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

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Chapter 6

Summary and future prospects

Since its isolation in 1969, the anthracycline doxorubicin (**1**) has become one of the most oft-used anti-cancer drugs, this in spite of its cardiotoxicity. More than a thousand analogs have been isolated from nature and prepared by organic synthesis, but the vast majority of these compounds did not outperform doxorubicin in terms of efficacy and cardiotoxicity. The exception appeared to be aclarubicin (**2**), which is much less cardiotoxic, however this close structural analog of doxorubicin is currently not in clinical use outside China and Japan. It has recently been shown that both anthracyclines **1** and **2** are able to induce eviction of histones from chromatin, and it has been hypothesized this is the main mode of action behind antitumor activity.

The work described in this Thesis entails the synthesis of anthracyclines inspired by the structures of doxorubicin and aclarubicin, with the aim to establish structure-activity relationships for these compounds. To this end, hybrid structures featuring structural elements of both anthracyclines have been prepared, as well as regioisomers, stereoisomers and other derivatives of doxorubicin. These should ultimately allow for the design of anthracyclines with reduced cardiotoxicity and better efficacy.

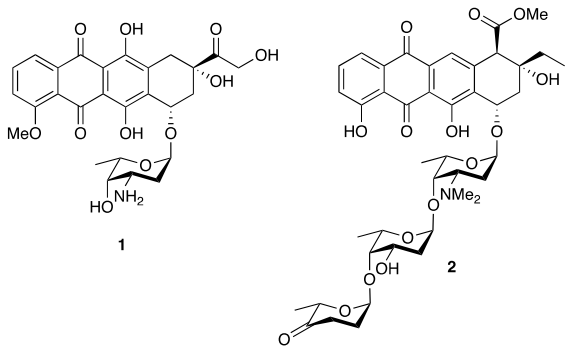


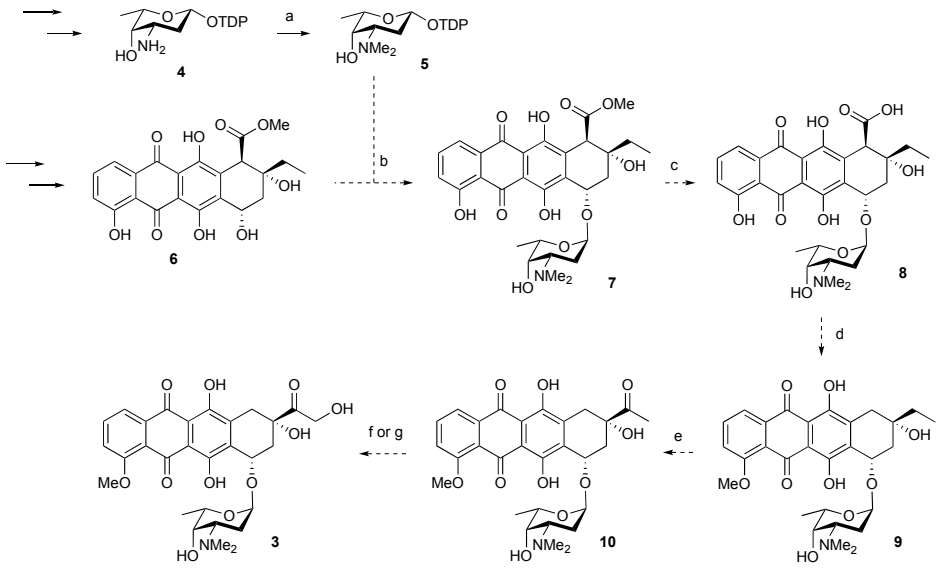
Figure 1. Structures of doxorubicin (**1**) and aclarubicin (**2**).

Chapter 1 presents a historical overview of the discovery of the first anthracyclines and their use in cancer treatment, and discusses some relevant routes of synthesis of 2-deoxyglycosides and anthracyclines.

Studies towards the synthesis of *N,N*-dimethyldoxorubicin are described in **Chapter 2**. This hybrid anthracycline combines structural elements from doxorubicin and aclarubicin. Since direct reductive alkylation of the amine in (semi-protected) doxorubicin led to undesired reduction of the ketone functionality, a new strategy had to be developed that is based on the glycosylation of an appropriately protected tetracycline aglycon with an orthogonally protected *ortho*-alkynylbenzoate glycosyl donor using the gold(I)-glycosylation chemistry developed by the group of Yu. This strategy proved fruitful, and the gold-promoted glycosylation proceeded with excellent α-stereoselectivity. The choice for a 4'-triethylsilyl protecting group facilitated the reductive alkylation whilst leaving the ketone intact, and final deprotection yielded *N,N*-dimethyldoxorubicin.

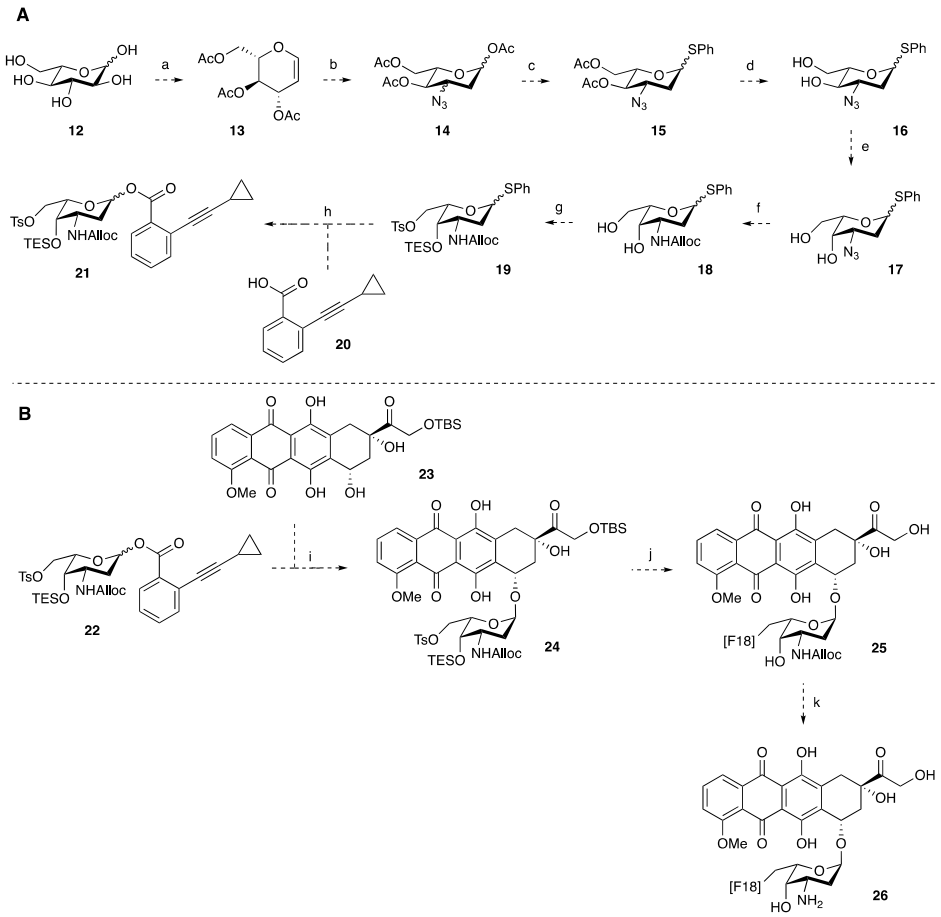
Although a large variety of anthracyclines are readily available through organic synthesis, their eventual use as anti-cancer drugs would require much larger quantities than those that can be generated through the here-described synthetic routes at competitive costs. Clinical doxorubicin is currently prepared through fermentation by a *Streptomyces peucetius* mutant, followed by chemical 14-hydroxylation. A chemo-enzymatic synthesis of *N,N*-dimethyldoxorubicin could also be envisaged, as outlined in Scheme 1. The combination of two or more biosynthetic pathways has been used in combinatorial biosynthesis approaches to obtain compounds that are not enzymatically produced or generated in minimal amounts. This concept has been used in the production of modified complex polyketides[1] and has already been applied to *S. galilaeus.*[2] In the biosynthesis of aclarubicin by *S. galilaeus*, dimethylation of the amine in TDP-daunosamine is performed by the aminomethylase enzyme *aknX2*.[3] Expression of this enzyme and the corresponding rhodosaminyl transferase into *S. peucetius* could enable the biosynthesis of *N,N*-dimethyldoxorubicin. In a similar manner, additional doxorubicin and aclarubicin inspired structures as described in Chapter 3 that could be prepared through manipulation of anthracycline biosynthesis machineries.

It would also be of interest to study the biodistribution of anthracyclines in the body using PET imaging. This has been done in the past using [18F]-labeled micelles[5,6] and nanoparticles[7] carrying doxorubicin as the toxic payload, but not on the stand alone drugs. As 14-fluorinated daunorubicin was shown to be a tenfold less potent than its parent compound,[8] [18F]-labelled doxorubicin (**11**) might be a better alternative. This compound would bear an [18F]-moiety on the 6-position of the sugar. 6',6',6'-Trifluoro-hydroxyrubicin has earlier been shown to exhibit higher potency against murine leukemia P388 than its parent compound,[9] and the modification in **11** is therefore expected to be well tolerated in terms of activity.



Scheme 1. Proposed biosynthesis of *N,N*-dimethyldoxorubicin (**3**) by mutant *S. peucetius*. (a) Dimethylation of TDP-daunosamine by *AknX2*; (b) Glycosylation on C-7 by rhodosaminyl transferase; (c) Demethylation of the acid at C-10 (*DnrP*); (d) Decarboxylation and methylation of the C-4 phenol (*DnrK*); (e) Oxidation at C-13 (*DoxA*); (f) Chemical hydroxylation of C-14 by *i.* Bromination of C-14; *ii.* Hydrolysis; (g) Enzymatic hydroxylation at C-14 by enzymatic overexpression of *DoxA*, as in mutant ATCC 27952.[4]

The synthesis of the envisaged 6-hydroxydaunosaminyl donor **21** would commence from L-glucose **12** in Scheme 2A, which can easily be obtained in 5 steps from cheap and commercially available sodium α-D-glucoheptonate.[10] This would then be converted to L-glucal **13** by means of peracetylation, anomeric bromination and Zn/Cu-mediated elimination of the 1-bromide and 2-*O*-acetate. Using the chemistry described in Chapter 2, mixture of azides **14** would be obtained. Installation of an anomeric thiophenyl moiety, followed by deacylation would yield diol **16**. Inversion of the 4-position would be accomplished by triflation of both the 4- and 6-hydroxyl groups, followed by reaction with tetrabutylammonium nitrate to yield *galacto*-conformed diol **17**. The azide would then be switched for an Alloc group, after which tosylation of the primary alcohol and silylation of the secondary alcohol would yield **19**. Silver-mediated hydrolysis of the anomeric thiophenyl group, followed by esterification to *ortho*-cyclopropylethynylbenzoic acid **20** would yield alkynylbenzoate donor 21. Glycosylation under Yu's gold(I)-catalyzed conditions would then give **24** (Scheme 2B). At this stage, treatment with [18F]KF·K_{222} would substitute the tosylate for the desired [18F]-moiety,[11] as well as remove the silyl ethers. Final removal of the Alloc group would yield 6'-[18F]-doxorubicin **11**.

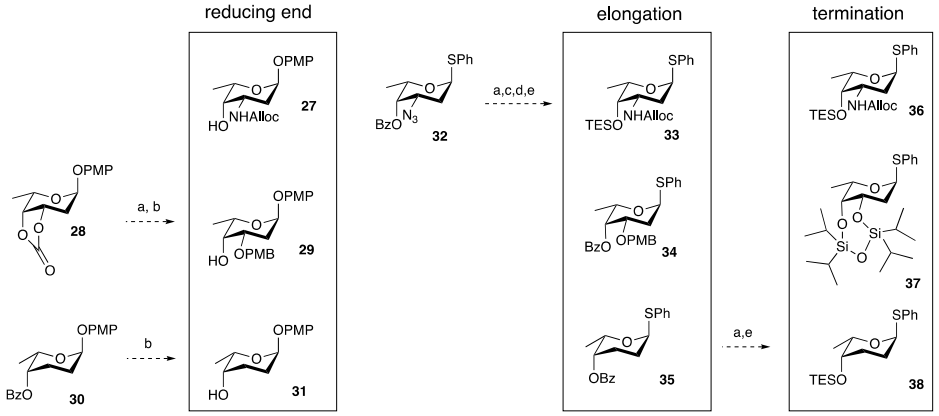


Scheme 2. Proposed synthesis of 6'-[18F]-doxorubicin (**11**). *Reagents and conditions:* (a) *i.* Ac_2O, NaOAc, 140 °C; *ii.* HBr/AcOH, Ac_2O, DCM; *iii.* Zn, AcOH, NaOAc, Ac_2O, $CuSO_4{\cdot}5H_2O$, MeCN; (b) *i.* H_2O, 80 °C, then NaN_3, AcOH; *ii.* Ac_2O, pyr.; (c) thiophenol, $BF_3{\cdot}OEt_2$, DCM, -78 °C to 0 °C; (d) NaOMe, MeOH; (e) *i.* Tf_2O, pyr., DCM, 0°C; *ii.* $TBANO_2$, MeCN; (f) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$; (g) *i.* TsCl, pyr., DCM, -20 °C; then TESOTf, pyr., -20 °C; (h) *i.* $AgNO_3$, 2,6-lutidine, THF/H_2O; *ii.* EDCI·HCl, DIPEA, DMAP, DCM; (i) PPh_3AuNTf_2 (10 mol%), DCM; (j) [18F]KF·K_{222}, K_2CO_3, DMSO; (k) $Pd(PPh_3)_4$, NDMBA, DCM.

Chapter 3 describes the synthesis of a library of nine doxorubicin/aclarubicin hybrid structures, filling the chemical space between these two anthracyclines. The assembly of these compounds relied on the use of Yu's *ortho*-alkynylbenzoate glycosylation method explored in Chapter 2 to construct the α-glycosidic bond between the respective aglycone and mono-/di-/trisaccharide moieties. The relevant di- and trisaccharide donors were assembled by (iterative) α-selective IDCP-mediated glycosylation reactions, and the anthracycline aglycones were obtained from acidic hydrolysis of the parent anthracyclines. Further highlights in these syntheses are the orthogonal removal of the anomeric *p*-methoxyphenolate over the PMB group present

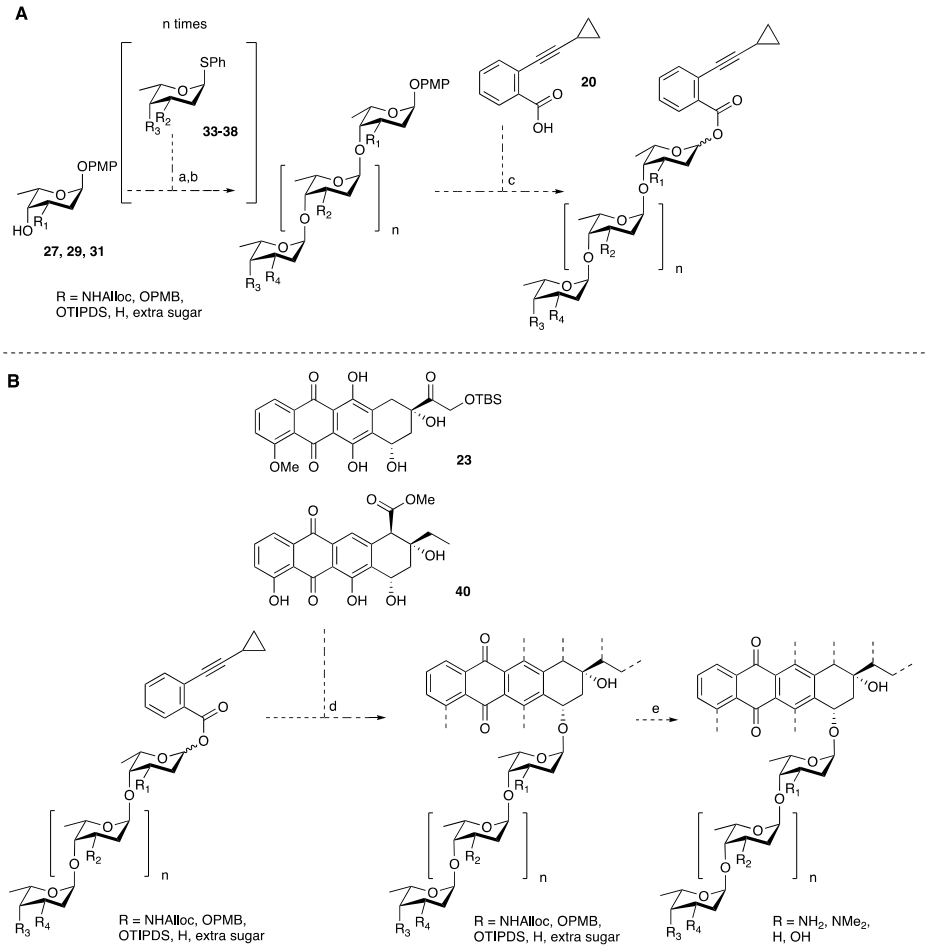
on the oliose moiety and the *post*-glycosylation introduction of the dimethylamine functionality.

It would be of interest to investigate the influence of switching the order of the sugars (rhodosamine, oliose, cinerulose A) in the trisaccharide found in aclarubicin on the biological activities of the resultant compounds. Additionally, longer chains (4 or more sugars) could be envisaged. To this end, nine monosaccharide building blocks are envisaged, as depicted in Scheme 3.



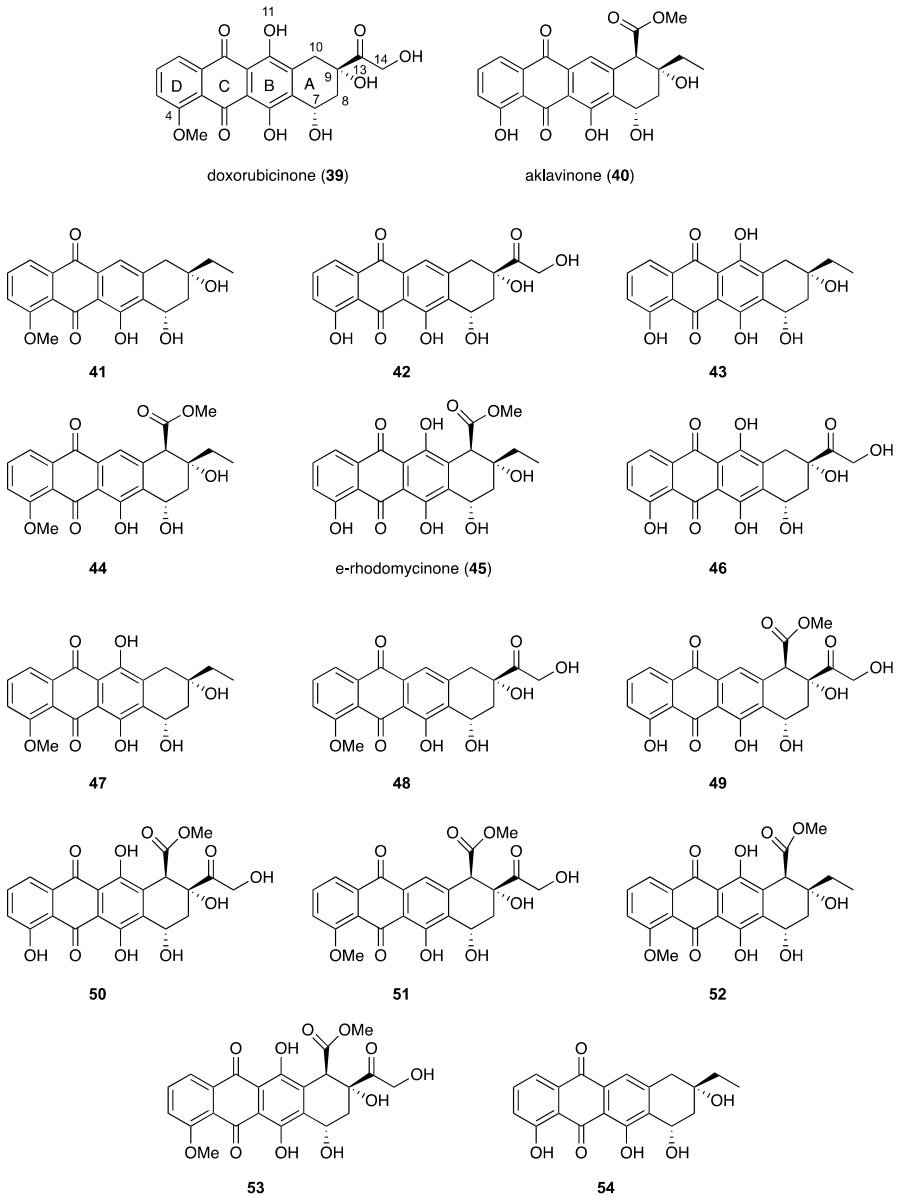
Scheme 3. Building blocks for aclarubicin-inspired sugar chain in different sugar order. *Reagents and conditions:* (a) NaOMe, MeOH; (b) *i.* Bu_2SnO, tol., 100 °C; *ii.* PMB-Cl, TBABr, tol.; (c) PPh_3, THF, H_2O, 50 °C; (d) Alloc-OSu, $NaHCO_3$, THF, H_2O; (e) TESOTf, pyr., DCM.

One of each of the three sugars is designed to be at the reducing end of the protected trisaccharides to give glycosyl acceptors **27**, **29** and **31**. These all feature a *p*-methoxyphenyl group at the reducing end, and a free hydroxyl group on the 4-position. As cinerulose A features a ketone on the 4-position and would not allow for further glycosylation, it is replaced by rhodinose. The three thioglycosides **33**, **34** and **35** serve as donors for elongation of the saccharide chain. They all feature a bulky group on the 4-position that should facilitate α-selective glycosylation. Finally, thioglycosides **36**, **37** and **38** could serve as the end of the chain and are protected with silyl ethers that can be deblocked after glycosylation to the desired aglycone.



Scheme 4. Glycosylations and deprotections for aclarubicin-inspired sugar chain in different sugar order. *Reagents and conditions:* (a) *i.* IDCP, Et_2O, DCE (4:1 v/v); *ii.* NaOMe, MeOH for benzoyl esters, HF·pyridine, pyr. for silyl ethers; c) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM; (d) PPh_3AuNTf_2 (10 mol%), DCM; (e) HF·pyridine, pyr. for silyl ethers; $Pd(PPh_3)_4$, NDMBA, DCM for Alloc groups; DDQ, DCM/pH 7 phosphate buffer for PMB ethers; aq. CH_2O, $NaBH(OAc)_3$, EtOH for demethylation.

As in Chapter 3, iterative IDCP glycosylation and deblocking would then yield the protected saccharides (Scheme 4). The initially chosen acceptor at the reducing end (**27**, **29**, or **33**) can be elongated *n*-times with thioglycoside donors **33**, **34** and **35** and finally terminated with **36**, **37** or **38** to achieve the desired saccharide chain length and composition. Finally, the *p*-methoxyphenolate would be removed oxidatively, followed by esterification to yield the corresponding *ortho*-alkynylbenzoate donors. Glycosylation to the desired aglycone is then followed by global deprotection and, if desired, reductive dimethylation onto the amine to yield the target compounds.

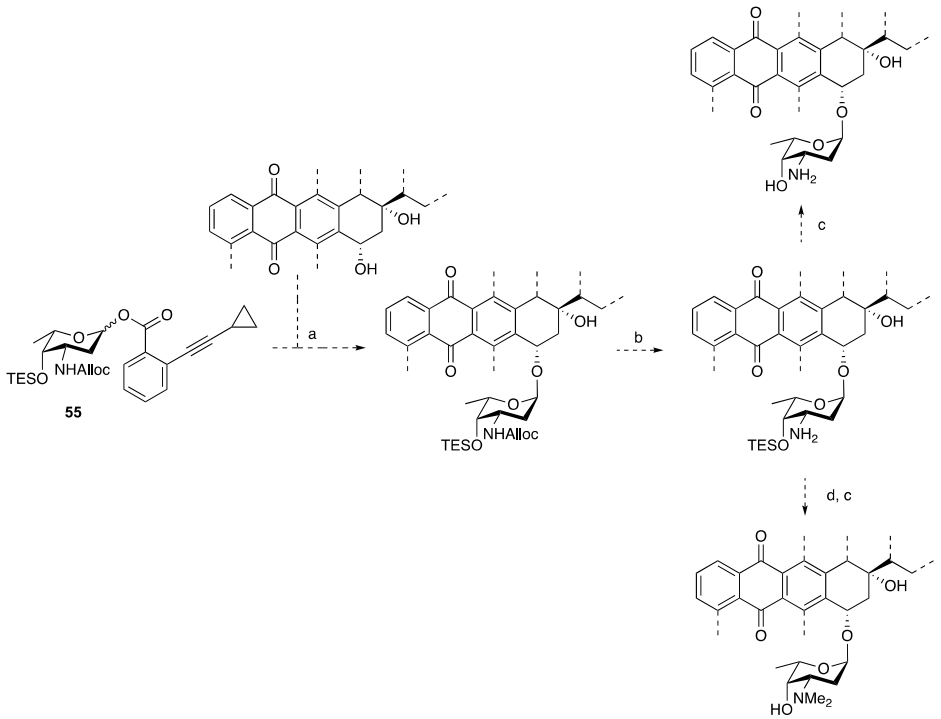


Scheme 5. Doxorubicinone (**39**), aklavinone (**40**) and hybrid aglycones **41-54**, aimed to fill the chemical space between these two anthracyclines.

As Chapter 3 explored the chemical space of the saccharides found in doxorubicin and aclarubicin, it would be of interest to prepare variants differing in their aglycone moieties as well. The chemical differences between doxorubicinone and aklavinone can be divided into 4 mutations: methylation of the 4-phenolate, hydroxylation of the 11-

position, presence/absence of a methyl ester on the 10-position and the oxidation pattern of the 9-ethyl tail. In this manner, 2^4 = 16 aglycones can be envisaged, which are depicted in Scheme 5.

These aglycones would be obtained through (manipulation of) the biosynthetic pathways of known anthracyclines, or chemical derivatization. These aglycones could then be glycosylated to the daunosamine donor described in Chapter 3 (see Scheme 6) to yield the corresponding hybrid anthracyclines. Deprotection of the Alloc group can either be followed by global desilylation, or first be subject to reductive dimethylation and then desilylation to yield the anthraquinone daunosamines or rhodosamines.



Scheme 6. Proposed synthesis of anthracyclines with different aglycones. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM; (b) $Pd(PPh_3)_4$, NDMBA, DCM; (c) HF·pyridine, pyr.; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH.

Chapter 4 describes the synthesis of a series of analogs of doxorubicin that differ in the nature of the functionality at the 3'-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. The latter series were prepared in a single step from doxorubicin,

whereas the other compounds were assembled from the relevant *ortho*-alkynylbenzoate donors and protected doxorubicinone. Rather than preparing the glycosides through deoxygenation and amination of L-fucose or L-rhamnose, certain rare sugars can also be obtained from natural source, a strategy applied for the synthesis of the 3'-methyl-doxorubicins. Methanolysis of vancomycin facilitated the isolation of its sugar moiety vancosamine, which could be appropriately functionalized and appended to the doxorubicinone aglycone.

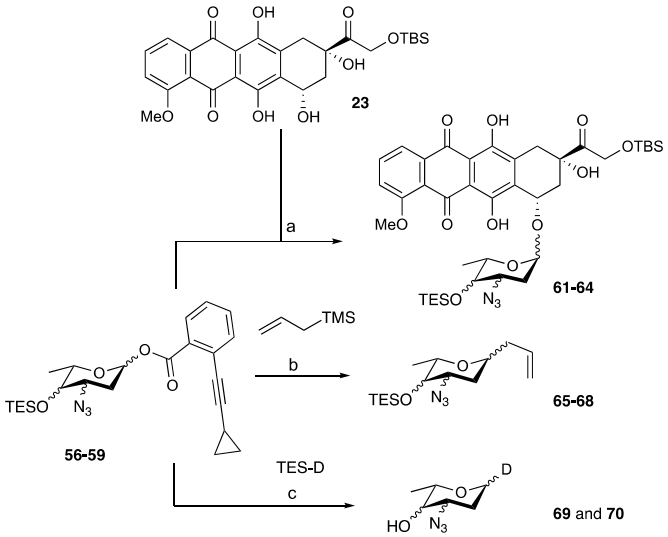
Chapter 5 describes the synthesis of stereo- and regio-isomers within the aminosugar moiety of doxorubicin. Epimers of the 3'- and 4'- position were prepared, along with their *N,N*-dimethylated variants. Additionally, switching the 3'- and 4'-position yielded two *iso*-doxorubicins.

The glycosylations of the aminosugar donors to the doxorubicin aglycone in this Chapter proceeded with varying stereoselectivity, and it would be beneficial to gain further insight into the underlying glycosylation reaction mechanism. To this end, a method by Hansen *et al.* (Figure 2) was applied that allows for direct comparative quantification of the stereoselectivity of the reactive intermediates (oxocarbenium ions) through DFT calculations, as a function of the conformation of these ions.[12–14] Through this computational method, globes are generated which depict the conformational energy landscape (CEL) for the corresponding oxocarbenium ion generated from the glycosyl donor of choice. The energy minima computed in this fashion are then divided between top- and bottom face selective families to give an α:β ratio that can be compared to that obtained in the corresponding chemical glycosylation reactions employing triethylsilane of allyl-TMS as nucleophiles.

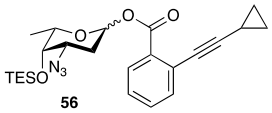
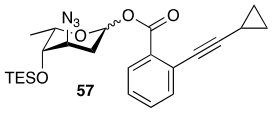
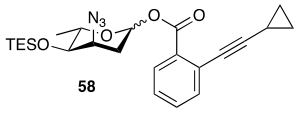
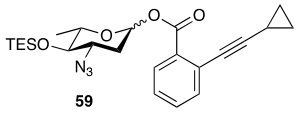
Thus, daunosamine, 3-epidaunosamine, ristosamine and acosamine donors used in Chapter 2 and 5, alkynylbenzoate donors **56**-**59** were prepared and subjected to gold(I)-catalyzed glycosylation to nucleophiles allyltrimethylsilane (allylTMS) and 14-*O*-TBS-doxorubicinone **23**. AllylTMS is a weak nucleophile, that generally does not react following an S_N2-type displacement mechanism.[15,16]

This computational model has not yet been used to probe the influence of (long range) neighboring group participation and therefore the amines in the donors are protected as an azide rather than the Alloc carbamate used in Chapter 5. Furthermore, the TES group was replaced by a TMS group to decrease the required computational costs. The results of the glycosylations performed with these four donors **56-59** as well as the computed stereoselectivities are shown in Table 3.

Table 1. Glycosylation stereoselectivities of *ortho*-alkynylbenzoate donors **56**-**59** to 14-*O*-TBS-doxorubicinone (**23**), allylTMS and TES-D, and *in silico* modelled α:β ratio based on oxocarbenium ion conformations.



Reagents and conditions: (a) 14-*O*-TBS-doxorubicinone (**23**) (1.5 eq), PPh_3AuNTf_2, 0.05M in DCM, RT; **(b)** allylTMS (8 eq), PPh_3AuNTf_2, 0.05M in DCM. The glycosylations with TES-D required stoichiometric amounts of gold catalyst and the resultant products were isolated as their 4-alcohols.

Entry	Donor	Acceptor **23** α:β-ratio (yield)	AllylTMS α:β-ratio (yield)	TES-D α:β-ratio (yield)	*In silico* computed α:β ratio
1	 **56**	>98:2 (79%)	>98:2 (67%)	-	>98:2
2	 **57**	>98:2 (84%)	>98:2 (83%)	-	>98:2
3	 **58**	75:25 (78%)	>98:2 (66%)	93:7 (83%)	83:17
4	 **59**	75:25 (91%)	≥90:10 (60%)	66:34 (78%)	41:59

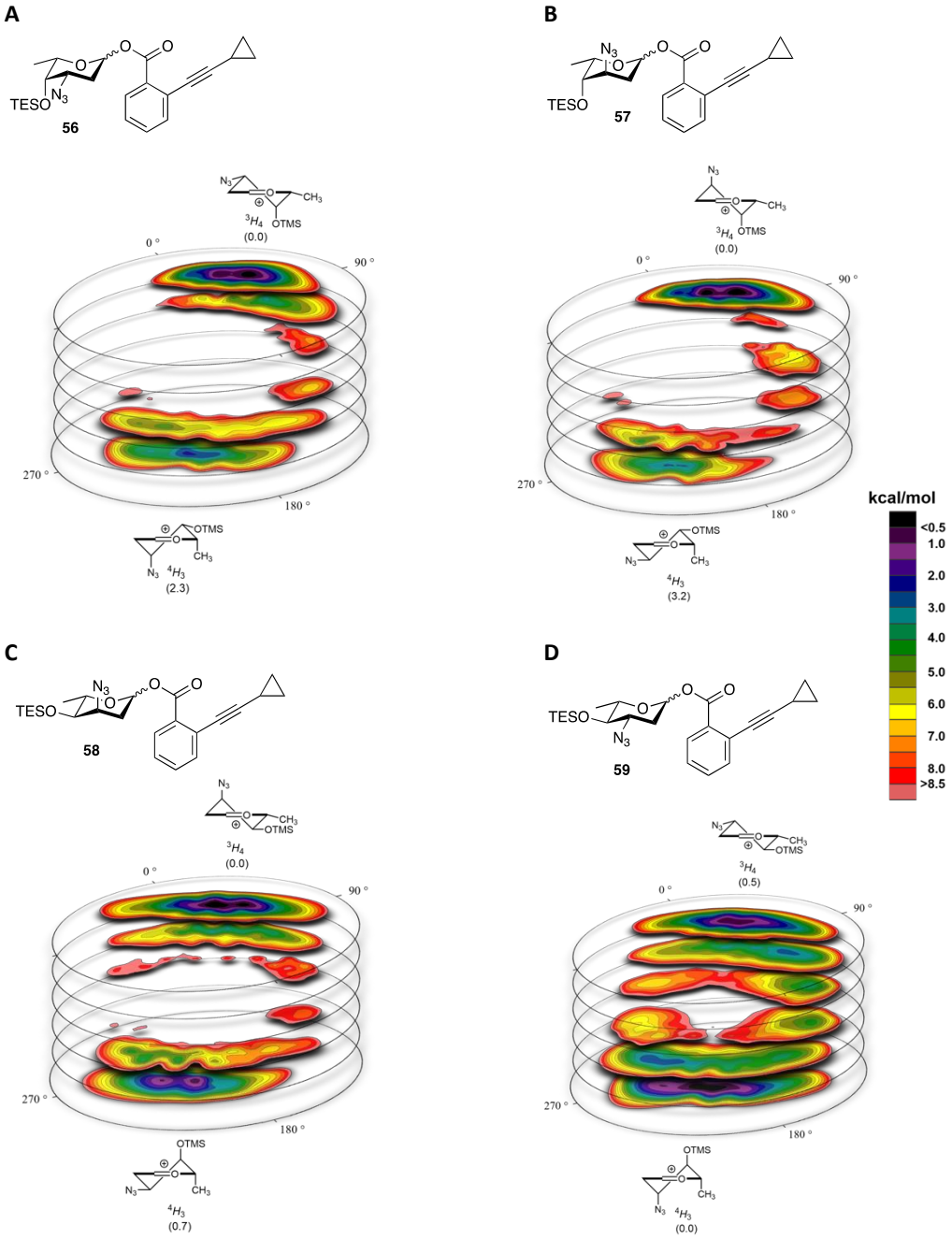


Figure 3. CEL maps of oxocarbenium ions in which the found local minima are indicated with their respective energies. (**A**) CEL map of daunosaminyl donor **56** derived oxocarbenium ions; (**B**) CEL map of 3-*epi*-daunosaminyl donor **57** derived oxocarbenium ions; (**C**) CEL map of ristosaminyl donor **58** derived oxocarbenium ions; (**D**) CEL map of acosaminyl donor **59** derived oxocarbenium ions.

Glycosylation of daunosaminyl donor **56** and 3-*epi*-daunosamine **57** to doxorubicinone-acceptor **23** as well as allylTMS under the agency of PPh_3AuNTf_2 proceeded in excellent stereoselectivity (>98:2). The *in silico* generated CEL maps for the oxocarbenium ions derived from these donors are shown in Figure 3A and 3B. Both feature clear energy minima for the $^3H_4$ oxocarbenium ions, which upon top-side attack yield the corresponding α-glycosides. The computed stereoselectivity predicted by these maps is a >98:2 mixture, in perfect agreement with the experimental glycosylation. Ristosamine donor **58** gave a 75:25 α:β mixture upon glycosylation to acceptor **23**, but proceeded α-selectively when using allylTMS as the acceptor instead. As this discrepancy may be the result of steric factors induced by the weak nucleophile allylTMS, the model glycosylation was also performed using TES-D as the nucleophile to yield a 93:7 mixture. In this case, a stoichiometric amount of gold(I) catalyst was required to drive the reaction to completion and the product was obtained without the silyl ether. The CEL map generated for the ristosaminyl oxocarbenium ions shows two relevant energy minima both for the $^3H_4$ and the $^4H_3$ conformations (0.7 kcal/mol difference in favor of $^3H_4$), predicting a 75:25 α:β mixture. The coupling of acosamine donor **59** to acceptor **23** proceeded with moderate stereoselectivity (3:1 α:β), whereas the coupling to allylTMS gave a 9:1 α:β mixture instead. Conversely, the CEL method gave two distinct energy minima (0.5 kcal/mol difference in favor of $^4H_3$), predicting the addition reaction to be slightly β-selective (41:59). Subjection of this donor to TES-D and a stoichiometric amount of PPh_3AuNTf_2 yielded a 66:34 mixture of anomers. Discrepancy between the ratio as predicted by the CEL method and the selectivities found in the experiment can be attributed to several factors. First, the reactive intermediates generated during gold(I)-mediated glycosylation of *ortho*-alkynylbenzoates are likely not the bare oxocarbenium ions. Furthermore, the relatively high temperature at which these glycosylations were performed (25 °C) may allow S_N2-like pathways to occur.

Overall, it appears that the computational method is able to give an indication of the stereoselectivity obtained in glycosylations with 2,3,6-dideoxy-3-azido alkynylbenzoate donors. It was shown that daunosaminyl- and 3-*epi*-daunosaminyl oxocarbenium ions give 1,5-*trans*-selective glycosylation, in line with the computed ratio, and that ristosaminyl- and acosaminyl are predicted to – and proceed – in an aselective fashion. Furthermore, the *C*-allyl glycosides obtained could be used to prepare more stable counterparts of commonly unstable 2-deoxy *O*-glycosides.

Within the context of regioisomers of doxorubicin, fucosamine-doxorubicinones **71** and **72** were envisaged (Figure 4). In these compounds, the amine function is shifted to the 2-position with respect to doxorubicin. Additionally, elongation of **71** with the terminal disaccharide found in aclarubicin was envisaged to yield trisaccharide **73**.

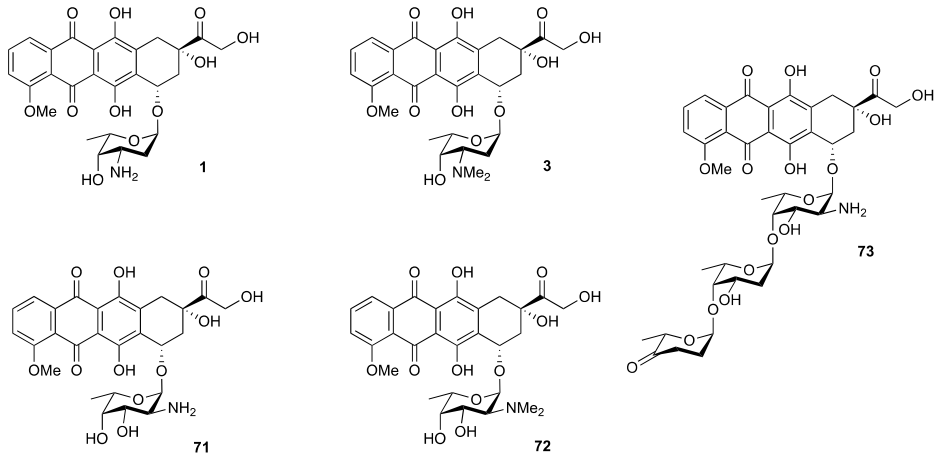
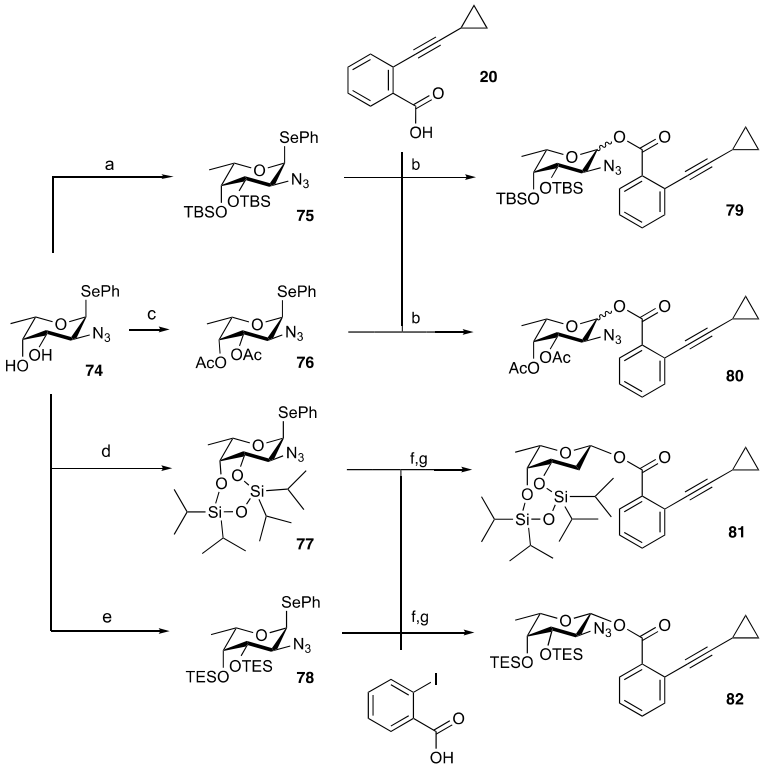


Figure 4. Doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**3**), in addition to their regio-isomers fucosamine-doxorubicinones **71** and **72** and trisaccharide **73**.

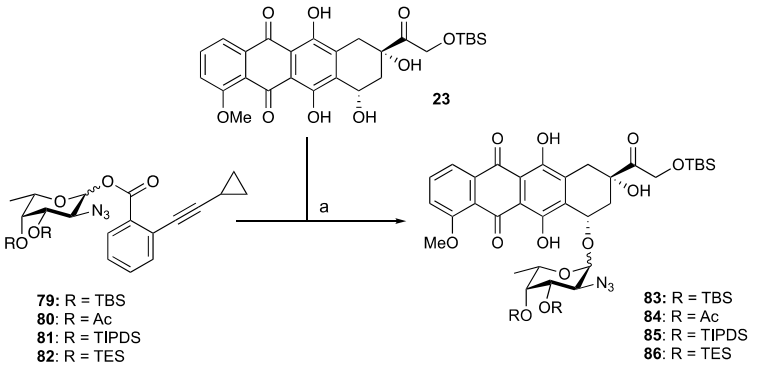
The synthesis of alkynylbenzoates **79**-**82** in Scheme 7 commenced with L-azidoselenofucoside **74**, prepared according to Hagen *et al*.[17] This diol was then protected with TBS, TES, acetyl or TIPDS groups to yield **75**-**78**. TBS and acetyl protected selenides **75** and **76** were then subjected to NIS-mediated hydrolysis, after which the hemiacetals were esterified to *ortho*-cyclopropylethynylbenzoic acid **20** to yield the corresponding anomeric alkynylbenzoates. This same procedure proved very low yielding for TES- and TIPDS-protected **77** and **78**, and these were subjected to esterification to iodobenzoic acid instead. Final Sonogashira coupling to cyclopropylacetylene yielded the *ortho*-alkynylbenzoates **79**-**82**.



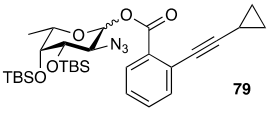
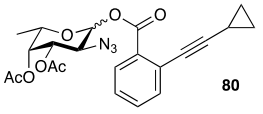
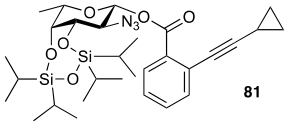
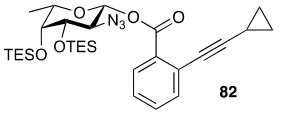
Scheme 7. Synthesis of four fucosazide *ortho*-alkynylbenzoate donors **79**-**82**. *Reagents and conditions:* (a) TBSOTf, pyr., DMF, 0 °C to RT, quant.; (b) *i.* NIS, MeCN/H_2O; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 70% over 2 steps (1:9 α:β) for **70**, 90% over 2 steps (1:5 α:β) for **76**; (c) Ac_2O, DMAP, pyr. 100 °C, quant.; (d) TIPDS-Cl_2, imidazole, pyr., 82%; (e) TESOTf, pyr., 88%; (f) *i.* $AgNO_3$, 2,6-lutidine, H_2O, THF; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 66% over 2 steps from **77**, 55% over 2 steps from **78**; (g) cyclopropylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 62% for **81**, 88% for **82**.

Table 3 shows the glycosylation of *ortho*-alkynylbenzoates **79-82** to doxorubicinone acceptor **23** under PPh_3AuNTf_2 catalysis, towards the synthesis of fucosamine-doxorubicinones **71** and **72**. The yields were modest to good for all four donors, but the stereoselectivityies of the glycosylations were poor. It has earlier been shown in the context of preactivation glycosylations (Ph_2SO, Tf_2O, TTBP, -80 °C to -40 °C) that the stereochemical outcome of fucosazidylation is very dependent on the acceptor nucleophilicity and is much more likely to proceed through S_N2-like pathways than for the 2-deoxyglycosides in this Thesis.[17] Unfortunately, only minimal amounts of the desired α-glycosidic products **79** and **81** could be isolated. Deprotection of the azide under Staudinger conditions proved unsuccessful, as the intermediate iminophosporane underwent attack of the tertiary 9-hydroxyl function, finally leading to aromatization of the attached ring as earlier shown for aklavinone **40** (Chapter 3, Scheme 7).

Table 2. Glycosylation of fucosazide *ortho*-alkynylbenzoates **79-82** to doxorubicinone-acceptor **23**.



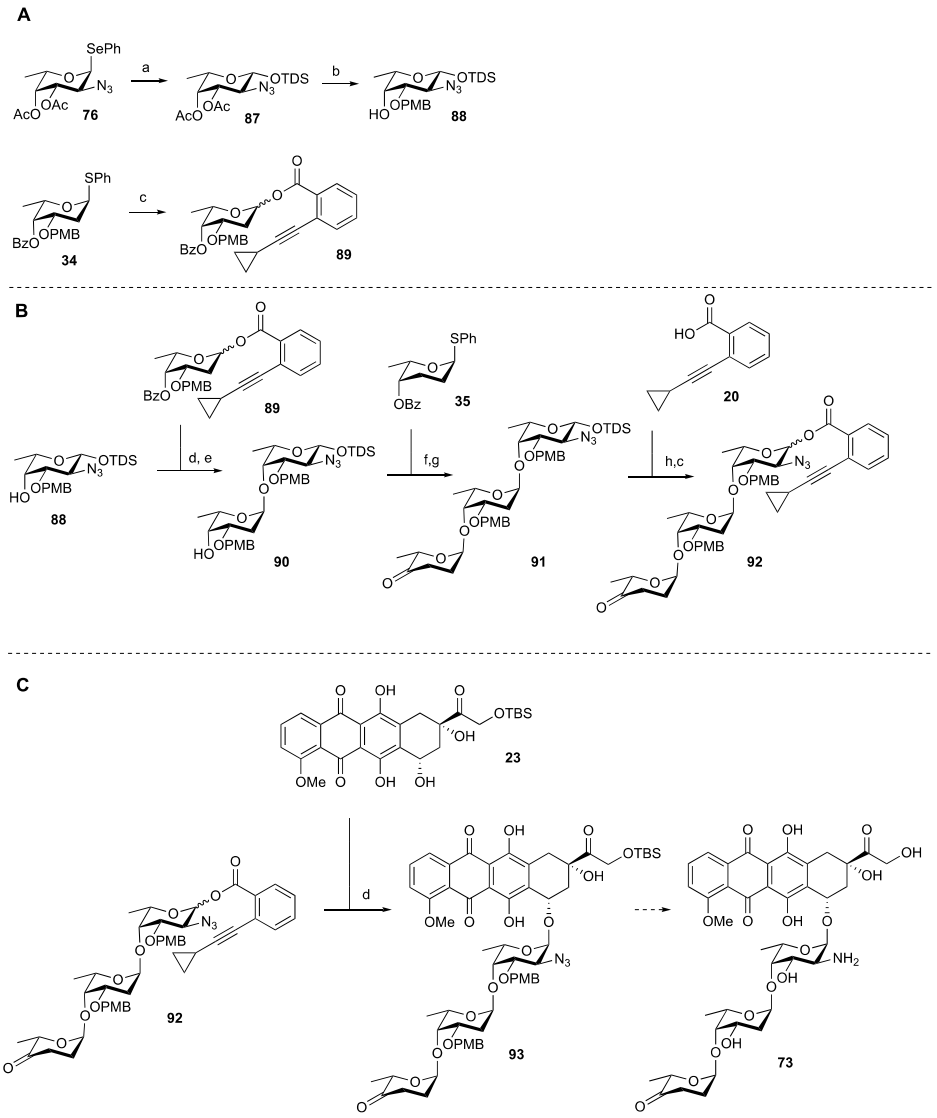
Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), 0.05M in DCM.

Entry	Donor	Yield (α:β ratio)
1	 **79**	91% (3:1 α:β)
2	 **80**	52% (1.5:1 α:β)
3	 **81**	68% (2.6:1 α:β)
4	 **82**	67% (2.2:1 α:β)

The use of the tin(II)-thiophenolate conditions developed by Romea *et al*., successfully applied by the group of Roush in their total synthesis of spinosyn A, might circumvent this issue.[18,19]

Progress in the synthesis of fucosamine-trisaccharide doxorubicinone **68** is depicted in Scheme 8. Fucosazide acceptor **83** (Scheme 8A) was prepared by hydrolysis of selenoglycoside **71**, followed by installation of an anomeric dimethylthexyl silyl ether

(TDS) to furnish **82**. Deacylation providing the diol, followed by installation of a 3-PMB group through the stannylene acetal gave acceptor **83**. As appendage of the oliosyl moiety on this alcohol using thioglycoside **30** proved to be low-yielding (using IDCP) or aselective (2.2:1 α:β using NIS, TfOH, -78 °C to -40 °C), alkynylbenzoate **84** was prepared instead. Subjection of a mixture of fucosazide acceptor **83** and olioside **84** to catalytic PPh_3AuNTf_2 (-78 °C to RT) gave the desired disaccharide **85** in good yield after removal of the 4'-benzoate. Subjection to rhodinoside **35** in the presence of IDCP gave the desired trisaccharide stereoselectively. Removal of the terminal benzoate and oxidation of the resultant alcohol, using Dess-Martin periodinane furnished the terminal cineruloside **86**. Removal of the reducing end TDS ether was accomplished using HF·pyr complex, after which the resultant hemiacetal was subjected to Steglich esterification to *ortho*-cyclopropylethynylbenzoic acid **20**, giving trisaccharide donor **87**. Glycosylation of this donor to doxorubicinone-acceptor **55** under the agency of PPh_3AuNTf_2 proceeded in moderate yield and stereoselectivity to give a mixture from which α,α,α-trisaccharide **88** could be isolated. Deprotections to obtain **73** remain to be done upon successful deprotection of the azide towards the monosaccharidic fucosamines.



Scheme 8. Towards the synthesis of 2-fucosamine-trisaccharide **73**. *Reagents and conditions:* (a) *i.* NIS, MeCN, H_2O; *ii.* TDS-Cl, imidazole, DCM, 94% over 2 steps; (b) *i.* NaOMe, MeOH; *ii.* Bu_2SnO, toluene, 105 °C, then PMB-Cl, TBABr, toluene, 90 °C, 92% over 2 steps; (c) *i.* NIS, MeCN, H_2O; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 84% over 2 steps (1:2.5 α:β) for **89**, 48% (1:1.5 α:β) for **92**; (d) PPh_3AuNTf_2, DCM, -78 °C to RT, 84% (14:1 α:β) for **90**, 47% (>7.7:1 α:β) for **93**; (e) NaOMe, MeOH, DCM, 63% for **90**, 80% for **91**; (f) *i.* IDCP, Et_2O,DCE; *ii.* NaOMe, MeOH, 80% over 2 steps; (g) Dess-Martin periodinane, $NaHCO_3$, DCM, 80%; (h) HF·pyr., THF, pyr., 92%.

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-*d*5 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).

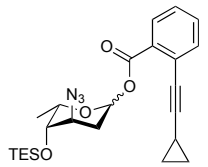
General procedure A: Silver-mediated hydrolysis of selenoglycosides
To a solution of thioglycoside or selenoglycoside in THF/H_2O (10:1 v/v, 0.16M) were added 2,6-lutidine (3 eq.) and $AgNO_3$ (3.5 eq.) and the reaction mixture was stirred overnight in the dark under regular atmosphere. Ethyl acetate and Na_2SO_4 were added and the reaction mixture was stirred for 1 h, filtered over Celite and concentrated *in vacuo* to give the crude hemiacetals.

General procedure B: Esterification with alkynylbenzoic acid or 2-iodobenzoic acid
To the hemi-acetal in DCM (0.1 M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3 eq) and freshly saponified *ortho*-cyclopropylethynylbenzoic acid (**20**) (3 eq) or 2-iodobenzoic (1.5 eq). After disappearance of the starting hemiacetal, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography gave the corresponding anomeric benzoates.

General procedure C: *O*-glycosylations of alkynylbenzoate donors
To a solution of the alkynylbenzoate donor and 14-*O*-tert-butyldimethylsilyl-doxorubicinone **23** (1.5 eq) in DCM (0.05M), were added activated molecular sieves (4Å) and the mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (1 mL/mmol, 0.1 eq) in DCM was added dropwise. After stirring 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography gave the anthracycline glycosides.

General procedure D: *C*-glycosylations using allyltrimethylsilane: To solution of donor (1 eq) and allyltrimethylsilane (8 eq) in DCM (0.05 M) were added 4Å MS and the reaction mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise. After stirring for 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (1:99 Et_2O:pentane) afforded the *C*-glycosides. Flamedried molecular sieves contained too little water and gave rise to glycal formation, fresh molecular sieves shortly exposed to air (ca. 30 seconds) allowed formation of the desired products.

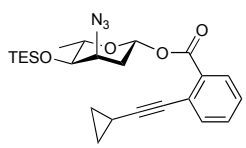
***o*-Cyclopropylethynylbenzoyl-3-*epi*-azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (57)**



Alcohol **24** (Chapter 5) (838 mg, 3.00 mmol) was dissolved in pyridine (10 mL), to which TESOTf (1.5 ml, 6.8 mmol, 2.2 eq) was added at 0 °C. After stirring for 1 h, Et_2O was added and the reaction mixture was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 EtOAc:pentane) afforded the silyl ether as a colorless oil (999 mg, 2.54 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.91 (m, 2H), 6.88 – 6.76 (m, 2H), 5.46 (dd, *J* = 4.4, 1.9 Hz, 1H), 4.24 (qd, *J* = 6.6, 1.6 Hz, 1H), 3.42 – 3.27 (m, 1H), 2.38 (dt, *J* = 14.8, 4.2 Hz, 1H), 2.04 (dddd, *J* = 14.5, 3.2, 1.9, 0.9 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 10H), 0.65 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 151.3, 117.6, 114.6, 95.0, 69.9, 63.8, 57.9, 55.8, 27.5, 16.7, 7.0, 4.9. HRMS: [M +Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.19760; found 416.19757.

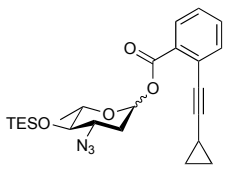
The above glycoside (394 mg, 1.0 mmol) was hydrolysed according to general procedure A. Column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the corresponding hemi-acetal. This hemi-acetal was esterified with cyclopropylethynyl benzoic acid **20** (559 mg, 3.00 mmol, 3 eq) according to general procedure B. Column chromatography 2:98 Et_2O:pentane afforded the title compound as a colorless oil (286 mg, 0,628 mmol, 63%, 1:3 α:β). Spectral data for the β -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.50 – 7.45 (m, 1H), 7.44 – 7.38 (m, 1 H), 7.34 – 7.27 (m, 1H), 6.23 (dd, J = 6.9, 2.8 Hz, 1H), 4.10 (qd, J = 6.7, 3.1 Hz, 1H), 4.00 (td, J = 6.0, 3.9 Hz, 1H), 3.56 (dd, J = 5.6, 3.1 Hz, 1H), 2.29 (ddd, J = 13.6, 6.9, 3.9 Hz, 1H), 1.91 (ddd, J = 13.6, 6.4, 2.9 Hz, 1H), 1.52 (tt, J = 6.8, 5.5 Hz, 1H), 1.29 (d, J = 6.7 Hz, 3H) , 1.00 (t, J = 7.9 Hz, 9H), 0.92-0.88 (m, 2H), 0.73-0.58 (m, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.6, 134.5, 132.0, 130.8, 130.4, 127.1, 125.4, 114.6, 101.5, 99.7, 91.8, 74.7, 71.9, 70.6, 59.7, 31.4, 16.8, 9.0, 7.0, 4.6, 0.9. HRMS: [M + H$^+$] calculated for $C_{24}H_{34}N_3O_4Si$ 456.23131; found 456.23112.

***o*-Cyclopropylethynylbenzoyl-4-*O*-triethylsilyl-2,3,6-trideoxy-3-azido-β-L-ribohexapyranoside (58)**



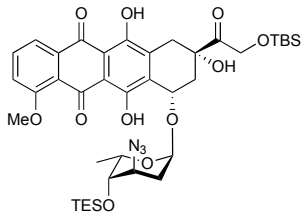
Glycoside **33** (Chapter 5) (797 mg, 2.00 mmol) was hydrolysed according to general procedure A. Column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the hemi-acetal. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** (1.12 mg, 3.0 mmol, 3 eq) according to general procedure B. Column chromatography (3:97 Et_2O:pentane) afforded the title compound as a colorless oil (453 mg, 0.950 mmol, 49%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H, Ar), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H, , Ar), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.30 – 7.25 (m, 1H, Ar), 6.19 (dd, *J* = 8.8, 2.4 Hz, 1H, H-1), 4.12 – 3.95 (m, 2H, H-3, H-5), 3.64 (dd, *J* = 8.2, 3.2 Hz, 1H, H-4), 2.21 (ddd, *J* = 13.4, 4.5, 2.5 Hz, 1H, H-2$_{eq}$), 1.97 (ddd, *J* = 13.4, 8.8, 3.3 Hz, 1H, H-2$_{ax}$), 1.57 – 1.45 (m, 1H, C-propyl -CH-), 1.29 (d, *J* = 6.4 Hz, 3H, H-6), 1.01 (t, *J* = 7.9 Hz, 9H, TES -CH_3), 0.93 – 0.85 (m, 4H, C-propyl -CH_2-), 0.68 (qd, *J* = 8.3, 7.9, 1.6 Hz, 6H, TES -CH_2-). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.31 (C=O), 134.4 (Ar), 132.0 (Ar), 131.0 (Ar), 130.7 (Ar), 127.0 (Ar), 125.1 (Ar), 99.7 (-C≡C-), 91.4 (C-1), 74.6 (C-4), 74.5 (-C≡C-), 72.0 (C-5), 60.0 (C-3), 34.3 (C-2), 18.5 (C-6), 9.0 (C-propyl -CH_2-) 9.0 (C-propyl -CH_2), 7.0 (TES -CH_3), 5.0 (TES -CH_2), 0.8 (C-propyl -CH-). IR (thin film, cm^{-1}): 2956, 2938, 2912, 2231, 2098 (N_3), 1728, 1597, 1279, 1239, 1065. HRMS: [M+Na]$^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133Na found 478.2133.

***o*-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-triethylsilyl-L-rhamnopyranoside (59)**



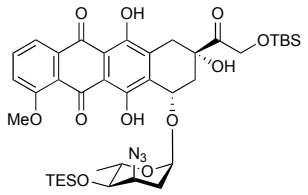
Glycoside **14** (Chapter 5) (862 mg, 2.19 mmol) was hydrolysed according to general procedure A. The crude hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** (1.22 g, 6.57 mmol, 3 eq) according to general procedure B. Column chromatography (3:97 Et_2O:pentane) afforded the title compound as a pale-yellow oil (614 mg, 1.30 mmol, 59%, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, J = 7.9, 1.4 Hz, 1H), 7.51 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (td, J = 7.6, 1.4 Hz, 1H), 7.32 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H), 6.01 (dd, J = 9.9, 2.3 Hz, 1H), 3.56 – 3.50 (app m, 1H), 3.50 – 3.46 (app m, 1H), 3.20 (t, J = 9.0 Hz, 1H), 2.48 (ddd, J = 12.5, 4.9, 2.2 Hz, 1H), 1.94 (td, J = 12.5, 10.0 Hz, 1H), 1.55 (tt, J = 7.5, 5.5 Hz, 1H), 1.36 (d, J = 6.2 Hz, 3H), 1.03 (t, J = 7.9 Hz, 9H), 0.94 – 0.90 (m, 4H), 0.73 (qd, J = 8.3, 7.9, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.2, 134.3, 132.1, 130.7, 130.5, 127.0, 125.1, 99.8, 92.2, 75.7, 74.5, 63.3, 35.4, 18.2, 8.9, 6.9, 5.2, 0.7. HRMS: [M+Na]$^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133; found 478.2139.

7-[3-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (62)



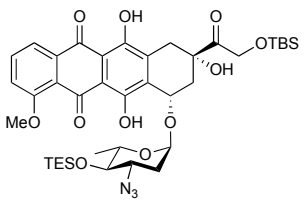
According to general procedure C, glycosyl donor **57** (50 mg, 0.11 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (90 mg, 0.17 mmol 1.5 eq). Column chromatography (5:95 Et_2O:pentane - 2:98 – 20:80 acetone:toluene) afforded the title compound as a red solid (70 mg, 90 μmol, 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.24 (s, 1H), 8.05 – 7.97 (m, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.21 (dd, *J* = 3.9, 2.2 Hz, 1H), 5.10 (s, 1H), 5.05 – 4.86 (m, 2H), 4.30 – 4.12 (m, 1H), 4.09 (s, 3H), 3.68 (q, *J* = 3.7 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.19 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.98 (d, *J* = 18.9 Hz, 1H), 2.34 (dt, *J* = 14.9, 2.2 Hz, 1H), 2.28 – 2.10 (m, 2H), 1.78 – 1.68 (m, 1H), 1.35 – 1.18 (m, 7H), 1.07 – 0.91 (m, 21H), 0.66 (q, *J* = 7.9 Hz, 7H), 0.15 (d, *J* = 5.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.2, 187.2, 186.7, 161.1, 156.5, 156.1, 135.8, 134.5, 134.3, 134.2, 132.1, 129.4, 129.3, 121.0, 119.9, 118.4, 111.5, 111.3, 99.3, 77.1, 69.4, 66.9, 63.6, 58.8, 56.8, 35.7, 34.1, 28.0, 26.0, 16.8, 7.0, 4.9, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_3Na$ 820.32737; found 820.3266.

7-[3-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-rhamnopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (63)



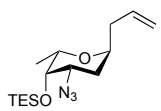
According to general procedure B glycosyl donor **58** (46 mg, 0.10 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (79 mg, 0.15 mmol 1.5 eq). Column chromatography (1:9 Et_2O:pentane, then 5:95 – 10:90 acetone:toluene) afforded the title compound as a red solid (62 mg, 78 μmol, 78%, 3:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.18 (s, 1H), 7.97 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.44 (s, 1H), 5.35 (d, *J* = 4.3 Hz, 1H), 5.20 (dd, *J* = 3.7, 2.2 Hz, 1H), 5.13 – 4.81 (m, 2H), 4.15 (dq, *J* = 9.1, 6.3 Hz, 1H), 4.08 (s, 3H), 3.82 (q, *J* = 3.4 Hz, 1H), 3.57 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.15 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.91 (d, *J* = 18.9 Hz, 1H), 2.30 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.13 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.86 (dt, *J* = 14.9, 4.2 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.03 – 0.95 (m, 18H), 0.68 (qd, *J* = 8.3, 7.9, 2.3 Hz, 6H), 0.16 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.6, 187.1, 186.6, 161.0, 156.4, 156.1, 135., 135.6, 134.7, 134.4, 120.9, 119.9, 118.4, 111.4, 111.2, 98.1, 76.9, 74.8, 68.4, 66.8, 65.5, 59.5, 56.8, 35.7, 34.0, 26.0, 18.0, 7.0, 5.0, -5.2, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.21325; found 478.2133.

7-[4-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (64)



According to general procedure C, glycosyl donor **59** (78 mg, 0.17 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (132 mg, 0.250 mmol 1.5 eq). Column chromatography (4:96 Et_2O:pentane, then 1:199 acetone:toluene) and size-exclusion chromatography (Sephadex LH-20, eluent: 1:1 v/v DCM:MeOH) afforded the title compound as a red solid (120 mg, 0.15 mmol, 91%, 3:1 α:β). Spectal data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.99 (s, 1H), 13.21 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.48 (d, *J* = 3.9 Hz, 1H), 5.25 (dd, *J* = 4.2, 2.1 Hz, 1H), 5.03 – 4.85 (m, 2H), 4.50 (s, 1H), 4.11 (s, 3H), 3.79 (dq, *J* = 9.0, 6.3 Hz, 1H), 3.45 (ddd, *J* = 12.4, 9.1, 4.8 Hz, 1H), 3.17 (t, *J* = 17.7 Hz, 1H), 2.93 (d, *J* = 18.8 Hz, 1H), 2.35 (dt, *J* = 14.9, 2.1 Hz, 1H), 2.26 – 2.15 (m, 2H), 1.77 (td, *J* = 13.5, 4.1 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.99 (s, 9H), 0.71 (qd, *J* = 8.3, 7.9, 2.5 Hz, 6H), 0.17 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 187.0, 186.6, 161.0, 156.3, 155.7, 135.8, 135.4, 134.2, 133.6, 120.7, 119.8, 118.5, 111.4, 111.3, 100.1, 76.2, 70.1, 66.7, 61.2, 56.7, 35.7, 35.4, 33.8, 29.7, 25.9, 18.6, 18.1, 6.9, 5.2, -5.4, -5.4. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.3267; found 820.3279.

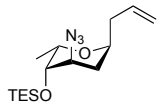
3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-fucopyranosyl)-1-propene (65)



According to general procedure D, the title compound was obtained from glycosyl donor **56** as a colorless oil (22 mg, 71 μmol, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.17 – 5.00 (m, 2H), 3.98 – 3.89 (m, 2H), 3.85 (tdd, *J* = 7.2, 5.6, 2.0 Hz, 2H), 2.28 (dtt, *J* = 14.1, 6.9, 1.4 Hz, 1H), 2.16 (dddt, *J* = 14.3, 7.2, 6.0, 1.3 Hz, 1H), 1.83 (ddd, *J*

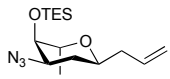
= 13.7, 5.3, 2.9 Hz, 1H), 1.52 (ddd, *J* = 13.7, 9.2, 3.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.64 (td, *J* = 8.0, 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 117.2, 71.9, 71.1, 64.7, 59.7, 38.9, 33.6, 14.2, 7.0, 4.9.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-xylopyranosyl)-1-propene (66)



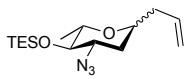
According to general procedure D, the title compound was obtained from glycosyl donor **57** as a colorless oil (27 mg, 87 μmol, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16 – 5.01 (m, 2H), 4.09 (qd, *J* = 6.9, 5.5 Hz, 1H), 3.71 (dtd, *J* = 12.1, 6.3, 2.3 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.56 (ddd, *J* = 11.9, 9.6, 4.7 Hz, 1H), 2.26 (dtt, *J* = 13.6, 6.8, 1.3 Hz, 1H), 2.17 (dddt, *J* = 14.2, 7.1, 5.8, 1.4 Hz, 1H), 1.95 (ddd, *J* = 13.1, 4.7, 2.3 Hz, 1H), 1.33 – 1.25 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.73 – 0.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.33, 117.44, 73.80, 73.01, 67.09, 60.39, 40.17, 36.59, 11.81, 6.86, 4.94. HRMS: $[M-N_2+H]^+$ calculated for $C_{15}H_{30}NO_2Si$: 284.2040; found 284.2046.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-ribohexopyranosyl)-1-propene (67)



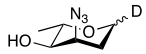
According to general procedure D, the title compound was obtained from glycosyl donor **58** as a colorless oil (22 mg, 74 μmol 74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.99 (qd, *J* = 6.9, 3.6 Hz, 1H), 3.73 (dtd, *J* = 8.6, 6.5, 3.4 Hz, 1H), 3.64 (t, *J* = 3.2 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.47 (dtt, *J* = 13.8, 6.8, 1.4 Hz, 1H), 2.34 – 2.23 (m, 1H), 1.94 (ddd, *J* = 12.8, 10.1, 8.7 Hz, 1H), 1.74 (dt, *J* = 12.7, 3.8 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.71 – 0.62 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.75, 117.30, 72.73, 72.69, 69.00, 57.33, 39.59, 30.21, 16.32, 6.93, 5.06. HRMS: $[M-N_2+H]^+$ calculated for $C_{15}H_{30}NO_2Si$: 284.2040; found 284.2047.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-β-L-rhamnopyranosyl)-1-propene (68)



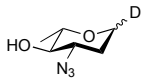
According to general procedure D, the title compound was obtained from glycosyl donor **59** as a colorless oil (25 mg, 60 μmol, 60%). Spectral data for the α-anomer: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.81 – 5.71 (m, 1H), 5.16 – 5.05 (m, 2H), 4.02 – 3.95 (m, 1H), 3.84 – 3.74 (m, 1H), 3.54 – 3.45 (m, 2H), 3.09 (t, *J* = 8.6 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.31 – 2.23 (m, 1H), 2.00 (dddd, *J* = 13.4, 4.8, 2.1, 0.5 Hz, 1H), 1.82 (ddd, *J* = 13.4, 11.7, 5.8 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 13H), 0.72 – 0.65 (m, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.5, 117.5, 76.6, 71.3, 70.1, 62.0, 35.7, 32.9, 18.7, 7.0, 5.4.

1-Deutero-2,3-dideoxy-3-azido-L-ribohexapyranoside (69)



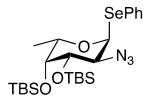
To a solution of donor **58** (46 mg, 0.1 mmol) in DCM (2 mL) were added TES-D (127 μL, 94 mg, 0.8 mmol 8 eq) and 4 Å MS. A freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (100 μL 0.01 mmol, 0.1 eq) and the reaction mixture was stirred for 1h, filtered and concentrated *in vacuo*. Column chromatography (0:100 – 30:70 Et_2O:pentane) afforded the title compound as a colourless oil (13 mg, 83 μmol, 83%, 93:7 α:β). Spectal data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.10 (q, *J* = 3.4 Hz, 1H), 3.74 – 3.70 (m, 0.93H,), 3.51 (dq, *J* = 9.1, 6.2 Hz, 1H), 3.34 (td, *J* = 9.2, 3.6 Hz, 1H), 2.04 – 1.87 (m, 3H), 1.27 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 73.2, 73.0, 61.7, 61.6, 61.4, 61.1, 30.2, 18.1. ^{2}H NMR (77 MHz, Chloroform-*d*) δ 3.65 (D-1α).

1-Deutero-2,3-dideoxy-3-azido-L-rhamnopyranoside (70)



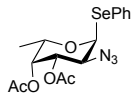
To a solution of donor **59** (46 mg, 0.1 mmol) in DCM (2 mL) were added TES-D (127 μL, 94 mg, 0.8 mmol 8 eq) and 4 Å MS. A freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (100 μL 0.01 mmol, 0.1 eq) and the reaction mixture was stirred for 1h. More PPh_3AuNTf_2 was added (in 1.1 mL DCM, 0.11 mmol, 1.1 eq) and the reaction mixture was stirred for another 1 h, filtered and concentrated *in vacuo*. Column chromatography (0:100 – 50:50 Et_2O:pentane) afforded the title compound as a colorless oil (12 mg, 78 μmol, 78%, >10:1 α:β). Spectal data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.97 (dq, *J* = 5.1, 1.7 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.27 (dq, *J* = 9.0, 6.1 Hz, 1H), 3.15 (t, *J* = 9.1 Hz, 1H), 2.02 (ddd, *J* = 13.1, 4.9, 1.8 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 76.6, 76.1, 65.6, 65.5, 65.4, 65.3, 65.1, 65.1, 64.4, 30.9, 18.2.

Phenyl 2-azido-3,4-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-seleno-α-L-fucopyranoside (75)



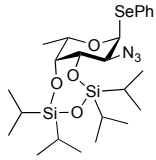
To an ice-cooled solution of diol **74**[17] (690 mg, 2.10 mmol) in DMF (4 mL) and pyridine (1.05 mL, 12.9 mmol, 6.15 eq), *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.44 mL, 6.29 mmol, 3.00 eq) was added dropwise. After stirring for 3 days while warming up to ambient temperature, the resulting solution was quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted five times with Et_2O. The combined organic layers were concentrated *in vacuo*, subsequently partitioned between Et_2O and H_2O and the organic layer successively washed four times with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 – 10:90 toluene:pentane) afforded the title compound as a colorless oil (1.17 g, 2.10 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 2H), 7.33 – 7.27 (m, 3H), 5.99 (d, *J* = 4.9 Hz, 1H), 4.28 (q, *J* = 6.5 Hz, 1H), 4.18 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.88 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.80 (d, *J* = 2.2 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H), 0.98 (s, 9H), 0.27 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 129.0, 128.8, 127.7, 86.0, 77.5, 77.2, 76.8, 74.7, 73.9, 70.4, 62.6, 29.8, 26.5, 26.2, 18.6, 17.2, -3.4, -3.8, -4.4, -4.4.

Phenyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-seleno-α-L-fucopyranoside (76)



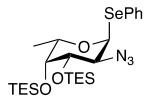
Diol **74** (1.68 g, 5.10 mmol) was dissolved in pyridine (25 mL) and acetic anhydride (40 mL), whereupon a catalytic amount of 4-dimethylaminopyridine was added. After heating to 100 °C and stirring for 1 hour, the resulting solution was diluted with DCM, quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted with DCM. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a viscous orange oil (2.10 g, 5.10 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.54 (m, 2H), 7.29 – 7.23 (m, 3H), 5.95 (d, *J* = 5.4 Hz, 1H), 5.31 (d, *J* = 3.3 Hz, 1H), 5.12 (dd, *J* = 10.9, 3.2 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 4.24 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.4, 134.5, 129.0, 127.9, 127.8, 84.2, 77.5, 77.2, 76.8, 71.4, 69.9, 67.2, 58.5, 20.4, 20.4, 15.6. HRMS: $[M+H]^+$ calculated for $C_{16}H_{20}N_3O_5Se$ 412.3150; found 413.2546.

Phenyl-2-azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-1-seleno-α-L-fucopyranoside (77)



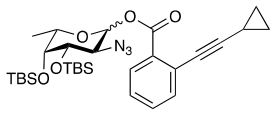
To a solution of diol **74** (328 mg, 1.00 mmol) in pyridine (5 mL) were added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.36 mL, 0.35 mg, 1.1 mmol, 1.1 eq) and imidazole (136 mg, 2 mmol, 2 eq). After stirring for two days, Et_2O (100 mL) was added and the mixture was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 5:95 Et_2O:pentane) afforded the title compound as a pale-yellow oil (470 mg, 0.820 mmol, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.49 (m, 2H), 7.27 (dd, *J* = 5.2, 2.1 Hz, 3H), 5.87 (d, *J* = 5.2 Hz, 1H), 4.35 (dt, *J* = 7.1, 5.9 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.04 (ddd, *J* = 10.9, 5.1, 1.3 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.17 – 0.92 (m, 28H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 129.2, 129.0, 129.0, 127.8, 85.7, 75.9, 73.2, 69.2, 62.1, 17.8, 17.8, 17.5, 17.3, 17.3, 17.3, 17.2, 17.2, 16.8, 14.8, 13.6, 13.2, 12.8. HRMS: $[M - N_2 + H]^+$ calculated for $C_{24}H_{42}NO_4SeSi_2$ 544.1818; found 544.1813.

Phenyl-2-azido-3,4-*O*-di-triethylsilyl-2-deoxy-1-seleno-α-L-fucopyranoside (78)



To a solution of diol **74** (328 mg, 1.00 mmol) in pyridine (5 mL) was added triethylsilyl triflate (0.65 mL, 3 mmol, 3 eq). After stirring overnight Et_2O was added and the reaction mixture was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (0:100 - 5:95 Et_2O:pentane) afforded the title compound as a pale-yellow oil (490 mg, 0.880 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.50 (m, 2H), 7.34 – 7.12 (m, 3H), 5.93 (d, *J* = 5.1 Hz, 1H), 4.25 – 4.17 (m, 1H), 4.14 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.73 (dd, *J* = 2.6, 1.0 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.01 (dt, *J* = 23.0, 7.9 Hz, 18H), 0.81 – 0.59 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 129.1, 129.0, 127.7, 85.9, 74.7, 73.8, 70.2, 62.4, 16.8, 7.1, 5.4, 5.1.

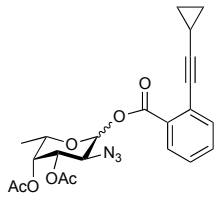
***o*-Cyclopropylethynylbenzoyl 2-azido-3,4-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-α-L-fucopyranoside (79)**



To a solution of fucosyl selenide **75** (1.17 g, 2.10 mmol) in 10:1 MeCN:H_2O (38.5 mL, v/v) was added *N*-iodosuccinimide (590 mg, 2.62 mmol, 1.25 eq). After stirring for 1 hour, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic

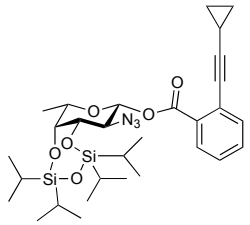
layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 – 20:80 toluene:pentane) afforded the intermediate lactol, a white crystalline solid, as a mixture of anomers (798 mg, 1.91 mmol, 91%, 1:2 α:β). The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (1.5:98.5 – 2.5:97.5 EtOAc:pentane) afforded β-anomer (249 mg, 0.425 mmol, 22%) and an α:β anomeric mixture (619 mg, 1.06 mmol, 55%, 1:5 α:β), as colorless oils. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.7, 1.5 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1H), 3.84 (dd, *J* = 10.1, 8.3 Hz, 1H), 3.71 (q, *J* = 6.4 Hz, 1H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.54 (dd, *J* = 10.1, 2.4 Hz, 1H), 1.53 (tt, *J* = 9.4, 5.2 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 18H), 0.90 (s, 2H), 0.89 (s, 2H), 0.19 (s, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 134.5, 132.3, 130.9, 130.2, 127.1, 125.6, 100.1, 94.1, 77.5, 76.8, 74.8, 74.7, 74.0, 72.5, 63.5, 26.4, 26.3, 18.7, 18.6, 17.5, 9.1, 9.0, 0.9, -3.4, -3.5, -4.2, -4.4. HRMS: $[M+Na]^+$ calculated for $C_{30}H_{47}N_3O_5Si_2Na$ 6082952; found 608.2946.

***o*-Cyclopropylethynylbenzoyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-L-fucopyranoside (80)**



To a solution of fucosyl selenide **76** (796 mg, 1.93 mmol) in 10:1 MeCN:H_2O (35.2 mL, v/v) was added *N*-iodosuccinimide (542 mg, 2.41 mmol, 1.25 eq). After stirring for 2 hours, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the intermediate lactol, an orange wax, as a mixture of anomers (517 mg, 1.93 mmol, 98%, 1:1 α:β). The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (2.5:97.5 – 33.3:66.7 EtOAc:pentane) afforded isolated α and β title benzoates **80α** (100 mg, 0.227 mmol, 15%) and **80β** (515 mg, 1.17 mmol, 77%), as slow crystallizing green oils. Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 5.49 (dd, *J* = 11.0, 3.2 Hz, 1H), 5.41 (dd, *J* = 3.2, 1.3 Hz, 1H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.07 (dd, *J* = 11.0, 3.7 Hz, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 1.67 – 1.58 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.97 – 0.87 (m, 3H), 0.86 – 0.79 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.9, 164.4, 135.1, 132.4, 131.0, 130.3, 127.4, 125.0, 99.9, 91.5, 77.5, 76.8, 74.9, 70.2, 69.9, 67.7, 57.2, 29.8, 20.8, 20.7, 16.1, 9.1, 9.0, 0.6. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H), 5.85 (d, *J* = 8.5 Hz, 1H), 5.29 (d, *J* = 3.3 Hz, 1H), 5.06 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.06 (q, *J* = 6.3 Hz, 1H), 3.98 (dd, *J* = 10.8, 8.5 Hz, 1H), 2.19 (s, 3H), 2.08 (s, 3H), 1.59 – 1.50 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 2H), 0.91 (d, *J* = 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.4, 163.3, 134.1, 132.2, 130.5, 129.5, 126.8, 125.2, 99.9, 93.0, 77.5, 76.8, 74.2, 71.6, 70.0, 69.2, 59.8, 20.3, 20.3, 15.7, 8.6, 0.5. HRMS: $[M+Na]^+$ calculated for $C_{22}H_{23}N_3O_7Na$ 441.1536; found 464.1428.

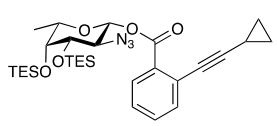
***o*-Cyclopropylethynylbenzoyl-2-azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-β-L-fucopyranoside (81)**



Selenoglycoside **77** (470 mg, 0.820 mmol, 1 eq) was hydrolysed according to general procedure A. The resulting crude lactol was esterified with 2-iodobenzoic acid (305 mg, 1.23 mmol, 1.5 eq) according to general method B. Column chromatography (1:99 – 5:95 EtOAc:pentane) afforded the title compound as a white solid (289 mg, 55%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (t, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 5.61 (d, *J* = 8.6 Hz, 1H), 4.09 (d, *J* = 3.1 Hz, 1H), 4.04 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.86 – 3.75 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 3H), 1.19 – 1.02 (m, 28H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 141.9, 133.5, 132.8, 132.0, 128.0, 95.1, 93.5, 77.2, 72.5, 71.8, 17.6, 17.6, 17.5, 17.2, 17.2, 17.0, 14.6, 13.5, 13.1, 12.6. HRMS $[M+Na]^+$ calculated for $C_{25}H_{40}IN_3O_6Si_2$: 684.1398, found 684.1390. To a solution of the above benzoate (289 mg, 0.45 mmol, 1 eq). in triethylamine (1.5 mL) and THF (1 mL) were added ethynyl cyclopropane (89 mg, 0.11 mL, 1.3 mmol, 3 eq), bis(triphenylphosphine)palladium dichloride (35 mg, 0.05 mmol, 0.1 eq and 10 mg) and copper iodide (0.05 mmol, 0.1 eq). The reaction mixture was stirred overnight, filtered over Celite and stirred for 1 hour with sat. aq. NH_4Cl. Pentane was added and the aqueous layer was extracted with 1% EtOAc in pentane.

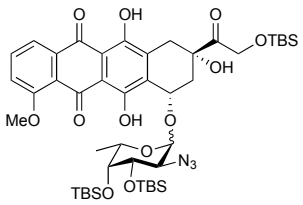
Combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 - 1:90 Et_2O in pentane) afforded the title compound as a yellow oil (231 mg 0.400 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 5.63 (d, *J* = 8.6 Hz, 1H), 4.08 (dd, *J* = 3.2, 1.0 Hz, 1H), 4.02 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.85 – 3.75 (m, 2H), 1.58 – 1.47 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.10 (qd, *J* = 8.8, 5.7 Hz, 28H), 0.92 – 0.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 134.4, 132.3, 131.0, 130.3, 127.0, 125.5, 100.1, 93.2, 77.3, 74.6, 72.6, 71.7, 63.2, 17.7, 17.7, 17.5, 17.2, 17.2, 17.2, 17.0, 14.6, 13.5, 13.2, 12.7, 9.0, 0.8. HRMS: $[M+Na]^+$ calculated for $C_{30}H_{45}N_3O_6Si_2Na$ 622.27391; found 622.2744.

_o_-Cyclopropylethynylbenzoyl-2-azido-3,4-_O_-di-triethylsilyl-2-deoxy-β-L-fucopyranoside (82)



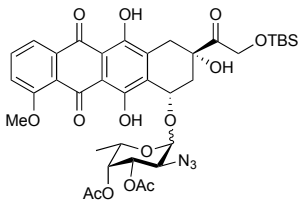
Selenoglycoside **78** (390 mg, 0.500 mmol) was hydrolysed according to general procedure A. The crude hemi-acetal was esterified with 2-iodobenzoic acid (186 mg, 0.750 mmol, 1.5 eq) according to general method B. Purification by column chromatography (2:98 – 5:95 EtOAc:pentane) afforded the title compound as a pale-yellow oil (200 mg, 0.330 mmol, 66%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (ddd, *J* = 7.5, 5.8, 1.4 Hz, 2H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.7 Hz, 1H), 5.62 (d, *J* = 8.4 Hz, 1H), 3.84 (dd, *J* = 10.0, 8.4 Hz, 1H), 3.73 – 3.59 (m, 2H), 3.53 (dd, *J* = 10.0, 2.6 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.00 (dt, *J* = 7.9, 4.4 Hz, 18H), 0.79 – 0.59 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 142.0, 133.5, 132.7, 132.0, 128.1, 95.2, 94.4, 74.6, 73.8, 72.5, 63.4, 17.0, 7.1, 5.3, 5.0. HRMS: $[M+Na]^+$ calculated for $C_{25}H_{42}IN_3O_5Si_2Na$ 670.1600; found 670.1612. To a solution of the above benzoate (193 mg, 0.320 mmol, 1 eq) in triethylamine (1 mL) were added cyclopropyl acetylene (80 µL, 0.96 mmol, 3 eq), bis (triphenylphosphine) palladium dichloride (21 mg, 0.03 mmol, 0.1 eq) and CuI (6 mg, 0.03 mmol, 0.1 eq). After stirring overnight sat aq. NH_4Cl was added and the resulting mixture was stirred for 1 hour. Pentane was added and the aqueous layer was extracted with 1% EtOAc in pentane. Combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 1:90 Et_2O:pentane) afforded the title product as a pale-yellow oil (100 mg, 0.180 mmol, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 5.65 (d, *J* = 8.5 Hz, 1H), 3.83 (dd, *J* = 10.1, 8.4 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.51 (dd, *J* = 10.1, 2.6 Hz, 1H), 1.52 (dt, *J* = 7.8, 5.8 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.00 (td, *J* = 8.0, 2.3 Hz, 18H), 0.92 – 0.87 (m, 4H), 0.79 – 0.61 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 134.5, 132.4, 131.1, 130.2, 127.1, 125.7, 100.2, 94.1, 74.6, 73.9, 72.5, 63.5, 17.0, 9.0, 7.2, 7.0, 5.4, 5.1, 0.9. HRMS: $[M+H]^+$ calculated for $C_{30}H_{48}N_3O_5Si_2$ 586.3127; found 586.2771.

7-[2-Azido-3,4-di-_O_-tert-butyldimethylsilyl-2-deoxy-α-L-fucopyranoside]-14-_O_-_tert_-butyldimethylsilyl-doxorubicinone (83)



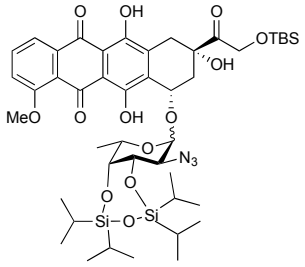
According to general procedure C, glycosyl donor **79** (114 mg, 0.195 mmol) was coupled to 14-*O*-TBS-doxorubicinone **23** (123 mg, 0.236 mmol, 1.2 eq). Purification by column chromatography (5:95 EtOAc:pentane then 1:399 acetone:toluene) afforded protected the title compound as a red amorphous solid (164 mg, 0.177 mmol, 91%, 3:1 α:β). Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.98 (s, 1H), 13.12 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 2.7 Hz, 1H), 5.38 (t, *J* = 2.9 Hz, 1H), 4.94 (d, *J* = 20.0 Hz, 1H), 4.87 (d, *J* = 20.1 Hz, 1H), 4.58 (s, 1H), 4.06 (s, 3H), 3.98 (q, *J* = 6.5 Hz, 1H), 3.80 – 3.70 (m, 3H), 3.17 (d, *J* = 19.1 Hz, 1H), 2.93 (d, *J* = 19.0 Hz, 1H), 2.29 (d, *J* = 14.0 Hz, 1H), 2.23 – 2.18 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.90 (s, 9H), 0.15 (br. s, 6H), 0.14 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 186.8, 186.7, 161.0, 156.3, 155.6, 135.7, 135.4, 134.4, 133.3, 120.8, 119.7, 118.5, 111.6, 111.5, 99.3, 77.5, 77.3, 76.8, 74.9, 71.4, 69.4, 67.8, 66.6, 60.9, 56.8, 35.9, 34.5, 29.8, 26.3, 26.2, 26.0, 18.7, 18.7, 18.6, 17.4, -3.3, -3.6, -4.4, -4.7, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{69}N_3O_{12}Si_3Na$ 950.40812; found 950.4079.

7-[2-Azido-3,4-di-*O*-acetyl-2-deoxy-α,β-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (84)



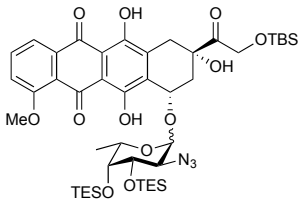
According to general procedure C, glycosyl donor **80** (21.7 mg, 49.2 µmol) was coupled to 14-*O*-TBS-doxorubicinone **23** (22.2 mg, 49.2 µmol, 1 eq). Purification by column chromatography (5:95 EtOAc:pentane - 4:96 – 7:93 acetone:toluene) afforded the title compound as a red solid (20 mg, 25.5 µmol, 52%, 1.5:1 α:β). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.15 (s, 1H), 14.08 (s, 1H), 13.25 (s, 1H), 13.22 (s, 1H), 8.04 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.03 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 2H), 7.78 (t, *J* = 7.9 Hz, 0H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 0H), 5.60 (d, *J* = 4.0 Hz, 1H), 5.58 (t, *J* = 3.1 Hz, 1H), 5.41 (dd, *J* = 3.9, 2.3 Hz, 1H), 5.35 (d, *J* = 3.1 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 5.09 (dd, *J* = 11.3, 3.2 Hz, 1H), 4.99 (d, *J* = 20.0 Hz, 1H), 4.91 (app. s, 2H), 4.87 (d, *J* = 20.0 Hz, 0H), 4.86 – 4.82 (m, 1H), 4.62 (s, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.09 (s, 5H), 4.07 (s, 1H), 3.75 (s, 1H), 3.73 – 3.62 (m, 3H), 3.30 – 3.22 (m, 2H), 3.16 (d, *J* = 19.4 Hz, 1H), 3.06 (d, *J* = 19.1 Hz, 1H), 2.57 (d, *J* = 14.8 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.18 (s, 4H), 2.11 (s, 2H), 2.05 (s, 2H), 2.01 (s, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 9H), 0.95 (s, 7H), 0.15 (s, 6H), 0.13 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 211.1, 187.2, 186.9, 186.8, 170.6, 170.5, 169.9, 169.9, 161.2, 161.2, 156.7, 156.4, 155.8, 155.6, 135.9, 135.9, 135.8, 135.7, 135.6, 134.5, 132.9, 132.7, 121.0, 121.0, 120.0, 118.6, 116.1, 114.9, 111.9, 111.7, 111.6, 111.2, 102.4, 99.8, 77.5, 77.1, 77.0, 76.8, 72.0, 70.8, 70.5, 70.5, 69.7, 69.6, 69.5, 68.7, 66.9, 66.8, 65.7, 61.0, 57.4, 56.9, 56.9, 36.1, 35.5, 34.7, 34.5, 26.0, 20.8, 20.8, 18.7, 16.1, 16.1, -5.2, -5.2. HRMS: $[M+Na]^+$ calculated for $C_{37}H_{45}N_3O_{14}SiNa$ 806.2563; found 806.2581.

7-[2-Azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (85)



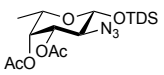
According to general procedure C, glycosyl donor **81** (24 mg, 50 µmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **23** (40 mg, 80 µmol, 1.5 eq). Column chromatography (1:199 - 50:50 EtOAc:toluene) gave the title compound as a red solid (31 mg, 31 µmol, 68%, 2.6: 1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.03 (s, 2H), 13.29 (s, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.78 (t, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 5.45 (d, *J* = 4.1 Hz, 1H), 5.39 (s, 1H), 5.05 – 4.72 (m, 3H), 4.38 (s, 1H), 4.14 (d, *J* = 2.3 Hz, 1H), 4.13 (s, 1H), 4.11 – 4.10 (m, 1H), 4.09 (s, 3H), 3.61 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.31 – 3.20 (m, 1H), 3.11 (d, *J* = 19.1 Hz, 1H), 2.34 (d, *J* = 14.5 Hz, 2H), 2.26 – 2.14 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 4H), 1.25 (s, 29H), 0.96 (s, 9H), 0.14 (d, *J* = 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.1, 187.0, 161.2, 156.4, 155.7, 135.8, 135.6, 134.4, 133.2, 121.1, 119.9, 118.6, 111.8, 111.6, 100.3, 77.5, 73.8, 72.9, 69.1, 67.5, 66.8, 60.5, 56.8, 36.0, 34.5, 26.0, 17.7, 17.7, 17.6, 17.4, 17.3, 17.3, 17.2, 17.1, 14.5, 13.9, 13.2, 12.7, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{67}N_3O_{13}Si_3Na$ 964.3879; found 964.3871.

7-[2-Azido-3,4-*O*-di-*O*-triethylsilyl-2-deoxy-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (86)



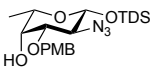
According to general procedure C, glycosyl donor **82** (82 mg, 0.15 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **23** (120 mg, 0.22 mmol, 1.5 eq). Column chromatography (5:95 EtOAc:pentane - 1:400 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) of the residue gave the title compound as a red solid (80 mg, 86 µmol, 67%, 2.2: 1 α:β). Spectral data for the α -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.01 (s, 1H), 13.20 (s, 1H), 8.02 – 7.95 (m, 1H), 7.79 – 7.68 (m, 1H), 7.38 (dt, *J* = 8.7, 1.4 Hz, 1H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.40 (dd, *J* = 3.8, 2.3 Hz, 1H), 5.00 – 4.81 (m, 2H), 4.58 (s, 1H), 4.08 (d, *J* = 0.9 Hz, 3H), 3.96 (q, *J* = 6.4 Hz, 1H), 3.78 – 3.66 (m, 3H), 3.58 – 3.47 (m, 1H), 3.43 – 3.33 (m, 1H), 3.29 – 2.95 (m, 2H), 2.33 – 2.11 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.07 – 0.84 (m, 27H), 0.79 – 0.50 (m, 12H), 0.18 – 0.08 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 186.9, 186.8, 161.1, 156.4, 155.7, 135.7, 135.5, 134.5, 133.3, 129.1, 128.3, 125.4, 120.9, 119.8, 118.5, 111.7, 111.5, 99.3, 77.5, 74.9, 71.0, 68.9, 66.6, 60.7, 56.8, 26.0, 17.0, 7.1, 7.0, 5.3, 4.9, -5.2, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{69}N_3O_{12}Si_3Na$ 950.4081; found 950.4103.

Thexyldimethylsilyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-β-L-fucopyranoside (87)



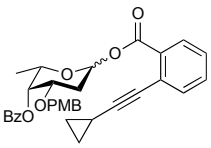
To a solution of fucosyl selenide **76** (2.10 g, 5.10 mmol) in 10:1 MeCN:H_2O (93.5 mL,v/v) was added *N*-iodosuccinimide (1.61 g, 7.14 mmol, 1.4 eq). After stirring for 30 minutes, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the intermediate lactol, an orange wax, as a mixture of anomers (1.37 g, 5.00 mmol, 98%, 1:1 α:β). This lactol was then dissolved in DCM (7.6 mL) and after adding imidazole (1.02 g, 15.0 mmol, 3 eq) the solution was stirred for 5 minutes, whereupon thexyldimethylsilyl chloride (1.5 mL, 7.5 mmol, 1.5 eq) was added. After stirring for 2.5 hours, the resulting solution was diluted with DCM and the organic layer successively washed with 1M aq. HCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 EtOAc:pentane) afforded the title compound as a colorless oil (1.99 g, 4.79 mmol, 96%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.15 (dd, *J* = 3.3, 1.0 Hz, 1H), 4.75 (dd, *J* = 10.9, 3.5 Hz, 1H), 4.54 (d, *J* = 7.6 Hz, 1H), 3.72 (q, *J* = 6.4 Hz, 1H), 3.55 (dd, *J* = 10.9, 7.6 Hz, 1H), 2.18 (s, 3H), 2.04 (s, 3H), 1.69 (hept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.92 – 0.88 (m, 12H), 0.21 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.0, 97.1, 77.5, 77.2, 76.8, 71.4, 69.7, 69.1, 63.4, 33.9, 25.0, 20.8, 20.8, 20.0, 19.9, 18.6, 18.5, 16.2, -2.0, -3.1.

Thexyldimethylsilyl 2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (88)



To a solution of diacetate **87** (1.87 g, 4.51 mmol) in MeOH (15 mL) was added sodium methoxide (51.7 mg, 0.968 mmol, 0.2 eq). After stirring overnight, the resulting solution was neutralized by the addition of acetic acid and then concentrated *in vacuo*, redissolved in toluene, filtered and concentrated *in vacuo* to afford the crude intermediate diol as a green oil. This diol was then dissolved in toluene (30 mL) together with dibutyltin oxide (1.36 g, 5.46 mmol, 1.2 eq). The resulting solution was stirred for 2.5 hours at 105 °C and successively coevaporated thrice with toluene to afford the *in situ* formed stannylene acetal as a viscous orange oil. The latter was then redissolved in toluene (30 mL) and tetra-*n*-butylammonium bromide (2.18 g, 6.76 mmol, 1.5 eq) and *p*-methoxybenzyl chloride (916 µL, 6.76 mmol, 1.5 eq) were added consecutively. After stirring at 90 °C for 1.5 hours, this was concentrated *in vacuo*, subsequently partitioned between DCM and H_2O and the organic layer dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the title compound as a colorless oil (1.88 g, 4.16 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.62 (s, 2H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.79 (s, 3H), 3.65 (br.s, 1H), 3.51 – 3.39 (m, 2H), 3.22 (dd, *J* = 10.1, 3.3 Hz, 1H), 2.45 (d, *J* = 2.4 Hz, 1H), 1.66 (hept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.91 – 0.86 (m, 12H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 129.6, 129.4, 114.0, 96.9, 79.0, 77.5, 77.2, 76.8, 71.7, 70.2, 68.3, 65.1, 55.3, 33.9, 24.9, 20.0, 19.9, 18.5, 18.4, 16.5, -1.9, -3.3. HRMS: $[M+Na]^+$ calculated for $C_{22}H_{37}N_3O_5SiNa$ 474.62822; found 474.2405.

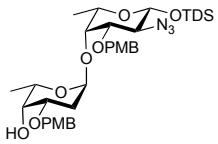
***o*-Cyclopropylethynylbenzoyl 4-*O*-benzoyl-2-deoxy-3-*O*-*p*-methoxybenzyl-α,β-L-fucopyranoside (89)**



To a solution of thiofucoside **34** (929 mg, 2.00 mmol) in 10:1 MeCN:H_2O (34.2 mL, v/v) was added *N*-iodosuccinimide (540 mg, 2.40 mmol, 1.2 eq). After stirring for 1 hour, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude intermediate lactol as a yellow oil. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the title compound as a yellow oil (912 mg, 1.69 mmol, 84%, 1:2.5 α:β). Spectral data for the α and β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.16 (m, 2H), 8.16 – 8.13 (m, 1H), 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.53 – 7.40 (m, 6H), 7.35 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.03 – 5.95 (m, 1H), 5.67 (app. br. s, 1H), 5.54 (app. d, *J* = 2.5 Hz, 1H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.42 – 4.38 (m, 1H), 4.29 – 4.19 (m, 1H), 3.89 (qd, *J* = 6.5, 0.8 Hz, 1H), 3.79 (s, 4H), 3.78 – 3.76 (m, 1H), 3.75 (s, 1H), 2.34 (ddd, *J* = 13.6, 9.1, 3.7 Hz, 1H), 2.24 – 2.14 (m, 3H), 1.51 (tt, *J* = 7.8, 5.3 Hz, 1H), 1.43 (tt, *J* = 8.1, 5.2 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 1H), 0.94 – 0.88 (m, 4H), 0.88 – 0.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 165.0, 164.5, 159.4, 159.4, 134.8, 134.4, 133.3, 133.3, 132.2, 132.0, 130.9,

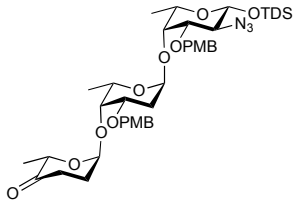
130.8, 130.8, 130.1, 130.0, 130.0, 129.9, 129.9, 129.6, 129.5, 128.6, 128.5, 127.4, 127.1, 125.2, 124.6, 114.0, 113.9, 100.1, 99.9, 93.8, 93.2, 77.5, 76.8, 75.1, 74.6, 73.6, 71.2, 71.1, 70.2, 70.1, 69.3, 68.5, 68.3, 55.4, 55.4, 32.4, 30.7, 17.2, 16.9, 9.1, 9.1, 9.1, 9.0, 0.8, 0.8. HRMS: $[M+Na]^+$ calculated for $C_{33}H_{32}O_7Na$ 563.20402; found 563.2048.

Thexyldimethylsilyl 2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (90)



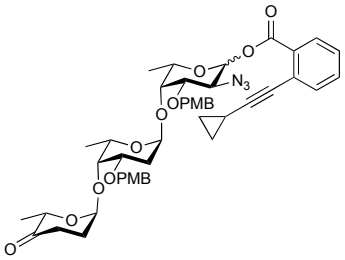
Method 1: Acceptor **88** (0.905 g, 2.00 mmol) and donor **34** (1.30 g, 2.81 mmol, 1.4 eq) were coevaporated thrice with toluene and then dissolved in DCM (25 mL), after which activated 4 Å molecular sieves were added and stirred for 30 minutes. This solution was then cooled to -78 °C, whereupon *N*-iodosuccinimide (631 mg, 2.81 mmol, 1.4 eq) and trifluoromethanesulfonic acid (52.8 µL 0.601 mmol, 0.3 eq) were added consecutively. After stirring for 30 minutes, the solution was allowed to warm up to -40 °C over the course of 30 minutes and was subsequently neutralized by the dropwise addition of triethylamine (646 µL) while stirring commenced for 10 minutes. Hereafter, the resulting solution was filtered, diluted with $CHCl_3$ and the organic layer successively washed with 10% aq. $Na_2S_2O_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (7:93 EtOAc:pentane) afforded the protected α-disaccharide (509 mg, 0.632 mmol, 32%) and an inseparable α:β mixture (1:2.2 α:β, 429 mg, 0.532 mmol, 26%) as colorless oils. *Method 2:* Acceptor **88** (45.2 mg, 0.1 mmol) and donor **89** (75.7 mg, 0.14 mmol, 1.4 eq, 1:2.5 α:β) were coevaporated thrice with toluene and then dissolved in DCM (2 mL), after which activated 4 Å molecular sieves were added, and stirred for 30 minutes. This solution was then cooled to -78 °C, whereupon freshly prepared PPh_3AuNTf_2 (0.1 M solution in DCM, 0.1 mL, 0.01 mmol, 0.1 eq) was added. After stirring overnight while warming up to ambient temperature, the resulting solution was filtered and concentrated *in vacuo*. Purification by column chromatography (6:94 -10:90 EtOAc:pentane) afforded the protected α-disaccharide as a colorless oil (67.9 mg, 0.084 mmol, 84%, 14:1 α:β). Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 – 8.07 (m, 2H), 7.55 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.55 (br. s, 1H), 5.10 (d, *J* = 2.6 Hz, 1H), 4.80 – 4.71 (m, 2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.56 (q, *J* = 6.5 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 7.6 Hz, 1H), 4.13 (ddd, *J* = 9.1, 6.5, 2.7 Hz, 1H), 3.80 (s, 3H), 3.79 (d, *J* = 3.1 Hz, 1H), 3.75 (s, 3H), 3.52 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.40 (q, *J* = 6.4 Hz, 1H), 3.16 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.18 – 2.09 (m, 2H), 1.70 (hept, *J* = 6.7 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.93 – 0.89 (m, 12H), 0.20 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 159.4, 159.3, 133.0, 130.3, 130.2, 129.9, 129.8, 129.7, 129.2, 128.4, 113.9, 113.9, 100.0, 97.3, 77.8, 77.5, 76.8, 75.0, 71.7, 71.4, 70.8, 70.1, 69.9, 65.9, 65.5, 55.4, 55.3, 34.0, 31.6, 25.1, 20.2, 20.1, 18.6, 18.6, 17.3, 17.1, -1.8, -2.7. HRMS: $[M+Na]^+$ calculated for $C_{43}H_{59}N_3O_{10}SiNa$ 828.38619; found 828.3885. To a solution of the above disaccharide benzoate (467 mg, 0.579 mmol) in MeOH (23 mL) and DCM (3 mL) was added sodium methoxide (0.50 g, 9.26 mmol, 16 eq) portion wise over the duration of 3 weeks, whereupon the resulting solution was neutralized by the dropwise addition of AcOH. The solution was then concentrated *in vacuo*, redissolved in DCM, filtered and concentrated *in vacuo*. Purification by column chromatography (10:90 – 40:60 EtOAc:pentane) afforded the title compound as a colorless oil (256 mg, 0.365 mmol, 63%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.92 – 6.85 (m, 4H), 4.98 (d, *J* = 3.4 Hz, 1H), 4.75 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.54 (s, 2H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 6.6 Hz, 1H), 3.96 (ddd, *J* = 11.9, 4.9, 2.9 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.76 – 3.73 (m, 2H), 3.49 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.37 (q, *J* = 6.4 Hz, 1H), 3.12 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.20 (s, 1H), 2.08 (dd, *J* = 12.6, 5.0 Hz, 1H), 1.94 (td, *J* = 12.3, 3.7 Hz, 1H), 1.69 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.93 – 0.87 (m, 12H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 159.3, 130.1, 129.8, 129.6, 129.2, 114.0, 113.9, 99.7, 97.2, 77.8, 77.5, 76.8, 74.6, 72.6, 71.4, 70.8, 69.9, 68.5, 66.1, 65.4, 55.3, 55.3, 34.0, 29.8, 25.0, 20.1, 20.1, 18.6, 18.6, 17.3, 17.0, -1.8, -2.8. HRMS: $[M+Na]^+$ calculated for $C_{36}H_{55}N_3O_9SiNa$ 724.35998; found 724.3614.

Thexyldimethylsilyl 2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (91)



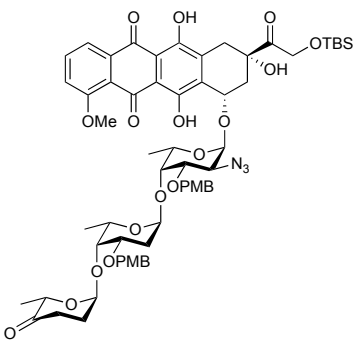
Acceptor disaccharide **90** (246 mg, 0.351 mmol) and donor **35** (161 mg, 0.491 mmol, 1.4 eq) were coevaporated thrice with toluene and then dissolved in 4:1 Et_2O:DCE (4 mL, v/v), after which activated 4 Å molecular sieves were added, and stirred for 1 hour. This solution was then cooled to 10 °C, whereupon iodonium di-*sym*-collidine perchlorate (658 mg, 1.40 mmol, 4 eq) was added. After stirring for 1 hour, the resulting solution was filtered, diluted with Et_2O and successively washed with 10% aq. $Na_2S_2O_3$, 1M aq. $CuSO_4$ and H_2O. The combined aqueous layers were then extracted with Et_2O and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (6:94 – 10:90 EtOAc:pentane), followed by size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH), afforded the crude protected trisaccharide. To a solution of this crude trisaccharide benzoate in MeOH (3 mL) and DCM (1 mL) was added sodium methoxide (72 mg, 1.37 mmol, 4.3 eq). After stirring for 3 days, the resulting solution was neutralized by the dropwise addition of acetic acid and concentrated *in vacuo*. Purification by column chromatography (10:90 – 40:60 EtOAc:pentane) afforded the trisaccharide as a white crystalline solid (208 mg, 0.255 mmol, 80% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 4H), 6.91 – 6.84 (m, 4H), 5.02 (d, *J* = 2.6 Hz, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.41 (q, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.22 (q, *J* = 6.5 Hz, 1H), 3.91 (td, *J* = 8.6, 2.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (s, 1H), 3.73 (s, 1H), 3.51 (s, 1H), 3.44 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.36 (q, *J* = 6.4 Hz, 1H), 3.10 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.13 – 2.02 (m, 3H), 1.92 (tt, *J* = 13.3, 4.0 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.91 – 0.87 (m, 12H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.1, 130.6, 129.7, 129.2, 129.0, 113.8, 113.7, 99.7, 98.5, 97.1, 77.7, 77.5, 76.8, 75.4, 74.2, 72.2, 71.3, 70.7, 69.8, 67.8, 67.5, 66.4, 65.4, 55.2, 33.9, 30.5, 29.7, 25.8, 24.9, 23.5, 20.1, 18.5, 17.5, 17.2, 17.1, -1.9, -2.8. HRMS: $[M+Na]^+$ calculated for $C_{42}H_{65}N_3O_{11}SiNa$ 838.42806; found 838.4315. To a solution of the above trisaccharide alcohol (208 mg, 0.255 mmol) in DCM (21.5 mL), $NaHCO_3$ (771 mg, 9.18 mmol, 36 eq) and Dess-Martin periodinane (260 mg, 0.612 mmol, 2.4 eq) were added consecutively. After stirring for 2 hours, 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ were added and vigorous stirring of the resulting biphasic mixture commenced for 1 hour, whereupon the organic layer was separated and the aqueous layer extracted thrice with DCM. The resulting combined organic layers were then successively washed with 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (10:90 – 30:70 EtOAc:pentane) afforded the title compound as a thick colorless oil (166 mg, 0.204 mmol, 80%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.91 – 6.85 (m, 4H), 5.06 – 4.99 (m, 2H), 4.76 – 4.67 (m, 2H), 4.62 – 4.55 (m, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 7.6 Hz, 1H), 4.27 (q, *J* = 6.4 Hz, 1H), 3.94 (ddd, *J* = 12.0, 4.6, 2.7 Hz, 1H), 3.84 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (d, *J* = 3.1 Hz, 1H), 3.46 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.37 (q, *J* = 6.4 Hz, 1H), 3.12 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.60 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.39 (ddd, *J* = 15.9, 7.6, 5.7 Hz, 1H), 2.27 (ddd, *J* = 14.0, 9.3, 4.8 Hz, 1H), 2.19 (dddd, *J* = 9.9, 7.6, 5.9, 2.7 Hz, 1H), 2.11 (dd, *J* = 12.3, 4.4 Hz, 1H), 2.02 (td, *J* = 12.1, 3.7 Hz, 1H), 1.67 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.87 (m, 12H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 159.3, 159.3, 130.5, 129.8, 129.4, 129.1, 113.9, 99.9, 97.8, 97.2, 77.8, 77.5, 76.8, 75.7, 74.6, 72.1, 71.8, 71.5, 70.8, 70.0, 67.6, 65.5, 55.4, 34.1, 34.0, 30.5, 29.8, 29.6, 25.0, 20.1, 20.1, 18.6, 18.6, 17.5, 17.3, 14.8, -1.8, -2.7. HRMS: $[M+Na]^+$ calculated for $C_{42}H_{63}N_3O_{11}SiNa$ 836.41241; found 836.4141.

***o*-Cyclopropylethynylbenzoyl 2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-L-fucopyranoside (92)**



To an ice-cooled solution of trisaccharide **91** (155 mg, 0.191 mmol) in pyridine (3.66 mL) and THF (7.63 mL), HF.pyr complex (70 wt% HF, 1.83 mL) was added dropwise. After stirring overnight while warming up to ambient temperature, the resulting solution was diluted with H_2O and the aqueous layer extracted with EtOAc. The organic layer was then successively washed with 1M aq. $CuSO_4$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (40:60 – 50:50 EtOAc:pentane) afforded the intermediate lactol. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (5:95 – 30:70 EtOAc:pentane) afforded title β benzoate (39 mg, 46.4 µmol, 26%) and an inseparable α/β mixture (32 mg, 38.1 µmol, 22%, 2.1:1 α:β) as light yellow oils. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.27 (m, 5H), 6.92 – 6.86 (m, 4H), 5.60 (d, *J* = 8.5 Hz, 1H), 5.07 (d, *J* = 2.8 Hz, 1H), 5.04 (app. t, *J* = 4.3 Hz, 1H), 4.78 (d, *J* = 12.1 Hz, 1H), 4.69 (q, *J* = 6.7 Hz, 1H), 4.66 – 4.61 (m, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.30 (q, *J* = 6.4 Hz, 1H), 3.97 (ddd, *J* = 11.8, 4.9, 2.6 Hz, 1H), 3.90 (d, *J* = 2.6 Hz, 1H), 3.86 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.82 – 3.80 (m, 1H), 3.75 (s, 3H), 3.65 (q, *J* = 6.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.61 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.40 (ddd, *J* = 15.6, 7.4, 5.5 Hz, 1H), 2.27 (app. td, *J* = 8.9, 4.6 Hz, 1H), 2.20 (app. ddt, *J* = 10.2, 6.2, 2.6 Hz, 1H), 2.13 – 2.09 (m, 1H), 2.05 (dd, *J* = 12.0, 3.9 Hz, 1H), 1.51 (tt, *J* = 7.5, 5.8 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.87 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 164.0, 159.5, 159.3, 134.5, 132.4, 130.8, 130.4, 130.2, 129.3, 129.2, 127.1, 125.6, 114.0, 113.9, 100.2, 100.0, 98.0, 93.6, 78.3, 77.5, 76.8, 75.5, 74.5, 74.1, 72.3, 72.2, 71.9, 71.7, 70.1, 67.7, 62.0, 55.4, 55.3, 34.1, 30.6, 29.6, 17.5, 17.1, 14.9, 9.1, 9.0, 0.9. HRMS: $[M+Na]^+$ calculated for $C_{46}H_{53}N_3O_{12}Na$ 862.35214; found 862.3541.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (93)



According to general procedure C, glycosyl donor **92** (18.0 mg, 21.4 µmol, 1:1.5 α:β) was coupled to 14-O-TBS-doxorubicinone **23** (13.6 mg, 25.7 µmol, 1.2 eq). Purification by column chromatography (20:80 EtOAc:pentane then 2:98 – 100:0 acetone:toluene) afforded a red amorphous solid (12.0 mg, 10.2 µmol, 47%, >7.7:1 α:β). A second purification by column chromatography (2:98 – 10:90 acetone:toluene) afforded the title compound as a red amorphous solid (10 mg, 8.5 µmol, 40%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 14.08 (s, 1H), 13.28 (s, 1H), 8.04 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.22 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.53 (d, *J* = 3.2 Hz, 1H), 5.39 (t, *J* = 3.1 Hz, 1H), 5.05 (t, *J* = 2.6 Hz, 1H), 5.01 (t, *J* = 4.2 Hz, 1H), 4.88 (d, *J* = 19.9 Hz, 1H), 4.84 (d, *J* = 19.9 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.18 (q, *J* = 6.4 Hz, 1H), 4.18 (s, 1H), 4.09 (s, 3H), 3.99 (q, *J* = 6.6 Hz, 1H), 3.94 (br. s, 1H), 3.87 (ddd, *J* = 13.0, 6.6, 3.3 Hz, 1H), 3.84 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.59 – 3.54 (m, 2H), 3.23 (dd, *J* = 19.0, 1.7 Hz, 1H), 3.09 (d, *J* = 18.9 Hz, 1H), 2.59 (ddd, *J* = 15.1, 9.0, 5.8 Hz, 1H), 2.39 (ddd, *J* = 15.7, 7.4, 5.5 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.24 – 2.19 (m, 1H), 2.20 – 2.13 (m, 1H), 2.07 – 2.01 (m, 2H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.96 – 0.93 (m, 3H), 0.15 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.3, 211.1, 187.2, 187.0, 161.2, 159.4, 159.3, 156.4, 155.7, 135.9, 135.7, 134.4, 133.2, 130.4, 129.5, 129.3, 129.1, 121.2, 120.0, 118.6, 114.0, 113.9, 111.9, 111.7, 100.0, 99.8, 97.9, 77.4, 76.9, 75.5, 75.2, 74.8, 72.2, 71.9, 71.6, 70.1, 68.9, 68.1, 67.8, 66.7, 59.2, 56.9, 55.5, 55.4, 36.0, 34.5, 34.1, 32.1, 31.6, 30.7, 30.5, 29.9, 29.6, 26.0, 22.8, 18.7, 17.4, 17.3, 14.9, 14.3, 0.1, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{61}H_{75}N_3O_{19}SiNa$ 1204.46562; found 1204.4666.

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