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

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Chapter 2

Synthesis of N,N-*dimethyldoxorubicin*

Introduction

Since its discovery in the late 1960s, the anthracycline doxorubicin (**1a**, Figure 1) has fulfilled a crucial role in anti-cancer treatment.[1] Unfortunately, its clinical use comes with a range of side-effects, most notably cardiotoxicity,[2–4] which can be lethal and occurs in a dose-dependent manner. Treatment with doxorubicin is therefore limited by this cardiotoxicity to a maximum cumulative dose, and afterwards, many patients require alternate treatments, which are not always available. Additionally, doxorubicin-induced cardiac damage persists even after remission, severely lowering the quality of life of cancer survivors. Besides cardiotoxicity, doxorubicin is also able to induce the formation of secondary tumors[5,6] and infertility, especially troublesome in younger patients.[7] In spite of these side-effects that strongly hamper treatment, doxorubicin remains on the World Health Organisation's List of Essential Medicines.[8] Although liposomal administration of doxorubicin[9] resulted in lowered cardiotoxicity, the synthesis of analogs did not result in a less cardiotoxic anthracycline.[10] The recent discovery of histone eviction as a mode of action for this drug[11] brings renewed interest into the anthracycline class of anti-cancer drugs. In order to better understand the structure-activity relationship (SAR) of doxorubicin and analogs thereof, and ultimately yield a better anthracycline anti-cancer drug than doxorubicin, this Chapter presents the synthesis of *N,N*-dimethyldoxorubicin (**3**, Figure 1): a hybrid structure combining structural elements from both doxorubicin (**1a**) and aclarubicin (**2**).

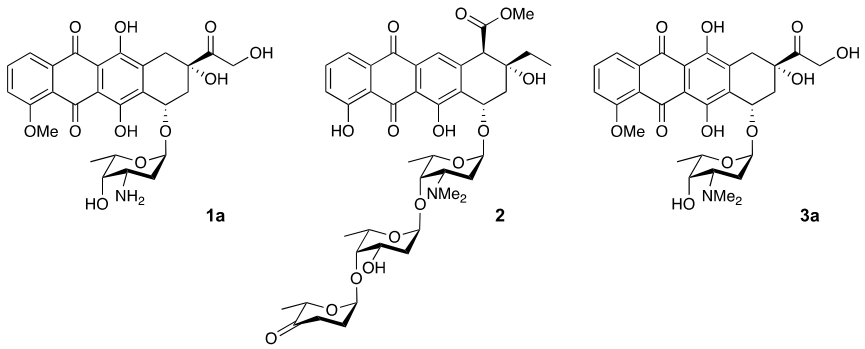
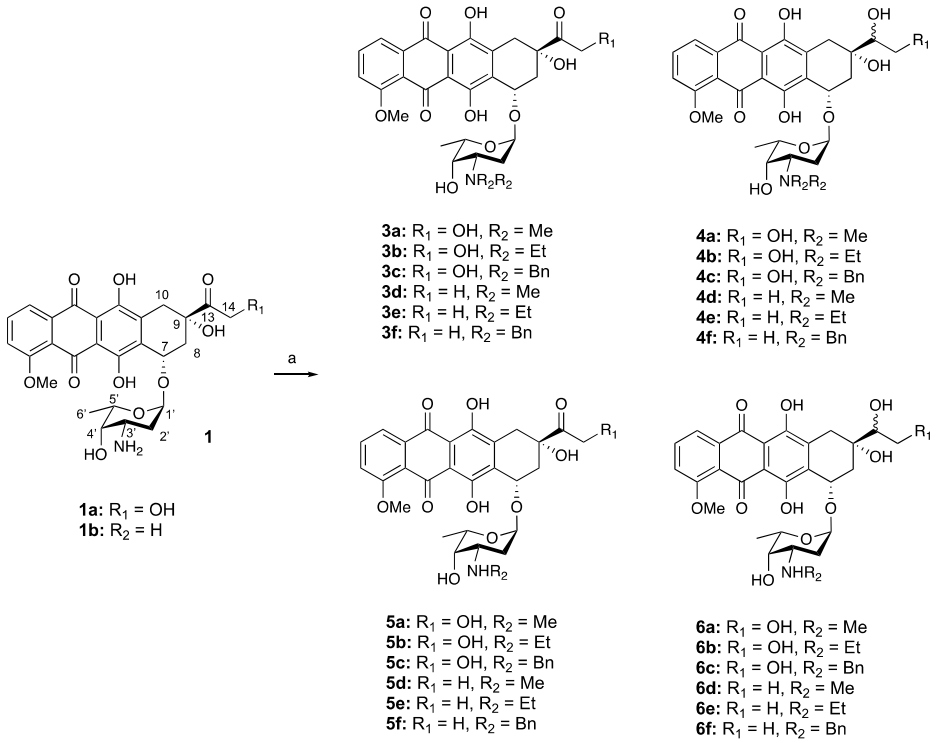


Figure 1. Doxorubicin (**1a**), aclarubicin (**2**) and the compound subject of this Chapter, *N,N*-dimethyldoxorubicin (**3a**).

Figure 1 shows the chemical structure of the cardiotoxic drug doxorubicin (**1a**), which has been shown to induce both DNA breaks and histone eviction.[11] Depicted as well is aclarubicin (**2**), a natural anthracycline that does not induce DNA damage, and is also less cardiotoxic in comparison to doxorubicin.[12] Considering the structures of these two drugs, a number of similarities and differences can be noted. Both compounds contain anthraquinone functions and share a general architecture, but they differ at places in substitution/oxidation pattern. Doxorubicin (**1a**) features an α-L-daunosamine as the single, monosaccharidic carbohydrate fragment. Aclarubicin features an α-L-rhodosamine (*N*,*N*-dimethyldaunosamine), that is further glycosylated on its 4-hydroxyl function with an α-(1→4) disaccharide composed of L-oliose and L-cinerulose A. Understanding of the structural basis of the difference in biological activities between doxorubicin (**1a**) and aclarubicin (**2**) would be greatly facilitated by the availability for evaluation of a series of hybrid structures of these two drugs. *N,N*-dimethyldoxorubicin (**3a**), combining the tetracycle present in doxorubicin and α-L-rhodosamine, the reducing sugar of aclarubicin (**2**) was envisaged as the first compound of such coherent set of hybrid anthracyclines.

N,N-dimethyldoxorubicin (**3a**), has been prepared previously by Tong *et al.*[13] They published a preparation that involves direct reductive alkylation of doxorubicin (**1a**) and daunorubicin (**1b**) to yield (di-)*N*-alkylated analogues **3a**-**3f** bearing two methyl, ethyl, and benzyl groups, respectively (Scheme 1). The yields were modest to low and were accompanied by unwanted reduction of the 13-(*bis*)-hydroxy ketone (**4a**-**4f**), mono-alkylated products (**5a**-**5f**) and compounds that had undergone both undesired transformations (**6a**-**6f**) in sometimes unspecified yields. Furthermore, the authors state that silica gel columns up to 7 feet (2.13 meters) were required to separate the products. They also found that the yields for reductive alkylation on daunorubicin (**1b**) (doxorubicin (**1a**) lacking the 14-OH group) were significantly higher.

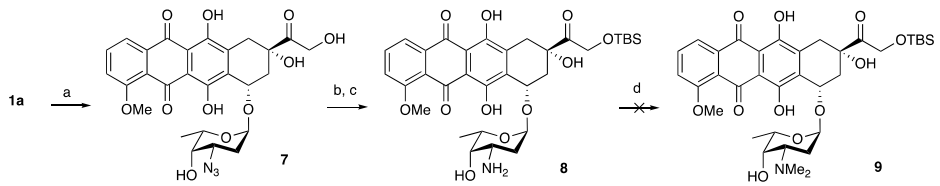


Scheme 1. Tong's synthesis of *N,N*-dimethyldoxorubicin (**3a**) and related dialkyl-doxorubicins and dialkyl-daunorubicins. *Reagents and conditions:* (a) aq. CH_2O, $NaBH_3CN$, MeCN, H_2O, 30 min, 43% for **3a**, 22% for **3b**, 3% for **3c**, 80% for **3d**, 37% for **3e**, 5% for **3f**.

Apparently, as also alluded to by the authors, the 13-*bis*-hydroxyketone moiety in doxorubicin (**1a**) is more susceptible to reduction than the hydroxyketone found in daunorubicin (**1b**). Borohydride reducing agents are known to reduce ketones when α-hydroxy substituents are present.[14,15] Attempts at reproducing the Tong method for the synthesis of *N,N*-dimethyldoxorubicin (**3a**) at the onset of the here-presented studies indeed led to extensive ketone reduction, incomplete amine alkylation, or both, and this synthesis route was therefore abandoned. The work described in this Chapter entails studies on the synthesis of *N,N*-dimethyldoxorubicin (**3a**), either by direct modification of doxorubicin (**1a**), or through glycosylation of the appropriately protected tetracycline aglycon with an orthogonally protected glycosyl donor using the gold(I)-glycosylation chemistry developed by the group of Yu.[16]

Results and discussion

One approach that would avoid ketone reduction as found in Tong's synthesis is shown in Scheme 2. In this strategy, the primary α-hydroxyl group that could direct the unwanted 13-ketone reduction is protected as its *tert*-butyldimethylsilyl ether (TBS). First, the amine in doxorubicin was protected as the azide by means of copper-catalyzed diazotransfer[17] to give **7**, following the procedure reported by Weil *et al*.[18] Subsequent regioselective silylation of the primary alcohol was followed by Staudinger reduction to give 14-*O*-TBS doxorubicin **8**. Reductive alkylation with formaldehyde using a sub-stoichiometric amount of sodium tris(acetoxy)borohydride ($NaBH(OAc)_3$), a milder reducing agent than $NaBH_3CN$, resulted in incomplete reductive alkylation and undesired ketone reduction. This might be a result of the intermediate methimine not being reactive enough towards borohydride reduction, due to hydrogen bonding with the 4'-hydroxyl group. As a result, the borohydride reduces the ketone instead.

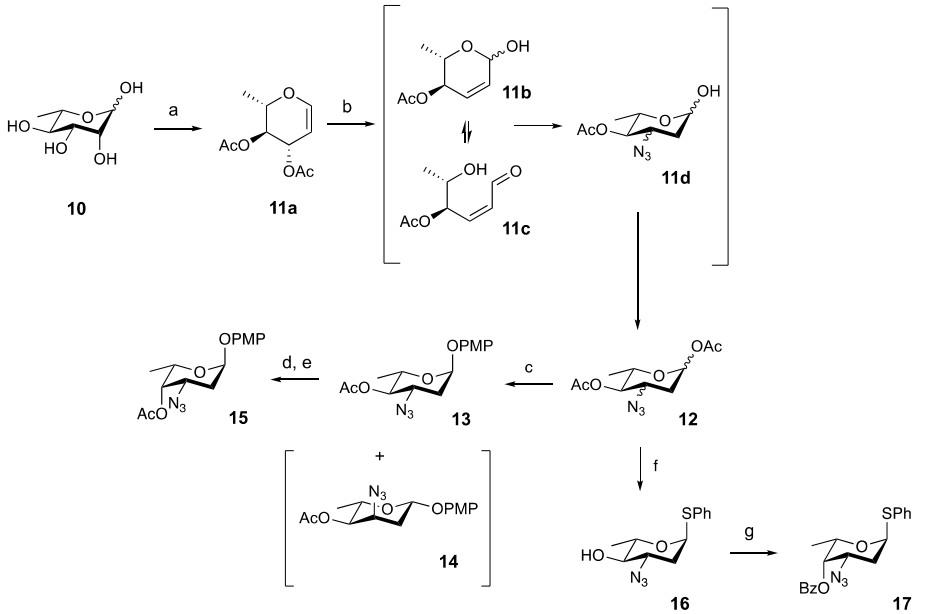


Scheme 2. Protection (steps a-c) of the 14-OH in doxorubicin (**1a**), in an attempt to prevent ketone reduction during reductive alkylation (step d). *Reagents and conditions:* (a) imidazole-1-sulfonyl azide hydrochloride, K_2CO_3, $CuSO_4 \cdot 5H_2O$, MeOH, 73%; (b) TBSCl, imidazole, DMF, 64%; (c) polymer-bound PPh_3, THF, H_2O, 50°C, 66%; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH.

The synthesis of *N,N*-dimethyldoxorubicin (**3a**) from an appropriately functionalized and protected donor glycoside and tetracycline aglycon was therefore investigated next. This strategy involves protecting both the 14- and the 4'-hydroxyl groups. Of note, such an approach should also allow for a larger variety of analogs to be prepared.

Since the discovery of doxorubicin (**1a**), a variety of strategies for the preparation of L-daunosaminyl donor glycosides has been published. Daunosamine can be obtained from acidic hydrolysis of doxorubicin itself, to yield daunosamine hydrochloride almost quantitatively.[19] Other methods for the preparation of daunosamine start from sugars (D-mannose[20], L-fucose[21], or L-rhamnose[21,22]) or even amino-acids (aspartic acid[23]). However, deriving large quantities of daunosamine from doxorubicin (€490 per gram[24]) was deemed too costly. Thus, preparation from either L-rhamnose or L-fucose was considered. L-fucose already possesses the correct stereochemistry on the 4-position, whereas L-rhamnose would require additional synthetic steps to invert this hydroxyl group. However, these additional steps are offset by the much lower cost of L-

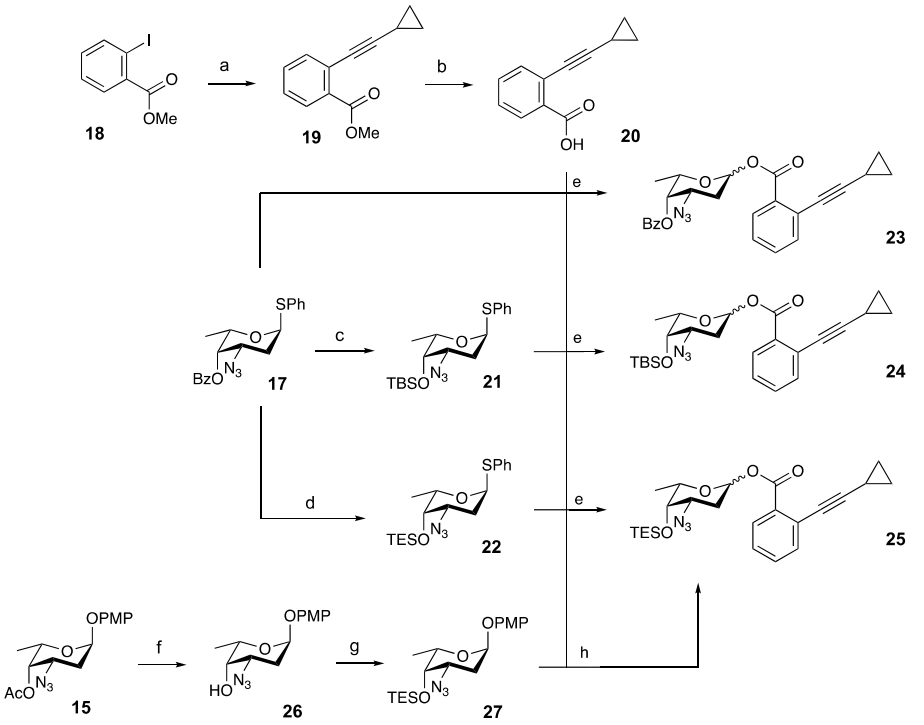
rhamnose (€275 per kg for L-rhamnose[25] versus $425 per 100 gram for L-fucose[26]) and also allowed for the preparation of daunosamine stereoisomers (see Chapter 5).



Scheme 2. Preparation of protected L-daunosamines **15** and **17**. *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii.* HBr/AcOH, Ac_2O, DCM; *iii.* Zn, AcOH, NaOAc, Ac_2O, $CuSO_4{\cdot}5H_2O$, MeCN, quant. over 3 steps; (b) *i.* H_2O, 80 °C, then NaN_3, AcOH; *ii.* Ac_2O, pyr., 83% over 2 steps; (c) *p*-methoxyphenol, TMSOTf, DCM, 0 °C, 50% of **13**, 10% of **14**, 83% total; (d) NaOMe, MeOH, 93%; (e) *i.* Tf_2O, pyr., DCM, 0 °C; *ii.* KOAc, 18-crown-6, DMF, 92% over 2 steps; (f) *i.* thiophenol, $BF_3{\cdot}OEt_2$, DCM, -78 to 0 °C; *ii.* NaOMe, MeOH, 39% over 2 steps; (g) *i.* Tf_2O, pyr., DCM, 0°C; *ii.* KOBz, 18-crown-6, DMF, 72% over 2 steps.

The synthesis of protected L-daunosamines **15** and **17** starting from L-rhamnose **10** commenced with the preparation of 3,4-di-*O*-acetyl-L-rhamnal **11a**.[27,28] To this end, L-rhamnose **10** was first peracetylated, then brominated at the anomeric position using HBr and finally subjected to a Zn/Cu-mediated elimination of the 1-bromide and 2-*O*-acetate in acetate buffer, to yield glycal **11a** in near quantitative yield over 3 steps. Heating this compound in water at 80 °C led to attack of water on the anomeric carbon to effect a shift of the 1,2-double bond to expel the acetate from C3 to give unsaturated alcohol **11b**. This alcohol is in equilibrium with 1,4-unsaturated aldehyde **11c**, which can undergo 1,4-addition of hydrazoic acid to give **12** as a mixture of 1- and 3- epimers, after anomeric acetylation. Treatment of this mixture with trimethysilyl trifluoromethanesulfonate (TMSOTf) in the presence of *p*-methoxyphenol afforded the corresponding anomeric *p*-methoxyphenyl acetals as a mixture of 1- and 3-epimers in 83% yield. From this, the desired α-configured C3-equatorial azide **13** could be separated in 50% overall yield (kedarosamine **14** was also isolated in 10% and used in

syntheses described in Chapter 5). Deacetylation, triflation and inversion[29] then gave **15**. In a similar vein, subjection of mixture **12** to $BF_3{\cdot}OEt_2$ and thiophenol followed by 4-deacetylation gave **16**. Triflation of the resultant equatorial alcohol was followed by S_N2-inversion of stereochemistry with potassium benzoate to finally give orthogonally protected **17**.

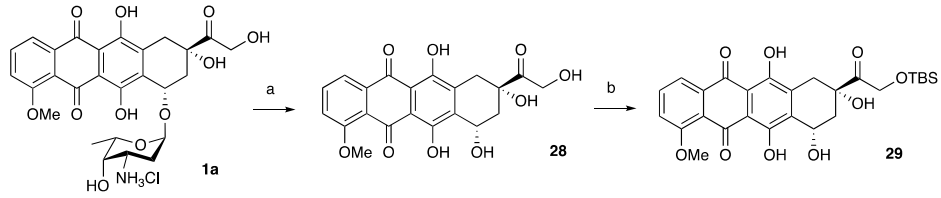


Scheme 3. Preparation of the L-daunosaminyl *ortho*-alkynylbenzoate donors **23**-**25**. *Reagents and conditions:* (a) cyclopropylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 96%; (b) aq. NaOH, THF; (c) *i*. aq. NaOH, dioxane, MeOH, 60°C; *ii. tert*-butyldimethylsilyl triflate, pyr., DMF, 83% over 2 steps; (d) *i*. aq. NaOH, dioxane, MeOH, 60°C; *ii.* triethylsilyl triflate, pyr., DMF, 95% over 2 steps; (e) *i. N*-iodosuccinimide, MeCN/H_2O (10:1, v/v); *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 68% for **23,** 43% for **24**, 20% for **25**, over 2 steps; (f) NaOMe, MeOH, 93%; (g) triethylsilyl triflate, pyr., DMF, quant.; (h) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (1:5.6 α:β).

Protected L-daunosaminyl thioglycoside **17** was then converted to its corresponding 4-silyl ether. Hydrolysis of the benzoate was followed by either *tert*-butyldimethylsilylation or triethylsilylation. The 4-hydroxyl function appeared unreactive towards silyl chlorides, even at elevated temperatures. Use of the corresponding silyl triflates afforded **21** and **22** in good yields. In order to convert these thioglycosides into their corresponding *ortho*-alkynylbenzoates, *ortho*-cyclopropylethynylbenzoic acid **20**[30] was prepared. According to the literature procedure,[31] methyl-2-iodobenzoate **18** was subjected to Sonogashira conditions

($Pd(PPh_3)_2Cl_2$, CuI, Et_3N) in the presence of cyclopropylacetylene to yield *ortho*-alkynylbenzoate methyl ester **19**. The carboxylic acid was then liberated by means of aqueous hydrolysis to give **20**. However, this acid proved to be particularly unstable, and undergoes intramolecular cyclisation to afford the corresponding *iso*-coumarins. This reagent was therefore best prepared fresh (by means of saponification) and used in excess in its Steglich esterification. Then, thioglycosides **17**, **21** and **22** were subjected to hydrolysis (*N*-iodosuccinimide in wet MeCN) to yield their corresponding hemiacetals. Steglich esterification of these with carboxylic acid **20** yielded the three different alkynylbenzoate donors. In this way, the α- and β-benzoates **23α** and **23β** (separated by column chromatography) were obtained in good yield over the two steps. Treatment of silyl ethers **21** and **22** led to extensive cleavage of the silyl protecting groups (giving **24** and **25** in 43% and 20% respectively, over two steps), presumably due to *in situ* generated molecular iodine, which is known to cleave silyl ethers in a catalytic fashion.[32] In an attempt to improve the yield of **25**, *p*-methoxyphenolate **15** was converted to its 4-*O*-triethylsilylether. Removal of the anomeric *p*-methoxyphenolate was achieved using the single-electron oxidant silver(II)-di(hydrogen picolinate) ($Ag(DPAH)_2$),[33,34] a reagent that was able to oxidize the *p*-methoxyphenolate into 1,4-benzoquinone under buffered conditions, thereby releasing the desired lactol. Ensuing esterification now gave alkynylbenzoate **25** in 75% over two steps. The glycosyl donors **23-25** were obtained as anomeric mixtures (with the β-product predominating). Because anomeric 2-deoxy *ortho*-alkynylbenzoates can interconvert under glycosylation conditions[35] and both anomers behave equally well in glycosylations,[31] this was expected to be of little influence on the outcome of the projected glycosylations.

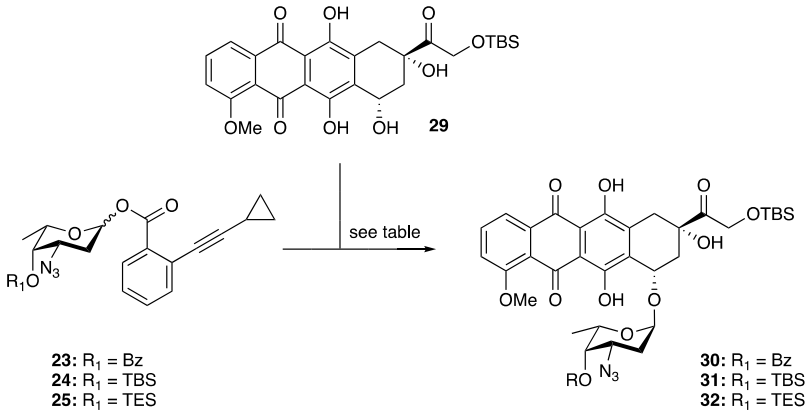
Attention was then turned to the synthesis of protected doxorubicinone aglycone acceptor **29**. Doxorubicinone (**28**) has been prepared by (lengthy) total synthesis[36–38] and formally from daunomycinone[39] but is more easily obtained by acidic hydrolysis of the glycosidic linkage in doxorubicin (**1a**), as shown in Scheme 4. This was followed by regioselective silylation of the primary alcohol to give acceptor **29** in near quantitative yield over the two steps.[40]



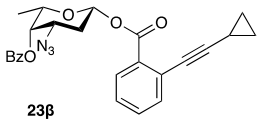
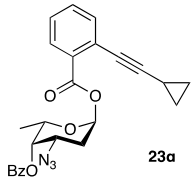
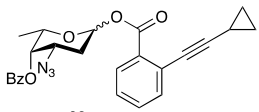
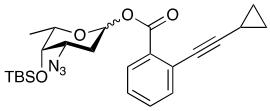
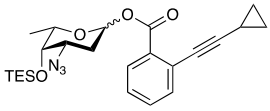
Scheme 4. Synthesis of doxorubicinone-acceptor **29**. *Reagents and conditions:* (a) *i.* aq. HCl, 90 °C; (b) TBS-Cl, imidazole, DMF, 97% over 2 steps.

Having both glycosylation partners in hand, their behavior in PPh_3AuNTf_2-mediated glycosylations was investigated. The results are summarized in Table 1.

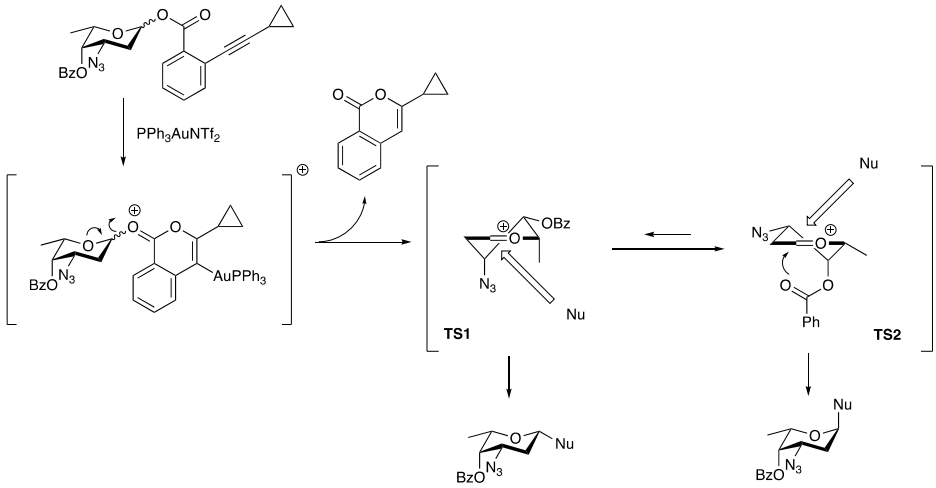
Table 1. Glycosylation of *ortho*-alkynylbenzoates **23**-**25** to doxorubicinone-acceptor **29**.



Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), 4Å MS, T, 0.05M in DCM.

Entry	Donor	Temperature	Acceptor **29** equiv.	Yield (α:β ratio)
1	 **23β**	-78 °C to RT	1	25% (>20:1 α:β)
2	 **23α**	-78 °C to RT	1	25% (>20:1 α:β)
3	 **23**	RT	1	71% (>20:1 α:β)
4	 **24**	RT	1.5	78% (>20:1 α:β)
5	 **25**	RT	1.5	73% (>20:1 α:β)

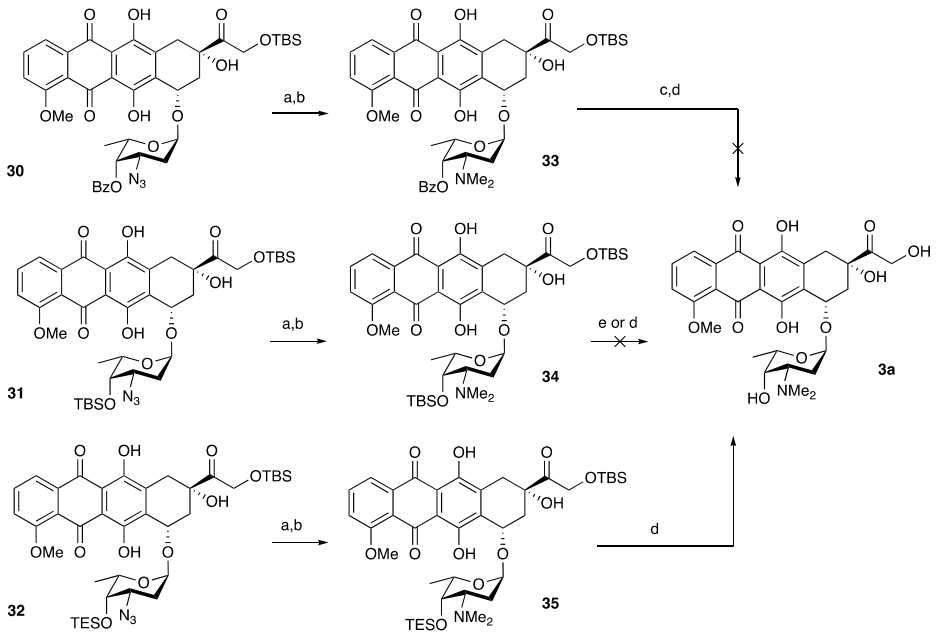
From entries 1 and 2 it appears that the anomeric stereochemistry of the prepared glycosyl donors is of little influence, as they performed equally well in the glycosylation reactions. Addition of a catalytic amount of PPh_3AuNTf_2 to a mixture of either donor **23α** or **23β** and acceptor **29** at -78 °C was followed by gradual warming up to RT to give **30** with excellent α-selectively in both cases. A rationale for the stereochemical outcome is shown in Scheme 5.



Scheme 5. Mechanistic rationale for the observed stereoselectivity of the glycosylation to donor **19**.

Association of the gold(I) catalyst to the triple bond in the anomeric alkynylbenzoate is followed by attack of the carbonyl onto the alkyne to yield an isochromenylium-gold complex, which can collapse to give an oxocarbenium-like intermediate. This species may adopt different conformations, of which the $^4H_3$ (TS1) and $^3H_4$ (TS2) are likely the most stable. Although the $^3H_4$-conformer places the large benzoate in a sterically unfavoured axial position, it may benefit from long-range anchimeric stabilization. Top-face attack on this species, provides the α-anomeric product, through a favorable chair-like transition state. Conversely, in the $^4H_3$ conformer, attack of the incoming nucleophile on the bottom face of the half-chair to allow for a chair like transition state, would lead to significant steric hindrance when passing the axial methyl and azide groups. The low yield of the reactions depicted in entries 1 and 2 is likely due to the observed poor solubility of the anthracycline acceptor in the reaction solvent at low temperature. Performing the same reaction at RT almost tripled the yield. At this temperature, the reaction was complete within 10 minutes, with the initial red suspension turning into a clear red liquid in mere seconds, maintaining the stereoselectivity of the reaction.

Donor glycosides featuring either a triethyl- or a *tert*-butyldimethylsilyl ether (Entries 4 and 5) gave excellent stereoselectivity upon glycosylation to give **31** and **32**. The oxocarbenium ion-like intermediates derived from these donors, likely prefer to adopt a $^3H_4$ conformation, which are selectively attacked on the α-face. In these reactions the amount of acceptor **29** was increased, to decrease the possibility of additional glycosylation onto the tertiary alcohol, a side-reaction observed in the usage of excess donor.[41] Excess acceptor **29** could be easily recovered through silica gel column chromatography of the glycosylation reaction mixtures.



Scheme 6. Final steps towards *N,N*-dimethyldoxorubicin (**3a**). *Reagents and conditions:* (a) polymer-bound PPh_3, THF/H_2O (10:1, v/v), 50 °C, 48% from **30**, 75% from **31**, 69% from **32**; (b) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 53% for **33**, 45% for **34**, 83% for **35**; (c) MeOH, reflux; (d) HF·pyr., THF/pyr., 66% from **35**; (e) TBAF, THF.

For all three obtained glycosidic products **30**-**32**, Staudinger reduction of the azide gave the corresponding free amines (Scheme 6). Subsequent *N*-dimethylation was achieved using a sub-stoichiometric amount of sodium tris(acetoxy)borohydride in the presence of aqueous formaldehyde to effect reductive alkylation and yield **33**-**35**. In contrast to the preparation of **9** (Scheme 2), little to no ketone reduction was observed here. Apparently, hydrogen bonding of the 4'-hydroxyl with the intermediate methimine is abolished upon protection of this function with either a benzoate or silyl ether. The final deprotections proved less facile, with attempts at removal of the benzoyl group in **33** (MeOH, reflux[42]) leading to degradation. The 4-OTBS group in **34** also proved to be

troublesome, with TBAF treatment giving a complex mixture and HF·pyridine unable to remove the 4-OTBS group, even after a prolonged reaction time (7 days). However, the TES group in **35** could be readily removed by treatment with HF·pyridine, to give the target *N,N*-dimethyldoxorubicin (**3a**) in 66% yield.

Conclusions

This Chapter describes the synthesis of *N,N*-dimethyldoxorubicin (**3a**), a hybrid structure combining structural elements from both doxorubicin (**1a**) and aclarubicin (**2**). As direct reductive alkylation on the natural drug proved troublesome, protected doxorubicin was prepared from carefully chosen glycosyl donors and acceptors. Gold(I) catalysis was able to promote the glycosylations, delivering the target compounds in good yields and excellent α-stereoselectivity. The final removal of the 4'-protecting group proved difficult but the use of the triethylsilyl group, which could be removed under mild conditions, allowed for the preparation of *N,N*-dimethyldoxorubicin (**3a**). The glycosylation methodology and protecting group strategy applied in this Chapter is further explored in the synthesis of doxorubicin/aclarubicin hybrid structures as described in Chapter 3.

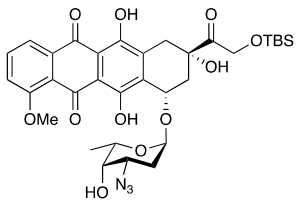
Experimental procedures and characterization data

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). ^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 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).

General procedure A: Au(I)-catalysed glycosylation

To a solution of the glycosyl donor (1 eq) and the required anthracycline acceptor (1-1.5 eq) in DCM (0.05M), 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) (0.1 eq) in DCM was added dropwise at the designated temperature. After stirring 30 minutes (for RT) or overnight (-20°C or lower), the mixture was filtered and concentrated *in vacuo*. Column chromatography (EtOAc:pentane or Et_2O:pentane and then acetone:toluene) followed by (if required) size-exclusion chromatography (Sephadex LH-20, DCM/MeOH, 1:1 v/v) gave the title compounds.

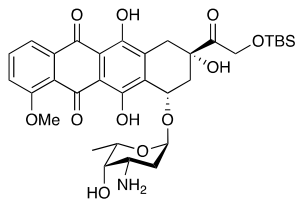
7-[3-Azido-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (7)



To a mixture of doxorubicin hydrochloride (**1a**) (200 mg, 0.340 mmol), potassium carbonate (72 mg, 0.51 mmol, 1.5 eq) and copper sulfate (cat. amount) in methanol (4 mL) was added imidazole-1-sulfonyl azide hydrochloride[17] (22 mg, 0.1035 mmol, 3.3 eq) and the reaction mixture was stirred overnight. The mixture diluted with water and extracted with DCM thrice. The combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (10:90 MeOH:DCM) gave 3'-azidodoxorubicin as a red solid (140 mg, 0.248 mmol, 72%). Spectral data was in accordance with that of literary precedence.[43] To a solution of the above azide (126 mg, 0.221 mmol) in DMF (4.4 mL) were added imidazole (38 mg, 0.55 mmol) and then *tert*-butyldimethylsilyl chloride (50 wt% in toluene, 85 μL, 1.1 eq) at 0°C and the resulting mixture was stirred for 3 days. Then, equal such portions of both imidazole and *tert*-butyldimethylsilyl chloride were added at 0°C and the mixture was stirred overnight. A third portion was added, and after 3 hours of stirring, the reaction mixture was poured into Et_2O and washed with H_2O thrice. The organic layer was then diluted with DCM, dried over Na_2SO_4 and concentrated *in vacuo* (the use of $MgSO_4$ for the drying of doxorubicinone-containing compounds led to extensive degradation). Column chromatography (2:98 – 20:80 acetone:toluene) gave the title compound as a red solid (90 mg, 0.13 mmol, 64%). ^1H NMR (400 MHz, Chloroform-*d*) δ 13.87 (s, 1H), 13.05 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.18 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.87 (d, *J* = 2.8 Hz, 2H), 4.35 (s, 1H), 4.07 (s, 5H), 3.74 (s, 1H), 3.60 (ddd, *J* = 12.8,

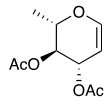
4.9, 2.4 Hz, 1H), 3.09 (dd, *J* = 18.6, 1.8 Hz, 1H), 2.76 (d, *J* = 18.8 Hz, 1H), 2.30 (d, *J* = 14.7 Hz, 2H), 2.14 (ddd, *J* = 29.8, 13.9, 4.0 Hz, 2H), 1.94 (dd, *J* = 13.2, 4.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 186.7, 186.4, 161.0, 156.2, 155.5, 135.8, 135.2, 133.8, 133.6, 120.5, 119.8, 118.6, 111.3, 111.2, 100.8, 70.3, 69.5, 67.2, 66.7, 56.7, 56.7, 35.5, 33.7, 28.5, 25.9, 18.7, 16.9, -5.2. HRMS: $[M + Na]^+$: calculated for $C_{33}H_{41}N_3O_{11}SiNa$: 706.2408; found 706.2401.

7-[3-Amino-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (8)



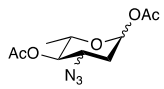
A suspension of **7** (200 mg, 0.292 mmol) and polymer-bound triphenylphosphine (490 mg, 1.46 mmol, 5 eq) in THF/H_2O (22 mL, 10:1 v/v) was stirred at 50°C overnight. It was then filtered off and concentrated *in vacuo*. Column chromatography (5:95 – 20:80 MeOH:DCM) gave the title compound as a red solid (127 mg, 0.193 mmol, 66%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (s, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 5.37 (s, 1H), 4.23 (q, *J* = 6.4 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 2.95 (d, *J* = 18.5 Hz, 1H), 2.74 (d, *J* = 18.5 Hz, 1H), 2.28 (d, *J* = 14.6 Hz, 1H), 2.13 – 2.00 (m, 1H), 2.00 – 1.80 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 9H), 0.14 (d, *J* = 3.3 Hz, 6H). ^{13}C NMR (101 MHz, MeOD) δ 213.3, 162.3, 157.2, 137.2, 136.1, 135.4, 121.2, 120.4, 120.2, 112.2, 112.0, 112.0, 101.7, 77.3, 71.4, 69.2, 68.2, 67.3, 57.1, 48.2, 40.3, 37.2, 33.8, 30.9, 26.4, 19.5, 17.3, -5.1.

3,4-Di-*O*-acetyl-L-rhamnal (11)



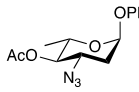
Commercially available L-rhamnose monohydrate **10** (20.0 g, 110.0 mmol) was suspended in pyridine (100 mL) and acetic anhydride (128 mL). After stirring for three days, the resulting solution was concentrated *in vacuo* and additionally coevaporated with toluene to afford crude per-*O*-acetyl-L-rhamnose as a viscous orange oil. The material was carried on without further purification. This tetraacetate was dissolved in DCM (70 mL) and acetic anhydride (3.6 mL), whereupon hydrobromic acid (33 wt. % HBr in AcOH, 33 mL) was added dropwise. After stirring for 3 hours, the resulting solution was concentrated *in vacuo* to afford the crude rhamnosyl bromide as a viscous green oil. The material was continued without further purification. To a stirring suspension of copper sulfate pentahydrate (3.50 g, 22.0 mmol, 0.2 eq), sodium acetate (16.2 g, 198.0 mmol, 1.8 eq), acetic acid (12.6 mL, 220.0 mmol, 2 eq) and acetic anhydride (14.5 mL, 154.0 mmol, 1.4 eq), in MeCN (50 mL) was added zinc dust (14.4 g, 220.0 mmol, 2 eq) and the resulting suspension was stirred for 45 minutes. Subsequently, a solution of the rhamnosyl bromide in MeCN (250 mL) was added *via* a dripping funnel over the duration of 40 minutes to the mixture of activated zinc. After stirring for 2 hours, the resulting suspension was diluted with DCM, filtered over Celite and successively washed with sat. aq. $NaHCO_3$. The aqueous layer was then extracted with DCM and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a light-yellow oil (23.6 g, 110.0 mmol, 100% over 3 steps). Spectral data was in accordance with that of literary precedence.[28]

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-L-rhamno/fucopyranoside (12)**[22]



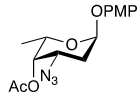
Glycal **11** (25.9 g, 121 mmol) in was emulsified in H_2O (170 mL) and heated at 80°C for 2 h. After cooling to room temperature, acetic acid (25.2 mL) and NaN_3 (10.9 g, 297 mmol, 1.4 eq) were added and the reaction mixture was stirred overnight. Sat. aq. $NaHCO_3$ was added and the reaction mixture was extracted thrice with EtOAc. Combined organics were dried over $MgSO_4$ and concentrated in vacuo. To the crude product in DCM (210 mL) were added pyridine (60 mL) and acetic anhydride (60 mL) and the reaction mixture was stirred overnight. It was then concentrated *in vacuo* and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford **8** as an orange oil. (25.4 g, 98.9 mmol, 82% over 2 steps).

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-rhamnopyranoside (13)**



12 (11.6 g, 45.0 mmol) and *p*-methoxyphenol (8.38 g, 67.5 mmol, 1.5 eq) were coevaporated thrice with toluene and subsequently dissolved in DCM (225 mL). Activated 4Å molecular sieves were added, and the mixture was allowed to stir for 30 minutes. Thereafter, TMSOTf (2.44 mL, 13.5 mmol, 0.3 eq) was added at 0°C and the mixture was stirred for a further 4 hours at that temperature. It was then filtered into sat. aq. $NaHCO_3$, after which the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (7:93 EtOAc:pentane) gave the title compound as a white solid (7.20 g, 22.4 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.92 (m, 2H), 6.92 – 6.78 (m, 2H), 5.47 (d, *J* = 2.7 Hz, 1H), 4.75 (t, *J* = 9.8 Hz, 1H), 4.07 (ddd, *J* = 12.3, 9.9, 5.0 Hz, 1H), 3.93 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.77 (s, 3H), 2.36 (ddd, *J* = 13.3, 4.9, 1.1 Hz, 1H), 2.14 (s, 3H), 1.86 (td, *J* = 12.9, 3.5 Hz, 1H), 1.13 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 155.0, 150.4, 117.6, 114.7, 95.5, 76.8, 75.5, 66.7, 57.6, 55.7, 35.5, 20.9, 17.6. HRMS: $[M + Na]^+$: calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

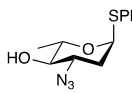
***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (15)**



To a solution of **13** (7.20 g, 22.4 mmol) in MeOH was added NaOMe (242 mg, 4.48 mmol, 0.2 eq) and the mixture was allowed to stir over 3 days. It was then neutralized by addition of Amberlite IR120 (H^+ form), filtered off and concentrated *in vacuo* to give the alcohol as a yellow oil (6.26 g, 22.4 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.94 (m, 2H), 6.88 – 6.79 (m, 2H), 5.47 (d, *J* = 2.8 Hz, 1H), 3.96 (ddd, *J* = 12.2, 9.5, 4.9 Hz, 1H), 3.83 (dq, *J* = 9.3, 6.2 Hz, 1H), 3.78 (s, 3H), 3.22 (td, *J* = 9.4, 4.1 Hz, 1H), 2.36 (ddd, *J* = 13.2, 4.9, 1.1 Hz, 1H), 2.26 (d, *J* = 4.2 Hz, 1H), 1.85 (td, *J* = 12.7, 3.5 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 150.6, 117.7, 114.7, 95.8, 76.8, 76.1, 68.5, 60.4, 55.8, 35.3, 17.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4$; 302.1111; found 302.1118.

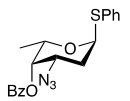
To a solution of the above compound (18.09 g, 64.8 mmol) in DCM (250 mL) and pyridine (25 mL), triflic anhydride (13.5 mL, 77.8 mmol, 1.2 eq) was added at 0°C. The mixture was allowed to stir for 1 hour, after which it was poured into 1M HCl solution. This was then extracted with DCM twice, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude triflate and 18-crown-6 (20.5 g, 77.8 mmol, 1.2 eq) were coevaporated thrice with toluene and dissolved in DMF (250 mL). To this was added KOAc (7.6 g, 77.8 mmol, 1.2 eq) and the mixture was stirred for 1 hour. It was then diluted with EtOAc and washed with H_2O five times and brine. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 - 7:93 EtOAc:pentane) gave the title compound as a yellow solid (19.2 g, 59.8 mmol, 92% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.91 (m, 2H), 6.91 – 6.75 (m, 2H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.22 (d, *J* = 2.5 Hz, 1H), 4.14 (q, *J* = 6.2 Hz, 1H), 4.05 (ddd, *J* = 12.3, 5.1, 3.0 Hz, 1H), 3.78 (s, 3H), 2.28 – 2.07 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.0, 150.7, 117.6, 114.8, 96.3, 76.8, 70.2, 66.0, 55.8, 54.6, 29.9, 20.9, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

Phenylthio-3-azido-4-*O*-benzoyl-2,3-dideoxy-α-L-rhamnopyranoside (16)[44]



A solution of **12** (12.9 g, 50.0 mmol) in DCM (250 mL) was cooled to -78 °C, after which thiophenol (5.25 mL, 51.5 mmol, 1.03 eq) and $BF_3{\cdot}OEt_2$ (15.4 mL, 125 mmol, 2.5 eq) were added dropwise. After being allowed to warm up to 0 °C, the reaction mixture was poured into sat. aq. $NaHCO_3$, extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. This crude product was then dissolved in MeOH (500 mL), after which methanolic NaOMe (5.4 M in MeOH) was added until pH>10. It was then quenched by addition of Amberlite (H^+ form), filtered and the filtrate was concentrated *in vacuo*. Column chromatography (4:96 – 5:95 EtOAc:pentane) gave the title compound as a clear oil (5.17 g, 19.5 mmol, 39% over 2 steps). Spectral data was in accordance with that of literary precedence.

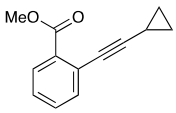
Phenylthio-3-azido-4-*O*-benzoyl-2,3-dideoxy-α-L-fucopyranoside (17)



To a solution of **16** (5.17 g, 19.5 mmol) in DCM (80 mL) and pyridine (8 mL), triflic anhydride (4.1 mL, 23.4 mmol, 1.2 eq) was added at 0°C. The mixture was allowed to stir for 1 hour, after which it was poured into 1M HCl solution. This was then extracted with DCM twice, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude triflate and 18-crown-6 (7.21 g, 27.3 mmol, 1.4 eq) were coevaporated thrice with toluene and dissolved in DMF (75 mL). To this was added potassium benzoate (4.37 g, 27.3 mmol, 1.2 eq) and the mixture was stirred for 1.5 hours. It was then diluted with EtOAc and washed with H_2O five times and brine. The organic layer was then dried over $MgSO_4$

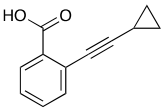
and concentrated *in vacuo*. Column chromatography (4:90 - 10:90 Et_2O:pentane) gave the title compound as a yellow oil (5.27 g, 14.3 mmol, 72% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.04 (m, 2H), 7.67 – 7.54 (m, 1H), 7.54 – 7.39 (m, 4H), 7.39 – 7.20 (m, 3H), 5.81 (d, *J* = 5.5 Hz, 1H), 5.60 – 5.39 (m, 1H), 4.59 (qd, *J* = 6.5, 1.3 Hz, 1H), 4.02 (ddd, *J* = 12.9, 4.7, 3.0 Hz, 1H), 2.57 (td, *J* = 13.2, 5.7 Hz, 1H), 2.21 (ddt, *J* = 13.3, 4.7, 1.2 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 134.3, 133.5, 131.4, 130.0, 129.4, 129.1, 128.6, 127.5, 83.7, 70.4, 66.4, 56.0, 30.8, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{19}H_{19}N_3O_3SNa$: 392.1045; found 392.1043.

Methyl *ortho*-cyclopropylethynylbenzoate (19)[31]



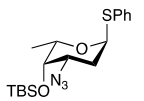
A flame dried flask was charged with methyl 2-iodobenzoate **18** (49.1 g, 200 mmol) and Et_3N (300 mL). The solution was degassed by sonication and cooled to 0°C. $Pd(PPh_3)_2Cl_2$ (2.81 g, 4.00 mmol, 0.02 eq) and CuI (762 mg, 4.00 mmol, 0.02 eq) were added. Cyclopropylacetylene (22.7 ml, 2.60 mmol, 1.3 eq) was then added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred overnight. 500 mL sat aq. NH_4Cl was added, stirred vigorously for 30 min and extracted pentane (600 mL) and EtOAc in pentane (600 mL, 1:99 v/v). Combined organics were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* Column chromatography (3:97 – 10:90 Et_2O:pentane) afforded the title compound as a pale-yellow oil (38.05 g, 192.3 mmol, 96%). Spectral data was in accordance with that of literary precedence.[45]

***ortho*-Cyclopropylethynylbenzoic acid (20)**



A solution of **19** in THF (5 mL/mmol) and 1M NaOH (5 mL/mmol) was stirred at 50°C for 8 hours. It was then poured into 1M HCl (6 mL/mmol) and extracted with DCM 3x. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The title acid thus obtained was used without further purification, due to its instability. Spectral data of the purified compound was in accordance with that of literary precedence.[45]

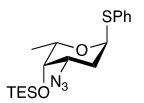
Phenylthio-3-azido-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-α-L-fucopyranoside (21)



A solution of **17** (753 mg, 2.04 mmol) in 1M NaOH (45 mL), dioxane (40 mL) and MeOH (40 mL) was stirred at 60 °C for 1 hour. It was then concentrated *in vacuo* and partitioned between EtOAc and aq. sat. NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alcohol.

This was then redissolved in DMF (3.4 mL) to which pyridine (342 µL, 4.25 mmol) and TBSOTf (370 µL, 2.04 mmol) were added at 0°C. After stirring overnight, additional such portions of pyridine and TBSOTf were added at the same temperature and again stirred overnight. The reaction mixture was then diluted with EtOAc, washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a clear oil (537 mg, 1.41 mmol, 69% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.38 (m, 2H), 7.38 – 7.16 (m, 3H), 5.68 (dd, *J* = 5.6, 1.3 Hz, 1H), 4.43 – 4.17 (m, 1H), 3.81 (ddd, *J* = 12.6, 4.2, 2.5 Hz, 1H), 3.73 – 3.61 (m, 1H), 2.53 (td, *J* = 12.8, 5.5 Hz, 1H), 2.00 (ddt, *J* = 12.9, 4.2, 1.2 Hz, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 131.5, 129.1, 127.3, 83.8, 70.7, 68.2, 58.5, 29.7, 26.1, 18.5, 17.7, -4.0, -4.3. HRMS: $[M + H]^+$ calculated for $C_{18}H_{30}N_3O_2Si$: 380.1828; found 380.1823.

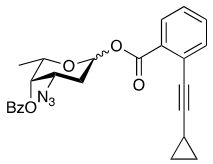
Phenylthio-3-azido-4-*O*-triethylsilyl-2,3-dideoxy-α-L-fucopyranoside (22)



A solution of **17** (810 mg, 2.19 mmol) in 1M NaOH (50 mL), dioxane (45 mL) and MeOH (45 mL) was stirred at 60°C for 1 hour. It was then concentrated *in vacuo* and partitioned between EtOAc and aq. sat. NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alcohol.

This was then redissolved in DMF (3.7 mL) to which pyridine (529 µL, 6.57 mmol, 3 eq) and TESOTf (891 µL, 3.94 mmol) were added at 0°C. After stirring for 1 hour, the reaction mixture was then diluted with EtOAc, washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a clear oil (792 mg, 2.09 mmol, 95% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.37 (m, 2H), 7.37 – 7.22 (m, 3H), 5.70 (d, *J* = 5.4 Hz, 1H), 4.26 (q, *J* = 6.5 Hz, 1H), 3.83 (ddd, *J* = 12.6, 4.2, 2.5 Hz, 1H), 3.79 – 3.65 (m, 1H), 2.53 (td, *J* = 12.8, 5.6 Hz, 1H), 2.10 – 1.93 (m, 1H), 1.20 (dd, *J* = 6.6, 0.8 Hz, 3H), 1.11 – 0.96 (m, 9H), 0.85 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.2, 129.1, 127.2, 83.7, 70.9, 68.2, 58.6, 29.6, 17.4, 7.1, 5.3. HRMS: $[M + H]^+$ calculated for $C_{18}H_{30}N_3O_2Si$: 380.1828; found 380.1823.

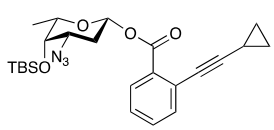
_o_-Cyclopropylethynylbenzoyl-3-azido-4-_O_-benzoyl-2,3-dideoxy-L-fucopyranoside (23)



To a solution of **17** (740 mg, 2 mmol) in MeCN:H_2O (18 mL, 10:1 v/v) was added *N*-iodosuccinimide (540 mg, 2.5 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated *in vacuo* to yield the lactol.

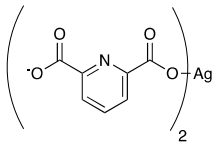
To a solution of the above crude lactol in DCM (5 mL) were added DIPEA (0.65 mL, 3.6 mmol, 1.8 eq), DMAP (244 mg, 2 mmol, 1 eq), EDCI·HCl (478 mg, 2.5 mmol, 1.25 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **20** (478 mg, 2.5 mmol, 1.25 eq). After stirring overnight, the mixture was 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 – 15:85 EtOAc:pentane) gave the title compound as a thick clear oil (604 mg, 1.36 mmol, α:β 1:3.6, 68% over 2 steps). Spectral data for the α -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.06 (m, 2H), 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 – 7.57 (m, 1H), 7.57 – 7.41 (m, 4H), 7.36 (td, *J* = 7.6, 1.5 Hz, 1H), 6.71 – 6.62 (m, 1H), 5.52 (d, *J* = 2.8 Hz, 1H), 4.45 (qd, *J* = 6.5, 1.3 Hz, 1H), 4.33 (ddd, *J* = 12.6, 4.8, 2.9 Hz, 1H), 2.41 (td, *J* = 13.1, 3.4 Hz, 1H), 2.23 (ddt, *J* = 13.4, 4.9, 1.5 Hz, 1H), 1.48 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.02 – 0.95 (m, 2H), 0.89 (ddt, *J* = 7.2, 5.0, 2.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.0, 135.0, 133.6, 132.2, 131.2, 131.1, 130.1, 129.4, 128.7, 127.5, 124.4, 99.0, 92.6, 75.3, 70.3, 68.5, 55.0, 29.0, 17.0, 9.1, 0.7. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.11 (m, 2H), 8.02 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.56 – 7.41 (m, 4H), 7.33 (td, *J* = 7.6, 1.5 Hz, 1H), 6.13 – 6.04 (m, 1H), 5.42 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.97 (qd, *J* = 6.4, 1.2 Hz, 1H), 3.82 (ddd, *J* = 12.0, 7.0, 3.2 Hz, 1H), 2.31 (td, *J* = 8.0, 7.4, 2.6 Hz, 2H), 1.59 – 1.47 (m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.02 – 0.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.3, 134.4, 133.6, 132.3, 130.9, 130.5, 130.1, 129.3, 128.6, 127.1, 125.1, 99.9, 92.8, 74.5, 71.8, 69.3, 57.8, 30.4, 16.8, 8.9, 0.7. HRMS: $[M + Na]^+$ calculated for $C_{25}H_{23}N_3O_5Na$: 468.1535; found 468.1537.

o-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-tert-butyldimethylsilyl-L-fucopyranoside (24)



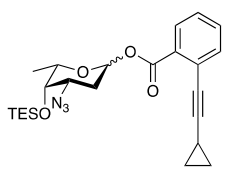
To a solution of **21** (483 mg, 1.27 mmol) in MeCN/H_2O (22 mL, 10:1 v/v) was added *N*-iodosuccinimide (357 mg, 1.59 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated in vacuo to yield the lactol. To a solution of this in DCM (6.4 mL) were added DIPEA (0.65 mL, 3.6 mmol, 1.8 eq), DMAP (153 mg, 1.27 mmol, 1 eq), EDCI·HCl (511 mg, 2.67 mmol, 3.2 eq) and freshly saponified o-cyclopropylethynylbenzoic acid **20** (763 mg, 3.81 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 – 10:90 EtOAc:pentane) gave the title compound as a thick clear oil (248 mg, 0.544 mmol, β only, 43% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 7.9, 1.4 Hz, 1H), 7.48 (dd, J = 7.8, 1.4 Hz, 1H), 7.42 (td, J = 7.6, 1.4 Hz, 1H), 7.37 – 7.25 (m, 1H), 5.96 (dd, J = 9.7, 2.4 Hz, 1H), 3.65 (qd, J = 6.4, 1.1 Hz, 1H), 3.61 (dd, J = 2.6, 1.2 Hz, 1H), 3.56 (ddd, J = 12.5, 4.2, 2.6 Hz, 1H), 2.25 (td, J = 12.0, 9.8 Hz, 1H), 2.09 (dddd, J = 11.7, 4.3, 2.4, 0.9 Hz, 1H), 1.58 – 1.46 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 0.97 (s, 10H), 0.90 – 0.87 (m, 4H), 0.20 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 134.3, 132.1, 130.9, 130.8, 127.1, 125.1, 99.8, 93.2, 74.6, 73.3, 69.7, 60.0, 29.1, 26.2, 18.5, 17.8, 8.9, 0.7, -4.0, -4.4. HRMS: $[M + Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$; 478.21325; found 478.21286.

Silver(II) bis-(hydrogen dipicolinate) monohydrate [46]



To a suspension of $AgNO_3$ (10.1 g, 60.0 mmol) in H_2O (3 L) was added dipicolinic acid (20.0 g, 120 mmol, 2 eq). Potassium persulfate (81.0 g, 300 mmol, 5 eq) was added over the course of 2h and the reaction mixture was stirred for 2 days. The black precipitate was filtered off, washed with H_2O and dried high vacuum to afford the title compound as a black solid (25.8 g, 56.0 mmol, 94%).

***o*-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (25)**

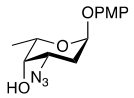


Method 1: To a solution of **22** (778 mg, 2.05 mmol) in MeCN/H_2O (35 mL, 10:1 v/v) was added *N*-iodosuccinimide (540 mg, 2.56 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated in vacuo to yield the lactol. To a solution of this in DCM (4.6 mL) were added DIPEA (1.3 mL, 7.2 mmol, 3.6 eq), DMAP (270 mg, 2.05 mmol, 1 eq), EDCI·HCl (845 mg, 4.42 mmol, 2.15 eq) and freshly saponified o-cyclopropylethynylbenzoic acid **20** (1.32 g, 6.6 mmol, 3.2 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 (1:99 - 2:98 EtOAc:pentane) gave the title compound as a white solid (191 mg, 0.42 mmol, β only, 20% over 2 steps).

Method 2: To a solution of **27** (583 mg, 1.48 mmol) in MeCN/H_2O (1:1 v/v, 80 mL) were added NaOAc (1.21 g, 14.8 mmol, 10 eq) and $Ag(DPAH)_2$ (2.71 g, 5.92 mmol, 4 eq) consecutively at 0°C. After stirring for 3 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. (* Column chromatography of the intermediate hemiacetals resulting from silver(I)-mediated deprotection is advised, as residual silver salts effecting the cyclisation of alkynylbenzoic acids and esters was observed)

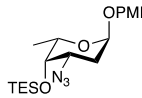
To a solution of the above hemiacetal in DCM (15 mL) were then added DMAP (183 mg, 1.48 mmol, 1 eq), DIPEA (1.16 mL, 6.67 mmol, 4.5 eq), EDCI·HCl (905 mg, 4.74 mmol, 3.2 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (827 mg, 4.44 mmol, 3 eq) and the mixture was stirred overnight. 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 (1.5:98.5) EtOAc:pentane and consecutive size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) gave the title compound as a white solid (507 mg, 1.11 mmol, 75%, 1:5.5 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.35 – 7.25 (m, 1H), 5.95 (dd, *J* = 9.7, 2.1 Hz, 1H), 3.70 – 3.52 (m, 3H), 2.25 (td, *J* = 12.0, 9.9 Hz, 1H), 2.08 (dt, *J* = 12.3, 3.5 Hz, 1H), 1.50 (h, *J* = 6.6 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.83 (m, 4H), 0.71 (q, *J* = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 148.4, 134.2, 132.0, 130.9, 130.7, 127.0, 125.0, 122.6, 99.8, 93.1, 73.1, 69.8, 60.0, 28.9, 17.4, 8.9, 7.1, 5.2, 0.7. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.37 (s, 1H), 6.54 (d, *J* = 11.2 Hz, 1H), 4.17 – 4.01 (m, 1H), 3.76 (s, 1H), 2.36 (ddd, *J* = 12.9, 9.8, 3.4 Hz, 1H), 2.02 (dd, *J* = 12.6, 3.9 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 2H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.83 (m, 4H), 0.71 (q, *J* = 7.6 Hz, 6H). HRMS: $[M + Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.21325; found 478.21286. IR (thin film, cm^{-1}): 2989, 2958, 2910, 2878, 2362, 2231, 2095 (N_3), 1724 (C=O), 1285, 1239.

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (26)**



15 (19.2 g, 59.8 mmol) was dissolved in MeOH (300 mL), to which NaOMe (650 mg, 12.0 mmol, 0.2 eq) was added. After stirring overnight, it was neutralized by addition of acetic acid and concentrated *in vacuo*. Column chromatography (15:85 - 30:70 EtOAc:pentane) gave the title compound as a light yellow solid (15.00 g, 53.7 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.92 (m, 2H), 6.92 – 6.79 (m, 2H), 5.55 (d, *J* = 3.0 Hz, 1H), 4.06 (q, *J* = 5.1 Hz, 1H), 4.01 (ddd, *J* = 12.3, 5.1, 2.8 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 3.1 Hz, 1H), 2.21 (td, *J* = 12.7, 3.6 Hz, 1H), 2.11 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.03 (d, *J* = 4.3 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 150.8, 117.6, 114.7, 96.2, 76.8, 69.8, 66.7, 57.1, 55.8, 29.0, 16.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4Na$; 302.1111; found 302.1118.

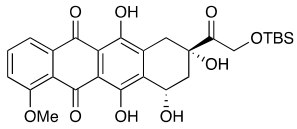
***p*-Methoxyphenyl-3-azido-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (27)**



To a solution of **26** (612 mg, 2.19 mmol) in DMF (3.7 mL) were added pyridine (0.53 mL, 6.6 mmol, 3 eq) and triethylsilyl triflate (0.89 mL, 3.9 mmol, 1.8 eq) at 0°C and the mixture was allowed to warm up to room temperature over 3 hours. It was then diluted with EtOAc and washed with H_2O thrice. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (pentane – 5:95 EtOAc:pentane) gave the title compound as a yellow oil (862 mg, 2.19 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 4.04 (d, *J* =

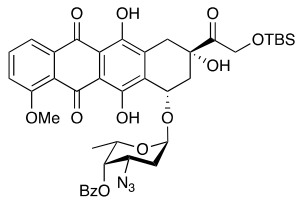
11.5 Hz, 1H), 3.94 (q, *J* = 6.3 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 1H), 2.28 (t, *J* = 12.5 Hz, 1H), 2.01 (d, *J* = 10.9 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.07 – 0.91 (m, 9H), 0.80 – 0.62 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.0, 117.6, 114.7, 96.4, 76.9, 70.8, 67.9, 57.6, 55.8, 28.8, 17.6, 7.2, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.19760; found 416.19727.

14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (29)[40]



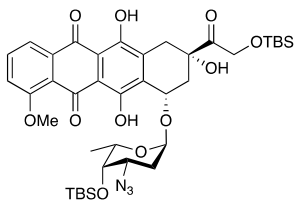
Commercially available doxorubicin hydrochloride (**1a**) (1.20 g, 2.07 mmol) was dissolved in 0.2M aq. HCl (120 mL) and heated to 90 °C. After stirring for 1.5 hours, the resulting solution was cooled to 0 °C, filtered and the filter was rinsed with MeOH, acetone and $CHCl_3$. This was combined with the filter residu and co-evaporated thrice with toluene to yield doxorubicinone **28**. This was then dissolved in DMF (10 mL), whereupon imidazole (366 mg, 5.38 mmol, 2.6 eq) and *tert*-butyldimethylsilyl chloride (315 mg, 2.09 mmol, 1.01 eq) were added consecutively. After stirring for 2.5 hours, additional imidazole (366 mg, 5.38 mmol, 2.6 eq) and *tert*-butyldimethylsilyl chloride (315 mg, 2.09 mmol, 1.01 eq) were added and stirring commenced for 30 minutes. The resulting solution was then diluted with DCM and the organic layer successively washed once with 1M aq. HCl and four times with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (10:90 – 100:0 acetone:toluene) afforded the title compound as a dark red solid (1.06 g, 2.01 mmol, 97% over 2 steps). Spectral data was in accordance with that of literary precedence.[40]

7-[3-Azido-4-*O*-benzoyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (30)



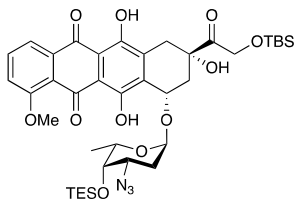
Prepared according to General Procedure A using donor **23** (α and/or β) and 14-*O*-TBS-doxorubicinone **29** (1-1.5 eq) at the desired temperature to give after column chromatography (10:90 EtOAc:pentane - 3:97 acetone:toluene) the title compound as a red solid. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.05 (s, 1H), 13.29 (s, 1H), 8.06 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.87 – 7.75 (m, 1H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.70 (d, *J* = 3.6 Hz, 1H), 5.44 (s, 1H), 5.36 – 5.30 (m, 1H), 4.89 (d, *J* = 1.6 Hz, 2H), 4.37 (s, 1H), 4.28 (q, *J* = 6.4 Hz, 1H), 4.10 (s, 3H), 3.83 (dt, *J* = 12.7, 4.2 Hz, 1H), 3.29 – 3.18 (m, 1H), 3.06 (d, *J* = 18.8 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.29 – 2.16 (m, 2H), 2.04 (dd, *J* = 13.2, 5.1 Hz, 1H), 1.31 – 1.20 (m, 3H), 0.96 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 187.4, 186.9, 161.2, 156.4, 155.9, 136.0, 135.7, 134.1, 133.6, 129.5, 129.4, 129.3, 120.0, 118.6, 111.8, 111.6, 100.8, 70.4, 70.2, 66.8, 66.7, 56.9, 54.9, 35.8, 34.1, 29.8, 26.0, 17.0. HRMS: $[M + Na]^+$ calculated for $C_{40}H_{45}N_3O_{12}SiNa$ 810.26702; found 810.2675.

7-[3-Azido-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (31)



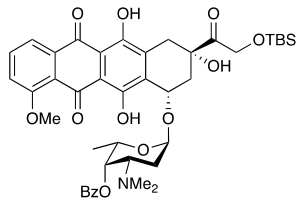
Prepared according to General Procedure A using donor **24** (90 mg, 0.198 mmol) and 14-*O*-TBS-doxorubicinone **29** (158 mg, 0.299 mmol, 1.5 eq) at RT to give after column chromatography (5:95 EtOAc:pentane – 2:98 - 20:80 acetone:toluene) the title compound as a red solid (125 mg, 0.157 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.15 (s, 1H), 7.98 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.22 (dd, *J* = 4.3, 2.1 Hz, 1H), 4.87 (d, *J* = 1.5 Hz, 2H), 4.48 (s, 1H), 4.08 (s, 3H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.68 (d, *J* = 2.4 Hz, 1H), 3.60 (ddd, *J* = 12.8, 4.4, 2.4 Hz, 1H), 3.15 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.88 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.25 – 2.08 (m, 2H), 1.83 (dd, *J* = 12.7, 4.3 Hz, 1H), 1.24 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 18H), 0.19 – 0.11 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.0, 186.7, 161.1, 156.4, 155.7, 135.8, 135.5, 134.0, 133.8, 120.8, 119.9, 118.6, 111.5, 111.4, 101.0, 70.4, 70.1, 68.4, 66.7, 57.3, 56.8, 35.6, 33.9, 28.4, 26.1, 26.0, 18.7, 18.5, 17.9, -4.1, -4.3, -5.3. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.32673; found 820.32770.

7-[3-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (32)



Prepared according to General Procedure A using donor **25** (191 mg, 0.419 mmol) and 14-O-TBS-doxorubicinone **29** (369 mg, 0.698 mmol, 1.67 eq) at RT to give after column chromatography (10:90 EtOAc:pentane and then 3:97 acetone:toluene) the title compound as a red solid (246 mg, 0.308 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 13.25 (s, 1H), 8.11 – 7.95 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.33 – 5.22 (m, 1H), 4.88 (d, *J* = 1.9 Hz, 2H), 4.50 (s, 1H), 4.09 (s, 3H), 3.95 (q, *J* = 6.4 Hz, 1H), 3.69 (s, 1H), 3.62 (ddd, *J* = 12.7, 4.2, 2.4 Hz, 1H), 3.22 (dd, *J* = 18.9, 1.5 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.32 (d, *J* = 14.8 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.82 (dd, *J* = 12.7, 4.3 Hz, 1H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.05 – 0.91 (m, 18H), 0.77 – 0.66 (m, 6H), 0.14 (d, *J* = 1.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.2, 161.2, 156.4, 155.9, 135.9, 135.6, 133.9, 121.0, 111.5, 101.0, 70.6, 70.0, 68.3, 66.8, 57.3, 56.8, 35.7, 34.0, 28.4, 26.0, 17.6, 7.1, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.32673; found 820.32770.

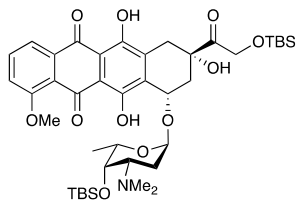
7-[3-Dimethylamino-4-*O*-benzoyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (33)



To a solution of **30** (20.4 mg, 25.9 µmol) in THF/H_2O (1.8 mL, 10:1 v/v) was added polymer-supported triphenylphosphine (3 mmol/g loading, 26 mg, 52 µmol, 2 eq) and the mixture was stirred overnight. Then, additional polymer-supported triphenylphosphine (26 mg, 52 µmol, 2 eq) was added and the mixture was allowed to stir another night. It was then filtered off and concentrated *in vacuo*. Column chromatography (20:80 acetone:toluene) gave the amine as a red solid (9.5 mg, 0.013 mmol, 48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.00 (s, 1H), 13.28 (s, 1H), 8.15 – 8.10 (m, 2H), 8.06 – 8.02 (m, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 5.34 (d, *J* = 3.3 Hz, 1H), 5.28 (d, *J* = 2.7 Hz, 1H), 5.00 – 4.83 (m, 2H), 4.26 (q, *J* = 6.4 Hz, 1H), 4.19 – 3.99 (m, 4H), 3.25 (dd, *J* = 18.8, 1.9 Hz, 2H), 3.04 (d, *J* = 18.9 Hz, 1H), 2.39 – 2.13 (m, 4H), 1.30 – 1.19 (m, 3H), 0.96 (s, 9H), 0.15 (s, 6H). HRMS: $[M + Na]^+$ calculated for $C_{40}H_{47}NO_{12}SiNa$ 762.2946; found 762.2946.

The above amine (9.5 mg, 12.5 µmol) was dissolved in EtOH (3.0 mL) and 37% aq. CH_2O (28 µL, 344 µmol, 27.5 eq) by sonication for 30 minutes. To this solution was then added $NaBH(OAc)_3$ (8.74 mg, 41.3 µmol, 1.95 eq) and it was stirred for 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95 – 30:70 acetone:toluene) gave the title compound as a red solid (5.2 mg, 6.58 µmol, 53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.01 (s, 1H), 13.29 (s, 1H), 8.13 – 8.09 (m, 2H), 8.05 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.62 – 7.56 (m, 1H), 7.47 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.69 (d, *J* = 3.7 Hz, 1H), 5.53 (s, 1H), 5.33 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 2H), 4.68 (s, 1H), 4.20 (q, *J* = 6.5 Hz, 1H), 4.10 (s, 3H), 3.25 (dd, *J* = 19.0, 1.9 Hz, 1H), 3.05 (d, *J* = 18.9 Hz, 1H), 2.50 (d, *J* = 12.4 Hz, 1H), 2.37 (dd, *J* = 14.9, 2.3 Hz, 1H), 2.27 – 2.17 (m, 7H), 2.11 (td, *J* = 13.0, 4.1 Hz, 1H), 1.96 (dd, *J* = 13.1, 4.2 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 187.3, 186.9, 166.4, 161.2, 156.6, 156.0, 135.9, 135.7, 134.2, 134.1, 133.3, 130.1, 128.6, 121.1, 120.0, 118.5, 111.6, 111.5, 101.7, 70.2, 69.3, 67.5, 66.8, 59.4, 56.9, 42.7, 35.8, 34.1, 29.6, 26.0, 17.3. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{51}NO_{12}SiNa$ 790.3259; found 790.3256.

7-[3-Dimethylamino-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (34)

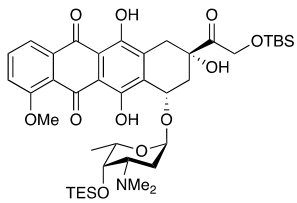


To a solution of **31** (115 mg, 0.144 mmol) in THF/H_2O (11 mL, 10:1 v/v) was added polymer-supported triphenylphosphine (3 mmol/g loading, 480 mg, 1.44 mmol, 10 eq) and the mixture was stirred overnight at 50°C. It was then filtered off and concentrated *in vacuo*. Column chromatography (2:98 – 100:0 acetone:toluene) gave the amine as a red solid (82.8 mg, 0.107 mmol, 75%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.47 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.19 (m, 1H), 4.89 (d, *J* = 2.0 Hz, 2H), 4.78 (s, 1H), 4.09 (s, 3H), 3.97 (q,

J = 6.5 Hz, 1H), 3.60 (d, *J* = 2.3 Hz, 1H), 3.18 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.96 (d, *J* = 18.9 Hz, 1H), 2.90 (dt, *J* = 12.0, 3.4 Hz, 1H), 2.33 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.13 (dd, *J* = 14.7, 4.0 Hz, 1H), 1.83 (td, *J* = 12.8, 4.0 Hz, 1H), 1.60 (dd, *J* = 13.0, 4.3 Hz, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 3.0 Hz, 18H), 0.14 (dd, *J* = 5.4, 1.5 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 187.1, 186.7, 161.1, 156.5, 155.9, 135.8, 135.6, 134.3, 134.1, 121.0, 119.9, 118.5, 111.5, 111.3, 101.6, 73.4, 69.6, 68.8, 66.7, 56.8, 47.7, 35.6, 34.1, 34.0, 26.3, 26.0, 18.7, 18.6, 18.2, -3.4, -3.6, -5.2, -5.3.

The above amine (32.9 mg, 42.6 µmol) was dissolved in a stock solution of ethanolic formaldehyde (2.1 mL, prepared by dissolving 31.7 µL of 37% aqueous formaldehyde in 21 mL EtOH). To this solution was then added $NaBH(OAc)_3$ (15.4 mg, 41.3 µmol, 1.7 eq) and it was then stirred for 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (4:96 acetone:toluene) gave the title compound as a red solid (15.3 mg, 19.1 µmol, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.29 (s, 1H), 8.03 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.26 (dd, *J* = 4.0, 2.1 Hz, 1H), 4.91 (d, *J* = 1.6 Hz, 2H), 4.86 (s, 1H), 4.09 (s, 3H), 3.90 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 1H), 3.21 (dd, *J* = 18.9, 1.9 Hz, 1H), 3.03 (d, *J* = 18.9 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.13 (d, *J* = 6.5 Hz, 7H), 1.98 (d, *J* = 15.4 Hz, 2H), 1.74 – 1.54 (m, 3H), 1.25 – 1.23 (m, 3H), 0.95 (d, *J* = 10.0 Hz, 18H), 0.18 – 0.04 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 187.3, 186.8, 161.2, 156.7, 156.1, 135.8, 135.7, 134.2, 119.9, 118.5, 111.5, 111.4, 101.9, 69.8, 69.6, 69.2, 66.8, 56.8, 42.9, 35.7, 34.0, 29.8, 26.3, 26.0, 18.9, 18.7, 18.3, -5.1, -5.2. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.38559; found 800.38605.

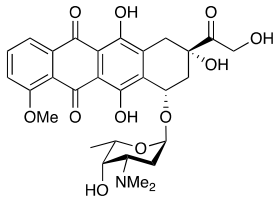
7-[3-Dimethylamino-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (35)



To a solution of **32** (620 mg, 0.777 mmol) in THF/H_2O (10:1 v/v, 56 mL) was added polymer-supported triphenylphosphine (2.59 g, 7.8 mmol, 10 eq) and the resulting mixture was stirred at 50 °C for 3 days. It was then filtered, concentrated *in vacuo* and coevaporated with toluene thrice. Column chromatography (6:94 acetone:toluene) gave the free amine as a red solid (451 mg, 0.584 mmol, 75%) which was used immediately in the next step.

The above free amine (51 mg, 66 µmol) was then dissolved in EtOH (4.2 mL) and 37% aq. CH_2O (147 µL, 1.82 mmol, 27.5 eq) by sonication for 30 minutes. To this solution was then added $NaBH(OAc)_3$ (27.3 mg, 0.129 mmol, 1.95 eq) and it was then stirred for 1.5 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95 – 20:80 acetone:toluene) gave the title compound as a red solid (44 mg, 55 µmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.92 (s, 1H), 13.27 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 3.4 Hz, 1H), 5.25 (s, 1H), 4.91 (d, *J* = 3.0 Hz, 2H), 4.86 (s, 2H), 4.09 (s, 3H), 3.88 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 1H), 3.20 (d, *J* = 18.9 Hz, 1H), 3.01 (d, *J* = 18.9 Hz, 1H), 2.36 (d, *J* = 14.6 Hz, 1H), 2.14 (s, 6H), 2.11 – 2.07 (m, 1H), 1.97 (td, *J* = 12.9, 4.0 Hz, 1H), 1.67 (d, *J* = 9.6 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.07 – 0.77 (m, 18H), 0.77 – 0.52 (m, 6H), 0.14 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) 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, 101.8, 69.7, 69.6, 69.1, 66.8, 61.4, 42.9, 35.7, 34.0, 28.0, 26.0, 18.7, 18.0, 7.3, 5.6. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.38559; found 800.38605.

***N,N*-dimethyldoxorubicin (3a)**



To a solution of **35** (81 mg, 0.10 mmol) in THF (7 mL) and pyridine (3.5 mL) at 0 °C was added HF·pyr complex (70 wt% HF, 420 µL). The mixture was stirred for 30 minutes at that temperature, after which it was allowed to stir for 3 hours 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 THF was removed from the filtrate *in vacuo*. The crude product, still dissolved in pyridine, was subjected to column chromatography on neutral silica (DCM – 80:20 MeOH:DCM) to yield *N,N*-dimethyldoxorubicin (**2**) as a red solid (38 mg, 67 µmol, 66%). ^{1}H NMR (500 MHz, MeOD) δ 7.66 (t, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.42 (d, *J* = 3.4 Hz, 1H), 4.95 (s, 1H), 4.80 – 4.65 (m, 1H), 4.14 (q, *J* = 6.5 Hz, 1H), 3.92 (s, 2H), 3.83 (d, *J* = 6.0 Hz, 1H), 2.94 (d, *J* = 18.1 Hz, 1H), 2.68 (d, *J* = 18.3 Hz, 1H), 2.62 (d, *J* = 11.9 Hz, 1H), 2.42 (s, 3H), 2.29 (t, *J* = 13.1 Hz, 1H), 2.10

– 2.02 (m, 2H), 1.94 (td, *J* = 13.1, 4.1 Hz, 1H), 1.30 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, MeOD) δ 214.43, 187.37, 162.20, 157.08, 155.85, 137.03, 135.86, 135.40, 134.85, 121.03, 120.34, 112.11, 111.87, 102.06, 77.41, 70.94, 68.89, 67.80, 65.71, 62.28, 57.00, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 42.40, 36.86, 33.88, 28.63, 17.29. HRMS: $[M + H]^+$ calculated for $C_{29}H_{34}NO_{11}$ 572.21249; found 572.21246.

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