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

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Chapter 3

Design and synthesis of doxorubicin/aclarubicin hybrids

Introduction

Anthracyclines comprise one of the most successful classes of natural products in history from which chemotherapeutic agents have been derived.[1] Two archetypal anthracyclines are doxorubicin (**1**, Figure 1) and aclarubicin, also known as aclacinomycin A[2] (**12**), both effective anti-cancer agents that have been used for several decades in the clinic.[3] Today doxorubicin is prescribed in the Western world for the treatment of a variety of cancers. Aclarubicin finds widespread use in Asia, also for combating various cancers.[4] Although structurally closely related, doxorubicin and aclarubicin feature a few notable differences in both their glycan and aglycon moieties. These structural differences that cause anthracyclines to display distinct biological activities are at the basis of the remarkable (though as of yet poorly understood) differences in their clinical manifestation. Doxorubicin induces severe cumulative cardiotoxicity, and clinical treatment with doxorubicin is therefore limited to six to eight doses.[5–7] In contrast, aclarubicin is more than a tenfold less cardiotoxic[8] and recent research by the group of Neefjes has provided evidence that this difference in toxicity may be related to the differences in the modes of action of the two compounds.[9] Doxorubicin causes disruption of chromatin structure by inducing histone eviction, and causes DNA double strand cleavages. Aclarubicin is capable of evicting histones as well, but DNA strands remain unaffected in cells treated with this agent. Furthermore, the non-cardiotoxic chemotherapeutic agent etoposide is able to induce DNA breaks but not histone eviction. This has led to the hypothesis that anthracyclines that effect both DNA double strand cleavage and histone eviction are cardiotoxic, whereas histone eviction alone suffices for anticancer activity.

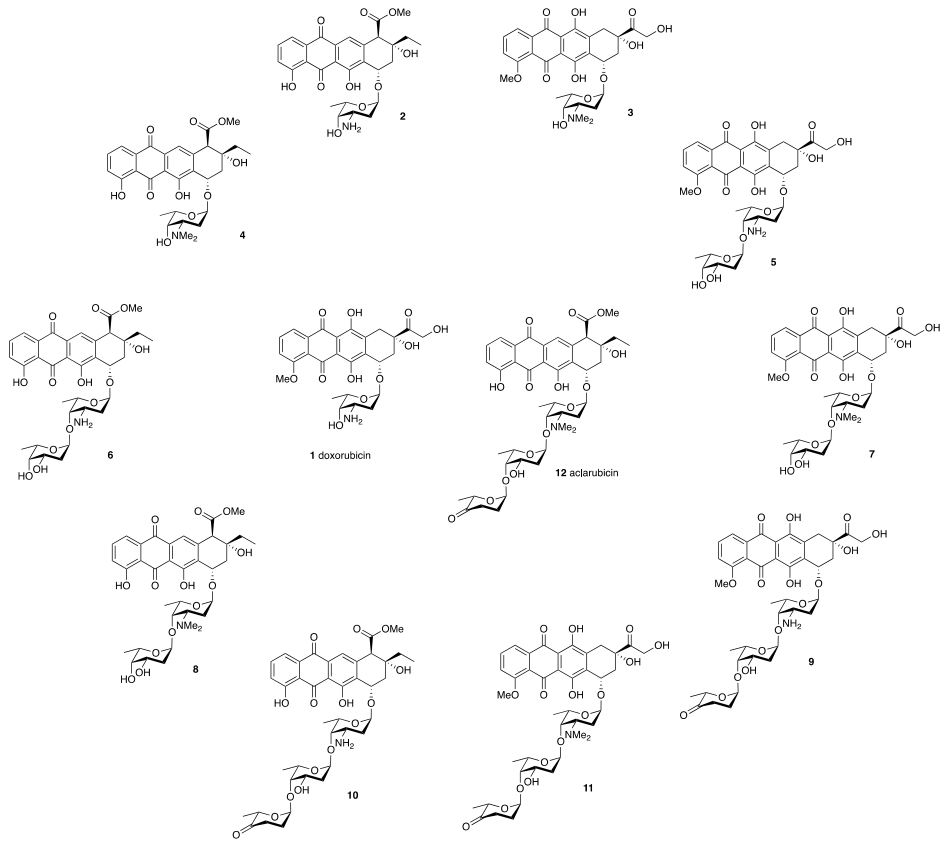
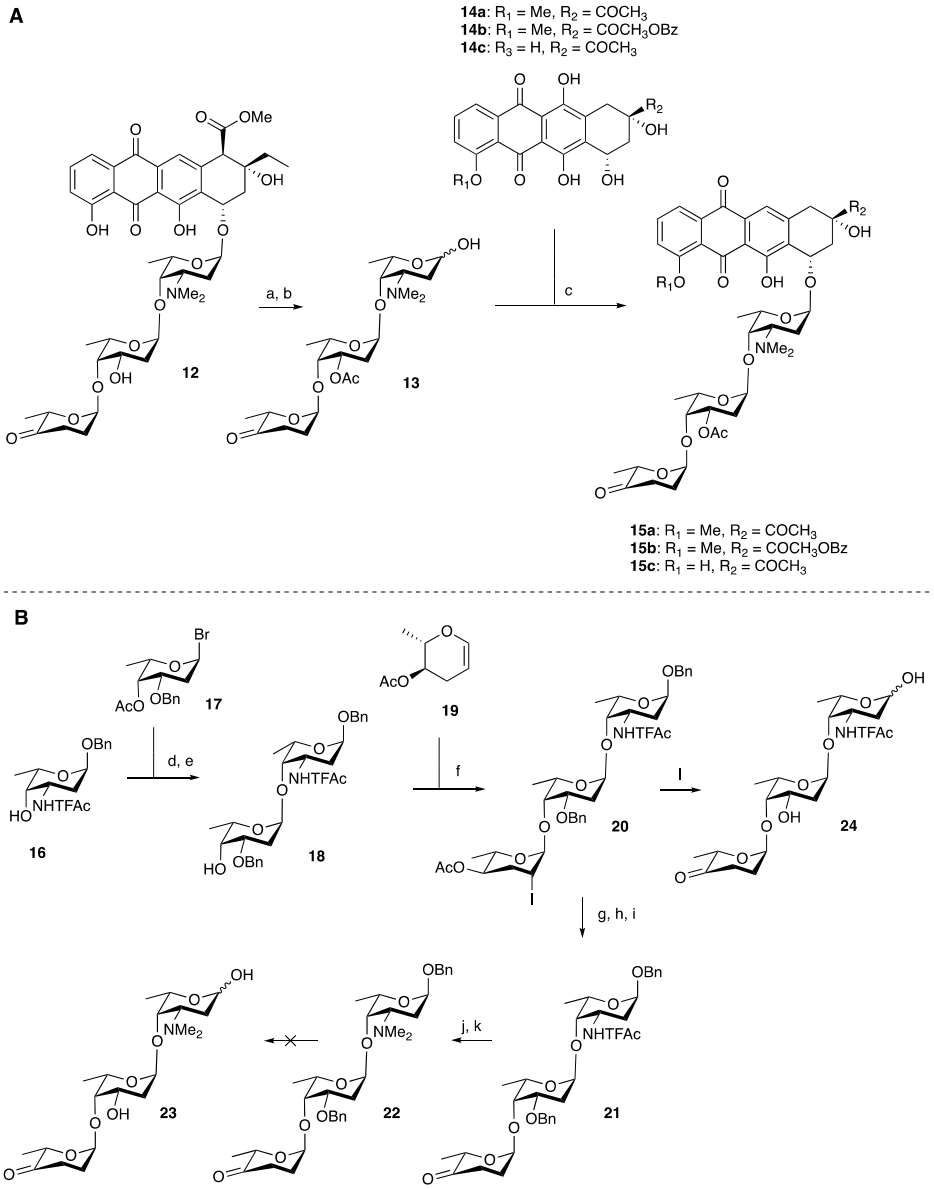


Figure 1. Chemical structures of doxorubicin (**1**), aclarubicin (**12**) and hybrid structures **2** – **11** subject of this Chapter.

Structural differences between doxorubicin and aclarubicin that may cause the diverging biological activities, can be divided into three categories: variation in the anthraquinone aglycon, in the (length of the) carbohydrate fragment and in the substitution pattern of the sole amine in both compounds. The anthraquinone portions have the same general architecture but vary at places in substitution/oxidation pattern. Doxorubicin features an α-L-daunosamine as the single, monosaccharidic carbohydrate fragment. Aclarubicin features an α-L-rhodosamine (*N*,*N*-dimethyldaunosamine), that is further glycosylated on its 4-hydroxyl function with an α-(1→4) disaccharide composed of L-oliose and L-cinerulose A. The differences in activity of doxorubicin and aclarubicin may be due to the difference in the overall architecture, or to one of the three distinguishing features as outlined above: the variant aglycon, the lack of *N*-methylation or the lack of additional deoxyfucose sugars. In order to assess whether distinct structural differences are at the basis of the divergent activity, a set of doxorubicin/aclarubicin hybrids (**2** – **11**, Figure 1) was designed, which comprises

anthracyclines composed of either of the two aglycons featuring a monosaccharide, a disaccharide or a trisaccharide glycan composed of the sugar configurations found in the parent structures, and with the amines bearing no or two methyl substituents.



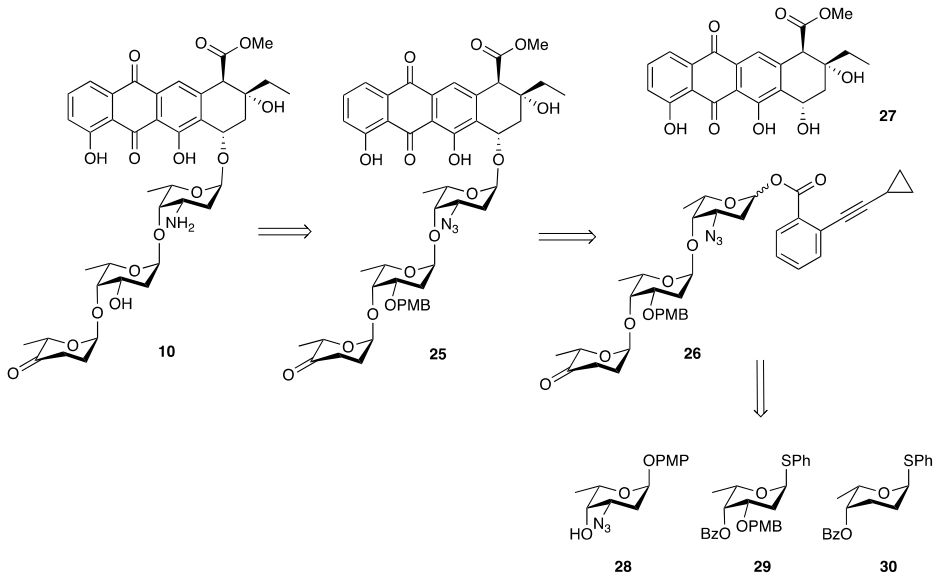
Scheme 1. Reported syntheses of the trisaccharide moiety found in aclarubicin (**12**). *Reagents and conditions:* (a) Ac_2O, pyr., 96%; (b) Pd/$BaSO_4$, MeOH, 98%; (c) Tf_2O, TBABr, *sym*-collidine, -70 °C, 33% for **15a**, 32% for **15b**, 20% for **15c**; (d) Ag_2O, $HgBr_2$, DCM, 0 °C to RT, 40%; (e) NaOMe, MeOH, 97%; (f) NIS, MeCN, 0 °C, 68%; (g) Pd/C, Et_3N, EtOH, 87%; (h) NaOMe, MeOH, 95%; (i) pyridinium dichromate, DCM, 91%; (j) K_2CO_3, MeOH, H_2O, 68%; (k) aq. CH_2O, $NaBH_3CN$, MeCN, 90%; (l) Pd/C, EtOAc, 85%.

Although the synthesis of anthraquinone monosaccharides has gathered considerable attention[10], only few studies on the synthesis of the di- and trisaccharide motifs discussed in this Chapter have been reported. Tanaka and co-workers, who reported the isolation and structure of aclarubicin (**12**), described the cleavage of the trisaccharide moiety from the parent drug for use in glycosylation to different aglycons.[11] They accomplished this feat by acetylation and hydrogenation ($Pd/BaSO_4$) of aclarubicin (**12**) to yield the (3'-) protected trisaccharide hemi-acetal **13**. Anomeric triflation in the presence of tetra-*n*-butylammonium bromide (TBABr) and *sym*-collidine was followed by addition of aglycones **14a**-**14c** to yield the corresponding anthraquinone trisaccharides **15a**-**15c**. Although this gave quick access to the desired compounds, the yields of these glycosylations were modest (20-33%) and did not allow for variations on the trisaccharide (i.e. free amine or shorter saccharide chain) nor did it result in any methodology on assembling the trisaccharide itself. Monneret *et al*. synthesized the protected trisaccharide found in aclarubicin in 1988.[12] Glycosylation of L-oliosyl bromide **17** under Koenigs-Knorr conditions to L-daunosaminyl acceptor **16** yielded the desired orthogonally protected disaccharide α-selectively in 40% yield. Deacetylation yielded **18** and was followed by addition of L-amicetosyl glycal **19** in the presence of *N*-iodosuccinimide to yield **20**. Removal of the 2"-iodide through hydrogenolysis was followed by Zemplén conditions (NaOMe, MeOH) to remove the 4"-acetyl, followed by pyridinium dichromate oxidation of the resultant alcohol to yield orthogonally protected cineruloside **21**. Removal of the trifluoroacetyl (K_2CO_3, MeOH) followed by reductive alkylation yielded protected aclarubicin trisaccharide **22**. Removal of the remaining benzyl groups to give **23** was unsuccessful and instead hydrogenolysis before installation of the dimethylamino motif was suggested, to yield *N*-trifluoroacetylated **24**, which is to be dimethylated post-glycosylation. Overall, the authors were able to prepare the trisaccharide motif but did not report on glycosylation studies with donor glycosides derived from the trisaccharide.

This Chapter describes the design and synthesis of a focused library of mono-, di- and trisaccharides filling the chemical space between doxorubicin (**1**) and aclarubicin (**12**). The synthesis strategy relies on α-selective iterative IDCP-mediated thioglycosylations to assemble the trisaccharide motif. Glycosylation to the anthraquinone moiety was accomplished by a method developed in the group of Yu (see also Chapter 2), wherein anomeric *ortho*-alkynylbenzoates are used as glycosylating agents in the presence of catalytic amounts of gold(I) species.

Results and discussion

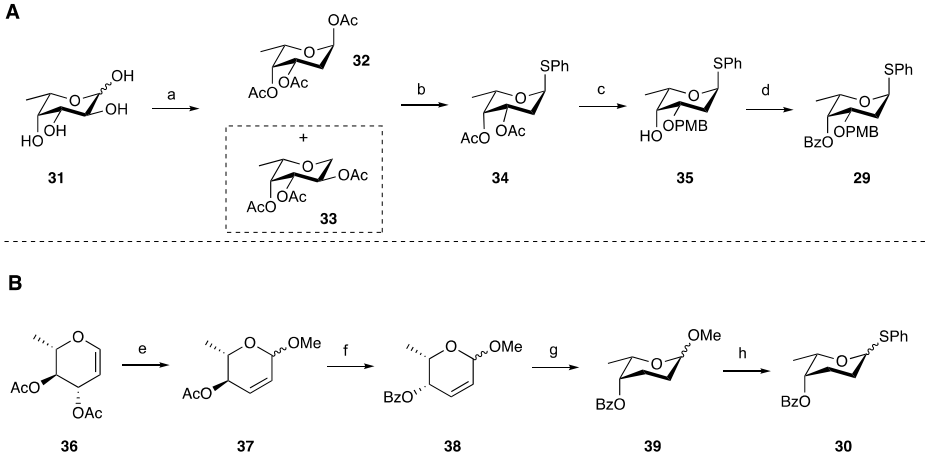
The retrosynthetic analysis for **10**, representative for the compounds prepared in this Chapter, is outlined in Scheme 2.



Scheme 2. Retrosynthesis of trisaccharide **10**, representative for the compounds prepared in this Chapter.

Orthogonally protected trisaccharide **25** contains a *p*-methoxybenzyl group on the 3''-hydroxyl function with the 3'-amine masked as an azide. Disconnection of the trisaccharide and the aglycon shows that *ortho*-alkynylbenzoate donor **26** can be attached to aklavinone (**27**, the aglycone found in aclarubicin) by means of the gold catalysis chemistry described in Chapter 2. The assembly of the trisaccharide motif may be effected by iterative IDCP-mediated thioglycosylations of L-daunosaminyl acceptor **28** (described in Chapter 2), L-oliosyl donor **29** and L-rhodinosyl donor **30**. The latter building blocks **29** and **30** are equipped with a C4-benzoate, allowing for long-range participation during the glycosylation reactions. Rhodinoside **30** serves as a precursor for the desired cinerulose moiety at the non-reducing end of the trisaccharide in **10**. The anomeric *p*-methoxyphenolate (OPMP) can be removed under mild oxidative conditions, thereby enabling introduction of the anomeric *ortho*-alkynylbenzoates required for the glycosylation reactions.

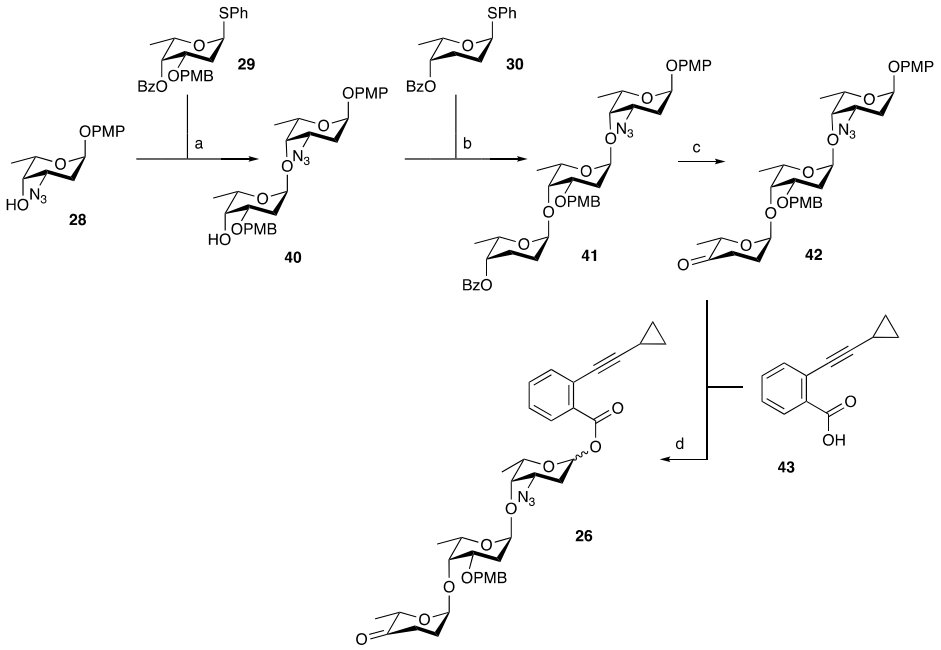
The synthesis of L-oliosyl donor **29** is depicted in Scheme 3A. According to the procedure reported by Gildersleeve *et al.*[13], L-fucose was transformed by sequential peracetylation, anomeric bromination (HBr) and radical-induced 1,2-*cis* migration



Scheme 3. Preparation of L-olioside and L-rhodinoside donors **29** and **30**. *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii.* HBr/AcOH, DCM; *iii.* Bu_3SnH, AIBN, toluene, 80 °C, 48% over 3 steps; (b) PhSH, $BF_3{\cdot}OEt_2$, DCM, -78 °C to 0 °C, 94% (10:1 α:β); (c) *i.* NaOMe, MeOH; *ii.* Bu_2SnO, toluene, 140 °C, then PMB-Cl, TBABr, toluene, 100 °C, o.n., 96% over 2 steps; (d) BzCl, pyr., DCM, 82%; (e) MeOH, $SnCl_4$, DCM, 80% (6:1 α:β); (f) *i.* NaOMe, MeOH; *ii.* benzoic acid, DEAD, PPh_3, THF, 0 °C, 70% over 2 steps (6:1 α:β); (g) Pd black, H_2, MeOH, 91%; (h) PhSH, $BF_3{\cdot}OEt_2$, DCM, -78 °C to -15 °C, 80% (α:β 1.2:1).

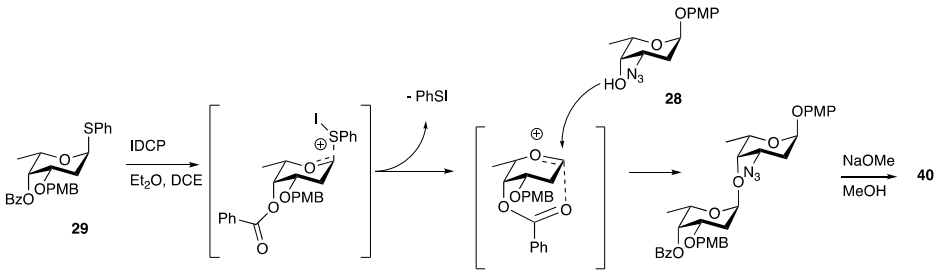
(Bu_3SnH, AIBN) of the 2-*O*-acetyl group to 2-deoxyfucoside **32**. In the latter step, the desired product was obtained together with tetrahydropyran **33** as a 3:1 mixture, as a result of quenching of the intermediate anomeric radical by tributyltin hydride *before* the 1,2-*cis*-migration - a phenomenon that was not observed by Gildersleeve and co-workers.[13] Regio-isomer **33** could be removed by crystallisation from ethanol. Next, installment of an anomeric thiophenyl group (PhSH, $BF_3{\cdot}OEt_2$) gave **34** as a 10:1 α:β mixture. Removal of the acetyl groups in **34** under Zemplén conditions was followed by installation of the 3-*O*-*p*-methoxybenzyl group using stannylene-acetal chemistry to yield **35** near quantitatively. A final benzoylation of the remaining 4-hydroxyl function yielded L-oliosyl donor **29**.

The synthesis of L-rhodinosyl donor **30** (Scheme 3B) commenced with L-rhamnal **36** (prepared in Chapter 2), using a method developed by Bhaté *et al*.[14] In this step, the C-3-acetate is eliminated in a Lewis acid mediated Ferrier rearrangement[15], after which methanol can attack the anomeric centre yielding methyl-*eno*-pyranoside **37**. This synthon was then deacetylated, after which the resulting allylic alcohol was subjected to a Mitsunobu-inversion with benzoic acid to give **38**.[16] Palladium-catalyzed hydrogenation of the double bond yielded the rhodinose-motif, after which installation of an anomeric thiophenyl moiety (PhSH, $BF_3{\cdot}OEt_2$, -78 °C to 0 °C) delivered donor **30** as a separable 1.2:1 α:β mixture.



Scheme 4. Preparation of trisaccharide *ortho*-alkynylbenzoate donor **26**. *Reagents and conditions:* (a) *i.* IDCP, Et_2O, DCE (4:1 v/v); *ii.* NaOMe, MeOH, 85% over 2 steps (α-only); (b) IDCP, Et_2O, DCE (4:1 v/v), 92% (α-only); (c) *i.* NaOMe, MeOH; *ii.* Dess-Martin periodinane, $NaHCO_3$, DCM, 98% over 2 steps; (d) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (2:3 α:β).

With the three building blocks **28**, **29** and **30** in hand, the synthesis of trisaccharide alkynylbenzoate donor **26** was undertaken as shown in Scheme 4. For the construction of the glycosidic linkages of the reactive and relatively acid labile 2,6-dideoxy and 2,3,6-trideoxyglycosides, iodonium di-collidinium perchlorate (IDCP) was explored as this reagent has previously been used for the synthesis of anthraquinone 2-deoxy saccharides[17] and for the activation of other reactive glycosyl donors.[18] Advantageous to this activation system is that it does not require addition of a strong (Lewis-) acid which can be detrimental to the 2-deoxy glycosidic bonds. Additionally, the reaction is buffered by the release of two equivalents of *sym*-collidine per donor activation event. Activation of thioglycoside **29** in the presence of acceptor **28** and IDCP in Et_2O/DCE stereoselectively yielded α-(1→4) linked disaccharide **40** after debenzoylation under Zemplén conditions. A stereochemical rationale for this selectivity is outlined in Scheme 5.

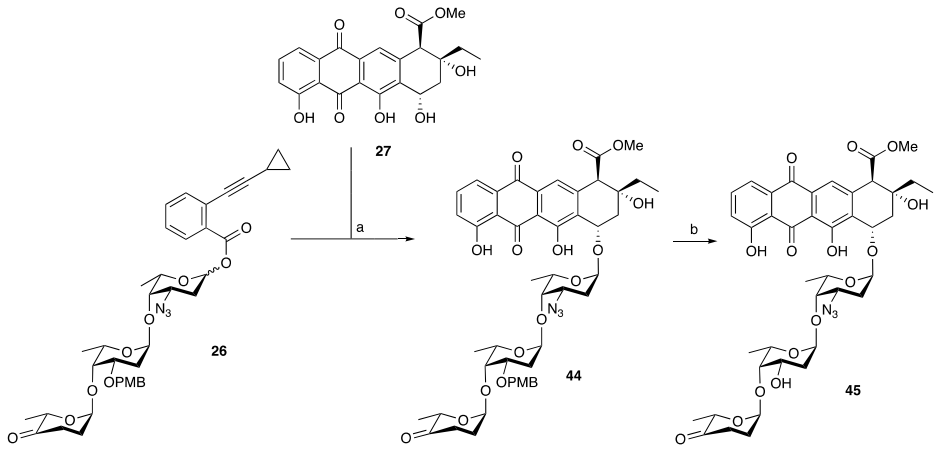


Scheme 5. Stereochemical rationale for α-glycosidic bond formation in **40**.

Upon treatment of donor **29** with IDCP, the formed oxocarbenium ion may be stabilized by electron density donation of the carbonyl of the 4-benzoate group as depicted in Scheme 5. The bottom face of the so-formed dioxolenium ion-like species is blocked, forcing acceptor **28** to attack the top face. The acceptor features a relatively poorly nucleophilic axial alcohol, with its reactivity further lowered by the neighboring 3-azide. In general, the decrease of acceptor nucleophilicity has been shown to promote α-selective glycosylations, possibly also taking place here.[19]

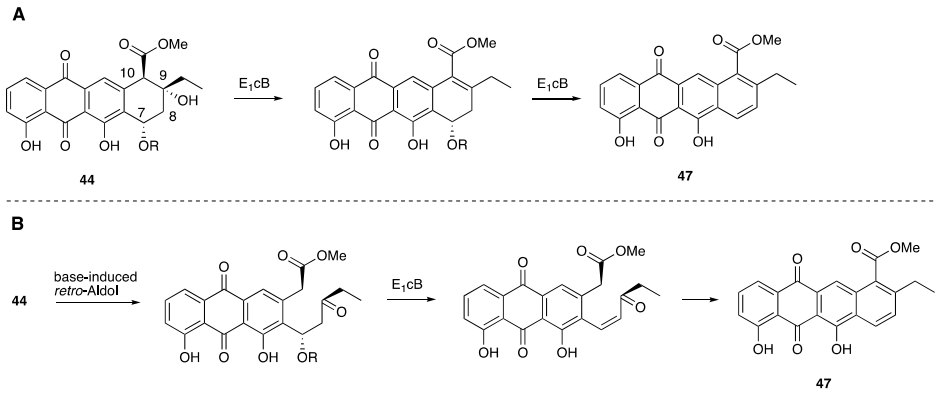
A mixture of disaccharide acceptor **40** and benzoyl-protected rhodinoside **30α** was subjected to IDCP to yield trisaccharide **41** in good yield and excellent α-selectivity. Deacylation of the benzoate in **41** and Dess-Martin oxidation of the resulting alcohol gave **42** near quantitatively. Treatment of **42** with ceric ammonium nitrate as the oxidant resulted in removal of both the anomeric *p*-methoxyphenyl protective group and the 3'-PMB group. DDQ removed solely the PMB group but left the anomeric phenolate intact. Gratifyingly, the silver(II)-mediated reaction conditions described in Chapter 2 were able to effect the orthogonal deprotection of the PMP group when a stoichiometric amount of the oxidant was used (more than 2 equivalents of $Ag(DPAH)_2$ resulted in partial removal of the PMB group). A final condensation of the so-obtained hemi-acetal with carboxylic acid **43** (described in Chapter 2) under Steglich conditions, yielded donor trisaccharide **26** ready for use in glycosylation events using Yu's gold-mediated glycosylation method.[20]

The synthesis of aklavinone (**27**), the acceptor chosen for the assembly of **10**, has been reported by several groups following the discovery of aclarubicin (**12**), both in racemic and enantiopure fashion.[21–27] More conveniently, acidic hydrolysis of aclarubicin (**12**) provides aglycon acceptor **27** quantitatively.[28] This set the stage for the key glycosylation envisaged, as shown in Scheme 6. Subjection of trisaccharide donor **26** and aklavinone (**27**) to a catalytic amount of PPh_3AuNTf_2 at -20 °C gave the desired trisaccharide **44** in 85% yield.



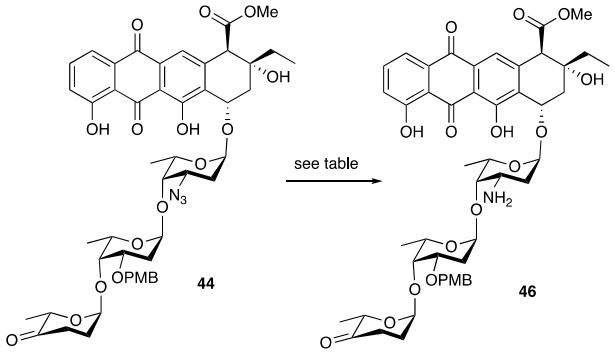
Scheme 6. Glycosylation of trisaccharide donor **26** to aklavinone **27** and ensuing attempted deprotections. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), 4 Å MS, DCM, 85% (8:1 α:β); (b) DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), quant.

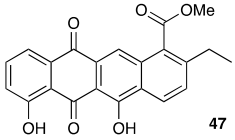
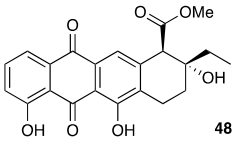
The stereoselectivity of the reaction was good (8:1 α:β), and the α-glycoside could be obtained in pure form by silica gel column chromatography. Removal of the PMB-ether was achieved using a large excess of DDQ in a biphasic, phosphate buffered system to yield the corresponding alcohol **45** quantitatively. Final azide deprotection however proved troublesome. Table 1 depicts the results from attempts at the reduction of the azide present in **44** into the desired amine, using phosphines, thiolates, hydrogenation and tin-hydride reagents. The Staudinger conditions as used in Chapter 2 (PPh_3, THF/H_2O) led to the formation of bisanhydroaklavinone **47**. This product has also been described in literature,[29,30] and has been referred in literature to as aclacinomycin F.[31] Two mechanistic explanations for the formation of **47** in the attempted azide reduction of **44** are given in Scheme 7.



Scheme 7. *Retro*-aldol / E_1cB pathway giving rise to fully aromatized aklavinone **47**.

Table 1. Azide-deprotecting conditions attempted on **44**.

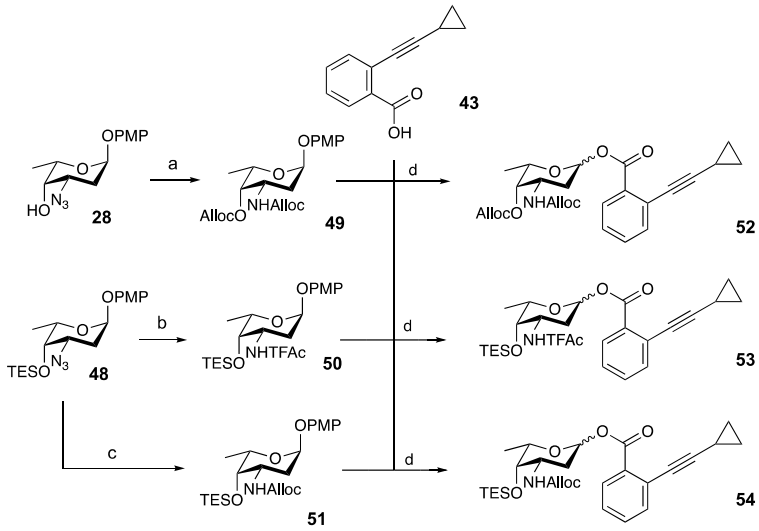


Entry	Deprotection conditions	Observed product(s)
1	PPh_3, THF/H_2O, 50 °C	 **47**
2	H_2S, THF/pyr.	**47**
3	1,3-propanedithiol, Et_3N, DMF	**47**
4	PtO_2, morpholine, H_2, THF	 **48**
5	PMe_3, THF/H_2O	Complex mixture
6	Lindlar's catalyst, MeOH	Complex mixture
7	Zn/NH_4Cl, MeOH/H_2O	Complex mixture
8	$Sn(SPh)_3HEt_3N$, THF	Complex mixture
9	Bu_2SnH_2	No conversion

E_1cB elimination, facilitated by the relatively acidic proton at C-10, would result in *net* dehydration over C-9 and C-10. This results in increased acidity of the C-8 protons, giving again a good E_1cB substrate, releasing the glycoside and resulting in fully aromatized **47**. Alternatively, the β-hydroxy ester might be able to undergo *retro*-aldol reaction to yield the corresponding keto-esters under basic condition. Base-induced elimination of the glycoside on C-7 in an E_1cB fashion is then facilitated by the newly

formed double bond being conjugated to the anthraquinone moiety. Then, aldol condensation closes the D-ring again, with a final dehydration process facilitated by full aromatization of this ring to also yield **47**. Subjection of **44** to a thiolate-based azide reduction (entries 2 and 3) resulted in the same degradation product. Hydrogenation of the azide was attempted using Adam's catalyst (PtO_2), which is known to be able to reduce azides whilst leaving benzyl groups intact.[32,33] Unfortunately cleavage of the benzylic trisaccharide could not be prevented, even when poisoning this catalyst with morpholine. Other procedures evaluated include the use of trimethylphosphine, Lindlar's catalyst (palladium on calcium carbonate), Zn/NH_4Cl, $Sn(SPh)_3HEt_3N$[34] and dibutyltin dihydride,[35] but all these reactions led to complex mixtures.

As the azide reduction required for the preparation of aklavinone-trisaccharide **10** proved very troublesome, other amine protecting groups were investigated, in the first instance for the preparation of monosaccharidic anthracyclines **2** and **4**.

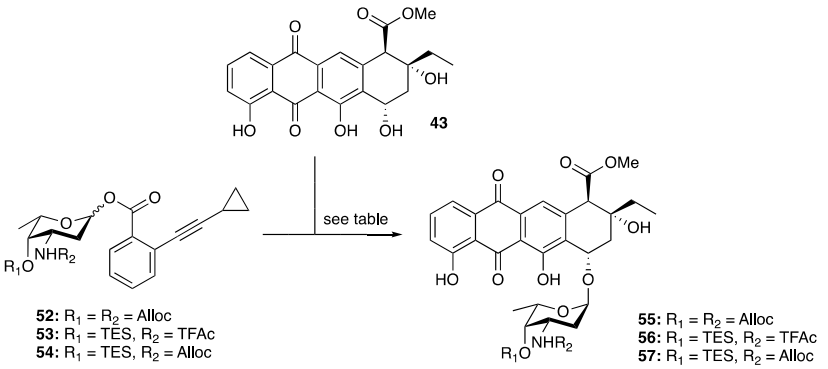


Scheme 8. Preparation of L-daunosamine *ortho*-alkynylbenzoate donors **52**-**54**. *Reagents and conditions:* (a) *i*. polymer-bound PPh_3, THF, H_2O; *ii.* allylchloroformate, pyr., DCM, -20 °C, 42% over 2 steps; (b) *i.* PPh_3, THF, H_2O; *ii.* trifluoroacetic anhydride, Et_3N, DCM, 91% over 2 steps; (c) polymer-bound PPh_3, THF, H_2O; *ii.* allylchloroformate, pyr., DCM, -20 °C, 88% over 2 steps; (d) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 98% over 2 steps for **51** (1:20 α:β), 66% over 2 steps for **52** (1:4 α:β), 73% over 2 steps for **53** (β only).

Protected L-daunosamine **28** (Chapter 2) was subjected to Staudinger reduction of the azide, followed by Alloc protection of both the amine and the hydroxyl group to yield **49**. Staudinger reduction of 4-silylated **48** (Chapter 2), followed by *N*-acylation with

either trifluoroacetic anhydride or allyl chloroformate yielded **50** and **51**, respectively. Conversion of *p*-methoxyphenyl acetals **49**-**51** proceeded analogously to the preparation of trisaccharide donor **26** in Scheme 4 to give *ortho*-alkynylbenzoates **52**-**54** in good yields.

Table 2. Glycosylation of *ortho*-alkynylbenzoates **52**-**54** to aklavinone **27**.



Reagents and conditions: (a) 2 eq of. **27**, PPh_3AuNTf_2 (10 mol%), 4 Å MS, T, 0.05M in DCM.

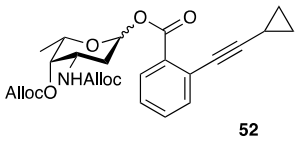
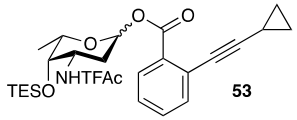
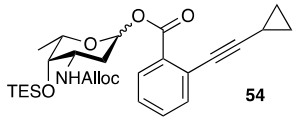
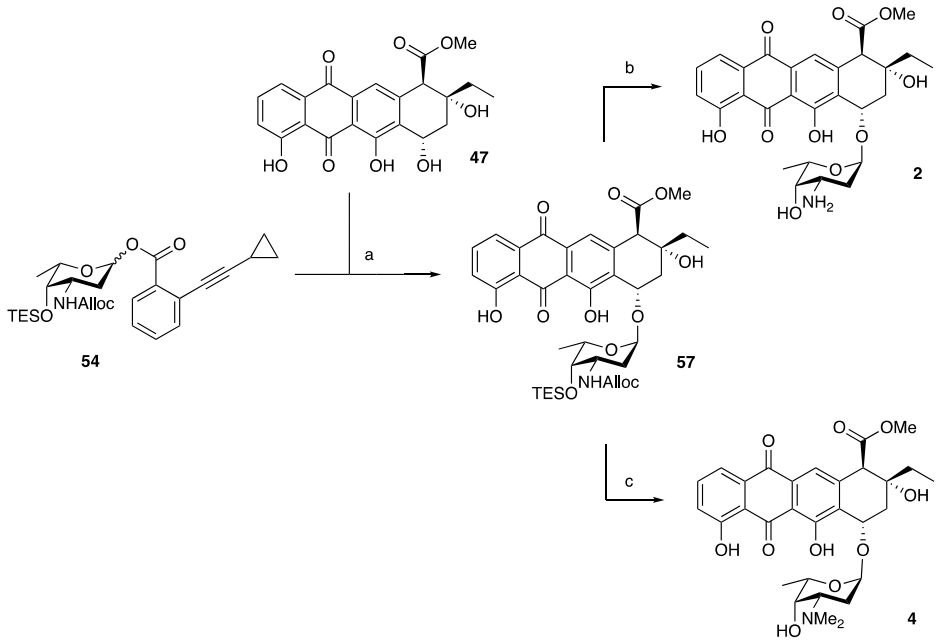
Entry	Donor	Temperature	Yield (α:β ratio).
1	 **52**	RT	58% (6.6:1 α:β)
2	-	-20 °C	93% (6.7:1 α:β)
3	-	-78 °C to RT	87% (6.3:1 α:β)
4	 **53**	RT	59% (>20:1 α:β)
5	 **54**	-20 °C	73% (>20:1 α:β)

Table 2 shows the glycosylation of *ortho*-alkynylbenzoates **52**-**54** to aklavinone **27** under PPh_3AuNTf_2 catalysis, towards the synthesis of **2** and **4**. The first three entries show the influence of temperature on the reaction outcome using donor **52**. All three reactions, performed at different temperatures (RT, -20 °C and -78 °C to -20 °C) gave a similar outcome in terms of stereoselectivtity (α/β = 6.3-6.7:1) providing inseparable

anomeric mixtures of **55**. The flexible 4-*O*-Alloc group may not be able to block the bottom-face of the ring as well as the bulky silyl ether, in the analogous building block, used in Chapter 2. By lowering the reaction temperature from RT to -20 °C, the yield of the glycosylation was significantly improved. Entries 4 and 5 show that *N*-trifluoroacetate and *N*-allyloxycarbamate protected donors **53** and **54** both provide

stereoselective glycosylations to yield **56** and **57**, respectively. Upon treatment of **55** with $Pd(PPh_3)_4$ and Me_2NTMS/TMSOAc as allyl-scavenger system,[36] **2** was obtained as a still inseparable anomeric mixture. Desilylation of **56** proceeded uneventfully but attempts at removal of the trifluoroacetamide (excess NaOMe, MeOH[22]) resulted in degradation of the aglycone moiety, as previously shown in Scheme 7.

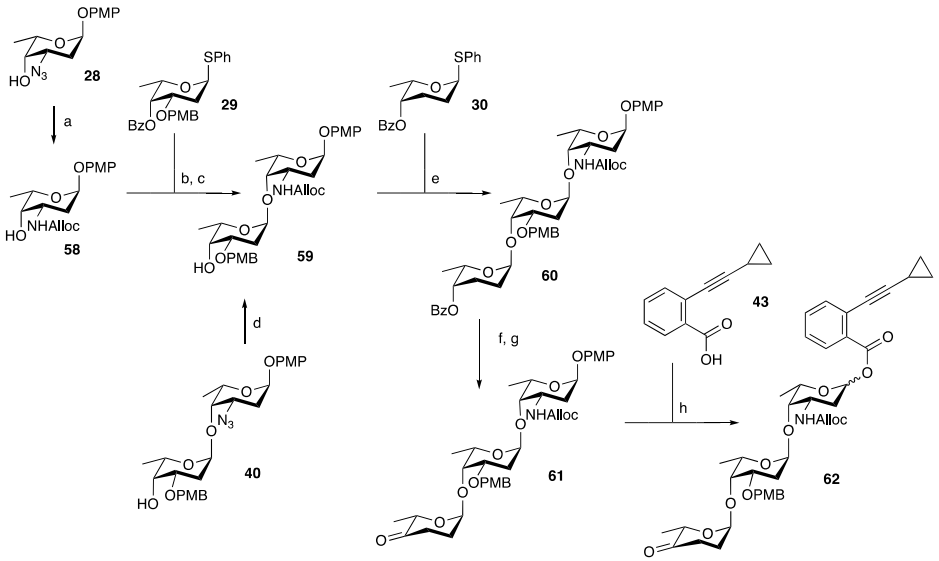


Scheme 9. Synthesis of aklavinone-monosaccharides **2** and **4**. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM, -20 °C, 73% (>20:1 α:β); (b) *i.* $Pd(PPh_3)_4$, NDMBA, DCM; *ii.* HF·pyridine, pyr., 40% over 2 steps; (c) *i.* $Pd(PPh_3)_4$, NDMBA, DCM; *ii.* aq. CH_2O, $NaBH(OAc)_3$, EtOH; *iii.* HF·pyridine, pyr., 43% over 3 steps.

Palladium-catalyzed removal of the *N*-Alloc group in **57** was performed using a catalytic amount of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid (NDMBA) as the allyl-scavenger,[37] as shown in Scheme 9. The use of the Me_2NTMS-TMSOAc-$Pd(PPh_3)_4$ system[36,37] was found to be inferior, as it often led to prolonged reaction times and significant formation of *N*-allylated products. This was followed by desilylation using HF·pyr complex to give known monosaccharide **2** in decent yield over 2 steps.[38]

The corresponding dimethylamine **4** could be prepared by the same removal of the Alloc group, followed by reductive alkylation to formaldehyde using $NaBH(OAc)_3$ and a final desilylation. The spectral data of **4** is in agreement with that described in the literature.[39]

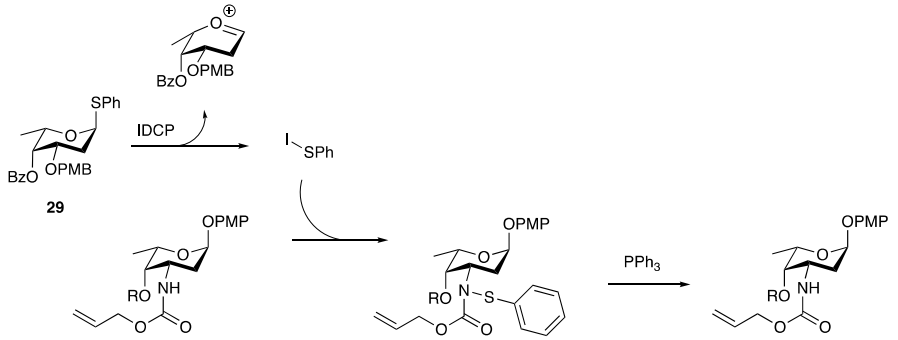
With the lessons learned from the synthesis of **2** and **4**, it was decided to switch the strategy for the preparation of the envisaged aklavinone trisaccharides to include the use of an Alloc carbamate as the amine protecting group, as shown for the synthesis of **10** in Scheme 10.



Scheme 10. Preparation of the *N*-allyloxycarbonyl protected trisaccharide donor **62**. *Reagents and conditions:* (a) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$, 89%; (b) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, 90%; (c) NaOMe, MeOH, 90%; (d) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$, 95%; (e) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, quant.; (f) NaOMe, MeOH, 85%; (g) Dess-Martin periodinane, $NaHCO_3$, DCM, 97%; (h) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (1:7 α:β).

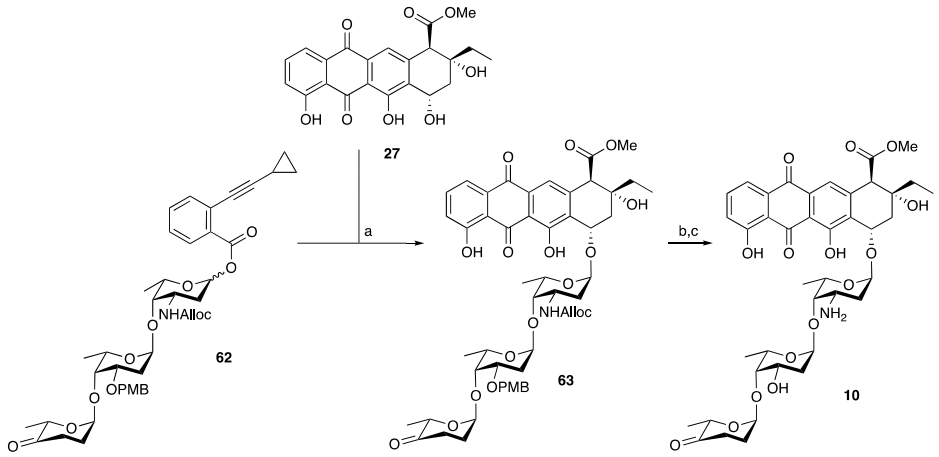
Azide acceptor **28** could easily be transformed into its Alloc counterpart **58** by treatment with triphenylphosphine in wet THF, followed by addition of *N*-allyloxycarbonylsuccinimide. Treatment of thioglycoside **29** and acceptor **58** with IDCP, as described in Scheme 4, gave the resulting disaccharide **59** in excellent yield and anomeric ratio after debenzoylation. During the course of the IDCP-glycosylation, it was observed that the released phenylthio-iodide was captured by the *N*-allyloxycarbamate moiety present in the acceptor.[17,40] As depicted in Scheme 11, addition of triphenylphosphine after the glycosylation to the resultant sulfenamide

cleaved the undesired N-S bond with release of phenylthio-(triphenylphosphonium) iodide and returned the carbamate function. This phenomenon can also occur in the preactivation of thioglycosides with the Tf_2O-diphenylsulfoxide promotor system when a carboxybenzyl-protected amine was present.[41]



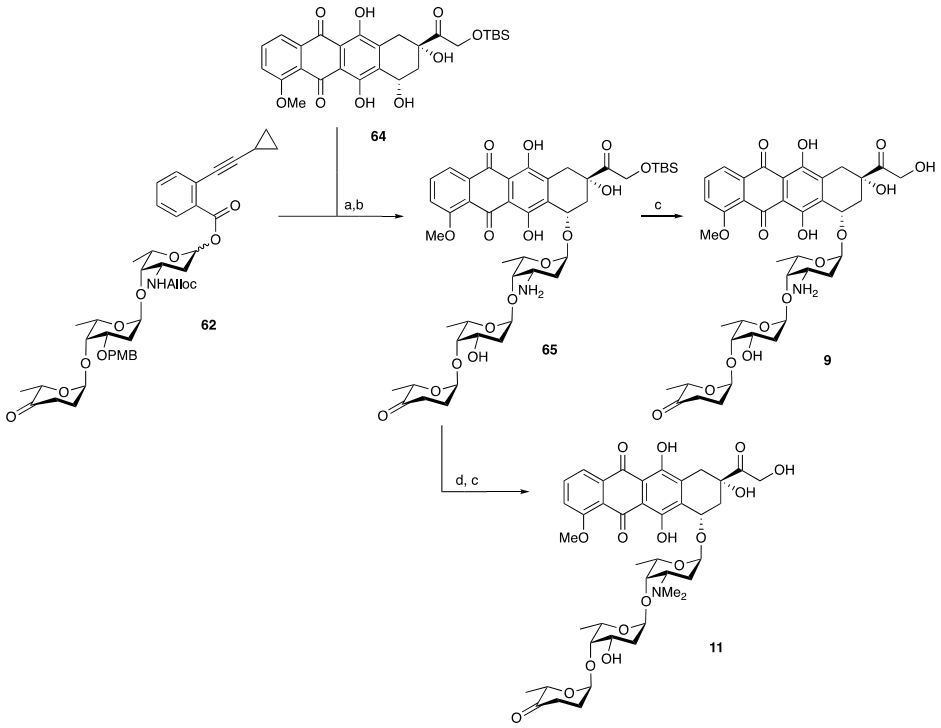
Scheme 11. Sulfenamide formation during IDCP-mediated glycosylation of *N*-Alloc-containing glycosides, and return of the carbamate upon addition of PPh_3.

Alloc-protected disaccharide **59** could also be prepared from 3-azide disaccharide **40** using the same procedure emplyed for the conversion of acceptor **28** to **58**. In the next glycosylation event, the addition of IDCP to the mixture of disaccharide acceptor **59** and thioglycoside **30** furnished trisaccharide **60** quantitatively. Deacylation of the C-4‴-benzoate, followed by Dess-Martin oxidation of the resulting alcohol gave cineruloside trisaccharide **61**. Conversion to the *ortho*-alkynylbenzoate proceeded analogously to the preparation of **26** in Scheme 4 to give *N*-Alloc protected trisaccharide donor **62**.



Scheme 12. Synthesis of aklavinone-trisaccharide **10**. Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), DCM, -20°C, 71%; (b) DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), 90%; (c) $Pd(PPh_3)_4$, NDMBA, DCM, 61%.

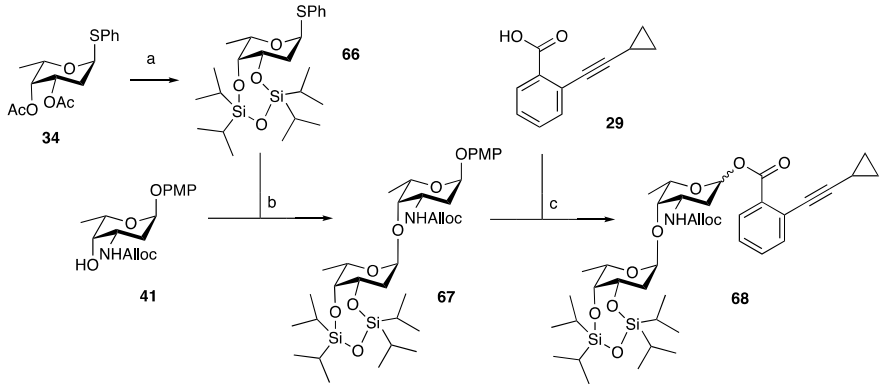
Subjection of a mixture of donor **62** and aklavinone **27** to Yu's conditions (10 mol% PPh_3AuNTf_2) at -20 °C gave the protected trisaccharide anthracycline with complete α-selectivity. DDQ-oxidation of the PMB group (in DCM and pH 7 phosphate buffer) proceeded uneventfully to give **63** and leave only the Alloc group for the final deprotection. The amine was liberated using the Pd/NMDBA system to give trisaccharide amine **10**, whose spectral data was in perfect agreement with literature precedent.[42]



Scheme 13. Synthesis of doxorubicinone-trisaccharides **9** and **11**. *Reagents and conditions:* (a) *i.* PPh_3AuNTf_2 (10 mol%), DCM; *ii.* DDQ, DCM, pH 7 phosphate buffer (18:1, v/v), 57% over 2 steps; (b) $Pd(PPh_3)_4$, NDMBA, DCM, 81%; (c) HF·pyridine, pyr., 73% for **9**, 73% for **11**; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 52%.

Attention was next focused on the synthesis of doxorubicinone-derived trisaccharides **9** and **11**, as depicted in Scheme 13. Subjecting *N*-allyloxycarbonyl protected trisaccharide donor **62** and an excess of 14-*O*-TBS-doxorubicinone **64** (described in Chapter 2) to catalytic PPh_3AuNTf_2 gave the desired trisaccharide **65** with excellent α-selectivity after oxidative removal of the PMB group (DDQ) and the Alloc group. The use of the azide-containing donor **26** was also able to give the corresponding protected doxorubicinone trisaccharide in excellent yield and α-selectivity, but the azide deprotection yielded complex mixtures (see the Experimental section for details).

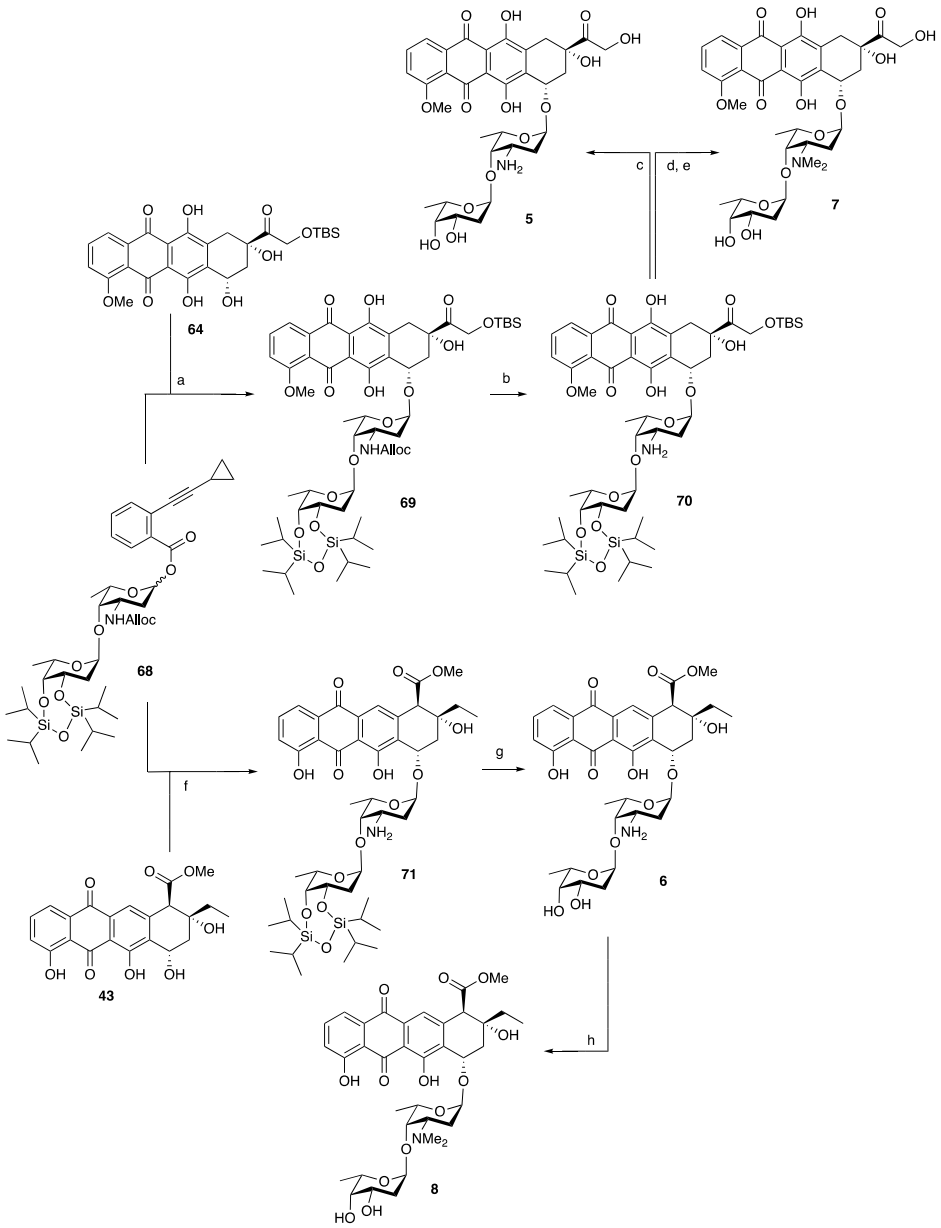
Treatment with Olah's reagent (HF·pyridine complex) finally gave trisaccharide amine **9**. The corresponding dimethylamine **11** was obtained from the reductive alkylation of formaldehyde and amine **65**, followed by desilylation. The obtained spectral data matched those described in the literature.[11]



Scheme 14. Synthesis of disaccharide *ortho*-alkynylbenzoate donor **68**.
Reagents and conditions: (a) *i.* NaOMe, MeOH; *ii.* tetraisopropyldisiloxane dichloride, pyr., 67% over 2 steps; (b) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, 89%; (c) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 84% over 2 steps (1:8 α:β).

In the preparation of anthracycline disaccharides **5**-**8**, the terminal diol was protected as its tetraisopropyldisiloxyl ether, as the previous and this Chapter has shown that silyl ethers can be readily removed from anthraquinone glycosides. The steric bulk of this protecting group should allow for effective blocking of the *beta*-face of the donor to facilitate the α-selective preparation of the disaccharide. Thus, L-olioside **66** was prepared as depicted in Scheme 14 from acetate **34** by removal of the acetyl esters and treatment of the resulting diol with tetraisopropyldisiloxane dichloride. A mixture of this thioglycoside and acceptor **41** was subjected to IDCP to give the desired disaccharide **67** in excellent yield and stereoselectivity. The disaccharide was converted to the corresponding Yu donor with the oxidation-Steglich esterification sequence as described earlier in this Chapter to give **68**.

The preparation of disaccharide donor **68** set the stage for coupling to the two aglycone acceptors **64** and **43** as outlined in Scheme 15. Treatment of a mixture of donor **68** and acceptor **64** with PPh_3AuNTf_2 proceeded stereoselectively to give **69**. Ensuing Alloc removal proceeded quantitatively to give **70**, after which HF·pyridine-mediated desilylation yielded 4'-oliosyl-doxorubicin **5**. Subjecting amine **70** to reductive alkylation (aq. CH_2O, $NaBH(OAc)_3$) followed by desilylation resulted in dimethylated **7**.



Scheme 15. Synthesis of anthraquinone disaccharides **5**-**8**. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM, 64%; (b) $Pd(PPh_3)_4$, NDMBA, DCM, quant.; (c) HF·pyridine, pyr., 76%; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 71%; (e) HF·pyridine, pyr., 81%; (f) *i.* PPh_3AuNTf_2 (10 mol%), -20 °C, DCM; *ii.* $Pd(PPh_3)_4$, NDMBA, DCM, 87% over 2 steps; (g) HF·pyridine, pyr., 41%; (h) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 34%.

Subjection of donor **68** and aklavinone **27** to gold(I)-mediated glycosylation proceeded stereoselectively, followed by removal of the Alloc group to give **71**. Final removal of the disiloxane moiety (HF·pyridine) gave disaccharide **6**. Double reductive methylation of the amine in **71** was followed by desilylation. Unfortunately, the HF·pyridine mediated desilylation was accompanied by loss of methyl groups of the amine. This *N*-demethylation was not observed in the preparation of **7**. It is known that the dihydroxyanthraquinone moiety in this compound is a powerful redox mediator, which might have effected this degradation.[47] Therefore, the double reductive *N*-methylation was performed on fully deprotected **6** to give the desired disaccharide **7** in acceptable yield, and with spectral data in agreement with literature precedent.[43]

Conclusions

The reasons behind the different biological activity profiles of doxorubicin and aclarubicin remain poorly understood. The preparation of hybrid structures filling the chemical space between these two natural compounds should aid in understanding these differences, with possible implications for the design of new anthracyclines for use in the clinic. This Chapter describes the synthesis of two monosaccharides (**3** and **4**), 4 disaccharides (**5**-**8**) and 3 trisaccharides (**9**-**11**), differing in *N*-methylation pattern and aglycon. The compounds **2**[38], **3**[44], **4**[39], **8**[43], **10**[42] and **11**[11] have been reported before, whereas **5**, **6**, **7** and **9** are new. The assembly of the compounds reported here relied on the use of Yu's *ortho*-alkynylbenzoate glycosylation method, which uses catalytic amounts of gold(I) to activate glycosyl donors. The relevant di- and trisaccharide donors were assembled by (iterative) stereoselective IDCP-mediated thioglycosylation, and the anthracycline aglycones were obtained from acidic hydrolysis of the parent anthracyclines. The library of doxorubicin/aclarubicin hybrids **1** – **12** should aid in establishing a proper structure-activity relationship to explain the different biological activities of these two drugs. The chemistry disclosed here should be amenable for the generation of a wider variety of anthracyclines.

Experimental procedures and characterization data

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

General procedure A: *p*-Methoxyphenolate oxidative deprotection

To a solution of the *p*-methoxyphenyl glycoside in 1:1 MeCN:H_2O (0.02M, v/v) were added NaOAc (10 eq) and then $Ag(DPAH)_2\cdot H_2O$ (2.1 eq for trisaccharides, 4 eq for monosaccharides) portionwise over 30 minutes at 0°C. The mixture was stirred until disappearance of the starting material; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo* gave the crude lactols.

General procedure B: Alkynylbenzoate esterification

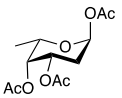
A solution of *ortho*-cyclopropylethynylbenzoic acid methyl ester (for preparation, see Chapter 2) in THF (5 mL/mmol) and 1M NaOH (5 mL/mmol) was stirred at 50 °C for at least 5 hours. It was then poured into 1M HCl (6 mL/mmol) and extracted with DCM thrice. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The resultant acid **43** was then used without further purification.

To a solution of the above crude lactol in DCM (0.1M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3.2 eq) and the above carboxylic acid **43** (3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (EtOAc:pentane) gave the title alkynylbenzoates.

General procedure C: Au(I)-catalysed glycosylation

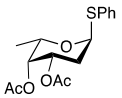
To a solution of the glycosyl donor and the required anthracycline acceptor (1-2 eq) in DCM (0.05M mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise at the designated temperature. After stirring 30 minutes (for RT) or overnight (-20°C or lower), the mixture was filtered and concentrated *in vacuo*. Column chromatography (EtOAc:pentane or Et_2O:pentane and then acetone:toluene) followed by (if required) size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the title glycosides.

1,3,4-Tri-*O*-acetyl-2-deoxy-α-L-fucopyranoside (32)[13]



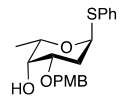
Commercially available L-fucose **31** (7.42 g, 45.2 mmol) was dissolved in pyridine (80 mL) and acetic anhydride (65 mL) and heated to 100 °C. After stirring for 1.5 hours, the resulting solution was concentrated *in vacuo* and additionally coevaporated twice with toluene to afford crude tetraacetyl-L-fucose as a viscous orange oil. The latter was then dissolved in DCM (40 mL), whereupon hydrobromic acid (33 wt. % HBr in AcOH, 40 mL) was added dropwise. After stirring overnight at ambient temperature, the resulting solution was poured onto a stirring suspension of Na_2CO_3 (40.0 g) in DCM (1 L) and left to stir for 1 hour, after which the suspension was filtered and subjected to the aforementioned work-up once more. The resulting solution was then concentrated *in vacuo* to afford the crude fucosyl bromide as an orange oil. This was then dissolved in toluene (1.5 L) in a two-necked 2L round-bottom flask. After the addition of azobisisobutyronitrile (742 mg, 4.52 mmol, 0.10 eq), it was stirred at 80 °C for 30 minutes, whereupon a solution of tributyltin hydride (18.2 mL, 58.0 mmol, 1.3 eq) was added *via* a syringe pump over the duration of 16 hours at the aforementioned temperature. Stirring of the resulting solution commenced for a further 2 hours and was subsequently concentrated *in vacuo*. Purification by column chromatography (20:80 – 40:60 EtOAc:pentane) afforded a mixture of the title compound and its 1-deoxy regioisomer **20** (11.08 g, containing 30.3 mmol desired product, 67% over 3 steps) as a white solid. Crystallisation from hot EtOH yielded the pure title compound (5.93 g, 21.6 mmol, 48% over 3 steps). Spectral data of the title compound was in accordance with that of literary precedence.[13]

Phenyl 2-deoxy-3,4-di-*O*-acetyl-thio-α-L-fucopyranoside (34)[13]



To a solution **32** (5.92 g, 21.6 mmol) in DCM (220 mL) at -78 °C, were added thiophenol (2.3 mL, 22.5 mmol, 1.04 eq) and $BF_3{\cdot}OEt_2$ (7.5 mL, 54 mmol, 2.5 eq) dropwise consecutively. The resulting solution was stirred at that temperature for 2 hours, after which it was slowly warmed up to -20 °C. It was then quenched by addition of Et_3N and concentrated *in vacuo*. Column chromatography (20:80 EtOAc:pentane) gave a residu which was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ twice and concentrated *in vacuo* to give the title compound as a white solid (7.00 g, 21.6 mmol, quant., 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[13]

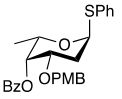
Phenyl 2-deoxy-3-*O*-*p*-methoxybenzyl-thio-α-L-fucopyranoside (35)[13]



A solution of **34** (1.62 g, 5.00 mmol) and NaOMe (cat. amount) in MeOH (100 mL) was stirred overnight. It was then quenched by addition of Amberlite IR120 (H^+ form), filtered and concentrated *in vacuo* to give the intermediate diol.

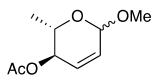
This diol was suspended in toluene (80 mL) and after the addition of dibutyltin oxide (1.25 g, 5.00 mmol, 1 eq), was heated to reflux in a Dean-Stark apparatus overnight. Thereafter, tetra-*n*-butylammonium bromide (3.22 g, 10.0 mmol, 2 eq) and 4-methoxybenzyl chloride (2.03 mL, 15.0 mmol, 3 eq) were added consecutively and stirring commenced overnight at 90 °C. Hereafter, the resulting solution was concentrated *in vacuo* and purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the title compound as a yellow wax (1.73 g, 4.80 mmol, 96% over 2 steps, 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[13]

Phenyl 4-*O*-benzoyl-2-deoxy-1-thio-α-L-fucopyranoside (29)



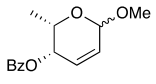
To a solution of **35** (10.7 g, 29.8 mmol) in pyridine (150 mL) and DCM (30 mL) was added benzoyl chloride (11.3 mL, 89.4 mmol, 3 eq). After stirring overnight, MeOH was added to quench and the mixture was concentrated *in vacuo*. Column chromatography (4:96 – 5:95 EtOAc:pentane) gave the title compound as a light yellow solid (11.3 g, 24.3 mmol, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.07 (m, 2H), 7.63 – 7.51 (m, 1H), 7.51 – 7.35 (m, 4H), 7.35 – 7.17 (m, 5H), 6.89 – 6.77 (m, 2H), 5.80 (d, *J* = 5.6 Hz, 1H), 5.62 (d, *J* = 2.9 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.01 (ddd, *J* = 12.3, 4.8, 2.9 Hz, 1H), 3.78 (s, 3H), 2.60 – 2.44 (m, 1H), 2.15 (ddt, *J* = 13.5, 4.9, 1.2 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 133.2, 131.2, 130.0, 129.6, 129.1, 128.5, 127.3, 114.0, 84.6, 72.1, 70.1, 69.5, 66.4, 55.4, 32.6, 17.0. HRMS: $(M + Na)^+$ calculated for $C_{27}H_{28}O_5SNa$ 487.1555, found 487.1552.

Methyl 4-*O*-acetyl-2,3-dideoxy-α,β,-L-*erythro*-hex-2-enopyranoside (37)[14]



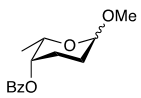
To a solution of L-rhamnal **36** (18.1 g, 84.6 mmol) in DCM (380 mL) and MeOH (7.2 mL, 178 mmol, 2.1 eq) was added tin(IV) chloride (1M $SnCl_4$ solution in DCM, 4.23 mL, 4.23 mmol, 0.05 eq) dropwise. After stirring for 40 minutes, the resulting solution was poured onto sat. aq. $NaHCO_3$ and the organic layer was washed with additional sat. aq. $NaHCO_3$. The combined aqueous layers were then extracted with DCM and the resulting combined organic layers were successively washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (20:80 EtOAc:pentane) afforded the title compound as a light brown oil (12.7 g, 68.0 mmol, 80%, 6:1 α:β). The material was carried on without further purification. Spectral data of the major α-anomer was in accordance with that of literary precedence.[14]

Methyl 4-*O*-benzoyl-2,3-dideoxy-α,β-L-*threo*-hex-2-enopyranoside (38)[16]



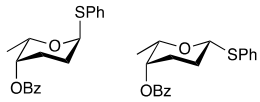
To a solution of **37** (12.7 g, 68.0 mmol, 6:1 α:β) in MeOH (85 mL) was added sodium methoxide (0.735 g, 13.6 mmol, 0.2 eq). After stirring for 1 hour, the resulting solution was neutralized by addition of acetic acid and then concentrated *in vacuo*. Purification by column chromatography (30:70 – 40:60 Et_2O:pentane) afforded the allylic alcohol as a yellow oil (8.04 g, 55.8 mmol, 82%, 6:1 α:β). This was then dissolved in THF (370 mL) and benzoic acid (10.2 g, 83.7 mmol, 1.5 eq) and triphenylphosphine (22.0 g, 83.7 mmol, 1.5 eq) were added consecutively. Subsequently, the solution was cooled to 0 °C, whereupon diethyl azodicarboxylate (13.8 mL, 86.5 mmol, 1.55 eq) was added dropwise. After stirring for 1.5 hours, the resulting solution was concentrated *in vacuo*, diluted with DCM and the organic layer successively washed twice with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the title compound as a colourless oil (9.64 g, 38.8 mmol, 70%, 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[16]

Methyl 4-*O*-benzoyl-2,3-dideoxy-α-L-*threo*-hexopyranoside (39)



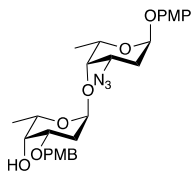
A solution of **38** (6.06 g, 24.4 mmol, 10:1 α:β) in MeOH (120 mL) was degassed with argon, whereupon palladium black (740 mg) was added, followed by the subsequent sparging of H_2(g) through the suspension. After stirring overnight, the resulting suspension was filtered over Celite and concentrated *in vacuo*. Purification by column chromatography (3:97 – 4:96 EtOAc:pentane) afforded the title compound as a colourless oil (5.56 g, 22.2 mmol, 91%, >16:1 α:β). Spectral data of the major α anomer was in accordance with that of literary precedence.[45]

Phenyl 4-*O*-benzoyl-2,3-dideoxy-1-thio-α,β-L-fucopyranoside (30α and 30β)



To a solution of **39** (3.05 g, 12.2 mmol) in DCM (60 mL) at -78°C were added thiophenol (1.30 mL, 12.7 mmol, 1.04 eq) and $BF_3{\cdot}OEt_2$ (3.75 mL, 30.5 mmol, 2.5 eq) dropwise. The mixture was allowed to warm up to -15°C over 4 hours, after which it was poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:98 – 10:90 EtOAc:pentane) gave the α-anomer and the β-anomers as clear oils (3.19 g, 9.71 mmol, 80%, α:β 1.2:1). Analytical data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 8.03 (m, 2H), 7.66 – 7.55 (m, 1H), 7.55 – 7.39 (m, 4H), 7.39 – 7.16 (m, 4H), 5.73 (d, *J* = 5.3 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.61 (qd, *J* = 6.6, 1.5 Hz, 1H), 2.44 (tt, *J* = 13.8, 5.1 Hz, 1H), 2.17 (tdd, *J* = 13.7, 4.4, 2.9 Hz, 1H), 2.13 – 2.00 (m, 1H), 1.87 (dt, *J* = 14.2, 3.5 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.44, 133.25, 131.12, 129.86, 129.05, 128.59, 126.99, 84.98, 69.96, 66.35, 25.65, 24.77, 17.27. HRMS: $(M + Na)^+$ calculated for $C_{19}H_{20}O_3SNa$ 351.10254; found 351.10250.

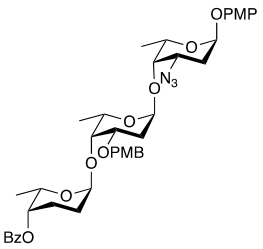
***p*-Methoxyphenyl-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (40)**



To a solution of the glycosyl acceptor **28** (1.54 g, 5.5 mmol, 1 eq) and the glycosyl donor **29** (3.58 g, 7.7 mmol, 1.4 eq) in 4:1 Et_2O:DCE (110 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidinium perchlorate (10.3 g, 22.0 mmol, 4 eq) was added. After 4 hours, the mixture was diluted with Et_2O and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (12:88 – 20:80 EtOAc:pentane) of the residue gave the crude

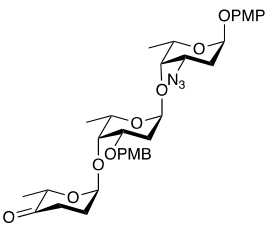
disaccharide. This was then dissolved in in MeOH (110 mL) and DCM (55 mL), after which NaOMe was added to pH=10. After stirring over 2 nights, it was neutralized by addition of Amberlite IR-120 (H^+ form), filtered and concentrated *in vacuo*. Column chromatography (30:70 – 50:50 EtOAc:pentane) gave the title compound as a thick yellow oil (2.51 g, 4.74 mmol, 85% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.17 (m, 2H), 7.06 – 6.95 (m, 2H), 6.95 – 6.76 (m, 4H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.05 (d, *J* = 3.7 Hz, 1H), 4.54 (q, *J* = 11.0 Hz, 2H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.17 (ddd, *J* = 12.6, 4.7, 2.8 Hz, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.93 (ddd, *J* = 11.8, 5.1, 2.8 Hz, 1H), 3.84 (d, *J* = 2.9 Hz, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 3.3 Hz, 4H), 2.18 – 1.95 (m, 5H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 159.5, 154.9, 150.8, 130.2, 129.5, 117.6, 114.7, 114.1, 99.6, 96.3, 75.1, 73.0, 70.0, 68.4, 67.6, 66.7, 56.9, 55.8, 55.4, 30.1, 29.9, 17.6, 17.1. HRMS: $(M + Na)^+$ calculated for $C_{27}H_{35}N_3O_8Na$ 552.2322; found 552.2326.

***p*-Methoxyphenyl-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (41)**



To a solution of the glycosyl acceptor **40** (1.07 g, 2.00 mmol) and the glycosyl donor **30α** (877 mg, 2.67 mmol, 1.34 eq) in 4:1 Et_2O:DCE (41 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (3.75 g, 8.00 mmol, 4 eq) was added. After 75 minutes, the mixture was diluted with Et_2O and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (10:90 – 30:70 EtOAc:pentane) of the residue gave the title compound as a fluffy white solid (1.38 g, 1.85 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.04 (m, 2H), 7.64 – 7.50 (m, 1H), 7.50 – 7.38 (m, 2H), 7.31 – 7.22 (m, 4H), 7.05 – 6.92 (m, 2H), 6.92 – 6.76 (m, 4H), 5.55 (d, *J* = 2.5 Hz, 1H), 5.10 (d, *J* = 3.6 Hz, 1H), 5.05 (s, 1H), 4.98 (s, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.27 (q, *J* = 6.5 Hz, 1H), 4.14 (ddd, *J* = 12.5, 4.7, 2.9 Hz, 1H), 4.00 (q, *J* = 6.5 Hz, 1H), 3.97 – 3.86 (m, 2H), 3.79 (s, 3H), 3.78 (s, 4H), 2.31 – 2.13 (m, 2H), 2.13 – 1.96 (m, 4H), 1.92 (d, *J* = 14.3 Hz, 1H), 1.81 (d, *J* = 13.0 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.2, 154.9, 150.8, 133.1, 130.7, 129.8, 129.1, 128.5, 117.6, 114.7, 113.8, 99.7, 98.6, 96.3, 75.1, 74.6, 72.8, 70.7, 70.1, 68.3, 67.6, 65.6, 56.9, 55.8, 55.4, 30.8, 30.0, 24.5, 23.2, 17.8, 17.7, 17.3. HRMS: $(M + Na)^+$ calculated for $C_{40}H_{49}N_3O_{11}Na$ 770.3265; found 770.3269.

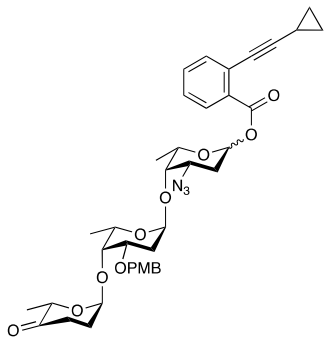
***p*-Methoxyphenyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (42)**



A solution of **41** (819 mg, 1.10 mmol) in dioxane (80 mL), MeOH (80 mL) and 1M NaOH solution (22 mL) was heated at 60°C for 1 hour. The mixture was then concentrated *in vacuo* and partitioned between EtOAc and sat. aq. NH_4Cl. The organic layer was further washed with sat. aq. NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude 4″-OH trisaccharide.

The above intermediate was then dissolved in DCM (100 mL), to which $NaHCO_3$ (3.20 g, 38.3 mmol, 35 eq) and Dess-Martin periodinane (1.11 g, 2.63 mmol, 2.4 eq) were added. After stirring for 2 hours, 10% aq. $Na_2S_2O_3$ (90 mL) was added and the mixture was stirred for a further 30 minutes. Then, it was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a light yellow thick oil (687 mg, 1.07 mmol, 98% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.19 (m, 2H), 7.03 – 6.93 (m, 2H), 6.93 – 6.76 (m, 4H), 5.55 (d, *J* = 2.4 Hz, 1H), 5.15 – 5.03 (m, 2H), 4.68 (q, *J* = 6.7 Hz, 1H), 4.65 – 4.46 (m, 2H), 4.30 (q, *J* = 6.5 Hz, 1H), 4.15 (ddd, *J* = 12.6, 4.8, 2.8 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.91 (ddd, *J* = 9.5, 6.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.72 (m, 4H), 2.62 (ddd, *J* = 15.2, 9.1, 5.9 Hz, 1H), 2.41 (ddd, *J* = 15.7, 7.5, 5.6 Hz, 1H), 2.35 – 2.15 (m, 2H), 2.14 – 1.96 (m, 4H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 159.2, 154.9, 150.8, 130.5, 129.1, 117.6, 114.7, 113.9, 99.7, 98.0, 96.3, 75.4, 74.7, 72.7, 71.9, 70.2, 68.1, 67.6, 56.9, 55.8, 55.4, 34.1, 30.7, 30.0, 29.7, 17.7, 14.9. HRMS: $(M + Na)^+$: calculated for $C_{33}H_{43}N_3O_{10}Na$ 664.2846; found 664.2858.

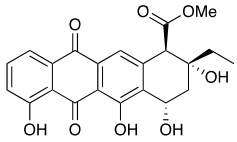
_o_-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-L-fucopyranoside (26)



To a solution of **42** (669 mg, 1.04 mmol) in 1:1 CH_3CN:H_2O (25 mL, v/v) were added NaOAc (853 mg, 10.4 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$[46] (1.00 g, 2.18 mmol, 2.1 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 130 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70 EtOAc:pentane) gave the trisaccharide lactol (479 mg, max. 0.891 mmol, 86%).

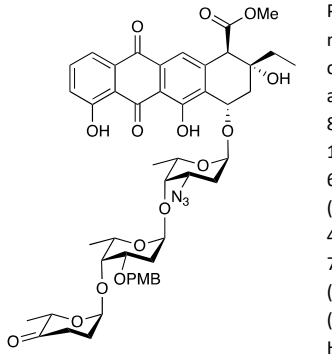
It was then subjected to General Procedure B, with final column chromatography of the residue (30:70 – 40:60 EtOAc:pentane) giving the title compound as a white solid (418 mg, 0.594 mmol, 91%, α:β 1:1.15). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.83 (m, 2H), 7.56 – 7.38 (m, 4H), 7.38 – 7.30 (m, 2H), 7.30 – 7.20 (m, 4H), 6.93 – 6.80 (m, 4H), 6.56 – 6.46 (m, 1H), 6.04 – 5.94 (m, 1H), 5.11 (q, *J* = 3.8 Hz, 4H), 4.69 (dq, *J* = 8.7, 6.7 Hz, 2H), 4.63 (s, 1H), 4.60 (s, 1H), 4.53 (dd, *J* = 11.5, 6.6 Hz, 2H), 4.23 (ddt, *J* = 30.3, 13.3, 6.5 Hz, 4H), 3.97 (d, *J* = 3.3 Hz, 2H), 3.92 (dtd, *J* = 13.6, 6.8, 2.7 Hz, 2H), 3.82 (s, 2H), 3.80 (dd, *J* = 4.1, 1.7 Hz, 2H), 3.76 (s, 3H), 3.74 – 3.66 (m, 3H), 2.62 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 2H), 2.47 – 2.34 (m, 2H), 2.34 – 2.04 (m, 11H), 2.00 (dd, *J* = 13.1, 4.6 Hz, 1H), 1.55 – 1.40 (m, 2H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.31 – 1.23 (m, 15H), 1.03 – 0.93 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 165.1, 164.4, 159.2, 135.0, 134.4, 132.3, 132.1, 131.4, 131.0, 130.6, 130.4, 129.2, 129.1, 127.5, 127.1, 124.4, 113.9, 99.9, 99.8, 98.9, 98.0, 98.0, 93.0, 92.8, 75.3, 74.8, 73.6, 73.0, 72.7, 72.4, 71.9, 70.2, 70.2, 69.8, 68.2, 68.1, 59.5, 56.9, 55.4, 55.4, 34.1, 30.6, 30.2, 29.7, 28.9, 17.7, 17.7, 14.9, 9.1, 9.0, 0.8. HRMS: $(M + Na)^+$ calculated for $C_{38}H_{45}N_3O_{10}Na$ 726.3003; found 726.3006.

Aklavinone (27)[28]



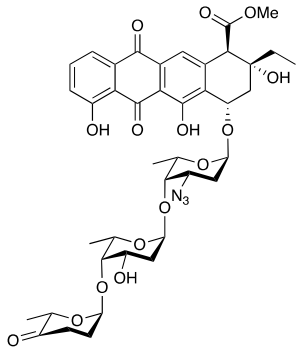
A solution of commercially available aclarubicin hydrochloride **12** (1.60 g, 1.89 mmol) in aq. HCl (0.2 M, 160 mL) was heated at 90°C for 1.5 hours. The resulting suspension was cooled down and extracted with DCM thrice. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (2.5:97.5 MeOH:DCM) gave the title compound as a yellow solid (778 mg, 1.89 mmol, quant.). Spectral data was in accordance with that of literary precedence.[28]

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (44)



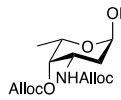
Prepared according to General Procedure C from donor **26** (52 mg, 0.071 mmol) and aklavinone **43** (2 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 - 5:95 acetone:toluene) the title compound as a yellow solid (56 mg, 0.060 mmol, 85%, α:β 8:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 11.96 (s, 1H), 7.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.73 – 7.60 (m, 2H), 7.38 – 7.09 (m, 3H), 6.93 – 6.82 (m, 2H), 5.52 (d, *J* = 3.7 Hz, 1H), 5.30 – 5.18 (m, 1H), 5.17 – 5.00 (m, 2H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.65 – 4.47 (m, 2H), 4.25 (q, *J* = 6.5 Hz, 1H), 4.18 (s, 1H), 4.15 – 4.00 (m, 2H), 3.96 (d, *J* = 2.7 Hz, 1H), 3.90 (ddd, *J* = 9.7, 7.0, 2.7 Hz, 1H), 3.82 (s, 3H), 3.78 – 3.65 (m, 5H), 2.69 – 2.50 (m, 2H), 2.40 (ddd, *J* = 15.6, 7.3, 5.4 Hz, 1H), 2.33 – 2.14 (m, 3H), 2.14 – 2.05 (m, 2H), 2.00 (td, *J* = 13.2, 4.0 Hz, 1H), 1.86 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.51 (dq, *J* = 14.4, 7.1 Hz, 1H), 1.37 – 1.16 (m, 6H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 192.7, 181.2, 171.3, 162.6, 162.1, 159.2, 142.6, 137.5, 133.5, 133.0, 130.9, 130.4, 129.1, 125.4, 124.9, 121.0, 120.3, 115.8, 114.8, 113.8, 101.2, 99.6, 97.9, 75.3, 74.4, 72.6, 71.8, 71.7, 71.4, 70.1, 68.0, 67.9, 57.0, 56.8, 55.4, 52.7, 34.0, 32.2, 30.6, 29.8, 29.6, 17.5, 14.8, 6.8. HRMS: $(M + Na)^+$ calculated for $C_{48}H_{55}N_3O_{16}Na$ 952.3480; found 952.3488.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (45)



To a biphasic mixture of **44** (213 mg, 0.204 mg) in DCM (34 mL) and phosphate buffer (2 mL, pH 7) was added DDQ (93 mg, 0.41 mmol, 2 eq) at 0°C after which the mixture was stirred at that temperature for 4 hours. Then, the same amount of DDQ was added and the mixture was stirred for another hour. It was then diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (3.5:96.5 – 20:80 acetone:toluene) gave the title compound as a yellow solid (189 mg, 0.204 mmol, 100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.72 (s, 1H), 12.01 (s, 1H), 7.83 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.38 – 7.29 (m, 1H), 5.52 (d, *J* = 3.7 Hz, 1H), 5.28 – 5.26 (m, 1H), 5.15 – 5.06 (m, 1H), 5.03 (d, *J* = 3.7 Hz, 1H), 4.49 (q, *J* = 6.7 Hz, 1H), 4.37 (q, *J* = 6.3 Hz, 1H), 4.18 (s, 1H), 4.15 – 4.03 (m, 3H), 3.79 – 3.62 (m, 7H), 2.59 – 2.39 (m, 4H), 2.34 – 2.23 (m, 1H), 2.23 – 1.98 (m, 3H), 1.86 (ddd, *J* = 12.7, 9.3, 3.7 Hz, 2H), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.51 (dq, *J* = 14.3, 7.1 Hz, 1H), 1.38 – 1.19 (m, 9H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 192.8, 181.4, 171.4, 162.7, 162.2, 142.7, 137.6, 133.6, 133.2, 125.0, 121.1, 120.4, 115.9, 114.9, 101.2, 100.3, 99.9, 82.8, 75.1, 71.9, 71.8, 71.4, 67.9, 67.4, 65.4, 57.1, 56.9, 52.7, 34.1, 33.6, 32.2, 29.9, 29.8, 27.7, 17.5, 17.2, 14.9, 6.8. HRMS: $(M + Na)^+$ calculated for $C_{40}H_{47}N_3O_{15}Na$ 832.2905; found 832.2916.

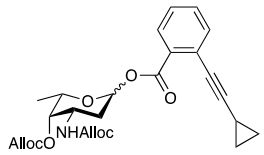
***p*-Methoxyphenyl-4-*O*-allyloxycarbonyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (49)**



To a solution of **28** (838 mg, 3.00 mmol) in THF:H_2O (16.5 mL, 10:1 v/v) was added triphenylphosphine (1.57 g, 6.00 mmol, 2 eq) and the mixture was stirred overnight. It was then filtered off and concentrated *in vacuo*.

The above crude amine was then dissolved in DCM (21.5 mL) and brought to 0°C. At this temperature, pyridine (1.45 mL, 18.0 mmol, 6 eq) and allyloxycarbonyl chloroformate (0.96 mL, 9.00 mmol, 3 eq) were added consecutively. After being allowed up to room temperature for 3 hours, another portion of both reagents was added again, and another after 2 more hours. Then after stirring overnight, H_2O (10 mL) was added and the mixture was stirred vigorously for 10 minutes. It was then washed with sat aq. $NaHCO_3$ and H_2O twice. Drying over $MgSO_4$ and concentration *in vacuo* gave a residue that was subjected to column chromatography (10:90 – 17:83 EtOAc:pentane) gave the di-Alloc glycoside as a yellow solid (528 mg, 1.26 mmol, 42% over 2 steps, 1:20 α:β). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 – 6.90 (m, 2H), 6.90 – 6.71 (m, 2H), 6.10 – 5.79 (m, 2H), 5.55 (d, *J* = 3.2 Hz, 1H), 5.46 – 5.18 (m, 4H), 4.99 (d, *J* = 2.9 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.73 – 4.61 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.56 – 4.47 (m, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 2.05 (ddt, *J* = 13.0, 5.3, 1.3 Hz, 1H), 1.97 (td, *J* = 12.7, 3.4 Hz, 1H), 1.14 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 155.3, 154.8, 150.8, 132.8, 131.4, 119.4, 118.1, 117.5, 114.7, 96.0, 75.4, 69.0, 66.0, 65.8, 55.8, 45.6, 31.1, 16.8. HRMS: $(M + Na)^+$ calculated for $C_{21}H_{27}NO_8Na$ 444.1634; found 444.1634.

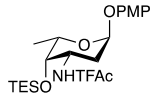
***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-4-*O*-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside (52)**



Prepared according to General Procedure A and B from the above glycoside (210 mg, 0.50 mmol), to give after column chromatography (4:96 Et_2O:pentane – 10:90 – 20:80 EtOAc:pentane) the title compound as a light yellow wax (237 mg, 0.49 mmol, 98% over 2 steps). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.43 (td, *J* = 7.6, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.4 Hz, 1H), 6.52 (t, *J* = 2.5 Hz, 1H), 6.08 – 5.79 (m, 2H), 5.49 – 5.16 (m, 4H), 5.07 (d, *J* = 2.9 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.60 (m, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.50 (t, *J* = 8.4 Hz, 1H), 4.43 (q, *J* = 6.5 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.61 (dd, *J* = 8.2, 5.2 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.97 – 0.72 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 155.3, 134.9, 132.7, 132.1, 131.4, 131.3, 130.9, 127.4, 124.9, 119.5, 118.0, 92.6, 74.9, 69.1, 68.1, 66.0, 45.8, 29.9, 16.9, 9.0, 0.7. Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (ddd, *J* = 8.0, 1.4, 0.5 Hz, 1H), 7.48 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.3, 1.4 Hz, 1H), 6.10 – 5.82 (m, 3H), 5.44 – 5.16 (m, 4H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.90 (d, *J* = 8.8 Hz, 1H), 4.68 (tdt, *J* = 14.1, 5.8, 1.4 Hz, 2H), 4.58 (d, *J* = 5.7 Hz, 2H), 4.21 – 4.09 (m, 1H),

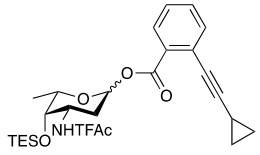
3.90 (q, *J* = 6.5 Hz, 1H), 2.12 (dddd, *J* = 12.2, 4.8, 2.5, 0.9 Hz, 1H), 1.94 (ddd, *J* = 13.0, 12.1, 9.9 Hz, 1H), 1.56 – 1.48 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.87 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 155.2, 134.3, 132.7, 132.2, 131.4, 130.9, 130.7, 127.1, 125.3, 119.4, 118.2, 100.0, 92.8, 74.5, 74.0, 71.6, 69.1, 66.1, 49.0, 31.6, 16.8, 9.0, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{26}H_{29}NO_8Na$ 506.1791; found 506.1796.

_p_-Methoxyphenyl-3-trifluoroacetylamino-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (50)



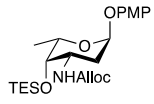
A solution of **48** (Chapter 2) (1.23 g, 4.40 mmol) and triphenylphosphine (4.6 g, 17.6 mmol, 4 eq) in THF:H_2O (10:1 v/v, 165 mL) was stirred overnight. It was then concentrated *in vacuo* and coevaporated twice with toluene before being used immediately in the next step. To a solution above free amine in DCM (150 mL) were added Et_3N (1.7 mL, 12.3 mmol, 2.8 eq) and trifluoroacetic anhydride (871 µL, 6.16 mmol, 1.4 eq) at 0 °C. The resulting mixture was stirred for 2 hours, after which it was quenched by addition of H_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 – 20:80 Et_2O:pentane) gave the title compound as a clear oil (2.03 g, 4.40 mmol, quant. over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 1H), 4.66 (s, 1H), 4.05 (d, *J* = 6.1 Hz, 1H), 3.80 (s, 1H), 3.77 (s, 3H), 2.12 (t, *J* = 12.5 Hz, 1H), 1.93 (d, *J* = 12.1 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.00 (t, *J* = 7.7 Hz, 9H), 0.78 – 0.58 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 156.7, 156.3, 156.0, 154.8, 150.9, 117.6, 114.7, 95.8, 70.8, 67.2, 55.7, 46.8, 30.0, 17.6, 7.1, 5.4. HRMS: [M + H]$^+$ calculated for $C_{21}H_{33}F_3NO_5Si$ 464.20746; found 464.20724.

***o*-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-*O*-triethylsilyl-3-*N*-trifluoroacetyl-L-fucopyranoside (36)**



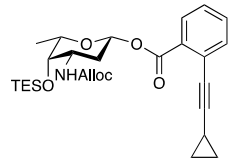
Prepared according to General Procedure A and B from (Chapter 2) (95 mg, 0.21 mmol), to give after column chromatography (4:96 - 20:80 EtOAc:pentane) the title compound as a light yellow wax (66 mg, 0.12 mmol, 68% over 2 steps, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 6.09 – 5.85 (m, 1H), 4.36 – 4.17 (m, 1H), 3.83 – 3.69 (m, 2H), 2.14 – 2.00 (m, 2H), 1.51 (pd, *J* = 6.2, 2.6 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.01 (td, *J* = 8.0, 2.7 Hz, 9H), 0.90 – 0.87 (m, 4H), 0.78 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 157.0, 156.6, 156.2, 155.9, 148.5, 134.3, 132.1, 130.8, 130.7, 127.0, 125.2, 122.7, 99.9, 92.9, 74.5, 69.7, 49.7, 30.6, 17.6, 9.0, 7.0, 5.4, 0.8. HRMS: [M + H]$^+$ calculated for $C_{21}H_{33}F_3NO_5Si$ 548.20560; found 548.20496.

***p*-Methoxyphenyl-3-N-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (51)**



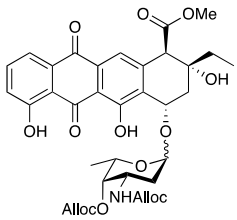
To a solution of **48** (Chapter 2) (862 mg, 2.19 mmol) in THF/H_2O (80 mL, 10:1 v/v) was added polymer-bound PPh_3 (1.46 g, 4.38 mmol, 2 eq) and the mixture was stirred overnight at 50 °C. Then, an additional portion of polymer-bound PPh_3 (0.73 g, 2.19 mmol, 1 eq) and the mixture was stirred an additional night at 50 °C. It was then filtered off and concentrated *in vacuo*. The resulting amine was dissolved in DCM (15.7 mL) to which pyridine (0.53 mL, 6.57 mmol, 3 eq) and allyl chloroformate (0.35 mL, 3.29 mmol, 1.5 eq) were added at -20 °C. After stirring at that temperature for 15 minutes, the reaction was allowed to warm up to RT, and poured into sat. aq. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 – 10:90 EtOAc:pentane) gave the title compound as a yellow oil (870 mg, 1.93 mmol, 88% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.05 – 6.90 (m, 2H), 6.86 – 6.73 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.51 (d, *J* = 2.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.76 (d, *J* = 9.1 Hz, 1H), 4.60 (qdt, *J* = 13.4, 5.8, 1.5 Hz, 2H), 4.35 – 4.27 (m, 1H), 4.01 (q, *J* = 6.5 Hz, 1H), 3.79 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.01 (td, *J* = 12.7, 3.5 Hz, 1H), 1.86 (dd, *J* = 12.5, 4.4 Hz, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.67 (qd, *J* = 7.9, 3.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 154.6, 151.1, 133.0, 117.8, 117.5, 114.7, 96.2, 71.4, 67.4, 65.7, 55.8, 47.5, 30.6, 17.7, 7.2, 5.4. HRMS: [M + Na]$^+$ calculated for $C_{23}H_{37}NO_6SiNa$: 474.2288; found 474.2288.

_o_-Cyclopropylethynylbenzoyl-3-_N_-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-β-L-fucopyranoside (54)



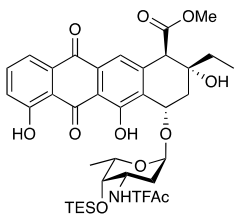
Prepared according to General Procedure A and B from **51** (225 mg, 0.500 mmol), to give after column chromatography (5:95 – 30:70 EtOAc:pentane) gave the title compound as a clear oil (158 mg, 0.308 mmol, 61% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.2, 5.7 Hz, 1H), 6.01 – 5.84 (m, 2H), 5.40 – 5.17 (m, 2H), 4.84 (d, *J* = 9.1 Hz, 1H), 4.59 (qdt, *J* = 13.3, 5.8, 1.5 Hz, 2H), 3.93 (qd, *J* = 9.0, 2.7 Hz, 1H), 3.78 – 3.62 (m, 2H), 2.00 – 1.87 (m, 2H), 1.51 (tt, *J* = 7.2, 5.8 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.82 (m, 4H), 0.67 (qd, *J* = 7.8, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 155.4, 134.3, 132.8, 132.0, 130.9, 127.0, 125.2, 117.9, 99.8, 93.4, 74.6, 73.1, 70.3, 65.8, 50.8, 31.1, 17.6, 9.0, 7.2, 5.4, 0.8. HRMS: [M + Na]$^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2444; found 536.2449.

7-[3-_N_-allyloxycarbonyl-4-_O_-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside]-aklavinone (55)



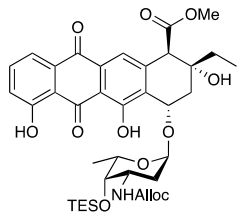
Prepared according to General Procedure C from donor **52** and aklavinone **43** (2 eq) at variable temperature to give after column chromatography (2:98 acetone:toluene) the title compound as a yellow solid. -78 °C to 0 °C (85%, 6.3:1 α:β), -20 °C (93%, 6.7:1 α:β) or RT (58%, 6.6:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.67 (d, *J* = 4.2 Hz, 1H), 11.99 (s, 1H), 7.86 – 7.78 (m, 1H), 7.75 – 7.59 (m, 2H), 7.27 (dd, *J* = 4.5, 1.2 Hz, 1H), 6.06 – 5.76 (m, 2H), 5.49 (d, *J* = 3.5 Hz, 1H), 5.44 – 5.12 (m, 5H), 5.01 – 4.95 (m, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 4.72 – 4.60 (m, 2H), 4.60 – 4.53 (m, 1H), 4.48 (d, *J* = 5.7 Hz, 1H), 4.30 (q, *J* = 6.6 Hz, 1H), 4.12 (d, *J* = 1.3 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.69 (s, 3H), 2.59 – 2.50 (m, 1H), 2.35 – 2.27 (m, 1H), 1.97 – 1.83 (m, 2H), 1.82 – 1.67 (m, 1H), 1.50 (dq, *J* = 13.8, 7.0 Hz, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 181.4, 171.5, 162.6, 162.2, 155.2, 142.8, 137.5, 133.6, 133.1, 131.4, 131.0, 129.1, 128.3, 124.9, 121.1, 120.3, 119.4, 117.9, 115.9, 114.8, 101.3, 75.1, 71.8, 71.5, 69.0, 66.1, 65.8, 57.1, 52.6, 45.6, 34.1, 32.2, 31.0, 16.8, 6.8. ^{13}C-GATED NMR ($CDCl_3$, 126 MHz) δ 101.3 ($J_{C1,\ H1}$ = 171.15 Hz). Spectral data for the β -anomer: ^{13}C-GATED NMR ($CDCl_3$, 126 MHz) δ 99.2 ($J_{C1,\ H1}$ = 158.60 Hz). HRMS: [M + Na]$^+$ calculated for $C_{36}H_{39}NO_{14}Na$ 732.2268; found 732.2285.

7-[2,3-Dideoxy-4-_O_-triethylsilyl-3-_N_-trifluoroacetyl-α-L-fucopyranoside]-aklavinone (56)



Prepared according to General Procedure C from donor **53** and aklavinone **43** (2 eq) at RT to give after column chromatography (10:90 – 20:80 EtOAc:pentane) the title compound as a yellow solid (54 mg, 0.072 mmol, 59%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.67 (s, 1H), 11.98 (s, 1H), 7.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.77 – 7.63 (m, 2H), 7.34 – 7.23 (m, 2H), 6.23 (d, *J* = 8.7 Hz, 1H), 5.48 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.11 (m, 1H), 4.24 – 4.17 (m, 1H), 4.14 (d, *J* = 6.6 Hz, 1H), 4.13 – 4.09 (m, 2H), 3.79 (d, *J* = 2.6 Hz, 1H), 3.70 (s, 3H), 2.54 (dd, *J* = 15.1, 4.4 Hz, 1H), 2.33 (dt, *J* = 15.0, 1.8 Hz, 1H), 2.03 (td, *J* = 12.8, 4.2 Hz, 1H), 1.82 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.75 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.51 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.31 – 1.20 (m, 83H), 1.09 (t, *J* = 7.4 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.76 – 0.57 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 181.4, 171.5, 162.7, 162.2, 156.7, 156.4, 156.1, 155.8, 142.7, 137.5, 133.6, 133.1, 131.0, 124.9, 121.1, 120.3, 115.9, 114.8, 101.1, 71.7, 71.6, 70.5, 67.4, 57.1, 52.6, 46.8, 34.1, 32.2, 30.0, 17.6, 7.0, 6.8, 5.4. HRMS: [M + Na]$^+$ calculated for $C_{36}H_{44}F_3NO_{11}SiNa$ 762.2922; found 762.2938.

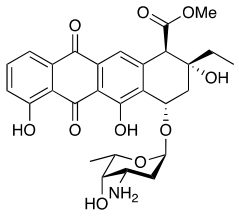
7-[3-_N_-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (57)



Prepared according to General Procedure C from donor **54** and aklavinone **43** (2 eq) at RT to give after column chromatography (4:96 Et_2O:pentane and then 1.5:98.5 acetone:toluene) the title compound as a yellow solid (149 mg, 0.201 mmol, 73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.66 (s, 1H), 12.04 (s, 1H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.86 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.28 – 5.12 (m, 3H), 4.63 (d, *J* = 8.8 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.21 (s, 1H), 4.15 – 4.01 (m, 2H), 3.86 (dq, *J* = 8.7, 4.1 Hz, 1H), 3.78 (s, 1H), 3.69 (s, 3H), 2.50 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.34 (d, *J* = 15.0 Hz, 1H), 1.92 (td,

J = 12.8, 4.1 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.49 (dq, *J* = 14.3, 7.3 Hz, 1H), 1.36 – 1.18 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.66 (qd, *J* = 7.9, 2.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 181.5, 171.6, 162.7, 162.3, 155.2, 142.9, 137.5, 133.7, 133.0, 132.9, 131.3, 124.9, 121.1, 120.3, 117.8, 115.9, 114.8, 101.6, 71.5, 71.4, 71.1, 67.6, 65.6, 57.2, 52.6, 47.4, 34.0, 32.2, 30.4, 17.6, 7.2, 6.8, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{38}H_{49}NO_{12}SiNa$ 774.2533; found 774.2525.

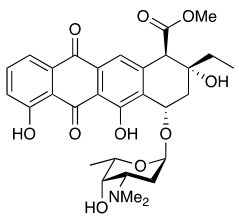
7-[α-L-Daunosamino]-aklavinone (2)



To a solution of **57** (60 mg, 0.081 mmol) in DCM (8.1 mL) were added *N,N*-dimethylbarbituric acid (38 mg, 0.24 mmol, 3 eq) and tetrakis(triphenylphosphine) palladium(0) (4.6 mg, 4.1 µmol, 0.05 eq). After stirring for 2.5 hours, the mixture was concentrated *in vacuo*. Column chromatography (DCM – 2:98 MeOH:DCM) gave the crude amine.

This was then redissolved in pyridine (6 mL) in a PTFE tube, after which HF.pyr complex (70 wt% HF, 710 µL) was added at 0°C. After 3.5 hours and 5.5 hours, additional HF.pyr complex (70 wt% HF, 355 µL each time) was added. After stirring for a total of 6.5 hours, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filter cake was rinsed thoroughly with MeOH:DCM (9:1 v/v). The combined filtrates were then concentrated *in vacuo*. Column chromatography (DCM – 20:80 MeOH:DCM) gave the title compound as a yellow solid (18 mg, 33 µmol, 41% over 2 steps). ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 7.77 – 7.61 (m, 2H), 7.53 (s, 1H), 7.31 – 7.20 (m, 1H), 5.49 (s, 1H), 5.14 (d, *J* = 4.7 Hz, 1H), 4.27 (q, *J* = 6.5 Hz, 1H), 4.08 (s, 1H), 3.73 (s, 2H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.57 – 3.47 (m, 1H), 2.52 (dd, *J* = 15.0, 5.2 Hz, 1H), 2.32 (d, *J* = 15.0 Hz, 1H), 2.03 (td, *J* = 12.9, 4.0 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.76 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.56 (dq, *J* = 13.9, 7.1 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 193.6, 182.3, 172.6, 163.7, 143.8, 138.5, 134.7, 134.0, 125.8, 121.2, 120.8, 117.0, 115.8, 101.7, 72.5, 72.1, 68.4, 68.1, 58.2, 53.0, 49.8, 48.4, 35.8, 33.3, 30.1, 17.0, 7.1. HRMS: $[M + H]^+$ calculated for $C_{28}H_{32}NO_{10}$ 542.2026; found 542.2031.

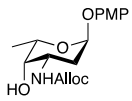
7-[α-L-Rhodosamino]-aklavinone (aklavin) (4)



To a solution of **57** (23.7 mg, 0.032 mmol) in DCM (3.2 mL) were added *N,N*-dimethylbarbituric acid (15 mg, 0.096 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (1.8 mg, 1.6 µmol, 0.05 eq). After stirring for 2.5 hours, the mixture was concentrated *in vacuo*. Column chromatography (DCM – 2:98 MeOH:DCM) gave the crude amine.

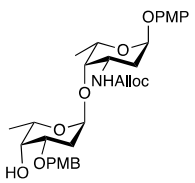
This was then redissolved in EtOH (7.7 mL) and 37% aq. CH_2O (79 µL, 30 eq) was added $NaBH(OAc)_3$ (67 mg, 0.32 mmol, 10 eq). The mixture was stirred for 2.5 hours before being quenched by addition of sat. aq. $NaHCO_3$. It was then poured into H_2O and extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude dimethylated amine. This was then redissolved in pyridine (3.2 mL) in a PTFE tube, after which HF.pyr complex (70 wt% HF, 125 µL) was added at 0 °C. Over the course of 4 hours, additional HF.pyr complex (70 wt% HF, 125 µL each time) was added 5 times. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was partitioned between DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) gave the title compound as a yellow solid (7.9 mg, 13.9 µmol, 43% over 3 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 12.01 (s, 1H), 7.83 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.55 (d, *J* = 3.9 Hz, 1H), 5.29 – 5.20 (m, 1H), 4.27 (s, 1H), 4.16 – 4.03 (m, 2H), 3.87 (s, 1H), 3.70 (s, 3H), 2.54 (dd, *J* = 15.2, 4.5 Hz, 1H), 2.45 (s, 6H), 2.33 (d, *J* = 15.2 Hz, 1H), 2.05 (td, *J* = 13.1, 12.6, 4.2 Hz, 1H), 1.89 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.76 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.52 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.38 (dd, *J* = 6.5, 2.1 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 181.4, 171.3, 162.8, 162.3, 142.8, 137.6, 133.6, 133.1, 131.2, 125.0, 121.1, 120.4, 115.9, 114.9, 101.1, 71.9, 71.4, 67.0, 65.8, 61.1, 57.2, 52.7, 42.0, 34.0, 32.2, 27.8, 17.0, 6.8. HRMS: $[M + H]^+$ calculated for $C_{30}H_{36}NO_{10}$ 570.2339; found 570.2921.

***p*-Methoxyphenyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (58)**



To a solution of **28** (838 mg, 3.00 mmol) in THF/H_2O (10:1 v/v, 16.5 mL) was added polymer-bound triphenylphosphine (3 mmol/g, 2.00g, 3 eq) and the mixture was stirred for 4 nights. To this mixture were then added $NaHCO_3$ (504 mg, 6 mmol, 2 eq), H_2O (10 mL) and finally *N*-(allyloxycarbonyloxy)succinimide (956 mg, 4.8 mmol, 1.6 eq). After stirring for 3 hours, it was partitioned between EtOAc and H_2O, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70:1– 40:60:1 EtOAc:pentane:Et_3N) gave the title compound as a white solid (904 mg, 2.67 mmol, 89% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.91 (m, 2H), 6.91 – 6.74 (m, 2H), 5.94 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1H), 5.48 (d, *J* = 3.4 Hz, 1H), 5.41 – 5.29 (m, 1H), 5.29 – 5.16 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.39 – 4.22 (m, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 1H), 2.08 (ddt, *J* = 13.2, 5.0, 1.1 Hz, 1H), 194 (bs, 1H), 1.87 (td, *J* = 12.9, 3.7 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 154.8, 150.9, 132.9, 118.0, 117.6, 114.7, 96.2, 77.5, 77.2, 76.8, 70.0, 65.8, 55.8, 47.1, 30.8, 16.9. HRMS: $[M + Na]^+$ calculated for $C_{17}H_{23}NO_6Na$ 360.1423; found 360.1416.

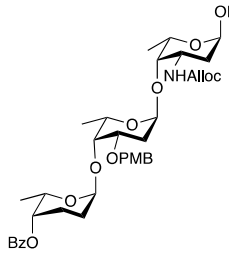
***p*-Methoxyphenyl-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (59)**



Method 1: To a solution of the glycosyl acceptor **58** (169 mg g, 0.5 mmol, 1 eq) and the glycosyl donor **29** (325 mg, 0.7 mmol, 1.4 eq) in 4:1 Et_2O:DCE (15 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (937 mg, 2.00 mmol, 4 eq) was added. After 30 minutes, triphenylphosphine (262 mg, 1.00 mmol, 2 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (15:85 – 20:80 EtOAc:pentane) of the residue gave the disaccharide. This was then dissolved in in MeOH (8.8 mL) and DCM (8.8 mL), after which NaOMe was added to pH=10. After stirring for a week, it was neutralized by addition of dry ice and concentrated *in vacuo*. Column chromatography (20:80 – 50:50 EtOAc:pentane) gave the title compound as a clear oil (232 mg, 0.39 mmol, 78% over 2 steps).

Method 2: To a solution of **40** (1.14 g, 2.15 mmol) in THF/H_2O (10:1 v/v, 24 mL) was added polymer-bound triphenylphosphine (3 mmol/g, 1.43 g, 2 eq) and the mixture was stirred overnight at 50°C. To this mixture were then added $NaHCO_3$ (470 mg, 5.59 mmol, 2.6 eq), H_2O (7.2 mL) and finally *N*-(allyloxycarbonyloxy)succinimide (557 mg, 2.8 mmol, 1.3 eq). After stirring for 2 nights, it was partitioned between EtOAc and H_2O, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70– 40:60 EtOAc:pentane) gave the title compound as a white solid (1.20 g, 2.04 mmol, 95% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 6.7 Hz, 2H), 7.05 – 6.96 (m, 2H), 6.96 – 6.87 (m, 2H), 6.87 – 6.77 (m, 2H), 6.21 (d, *J* = 8.2 Hz, 1H), 5.92 (ddt, *J* = 16.4, 10.9, 5.5 Hz, 1H), 5.51 (d, *J* = 3.1 Hz, 1H), 5.37 – 5.25 (m, 1H), 5.20 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.00 – 4.92 (m, 1H), 4.62 – 4.52 (m, 4H), 4.39 – 4.25 (m, 1H), 4.11 (q, *J* = 7.8, 7.1 Hz, 1H), 4.08 – 4.01 (m, 1H), 3.97 (td, *J* = 8.4, 3.1 Hz, 1H), 3.86 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.56 (s, 1H), 2.21 (s, 1H), 2.13 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.08 – 2.00 (m, 2H), 1.86 (td, *J* = 12.7, 3.5 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.9, 154.7, 151.1, 133.0, 130.0, 129.5, 117.6, 117.5, 114.6, 114.1, 101.4, 96.4, 81.5, 72.7, 70.2, 68.2, 67.5, 67.2, 65.7, 55.8, 55.4, 46.6, 31.8, 30.3, 17.4, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{31}H_{41}NO_{10}Na$ 610.2628; found 610.2632.

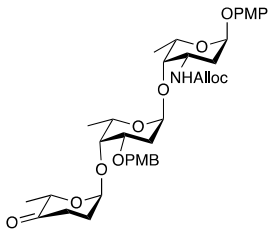
***p*-Methoxyphenyl-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (60)**



To a solution of the glycosyl acceptor **59** (120 g, 2.04 mmol) and the glycosyl donor **30α** (1.01 g, 2.86 mmol, 1.4 eq) in 4:1 Et_2O:DCE (62.5 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (3.82 g, 8.16 mmol, 4 eq) was added. After 35 minutes, triphenylphosphine (1.07g, 4.08 mmol, 2.00 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (10:90 – 30:70 EtOAc:pentane) of the residue gave the title

compound as a thick clear oil (1.59 g, 1.97 mmol, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.05 (m, 2H), 7.61 – 7.54 (m, 1H), 7.51 – 7.37 (m, 2H), 7.28 (d, *J* = 2.2 Hz, 2H), 7.04 – 6.94 (m, 2H), 6.92 – 6.85 (m, 2H), 6.85 – 6.76 (m, 2H), 6.16 (d, *J* = 8.3 Hz, 1H), 5.92 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.49 (d, *J* = 2.7 Hz, 1H), 5.34 – 5.16 (m, 2H), 5.04 (s, 1H), 5.03 – 4.94 (m, 2H), 4.72 – 4.50 (m, 5H), 4.40 – 4.25 (m, 1H), 4.17 – 4.01 (m, 2H), 3.99 – 3.88 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.56 (s, 1H), 2.29 – 2.15 (m, 2H), 2.14 – 1.98 (m, 3H), 1.94 (d, *J* = 14.0 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.2, 155.9, 154.7, 151.1, 133.1, 130.6, 130.5, 129.8, 129.0, 128.5, 117.7, 117.6, 114.6, 113.9, 101.5, 98.7, 96.4, 81.1, 77.5, 77.4, 77.2, 76.8, 74.9, 72.7, 70.6, 70.3, 70.3, 68.8, 67.5, 65.7, 65.7, 65.7, 55.8, 55.4, 46.6, 31.8, 31.3, 24.5, 23.1, 17.5, 17.2. HRMS: $[M + Na]^+$ calculated for $C_{44}H_{55}NO_{13}Na$ 828.3571; found 828.3586.

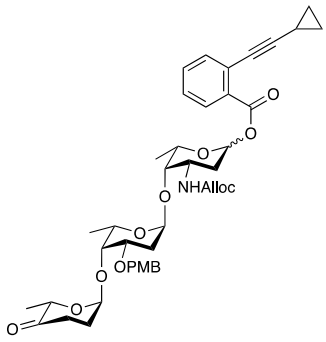
***p*-Methoxyphenyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (61)**



Trisaccharide **60** (1.20 g, 2.04 mmol) was dissolved in in MeOH (40 mL) and DCM (40 mL), after which NaOMe was added to pH 10. After stirring for a week, it was neutralized by addition of dry ice and concentrated *in vacuo*. Column chromatography (50:50 – 75:25 EtOAc:pentane) gave the title compound as a white foam (1.21 g, 1.72 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.19 (m, 2H), 7.05 – 6.95 (m, 2H), 6.93 – 6.85 (m, 2H), 6.85 – 6.75 (m, 2H), 6.15 (d, *J* = 8.3 Hz, 1H), 5.97 – 5.86 (m, 1H), 5.49 (d, *J* = 3.1 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.99 (q, *J* = 1.5 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.70 – 4.46 (m, 4H), 4.43 – 4.34 (m, 1H), 4.31 (dt, *J* = 7.8, 4.3 Hz, 1H), 4.09 (q, *J* = 6.3 Hz, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.54 (s, 1H), 3.52 (s, 1H), 2.17 (td, *J* = 12.1, 3.7 Hz, 1H), 2.12 – 1.90 (m, 4H), 1.82 (td, *J* = 12.6, 3.5 Hz, 1H), 1.78 – 1.66 (m, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 155.9, 154.6, 151.1, 133.0, 130.6, 129.0, 117.7, 117.5, 114.6, 113.8, 101.4, 98.7, 96.4, 81.0, 74.9, 72.7, 68.9, 67.6, 67.5, 66.6, 55.8, 55.4, 46.6, 31.8, 31.3, 25.8, 23.6, 17.5, 17.1. HRMS: $[M + Na]^+$ calculated for $C_{37}H_{51}NO_{12}Na$ 724.3309; found 724.3322.

To a solution of the above alcohol (351 mg, 0.500 mmol) in in DCM (20 mL) were added $NaHCO_3$ (840 mg, 5.00 mmol, 10 eq) and Dess-Martin periodinane (530 mg, 1.25 mmol, 2.5 eq). After stirring for 1.5 hours, 10% aq. $Na_2S_2O_3$ (20 mL) was added and the mixture was stirred for a further 30 minutes. Then, it was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) gave the title compound as a white solid (341 mg, 0.487 mmol, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.20 (m, 2H), 7.06 – 6.99 (m, 2H), 6.92 – 6.85 (m, 2H), 6.85 – 6.76 (m, 2H), 6.16 (d, *J* = 8.2 Hz, 1H), 5.92 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.50 (d, *J* = 3.1 Hz, 1H), 5.36 – 5.15 (m, 2H), 5.10 (t, *J* = 4.3 Hz, 1H), 5.00 (dd, *J* = 3.7, 1.7 Hz, 1H), 4.72 – 4.45 (m, 5H), 4.38 – 4.25 (m, 1H), 4.08 (dq, *J* = 13.3, 6.4 Hz, 2H), 4.03 – 3.88 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.56 (s, 1H), 2.60 (ddd, *J* = 15.0, 8.9, 5.7 Hz, 1H), 2.41 (ddd, *J* = 15.6, 7.6, 5.5 Hz, 1H), 2.30 (ddt, *J* = 14.1, 8.9, 5.2 Hz, 1H), 2.25 – 1.99 (m, 4H), 1.84 (td, *J* = 12.7, 3.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 158.9, 155.4, 154.3, 150.7, 132.7, 130.0, 128.7, 117.3, 117.2, 114.2, 113.5, 101.1, 97.6, 96.0, 80.7, 74.7, 72.1, 71.5, 69.9, 68.2, 67.1, 65.3, 55.4, 55.0, 46.2, 33.6, 31.4, 30.7, 29.1, 17.1, 17.0, 14.5. HRMS: $[M + Na]^+$ calculated for $C_{37}H_{49}NO_{12}Na$ 722.3153; found 722.3165.

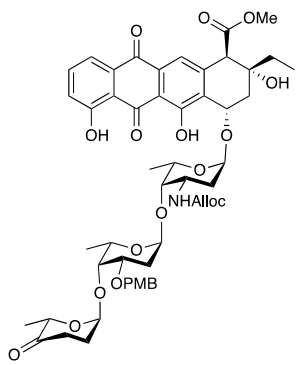
_o_-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-L-fucopyranoside (62)



To a solution of **61** (1.06 g, 1.51 mmol) in 1:1 CH_3CN:H_2O (70 mL, v/v) were added NaOAc (1.42 g, 15.1 mmol, 10 eq) and then $Ag(DPAH)_2{\cdot}H_2O$ (1.42 g, 3.10 mmol, 2.1 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 70 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (40:60 – 60:40 EtOAc:pentane) gave the crude trisaccharide hemiacetal.

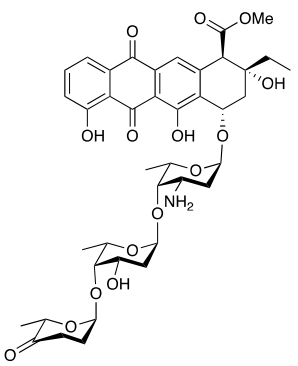
To a solution of the above crude hemiacetal in DCM (35 mL) were added DIPEA (2.42 mL, 13.6 mmol, 9 eq), DMAP (189 mg, 1.51 mmol, 1 eq), EDCI·HCl (943 mg, 4.83 mmol, 3.2 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **43** (837 mg, 4.53 mmol, 3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (20:80 – 40:60 EtOAc:pentane) gave the title compound as a white foam (872 mg, 1.14 mmol, 75% over 2 steps, α:β 1:7). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 – 7.16 (m, 3H), 6.93 – 6.79 (m, 2H), 6.36 (d, *J* = 8.0 Hz, 1H), 5.98 (dd, *J* = 10.0, 2.2 Hz, 1H), 5.90 (ddd, *J* = 16.3, 10.7, 5.4 Hz, 1H), 5.37 – 5.15 (m, 2H), 5.10 (t, *J* = 4.4 Hz, 1H), 5.03 – 4.97 (m, 1H), 4.75 – 4.45 (m, 5H), 4.08 (q, *J* = 6.6 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.90 (ddt, *J* = 12.4, 7.4, 4.1 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.76 (s, 3H), 3.49 (s, 1H), 2.60 (ddd, *J* = 15.0, 8.8, 5.7 Hz, 1H), 2.42 (ddd, *J* = 15.7, 7.7, 5.4 Hz, 1H), 2.31 (ddt, *J* = 13.9, 8.8, 5.2 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.10 (tt, *J* = 10.4, 5.5 Hz, 2H), 1.81 (td, *J* = 12.3, 9.9 Hz, 1H), 1.50 (tt, *J* = 7.8, 5.4 Hz, 1H), 1.36 – 1.27 (m, 6H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.87 (dd, *J* = 7.6, 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 164.3, 159.3, 155.8, 134.3, 132.9, 132.0, 130.3, 129.1, 127.0, 125.2, 117.7, 113.9, 101.8, 99.8, 98.0, 93.2, 80.3, 75.1, 74.5, 72.9, 72.4, 71.9, 70.3, 68.7, 65.7, 55.4, 50.0, 34.0, 32.2, 31.1, 29.5, 17.4, 14.8, 9.0, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{51}NO_{12}Na$ 784.3309; found 784.3322.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-_N_-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (63)



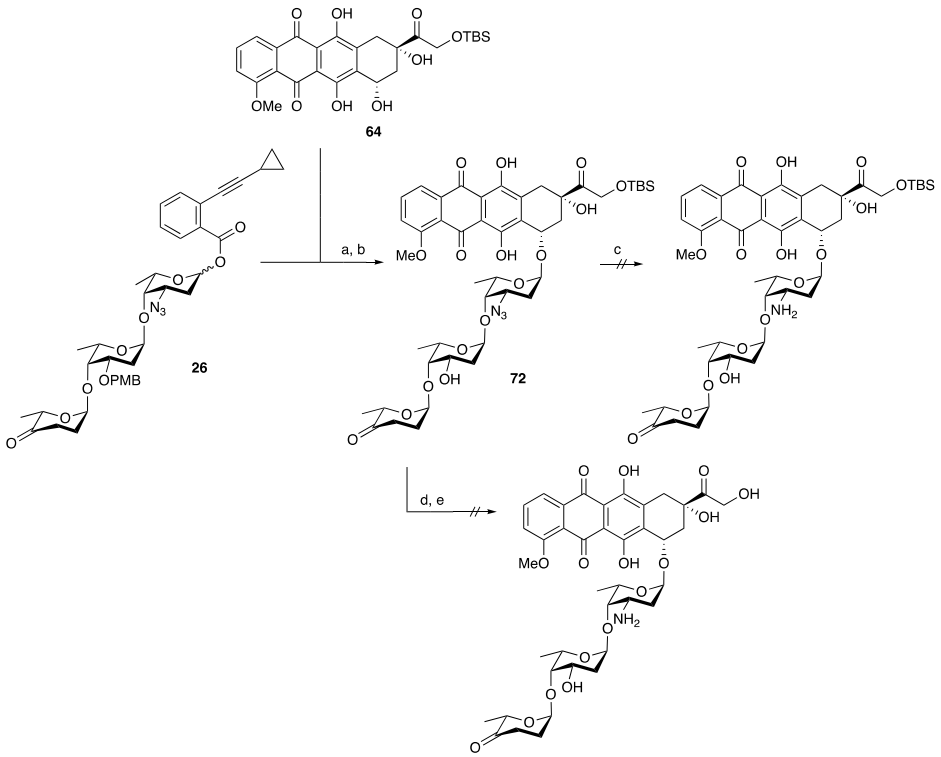
Prepared according to General Procedure C from donor **62** (211 mg, 0.276 mmol) and aklavinone **43** (2 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 – 20:80 acetone:toluene) the title compound as a yellow solid (210 mg, 0.213 mmol, 77%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.66 (s, 1H), 12.01 (s, 1H), 7.82 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.34 – 7.21 (m, 2H), 6.93 – 6.82 (m, 2H), 6.07 (d, *J* = 7.8 Hz, 1H), 5.83 (ddt, *J* = 16.0, 10.8, 5.6 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.30 – 5.06 (m, 4H), 4.98 (s, 1H), 4.71 – 4.62 (m, 1H), 4.62 – 4.49 (m, 2H), 4.46 (ddt, *J* = 6.9, 5.5, 1.5 Hz, 2H), 4.22 (s, 2H), 4.12 (s, 1H), 4.09 – 3.90 (m, 3H), 3.87 (d, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.55 (s, 1H), 2.66 – 2.47 (m, 2H), 2.42 (ddd, *J* = 15.7, 7.6, 5.5 Hz, 1H), 2.36 – 2.25 (m, 2H), 2.25 – 2.04 (m, 3H), 2.00 (dd, *J* = 12.9, 4.5 Hz, 1H), 1.74 (dq, *J* = 13.5, 6.0, 4.3 Hz, 2H), 1.50 (dq, *J* = 14.6, 7.1 Hz, 1H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.28 – 1.24 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 192.8, 181.4, 171.5, 162.6, 162.2, 159.3, 155.5, 142.7, 137.4, 133.5, 133.0, 133.0, 131.1, 130.3, 129.1, 124.8, 121.0, 120.3, 117.5, 115.8, 114.8, 113.9, 101.6, 101.5, 98.0, 80.9, 75.0, 72.5, 71.8, 71.4, 70.3, 68.5, 67.7, 65.5, 57.1, 55.4, 52.6, 46.5, 34.0, 32.2, 31.6, 31.1, 29.5, 17.4, 17.3, 14.8, 6.8. HRMS: $[M + Na]^+$ calculated for $C_{52}H_{61}NO_{18}Na$ 1010.3786; found 1010.3796.

3',3'-Didesmethyl-aclarubicin (Aclacinomycin K) (10)



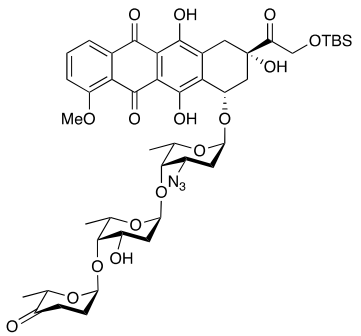
To a biphasic mixture of **63** (210 mg, 0.213 mmol) in DCM (36 mL) and phosphate buffer (3.6 mL, pH=7) was added DDQ (484 mg, 2.13 mmol, 10 eq) at 0°C after which the mixture was stirred at that temperature for 90 minutes. It was diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95– 10:90 acetone:toluene) gave the intermediate free 3''-hydroxyl as a yellow solid (155 mg, 0.179 mmol, 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.65 (s, 1H), 12.00 (s, 1H), 7.81 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.75 – 7.60 (m, 2H), 7.32 – 7.25 (m, 1H), 6.05 (d, *J* = 7.8 Hz, 1H), 5.83 (ddt, *J* = 16.3, 10.7, 5.5 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.27 – 5.06 (m, 4H), 4.95 (d, *J* = 3.5 Hz, 1H), 4.53 – 4.38 (m, 3H), 4.28 – 4.18 (m, 2H), 4.18 – 4.06 (m, 3H), 3.86 (dd, *J* = 12.2, 6.5 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.70 (s, 3H), 3.55 (s, 1H), 2.59 – 2.38 (m, 4H), 2.31 (d, *J* = 15.0 Hz, 1H), 2.24 – 2.06 (m, 2H), 2.01 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.92 (td, *J* = 12.4, 3.8 Hz, 1H), 1.83 – 1.68 (m, 2H), 1.49 (dq, *J* = 14.7, 7.2 Hz, 1H), 1.36 – 1.24 (m, 9H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 192.8, 181.4, 171.5, 162.6, 162.2, 155.5, 142.7, 137.4, 133.6, 133.0, 133.0, 131.1, 124.8, 121.0, 120.3, 117.5, 115.9, 114.8, 101.6, 101.6, 100.3, 82.1, 81.2, 71.9, 71.5, 71.4, 67.9, 67.7, 65.5, 65.0, 57.1, 52.6, 46.6, 34.4, 34.0, 33.5, 32.2, 31.6, 27.6, 17.3, 16.9, 14.8, 6.8. HRMS: $[M + Na]^+$ calculated for $C_{44}H_{53}NO_{17}Na$ 890.3211; found 890.3220.

A solution of the above compound (155 mg, 0.179 mmol) and *N,N*-dimethylbarbituric acid (125 mg, 0.806 mmol, 4.5 eq) in DCM (18 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (10.0 mg, 0.0090 mmol, 0.05 eq) was added and the mixture was allowed to stir for 15 minutes. It was then directly subjected to column chromatography on neutral silica (0:100 – 3:97 MeOH:DCM), followed by size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) twice and finally column chromatography on neutral silica (3:97 MeOH:DCM) to give the title compound as a yellow solid (86 mg, 0.11 mmol, 61%). ^{1}H NMR (500 MHz, Chloroform-*d* + MeOD) δ 7.81 (dt, *J* = 7.4, 2.0 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.30 (d, *J* = 1.2 Hz, 1H), 5.47 (t, *J* = 2.5 Hz, 1H), 5.26 (dd, *J* = 4.4, 1.8 Hz, 1H), 5.10 (t, *J* = 6.2 Hz, 1H), 4.99 (d, *J* = 3.6 Hz, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 4.17 – 4.04 (m, 3H), 3.74 (s, 1H), 3.70 (s, 3H), 3.50 (d, *J* = 2.4 Hz, 1H), 2.99 (ddd, *J* = 10.9, 6.3, 2.4 Hz, 1H), 2.56 – 2.37 (m, 4H), 2.30 (dt, *J* = 14.9, 1.8 Hz, 2H), 2.21 – 2.12 (m, 1H), 2.09 (dd, *J* = 12.4, 4.6 Hz, 1H), 1.91 (td, *J* = 12.4, 3.8 Hz, 1H), 1.75 (ddd, *J* = 14.1, 9.4, 5.7 Hz, 3H), 1.50 (dp, *J* = 13.8, 7.0 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$ + MeOD) δ 210.3, 192.7, 181.4, 171.4, 162.4, 162.0, 142.6, 137.4, 133.5, 133.0, 131.2, 124.8, 120.9, 120.2, 115.8, 114.7, 101.6, 100.9, 100.0, 81.9, 81.8, 71.9, 71.6, 70.9, 68.1, 67.5, 65.1, 57.1, 52.6, 46.6, 34.2, 34.2, 33.8, 33.5, 32.1, 27.6, 17.4, 17.0, 14.7, 6.6. HRMS: $[M + H]^+$ calculated for $C_{40}H_{50}NO_{15}$ 784.3181; found 784.3196.



Scheme 16. Attempted synthesis of doxorubicinone trisaccharides **9** and **11** using the azide as amine protecting group. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), 4 Å MS, DCM, 95%; DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), quant.; (c) PPh_3, THF/H_2O; (d) TBAF, pH 7 phosphate buffer, THF, 91%; (e) H_2S, THF/pyr. or 1,3-propanedithiol, Et_3N, DMF.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (72)

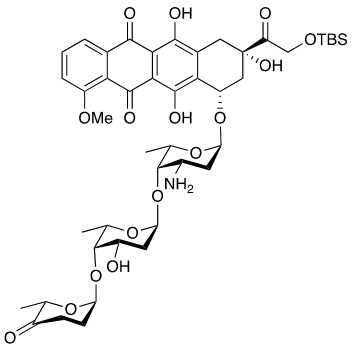


Prepared according to General Procedure C from donor **26** (226 mg, 0.322 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **64** (1.5 eq) to give after column chromatography (30:70 EtOAc:pentane and then 3.5:96.5 – 5:95 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) the protected anthracycline trisaccharide as a red solid (320 mg, 0.306 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.98 (s, 1H), 13.23 (s, 1H), 8.02 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.35 – 7.21 (m, 2H), 6.95 – 6.83 (m, 2H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.29 – 5.22 (m, 1H), 5.13 – 5.01 (m, 2H), 4.87 (d, *J* = 2.2 Hz, 2H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.66 – 4.49 (m, 2H), 4.41 (s, 1H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.10 (s, 3H), 4.01 (q, *J* = 6.7 Hz, 1H), 3.96 (d, *J* = 2.7 Hz, 1H), 3.90 (ddd, *J* = 9.8, 7.2, 2.6 Hz, 1H), 3.83 (s, 3H), 3.77 – 3.66 (m, 2H), 3.28 – 2.88 (m, 2H), 2.62 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.41 (ddd, *J* = 15.6, 7.4, 5.5 Hz, 1H), 2.34 – 2.14 (m, 4H), 2.14 – 2.05 (m, 2H), 1.97 (td, *J* = 12.8, 4.0 Hz, 1H), 1.81 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 4H), 1.00 – 0.94 (m, 13H), 0.15 (d, *J* = 1.5 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 211.1, 187.2, 186.8, 161.2, 159.3, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 130.4, 129.2, 120.9, 120.0, 118.6, 113.9, 111.6, 111.5, 100.8,

99.6, 98.0, 75.3, 74.4, 72.6, 71.8, 70.2, 70.1, 68.1, 66.8, 56.8, 56.7, 55.4, 35.7, 34.1, 30.6, 29.7, 26.0, 18.7, 17.7, 17.6, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{53}H_{67}N_3O_{17}SiNa$ 1068.4137; found 1068.4141.

To a biphasic mixture of the above compound (226 mg, 0.216 mmol) in DCM (36 mL) and phosphate buffer (2 mL, pH=7) was added DDQ (53.9 mg, 0.24 mmol, 1.1 eq) at 0°C after which the mixture was stirred at that temperature for 2.5 hours. Then, the same amount of DDQ was added and the mixture was stirred for a further 3 hours. It was diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (3.5:96.5 – 8:92 – 20:80 acetone:toluene) gave the title compound as a red solid (158 mg, 0.171 mmol, 79%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.17 (s, 1H), 8.06 – 7.93 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.49 – 7.35 (m, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.31 – 5.17 (m, 1H), 5.17 – 5.07 (m, 1H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.95 – 4.79 (m, 2H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.43 – 4.31 (m, 2H), 4.16 – 4.05 (m, 4H), 4.01 (q, *J* = 6.4 Hz, 1H), 3.80 – 3.63 (m, 4H), 3.28 – 2.82 (m, 2H), 2.55 – 2.37 (m, 3H), 2.29 (d, *J* = 15.2 Hz, 1H), 2.24 – 2.07 (m, 3H), 2.02 (td, *J* = 12.9, 12.4, 3.8 Hz, 1H), 1.85 (ddt, *J* = 17.3, 9.5, 4.2 Hz, 2H), 1.35 – 1.18 (m, 9H), 0.96 (s, 9H), 0.15 (d, *J* = 1.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 210.2, 187.0, 186.7, 161.1, 156.3, 155.7, 135.9, 135.5, 133.9, 133.7, 120.8, 119.9, 118.6, 111.5, 111.4, 100.8, 100.3, 99.9, 82.7, 75.0, 71.9, 70.1, 67.9, 67.4, 66.7, 65.3, 56.8, 56.8, 34.0, 33.9, 33.6, 29.6, 27.6, 26.0, 18.7, 17.6, 17.1, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{45}H_{59}N_3O_{16}SiNa$ 948.3562; found 948.3564.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (65)



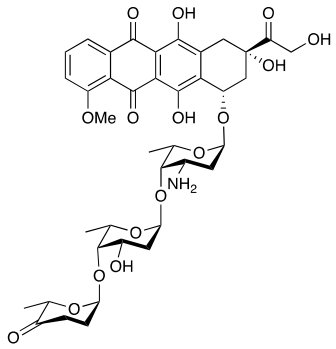
Prepared according to General Procedure C from donor **62** (422 mg, 0.552 mmol) and doxorubicinone acceptor **64** (Chapter 2) (1.5 eq) to give after column chromatography (20:80 – 100:0 EtOAc:pentane) the crude anthracycline trisaccharide.

To a solution of the above trisaccharide in DCM (93 mL) and phosphate buffer (9.3 mL, pH=7) was added DDQ (1.25 g, 5.52 mmol, 10 eq) at 0°C after which the mixture was stirred at that temperature for 45 minutes. It was then stirred at room temperature for an additional 2.5 hours, after which it was diluted with DCM and washed with H_2O four times. The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95– 12:88 acetone:toluene) gave the free 3''-hydroxyl anthracycline trisaccharide as a red solid (310 mg, 0.315 mmol, 57% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.24 (s, 1H), 8.03 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 5.84 (ddt, *J* = 16.2, 10.8, 5.5 Hz, 1H), 5.51 (d, *J* = 3.7 Hz, 1H), 5.26 (td, *J* = 3.4, 1.7 Hz, 1H), 5.23 – 5.05 (m, 2H), 4.99 – 4.93 (m, 1H), 4.90 (d, *J* = 2.8 Hz, 2H), 4.58 – 4.41 (m, 4H), 4.19 – 4.10 (m, 3H), 4.09 (s, 3H), 3.93 – 3.82 (m, 1H), 3.78 – 3.70 (m, 2H), 3.58 (s, 1H), 3.20 (dd, *J* = 18.7, 1.8 Hz, 1H), 2.97 (d, *J* = 18.9 Hz, 1H), 2.55 – 2.39 (m, 3H), 2.29 (d, *J* = 14.8 Hz, 1H), 2.24 – 2.02 (m, 4H), 1.92 (ddd, *J* = 14.0, 10.0, 3.8 Hz, 2H), 1.83 – 1.72 (m, 1H), 1.37 – 1.22 (m, 10H), 0.96 (s, 9H), 0.14 (d, *J* = 2.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 209.9, 187.2, 186.8, 161.1, 156.5, 156.0, 155.6, 135.8, 135.6, 134.2, 134.0, 133.0, 121.0, 119.9, 118.5, 117.6, 111.6, 111.4, 101.6, 100.9, 100.3, 82.2, 81.1, 72.0, 69.8, 67.9, 66.8, 65.6, 65.0, 56.8, 46.6, 35.8, 34.4, 34.2, 33.5, 31.4, 27.6, 26.0, 18.7, 17.5, 16.9, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{49}H_{65}NO_{18}SiNa$ 1006.3869; found 1006.3876.

A solution of the above compound (159 mg, 0.162 mmol) and *N,N*-dimethylbarbituric acid (115 mg, 0.729 mmol, 4.5 eq) in DCM (16.3 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (9.0 mg, 81 µmol, 0.05 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography on neutral silica (0:100 – 3:97 MeOH:DCM) to give the title compound as a red solid (118 mg, 0.131 mmol, 81%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 7.97 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.75 (t, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 5.23 (dd, *J* = 4.1, 2.2 Hz, 1H), 5.10 (t, *J* = 6.1 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 1H), 4.94 – 4.81 (m, 2H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.13 (ddd, *J* = 12.2, 4.7, 2.7 Hz, 1H), 4.08 (s, 3H), 4.03 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 1H), 3.52 (d, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 18.8, 1.9 Hz, 1H), 3.00 (ddd, *J* = 12.4, 4.7, 2.4 Hz, 1H), 2.89 (d, *J* = 18.7 Hz, 1H), 2.56 – 2.38 (m, 3H), 2.30 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.23 – 2.00 (m, 3H), 1.89 (td, *J* = 12.4, 3.8 Hz, 1H), 1.75 (td, *J* = 12.9, 3.9 Hz, 1H), 1.68 (dd, *J* = 13.1, 4.5 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 9H), 0.14 (d, *J* = 1.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 210.0, 186.9, 186.6, 161.1,

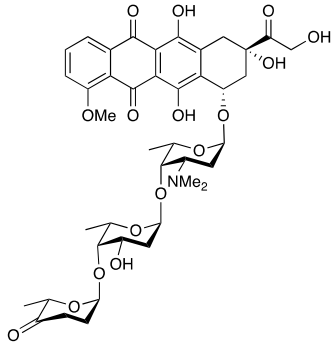
156.4, 155.8, 135.7, 135.5, 134.1, 120.8, 119.8, 118.5, 111.4, 101.4, 100.8, 100.2, 82.3, 81.7, 71.9, 69.6, 68.4, 67.4, 66.6, 65.2, 56.7, 46.8, 35.6, 34.4, 33.9, 33.5, 27.7, 26.0, 18.7, 17.7, 17.2, 14.8. HRMS: $[M + H]^+$ calculated for $C_{45}H_{62}NO_{16}Si$ 900.3838; found 900.3836.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (9)



To a solution of **65** (19.7 mg, 21.9 µmol) in pyridine (0.7 mL) and THF (1.4 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 86 µL) at 0°C. After 3 hours, an additional such portion of HF.pyr complex was added. After stirring one more hour, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was poured into DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 4:96 MeOH:DCM) gave the title compound as a red solid (12.7 mg, 16.2 µmol, 74%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.94 (s, 1H), 8.13 – 7.89 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.52 – 7.31 (m, 1H), 5.51 (d, *J* = 3.8 Hz, 1H), 5.36 – 5.27 (m, 1H), 5.09 (t, *J* = 6.1 Hz, 1H), 5.01 (d, *J* = 3.7 Hz, 1H), 4.81 – 4.68 (m, 2H), 4.49 (q, *J* = 6.6 Hz, 1H), 4.23 (q, *J* = 6.4 Hz, 1H), 4.16 – 4.05 (m, 4H), 4.01 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 1H), 3.52 (s, 1H), 3.25 (dd, *J* = 18.9, 2.0 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.46 (dtt, *J* = 17.8, 10.3, 5.8 Hz, 4H), 2.32 (dt, *J* = 14.5, 2.1 Hz, 1H), 2.25 (t, *J* = 7.6 Hz, 1H), 2.22 – 2.05 (m, 4H), 1.89 (td, *J* = 12.3, 3.7 Hz, 1H), 1.76 (td, *J* = 12.9, 3.9 Hz, 1H), 1.70 (d, *J* = 4.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 210.0, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 121.0, 120.0, 118.6, 111.7, 111.5, 101.3, 100.9, 100.3, 82.4, 81.7, 72.0, 69.2, 68.5, 67.5, 65.6, 65.3, 56.8, 46.8, 35.6, 34.5, 34.1, 33.6, 27.7, 17.8, 17.2, 14.9. HRMS: $[M + H]^+$ calculated for $C_{39}H_{48}NO_{16}$: 786.2973; found 786.2982.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (11)

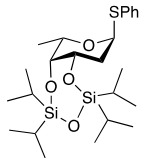


To a solution of **65** (48.0 mg, 53.3 µmol) in EtOH (10.8 mL) and 37% aq. CH_2O (132 µL, 30 eq) was added $NaBH(OAc)_3$ (21.5 mg, 0.101 mmol, 1.9 eq). The mixture was stirred for 1.5 hours before being poured into sat. aq. $NaHCO_3$. This was repetitively extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (10:90 – 40:60 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the free amine as a red solid (25.8 mg, 27.8 µmol, 52%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.24 (s, 1H), 8.01 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.45 – 7.36 (m, 1H), 5.53 (d, *J* = 3.8 Hz, 1H), 5.26 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.10 – 5.06 (m, 1H), 5.03 (d, *J* = 3.4 Hz, 1H), 4.97 – 4.82 (m, 2H), 4.77 (s, 1H), 4.55 (q, *J* = 6.4 Hz, 1H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.09 (d, *J* = 3.3 Hz, 4H), 3.92 (q, *J* = 6.6 Hz, 1H), 3.75 (s, 1H), 3.72 – 3.58 (m, 2H), 3.18 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.53 – 2.38 (m, 3H), 2.32 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.26 – 2.01 (m, 10H), 1.94 – 1.73 (m, 4H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.31 – 1.20 (m, 7H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.14 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 210.3, 187.1, 186.7, 161.1, 156.6, 155.9, 135.8, 135.6, 134.3, 134.1, 124.9, 121.0, 119.9, 118.5, 111.5, 111.4, 101.5, 100.3, 99.6, 83.1, 74.1, 71.9, 69.7, 68.6, 66.7, 65.4, 61.7, 56.8, 43.4, 35.6, 34.4, 34.0, 33.6, 30.4, 29.8, 27.7, 26.0, 18.1, 17.1, 14.9. HRMS: $[M + H]^+$ calculated for $C_{47}H_{66}NO_{16}Si$: 928.4151; found 928.4157.

To a solution of the above compound (20.6 mg, 22.2 µmol) in pyridine (1.4 mL) and THF (1.4 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 87 µL) at 0°C. Four more additional such amounts of HF.pyr complex were added over the course of 4.5 hours. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was poured into DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 10:90 MeOH:DCM) gave the title compound as a red solid (13.3 mg, 16.3 µmol, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.26 (s,

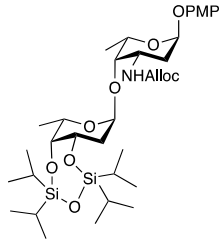
1H), 8.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.40 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.55 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.28 (m, 1H), 5.08 (dd, *J* = 7.0, 5.6 Hz, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.76 (d, *J* = 1.0 Hz, 2H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.49 (q, *J* = 6.7 Hz, 1H), 4.16 – 4.03 (m, 4H), 3.91 (q, *J* = 6.5 Hz, 1H), 3.76 (s, 1H), 3.71 – 3.60 (m, 2H), 3.26 (dd, *J* = 18.8, 2.0 Hz, 1H), 3.03 (d, *J* = 18.8 Hz, 1H), 2.54 – 2.40 (m, 3H), 2.34 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.24 – 2.12 (m, 7H), 2.10 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.03 (d, *J* = 15.0 Hz, 1H), 1.83 (td, *J* = 12.2, 3.8 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 210.3, 187.3, 186.9, 161.2, 156.5, 155.9, 135.9, 135.6, 134.2, 133.7, 121.1, 119.9, 118.5, 111.7, 111.5, 101.4, 100.3, 99.6, 83.1, 74.1, 71.9, 69.3, 68.8, 66.9, 65.6, 65.4, 61.8, 56.8, 43.5, 35.6, 34.4, 34.1, 33.7, 27.8, 18.2, 17.1, 14.9. HRMS: $[M + H]^+$ calculated for $C_{41}H_{52}NO_{16}$: 814.3286; found 814.3301.

Phenyl 2-deoxy-3,4-tetraisopropyldisiloxyl-1-thio-α-L-fucopyranoside (66)



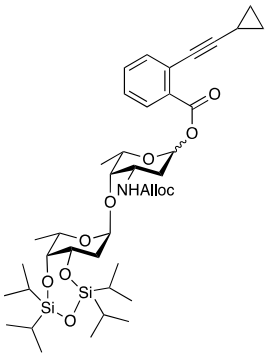
A solution of **34** (6.35 g, 19.6 mmol) and NaOMe (cat. amount) in MeOH (200 mL) was stirred overnight. It was then quenched by addition of Amberlite IR120 (H^+ form), filtered and concentrated *in vacuo* to give the intermediate diol. To a solution of this diol in pyridine (100 mL) was added tetraisopropyldisiloxane dichloride (8.3 mL, 25.5 mmol, 1.3 eq) and the resulting mixture was stirred overnight. It was then poured into Et_2O, washed with H_2O thrice and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:96 – 8:92 toluene:pentane) gave the title compound as a colourless oil (6.36 g, 13.2 mmol, 67%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.38 (m, 2H), 7.34 – 7.13 (m, 3H), 5.69 (d, *J* = 5.6 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.34 – 4.29 (m, 1H), 4.07 – 3.92 (m, 1H), 2.45 (td, *J* = 12.7, 5.8 Hz, 1H), 2.00 (ddt, *J* = 13.0, 4.6, 1.1 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.14 – 0.86 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 130.8, 129.0, 126.8, 84.6, 73.4, 71.4, 67.7, 34.1, 17.8, 17.8, 17.7, 17.6, 17.5, 17.5, 17.4, 17.3, 14.4, 14.2, 13.2, 12.7. HRMS: $[M + Na]^+$ calculated for $C_{24}H_{42}O_4SSi_2Na$ 505.2240; found 505.2238.

***p*-Methoxyphenyl-2-deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (67)**



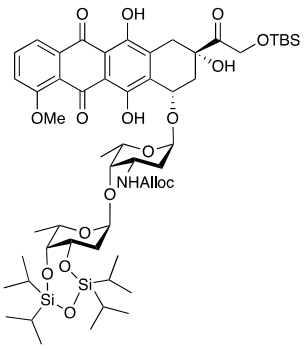
To a solution of the glycosyl acceptor **41** (901 mg, 2.67 mmol, 1 eq) and the glycosyl donor **66** (1.80 g, 3.73 mmol, 1.3 eq) in Et_2O:DCE (70 mL, 4:1 v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (5.00 mg, 10.7 mmol, 4 eq) was added. After 30 minutes, triphenylphosphine (1.40 g, 5.34 mmol, 2 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (5:95 – 10:90 EtOAc:pentane) of the residue gave the title compound as a white foam (1.69 g, 2.38 mmol, 89%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.05 – 6.93 (m, 2H), 6.93 – 6.70 (m, 2H), 6.16 (d, *J* = 7.9 Hz, 1H), 5.92 (ddt, *J* = 16.1, 10.9, 5.6 Hz, 1H), 5.52 (d, *J* = 3.2 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.93 (d, *J* = 3.7 Hz, 1H), 4.58 (qdt, *J* = 13.3, 5.6, 1.4 Hz, 2H), 4.41 (ddd, *J* = 12.2, 4.6, 2.5 Hz, 1H), 4.37 – 4.25 (m, 1H), 4.14 – 4.04 (m, 2H), 4.01 (s, 1H), 3.77 (s, 3H), 3.54 (s, 1H), 2.19 – 2.05 (m, 2H), 1.99 (dd, *J* = 12.6, 4.6 Hz, 1H), 1.89 (td, *J* = 12.7, 3.5 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.14 – 0.83 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 154.4, 150.9, 132.8, 117.4, 117.2, 114.4, 101.8, 96.2, 81.2, 73.0, 69.8, 68.0, 67.4, 65.4, 55.5, 46.4, 33.1, 31.5, 17.6, 17.5, 17.4, 17.3, 17.3, 17.2, 17.2, 17.2, 17.1, 17.1, 14.1, 13.9, 13.0, 12.4. HRMS: $[M + Na]^+$ calculated for $C_{35}H_{59}NO_{10}Si_2Na$ 732.35752; found 732.3587.

_o_-Cyclopropylethynylbenzoyl-2-deoxy-3,4-tetraisopropyldisiloxane-α-L-fucopyranosyl-(1→4)-3-N-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside (68)



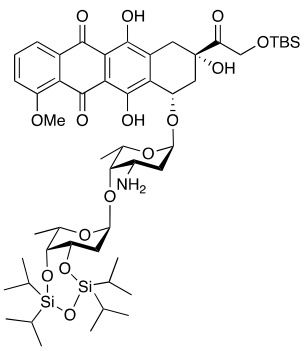
Prepared according to General Procedure A and B from **67** (1.69 g, 2.38 mmol) to give after column chromatography (10:90 – 20:80 EtOAc:pentane) the title compound as a white foam (1.54 g, 1.99 mmol, 84% over 2 steps, α:β 1:8). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 – 7.85 (m, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (ddd, *J* = 9.1, 6.0, 1.4 Hz, 1H), 7.35 – 7.24 (m, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.99 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.96 – 5.84 (m, 1H), 5.36 – 5.15 (m, 2H), 4.93 (d, *J* = 3.9 Hz, 1H), 4.56 (qdt, *J* = 13.3, 5.6, 1.5 Hz, 2H), 4.45 (ddd, *J* = 12.1, 4.5, 2.5 Hz, 1H), 4.11 – 4.06 (m, 1H), 4.01 (d, *J* = 2.5 Hz, 1H), 3.87 (dddd, *J* = 12.1, 7.1, 4.1, 2.6 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.48 – 3.44 (m, 1H), 2.22 (ddd, *J* = 11.9, 4.1, 2.2 Hz, 1H), 2.14 (td, *J* = 12.4, 4.0 Hz, 1H), 1.99 (dd, *J* = 12.4, 4.6 Hz, 1H), 1.85 (td, *J* = 12.3, 10.0 Hz, 1H), 1.51 (tt, *J* = 7.2, 5.7 Hz, 1H), 1.36 – 1.30 (m, 6H), 1.13 – 0.81 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 155.8, 134.2, 133.0, 132.0, 131.1, 130.8, 127.0, 125.1, 117.7, 102.3, 99.8, 93.2, 80.6, 74.5, 73.3, 73.0, 69.9, 68.4, 65.7, 50.1, 33.3, 32.2, 17.8, 17.8, 17.6, 17.5, 17.5, 17.5, 17.4, 17.3, 14.3, 14.2, 13.2, 12.7, 9.0, 8.9, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{40}H_{61}NO_{10}Si_2Na$ 794.37317; found 794.3749.

7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (69)



Prepared according to General Procedure C from donor **68** (722 mg, 1.00 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **64** (793 mg, 1.50 mmol, 1.5 eq) to give after column chromatography (5:95 – 20:80 EtOAc:pentane – 4:96 acetone:toluene) the title compound as a red solid (714 mg, 0.640 mmol, 64%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.09 (s, 1H), 7.93 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.07 (d, *J* = 7.8 Hz, 1H), 5.91 – 5.78 (m, 1H), 5.50 (d, *J* = 3.8 Hz, 1H), 5.27 – 5.18 (m, 2H), 5.13 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.98 – 4.86 (m, 3H), 4.61 – 4.37 (m, 4H), 4.13 (q, *J* = 6.5 Hz, 1H), 4.05 (d, *J* = 24.2 Hz, 6H), 3.90 – 3.77 (m, 1H), 3.55 (s, 1H), 3.09 (dd, *J* = 18.8, 2.0 Hz, 1H), 2.81 (d, *J* = 18.7 Hz, 1H), 2.29 (d, *J* = 14.6 Hz, 1H), 2.22 – 2.05 (m, 2H), 2.05 – 1.95 (m, 1H), 1.92 (dd, *J* = 13.1, 4.5 Hz, 1H), 1.78 (td, *J* = 12.9, 4.0 Hz, 1H), 1.30 (dd, *J* = 16.4, 6.4 Hz, 6H), 1.16 – 0.82 (m, 37H), 0.15 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 186.8, 186.4, 161.0, 156.3, 155.7, 135.7, 135.3, 134.0, 133.9, 132.9, 120.7, 119.8, 118.5, 117.5, 111.3, 111.2, 101.9, 101.0, 81.0, 73.2, 69.9, 69.7, 68.2, 68.0, 66.7, 65.5, 56.7, 46.6, 35.7, 34.0, 33.3, 31.3, 26.0, 18.7, 17.8, 17.7, 17.6, 17.5, 17.5, 17.5, 17.4, 17.3, 17.2, 14.3, 14.1, 13.1, 12.6, -5.2, -5.3. HRMS: $[M + Na]^+$ calculated for $C_{55}H_{83}NO_{17}Si_3Na$ 1136.48665; found 1136.4866.

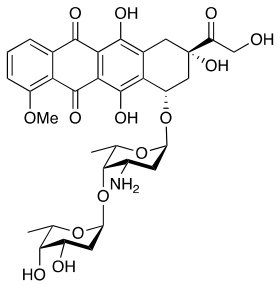
7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (70)



A solution of **69** (704 mg, 0.631 mmol) and *N*,*N*-dimethylbarbituric acid (440 mg, 2.84 mmol, 4.5 eq) in DCM (63 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (36.5 mg, 0.032 mmol, 0.05 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 50:50 acetone:toluene) to give the title compound as a red solid (650 mg, 0.631 mmol, 100%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.42 – 7.33 (m, 1H), 5.53 – 5.41 (m, 1H), 5.21 (dd, *J* = 4.1, 2.2 Hz, 1H), 4.98 (d, *J* = 3.7 Hz, 1H), 4.96 – 4.81 (m, 2H), 4.65 (s, 1H), 4.42 (ddd, *J* = 12.1, 4.6, 2.5 Hz, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 4.10 – 3.93 (m, 5H), 3.53 (s, 1H), 3.40 – 3.20 (m, 3H), 3.18 – 3.00 (m, 2H), 2.82 (d, *J* = 18.7 Hz, 1H), 2.29 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.21 – 2.09 (m, 2H), 2.05 – 1.93 (m, 1H), 1.76 (ddd, *J* = 27.6,

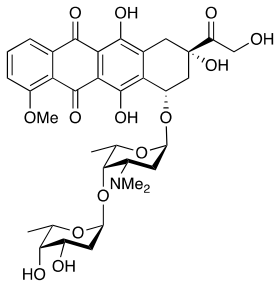
14.0, 4.2 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.13 – 0.75 (m, 36H), 0.15 (d, *J* = 1.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 186.7, 186.4, 161.0, 156.3, 155.6, 135.7, 135.3, 134.0, 132.1, 132.1, 128.6, 120.7, 119.7, 118.5, 111.3, 101.3, 101.1, 81.5, 73.3, 70.1, 69.6, 68.3, 67.8, 66.6, 56.7, 46.8, 35.6, 33.8, 33.4, 25.9, 18.7, 17.7, 17.7, 17.6, 17.6, 17.5, 17.5, 17.4, 17.3, 17.2, 14.2, 14.1, 13.1, 12.6. HRMS: $[M + H]^+$ calculated for $C_{51}H_{80}NO_{15}Si_3$ 1030.48358; found 1030.4855.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]- doxorubicinone (5)



To a solution of **70** (30.5 mg, 29.6 μmol) in pyridine (3.0 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 232 μL) at 0 °C. Over the course of 4 hours, 2 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (0:100 – 20:80 MeOH:DCM) gave the title compound as a red solid (15.1 mg, 22.4 μmol, 76%). ^{1}H NMR (500 MHz, Pyridine-d_5) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 3.0 Hz, 1H), 5.17 (d, *J* = 3.9 Hz, 1H), 5.12 (d, *J* = 2.3 Hz, 2H), 5.06 (d, *J* = 3.8 Hz, 1H), 4.36 (dt, *J* = 12.1, 3.9 Hz, 1H), 4.33 – 4.19 (m, 2H), 3.80 (d, *J* = 2.9 Hz, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.41 (t, *J* = 8.7 Hz, 1H), 3.34 – 3.12 (m, 2H), 2.51 (d, *J* = 14.4 Hz, 1H), 2.30 (td, *J* = 12.2, 3.9 Hz, 1H), 2.22 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.08 (dd, *J* = 12.3, 4.9 Hz, 1H), 1.97 (dd, *J* = 9.2, 2.8 Hz, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Pyr) δ 215.4, 187.5, 161.9, 157.5, 156.2, 135.2, 121.6, 120.1, 119.9, 112.3, 112.0, 101.9, 101.9, 81.6, 77.1, 72.4, 70.9, 69.0, 68.8, 66.7, 66.2, 57.1, 48.0, 37.9, 34.6, 34.4, 34.2, 18.1. HRMS: $[M + H]^+$ calculated for $C_{33}H_{40}NO_{14}$ 674.24488; found 674.2456.

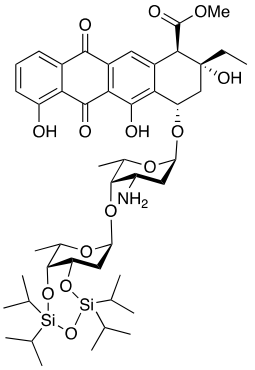
7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (7)



To a solution of **70** (102 mg, 99 μmol) in EtOH (20 mL) and 37% aq. CH_2O (245 μL, 30 eq) was added $NaBH(OAc)_3$ (40 mg, 0.193 mmol, 1.95 eq). The mixture was stirred for 1.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography chromatography (3:97 acetone:toluene) gave the dimethylated amine as a red solid (75 mg, 70.9 μmol, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.24 (s, 1H), 8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.43 – 7.37 (m, 1H), 5.54 (d, *J* = 3.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.01 (d, *J* = 3.4 Hz, 1H), 4.98 – 4.84 (m, 2H), 4.79 (s, 1H), 4.49 – 4.34 (m, 2H), 4.09 (s, 3H), 3.95 (t, *J* = 1.8 Hz, 1H), 3.91 (q, *J* = 6.5 Hz, 1H), 3.75 (s, 1H), 3.38 – 3.35 (m, 1H), 3.18 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.7, 2.3 Hz, 1H), 2.19 (s, 6H), 2.17 – 2.06 (m, 3H), 2.06 – 1.96 (m, 2H), 1.89 (td, *J* = 12.8, 4.0 Hz, 1H), 1.80 (dd, *J* = 13.0, 4.1 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.07 (ddt, *J* = 9.4, 7.4, 4.6 Hz, 24H), 0.96 (s, 9H), 0.14 (d, *J* = 2.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 187.2, 186.8, 161.1, 156.6, 156.0, 135.8, 135.6, 134.3, 134.2, 121.0, 119.9, 118.5, 111.5, 111.4, 101.5, 99.9, 74.1, 73.8, 70.6, 69.6, 68.8, 67.3, 66.7, 61.8, 56.8, 43.5, 35.7, 34.1, 33.4, 26.0, 18.1, 17.8, 17.8, 17.7, 17.6, 17.6, 17.5, 17.5, 17.4, 17.4, 14.4, 14.3, 13.2, 12.7. HRMS: $[M + H]^+$ calculated for $C_{53}H_{84}NO_{15}Si_3$ 1058.51488; found 1058.51488.

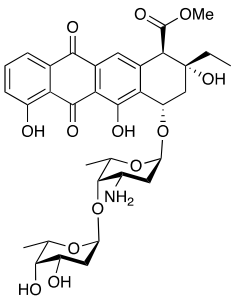
To a solution of the above compound (38 mg, 35.9 μmol) in pyridine (3.6 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 282 μL) at 0°C. Over the course of 4.5 hours, 3 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 10:90 MeOH:DCM) gave the title compound as a red solid (20.3 mg, 28.9 μmol, 81%). ^{1}H NMR (500 MHz, Chloroform-*d* + MeOD) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 5.55 (d, *J* = 4.0 Hz, 1H), 5.28 (s, 1H), 5.05 (d, *J* = 3.9 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 2H), 4.41 (q, *J* = 6.6 Hz, 1H), 4.14 – 4.03 (m, 4H), 3.97 (q, *J* = 6.6 Hz, 1H), 3.83 (d, *J* = 6.5 Hz, 1H), 3.24 (dd, *J* = 18.9, 5.9 Hz, 1H), 3.02 (dd, *J* = 19.2, 6.3 Hz, 1H), 2.39 – 2.08 (m, 8H), 2.07 – 1.80 (m, 4H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$ + MeOD) δ 213.6, 187.2, 186.8, 161.1, 155.9, 155.3, 135.9, 135.4, 133.8, 133.5, 120.8, 119.8, 118.6, 111.6, 111.4, 100.9, 99.2, 73.6, 71.0, 69.2, 68.6, 66.6, 65.4, 65.2, 61.7, 56.6, 43.0, 35.5, 33.8, 32.3, 28.7, 17.9, 16.6. HRMS: $[M + H]^+$ calculated for $C_{35}H_{44}NO_{14}$ 702.27619; found 702.2769.

7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (71)



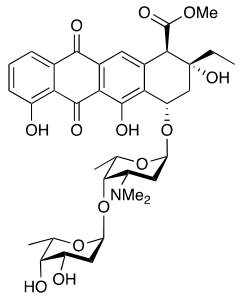
Prepared according to General Procedure C from donor **68** (623 mg, 0.806 mmol) and aklavinone **43** (665 mg, 1.61 mmol, 2.00 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 – 10:90 acetone:toluene) of the residue an inseparable mixture of the disaccharide anthracycline and acceptor, which was continued to the next step. A solution of the above mixture and *N,N*-dimethylbarbituric acid (562 mg, 3.60 mmol, 2.2 eq) in DCM (81 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (23 mg, 0.040 mmol, 0.025 eq) was added and the mixture was allowed to stir for 30 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 25:75 acetone:toluene) to give the title compound as a yellow solid (636 mg, 0.700 mmol, 86% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 5.47 (d, *J* = 2.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 1.8 Hz, 1H), 4.97 (d, *J* = 3.6 Hz, 1H), 4.42 (ddd, *J* = 12.0, 4.7, 2.5 Hz, 1H), 4.19 – 4.05 (m, 3H), 4.00 (d, *J* = 2.6 Hz, 1H), 3.70 (s, 3H), 3.51 (d, *J* = 2.5 Hz, 1H), 3.24 (qt, *J* = 9.3, 6.6, 5.6 Hz, 1H), 2.52 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.17 – 2.08 (m, 1H), 2.01 (dd, *J* = 12.3, 4.6 Hz, 1H), 1.86 – 1.68 (m, 3H), 1.49 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.17 – 0.85 (m, 31H).^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 181.2, 171.4, 162.5, 162.1, 142.7, 137.4, 133.4, 132.9, 131.2, 124.8, 120.9, 120.2, 115.7, 114.6, 101.7, 101.1, 81.7, 73.3, 71.6, 70.9, 70.2, 68.1, 67.8, 57.1, 52.6, 46.8, 33.9, 33.4, 32.2, 17.7, 17.7, 17.6, 17.5, 17.5, 17.4, 17.3, 17.3, 14.3, 14.1, 13.1, 12.6, 6.8. HRMS: $[M + H]^+$ calculated for $C_{46}H_{68}NO_{14}Si_2$ 914.4178; found 914.4173.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (6)



To a solution of **71** (91 mg, 0.10 mmol) in pyridine (10 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 393 µL) at 0°C. Over the course of 4.5 hours, 3 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and partitioned between DCM and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) followed by size-exclusion chromatography (Sephadex LH-20, eluent DCM:MeOH, 1:1) gave the title compound as a yellow solid (27.5 mg, 40.9 µmol, 41%). ^{1}H NMR (400 MHz, Chloroform-*d* + MeOD) δ 7.79 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.74 – 7.57 (m, 2H), 7.32 – 7.23 (m, 1H), 5.47 (t, *J* = 2.5 Hz, 1H), 5.27 – 5.20 (m, 1H), 4.97 (d, *J* = 3.5 Hz, 1H), 4.20 – 4.01 (m, 4H), 3.70 (s, 3H), 3.64 (d, *J* = 3.0 Hz, 2H), 3.61 – 3.52 (m, 2H), 3.11 (dd, *J* = 10.6, 6.7 Hz, 1H), 2.53 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.27 (d, *J* = 15.0 Hz, 1H), 1.97 (ddd, *J* = 22.5, 12.3, 4.2 Hz, 2H), 1.86 – 1.64 (m, 3H), 1.50 (dt, *J* = 14.6, 7.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.07 (q, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 181.4, 171.4, 162.5, 162.0, 142.6, 137.5, 133.5, 132.9, 131.1, 124.9, 121.0, 120.3, 115.8, 114.7, 101.3, 100.8, 81.1, 71.6, 70.9, 70.8, 68.0, 67.4, 65.4, 57.0, 52.6, 46.7, 34.1, 33.2, 32.7, 32.2, 17.3, 16.9, 6.7. HRMS: $[M + H]^+$ calculated for $C_{34}H_{42}NO_{13}$ 672.2656; found 672.2645.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (8)



To a solution of **6** (26.2 mg, 37.4 µmol) in EtOH (3.7 mL) and 37% aq. CH_2O (200 µL, 60 eq) was added $NaBH(OAc)_3$ (85 mg, 0.374 mmol, 10 eq). The mixture was stirred for 2.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (3:97 – 10:90 MeOH:DCM) gave the title compound as a yellow solid (8.8 mg, 12.6 µmol, 34%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.69 (s, 1H), 12.04 (s, 1H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.78 – 7.60 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.51 (d, *J* = 3.7 Hz, 1H), 5.27 (dd, *J* = 4.3, 1.9 Hz, 1H), 5.01 (s, 1H), 4.53 (dd, *J* = 14.2, 7.7 Hz, 1H), 4.17 – 4.05 (m, 2H), 4.00 (q, *J* = 6.6 Hz, 1H), 3.74 (d, *J* = 8.5 Hz, 1H), 3.63 (d, *J* = 3.1 Hz, 1H), 2.52 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.29 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.25 – 2.11 (m, 6H), 2.07 (dt, *J* = 10.9, 5.4 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.75 (dq, *J* = 14.6, 7.7, 7.3 Hz, 1H), 1.51 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.09 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 181.5, 162.7, 162.3, 142.8, 137.5, 133.6, 133.1, 124.9, 121.1, 120.3, 116.0, 114.8, 101.7, 99.2, 71.8, 71.7, 70.8, 68.5, 66.3, 66.0, 61.7, 57.3, 52.7, 43.4, 33.9, 33.2, 32.3, 18.0, 16.8, 6.8. HRMS: $[M + H]^+$ calculated for $C_{36}H_{46}NO_{13}$ 700.2969; found 700.2966.

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