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Synthesis of 3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl pyranonaphthoquinone analogues of medermycin

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The synthesis of an isomeric mixture of 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl analogues **6** of the *C*-glycosylpyranonaphthoquinone antibiotic medermycin is described. The key 3-acetyl-6-(4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone **8** was prepared *via* Stille coupling of 6-(3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4-naphthoquinone **17** with (α-ethoxyvinyl)tributylstannane followed by hydrolysis and oxidation of the resultant hydroquinone **18**. Bromonaphthoquinone **17** in turn was afforded by oxidative demethylation of 6-(4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene **16** formed by regioselective bromination of 6-(4-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene **10**. This latter naphthalene **10** was prepared *via* direct *C*-glycosylation of naphthol **12** with glycosyl donor **11** using $BF_3{\cdot}Et_2O$ in acetonitrile. The regioselectivity of the bromination of naphthalene **10** was independently determined by reductive monomethylation of the 6-(4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone **22** to naphthol **23** followed by selective *ortho* bromination to bromide **24** and methylation to **16**. Attempts to effect acetylation of 6-(4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene **16** and 3-bromo-6-(3-dimethylamino-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene **26** *via* Stille coupling with (α-ethoxyvinyl)tributylstannane were low yielding thereby establishing the necessity to use an azido group as a latent dimethylamino group and a more electrophilic bromonaphthoquinone as the coupling partner for the Stille reaction. Addition of 2-trimethylsilyloxyfuran **9** to 3-acetyl-6-(4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone **8** afforded the furofuran adducts **7** and **19** as an inseparable mixture of diastereomers. Oxidative rearrangement of this diastereomeric mixture using ceric ammonium nitrate afforded the inseparable diastereomeric furonaphthopyrans **6** and **20**.

Introduction

Medermycin is a unique member of the pyranonaphthoquinone family of antibiotics[1,2] in that it contains a β-*C*-glycoside linkage to an aminosugar, D-angolosamine. Medermycin was isolated[3] from a strain of *Streptomyces* K73 and was shown to exhibit activity against Gram-positive bacteria including *Staphylococcus aureus*. The structure of medermycin **1** was initially assigned as having the same skeleton as kalafungin **3** with the amino sugar moiety attached to the pyranonaphthoquinone nucleus at C-8. There was some confusion when Tanaka *et al.*[4,5] reported the isolation and structure of an antitumour agent lactoquinomycin and suggested that medermycin could be an isomer of lactoquinomycin based on apparent differences in their physicochemical properties and biological activities. This was resolved, however, when a synthesis of medermycin by Tatsuta *et al.*[6] allowed comparison of the synthetic and natural samples thereby establishing that all three samples were identical. Lactoquinomycin/medermycin were also shown to inhibit platelet aggregation.[7]

The situation recently changed when Morin and co-workers[8] provided chemical and spectroscopic evidence that necessitated the original structure of medermycin be revised to structure **2** wherein the *C*-glycoside is attached to the kalafungin skeleton at the C-10 position *para* to the hydroxyl group. Morin and co-workers[8] also established that Tatsuta *et al.*[6] had in fact inadvertantly synthesized medermycin with the revised structure **2** although Tatsuta *et al.*[6] had initially claimed a synthesis of medermycin with the original structure **1**. These recent studies by Morin and co-workers[8] also suggested revision of the previous structures for the related *C*-glycosyl pyranonaphthoquinone antibiotics lactoquinomycin B[9] and menoxymycin A[10] to structures **4** and **5**, respectively. However, more recently Wyeth researchers[11] presented sophisticated NMR evidence in support of the original structure for medermycin/lactoquinomycin A **1**.

Our synthetic efforts towards medermycin focused on the efficient introduction of a *C*-glycoside at C-8 on the pyranonaphthoquinone skeleton and have resulted in the synthesis of a 2-deoxyglucosyl analogue[12] and an azido analogue[13] of medermycin **1**. Given the significant biological activity exhibited by medermycin **1**, and the prevalence of other naphthoquinone antibiotics such as the quanoliranes, capomycins, urdamycins, amicenomycins, and saquayamicins in which the *C*-glycoside linkage is *ortho* to a phenolic group,[14] our synthetic programme provides access to a range of *C*-glycosidic pyranonaphthoquinones related to medermycin **1** that can be evaluated for biological activity.

To date only one synthesis of medermycin **2** has been reported[6] in which the pyranonaphthalene skeleton was assembled by addition of a *C*-glycosylsulfonylphthalide to an enone. Substantial functional group manipulation was required after construction of the *C*-glycoside linkage in order to access the required D-angolosaminide moiety and the dimethylamino group on the sugar was introduced in low yield in the final steps of the synthesis. We herein report the full details[13] of our synthesis of an azido analogue of medermycin **1** using a furofuran annulation – oxidative rearrangement strategy as previously used for the synthesis of kalafungin **3**[15] and related aglycones.[16]

Results and discussion

In our approach to the synthesis of the original structure of medermycin **1** we required a flexible strategy for construction of the *C*-glycoside moiety *ortho* to the phenolic group that was

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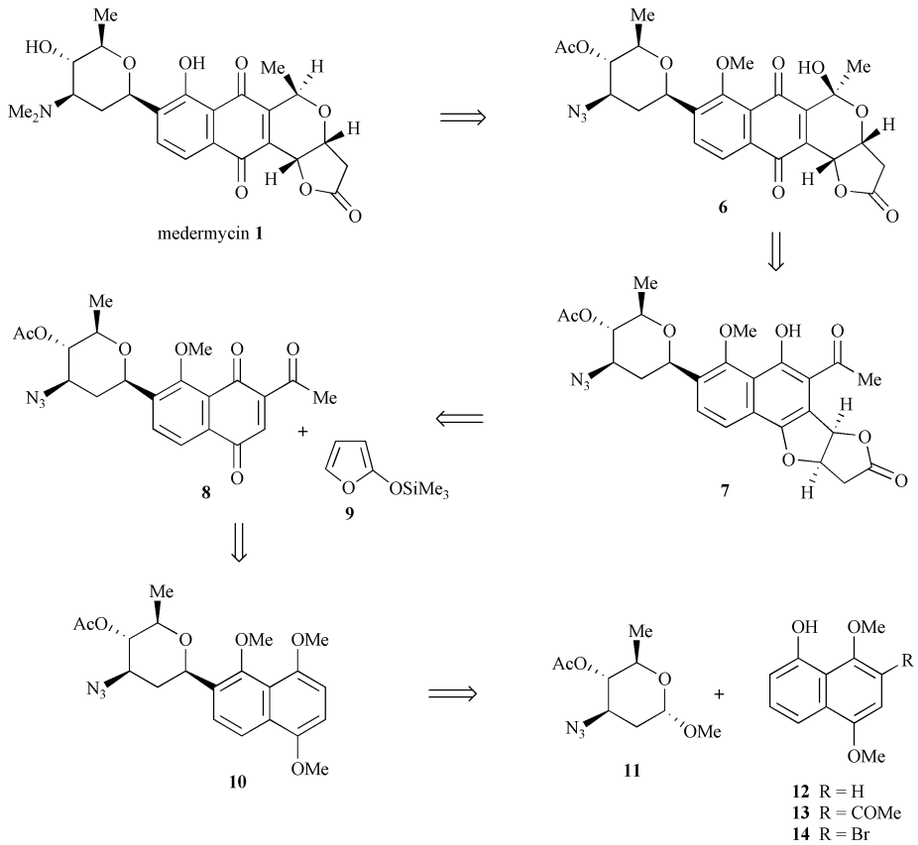
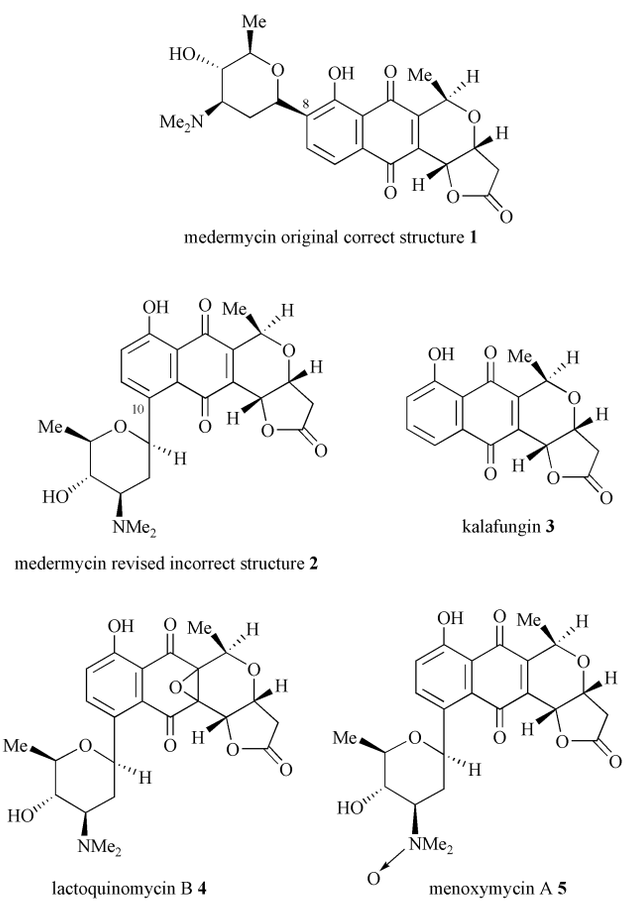


Scheme 1

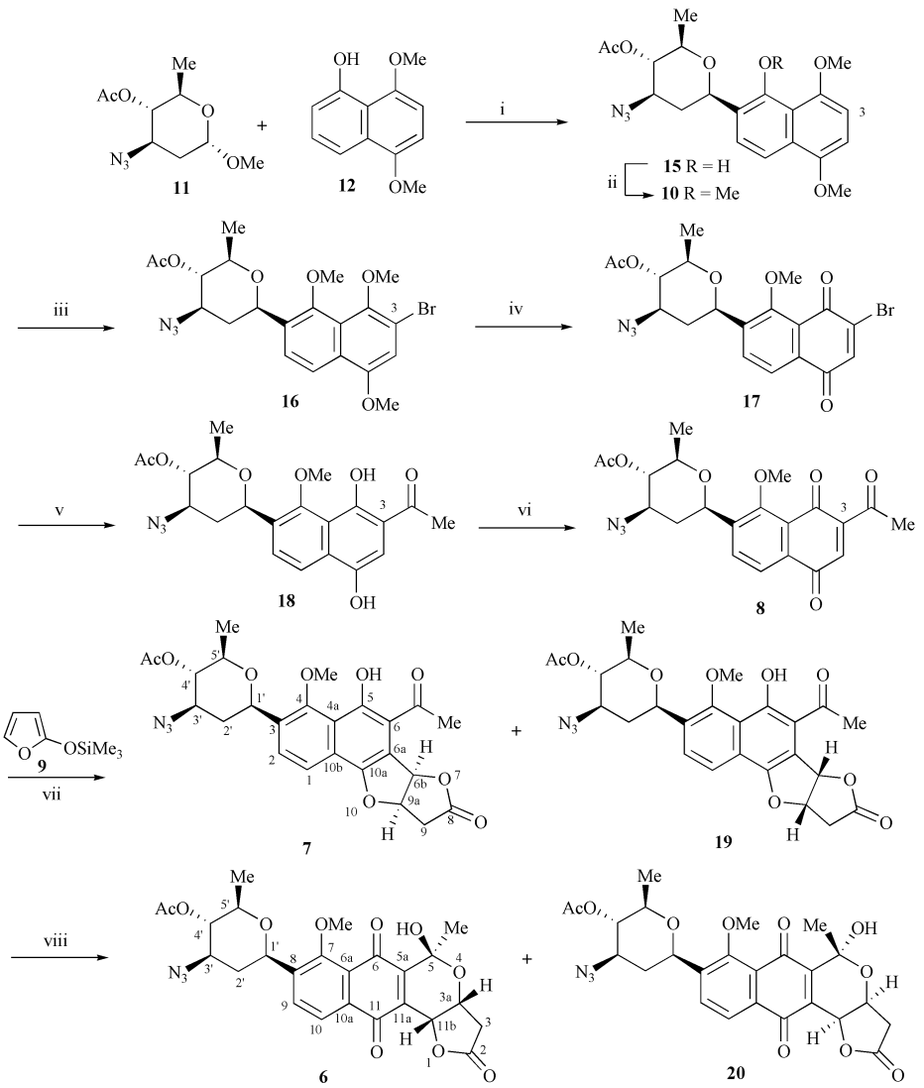


amenable to the construction of other analogues with varying *C*-glycoside moieties. A synthesis of an azido analogue **6** of medermycin was realized based on the retrosynthesis outlined (Scheme 1). Direct *C*-glycosylation of naphthol **12** with azido sugar **11** provides *C*-glycosylnaphthalene **10** that serves as an appropriate precursor to the key *C*-glycosyl acetylnaphthoquinone **8** required for the furofuran annulation with 2-trimethylsilyloxyfuran **9** providing adduct **7** that undergoes oxidative rearrangement to pyranonaphthoquinone **6**.

Preliminary investigations[17] established the necessity to use an azido group as a latent dimethylamino group in the glycosyl donor **11** due to problems encountered with quaternization of the dimethylamino group when undertaking further manipulation of the naphthol fragment after the *C*-glycosylation step. Furthermore it was also found[17] that use of 5-hydroxy-1,4-dimethoxynaphthalene **12** was essential to ensure good yields in the *C*-glycosylation step in that use of naphthols further substituted at C-3, only afforded low yields of the desired *C*-glycosides. Our synthetic strategy therefore focused on introduction of a bromine at C-3 of the initial *C*-glycoside **10** in preparation for subsequent introduction of an acetyl group at C-3 in naphthoquinone **8** which is essential for effective regiocontrol in the ensuing furofuran annulation step. Whilst direct *C*-glycosylation of 3-acetyl-5-hydroxy-1,4-dimethoxynaphthalene **13** or 3-bromo-5-hydroxy-1,4-dimethoxynaphthalene **14** with glycosyl donor **11** would have provided a more direct approach, the low yields observed in the *C*-glycosylation step using these naphthols precluded this strategy.[17]

Glycosyl donor **11** was readily prepared[17] from di-*O*-acetyl-D-rhamnal by adaptation of existing methodology for the synthesis of the L-isomer reported by Monneret and co-workers.[18] After substantial experimentation[17] to evaluate the optimum method for effecting the key *C*-glycosylation[19] step, arylation of azido *C*-glycosyl donor **11** with naphthol **12**[12] was optimally achieved in 60% yield using two equivalents of boron trifluoride (2.0 equiv.) in acetonitrile at 0 °C. Treatment of the resultant *C*-glycoside **15** with sodium hydride and methyl iodide in DMF then afforded methyl ether **10** in 82% yield (Scheme 2).

The next challenge in the synthesis was the introduction of a bromine substituent at C-3. It was envisaged that the resulting



Scheme 2 *Reagents, conditions and yields*: (i) $BF_3{\cdot}Et_2O$ (2.0 equiv.), CH_3CN, 0 °C (60%); (ii) NaH, DMF, MeI, 0 °C (82%); (iii) NBS (1.0 equiv.), CH_2Cl_2, 1.5 h (73%); (iv) $(NH_4)_2Ce(NO_3)_6$ (2.5 equiv.), CH_3CN, 5 min, (99%); (v) (α-ethoxyvinyl)tributylstannane (1.1. equiv.), $Pd(PPh_3)_4$, CuBr, 1,4-dioxane, 100 °C, 50 min, then CH_2Cl_2, aq. $Na_2S_2O_4$, then 0.5 M HCl (71%); (vi) Ag_2O, Et_2O; (vii) 9 (2.0 equiv.), CH_3CN, 0 °C; then SiO_2, MeOH, room temp., 18 h (40% over 2 steps); (viii) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv.), CH_3CN, 5 min (89%).

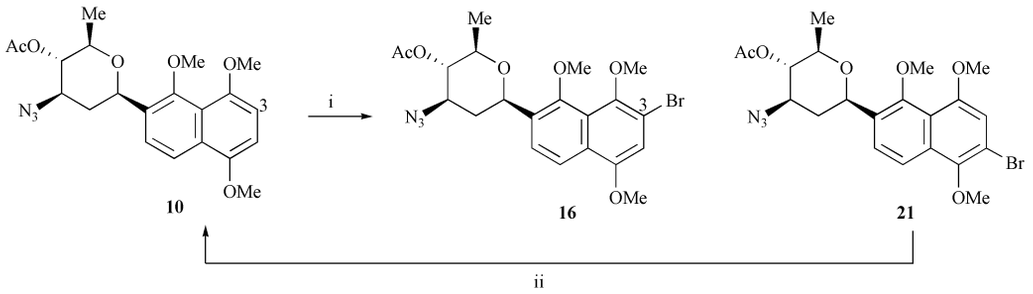
3-bromonaphthalene **16** would undergo palladium(0)-mediated coupling with (α-ethoxyvinyl)tributylstannane followed by hydrolysis to introduce an acetyl group at C-3. In our synthesis of a 2-deoxyglucosyl analogue of medermycin[12] introduction of a bromine at C-3 was achieved using a five step procedure *via* initial oxidation to a naphthoquinone. A substantial improvement was made in the present work when it was found that *C*-glycosylnaphthalene **10** underwent regioselective bromination at C-3 in a single step.

C-Glycosylnaphthalene **10** has three sites where electrophilic attack might occur. It was expected that bromination would predominate at C-3 and C-2 due to the presence of two electron-donating methoxyl substituents on the right-hand ring. Furthermore, the C-5 methoxy group is expected to favour C-3 bromination when resonance structures for the cationic intermediates are considered.

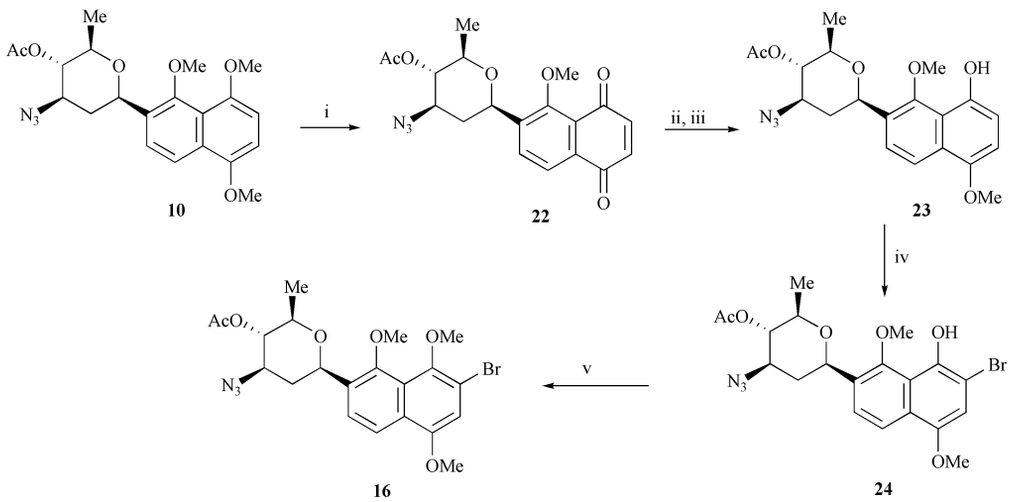
In the event, bromination of **10** occurred smoothly using *N*-bromosuccinimide in dichloromethane to give the desired 3-bromonaphthalene **16** in 73% yield and 2-bromonaphthalene **21** in 20% yield after column chromatography (Scheme 3). None of the C-8 brominated product was observed. High resolution mass spectrometry established the molecular formula $C_{21}H_{24}N_3O_6Br$ for the major regioisomer **16**. The mass spectrum featured two peaks of approximately equal intensity at *m*/*z* 493 and *m*/*z* 495, consistent with the introduction of a bromine atom. The ^1H NMR spectrum featured a one-proton singlet at δ 6.94, which was assigned to 2-H. 7-H and 8-H both resonated as doublets with $J_{7,8}$ 8.8 Hz, at δ 8.05 and δ 7.59 respectively. Accurate mass determination also established the molecular formula $C_{21}H_{24}N_3O_6Br$ for the minor regioisomer **21**. A one-proton singlet observed at δ 6.94 in the ^1H NMR spectrum was assigned to 3-H. 7-H and 8-H resonated as doublets at δ 7.90 and δ 7.64 respectively.

Unambiguous confirmation of the regiochemical assignment of the major regioisomer was achieved by preparing 3-bromonaphthalene **16** *via* an independent route (Scheme 4). Thus, oxidative methylation of trimethoxynaphthalene **10** afforded naphthoquinone **22** which underwent reductive monomethylation to naphthol **23**. Selective *ortho*-bromination of naphthol **23** then afforded 3-bromonaphthol **24** that upon methylation furnished 3-bromotrimethoxynaphthalene **16** for which the ^1H NMR spectrum was identical to the major bromide obtained from the one-step bromination of **10**.

It was found that the 2-bromo regioisomer **21** could be efficiently recycled by performing a lithium–bromine exchange using 1.0 equivalent of *n*-butyllithium in tetrahydrofuran and quenching the resulting aryllithium with water to give debrominated compound **10** which could then be recycled into the synthesis. Surprisingly, the acetyl group survived this operation intact, although it was found that by-products of higher polarity (and lower yields of **10**) were obtained when excess *n*-butyllithium was used.



Scheme 3 *Reagents, conditions and yields*: (i) NBS (1.0 equiv.), CH_2Cl_2, 1.5 h, **16** (73%), **21** (20%); (ii) BuLi, −78 °C to 0 °C, 1 h, then H_2O, 82%.



Scheme 4 *Reagents, conditions and yields*: (i) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O (71%); (ii) NaS_2O_6, H_2O, Et_2O; (iii) K_2CO_3, MeI, acetone; (iv) Br_2, CCl_4; (v) NaH, Me_2SO_4 42% over 4 steps.

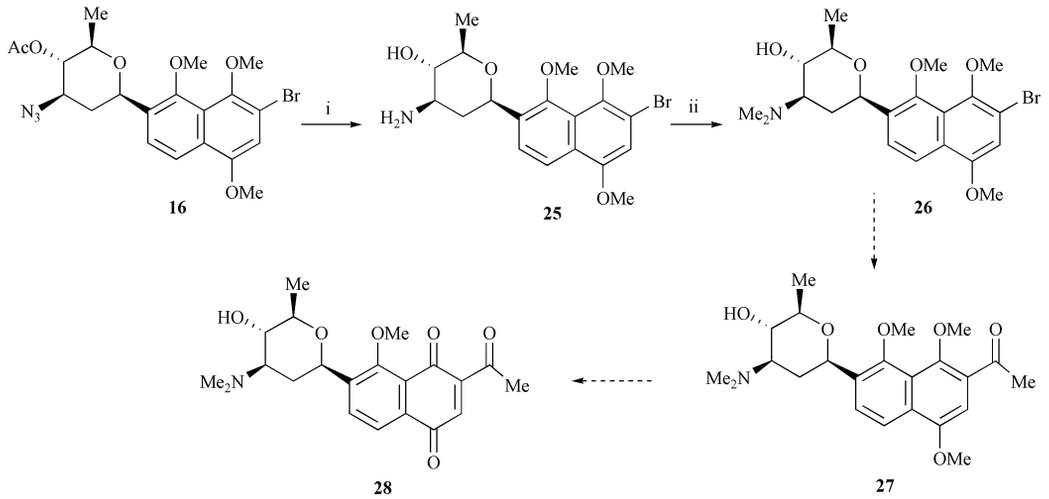
Since it was apparent from the reaction with *N*-bromosuccinimide that electrophilic attack on naphthalene **10** occurs preferentially at C-3, an electrophilic acylation strategy was investigated as a method to introduce an acetyl group at C-3 on naphthalene **10** which would obviate the need to proceed *via* bromide **16**. Towards this goal a variety of acetylation procedures were investigated. Initially attention focused on the use of an acetic acid–trifluoroacetic anhydride system,[20] which has previously been used successfully to acetylate related polyalkoxynaphthalenes.[21] Unfortunately, naphthalene **10** proved totally unreactive towards this system, even at elevated temperatures. Friedel–Crafts acetylation using acetyl chloride and aluminium chloride in dichloromethane also failed, with some decomposition observed using this system at elevated temperatures. Finally, **10** was exposed to the highly reactive mixed anhydride, acetyl triflate[22] at −40 °C, which disappointingly only afforded recovered starting material **10**. The very poor reactivity of naphthalene **10** towards acetylation was disappointing and our attention therefore turned to the palladium(0)-mediated coupling of bromonaphthalene **10** with (α-ethoxyvinyl)tributylstannane[23] as a method for introduction of the required acetyl group.

Despite extensive experimentation, attempts to convert the bromide in naphthalene **16** to an acetyl group *via* Stille coupling with (α-ethoxyvinyl)tributylstannane followed by acidic hydrolysis of the enol ether intermediate mainly resulted in recovered starting material. This outcome was disappointing given that an analogous transformation had been successfully achieved in the synthesis of a 2-deoxyglucosyl analogue of medermycin in which the *C*-glycoside lacked an azide group. Even when the bidentate ligand 1,1′-bis(diphenylphosphino)-ferrocene (dppf)[24] was used, very little reaction had occurred after 18 h and the starting bromide **16** was recovered in 92% yield. It was postulated that the phosphine ligands of the catalyst were undergoing a Staudinger reaction[25] with the azide function at C-3′. The Staudinger reaction is commonly used as a chemoselective method for the reduction of azides to primary amines. This hypothesis suggested that a superior coupling method might be achieved if the azide group were converted into a dimethylamino group prior to the Stille coupling.

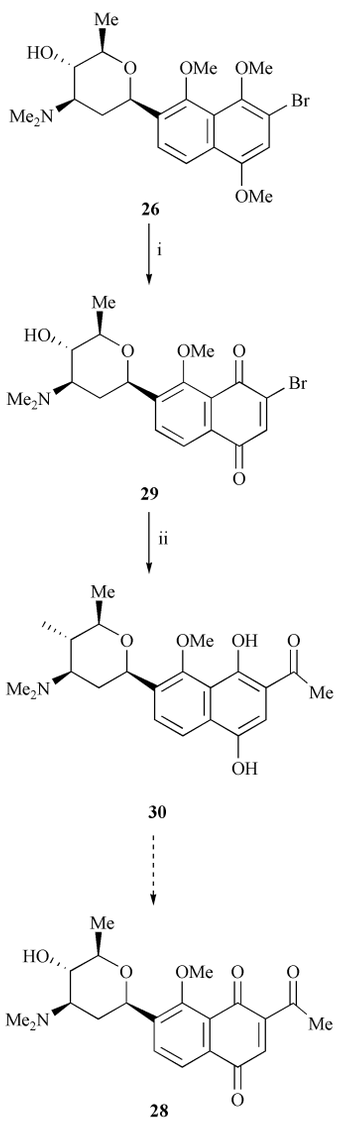
Reduction of the azide group in *C*-glycoside **16** to an amine with retention of the bromine was achieved *via* hydrogenation over platinum(IV) oxide in methanol. The acetate group at C-4′ was cleaved under these conditions affording amino-*C*-glycoside **25** in high yield (Scheme 5). Primary amine **25** was then converted to dimethylamino derivative **26** using sodium borohydride in acetonitrile at room temperature. With bromide **26** in hand, it was then disappointing to find that attempted Stille coupling–hydrolysis to 3-acetylnaphthalene **27** prior to oxidation to the desired naphthoquinone **28** was unsuccessful. Despite the use of many sets of conditions including the use of copper(I) co-catalysts[26] to effect this reaction only recovered bromide **26** was obtained.

In Stille reactions the oxidative addition to palladium(0) is usually the rate determining step and electron rich bromides such as **16** and **26** provide lower yields of coupled products than aryl bromides with electron withdrawing substituents.[27] *Ortho* substituents have also been proposed to coordinate to the palladium center with a detrimental effect on the rate of cross-coupling.[27] In the present work it was therefore decided that the best way to improve the Stille reaction was to use a more reactive bromide coupling partner which prompted the use of bromoquinones **17** and **29** for this reaction (Schemes 2,6). The use of simple 2- and 3-bromonaphthoquinones as electrophiles in palladium(0)- and copper(I)-catalyzed Stille couplings with various aryl, vinyl and alkyl stannanes has been successfully achieved by Echavarren *et al.*[28]

The viability of using *C*-glycosylnaphthoquinone **29** as coupling partner was first investigated (Scheme 6) in that use of bromonaphthoquinone **29** would obviate the need to carry out the reduction of the azide to a dimethylamino group at a later stage. Bromonaphthalene **26** was therefore oxidized using ceric



Scheme 5 *Reagents, conditions and yields*: (i) PtO_2, H_2, MeOH, 24 h (99%); (ii) $NaCNBH_3$, H_2CO, CH_3CN (93%).



Scheme 6 *Reagents, conditions and yields*: (i) CAN (2.5 equiv.), CH_3CN, 5 min (85%); (ii) (α-ethoxyvinyl)tributylstannane (1.1 equiv.), $Pd(PPh_3)_4$, CuBr, 1,4-dioxane, 100 °C, 50 min; then CH_2Cl_2, aq. $Na_2S_2O_4$, then 0.5 M HCl (22%).

ammonium nitrate to give the desired naphthoquinone **29** in 85% yield after chromatography. Coupling of bromoquinone **29** with (α-ethoxyvinyl)tributylstannane was then attempted using $Pd(PPh_3)_4$ and copper(I) bromide in 1,4-dioxane at 100 °C. TLC analysis of the reaction indicated that complete consumption of starting material had occurred within 50 min and the reaction mixture was then subjected to a reductive hydrolysis with sodium dithionite and 0.5 M hydrochloric acid. Care was taken to ensure extraction of the tertiary amine product by treatment of the aqueous phase with sodium bicarbonate, however, disappointingly only a 22% yield of acetyl hydroquinone **30** was obtained.

The high resolution mass spectrum of compound **30** contained a molecular ion at *m*/*z* 389.1841, establishing the molecular formula $C_{21}H_{27}NO_6$. A strong peak at 1625 cm^{-1} in the infrared spectrum was assigned to the *ortho*-hydroxy ketone. A singlet in the ^1H NMR spectrum at δ 7.06 was assigned to 2-H and 7-H and 8-H resonated as mutually coupled doublets, at δ 7.99 and δ 7.74 respectively. In the ^{13}C NMR spectrum a new peak at δ 205.0 was consistent with the introduction of a methyl ketone.

Bromoquinone **29** was poorly soluble in 1,4-dioxane (and even less soluble in toluene, another reaction solvent commonly used to effect Stille couplings), suggesting that more efficient coupling might depend on solubilising **29** in the reaction medium. To this end, a coupling experiment was attempted using dimethylsulfoxide as an additive; however, this led to no improvement in yield. In other experiments attention was paid to exhaustive extraction of the aqueous phases with a variety of organic solvents. However, the initial yield of 22% was not improved. Frustratingly, the success of the reaction even when using the optimized conditions appeared to be highly variable. These problems were exacerbated when attempts to oxidize *C*-glycosylhydroquinone **30** to the key naphthoquinone **28** using silver(I) oxide, manganese(IV) oxide and ceric ammonium nitrate afforded only complex mixtures.

These latter disappointing results forced us to return to the use of azido *C*-glycosylbromonaphthoquinone **17** (Scheme 2) as the electrophilic coupling partner for the Stille reaction. Thus, treatment of 3-bromonaphthalene **16** with ceric ammonium nitrate afforded bromonaphthoquinone **17** in high yield. High resolution mass spectrometry established the molecular formula $C_{19}H_{18}N_3O_6Br$ for compound **16** and the infrared spectrum revealed a strong band at 1673 cm^{-1}, attributed to the quinone carbonyl groups. In the ^1H NMR spectrum a single methoxy group resonated at δ 3.93, consistent with oxidative demethylation, while a large downfield shift was observed for 2-H, which resonated at δ 7.50. 7-H and 8-H resonated as an unresolved multiplet at δ 7.96–7.91. In the ^{13}C NMR spectrum, two peaks attributed to the quinone carbonyl carbons were observed at δ 182.6 and δ 177.1. Retention of bromine was evident in the mass spectrum, which exhibited two molecular ions of approximately equal intensity at *m*/*z* 465 and 463.

Stille coupling of bromonaphthoquinone**17** with (α-ethoxyvinyl)tributylstannane proceeded smoothly and bromonaphthoquinone **17** was entirely consumed within 50 min (Scheme 2). After treatment with aqueous dithionite and hydrochloric acid the desired acetylhydroquinone **18** was furnished in 71% yield after chromatography. This compound was somewhat unstable on silica, and it was very important to use as small a column as possible, in conjunction with a fast eluent (hexanes–ethyl acetate, 1 : 1) in order to obtain this optimum yield. The high resolution mass spectrum of compound **18** contained a molecular ion at *m*/*z* 429.1549, establishing the molecular formula $C_{21}H_{23}N_3O_7$. A strong peak in the infrared spectrum at 1626 cm^{-1} was consistent with the presence of the carbonyl group of an *ortho* hydroxy aromatic ketone. In the ^1H NMR spectrum, 2-H resonated as a singlet at δ 7.00, while two mutually coupled doublets at δ 7.94 and δ 7.73 ($J_{7,8}$ 8.7 Hz) were assigned to 7-H and 8-H respectively. Inspection of the ^{13}C NMR spectrum revealed the loss of the two quinone carbons and the appearance of a peak at δ 204.5, which was assigned to the ketone carbonyl.

3-Acetylhydroquinone **18** was then oxidized to 3-acetylnaphthoquinone **8** using silver(I) oxide in diethyl ether (Scheme 2), however, attempts to purify 3-acetylnaphthoquinone **8** were fruitless and severe decomposition occurred upon attempted purification by chromatography. Use of flash silica pre-treated with triethylamine made little or no difference to the outcome. Quinone **8** also appeared to be somewhat unstable in solution, and underwent decomposition during storage; the material was therefore used immediately in crude form for the subsequent reaction with 2-trimethylsilyloxyfuran **9**.

With the key naphthoquinone **8** in hand, albeit in crude form, attention shifted to the final phase of the synthesis namely, use of a 2-trimethylsilyloxyfuran addition–oxidative rearrangement strategy to establish the pyranonaphthoquinone skeleton present in medermycin **1** (Scheme 2). Towards this end, 2-trimethysilyloxyfuran **9** (2.0 equiv.) was added to a solution of *C*-glycosylnaphthoquinone **8** in acetonitrile at 0 °C. After an hour a small amount of methanol and silica were added and the mixture was left to stir at room temperature overnight. Subsequent work up and chromatography afforded a mixture of furonaphthofurans **7** and **19** in 40% yield. The ratio of diastereomers **7 : 19** was 1 : 1 as determined by ^1H NMR analysis. In some experiments this ratio was somewhat less (or more) than 1 : 1, probably due to discarding of impure early or late fractions during chromatography. Purification was difficult due to the instability of adducts **7** and **19** on silica gel.

Accurate mass determination established the molecular formula $C_{25}H_{25}N_3O_9$ for the mixture of adducts **7** and **19**. The infrared spectrum featured a broad band at 3502 cm^{-1}, which was assigned to the hydroxyl group and a strong band at 1775 cm^{-1} was assigned to the newly introduced γ-lactone carbonyl. The ^1H NMR spectrum was complicated by the presence of the two diastereomers. The bridgehead proton 6_b-H resonated as a doublet at δ 6.45 ($J_{6b,9a}$ 6.3 Hz), while the corresponding signal for the diastereomeric proton 6_b*-H appeared as a doublet at δ 6.46 ($J_{6b*,9a*}$ 6.3 Hz). The other bridgehead protons H-9_a and H-9_a* overlapped to give an unresolved multiplet at δ 5.53–5.50. The coupling constant $J_{6b,9a}$ 6.3 Hz was consistent with the proposed formation of a *cis*-fused 2*H*-furo[3,2-*b*]naphtho-[2,3-*d*]furan ring system.[12,15] An unresolved multiplet at δ 3.15–3.12 was assigned to 9-H and 9*-H. A singlet at δ 2.81 was assigned to the methyl ketone protons of both diastereomers. In one diastereomer 1-H and 2-H resonated as mutually coupled doublets at δ 7.80 and 7.73 respectively, while in the other diastereomer 1*-H and 2*-H gave rise to separate resonances at δ 7.79 and 7.75 respectively. Resonances for certain protons on the azido sugar moiety also exhibited chemical shift differences between the two diastereomers, for example a doublet of doublets of doublets at δ 2.38 ($J_{2'eq,1'}$ 1.9 Hz, $J_{2'eq,3'}$ 4.9 Hz and $J_{2'eq,2'ax}$ 13.2 Hz) was assigned to $2_{eq}'$-H, whereas a virtually identical signal at δ 2.34 was assigned to $2_{eq}'$*-H. $2_{ax}'$-H and $2_{ax}'$*-H resonated at δ 1.71 and 1.78 respectively, while 1′-H and 1′*-H gave rise to doublets of doublets at δ 5.01 and 5.04 respectively. This ^1H NMR data did not allow individual resonances to be assigned to either **7** or **19**.

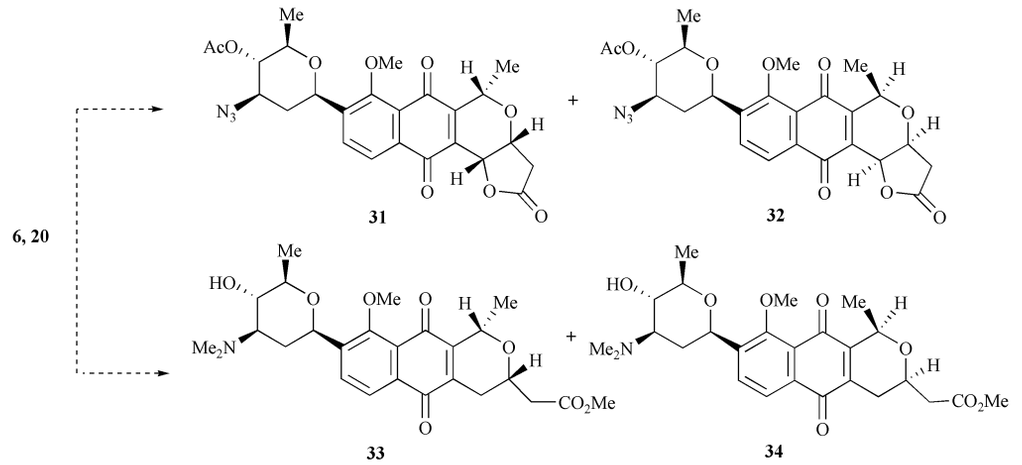
The ^{13}C NMR spectrum was also complicated by splitting of peaks due to the presence of two diastereomers although where chemical shift differences were observed they were small, typically of the order of 0.1–0.2 ppm. A comparison of key carbon resonances with those obtained for similar 2-deoxyglucosyl furonaphthofuran adducts[12] was consistent with the proposed structure.

With the furonaphthofuran adducts **7** and **19** in hand as a 1 : 1 mixture of diastereomers, attention next turned to the oxidative rearrangement step (Scheme 2). The reaction proceeded smoothly using ceric ammonium nitrate in aqueous acetonitrile to give a mixture of the diastereomeric lactols **6** and **20** in 89% yield, and in a 1 : 1 ratio as measured by analysis of the ^1H NMR spectrum. The crude material was of satisfactory purity based on inspection of the ^1H NMR spectrum, which was fortuitous given that attempts to purify lactols **6** and **20** by conducting chromatography using solvents chilled to −30 °C were unsuccessful due to severe decomposition of the lactols on the column. By necessity, therefore, the two diastereomers **6** and **20** were characterized as an inseparable 1 : 1 mixture.

The high resolution mass spectrum of lactols **6** and **20** contained a molecular ion at *m*/*z* 527.1526, confirming the molecular formula $C_{25}H_{25}N_3O_{10}$. The infrared spectrum contained a broad band at 3417 cm^{-1}, which was assigned to the OH stretch. Strong bands at 1774, 1743 and 1668 cm^{-1} were assigned to the γ-lactone, acetate and quinone carbonyls respectively. As expected, the ^1H NMR spectrum was complicated by the presence of two diastereomers. The geminal protons 3A-H and 3B-H gave rise to doublets at δ 2.95 and δ 2.74 respectively, with coupling constant, $J_{3A,3B}$ 20.2 Hz. The analogous protons 3A*-H and 3B*-H in the alternative diastereomer gave rise to separate signals slightly further upfield. Doublets at δ 5.27 and δ 5.28 were assigned to the bridgehead protons 11_b-H and 11_b*-H respectively. The resonances for 3_a-H and 3_a*-H overlapped and appeared as an unresolved multiplet at δ 4.91–4.85. The coupling constant observed for $J_{11b,3a}$ was 2.8 Hz in both diastereomers, which is consistent with the presence of a *cis*-fused 2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran system.[12,15] A distinct separation of the methoxy resonances for the two diastereomers was observed with the appearance of two singlets at δ 3.94 (OMe) and 3.88 (OMe*), while the methyl ketone groups for the two diastereomers were coincident resonating as a singlet at δ 1.80. Differences between the two diastereomers were also observed in the chemical shifts of certain protons on the azido sugar moiety, although 1′-H and 1′*-H together gave rise to a broad multiplet at δ 5.13–5.07. $2'_{eq}$-H and $2'_{eq}$*-H resonated at δ 2.38 and δ 2.43 respectively, while the axial protons $2'_{ax}$-H and $2'_{ax}$*-H gave rise to overlapping signals at δ 1.66–1.54.

The ^{13}C NMR spectrum was likewise complicated by the doubling up of many signals due to the presence of the two diastereomers and was consistent with that reported for related compounds.[12,15] Only two diastereomers were evident in the ^1H and ^{13}C NMR spectra, indicating that only one relative configuration at the lactol carbon was present. The assignment made in the present case places the hydroxyl group axial, where additional stability is gained from the anomeric effect.[29] This assignment was supported by the comparison of the ^1H NMR chemical shifts for the bridgehead proton 3_a-H and the 5-Me group, with those observed for 2-deoxyglucosyl analogues.[12]

With lactols **6** and **20** in hand, it was hoped that subsequent reduction with triethylsilane and trifluoracetic acid would afford the diastereomeric ethers **31** and **32** (Scheme 7) in which axial delivery of hydride takes place as reported by Kraus *et al.*[30] Despite carrying out this reaction at −10 °C over



Scheme 7 *Reagents, conditions and yields*: (i) CF_3CO_2H, Et_3SiH, CH_2Cl_2, −10 °C, 72 h; (ii) H_2, Pd-C, MeOH then H_2CO, $NaBH_3CN$–$ZnCl_2$, MeOH then CH_2N_2.

three days using a similar procedure developed for the capricious reduction of similar 2-deoxyglucosyl lactols,[12] it was disappointing to only observe substantial decomposition to baseline materials in this case.

A second approach to the reduction of lactols **6** and **20**, made use of catalytic hydrogenation as successfully used for the synthesis of deoxyfrenolicin.[31] It was envisaged that catalytic hydrogenation of lactols **6** and **20** would effect reduction of the azide group to an amino group and hydrogenolysis of the γ-lactone to a carboxylic acid that would undergo esterification with diazomethane to afford esters **33** and **34** after '*in situ*' reductive methylation of the resultant amino functionality. With these ideas in mind, lactols **6** and **20** were subjected to catalytic hydrogenation over palladium on charcoal in methanol for three hours. After filtration to remove the catalyst, aqueous formaldehyde and zinc-modified cyanoborohydride in methanol were added to effect reductive methylation. Finally after 6 h, the reaction mixture was treated with excess diazomethane, however, this procedure resulted in substantial loss of material and the formation of several products presumably due to the competitive formation of quinone methide intermediates upon reduction of the quinone to a hydroquinone.

In summary, an efficient synthesis of azido *C*-glycosylpyranonaphthoquinones **6** and **20** has been achieved providing analogues of the naturally occurring antibiotic medermycin **1** for biological evaluation. In light of the difficulties experienced with the final reduction of the azide and lactol groups in **6** and **20**, the work reported herein has necessitated a change in direction for our synthesis of medermycin **1**.

Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption spectra are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s = strong, m = medium, w = weak and br = broad. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker DRX 400 (400 MHz) spectrometer at ambient temperature. All *J*-values are given in Hz. Chemical shifts are expressed in parts per million downfield shift from tetramethylsilane as an internal standard, and reported as position (δ_H), relative integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, m = multiplet) and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 200 (50.3 MHz) or a Bruker DRX 400 (100.5 MHz) spectrometer at ambient temperature with complete proton decoupling. When NMR data are reported for isomeric mixtures, resonances for the minor isomer are denoted by an asterisk (*). Low resolution mass spectra were recorded on a VG70-250S, a VG70-SD or a AEI model MS902 double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70eV (EI, DEI, CI and DCI). High resolution mass spectra were recorded at nominal resolution of 5000 or 10,000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Low resolution chemical ionisation mass spectra were also recorded on a Hewlett Packard 5989A mass spectrometer using ammonia as reagent gas with the sample dissolved in methanol. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was performed using 0.2 mm thick pre-coated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualised by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. Optical rotations were recorded on an Optical Activity POLAAR 2001 polarimeter using a 5 dm^{-3} cell. Samples were prepared in the solvent indicated at the concentration specified (measured in g 100 cm^{-3}).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene 10

To a cooled (0 °C) solution of *C*-glycosylnaphthol **15**[17] (1.52 g, 3.79 mmol) in *N,N*-dimethylformamide (50 mL) was added sodium hydride (228 mg of a 60% dispersion in oil, 5.75 mmol). The mixture was stirred at 0 °C under an atmosphere of nitrogen for 5 min then methyl iodide (1.22 mL, 37.9 mmol) was added dropwise. The mixture was stirred for a further 2 h then quenched with water (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with water (3 × 100 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (hexanes–ethyl acetate, 3 : 1 as eluent) gave *6-(4′-O-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino-*hexopyranosyl)-1,4,5-trimethoxynaphthalene* **10** (1.25 g, 82%) as a pale foam (Found: C, 60.9; H, 5.9; N, 9.8%; M^+, 415.1740. $C_{21}H_{25}N_3O_6$ requires: C, 60.7, H, 6.1, N, 10.1%; M, 415.1743); $[a]_D^{22}$ +16.9 (*c* 0.5 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2935, 2835, 2096 (N_3), 1746 (C=O), 1602, 1584, 1414, 1351 and 1260; δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.83 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.2 and $J_{2'ax,2'eq}$ 13.2, $2'_{ax}$-H), 2.16 (3 H, s, OAc), 2.35 (1 H, ddd, $J_{2'eq,1'}$ 1.6, $J_{2'eq,2'ax}$ 13.2 and $J_{2'eq,3'}$ 4.8, $2'_{eq}$-H), 3.60–3.66 (2 H, m, 3′-H and 5′-H), 3.85 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.80 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6,

4′-H), 5.06 (1 H, dd, $J_{1',2'ax}$ 11.2 and $J_{1',2'eq}$ 1.6, 1′-H), 6.73 (1 H, d, $J_{3,2}$ 8.5, 3-H), 6.79 (1 H, d, $J_{2,3}$ 8.5, 2-H), 7.58 (1 H, d, $J_{8,7}$ 8.8, 8-H) and 8.07 (1 H, d, $J_{7,8}$ 8.8, 7-H); δ_C(100 MHz; $CDCl_3$) 18.7, 21.6, 38.6, 56.6, 57.4, 62.4, 63.7, 73.0, 75.6, 76.2, 104.8, 107.0, 119.6, 121.1, 124.5, 129.3, 131.6, 150.4, 150.5, 153.2 and 170.9; *m*/*z* (EI) 415 (M^+, 2%), 401 (2), 388 (52), 387 (100), 300 (12), 284 (17), 255 (19), 247 (17), 246 (51), 244 (71), 231 (45), 229 (49), 215 (23) and 201 (25).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene 16 and 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-2-bromo-1,4,5-trimethoxynaphthalene 21

To a solution of naphthalene **10** (379 mg, 0.912 mmol) in dichloromethane (15 mL) was added *N*-bromosuccinimide (163 mg, 0.916 mmol) in a single portion. The mixture was stirred for 90 min, then quenched with saturated sodium sulfite solution (10 mL) and stirred for an additional 5 min. The phases were separated, and the aqueous phase was extracted with dichloromethane (5 mL). The combined organic phases were then washed with water (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (hexanes–ethyl acetate, 85 : 15) afforded the following:

(i) 6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5- trimethoxynaphthalene 16. (328 mg, 73%) as a pale yellow foam (Found (EI): M^+, 493.0850 and 495.0837. $C_{21}H_{24}N_3O_6Br$ requires M, 493.0848 and 495.08280); $[\alpha]_D^{22}$ +23.9 (*c* 0.4 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2923, 2850, 2098 (N_3), 1744 (C=O), 1588, 1458, 1329 and 1226; δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.84 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.4 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$-H), 2.17 (3 H, s, OAc), 2.32 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,2'ax}$ 13.2 and $J_{2'eq,3'}$ 4.9, 2′$_{eq}$-H), 3.81–3.65 (2 H, m, 3′-H and 5′-H), 3.83 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.96 (3 H, s, OMe), 4.82 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′-H), 5.08 (1 H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 2.0, 1′-H), 6.94 (1 H, s, 2-H), 7.59 (1 H, d, $J_{8,7}$ 8.8, 8-H) and 8.05 (d, 1H, $J_{7,8}$ 8.8, H-7); δ_C(100 MHz; $CDCl_3$) 18.0, 20.9, 38.0, 56.0, 61.7, 61.8, 63.4, 72.0, 75.0, 75.4, 108.8, 115.1, 119.5, 123.0, 124.0, 127.9, 132.2, 145.6, 151.2, 152.2 and 170.1; *m*/*z* (EI) 495/493 (M^+, 49%), 467/465 (M − N_2, 7), 324 (14), 309 (12), 178 (18) and 43 (100).

(ii) 6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-2-bromo-1,4,5- trimethoxynaphthalene 21. (91 mg, 20%) as a yellow oil (Found (EI): M^+, 493.0847 and 495.0821. $C_{21}H_{24}N_3O_6Br$ requires M, 493.0848 and 495.0828); $[\alpha]_D^{22}$ +16.4 (*c* 0.3, CH_2Cl_2); ν_{max} (film)/cm^{-1} 2934, 2840, 2098 (N_3), 1746 (C=O), 1574, 1447, 1374 and 1227; δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.82 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.3 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$-H), 2.17 (3 H, s, OAc), 2.34 (1 H, ddd, $J_{2'eq,1'}$ 1.9, $J_{2'eq,2'ax}$ 13.2 and $J_{2'eq,3'}$ 4.8, 2′$_{eq}$-H), 3.80–3.65 (2 H, m, 3′-H and 5′-H), 3.83 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.80 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′-H), 5.04 (1 H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 1.9, 1′-H), 6.94 (1 H, s, 6-H), 7.64 (1 H, d, $J_{8,7}$ 8.8, 8-H) and 7.90 (1 H, d, $J_{7,8}$ 8.8, 7-H); δ_C (100 MHz; $CDCl_3$) 18.7, 21.6, 38.5, 57.2, 62.1, 62.3, 63.9, 72.8, 75.6, 76.1, 110.7, 113.1, 119.7, 120.5, 126.2, 131.8, 132.1, 147.7, 153.3, 153.9 and 170.9; *m*/*z* (EI) 495/493 (M^+, 100%), 457 (31), 415 (11), 324 (30), 309 (45) and 281 (14).

Recycling of 2-bromonaphthalene 21

To a cooled (−78 °C) solution of 2-bromonaphthalene **21** (50 mg, 0.101 mmol) in tetrahydrofuran (1 mL) stirring under an atmosphere of nitrogen was added *n*-BuLi as a solution in hexanes (1.50 M, 71 μL, 0.106 mmol). The mixture was allowed to warm gradually to 0 °C over 1 h, then quenched with saturated sodium hydrogen carbonate solution (5 mL). The mixture was extracted with diethyl ether (2 × 10 mL), and the combined ethereal phases were washed with water (10 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes–ethyl acetate 4 : 1) to give *6-(4′-O-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-1,4,5-trimethoxynaphthalene* **10** (34 mg, 82%) as a pale foam. The ^{1}H NMR data was identical to that reported above.

6-(3′-Amino-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene 25

To a solution of *C*-glycosyl-3-bromonaphthalene **16** (318 mg, 0.644 mmol) in methanol (20 mL) was added platinum(IV) oxide hydrate (32 mg). The reaction vessel was placed under vacuum using a water aspirator, and the atmosphere was replaced with hydrogen by means of a balloon. This purging process was repeated two times. The reaction mixture was stirred under an atmosphere of hydrogen for 24 h before being filtered through Celite and concentrated *in vacuo.* Purification by flash column chromatography (dichloromethane–methanol, 4 : 1 as eluent) gave *6-(3′-amino-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene* **25** (280 mg, 99%) as a pale foam (Found: M^+, 425.0837 and 427.0825. $C_{19}H_{24}NO_5Br$ requires M, 425.0838 and 427.0817); $[\alpha]_D^{22}$ +27.2 (*c* 0.4 in CH_3OH); ν_{max} (film)/cm^{-1} 3354 (NH, OH), 2932, 1588 and 1328; δ_H(400 MHz; CD_3OD) 1.34 (3 H, d, $J_{6',5'}$ 6.1, 6′-H); 1.66 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.3 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$-H), 2.15 (1 H, ddd, $J_{2'eq,1'}$ 1.8, $J_{2'eq,3'}$ 4.1 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$-H), 2.98–2.95 (1 H, m, 3-H′), 2.99 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.2, 4′-H), 3.51–3.47 (1 H, m, 5′-H), 3.80 (3 H, s, OMe), 3.83 (3 H, s, OMe), 3.96 (3 H, s, OMe), 5.10 (1 H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 1.8, 1′-H), 7.04 (1 H, s, 2-H), 7.61 (1 H, d, $J_{8,7}$ 8.9, 8-H) and 8.02 (1 H, d, $J_{7,8}$ 8.9, 7-H); δ_C(100 MHz; CD_3OD) 17.2, 39.7, 54.0, 55.1, 60.7, 62.3, 72.1, 76.9, 77.4, 108.2, 114.6, 118.5, 122.8, 124.2, 127.5, 133.5, 145.4, 151.1 and 152.1; *m*/*z* (EI) 427/425 (M^+, 26%), 396/394 (M=OMe, 100), 352/350 (24), 338/336 (43), 322/320 (91), 311/309 (30) and 213 (29).

3-Bromo-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4,5-trimethoxynaphthalene 26

To a solution of *C*-glycosyl-3-bromonaphthalene **25** (280 mg, 0.657 mmol) in acetonitrile (5 mL) was added aqueous formaldehyde (36%, 1.02 mL, 13.2 mmol), followed by sodium cyanoborohydride (132 mg, 2.10 mmol). After 15 min the solution was found to be alkaline (tested using red Litmus paper) and acetic acid was added dropwise until the solution was nearly neutral. The mixture was stirred for a further 2 h, adjusting the pH with acetic acid as necessary. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with saturated sodium hydrogen carbonate solution (2 × 20 mL). The organic phase was then dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (ethyl acetate-hexanes, 4:1) gave *3-bromo-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-1,4,5-trimethoxynaphthalene* **26** (270 mg, 93%) as a pale foam (Found: M^+, 453.1156 and 455.1137; $C_{21}H_{28}NO_5Br$ requires M, 453.1154 and 455.1130); $[\alpha]_D^{22}$ +16.1 (*c* 1.0 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3458 (OH), 2932, 2833, 1587 and 1504; δ_H(400 MHz; $CDCl_3$) 1.43 (3 H, d, $J_{6',5'}$ 6.1, 6′-H), 1.63 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.0 and $J_{2'ax,2'eq}$ 12.7, 2′$_{ax}$-H), 1.98 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,3'}$ 3.6 and $J_{2'eq,2'ax}$ 12.7, 2′$_{eq}$-H), 2.32 (6 H, s, NMe_2), 2.77–2.71 (1 H, m, 3′-H), 3.23 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.7, 4′-H), 3.61–3.56 (1 H, m, 5′-H), 3.85 (3 H, s, OMe), 3.86 (1 H, br s, O*H*), 3.87 (3 H, s, OMe), 3.96 (3H, s, OMe), 5.07 (1 H, dd, $J_{1',2'eq}$ 2.0 and $J_{1',2'ax}$ 11.0, 1′-H), 6.93 (1 H, s, 2-H), 7.63 (1 H, d, $J_{8,7}$ 8.8, 8-H) and 8.04 (1 H, d, $J_{7,8}$ 8.8, 7-H); δ_C (100 MHz; $CDCl_3$) 19.5, 29.6, 41.0, 56.7, 62.5, 64.1, 68.2, 72.4, 73.6, 78.4, 109.3, 115.6, 120.0, 123.9, 125.2, 128.4, 134.6, 146.4, 151.8,

152.9; *m/z* (EI) 453/455 (M^+, 9%), 396/394 (11), 326/324 (27), 311/309 (9) and 71 (100).

3-Bromo-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone 29

To a solution of bromonaphthalene **26** (306 mg, 0.692 mmol) in acetonitrile (8 mL) was added a solution of ceric ammonium nitrate (948 mg, 1.72 mmol) in water (4 mL). After 5 min saturated sodium hydrogen carbonate solution (5 mL) was added, and the mixture extracted with dichloromethane (2 × 25 mL). The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate–hexanes, 4 : 1, short column) afforded *3-bromo-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-5-methoxy-1,4-naphthoquinone* **29** (242 mg, 85%) as a red–brown foam (Found: M^+, 423.0691 and 425.0662. $C_{19}H_{22}NO_5Br$ requires M, 423.0681 and 425.0661); $[\alpha]_D^{22}$ +19.3 (*c* 0.3 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3307 (OH), 2937, 2869, 1673 (quinone C=O), 1599, 1574, 1282 and 1082; δ_H(400 MHz; $CDCl_3$) 1.38 (3 H, d, $J_{6',5'}$ 6.0, 6′-H), 1.51 (1 H, ddd, $J_{2'ax,2'eq}$ 12.1 and $J_{2'ax,1'} = J_{2'ax,3'}$ 10.6, 2′$_{ax}$-H), 2.38 (1 H, ddd, $J_{2'eq,1'}$ 1.9, $J_{2'eq,3'}$ 3.9 and $J_{2'eq,2'ax}$ 12.1, 2′$_{eq}$-H), 2.79 (6 H, s, NMe_2), 2.81 (1 H, s, O*H*), 2.87–2.76 (1 H, m, 3′-H), 3.41 (1 H, dd, $J_{4',5'} = J_{4',3'}$ 9.4, 4′-H), 3.61–3.54 (1 H, m, 5′-H), 3.88 (3 H, s, OMe), 4.85 (1 H, dd, $J_{1',2'ax}$ 10.6 and $J_{1',2'eq}$ 1.9, 1′-H), 7.87 (2 H, m, 7-H and 8-H) and 7.45 (1 H, s, 2-H); δ_C (100 MHz; $CDCl_3$): 17.8, 30.8, 40.0, 62.7, 67.4, 70.0, 71.7, 76.7, 122.5, 123.5, 133.0, 133.2, 138.9, 141.6, 142.4, 157.4, 176.4 and 181.9; *m/z* (EI) 427/425 (M^+, 1%), 394/392 (1), 218 (7) and 130 (100).

3-Acetyl-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4-dihydroxy-5-methoxynaphthalene 30

To a solution of bromoquinone **29** (30 mg, 0.070 mmol) in dioxane (1 mL) was added copper(I) bromide (0.5 mg, 0.003 mmol), tetrakis(triphenylphosphine)palladium(0) (4.3 mg, 0.004 mmol) and (α-ethoxyvinyl)tributylstannane[32] (26 mg, 0.072 mmol). The reaction was stirred at 100–110 °C under an atmosphere of nitrogen for 105 min, then allowed to cool to room temperature. The mixture was then diluted with dichloromethane–ether (2 : 1, 10 mL) and shaken in a separating funnel with a solution of sodium dithionite (0.8 g) in water (5 mL) for 2 min. The phases were separated, and the aqueous phase was adjusted to pH 8 using saturated sodium hydrogen carbonate solution. The aqueous phase was then extracted with dichloromethane (2 × 5 mL) and the combined dichloromethane phases were subsequently washed with saturated sodium hydrogen carbonate solution (2 × 5 mL) and dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane–methanol, 9 : 1, short column) afforded *3-acetyl-6-(3′-dimethylamino-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-1,4-dihydroxy-5-methoxynaphthalene* **30** (6 mg, 22%) as a fluorescent yellow oil (Found (EI): M^+, 389.1841. $C_{21}H_{27}NO_6$ requires M, 389.1838); $[\alpha]_D^{22}$ +4 (*c* 0.01 in CH_2Cl_2); υ_{max} (film)/cm^{-1} 3242 (OH), 2934, 1625 (*o*-hydroxyacetophenone), 1386, 1244 and 1080; δ_H(200 MHz; $CDCl_3$ and CD_3OD) 1.44 (3 H, d, $J_{6',5'}$ 5.9, 6′-H), 1.55 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 10.1 and $J_{2'ax,2'eq}$ 13.1, 2′$_{ax}$-H), 2.30–2.20 (1 H, m, 2′$_{eq}$-H), 2.62 (6 H, s, NMe_2), 2.65 (3 H, s, COMe), 3.35–3.20 (1 H, m, 3′-H), 3.41 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 8.9, 4′-H), 3.65–3.57 (1 H, m, 5′-H), 3.91 (3 H, s, OMe), 4.97 (1 H, br d, $J_{1',2'ax}$ 10.1, 1′-H), 7.06 (1 H, s, 2-H), 7.74 (1 H, d, $J_{8,7}$ 8.7, 8-H) and 7.99 (1 H, d, $J_{7,8}$ 8.7, 7-H); δ_C (50 MHz; $CDCl_3$ and CD_3OD) 18.6, 28.1, 31.7, 38.5, 43.0, 64.0, 68.9, 70.8, 72.6, 105.4, 107.2, 114.0, 115.6, 119.8, 128.1, 131.9, 144.8, 155.3, 159.2 and 205.0; *m/z* (EI) 389 (M^+, 6%), 356 (23), 330 (13), 312 (33) and 71 (100).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-5-methoxy-1,4-naphthoquinone 17

To a solution of 3-bromonaphthalene **16** (100 mg, 0.202 mmol) in acetonitrile (10 mL) was added a solution of ceric ammonium nitrate (276 mg, 0.503 mmol) in water (2 mL). After stirring for 5 min, the mixture was diluted with dichloromethane (50 mL) and washed with water (2 × 50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by passage through a small plug of flash silica gel (hexanes–ethyl acetate, 1 : 1 as eluent) afforded *6-(4′-O-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-3-bromo-5-methoxy-1,4-naphthoquinone* **17** (93 mg, 99%) as a bright orange foam (Found (EI): M^+, 463.0382. $C_{19}H_{18}N_3O_6{}^{79}Br$ requires M, 463.0379); $[\alpha]_D^{22}$ −5.9 (*c* 0.05 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2936, 2099 (N_3), 1745 (ester C=O), 1673 (quinone C=O), 1599, 1574 and 1226; δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.60 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.3 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$-H), 2.41 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,2'ax}$ 13.2 and $J_{2'eq,3'}$ 4.9, 2′$_{eq}$-H), 2.17 (3 H, s, OAc), 3.68–3.64 (1 H, m, 5′-H), 3.79–3.73 (1 H, m, 3′-H), 3.93 (3 H, s, OMe), 4.78 (1 H, dd, $J_{4',5'} = J_{4',3'}$ 9.6, 4′-H), 4.89 (1 H, dd, $J_{1',2'eq}$ 2.0 and $J_{1',2'ax}$ 11.3, 1′-H), 7.50 (1 H, s, 2-H) and 7.96–7.91 (2 H, m, 7-H and 8-H); δ_C(100 MHz; $CDCl_3$) 18.6, 21.6, 38.2, 62.0, 63.4, 72.6, 75.7, 75.8, 123.2, 124.3, 133.7, 133.9, 139.6, 142.4, 143.4, 158.2, 170.8, 177.1 and 182.6; *m/z* (EI) 465/463 (M^+, 12%), 363/361 (21), 319 (13), 295/293 (59) and 43 (100).

3-Acetyl-6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-1,4-dihydroxy-5-methoxynaphthalene 18

To a solution of bromoquinone **17** (96 mg, 0.207 mmol) in dioxane (2 mL) was added copper(I) bromide (1.6 mg, 0.011 mmol), tetrakis(triphenylphosphine)palladium(0) (12.7 mg, 0.011 mmol) and (α-ethoxyvinyl)tributylstannane[32] (80 mg, 0.222 mmol). The reaction was stirred at 100–105 °C under an atmosphere of nitrogen for 50 min, then concentrated *in vacuo*. The dark brown oil was dissolved in dichloromethane (10 mL) and shaken in a separating funnel with a solution of sodium dithionite (2.1 g) in water (10 mL) for 2 min. The phases were separated, and the organic phase was washed with hydrochloric acid (0.5 M, 10 mL) and water (10 mL). The organic phase was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate–hexanes, 3 : 2, base-treated silica) gave *3-acetyl-6-(4′-O-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-arabino-hexopyranosyl)-1,4-dihydroxy-5-methoxynaphthalene* **18** (62 mg, 71%) as a fluorescent yellow–tinted brown oil (Found (EI): M^+, 429.1549. $C_{21}H_{23}N_3O_7$ requires M, 429.1536); $[\alpha]_D^{22}$ −7 (*c* 0.02 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 3386 (OH), 2956, 2099 (N_3), 1745 (ester C=O) and 1626 (*o*-hydroxyacetophenone); δ_H (400 MHz; $CDCl_3$) 1.29 (3 H, d, $J_{6',5'}$ 6.1, 6′-H), 1.79 (1 H, ddd, $J_{2'ax,1'} = J_{2'ax,3'}$ 11.4 and $J_{2'ax,2'eq}$ 13.2, 2′ax-H), 2.17 (3 H, s, OAc), 2.35 (1 H, ddd, $J_{2'eq,1'}$ 1.9, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$-H), 2.61 (3 H, s, COMe), 3.81–3.66 (2 H, m, 3′-H and 5′-H), 3.92 (3 H, s, OMe), 4.81 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′-H), 5.06 (1 H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 1.9, 1′-H), 5.85 (1 H, br s, O*H*), 7.00 (1 H, s, 2-H), 7.73 (1 H, d, $J_{8,7}$ 8.7, 8-H), 7.94 (1 H, d, $J_{7,8}$ 8.7, 7-H) and 12.92 (1 H, s, O*H*); δ_C (100 MHz; $CDCl_3$) 18.2, 18.6, 21.6, 28.0, 38.5, 62.2, 64.1, 72.6, 76.2, 107.8, 113.6, 119.4, 120.5, 128.9, 132.4, 132.5, 143.6, 156.3, 158.6, 171.1 and 204.5; *m/z* (EI) 429 (M^+, 25%), 325 (10), 257 (31) and 43 (100, CH_3CO).

(6b*R*, 9a*R*)-6-Acetyl-3-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-6b,9a-dihydro-5-hydroxy-4-methoxyfuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 7 and (6b*S*, 9a*S*)-6-acetyl-3-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-6b,9a-dihydro-5-hydroxy-4-methoxyfuro[3,2-*b*]naphtho[2,1-*d*]furan-8(9*H*)-one 19

To a solution of hydroquinone **18** (96 mg, 0.225 mmol) in diethyl ether (5 mL) was added silver(I) oxide (104 mg, 0.449

mmol). The mixture was stirred vigorously for 3 h, then filtered through Celite and the filtrate concentrated *in vacuo*. The resulting red oil was dissolved in dry acetonitrile (3 mL) and cooled to 0 °C. 2-(Trimethylsilyloxy)furan (74 μL, 0.51 mmol) was added dropwise as a solution in acetonitrile (0.5 mL), and the mixture was stirred for 1 h. Silica gel (25 mg) and methanol (0.25 mL) were subsequently added, and the mixture left to stir at room temperature overnight. The mixture was then diluted with dichloromethane (20 mL), washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (hexanes–ethyl acetate, 3 : 2, short column) gave the *title compounds* **7** and **19** (46 mg, 40%; 1 : 1 mixture by ^{1}H NMR)† ‡ as a yellow oil (Found (EI): M^+, 511.1590. $C_{25}H_{25}N_3O_9$ requires M, 511.1591); υ_{max} (film)/cm^{-1} 3502 (OH), 2936, 2100 (N_3), 1775 (γ-lactone C=O) and 1743 (ester C=O); δ_H (400 MHz; $CDCl_3$) 1.26 (3 H, d, $J_{6',5'}$ 6.1, 6′*-H), 1.28 (3 H, d, $J_{6',5'}$ 6.1, 6′-H), 1.71 (1 H, ddd, $J_{2'ax,1'}$ = $J_{1'ax,3'}$ 11.4 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$-H), 1.78 (1 H, ddd, $J_{2'ax,1'}$ = $J_{2'ax,3'}$ 12.3 and $J_{2'ax,2'eq}$ 13.2, 2′$_{ax}$*-H), 2.16 (6 H, s, OAc/OAc*), 2.34 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,3'}$ 5.2 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$*-H), 2.38 (1 H, ddd, $J_{2'eq,1'}$ 1.9, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$-H), 2.81 (6 H, s, COMe/COMe*), 3.15–3.12 (4 H, m, 9-H/9*-H), 3.81–3.64 (4 H, m, 3′-H/3′*-H and 5′-H/5′*-H), 3.92 (3 H, s, OMe*), 3.93 (3 H, s, OMe), 4.76 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′-H), 4.79 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′*-H), 5.01 (1 H, dd, $J_{1',2'ax}$ 11.4 and $J_{1',2'eq}$ 1.9, 1′-H), 5.04 (1 H, dd, $J_{1',2'ax}$ 12.3 and $J_{1',2'eq}$ 2.0, 1′*-H), 5.53–5.50 (2 H, m, 9a-H/9a*-H), 6.45 (1 H, d, $J_{6b,9a}$ 6.3, 6b-H), 6.46 (d, 1 H, $J_{6b,9a}$ 6.3, 6b*-H), 7.73 (1 H, d, $J_{1,2}$ 8.6, 1-H), 7.75 (1 H, d, $J_{1,2}$ 8.6, 1*-H), 7.79 (1 H, d, $J_{2,1}$ 8.6, 2*-H) and 7.80 (1 H, d, $J_{2,1}$ 8.6, 2-H)§; δ_C(100 MHz; $CDCl_3$) 18.6, 21.6, 31.4, 36.2, 38.5*/38.5, 62.2, 64.3*/64.2, 72.6/72.4*, 75.7*/75.6, 76.0, 81.5/81.5*, 86.5, 111.8*/111.7, 113.3*/113.1, 119.9*/119.8, 121.6, 126.8, 129.9*/129.9, 134.4/134.3*, 151.0/150.9*, 156.4*/156.3, 160.6/160.5*, 170.8, 174.8/174.7* and 203.2; *m*/*z* (EI) 511 (M^+, 1%), 495 (1), 493 (1), 467 (1), 368 (1), 314 (1), 256 (1) and 149 (100).

(3a*R*, 5*S*, 11b*R*)-3,3a,5,11b-Tetrahydro-8-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-7-methoxy-5-methyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione 6 and (3a*S*, 5*R*, 11b*S*)-3,3a,5,11b-tetrahydro-8-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-5-hydroxy-7-methoxy-5-methyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]-pyran-2,6,11-trione 20

To a solution of adducts **7** and **19** (27 mg, 0.052 mmol) in acetonitrile (5 mL) was added a solution of ceric ammonium nitrate (58 mg, 0.106 mmol) in water (0.5 mL), and the mixture was stirred for 5 min. The mixture was then diluted with dichloromethane (25 mL), washed with water (2 × 25 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the *title compounds* **6** and **20** (22 mg, 89%; *ca*. 3 : 2 mixture of diastereomers by ^{1}H NMR) as a yellow oil (Found (EI): M^+, 527.1526. $C_{25}H_{25}N_3O_{10}$ requires M, 527.1540); ν_{max} (film)/cm^{-1} 3417 (OH), 2982, 2939, 1774 (γ-lactone C=O), 1743 (ester C=O) and 1668 (quinone C=O); δ_H(400 MHz; $CDCl_3$) 1.28 (3 H, d, $J_{6',5'}$ 6.2, 6′*-H), 1.29 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.66–1.54 (2 H, m, 2′$_{ax}$-H/2′$_{ax}$*-H), 1.80 (6 H, s, 5-Me/5-Me*), 2.16 (6 H, s, OAc/OAc*), 2.38 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,3'}$ 4.9 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$-H), 2.43 (1 H, ddd, $J_{2'eq,1'}$ 2.0, $J_{2'eq,3'}$ 4.8 and $J_{2'eq,2'ax}$ 13.2, 2′$_{eq}$*-H), 2.73 (1 H, apparent d, $J_{3B,3A}$ 20.3, 3B-H), 2.74 (1 H, apparent d, $J_{3B,3A}$ 20.3, 3B*-H), 2.94 (1 H, dd, $J_{3A,3a}$ 5.2 and $J_{3A,3B}$ 20.3, 3A-H), 2.95 (1 H, dd, $J_{3A,3a}$ 4.7 and $J_{3A,3B}$ 20.2, 3A*-H), 3.79–3.61 (4 H, m, 3′-H/3′*-H and 5′-H/5*-H), 3.88 (3 H, s, OMe*), 3.94 (3 H, s, OMe), 4.76 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′*-H), 4.77 (1 H, dd, $J_{4',3'} = J_{4',5'}$ 9.6, 4′-H), 4.91–4.85 (2 H, m, 3a-H/3a*-H), 5.13–5.07 (2 H, br m, 1′-H/1′*-H), 5.27 (1 H, d, $J_{11b,3a}$ 2.8, 11b-H), 5.28 (1 H, d, $J_{11b,3a}$ 2.8, 11b*-H), 7.92 (1 H, d, $J_{10,9}$ 8.0, 10*-H), 7.93 (1 H, d, $J_{10,9}$ 8.0, 10-H), 7.96 (1 H, d, $J_{9,10}$ 8.0, 9*-H) and 7.97 (1 H, d, $J_{9,10}$ 8.0, 9-H)¶; δ_C(100 MHz; $CDCl_3$) 18.6, 21.5/21.3*, 28.2/28.1*, 37.2, 38.2/38.1*, 61.9, 63.7/63.5*, 67.8/67.8*, 69.3/69.2*, 72.6*/72.5, 75.7, 75.8, 93.9/93.8*, 123.9, 124.1, 127.6/127.0*, 131.1/130.2*, 133.7/133.5*, 143.5/143.3*, 148.2, 157.6*/157.5, 170.3, 174.9, 183.0/182.6* and 185.3*/184.6; *m*/*z* (EI) 527 (M^+, 1%), 467 (M–CH_3CO_2H, 23), 439 (8), 311 (9), 295 (9) and 44 (CH_3CHO^+, 100).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone 22

A solution of ceric ammonium nitrate (766 mg, 1.4 mmol) in water (0.7 mL) was added dropwise to a stirred solution of *C*-glycosyltrimethoxynaphthalene **10** (290 mg, 0.7 mmol) in acetonitrile (5 mL) at 0 °C. The reaction mixture briefly turned blue then turned yellow. Water (10 mL) was added and the reaction mixture diluted with dichloromethane (10 mL) then washed with water (10 mL). The combined organic extracts were dried over magnesium sulfate and the solvent removed at reduced pressure. Careful purification of the residue by flash chromatography (hexanes–ethyl acetate, 2 : 1 as eluent) gave 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-5-methoxy-1,4-naphthoquinone **22** (190 mg, 71%) as a glassy foaming yellow solid; mp 72–74 °C (Found: C, 58.9; H, 5.0; N, 10.6%. $C_{19}H_{19}N_3O_6$ requires C, 59.2; H, 5.0; N, 10.9%); $[\alpha]_D^{22} = -65.6$ (*c* 0.25 in CH_2Cl_2); υ_{max} (film)/cm^{-1} 2982, 2938 (CH), 2099 (N_3), 1744, 1666 (C=O) and 1228 (C=O); δ_H(200 MHz; $CDCl_3$) 1.26 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.55–1.66 (1 H, m, 2′$_{ax}$-H), 2.14 (3 H, s, CH_3CO), 2.34–2.43 (1 H, m, 2′$_{eq}$-H), 3.59–3.88 (2 H, m, 3′-H and 5′-H), 3.90 (3 H, s, OMe), 4.74 (1 H, dd, $J_{4',3'}$ 9.6 and $J_{4',5'}$ 9.6, 4′-H), 4.87 (1 H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 1.9, 1′-H), 6.88 (1 H, d, *J* 10.3, 2-H or 3-H), 6.92 (1 H, d, *J* 10.3, 3-H or 2-H), 7.89 (1 H, d, *J* 8.0, 7-H or 8-H) and 7.93 (1 H, d, *J* 8.0, 8-H or 7-H); δ_C (200 MHz; $CDCl_3$) 17.8, 20.8, 37.5, 61.2, 62.4, 71.8, 74.8, 75.1, 123.2, 123.4, 132.2, 133.3, 136.8, 140.3, 142.2, 156.6, 170.0, 184.16 and 184.18; *m*/*z* (EI) 385 (M^+, 3%), 283 (5), 215 (15), 83 (30), 43 (CH_3CO, 88), 28 (100).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-4-hydroxy-1,5-dimethoxynaphthalene 23

A solution of the above quinone **22** (50 mg, 0.13 mmol) in dichloromethane (10 mL) was shaken with saturated aqueous sodium dithionite (5 mL) until the yellow colour disappeared (5 min). The organic extract was dried by filtration through a short column of magnesium sulfate and the solvent removed at reduced pressure to give the crude hydroquinone (46 mg) as an unstable pale brown oil; δ_H (200 MHz; $CDCl_3$) 1.27 (3 H, d, $J_{6',5'}$ 6.2, 6′-H), 1.89–2.08 (1 H, m, 2′$_{ax}$-H), 2.18 (3 H, s, CH_3CO), 2.18–2.29 (1 H, m, 2′$_{eq}$-H), 3.62–3.85 (2 H, m, 3′-H and 5′-H), 3.91 (3 H, s, OCH_3), 4.84 (1 H, dd, $J_{4',3'}$ 9.5 and $J_{4',5'}$ 9.6, 4′-H), 4.95 (1 H, dd, $J_{1',2'ax}$ 11.3 and $J_{1',2'eq}$ 2.0, 1′-H), 6.75 (2 H, s, 2-H and 3-H), 7.50 (1 H, d, $J_{8,7}$ 8.9, 8-H), 8.00 (1 H, d, $J_{7,8}$ 8.9, 7-H) and 8.82 (1 H, br s, OH).

A two-neck flask containing this crude dihydroquinone (46 mg) was evacuated for 1 hour and dry degassed acetone (3 mL) was added by syringe under nitrogen. Potassium carbonate (83 mg, 0.6 mmol) was added and the reaction mixture darkened. Dimethyl sulfate (37 μL, 0.36 mmol) was added and a

† In a separate experiment, a non-1 : 1 ratio of diastereomers was obtained, allowing signals to be grouped according to diastereomer based on the difference in integration between the two diastereomers. Signals belonging to the different diastereomers are distinguished by the presence or absence of an asterisk (*). For the ^{13}C NMR data, signals which were coincidental for both diastereomers are reported as a single value. Assignment of an individual set of resonances to a specific diastereomer was not made.

‡ ^{1}H and ^{13}C NMR spectra were complicated by the presence of residual butenolide obtained from hydrolysis of 2-trimethylsilyloxyfuran **9**.

§ Resonances due to the phenolic OH were not observed.

¶ Resonances due to the phenolic OH were not observed.

lightening of the reaction mixture was then observed. The reaction mixture was heated at reflux for 25 min then cooled and filtered through a plug of Celite. The solvent was evaporated at reduced pressure to afford crude 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-4-hydroxy-1,5-dimethoxynaphthalene **23** (42 mg) as an unstable red oil; δ_H (200 MHz; $CDCl_3$) 1.27 (3 H, d, $J_{6',5'}$ 6.1, 6′-H), 1.95–2.07 (1 H, m, $2'_{ax}$-H), 2.22 (3 H, s, CH_3CO), 2.20–2.28 (1 H, m, $2'_{eq}$-H), 3.64–3.95 (2 H, m, 3′-H and 5′-H), 3.93 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 4.83 (1 H, dd, $J_{4',3'}$ 9.5 and $J_{4',5'}$ 9.6, 4′-H), 4.97 (1 H, dd, $J_{1',2'ax}$11.3 and $J_{1',2'eq}$ 2.0, 1′-H), 6.75 (1H, d, *J* 8.2, 2-H or 3-H), 6.83 (1H, d, *J* 8.2, 3-H or 2-H), 7.50 (1 H, d, $J_{8,7}$ 8.9, 8-H), 8.07 (1 H, d, $J_{7,8}$ 8.9, 7-H) and 8.83 (1 H, br s, OH).

6-(4′-*O*-Acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene 16 from 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-4-hydroxy-1,5-dimethoxynaphthalene 24

A solution of bromine (23 mg, 0.144 mmol) in carbon tetrachloride (0.5 mL) was carefully added dropwise to a stirred solution of crude naphthol **23** (42 mg) in carbon tetrachloride (1 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 5 min then quenched with saturated aqueous sodium thiosulfate (5 mL) and diluted with dichloromethane (10 mL). The organic layer was washed with water (10 mL) and the aqueous layer extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried over magnesium sulfate and evaporated to give crude 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-4-hydroxy-1,5-dimethoxynaphthalene **24** (45 mg) as an unstable tan oil that rapidly darkened on standing; δ_H (200 MHz, $CDCl_3$) 1.24–1.28 (3 H, d, 6′-H), 1.70–1.92 (1 H, m, $2'_{ax}$-H), 2.16 (3 H, s, CH_3CO), 2.25-2.35 (1 H, m, $2'_{eq}$-H), 3.65–3.90 (2 H, m, 3′-H and 5′-H), 3.81 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.80 (1 H, dd, $J_{4',3'}$ 9.6 and $J_{4',5'}$ 9.6, 4′-H), 5.05 (1 H, dd, $J_{1',2'ax}$ 9.5 and $J_{1',2'eq}$ 1.9, 1′-H), 6.92 (1H, s, 2-H), 7.57 (1 H, d, $J_{8,7}$ 8.8, 8-H) and 8.04 (1 H, d, $J_{7,8}$ 8.8, 7-H).

To a slurry of sodium hydride (10 mg, 60% dispersion in oil, 0.24 mmol) in dry DMF (1 mL) at 0 °C was added dropwise a solution of this crude naphthol **24** (45 mg) in dry DMF (1 mL). The reaction mixture turned a deep brown colour. Dimethyl sulfate (25 μl, 0.24 mmol) was then added and the reaction mixture stirred for 5 min at 0 °C then quenched with water (1 mL). The reaction mixture was extracted with dichloromethane (10 mL), washed with water (3 × 10 mL), dried over magnesium sulfate and concentrated under reduced pressure. The resultant residue was purified by flash chromatography (hexanes–ethyl acetate, 4 : 1 as eluent) to give 6-(4′-*O*-acetyl-3′-azido-2′,3′,6′-trideoxy-β-D-*arabino*-hexopyranosyl)-3-bromo-1,4,5-trimethoxynaphthalene **16** (30 mg, 42% from **22**) as a pale yellow oil for which the ^{1}H NMR, IR and MS data were in agreement with that reported above.

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