 17.6, 9.0, 7.1, 5.4, 0.8. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 1H), 7.93 (td, *J* = 8.8, 8.4, 2.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.37 (m, 1H), 6.59 (s, 1H), 4.86 (ddd, *J* = 13.7, 3.8, 2.4 Hz, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.13 (s, 1H), 3.16 (s, 3H), 2.65 (td, *J* = 13.2, 3.5 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.65 – 1.59 (m, 1H), 1.28 (s, 3H), 0.92 (dq, *J* = 6.3, 2.3 Hz, 9H), 0.89 – 0.80 (m, 4H), 0.66 (qd, *J* = 7.9, 3.3 Hz, 6H). HRMS: $[M + Na]^+$ calculated for $C_{27}H_{36}F_3NO_5SiNa$ 562.22071; found 562.22058.

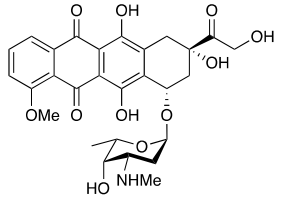


7-[3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (41)



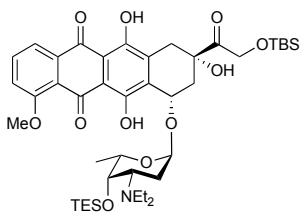
14-O-TBS-doxorubicinone **22** (560 mg, 1.06 mmol, 2 eq) and donor **40** (286 mg, 0.530 mmol, 1 eq) were coevaporated thrice with toluene and then dissolved in DCM (10.6 mL), after which freshly activated 4 Å molecular sieves were added, and stirred for 30 minutes, whereupon freshly prepared PPh_3AuNTf_2 (0.05 M solution in DCM, 1.06 mL, 0.1 eq) was added. After stirring for 5 minutes, the resulting solution was diluted with DCM, filtered over Celite and concentrated *in vacuo*. Purification by column chromatography (10:90 EtOAc:pentane and then 3:97 acetone:toluene) gave the title compound as a red solid (330 mg, 0.374 mmol, 71%). Spectral data for the major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.96 (s, 1H), 13.19 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.60 (d, *J* = 3.3 Hz, 1H), 5.28 – 5.19 (m, 1H), 4.97 – 4.84 (m, 2H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.28 (s, 1H), 4.09 (s, 3H), 4.02 (s, 1H), 3.18 (d, *J* = 18.8 Hz, 1H), 3.04 (s, 3H), 2.91 (d, *J* = 18.7 Hz, 1H), 2.43 (td, *J* = 13.2, 4.0 Hz, 1H), 2.35 (d, *J* = 14.9 Hz, 1H), 2.20 (dd, *J* = 14.8, 4.1 Hz, 1H), 1.68 (dd, *J* = 12.2, 3.7 Hz, 1H), 1.64 (s, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.04 – 0.90 (m, 18H), 0.70 – 0.53 (m, 6H), 0.16 (d, *J* = 2.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 187.2, 186.7, 161.1, 156.5, 155.9, 135.9, 135.6, 134.3, 133.9, 120.9, 120.0, 118.5, 111.5, 111.4, 101.2, 70.9, 70.7, 68.5, 66.9, 56.8, 53.1, 35.9, 34.0, 27.2, 26.0, 7.1, 5.5. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{58}F_3NO_{12}Si_2Na$ 904.33418; found 904.33459.

***N*-methyl-doxorubicin (8)**



To a solution of **41** (101 mg, 0.115 mmol) in pyridine (4.5 mL) and Et_3N (2.25 mL) was added triethylamine trihydrofluoride (2.25 mL). After stirring for 1 h, it was poured into sat. aq. $NaHCO_3$. The organic layer was separated and thrice washed with sat. aq. $NaHCO_3$ after which it was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting acetamide was dissolved in MeOH (9 mL), to which NaOMe (17 mg, 0.29 mmol, 2.5 eq) was added, rendering the solution blue. After 20 minutes, dry ice was added until the red colour had returned and the mixture was poured into brine. This was then repetitively extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (10:90 – 20:80 MeOH:DCM) gave the title compund as a red solid (15 mg, 26 µmol, 23% over 2 steps). ^{1}H NMR (500 MHz, MeOD) δ 7.87 – 7.67 (m, 2H), 7.60 – 7.40 (m, 1H), 5.44 (s, 1H), 4.97 (s, 1H), 4.79 – 4.69 (m, 2H), 4.26 (q, *J* = 6.4 Hz, 1H), 4.00 (s, 3H), 3.84 (s, 1H), 3.49 (ddd, *J* = 11.3, 5.9, 2.8 Hz, 1H), 3.00 (d, *J* = 18.6 Hz, 1H), 2.80 (d, *J* = 18.5 Hz, 1H), 2.64 (s, 3H), 2.32 (d, *J* = 14.7 Hz, 1H), 2.12 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.05 – 1.97 (m, 3H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 214.84, 187.83, 187.58, 162.41, 157.24, 156.00, 137.24, 136.13, 135.48, 135.12, 121.31, 120.47, 112.32, 112.06, 100.96, 76.99, 71.31, 67.82, 66.01, 65.67, 57.13, 56.15, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 37.23, 33.65, 30.35, 28.28, 16.97. HRMS: $[M + H]^+$ calculated for $C_{29}H_{31}NO_{11}$ 558.19699; found 558.19684.

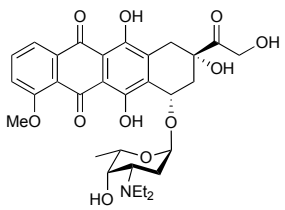
7-[3-Diethylamino-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (47)



To a solution of **46** (Chapter 2) (239 mg, 0.300 mmol) in THF/H_2O (25 mL, 1:1, v/v) was added polymer bound PPh_3 (3 mmol/g PPh_3 loading, 667 mg, 2.00 mmol, 6.7 eq) and the reaction mixture was stirred for 3 days at 50°C. Additional polymer bound PPh_3 (500 mg, 1.5 mmol, 5 eq) was added and the reaction mixture was stirred for 3 more days at the same temperature. The reaction mixture was then allowed to cool to room temperature and filtered off, the filtrate was concentrated *in vacuo* and co-evaporated with toluene. Column chromatography (3:97 – 10:90 acetone:toluene) gave the intermediate amine (148 mg, 0.193 mmol, 64%). To a solution of the amine thus obtained (141 mg, 0.183 mmol) in EtOH (15 mL) was added acetaldehyde (50% w/w in EtOH, 1.1 mL, 11 mmol, 60 eq). After stirring for 30 minutes, $NaBH(OAc)_3$ (74 mg, 0.35 mmol, 1.9 eq) was added and the reaction mixture was stirred for 5 hours. Sat aq. $NaHCO_3$ was added and the solution was extracted with DCM thrice. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (4:96 – 5:95 acetone:toluene) afforded the title compound as a red

solid (71 mg, 86 μmol, 30% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.91 (s, 1H), 13.25 (s, 1H), 8.01 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.45 – 7.36 (m, 1H), 5.53 (d, *J* = 3.8 Hz, 1H), 5.27 (dd, *J* = 4.0, 2.2 Hz, 1H), 4.99 – 4.82 (m, 3H), 4.09 (s, 3H), 3.88 (q, *J* = 6.3 Hz, 1H), 3.73 (s, 1H), 3.18 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.99 (d, *J* = 18.9 Hz, 1H), 2.57 (q, *J* = 6.9 Hz, 5H), 2.36 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.21 – 1.97 (m, 2H, H-8), 1.64 (dd, *J* = 12.8, 3.5 Hz, 1H), 1.31 – 1.18 (m, 6H), 1.07 – 0.92 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 6H), 0.66 (qd, *J* = 8.3, 7.9, 1.7 Hz, 6H), 0.14 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.6, 187.2, 186.8, 161.1, 156.6, 156.0, 135.8, 135.7, 134.5, 134.2, 121.1, 119.9, 118.5, 111.5, 111.4, 101.9, 77.4, 71.1, 69.6, 69.4, 66.8, 56.8, 56.7, 41.9, 35.6, 34.1, 27.8, 26.0, 18.7, 18.2, 11.2, 7.3, 5.6, -5.1, -5.3. HRMS: $(M + H)^+$ calculated for $C_{43}H_{66}NO_{11}Si_2$ 828.4175; found 828.4161.

***N,N*-diethyldoxorubicin (9)**

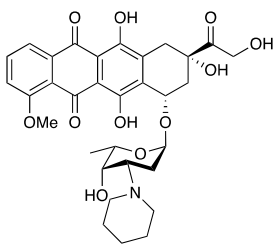


47 (52 mg, 63 μmol) was dissolved in pyridine (2 mL) and cooled to 0°C. HF·pyridine (70 wt% HF, 0.48 mL) was added and the reaction mixture was stirred for 5h at this temperature. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and the filtrate was diluted with DCM, washed with H_2O and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was subjected to column chromatography on neutral silica (0:100 - 15:85 MeOH:DCM) to afford the title compound as a red solid (37 mg, 62 μmol, 98%). ^{1}H NMR (500 MHz, , $CDCl_3$) δ 13.94 (s, 1H), 13.20 (s, 1H), 8.01 (dd, J = 7.7, 1.0 Hz, 1H), 7.79 (dd, J = 8.5, 7.7 Hz, 1H), 7.41 (dd, J = 8.6, 1.1 Hz, 1H), 5.56 (d, J = 2.7 Hz, 1H), 5.30 (dd, J = 4.0, 2.1 Hz, 1H), 4.83 (s, 1H), 4.77 (s, 2H), 4.10 (s, 3H), 4.03 – 3.87 (m, 1H), 3.69 (t, J = 1.9 Hz, 1H), 3.23 (dd, J = 18.8, 2.0 Hz, 1H), 2.97 (d, J = 18.8 Hz, 1H), 2.74 – 2.57 (m, 5H), 2.39 (dt, J = 14.6, 2.2 Hz, 1H), 2.16 (dd, J = 14.7, 4.0 Hz, 1H), 1.97 – 1.67 (m, 2H), 1.40 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 120.9, 119.9, 118.6, 111.6, 111.5, 101.1, 76.9, 69.6, 67.2, 66.2, 65.6, 56.8, 55.2, 41.6, 35.5, 34.1, 28.3, 17.4, 11.1. HRMS: $(M + H)^+$ calculated for $C_{31}H_{38}NO_{11}$ 600.2445; found 600.2439.

General Procedure A: *N*-cyclic doxorubicins

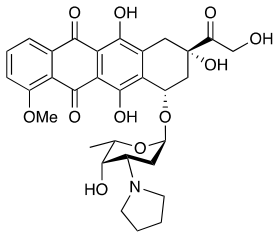
To a solution of doxorubicin·HCl in DMF (0.033M) were added triethylamine (3 eq) and the corresponding diiodoalkane or diiodoether (18 eq). The mixture was allowed to stir for 5 days, or until LCMS showed disappearance of the starting material. It was then poured into H_2O, extracted with $CHCl_3$ repetitively, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (MeOH:DCM) gave the title compounds as red solids.

***N*-piperidinodoxorubicin (10)**



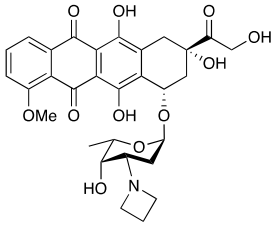
Prepared according to General Procedure A from doxorubicin·HCl (100 mg) and diiodopentane to give the title compound as a red solid (81 mg, 0.13 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-d_3) δ 14.63 (s, 1H), 13.57 (s, 1H), 8.17 – 8.01 (m, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 5.89 (d, *J* = 3.5 Hz, 1H), 5.61 (d, *J* = 20.0 Hz, 1H), 5.53 – 5.39 (m, 2H), 4.79 (q, *J* = 6.6 Hz, 1H), 4.46 (s, 1H), 3.98 (s, 3H), 3.66 – 3.36 (m, 6H), 3.23 (t, *J* = 6.9 Hz, 1H), 2.88 (dt, *J* = 14.5, 2.3 Hz, 1H), 2.59 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.46 (dh, *J* = 17.0, 3.8 Hz, 2H), 1.81 (dtt, *J* = 11.1, 8.1, 4.6 Hz, 1H), 1.74 – 1.57 (m, 4H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.44 (p, *J* = 7.5 Hz, 1H), 1.40 – 1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.8, 187.6, 161.9, 157.6, 156.1, 121.5, 120.0, 112.2, 111.9, 101.1, 76.9, 70.9, 68.3, 66.5, 66.4, 62.0, 57.2, 53.9, 51.1, 37.9, 34.2, 28.0, 24.4, 17.9, 8.3, 7.8. HRMS: $[M + H]^+$ calculated for $C_{32}H_{38}NO_{11}$ 612.2445; found 612.2242.

***N*-pyrrolidinodoxorubicin (11)**



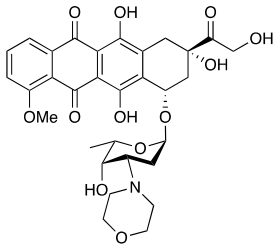
Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and diiodopropane to give the title compound as a red solid (27 mg, 45 µmol, 53%). HRMS: $[M + H]^+$ calculated for $C_{31}H_{36}NO_{11}$ 598.2288; found 598.2291.

***N*-azetidinodoxorubicin (12)**



Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and diiodopropane to give the title compound as a red solid (17 mg, 29 µmol, 34%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.81 – 7.57 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 3.6 Hz, 1H), 4.78 – 4.62 (m, 2H), 4.15 (q, *J* = 6.6 Hz, 1H), 3.94 (d, *J* = 17.7 Hz, 7H), 3.69 (d, *J* = 2.7 Hz, 1H), 3.41 (s, 1H), 2.97 – 2.87 (m, 1H), 2.68 (d, *J* = 18.4 Hz, 1H), 2.34 (p, *J* = 7.8 Hz, 2H), 2.26 (d, *J* = 14.6 Hz, 1H), 2.05 (dd, *J* = 14.6, 4.9 Hz, 1H), 1.87 (dt, *J* = 9.5, 4.6 Hz, 1H), 1.77 (td, *J* = 12.7, 3.9 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 214.7, 187.6, 187.4, 162.3, 157.2, 155.9, 137.2, 135.9, 135.4, 135.1, 121.1, 120.3, 112.2, 111.9, 100.9, 77.0, 71.1, 67.9, 65.7, 64.7, 62.0, 57.1, 53.5, 37.1, 33.6, 26.5, 17.2, 16.9. HRMS: $[M + H]^+$ calculated for $C_{30}H_{34}NO_{11}$ 584.2132; found 584.2129.

***N*-morpholinodoxorubicin (13)**



Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and bis(2-iodo)ethyl ether to give the title compound as a red solid (32 mg, 52 µmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 13.20 (s, 1H), 8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.46 – 7.36 (m, 1H), 5.56 (d, *J* = 3.1 Hz, 1H), 5.28 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.74 (d, *J* = 15.8 Hz, 3H), 4.09 (s, 3H), 3.96 (q, *J* = 6.7 Hz, 1H), 3.71 (dt, *J* = 12.3, 4.1 Hz, 6H), 3.23 (dd, *J* = 18.8, 1.9 Hz, 1H), 2.97 (d, *J* = 18.8 Hz, 1H), 2.49 – 2.32 (m, 4H), 2.17 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.78 (dd, *J* = 11.2, 4.1 Hz, 2H), 1.39 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 213.8, 187.2, 186.7, 161.1, 156.4, 155.7, 136.0, 135.5, 133.9, 133.6, 125.6, 120.9, 120.0, 118.6, 111.6, 111.5, 101.1, 70.0, 67.1, 66.9, 65.6, 65.1, 58.8, 56.8, 49.8, 35.6, 34.0, 30.4, 29.8, 27.5, 17.3. HRMS: $[M + H]^+$ calculated for $C_{31}H_{36}NO_{12}$ 614.2238; found 614.2241.

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