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Synthesis of Daunorubicin Analogues Containing Truncated Aromatic Cores and Unnatural Monosaccharide Residues

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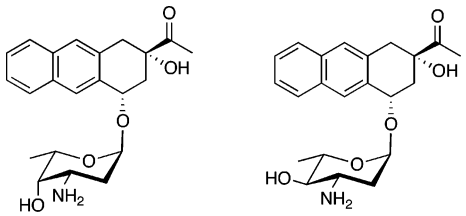

The anthracycline antibiotics daunorubicin and doxorubicin have been used widely as anticancer drugs, but their cardiotoxicity limits their clinical use. We describe here the preparation of a small panel of daunorubicin analogues in which the anthraquinone core is replaced with simpler aromatic moieties that lack a quinone functionality. The targets consist of a functionalized 1,2,3,4-tetrahydro-naphthalene or 1,2,3,4-tetrahydro-anthracene core bound to one of three monosaccharides: daunosamine, acosamine, or 4-amino-2,3,6-trideoxy-L-*threo*-hexopyranose. Key steps in the synthesis included an enantioselective ring opening of benzo-fused norbornene derivatives for the preparation of the core structures and the use of silver hexafluorophosphate-promoted thioglycoside activation in the glycosylation of these cores. Evaluation of these compounds against the MCF-7 cancer cell line demonstrated that the identity of the carbohydrate moiety appeared to have little influence on the cytotoxicity. Moreover, the analogues with the 1,2,3,4-tetrahydro-naphthalene core showed no cytotoxicity, while those possessing the 1,2,3,4-tetrahydro-anthracene moiety were more active. The IC_{50} values for the latter group of compounds were in the range of 94−134 μM, compared to 17 μM for doxorubicin and 5 μM for daunorubicin.

Introduction

The anthracycline antibiotics daunorubicin (**1**, Chart 1) and doxorubicin (**2**), first isolated in the 1960s from *Streptomyces peucetius*,[1] have found widespread clinical use as anticancer agents.[2] Synthetic analogues of these natural products, for example epirubicin (**3**)[3] and idarubicin (**4**),[4] have also entered the clinic, and a very large number of other analogues have been synthesized and their cytotoxicity has been evaluated (e.g., **5** and **6**).[5] These compounds, all of which contain an anthraquinone core attached to a carbohydrate moiety, are inhibitors of topoisomerases, enzymes that manage the topology of DNA.[6] More specifically, doxorubicin and its analogues function as topoisomerase poisons through stabilization of the "cleavable

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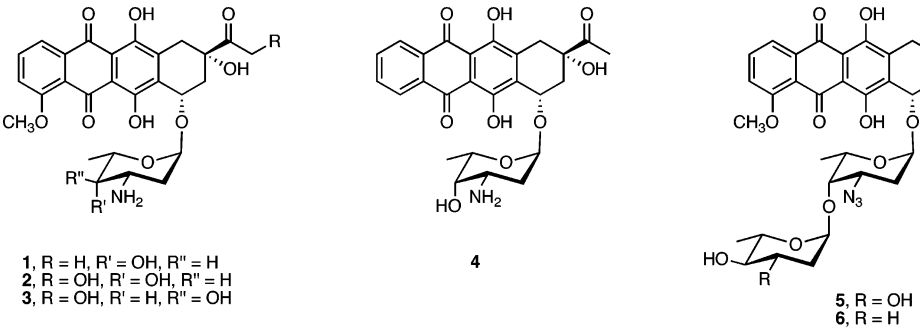
CHART 1



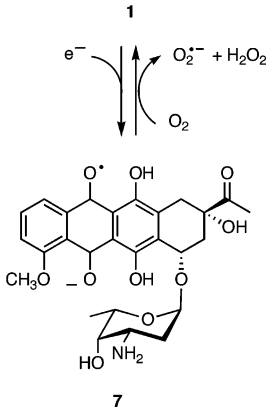
1, R = H, R' = OH, R'' = H
2, R = OH, R' = OH, R'' = H
3, R = OH, R' = H, R'' = OH

4

5, R = OH
6, R = H

complex" that forms as part of the catalytic cycle of the enzyme.[7] While the structure of the ternary complex that forms between the DNA, the drug, and the enzyme has remained elusive, the binding of anthracyclines to DNA is known to involve the intercalation of the anthraquinone moiety between DNA base pairs while the saturated ring of the aglycone and the carbohydrate binds in the minor groove.[8]

Despite their clinical use in the treatment of cancer, a limitation of these compounds is their cardiotoxicity, which is often irreversible.[9] The mechanisms underlying anthracycline-induced cardiotoxocity are complex, but a major cause is believed to be a process that begins with the one-electron reduction of the quinone moiety to the corresponding semiquinone (e.g., **7**, Figure 1).[10] In the presence of oxygen, this



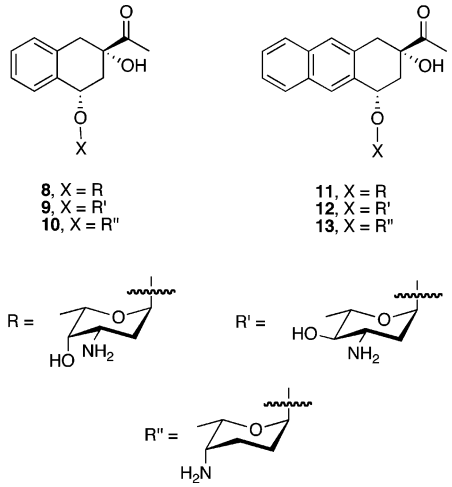
1

7

FIGURE 1. Generation of reactive oxygen species from daunorubicin.

semiquinone is reoxidized to the parent quinone together with the generation of superoxide anion and, through dismutation, hydrogen peroxide. These reactive oxygen species lead to oxidative stress in cardiac tissues, which have comparatively low concentrations of enzymes that detoxify these oxidants.[11]

CHART 2



8, X = R
9, X = R'
10, X = R''

11, X = R
12, X = R'
13, X = R''

Mindful of these issues, we were curious if daunorubicin analogues containing simplified aromatic moieties lacking the quinone moiety would possess cytotoxic activity against cancer cells but potentially be less cardiotoxic. Despite the large number of anthracycline derivatives that have been synthesized, little work has been focused on the preparation of compounds without the full anthraquinone moiety.[12] We report here the synthesis and testing of a small panel of such analogues (**8**−**13**, Chart 2), consisting of a simplified core structure bound to one of three monosaccharides: daunosamine, acosamine, or 4-amino-2,3,6-trideoxy-L-*threo*-hexopyranose.

Results and Discussion

When designing a route to the targets, we envisioned that their synthesis could be achieved by the regioselective glycosylation of diol **14** or **15** (Chart 3) with the appropriate thioglycoside (**16**−**18**), followed by deprotection and reduction of the azido group to the amine. It was therefore necessary to prepare these five building blocks first. The 1,2,3,4-tetrahydronaphthalene diol **14** has been synthesized previously[13] but only in racemic form, and thus we chose to develop an enantioselective approach to this compound as well as the 1,2,3,4-

(7) (a) Zunino, F.; Capranico, G. *Anti-Cancer Drug Des.* **1990**, *5*, 307−317. (b) Fortune, J. M. Osheroff, N. *Prog. Nucleic Acid Res. Mol. Biol.* **2000**, *64*, 221−253.

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(10) Minotti, G.; Menna, P.; Salvatorelli, E.; Cairo, G.; Gianni, L. *Pharmacol. Rev.* **2004**, *56*, 185−229.

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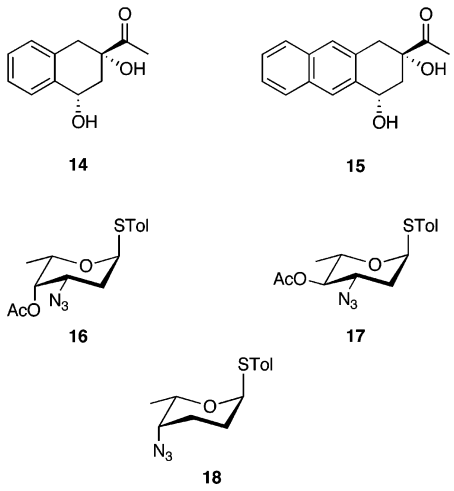
(13) Momose, T.; Ozaki, Y. *Chem. Pharm. Bull.* **1976**, *24*, 1631−1636.

CHART 3



tetrahydro-anthracene derivative, **15**. Although thioglycosides **16**−**18** have not been reported, we anticipated that existing methodology could be applied to their preparation.

Synthesis of 1,2,3,4-Tetrahydro-naphthalene Core, 14. The preparation of **14** began with the oxanorbornene derivative **19** (Scheme 1), which could be straightforwardly obtained from anthranilic acid and furan.[14] Conversion of bicyclic olefin **19** into allylic alcohol **20** was achieved using a nickel-catalyzed asymmetric ring opening reaction developed by Lautens and Rovis,[15] which afforded the product in 85% yield and in excellent enantioselectivity (98% ee) as determined by chiral HPLC. Subsequent protection of the alcohol as the *tert*-butyldiphenylsilyl ether proceeded uneventfully yielding **21** in 85% yield.

We next needed to add water across the alkene in a regioselective manner, and a number of methods were explored to effect this transformation. All attempts using hydroboration failed to give any of the desired product (**22**); however, a two step sequence involving epoxidation and reductive opening of the resulting oxirane was successful. Thus, **21** was treated with DMDO to give a product, assumed to be the corresponding epoxide, which was not isolated but instead was reacted with lithium aluminum hydride. Under these conditions, the expected alcohol, **22**, was obtained in 80% overall yield as a 95:5 mixture of isomers, although the stereochemistry of the products was not unequivocally established. Replacing DMDO with *m*-CPBA in the epoxidation step also gave the product but in much lower yield (30%) together with a number of byproducts. With alcohol **22** in hand, its oxidation to ketone **23** could be achieved in 90% yield upon reaction with IBX.

The last of the key steps in the preparation of **14** was the stereoselective introduction of the two-carbon side chain at C3 of the saturated ring in **23**, which we hoped to achieve via the addition of an isopropenyl group. After significant experimentation, the best conditions were found to involve the pretreatment of **23** with cerium(III) chloride at low temperature, followed by addition of isopropenyl magnesium bromide.[16] These conditions afforded an 80% yield of a mixture of the two possible stereosiomers, **24** and **25**, in an 87:13 ratio. Separation of these diastereomers by chromatography afforded pure **24**, a crystalline compound. A single-crystal X-ray study verified that the isopropenyl and siloxy groups were on opposite sides of the molecule.[17]

With a reliable route to **24** in place, its conversion to ketone **26** was achieved in 75% yield by first reaction with ozone and then with triethylamine.[18] While cleavage of the intermediate ozonide could also be carried out with more traditional reducing agents (e.g., dimethylsulfide and triphenylphosphine), the yields were consistently lower. Finally, removal of the silyl ether with tetra-*n*-butylammonium fluoride afforded **14** in 90% yield. Using the route illustrated in Scheme 1, **14** could be obtained in eight steps and in 23% overall yield from **19**.

Synthesis of 1,2,3,4-Tetrahydro-anthracene Core, 15. We anticipated that tetrahydro-anthracene derivative **15** could be obtained via a route analogous to that used for the preparation of **14**, starting from **27** (Scheme 2). Thus, we synthesized oxanorbornene derivative **27** using previously reported methods[19] and subjected it to the ring-opening protocol successfully employed to prepare **20** from **19**. This transformation was both high yielding and highly enantioselective when **19** was used as the substrate. Unfortunately, with **27**, the product was produced in both lower yield and with significantly lower enantioselectivity. After extensive optimization of the reaction (changing ligand and catalyst concentration as well as reaction times), the best result obtained was a 64% yield of the product (**28**) in 55% ee (chiral HPLC). Attempts to resolve the enantiomers at this stage by acylation with (*S*)-acetyl mandelic acid led to decomposition of **28**, and therefore this mixture of enantiomers was carried forward, with the goal of separating the stereoisomers at a later stage.

The synthesis of the tetrahydro-anthracene core continued from **28** by protection of the alcohol as the corresponding *tert*-butyldiphenylsilyl ether affording **29** (86% yield). Epoxidation of alkene **29** followed by reaction with lithium aluminum hydride provided a 63% yield of alcohol **30**, which was then oxidized to ketone **31** in 86% yield. As was done for the synthesis of **14**, the two carbon side chain at C3 was introduced via a cerium(III) mediated addition of isopropenyl magnesium bromide to **31**. In this case, the reaction proceeded in 70% yield and provided an 85:15 ratio of diastereomers, in which the isomer with the hydroxyl and *tert*-butyldiphenylsiloxy groups cis (**32-cis**) predominated. Support of the relative stereochemistry of these groups could be obtained by comparison of the ^{1}H NMR spectrum for **32-cis** with those of **24**, for which a crystal structure[17] had confirmed the stereochemistry, and its stereoisomer, **25** (Scheme 1). For example, the signal for the hydrogen on the carbon bearing the secondary hydroxyl group appeared as a doublet of doublets with two equal coupling constants (∼4 Hz) in both **24** and **32-cis**, while in **25** this signal appeared as a doublet of doublets with couplings of different magnitudes (9.7 and 5.8 Hz). In addition, the chemical shift difference between the hydrogens on the benzylic methylene carbon differed by less than 0.1 ppm in **24** and **32-cis**, while in **25** the resonances for these hydrogens were separated by over 0.4 ppm. Ozonolysis of the alkene in **32-cis** proved unsuccessful,

(14) Stiles, M.; Miller, R. G.; Burckhardt, U. *J. Am. Chem. Soc.* **1963**, *85*, 1792−1797.
(15) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247.
(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.
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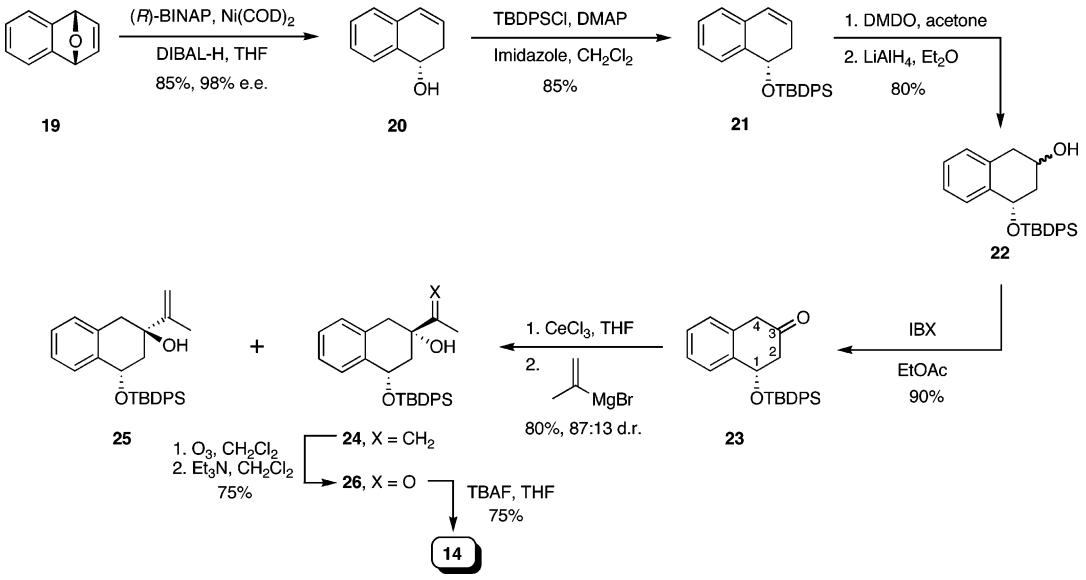
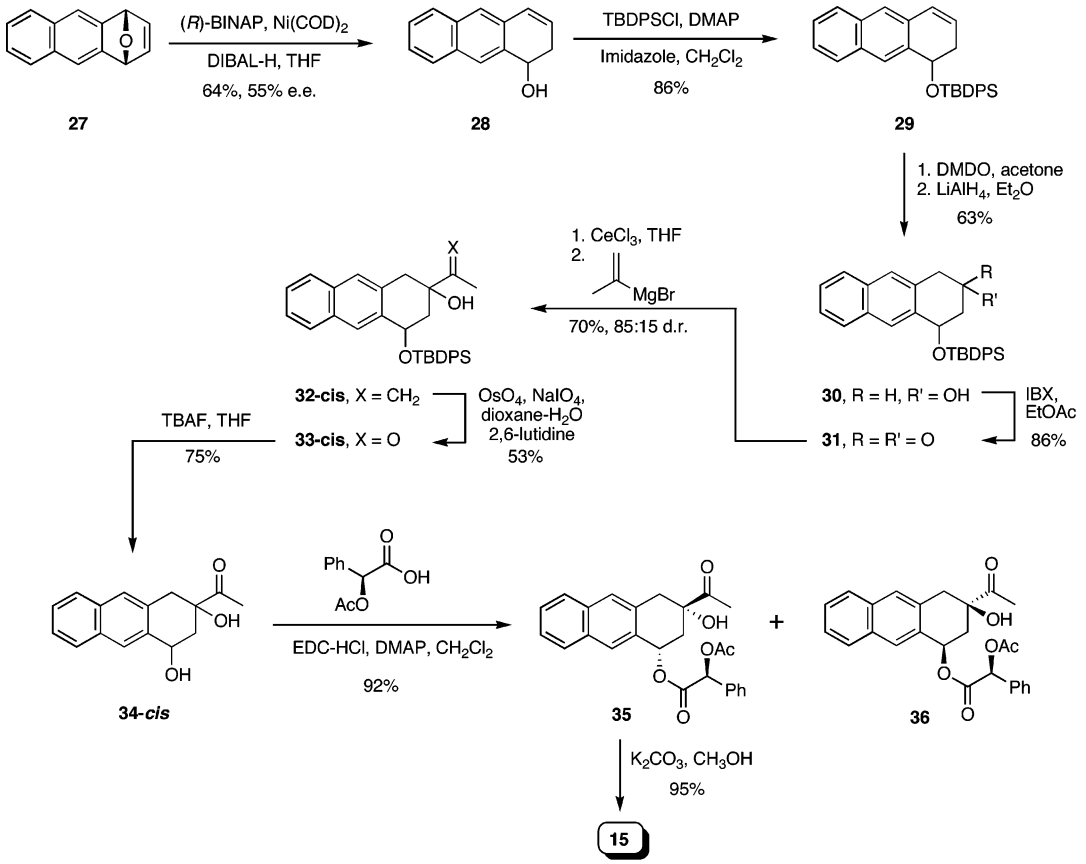
SCHEME 1



SCHEME 2

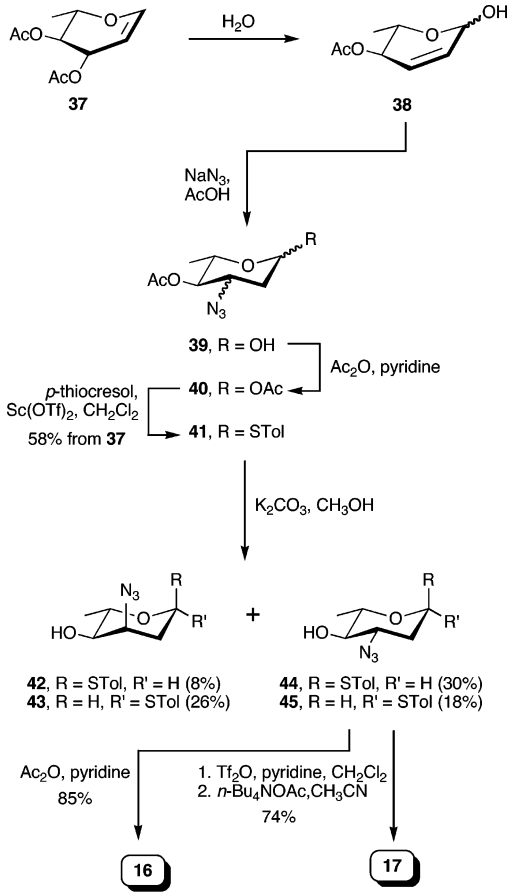


but a variant of the Lemieux−Johnson reaction[20] provided a 53% yield of ketone **33-cis**, which was deprotected to diol **34-cis**, in 75% yield, upon reaction with tetra-*n*-butylammonium fluoride.

At this stage, selective acylation of the secondary hydroxyl group with (*S*)-acetyl mandelic acid was possible, and this reaction gave a combined 92% yield of two diastereomeric tertiary alcohols **35** and **36**, which could be separated by chromatography. We had hoped that one of these two compounds would be crystalline, which would allow us to unequivocally determine the absolute configuration of the stereocenters at C1 and C3 in the tetrahydro-anthracene core; however, all attempts to crystallize either **35** or **36** failed. Faced with this difficulty, we carried forward the major product (**35**) on the assumption that the oxanorbornene ring opening (**27** → **28**), the reaction in which the absolute stereochemistry is set,

(20) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219.

SCHEME 3



would give the same enantiomer as the major product in both naphthalene and anthracene-derived bicyclic systems, **19** and **27**, respectively. Removal of the auxiliary in **35** upon reaction with base yielded **15** in 95% yield. The route shown in Scheme 2 afforded **15** in 7% yield and 10 steps from 1,4-epoxy-1,4-dihydroanthracene, **27**.

Synthesis of Glycosyl Donors 16 and 17. The synthesis of thioglycoside **16** and **17** began from 3,4-di-*O*-acetyl rhamnal, **37**,[21] and is illustrated in Scheme 3. Using previously described methods, **37** was converted into azidosugar **39** in two steps: conversion of the glycal to the pseudoglycal **38**[22] and then addition of azide ion.[21] This transformation provided all four possible stereoisomers, which, as reported,[21] could not be separated. Acetylation yielded **40**, again as an inseparable mixture, which was then converted[23] to thioglycoside **41** in 58% overall yield from **37**. Like diacetate **40**, the mixture of thioglycosides **41** was also inseparable by chromatography; however, deprotection of the acetate provided a mixture that could be separated, and thus thioglycosides **42**, **43**, **44**, and **45** were obtained as pure compounds in 8%, 26%, 30%, and 18%, respectively. While this route gave the desired products, **44** and **45**, in relatively modest yields, it is efficient and could be used to synthesize gram-scale amounts of these thioglycosides.

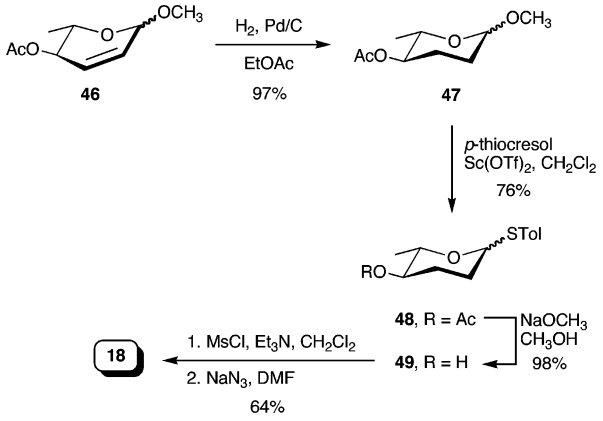
Assigning the stereochemistry at C3 and C1 in **42**−**45** could be straightforwardly done using ^{1}H NMR spectroscopy. For the compounds with L-*ribo* stereochemistry, **42** and **43**, the signal for H3 appeared as a doublet of doublet of doublets with $^3J_{3,2eq} \sim {}^3J_{3,2ax} \sim {}^3J_{3,4} \sim 3.3$ Hz, as would be expected for the equatorially oriented H3. In the case of the isomers with L-*arabino* stereochemistry, in which H3 is axially disposed, the resonance for H3 appeared as a doublet of doublet of doublets with $^3J_{3,2ax} \sim 12.0$ Hz, $^3J_{3,4} \sim 9.5$ Hz, and $^3J_{3,2eq} \sim 5.0$ Hz, again consistent with expectations. The anomeric stereochemistry could also be deduced from the ^{1}H NMR spectra. For the α-glycosides, **42** and **44**, the resonance for H1 appeared as a doublet with $^3J_{1,2ax} \sim 4-6$ Hz, and for the *β*-glycosides **43** and **45**, this signal appeared as a doublet of doublets with $^3J_{1,2ax} \sim 11.5$ Hz and $^3J_{1,2eq} \sim 2.5$ Hz.

(21) Renneberg, B.; Li, Y.-M.; Laatsch, H.; Fiebig, H.-H. *Carbohydr. Res.* **2000**, *329*, 861−872.

(22) Hollenbeak, K. H.; Kuehne, M. E. *Tetrahedron* **1974**, *30*, 2307−2316.

(23) Yadav, J. S.; Reddy, B. V. S.; Murthy, C. V. S. R.; Kumar, G. M. *Synlett* **2000**, 1450−1451.

SCHEME 4



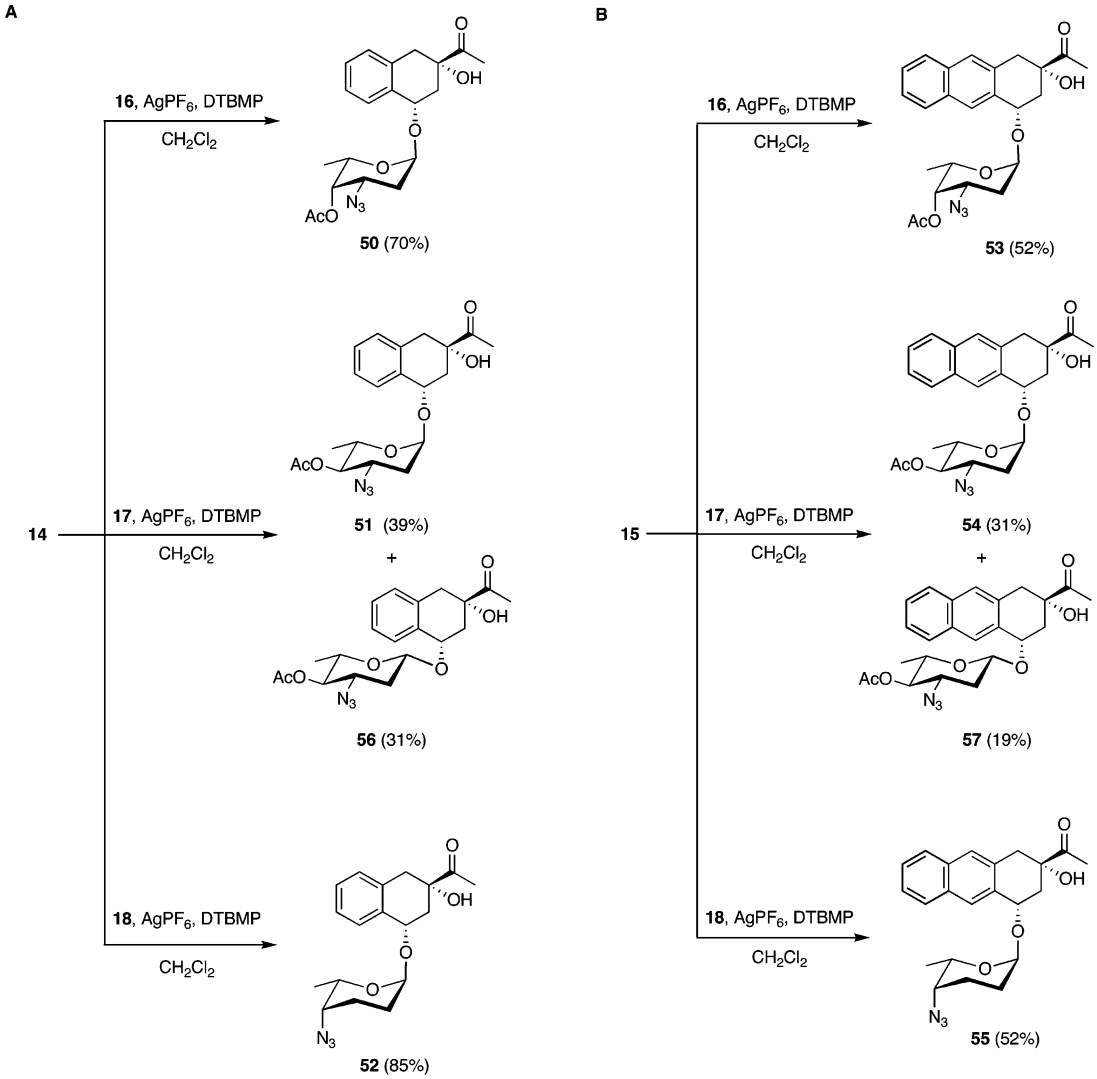
With sufficient quantities of **44** and **45** in hand, they could be converted efficiently into **16** and **17**. Although for the purposes of characterization **44** and **45** were separated, they were used as a mixture in subsequent transformations as we expected that the stereochemistry at C1 would be irrelevant to the outcome of the glycosylation reactions for which they were synthesized (vide supra). The preparation of **16** was achieved in one step and 85% yield from the mixture of **44** and **45** upon reaction with acetic anhydride and pyridine. Conversion to thioglycoside **17** required two steps, treatment with trifluoromethanesulfonic anhydride and pyridine to generate the corresponding triflate intermediate and then reaction with tetra-*n*-butylammonium acetate, thus giving the expected product in 74% overall yield.

Synthesis of Glycosyl Donors 18. The synthesis of thioglycoside **18** started from the known alkene **46**[24] (Scheme 4), which was prepared in one step from 3,4-di-*O*-acetyl rhamnal (**37**, Scheme 3). Hydrogenation of **46** provided the 2,3-dideoxy methyl glycoside **47** in excellent (97%) yield, and this product was subsequently converted to thioglycoside **48** in 76% yield upon reaction with *p*-thiocresol and scandium triflate. Deacetylation gave alcohol **49**, which was converted into **18** via formation of the 4-*O*-mesyl intermediate and substitution with azide ion. Thioglycoside **18** was obtained in 64% overall yield from **48**.

Glycosylation Reactions. Having implemented routes to both the core structures **14** and **15** and the thioglycoside donors **16**−**18**, we explored their coupling. We initially attempted the glycosylation of **14** with **16**−**18** by treatment of the donor and acceptor with *N*-iodosuccinimide and silver trifluoromethane-

(24) Brimacombe, J. S.; Doner, L. W.; Rollins, A. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2977−2979.

SCHEME 5



sulfonate,[25] an often used promoter system for the activation of thioglycosides. However, under these conditions, none of the product was formed and decomposition of **14** was observed. We then focused on a less commonly used method for thioglycoside activation: the use of silver hexafluorophosphate.[26] This method was reported to be highly α-selective for the synthesis of 2-deoxy-glycosides and has been used previously for the glycosylation of anthracyclines.[5e,g] As shown in Scheme 5, activation of **16**−**18** with silver hexafluorophosphate in the presence of **14** gave glycoside products in good to excellent yields (70−85%). Similar reaction of **15** with these thioglycosides also gave the expected products, but the yields were more modest (∼50%). In these cases, a large amount of hydrolyzed donor was produced, and the unreacted acceptor could also be recovered.

These reactions were all done with a 1:1 ratio of donor to acceptor, and in an attempt to improve the modest yields obtained in the glycosylation of **15**, we explored the use of an excess of donor. However, the use of such conditions led to the formation of significant amounts of the product in which both the secondary and tertiary hydroxyl groups were glycosylated.

The stereochemistry of the glycoside products could be determined using ^{1}H NMR spectroscopy, as described above for thioglycosides **42**−**45**. In the α-glycosides, the signal for H1 appeared as a doublet with $^3J_{1,2ax} \sim 4-6$ Hz and $^3J_{1,2eq} \sim 0$ Hz, while for the *β*-glycosides this resonance appeared as a doublet of doublets with $^3J_{1,2ax} \sim 9.5$ Hz and $^3J_{1,2eq} \sim 2.0$ Hz. For thioglycosides **16** and **18**, these glycosylations were highly α-selective as has been reported previously.[5e,g,26] However, in glycosylations with **17**, significant quantities of the *β*-glycoside products, **56** and **57**, were also produced.

To rationalize the poor stereoselectivity of glycosylations with **17**, we considered that the acetoxy group at C4 might be influencing the reaction through remote participation. As outlined in Figure 2, participation of the acetoxy group in the oxacarbenium ion (**58**) that is generated upon activation could lead to the formation of a bicyclic intermediate, **59**, which would necessarily provide the *β*-glycoside, **60**. In contrast, direct attack of the nucleophile on **58** would afford the α-glycoside. Analogous participation events have been previously proposed.[27] Although the formation of **59** would be expected to be a high-energy process, the deoxygenation at C2 would facilitate the required ring conformational change by reducing the magnitude

(25) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313−3416.

(26) Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946−949.

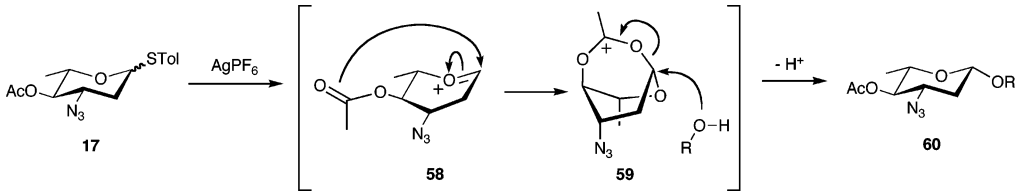
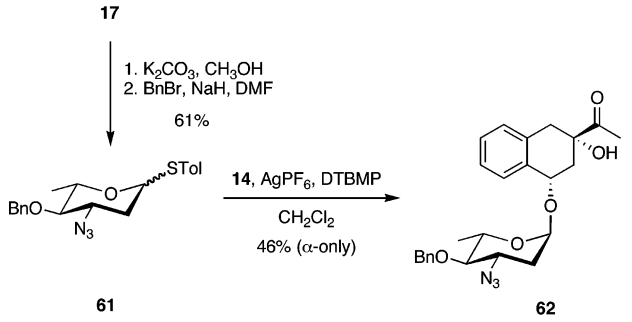


FIGURE 2. Proposed mechanism to account for the formation of β-glycosides in glycosylations with thioglycoside **17**.

SCHEME 6



of eclipsing interactions along the C2−C3 bond. In addition, due to the small size of the azide moiety and the deoxygenation at C6, any unfavorable steric interactions between the groups at C3 and C5 would be less than in a ring in which each of these carbons carried a protected hydroxyl group.

To further probe the plausibility of the pathway shown in Figure 2, we synthesized an analogue of **17** in which the acetoxy group was replaced with a nonparticipating benzyl group, **61** (Scheme 6). Subsequent glycosylation of **14** with **61** provided only the α-glycoside product, **62**, in 46% yield; the remainder of the mass balance was unreacted alcohol and hydrolyzed donor. This result provides additional support for the proposal that glycosylations with **17** proceed through the reaction manifold outlined in Figure 2.

Deprotection Reactions. With all of the coupled products in hand, each was converted to the final targets **8**−**13** by first removal of the acetate groups (if necessary) and finally reduction of the azide to the amine using Staudinger reduction (Scheme 7). The yield for these reactions ranged from modest to good. As was observed in the glycosylations, these deprotection and reduction reactions proceeded in better yield for the tetrahydro-naphthalene series (**50**−**52**) than for the tetrahydro-anthracene series (**53**−**55**). We are unsure as to the origin of the modest yields in the conversion of **53**−**55** into the final targets. Although the reactions were all clean by TLC, following purification by chromatography, only the modest yields of the products were obtained.

Evaluation of Cytotoxicity of 8−13 against MCF-7 Breast Cancer Cells. Each of the six target compounds **8**−**13** was evaluated for cytotoxic activity against MCF-7 breast cancer cells, and the data were compared to those obtained with doxorubicin and daunorubicin. As an initial screen, each compound was tested in a standard cytotoxocity assay[28] at 100 μM (Table 1), which showed that the tetrahydro-naphthalene compounds **8**−**10** had no cytotoxic effect, while the tetrahydro-anthracene derivatives **11**−**13** were of modest cytotoxicity. To further probe the potency of **11**−**13**, IC_{50} values of each were determined (Table 1), and these compounds were shown to be less cytotoxic than either doxorubicin or daunorubicin. These results suggest that a minimum of two aromatic rings are required for the cytotoxicity and that analogues possessing a 1,2,3,4-tetrahydro-tetracene core may possess better activity still. It is also interesting to note that in these series of compounds, the structure of the carbohydrate moiety appears to play a minor role in determining the cytotoxicity, as **11**−**13** have comparable IC_{50} values.

Conclusions

In summary, we report here the synthesis of a panel of daunorubicin analogues, **8**−**13**, consisting of a functionalized 1,2,3,4-tetrahydro-naphthalene or 1,2,3,4-tetrahydro-anthracene moiety appended to one of three monosaccharide residues. Key steps in the synthesis of these compounds were (1) the preparation of the tetrahydro-naphthalene and tetrahydro-anthracene cores via the enantioselective opening of benzo-fused norbornene derivatives[15] and (2) the use of silver hexafluoro-phosphate[26] as a promoter in the glycosylation of these cores with thioglycoside donors. Evaluation of these compounds against MCF-7 cancer cells revealed that the compounds containing the 1,2,3,4-tetrahydro-naphthalene core (**8**−**10**) showed no cytotoxicity, while those with the 1,2,3,4-tetrahydro-anthracene moiety (**11**−**13**) were more active, suggesting that further extension of the core may provide compounds with increased cytotoxicity.

Experimental Section

General Procedure for the Glycosylation of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Cores. A mixture of thioglycoside (0.5 mmol), compound **14** or **15** (0.5 mmol), and DTBMP (1.46 mmol) was dissolved in CH_2Cl_2 (10 mL). Molecular sieves (4 Å, freshly activated) were added, and the reaction mixture was stirred for 1.5 h under an inert atmosphere. The reaction mixture was cooled to 0 °C, and powdered $AgPF_6$ (1.46 mmol) was added. Stirring was maintained for 2−3 h. Et_3N (5 mL) was then added, and the solution was filtered through Celite to give a solution that was concentrated. Purification of the residue by column chromatography afforded the desired products.

General Procedure for the Removal of the Acetate Group for 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Glycosides. Protected glycosides (0.47 mmol) were dissolved in dry CH_3OH (5 mL), and K_2CO_3 (0.065 g, 0.47 mmol) was added. The mixture was stirred for 24 h, concentrated, and purified via column chromatography to afford the desired products.

General Procedure for the Reduction of 1,2,3,4-Tetrahydro-naphthyl and 1,2,3,4-Tetrahydro-anthranyl Azido Glycosides. Azido glycosides (0.3 mmol) and triphenylphosphine (0.6 mmol) were dissolved in a solution of THF (10 mL) and water (1 mL),

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(28) (a) Cory, A. H.; Owen, T. C.; Barltrop, J. A.; Cory, J. G. *Cancer Commun.* **1991**, *3*, 207−212. (b) Barltrop, J. A.; Owen, T. C.; Cory, A. H.; Cory, J. G. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 611−614.

SCHEME 7

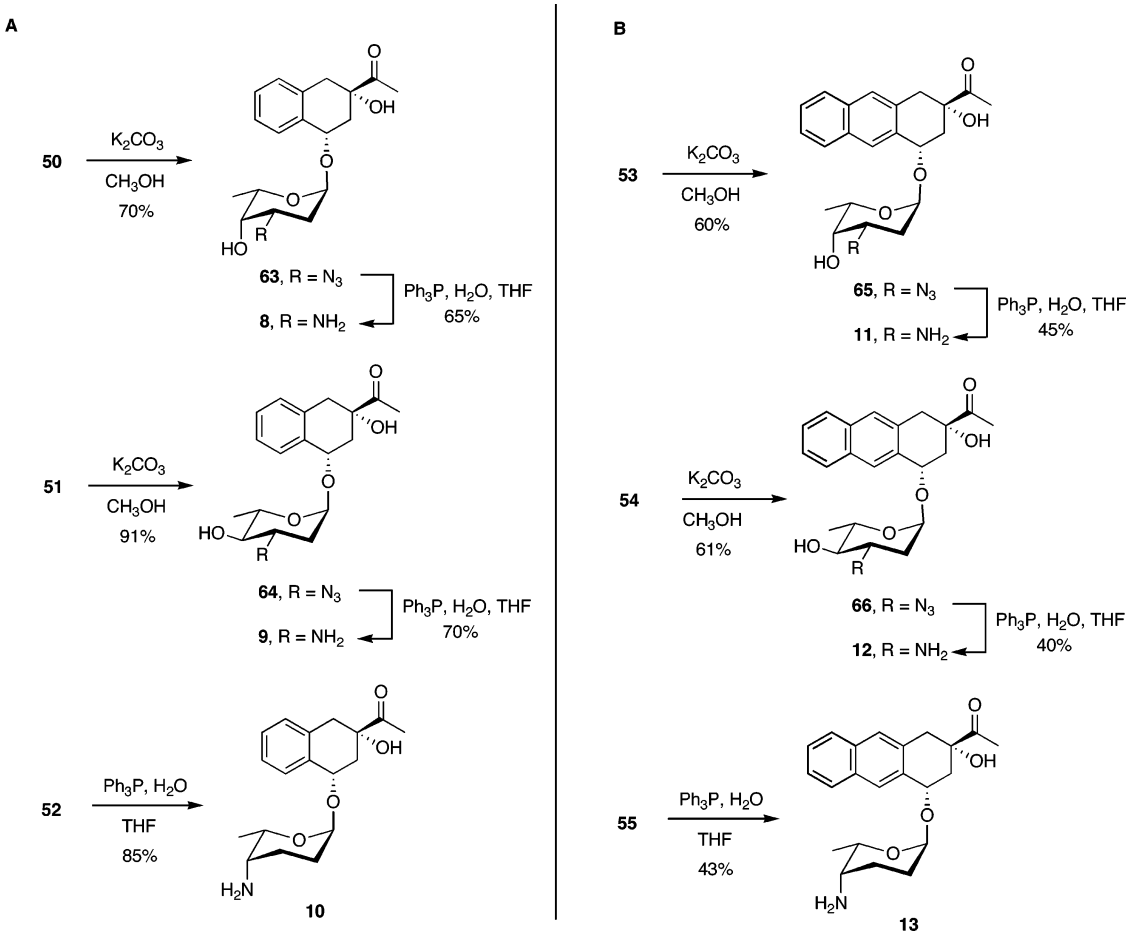

TABLE 1. Cytotoxicity of 8−13 against MCF-7 Breast Cancer Cells

compound	% inhibition at 100 μM	IC_{50} (μM)
8	0	ND[a]
9	0	ND[a]
10	0	ND[a]
11	47	111
12	22	134
13	58	94
daunorubicin	ND[a,b]	5
doxorubicin	ND[a,c]	17

[a] Not determined. [b] 99% inhibition at 40 μM. [c] 97% inhibition at 40 μM.

and the reaction mixture was stirred for 3−12 h at 55 °C. Concentration followed by purification by column chromatography afforded the desired products.

(1*S*,3*S*)-1-*O*-(3-Amino-2,3,6-deoxy-β-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (8). Yield 70%; R_f = 0.15 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −120.3 (*c* 0.6, CH_3OH). ^1H NMR (400 MHz, CD_3OD): δ_H 7.18−7.38 (m, 4H, Ar), 5.16 (d, 1H, $J_{1,2ax}$ = 3.1 Hz, H-1), 4.80−4.89 (m, 1H, H-1_a), 4.13 (q, 1H, $J_{5,6}$ = 6.7 Hz, H-5), 3.63−3.71 (m, 2H, H-3, H-4), 3.10 (d, 1H, $J_{4ax,4eq}$ = 16.1 Hz, H-4_aax), 2.91 (d, 1H, $J_{4ax,4eq}$ = 16.1 Hz, H-4_aeq), 2.49 (m, 1H, H-2_aeq), 2.23 (s, 3H, C(O)CH_3), 1.98−2.09 (m, 2H, H-2ax, H-2_aax), 1.83−1.90 (m, 1H, H-2eq), 1.27 (d, 3H, $J_{5,6}$ = 6.7 Hz, H-6). ^{13}C NMR (100 MHz, CD_3OD): δ_C 213.4 (C=O), 136.6 (Ar), 135.3 (Ar), 130.1 (Ar), 130.0 (Ar), 129.3 (Ar), 127.4 (Ar), 97.9 (C-1), 78.8 (C-3_a), 75.4 (C-1_a), 68.0 (C-4), 67.8 (C-5), 48.5 (C-3), 40.0 (C-4_a), 39.6 (C-2_a), 29.8 (C-2), 24.4 (C(O)CH_3), 17.0 (C-6). ESI HRMS calcd for $C_{18}H_{26}NO_5$: 336.1811 $[M + H]^+$. Found: 336.1806.

(1*S*,3*S*)-1-*O*-(3-Amino-2,3,6-deoxy-β-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (9). Yield 65%; R_f = 0.18 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −80.4 (*c* 0.3, CH_3OH). ^1H NMR (500 MHz, CD_3OD): δ_H 7.19−7.38 (m, 4H, Ar), 5.11 (d, 1H, $J_{1,2ax}$ = 3.8 Hz, H-1), 4.82 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 5.1 Hz, H-1_a), 3.84−3.90 (m, 1H, H-5), 3.37−3.45 (m, 1H, H-3), 3.08−3.18 (m, 2H, H-4, H-4_aax), 2.93 (d, 1H, $J_{4ax,4eq}$ = 16.2 Hz, H-4_aeq), 2.50 (dd, 1H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2ax}$ = 5.1 Hz, H-2_aax), 2.22 (s, 3H, C(O)CH_3), 2.16−2.22 (m, 1H, H-2eq), 2.05 (dd, 1H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2eq}$ = 5.1 Hz, H-2_aeq), 1.82 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.8 Hz, $J_{1,2ax}$ = 3.8 Hz, H-2ax), 1.34 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6). ^{13}C NMR (125 MHz, CD_3OD): δ_C 213.2 (C=O), 136.5 (Ar), 135.4 (Ar), 130.1 (Ar), 129.3 (Ar), 128.9 (Ar), 127.4 (Ar), 97.3 (C-1), 78.8 (C-3_a), 75.3 (C-1_a), 75.0 (C-4), 70.2 (C-5), 51.4 (C-3), 48.5 (C-4_a), 40.2 (C-2_a), 39.6 (C-2), 24.3 (C(O)CH_3), 17.9 (C-6). ESI HRMS calcd for $C_{18}H_{26}NO_5$: 336.1811 $[M + H]^+$. Found: 336.1808.

(1*S*,3*S*)-1-*O*-(4-Amino-2,3,4,6-tetradeoxy-β-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (10). Yield 85%; R_f = 0.25 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −70.6 (*c* 0.5, CH_3OH). ^1H NMR (500 MHz, CD_3OD): δ_H 7.20−7.35 (m, 4H, Ar), 5.18 (d, 1H, $J_{1,2ax}$ = 3.3 Hz, H-1), 4.83 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 5.8 Hz, H-1_a), 4.78 (s, 1H, 3°-OH), 4.30−4.40 (m, 1H, H-5), 3.35 (br s, 1H, H-4), 3.10 (d, 1H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aax), 2.93 (d, 1H, $J_{4ax,4eq}$ = 16.0 Hz, H-4_aeq), 2.50 (dd, 1H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{1,2eq}$ = 5.8 Hz, H-2_aax), 2.25−2.32 (m, 1H, H-3eq), 2.26 (s, 3H, C(O)CH_3), 2.17 (dd, 1H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{1,2eq}$ = 5.8 Hz, H-2_aeq), 1.82−1.92 (m, 2H, H-3ax, H-2ax), 1.65−1.72 (m, 1H, H-2eq), 1.24 (d, 3H, $J_{5,6}$ = 6.8 Hz, H-6). ^{13}C NMR (125 MHz, CD_3OD): δ_C 213.4 (C=O), 136.7 (Ar), 135.3 (Ar), 130.0 (Ar), 129.2 (Ar), 128.8 (Ar), 127.4 (Ar), 98.4 (C-1), 78.8 (C-3_a), 75.4

(C-1_a), 65.0 (C-5), 50.5 (C-4), 48.5 (C-4_a), 40.1 (C-2_a), 39.7 (C-3), 24.3 (C(O)*C*H_3), 23.4 (C-2), 17.5 (C-6). ESI HRMS calcd for $C_{18}H_{26}NO_4$: 320.1862 $[M + H]^+$. Found: 320.1877.

(1*S*,3*S*)-1-*O*-(3-Amino-2,3,6-deoxy-*β*-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (11). Yield 40%; R_f = 0.15 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −110.6 (*c* 0.3, CH_3OH). ^1H NMR (400 MHz, CD_3OD): δ_H 7.72−7.84 (m, 3H, Ar), 7.61 (s, 1H, Ar), 7.37−7.46 (m, 2H, Ar), 5.04 (br s, 1H, H-1), 4.96 (dd, 1H, $J_{1,2ax} = J_{1,2eq}$ = 5.9 Hz, H-1_a), 4.80 (s, 1H, 2°-OH), 4.11 (q, 1H, $J_{5,6}$ = 6.5 Hz, H-5), 3.50−3.55 (m, 1H, H-3), 3.28−3.36 (m, 1H, H-4), 3.20 (d, 1H, $J_{4ax,4eq}$ = 15.7 Hz, H-4_aax), 3.11 (d, 1H, $J_{4ax,4eq}$ = 15.7 Hz, H-4_aeq), 2.60 (dd, 1H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2ax}$ = 5.9 Hz, H-2_aax), 2.24 (s, 3H, C(O)CH_3), 2.01 (dd, 1H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2eq}$ = 5.9 Hz, H-2_aeq), 1.76−1.86 (m, 2H, H-2ax, H-2eq), 1.28 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 213.4 (C═O), 135.6 (Ar), 134.6 (Ar), 133.7 (Ar), 133.5 (Ar), 128.7 (Ar), 128.0 (Ar), 127.9 (Ar), 126.9 (Ar), 126.6 (Ar), 126.5 (Ar), 97.6 (C-1), 74.4 (C-3_a), 71.9 (C-1_a), 71.1 (C-4), 68.3 (C-5), 48.2 (C-3), 47.8 (C-4_a), 40.8 (C-2_a), 39.6 (C-2), 32.8 (C(O)*C*H_3), 17.1 (C-6). ESI HRMS calcd for $C_{22}H_{28}NO_5$: 386.1967 $[M + H]^+$. Found: 386.1962.

(1*S*,3*S*)-1-*O*-(3-Amino-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (12). Yield 45%; R_f = 0.15 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −63.1 (*c* 0.2, CH_3OH). ^1H NMR (600 MHz, CD_3OD): δ_H 7.74−7.84 (m, 3H, Ar), 7.64 (s, 1H, Ar), 7.39−7.46 (m, 2H, Ar), 5.03 (d, 1H, $J_{1,2ax}$ = 3.5 Hz, H-1), 4.98 (dd, 1H, $J_{1,2ax} = J_{1,2eq}$ = 5.6 Hz, H-1_a), 3.87 (dq, 1H, $J_{4,5}$ = 9.7 Hz, $J_{5,6}$ = 6.6 Hz, H-5), 3.30−3.35 (m, 1H, H-3), 3.22 (d, 1H, $J_{4ax,4eq}$ = 15.3 Hz, H-4_aax), 3.13 (d, 1H, $J_{4ax,4eq}$ = 15.3 Hz, H-4_aeq), 3.05 (dd, 1H, $J_{4,5} = J_{3,4}$ = 9.7 Hz, H-4), 2.63 (dd, 1H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2ax}$ = 5.6 Hz, H-2_aax), 2.16 (ddd, 1H, $J_{2ax,2eq} = J_{2ax,3}$ = 12.4 Hz, $J_{1,2ax}$ = 3.5 Hz, H-2ax), 2.03 (dd, 1H, $J_{2ax,2eq}$ = 14.2 Hz, $J_{1,2eq}$ = 5.6 Hz, H-2_aeq), 1.74 (dd, $J_{2ax,2eq}$ = 12.4 Hz, $J_{2eq,3}$ = 3.4 Hz, H-2eq), 1.34 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6). ^{13}C NMR (125 MHz, CD_3OD): δ_C 213.4 (C═O), 135.6 (Ar), 134.8 (Ar), 133.9 (Ar), 133.7 (Ar), 128.8 (Ar), 128.3 (Ar), 128.2 (Ar), 127.2 (Ar), 126.8 (Ar), 126.7 (Ar), 96.7 (C-1), 79.3 (C-3_a), 76.7 (C-1_a), 74.7 (C-4), 70.2 (C-5), 48.9 (C-3), 39.2 (C-4_a), 41.1 (C-2_a), 39.7 (C-2), 24.4 (C(O)*C*H_3), 18.0 (C-6). ESI HRMS calcd for $C_{22}H_{28}NO_5$: 386.1967 $[M + H]^+$. Found: 386.1963.

(1*S*,3*S*)-1-*O*-(4-Amino-2,3,4,6-tetradeoxy-*β*-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (13). Yield 43%; R_f = 0.13 (10:1, CH_2Cl_2−CH_3OH); $[\alpha]_D$ −88.9 (*c* 0.2, $CHCl_3$). ^1H NMR (500 MHz, CD_3OD): δ_H 7.74−7.83 (m, 3H, Ar), 7.63 (s, 1H, Ar), 7.39−7.45 (m, 2H, Ar), 4.95−5.00 (m, 2H, H-1, H-1_a), 4.20−4.30 (m, 1H, H-5), 3.21 (d, 1H, $J_{4ax,4eq}$ = 15.5 Hz, H-4_aax), 3.11 (d, 1H, $J_{4ax,4eq}$ = 15.5 Hz, H-4_aeq), 2.80 (br s, 1H, H-4), 2.50 (dd, 1H, $J_{2ax,2eq}$ = 14.1 Hz, $J_{1,2ax}$ = 6.1 Hz, H-2_aax), 2.28 (s, 3H, C(O)CH_3), 2.16 (ddd, 1H, $J_{3ax,3eq} = J_{2ax,3ax}$ = 13.9 Hz, $J_{3ax,4}$ = 4.4 Hz, H-3ax), 2.03 (dd, 1H, $J_{2ax,2eq}$ = 13.9 Hz, $J_{1,2eq}$ = 6.1 Hz, H-2_aeq), 1.93 (ddd, 1H, $J_{2ax,2eq} = J_{2ax,3ax}$ = 13.9 Hz, $J_{2ax,3eq}$ = 4.3 Hz, H-2ax), 1.64−1.68 (m, 1H, H-3eq), 1.56−1.61 (m, 1H, H-2eq), 1.20 (d, 3H, $J_{5,6}$ = 6.7 Hz, H-6). ^{13}C NMR (125 MHz, CD_3OD): δ_C 213.7 (C═O), 136.0 (Ar), 134.8 (Ar), 133.8 (Ar), 133.7 (Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar), 127.1 (Ar), 126.6 (Ar), 97.7 (C-1), 79.4 (C-3_a), 74.3 (C-1_a), 67.7 (C-5), 49.6 (C-4), 41.0 (C-4_a), 39.8 (C-2_a), 39.8 (C-3), 26.6 (C-2), 24.6 (C(O)*C*H_3), 17.8 (C-6). ESI HRMS calcd for $C_{22}H_{28}NO_4$: 370.2018 $[M + H]^+$. Found: 370.2013.

(1*S*,3*S*)-1-Hydroxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (14). Ketone **26** (0.73 g, 1.64 mmol) was dissolved in THF (5 mL), and tetrabutylammonium fluoride in 1.0 M THF (1.49 g, 1.65 mmol) was added to the solution. The reaction mixture was stirred for 48 h, concentrated, and purified by chromatography (5:1, hexanes−EtOAc) to yield **14** (0.254 g, 75%) as an oil. R_f = 0.48 (1:1, hexanes−EtOAc); $[\alpha]_D$ +21.1 (*c* 0.8, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.46−7.48 (m, 1H, Ar), 7.26−7.31 (m, 2H, Ar), 7.11−7.14 (m, 1H, Ar), 4.90 (br s, 1H, H-1), 4.47 (s, 1H, 3°-OH), 3.72 (br d, 1H, *J* = 8.9 Hz, 2°-OH), 3.24 (d, 1H, $J_{4ax,4eq}$ = 16.5 Hz, H-4ax), 2.84 (dd, 1H, $J_{4ax,4eq}$ = 16.5 Hz, $J_{2eq,4eq}$ = 2.1 Hz, H-4eq), 2.38 (s, 3H, C(O)CH_3), 2.31 (dd, 1 H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2ax}$ = 4.6 Hz, H-2ax), 2.23 (ddd, 1H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2eq}$ = 4.6 Hz, H-2eq). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 210.9 (C═O), 136.9 (Ar), 131.5 (Ar), 130.2 (Ar), 129.4 (Ar), 128.4 (Ar), 127.1 (Ar), 78.5 (C-3), 67.1 (C-1), 38.2 (C-4), 36.9 (C-2), 24.0 (C(O)-CH_3). ESI HRMS calcd for $C_{12}H_{14}O_3Na$: 229.0841 $[M + Na]^+$. Found: 229.0835.

(*S*)-1-*tert*-Butyldiphenylsiloxy-3,4-dihydro-naphthalene (21). Alkene **20**[15] (3.2 g, 21.9 mmol), imidazole (3.73 g, 54.8 mmol), and DMAP (50 mg, 0.41 mmol) were dissolved in CH_2Cl_2 (50 mL). TBDPSCl (6.02 g, 21.9 mmol) was added to the solution, and the reaction mixture was stirred for 4 h. Once the reaction was complete, the mixture was concentrated and purified by chromatography (hexanes) to yield **21** (7.16 g, 85%) as a clear oil. R_f = 0.56 (hexanes); $[\alpha]_D$ −40.2 (*c* 1.4, C_6H_6). ^1H NMR (300 MHz, C_6D_6): δ_H 7.67−7.84 (m, 4H, Ar), 7.52−7.55 (m, 1H, Ar), 7.06−7.26 (m, 8H, Ar), 6.89−6.93 (m, 1H, Ar), 6.32 (br d, 1H, $J_{4,3}$ = 9.6 Hz, H-4), 5.60 (ddd, 1H, $J_{3,4}$ = 9.6 Hz, $J_{2ax,3}$ = 4.5 Hz, $J_{2eq,3}$ = 4.3 Hz, H-3), 5.05 (dd, 1H, $J_{1,2eq}$ = 7.1 Hz, $J_{1,2ax}$ = 6.9 Hz, H-1), 2.41 (dddd, 1H, $J_{2eq,2ax}$ = 16.9 Hz, $J_{1,2eq}$ = 7.1 Hz, $J_{2eq,3}$ = 4.3 Hz, $J_{2eq,4}$ = 1.8 Hz, H-2eq), 2.09 (dddd, 1H, $J_{2ax,2eq}$ = 16.9 Hz, $J_{1,2ax}$ = 6.9 Hz, $J_{2ax,3}$ = 4.5 Hz, $J_{2ax,4}$ = 1.8 Hz, H-2ax), 1.16 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, C_6D_6): δ_C 137.8 (Ar), 136.3 (3 × Ar), 136.2 (3 × Ar), 135.0 (Ar), 134.2 (Ar), 133.9 (Ar), 130.1 (Ar), 130.0 (Ar), 128.0 (2 × Ar), 127.9 (2 × Ar), 127.5 (C-4), 126.5 (Ar), 126.3 (C-3), 125.9 (Ar), 70.4 (C-1), 33.3 (C-2), 27.3 (*C*(CH_3)$_3$), 19.8 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{26}H_{28}OSiNa$: 407.1807 $[M + Na]^+$. Found: 407.1810.

(*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (22). Compound **21** (7.10 g, 18.5 mmol) was dissolved in CH_2Cl_2 (50 mL), and the resulting solution was added to DMDO (approximately 0.05−0.08 M solution in acetone, 400 mL). The reaction mixture was stirred for 2 h at 0 °C and then concentrated. The crude product was used without any further purification. R_f = 0.52 (15:1, hexanes−EtOAc). The epoxide (7.41 g, 18.5 mmol) was then dissolved in Et_2O (60 mL), and the mixture was cooled to 0 °C. $LiAlH_4$ (1.20 g, 31.5 mmol) was added to the mixture, and the solution was stirred for 70 min at room temperature. Excess EtOAc was added to quench the residual $LiAlH_4$, followed by 4 M NaOH (3 mL). The mixture was filtered through Celite and concentrated. The crude product was purified by chromatography (5:1, hexanes−EtOAc) to yield **22** as a 95:5 mixture of isomers, which were inseparable (5.95 g, 80% over two steps) as a clear oil. Data for the major isomer: R_f = 0.32 (5:1, hexanes−EtOAc); $[\alpha]_D$ −45.8 (*c* 1.3, $CHCl_3$). ^1H NMR (600 MHz, CD_3OD): δ_H 6.80−7.78 (m, 14H, Ar), 4.94 (dd, 1H, $J_{1,2ax} = J_{1,2eq}$ = 5.3 Hz, H-1), 4.47−4.51 (m, 1H, H-3), 3.17 (dd, 1H, $J_{4ax,4eq}$ = 16.2 Hz, $J_{4ax,3}$ = 7.5 Hz, H-4ax), 2.58 (dd, 1H, $J_{4eq,4ax}$ = 16.2 Hz, $J_{4eq,3}$ = 7.5 Hz, H-4eq), 2.23 (ddd, 1H, $J_{2ax,2eq}$ = 12.8 Hz, $J_{1,2ax}$ = 5.3 Hz, $J_{2ax,3}$ = 3.8 Hz, H-2ax), 1.67 (ddd, 1H, $J_{2ax,2eq}$ = 12.8 Hz, $J_{1,2eq}$ = 5.3 Hz, $J_{2eq,3}$ = 3.8 Hz, H-2eq), 1.05 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, C_6D_6): δ_C 138.6 (Ar), 137.1 (4 × Ar), 136.1 (Ar), 135.2 (Ar), 135.1 (Ar), 131.0 (Ar), 130.8 (Ar), 130.4 (Ar), 130.1 (Ar), 128.9 (2 × Ar), 128.8 (Ar), 128.6 (2 × Ar), 126.8 (Ar), 71.7 (C-1), 64.8 (C-3), 41.9 (C-4), 39.5 (C-2), 27.6 (*C*(CH_3)$_3$), 20.2 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{26}H_{30}O_2SiNa$: 425.1913 $[M + Na]^+$. Found: 425.1907. Anal. Calcd: C, 77.57; H, 7.51. Found: C, 77.84; H, 7.34.

(*S*)-1-*tert*-Butyldiphenylsiloxy-1,2,3,4-tetrahydro-naphtha-3-one (23). Alcohol **22** (5.0 g, 12.5 mmol) was dissolved in EtOAc (40 mL), and IBX (8.75 g, 31.3 mmol) was added. The resulting mixture was stirred for 6 h at 85 °C, whereupon the cloudy solution changed from colorless to light yellow. The suspension was filtered, concentrated, and then purified by chromatography (20:1, hexanes−EtOAc) to yield **23** (4.5 g, 90%) as a white solid. R_f = 0.70 (5:1, hexanes−EtOAc); $[\alpha]_D$ −64.8 (*c* 1.3, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ_H 7.67−7.78 (m, 2H, Ar), 7.36−7.49 (m, 6H, Ar), 7.23−7.32 (m, 3H, Ar), 7.08−7.19 (m, 2H, Ar), 6.90 (d, 1H, *J* = 7.4 Hz,

Ar), 4.82 (dd, 1H, $J_{1,2ax}$ = 4.5 Hz, $J_{1,2eq}$ = 3.2 Hz, H-1), 3.76 (d, 1H, $J_{4ax,4eq}$ = 19.9 Hz, H-4ax), 3.22 (d, 1H, $J_{4ax,4eq}$ = 19.9 Hz, H-4eq), 2.67 (dd, 1H, $J_{2ax,2eq}$ = 16.5 Hz, $J_{1,2ax}$ = 4.5 Hz, H-2ax), 2.09 (dd, 1H, $J_{2ax,2eq}$ = 16.5 Hz, $J_{1,2eq}$ = 3.2 Hz, H-2eq), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, C_6D_6): δ_C 205.5 (C-3), 138.5 (Ar), 136.3 (4 × Ar), 135.3 (Ar), 134.2 (Ar), 133.9 (Ar), 133.7 (Ar), 130.3 (Ar), 130.1 (Ar), 128.9 (Ar), 128.3 (2 × Ar), 127.9 (2 × Ar), 127.3 (Ar), 126.5 (Ar), 71.5 (C-1), 47.4 (C-4), 44.2 (C-2), 27.1 (*C*(CH_3)$_3$), 19.5 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{26}H_{28}O_2$SiNa: 423.1756 [M +Na]$^+$. Found: 423.1751.

(1*S*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-3-isopropenyl-1,2,3,4-tetrahydro-naphthalene (24). Cerium chloride heptahydrate (4.53 g, 18.4 mmol) and a magnetic stir bar were placed in a flask and heated to 140−142 °C in vacuo (0.1 Torr) for 24 h. The flask was cooled to rt, and ketone **23** (2.10 g, 5.25 mmol) and THF (20 mL) were added. The reaction mixture was vigorously stirred for 1.5 h after the mixture had become an orange paste. Isopropenylmagnesium bromide in THF (0.5 M, 18.9 mL, 9.45 mmol) was added over 10 min at 0 °C, and the solution was stirred for 4 h. The mixture was then treated with a saturated aq soln of NH_4Cl (50 mL), and EtOAc (50 mL) was added. The mixture was filtered through Celite, and the aq layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over Na_2SO_4 and purified by chromatography (15:1, hexanes−EtOAc) to yield **24** (1.86 g, 67%) as a white solid. The solid was recrystallized from hexane−Et_2O (1:1). Mp 95−98 °C; R_f = 0.65 (5:1, hexanes−EtOAc); $[\alpha]_D$ −10.5 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.92−7.82 (m, 14H, Ar), 5.08 (s, 1H, alkene), 4.94 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.8 Hz, H-1), 4.87 (br s, 1H, alkene), 4.59 (s, 1H, 3°-OH), 3.08 (br d, 1H, $J_{4ax,4eq}$ = 16.8 Hz, H-4ax), 3.03 (d, 1H, $J_{4ax,4eq}$ = 16.8 Hz, H-4eq), 2.30 (ddd, 1H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2eq}$ = 3.8 Hz, $J_{2eq,4}$ = 1.3 Hz, H-2eq), 2.00 (dd, 1H, $J_{2ax,2eq}$ = 14.0 Hz, $J_{1,2ax}$ = 3.8 Hz, H-2ax), 1.82 (s, 3H, =CCH_3), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 149.9 (alkene), 136.2 (2 × Ar), 135.8 (2 × Ar), 135.2 (Ar), 134.8 (Ar), 134.6 (Ar), 133.0 (Ar), 132.9 (Ar), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 125.8 (Ar), 110.0 (alkene), 73.1 (C-3), 70.6 (C-1), 41.6 (C-4), 40.5 (C-2), 26.9 (=CCH_3), 19.3 (*C*(CH_3)$_3$), 18.7 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{29}H_{34}O_2$SiNa: 465.2226 [M + Na]$^+$. Found: 465.2221. Anal. Calcd: C, 78.68; H, 7.74. Found: C, 78.35; H, 7.68.

(1*R*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-hydroxyl-3-isopropenyl-1,2,3,4-tetrahydro-naphthalene (25). Product **25** (0.278 g, 13%) was obtained as a clear oil. R_f = 0.62 (5:1, hexanes−EtOAc); $[\alpha]_D$ +15.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.03−7.82 (m, 14H, Ar), 5.22 (dd, 1H, $J_{1,2ax}$ = 9.7 Hz, $J_{1,2eq}$ = 5.8 Hz, H-1), 4.93 (s, 1H, alkene), 4.77 (br s, 1H, alkene), 3.10 (d, 1H, $J_{4ax,4eq}$ = 16.8 Hz, H-4ax), 2.68 (d, 1H, $J_{4ax,4eq}$ = 16.8 Hz, H-4eq), 1.87−2.00 (m, 2H, H-2ax, H-2eq), 1.72 (s, 3H, =CCH_3), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 150.9 (alkene), 136.2 (2 × Ar), 135.9 (2 × Ar), 135.2 (Ar), 134.8 (Ar), 134.6 (Ar), 133.0 (Ar), 132.9 (Ar), 130.1 (Ar), 129.8 (Ar), 129.6 (Ar), 129.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 125.8 (Ar), 109.4 (alkene), 74.5 (C-3), 69.4 (C-1), 42.7 (C-4), 40.4 (C-2), 26.6 (=CCH_3), 19.5 (*C*(CH_3)$_3$), 18.7 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{29}H_{34}O_2$SiNa: 465.2226 [M + Na]$^+$. Found: 465.2219.

(1*S*,3*S*)-1-*tert*-Butyldiphenylsiloxy-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (26). Alkene **24** (0.97 g, 2.19 mmol) was dissolved in CH_2Cl_2 and placed in a three-neck flask. The mixture was cooled to −78 °C, and ozone was bubbled through the solution for 5 min. Triethylamine (5.74 g, 21.9 mmol) was added, and the reaction mixture was further stirred for 24 h. The mixture was concentrated and purified by chromatography (20:1, hexanes−EtOAc) to yield **26** (0.73 g, 75%) as an oil. R_f = 0.53 (5:1, hexanes−EtOAc); $[\alpha]_D$ −29.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 6.80−7.80 (m, 14H, Ar), 5.25 (s, 1H, −OH), 4.96 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.8 Hz, H-1), 3.12 (br d, 1H, $J_{4ax,4eq}$ = 16.7 Hz, H-4ax), 3.01 (d, 1H, $J_{4ax,4eq}$ = 16.7 Hz, H-4eq), 2.35 (s, 3H, C(O)CH_3), 2.24 (ddd, 1H, $J_{2ax,2eq}$ = 14.3 Hz, $J_{1,2eq}$ = 3.8 Hz, $J_{2eq,4eq}$ = 2.0 Hz, H-2eq), 2.01 (dd, 1H, $J_{2ax,2eq}$ = 14.3 Hz, $J_{1,2ax}$ = 3.8 Hz, H-2ax), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 212.6 (C=O), 136.1 (4 × Ar), 135.3 (Ar), 134.8 (Ar), 133.1 (Ar), 132.6 (Ar), 132.5 (Ar), 130.2 (Ar), 129.9 (Ar), 129.6 (Ar), 129.5 (Ar), 129.4 (Ar), 128.0 (Ar), 127.7 (Ar), 127.6 (Ar), 126.1 (Ar), 78.5 (C-3), 70.0 (C-1), 38.9 (C-4), 37.6 (C-2), 26.9 (C(O)*C*H_3), 24.7 (*C*(CH_3)$_3$), 19.3 (C(*C*H_3)$_3$). ESI HRMS calcd for $C_{28}H_{32}O_3$SiNa: 467.2018 [M + Na]$^+$. Found: 467.2013.

(1*S*,3*S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-β-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (50). Yield 70%; R_f = 0.31 (3:1, hexanes−EtOAc); $[\alpha]_D$ −135.2 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.18−7.36 (m, 4H, Ar), 5.18−5.24 (m, 2H, H-4, H-1), 4.93 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.3 Hz, H-1$_a$), 4.45 (s, 1H, 3°-OH), 4.13 (q, 1H, $J_{5,6}$ = 6.4 Hz, H-5), 3.84 (ddd, 1H, $J_{2ax,3}$ = 13.0 Hz, $J_{3,4}$ = 4.7 Hz, $J_{2eq,3}$ = 3.4 Hz, H-3), 3.18 (d, 1H, $J_{4ax,4eq}$ = 17.0 Hz, H-4$_a$ax), 3.14 (d, 1H, $J_{4ax,4eq}$ = 17.0 Hz, H-4$_a$eq), 2.33 (s, 3H, C(O)CH_3), 2.25−2.28 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.19 (s, 3H, OC(O)CH_3), 2.07 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.0 Hz, $J_{1,2ax}$ = 4.1 Hz, H-2ax), 1.81 (dd, 1H, $J_{2ax,2eq}$ = 13.0 Hz, $J_{2eq,3}$ = 3.4 Hz, H-2eq), 1.22 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 211.9 (C=O), 170.3 (O*C*(O)CH_3), 133.8 (Ar), 131.6 (Ar), 129.9 (Ar), 129.2 (Ar), 129.1 (Ar), 126.1 (Ar), 94.2 (C-1), 77.9 (C-3$_a$), 71.9 (C-1$_a$), 69.8 (C-4), 65.8 (C-5), 54.2 (C-3), 38.9 (C-4$_a$), 36.1 (C-2$_a$), 29.3 (C-2), 24.5 (C(O)*C*H_3), 20.6 (OC(O)*C*H_3), 16.7 (C-6). ESI HRMS calcd for $C_{20}H_{25}N_3O_6$Na: 426.1641 [M + Na]$^+$. Found: 426.1638.

(1*S*,3*S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-β-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (51). Yield 39%; R_f = 0.38 (3:1, hexanes−EtOAc); $[\alpha]_D$ −157.3 (*c* 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.19−7.36 (m, 4H, Ar), 5.17 (d, 1H, $J_{1,2ax}$ = 4.1 Hz, H-1), 4.93 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.3 Hz, H-1$_a$), 4.72 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.7 Hz, H-4), 4.48 (s, 1H, 3°-OH), 3.82−3.96 (m, 2H, H-3, H-5), 3.18 (d, 1H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$ax), 3.06 (d, 1H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$eq), 2.35 (s, 3H, C(O)CH_3), 2.27−2.31 (m, 2H, H-2$_a$ax, H-2$_a$-eq), 2.16 (s, 3H, OC(O)CH_3), 2.07 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.1 Hz, $J_{1,2ax}$ = 4.1 Hz, H-2ax), 1.81 (dd, 1H, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2eq,3}$ = 4.1 Hz, H-2eq), 1.25 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 211.9 (C=O), 170.0 (O*C*(O)CH_3), 133.9 (Ar), 131.8 (Ar), 130.1 (Ar), 130.0 (Ar), 129.4 (Ar), 126.3 (Ar), 93.7 (C-1), 78.0 (C-3$_a$), 75.4 (C-1$_a$), 71.8 (C-4), 66.8 (C-5), 57.4 (C-3), 39.0 (C-4$_a$), 36.3 (C-2$_a$), 35.1 (C-2), 24.7 (C(O)*C*H_3), 20.9 (OC(O)*C*H_3), 17.5 (C-6). ESI HRMS calcd for $C_{20}H_{25}N_3O_6$Na: 426.1641 [M + Na]$^+$. Found: 426.1632.

(1*S*,3*S*)-1-*O*-(4-Azido-2,3,4,6-tetradeoxy-β-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (52). Yield 85%; R_f = 0.42 (3:1, hexanes−EtOAc); $[\alpha]_D$ −55.1 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.18−7.38 (m, 4H, Ar), 5.50 (d, 1H, $J_{1,2ax}$ = 3.0 Hz, H-1), 4.94 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.4 Hz, H-1$_a$), 4.78 (s, 1H, 3°-OH), 4.12 (dq, 1H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 3.54 (br s, 1H, H-4), 3.20 (d, 1H, $J_{4ax,4eq}$ = 17.1 Hz, H-4$_a$ax), 3.02 (d, 1H, $J_{4ax,4eq}$ = 17.1 Hz, H-4$_a$eq), 2.36 (s, 3H, C(O)CH_3), 2.22−2.31 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.07−2.16 (m, 1H, H-3ax), 1.90−2.02 (m, 2H, H-2eq, H-3eq), 1.42−1.49 (m, 1H, H-2ax), 1.30 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 212.2 (C=O), 133.8 (Ar), 132.2 (Ar), 130.2 (Ar), 130.0 (Ar), 129.1 (Ar), 126.1 (Ar), 94.2 (C-1), 78.2 (C-3$_a$), 71.4 (C-1$_a$), 66.1 (C-5), 59.8 (C-4), 39.0 (C-4$_a$), 36.0 (C-2$_a$), 24.7 (C(O)*C*H_3), 23.9 (C-3), 22.9 (C-2), 18.0 (C-6). ESI HRMS calcd for $C_{18}H_{23}N_3O_4$Na: 368.1586 [M + Na]$^+$. Found: 368.1583.

(1*S*,3*S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-β-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (53). Yield 57%; R_f = 0.33 (3:1, hexanes−EtOAc); $[\alpha]_D$ −91.1 (*c* 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.77−7.85 (m, 3H, Ar), 7.68 (s, 1H, Ar), 7.45−7.53 (m, 2H, Ar), 5.22−5.25 (m, 1H, H-4), 5.15 (d, 1H, $J_{1,2ax}$ = 4.0 Hz, H-1), 5.10 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.6 Hz, H-1$_a$), 4.43 (s, 1H, 3°-OH), 4.16 (q, 1H, $J_{5,6}$ = 6.6 Hz, H-5), 3.89 (ddd, 1H, $J_{2ax,3}$ = 13.1 Hz, $J_{3,4}$ = 4.8 Hz, $J_{2eq,3}$ = 4.0 Hz, H-3), 3.29 (d, 1H, $J_{4ax,4eq}$ = 16.6 Hz, H-4$_a$ax), 3.24 (d, 1H,

$J_{4ax,4eq}$ = 16.6 Hz, H-4$_a$eq), 2.39 (dd, 1H, $J_{2ax,2eq}$ = 14.8 Hz, $J_{1,2ax}$ = 3.6 Hz, H-2$_a$ax), 2.30 (dd, 1H, $J_{2ax,2eq}$ = 14.8 Hz, $J_{1,2eq}$ = 3.6 Hz, H-2$_a$eq), 2.25 (s, 3H, C(O)CH$_3$), 2.19 (s, 3H, OC(O)CH$_3$), 2.05 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.1 Hz, $J_{1,2ax}$ = 4.0 Hz, H-2ax), 1.78 (dd, 1H, $J_{2ax,2eq}$ = 13.1 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.27 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 211.5 (C═O), 170.5 (O*C*(O)CH$_3$), 133.8 (Ar), 131.8 (2 × Ar), 130.7 (Ar), 128.6 (Ar), 128.2 (Ar), 127.9 (Ar), 127.2 (Ar), 126.8 (Ar), 126.0 (Ar), 93.7 (C-1), 78.1 (C-3$_a$), 72.2 (C-1$_a$), 70.0 (C-4), 65.9 (C-5), 54.4 (C-3), 39.3 (C-4$_a$), 37.8 (C-2$_a$), 29.4 (C-2), 24.5 (C(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$), 16.9 (C-6). ESI HRMS calcd for $C_{24}H_{27}N_3O_6$Na: 476.1798 [M + Na]$^+$. Found: 476.1792.

(1*S*,3*S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (54). Yield 31%; R_f = 0.30 (3:1, hexanes−EtOAc); [α]$_D$ −110.4 (*c* 0.5, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.78−7.84 (m, 3H, Ar), 7.65 (s, 1H, Ar), 7.40−7.55 (m, 2H, Ar), 5.10 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.6 Hz, H-1$_a$), 5.02 (d, 1H, $J_{1,2ax}$ = 3.9 Hz, H-1), 4.74 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.8 Hz, H-4), 4.44 (s, 1H, 3°-OH), 3.88−4.00 (m, 2H, H-3, H-5), 3.30 (d, 1H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$ax), 3.24 (d, 1H, $J_{4ax,4eq}$ = 16.9 Hz, H-4$_a$eq), 2.28−2.43 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.26 (s, 3H, C(O)CH$_3$), 2.16 (s, 3H, OC(O)CH$_3$), 2.00 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.6 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2ax), 1.81 (dd, 1H, $J_{2ax,2eq}$ = 13.6 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.25 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 211.4 (C═O), 169.9 (O*C*(O)CH$_3$), 133.7 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.4 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.7 (Ar), 125.9 (Ar), 92.9 (C-1), 78.0 (C-3$_a$), 75.4 (C-1$_a$), 71.9 (C-4), 66.6 (C-5), 57.4 (C-3), 39.2 (C-4$_a$), 37.7 (C-2$_a$), 34.9 (C-2), 24.4 (C(O)-*C*H$_3$), 20.8 (OC(O)*C*H$_3$), 17.5 (C-6). ESI HRMS calcd for $C_{24}H_{27}N_3O_6$Na: 476.1798 [M + Na]$^+$. Found: 476.1793.

(1*S*,3*S*)-1-*O*-(4-Azido-2,3,4,6-tetradeoxy-*β*-L-*threo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (55). Yield 50%; R_f = 0.24 (5:1, hexanes−EtOAc); [α]$_D$ −28.9 (*c* 0.4, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.74−7.86 (m, 3H, Ar), 7.66 (s, 1H, Ar), 7.43−7.51 (m, 2H, Ar), 5.15 (d, 1H, $J_{1,2ax}$ = 3.5 Hz, H-1$_a$), 5.00−5.05 (m, 1H, H-1), 4.72 (s, 1H, 3°-OH), 4.15 (dq, 1H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.7 Hz, H-5), 3.56 (br s, 1H, H-4), 3.32 (d, 1H, $J_{4ax,4eq}$ = 16.0 Hz, H-4$_a$ax), 3.25 (d, 1H, $J_{4ax,4eq}$ = 16.0 Hz, H-4$_a$eq), 2.28−2.41 (m, 5H, H-2$_a$ax, H-2$_a$eq, C(O)CH$_3$), 2.22−2.31 (m, 2H, H-3$_a$ax, H-3$_a$eq), 2.12−2.22 (m, 1H, H-3eq), 1.90−2.00 (m, 2H, H-2ax, H-3ax), 1.40−1.47 (m, 1H, H-2eq), 1.35 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 211.9 (C═O), 133.7 (Ar), 131.8 (Ar), 131.6 (Ar), 130.8 (Ar), 128.8 (Ar), 128.2 (Ar), 127.9 (Ar), 127.1 (Ar), 126.6 (Ar), 125.9 (Ar), 93.3 (C-1), 78.3 (C-3$_a$), 71.4 (C-1$_a$), 66.1 (C-5), 59.9 (C-4), 39.4 (C-4$_a$), 37.2 (C-2$_a$), 24.6 (C(O)*C*H$_3$), 23.9 (C-3), 22.9 (C-2), 18.1 (C-6). ESI HRMS calcd for $C_{22}H_{25}N_3O_4$Na: 418.1743 [M + Na]$^+$. Found: 418.1737.

(1*S*,3*S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (56). Yield 31%; R_f = 0.17 (3:1, hexanes−EtOAc); [α]$_D$ +65.4 (*c* 0.3, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.11−7.48 (m, 4H, Ar), 5.12 (dd, 1H, $J_{1,2sx}$= $J_{1,2eq}$ = 2.9 Hz, H-1$_a$), 4.81 (dd, 1H, $J_{1,2ax}$ = 9.6 Hz, $J_{1,2eq}$ = 1.9 Hz, H-1), 4.70 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.5 Hz, H-4), 4.14 (s, 1H, 3°-OH), 3.48−3.61 (m, 2H, H-3, H-5), 3.10 (d, 1H, $J_{4ax,4eq}$ = 16.7 Hz, H-4$_a$ax), 2.99 (d, 1H, $J_{4ax,4eq}$ = 16.7 Hz, H-4$_a$eq), 2.36 (s, 3H, C(O)CH$_3$), 2.16−2.28 (m, 3H, H-2ax, H-2$_a$ax, H-2$_a$eq), 2.14 (s, 3H, OC(O)CH$_3$), 1.67−1.76 (m, 1H, H-2eq), 1.29 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 212.3 (C═O), 169.9 (O*C*(O)CH$_3$), 133.1 (Ar), 133.0 (Ar), 130.7 (Ar), 130.0 (Ar), 128.9 (Ar), 126.9 (Ar), 96.5 (C-1), 77.8 (C-3$_a$), 74.8 (C-1$_a$), 72.5 (C-4), 71.1 (C-5), 59.8 (C-3), 39.0 (C-4$_a$), 36.3 (C-2$_a$), 34.0 (C-2), 24.7 (C(O)*C*H$_3$), 20.9 (OC(O)*C*H$_3$), 17.6 (C-6). ESI HRMS calcd for $C_{20}H_{25}N_3O_6$Na: 426.1641 [M + Na]$^+$. Found: 426.1635.

(1*S*,*3S*)-1-*O*-(4-*O*-Acetyl-3-azido-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (57). Yield 19%; R_f = 0.15 (3:1, hexanes−EtOAc); [α]$_D$ +72.4 (*c* 0.2, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ_H 7.95 (s, 1H, Ar), 7.72−7.85 (m, 2H, Ar), 7.60 (s, 1H, Ar), 7.40−7.55 (m, 2H, Ar), 5.30 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 2.9 Hz, H-1$_a$), 4.85 (dd, 1H, $J_{1,2ax}$ = 9.6 Hz, $J_{1,2eq}$ = 1.9, H-1), 4.70 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.5 Hz, H-4), 4.00 (s, 1H, 3°-OH), 3.42−3.62 (m, 2H, H-3, H-5), 3.20 (s, 2H, H-4$_a$ax, H-4$_a$eq), 2.20−2.40 (m, 6H, H-2ax, H-2$_a$ax, H-2$_a$eq, *C*(O)CH$_3$), 2.15 (s, 3H, OC(O)CH$_3$), 1.67−1.80 (m, 1H, H-2eq), 1.30 (d, 3H, $J_{5,6}$ = 6.1 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 212.0 (C═O), 169.9 (O*C*(O)CH$_3$), 133.6 (Ar), 132.4 (Ar), 132.3 (Ar), 131.1 (Ar), 129.2 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.5 (Ar), 125.7 (Ar), 96.6 (C-1), 77.9 (C-3$_a$), 74.8 (C-1$_a$), 73.2 (C-4), 71.1 (C-5), 59.8 (C-3), 39.2 (C-4$_a$), 36.3 (C-2$_a$), 35.4 (C-2), 24.6 (C(O)*C*H$_3$), 20.9 (OC(O)*C*H$_3$), 17.5 (C-6). ESI HRMS calcd for $C_{24}H_{27}N_3O_6$Na: 476.1798 [M + Na]$^+$. Found: 476.1791.

(1*S*,3*S*)-1-*O*-(3-Azido-4-*O*-benzyl-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (62). Yield 46%; R_f = 0.32 (3:1, hexanes−EtOAc); [α]$_D$ −82.2 (*c* 1.0, CHCl$_3$). ^{1}H NMR (500 MHz, CDCl$_3$): δ_H 7.18−7.44 (m, 9H, Ar), 5.02 (d, 1H, $J_{1,2ax}$ = 4.1 Hz, H-1), 4.88−4.94 (m, 2H, H-1$_a$, PhC*H*$_2$), 4.67 (d, 1H, J = 10.5 Hz, PhC*H*$_2$), 4.55 (s, 1H, 3°-OH), 3.82−3.92 (m, 2H, H-3, H-5), 3.20 (d, 1H, $J_{4ax,4eq}$ = 16.1 Hz, H-4$_a$ax), 3.00−3.10 (m, 2H, H-4, H-4$_a$eq), 2.35 (s, 3H, C(O)-CH$_3$), 2.23−2.26 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.00 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.3 Hz, $J_{1,2ax}$ = 4.1 Hz, H-2ax), 1.81 (dd, 1H, $J_{2ax,2eq}$ = 13.3 Hz, $J_{2eq,3}$ = 4.1 Hz, H-2eq), 1.25 (d, 3H, J = 6.2 Hz, H-6). ^{13}C NMR (125 MHz, CDCl$_3$): δ_C 212.3 (C═O), 137.4 (Ar), 134.1 (Ar), 131.7 (Ar), 130.1 (Ar), 130.0 (Ar), 129.3 (Ar), 128.6 (2 × Ar), 128.4 (2 × Ar), 128.1 (Ar), 126.1 (Ar), 93.3 (C-1), 83.8 (C-4), 78.1 (C-3$_a$), 75.4 (Ph*C*H$_2$), 71.2 (C-1$_a$), 68.2 (C-5), 59.8 (C-3), 39.0 (C-4$_a$), 36.2 (C-2$_a$), 35.5 (C-2), 24.8 (C(O)*C*H$_3$), 18.2 (C-6). ESI HRMS calcd for $C_{25}H_{29}N_3O_5$Na: 474.2005 [M + Na]$^+$. Found: 474.2001.

(1*S*,3*S*)-1-*O*-(3-Azido-2,3,6-deoxy-*β*-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (63). Yield 91%; R_f = 0.31 (3:1, hexanes−EtOAc); [α]$_D$ −114.7 (*c* 0.8, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.18−7.37 (m, 4H, Ar), 5.13 (d, 1H, $J_{1,2ax}$ = 4.0 Hz, H-1), 4.90 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.4 Hz, H-1$_a$), 4.50 (s, 1H, 2°-OH), 4.01 (q, 1H, $J_{5,6}$ = 6.6 Hz, H-5), 3.70−3.80 (m, 2H, H-3, H-4), 3.15 (d, 1H, $J_{4ax,4eq}$ = 17.0 Hz, H-4$_a$ax), 3.02 (d, 1H, $J_{4ax,4eq}$ = 17.0 Hz, H-4$_a$eq), 2.32 (s, 3H, C(O)CH$_3$), 2.22−2.26 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.06 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.0 Hz, $J_{1,2ax}$ = 4.0 Hz, H-2ax), 1.75 (dd, 1H, $J_{2ax,2eq}$ = 13.0 Hz, $J_{2eq,3}$ = 4.0 Hz, H-2eq), 1.33 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6). ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 211.9 (C═O), 133.7 (Ar), 131.8 (Ar), 129.9 (Ar), 129.2 (Ar), 129.1 (Ar), 126.2 (Ar), 94.4 (C-1), 77.9 (C-3$_a$), 71.9 (C-1$_a$), 69.4 (C-4), 66.6 (C-5), 56.6 (C-3), 38.9 (C-4$_a$), 36.1 (C-2$_a$), 28.4 (C-2), 24.6 (C(O)*C*H$_3$), 16.7 (C-6). ESI HRMS calcd for $C_{18}H_{23}N_3O_5$Na: 384.1535 [M + Na]$^+$. Found: 384.1530.

(1*S*,3*S*)-1-*O*-(3-Azido-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-naphthalene (64). Yield 70%; R_f = 0.38 (3:1, hexanes−EtOAc); [α]$_D$ −74.6 (*c* 0.7, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.19−7.38 (m, 4H, Ar), 5.03 (d, 1H, $J_{1,2ax}$ = 3.5 Hz, H-1), 4.90 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.5 Hz, H-1$_a$), 4.54 (br s, 1H, 2°-OH), 3.68−3.83 (m, 2H, H-3, H-5), 3.13−3.21 (m, 2H, H-4, H-4$_a$ax), 3.01 (d, 1H, $J_{4ax,4eq}$ = 17.2 Hz, H-4$_a$-eq), 2.33 (s, 3H, C(O)CH$_3$), 2.23−2.27 (m, 2H, H-2$_a$ax, H-2$_a$eq), 2.00 (m, 1H, H-2eq), 1.69 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.9 Hz, $J_{1,2ax}$ = 3.5 Hz, H-2ax), 1.34 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ^{13}C NMR (100 MHz, CDCl$_3$): δ_C 212.1 (C═O), 133.9 (Ar), 131.8 (Ar), 130.0 (Ar), 129.9 (Ar), 129.2 (Ar), 126.1 (Ar), 93.6 (C-1), 78.0 (C-3$_a$), 75.9 (C-1$_a$), 71.4 (C-4), 68.4 (C-5), 60.0 (C-3), 38.8 (C-4$_a$), 36.1 (C-2$_a$), 34.8 (C-2), 24.6 (C(O)*C*H$_3$), 17.7 (C-6). ESI HRMS calcd for $C_{18}H_{23}N_3O_5$Na: 384.1535 [M + Na]$^+$. Found: 384.1531.

(1*S*,3*S*)-1-*O*-(3-Azido-2,3,6-deoxy-*β*-L-*lyxo*-hexopyranosyl)-3-acetyl-3-hydroxyl-1,2,3,4-tetrahydro-anthracene (65). Yield 61%; R_f = 0.34 (1:1, hexanes−EtOAc); [α]$_D$ −55.4 (*c* 0.2, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 7.77−7.86 (m, 3H, Ar), 7.67 (s, 1H, Ar), 7.45−7.52 (m, 2H, Ar), 5.09−5.16 (m, 2H, H-1$_a$, H-1), 4.50

(br s, 1H, 2°-OH), 4.08 (q, 1H, $J_{5,6}$ = 6.6 Hz, H-5), 3.82−3.87 (m, 1H, H-3), 3.76 (s, 1H, H-4), 3.37 (br s, 2H, H-4_aax, H-4_aeq), 2.38 (dd, 1H, $J_{2ax,2eq}$ = 14.7 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2_aax), 2.26−2.32 (m, 4H, H-2_aeq, C(O)CH_3), 2.05 (ddd, 1H, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 12.7 Hz, $J_{1,2ax}$ = 3.9 Hz, H-2ax), 1.75 (dd, 1H, $J_{2ax,2eq}$ = 12.7 Hz, $J_{2eq,3}$ = 3.9 Hz, H-2eq), 1.40 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 211.6 (C═O), 133.6 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.6 (Ar), 128.1 (Ar), 127.8 (Ar), 127.1 (Ar), 126.6 (Ar), 125.9 (Ar), 93.6 (C-1), 78.1 (C-3_a), 71.9 (C-1_a), 69.5 (C-4), 66.6 (C-5), 56.7 (C-3), 39.2 (C-4_a), 37.4 (C-2_a), 28.4 (C-2), 24.5 (C(O)*C*H_3), 16.8 (C-6). ESI HRMS calcd for $C_{22}H_{25}N_3O_5Na$: 434.1692 $[M + Na]^+$. Found: 434.1686.

(1*S*,3*S*)-1-*O*-(3-Azido-2,3,6-deoxy-*β*-L-*arabino*-hexopyranosyl)-3-acetyl-3-hydroxy-1,2,3,4-tetrahydro-anthracene (66). Yield 60%; R_f = 0.30 (1:1, hexanes−EtOAc); $[\alpha]_D$ −62.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H) 7.78−7.84 (m, 3H, Ar), 7.65 (s, 1H, Ar), 7.40−7.55 (m, 2H, Ar), 5.10 (dd, 1H, $J_{1,2ax}$ = $J_{1,2eq}$ = 3.5 Hz, H-1_a), 5.02 (d, 1H, $J_{1,2ax}$ = 3.5 Hz, H-1), 4.50 (br s, 1H, 2°-OH), 3.63−3.85 (m, 2H, H-3, H-5), 3.28−3.33 (m, 2H, H-4_aax, H-4_aeq), 3.20 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.5 Hz, H-4), 2.20−2.39 (m, 5H, H-2_aax, H-2_aeq, C(O)CH_3), 2.00 (m, 1H, H-2ax), 1.70−1.78 (m, 1H, H-2eq), 1.40 (d, 3H, $J_{5,6}$ = 6.2 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 211.7 (C═O), 133.7 (Ar), 131.7 (Ar), 131.6 (Ar), 130.6 (Ar), 128.5 (Ar), 128.2 (Ar), 127.8 (Ar), 127.1 (Ar), 126.6 (Ar), 125.8 (Ar), 92.9 (C-1), 78.1 (C-3_a), 76.6 (C-1_a), 71.6 (C-4), 68.4 (C-5), 60.0 (C-3), 39.2 (C-4_a), 37.5 (C-2_a), 34.7 (C-2), 24.5 (C(O)*C*H_3), 17.8 (C-6). ESI HRMS calcd for $C_{22}H_{25}N_3O_5Na$: 434.1692 $[M + Na]^+$. Found: 434.1688.

Cytotoxicity Assays. Compounds **8**−**13** were assayed against the MCF-7 breast cancer cell line using a cell proliferation assay that employs the bioreduction of a tetrazolium compound to a formazan to quantitate cell viability.[28] Cells (∼10 000/well) were incubated in the cell culture media (DMEM/high, 10% fetal bovine serum, 1% L-glutamine, 1% sodium pyruvate) in a 96-well plate for 24 h and then dosed with potential cytotoxic compounds in the serum-free media (DMEM-F12, 1 mg/mL human albumin, 5 mg/L human transferrin, 5 mg/L bovine insulin) and incubated for 72 h, at which point a solution of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) was added, and the plate was incubated for an additional 2 h. The dehydrogenase enzymes of viable cells reduce the MTS to formazan, which can be quantitated at 490 nm. When read against a control, this quantity has been shown to be a direct indication of the number of viable cells.

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Supporting Information Available: Experimental details for the preparation of compounds not described in the Experimental Section as well as associated characterization data, ^{1}H and ^{13}C NMR spectra of new compounds, and IC_{50} plots for **11**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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