Carbohydrate Derivatives of the Antitumour Alkaloid 9-Hydroxyellipticine

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The synthesis of L-arabinosyl derivatives of 2-naphthol and the quaternised ellipticines Celiptium (**2**) and Ellipravin (**3**) is reported. Naphth-2-yl 2′,3′,4′-tri-*O*-acetyl-α-L-arabinopyranoside was prepared under Königs–Knorr and Mitsunobu conditions in nonpolar aprotic solvents and using 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl fluoride as the glycosyl donor. These conditions were not applicable to the corresponding glycosidation reactions with the quaternised ellipticines **2** and **3** which are soluble only in polar solvents. Formation of the 9-(α-L-arabinopyranosyl)ellipticine derivatives **13** and **14** was achieved by using 2,3,4-tri-*O*-acetyl-L-arabinopyranosyl bromide in the presence of sodium methoxide in methanol. Improved yields were obtained under the same conditions by incorporation of an ether linker between the sugar and ellipticine to give derivatives **15** and **16**. The glycolate esters **17** and **18**, which were prepared using 2-(2′,3′,4′-tri-*O*-acetyl-α-L-arabinopyranosyl)glycolic acid, undergo hydrolysis suggesting that these compounds could function as prodrugs in vivo. Linear dichroism studies of the interaction of Celiptium (**2**) and the stable L-arabinosyl ellipticine derivatives **3**, **15** and **16** with calf thymus DNA are consistent with intercalation of the ellipticine chromophore, positioning the sugars at the 2- and 9-positions in the major and minor grooves of DNA.

Introduction

Ellipticine and 9-methoxyellipticine are plant alkaloids isolated from the leaves of the plant *Ochrosia elliptica*, of the *Apocynaceae* family.[1] While both compounds exhibit high in vitro anticancer activity against a number of experimental tumours,[2] poor aqueous solubility has precluded clinical trials with these compounds. Research to address this limitation identified hydroxylation at C-9, to give 9-hydroxyellipticine (**1**) (Figure 1, part a),[3] and quaternisation at N-2,[4] as key structural modifications that led to improved aqueous solubility, increased antitumour activity and altered tissue distribution. As a result of these studies, preclinical and clinical evaluations of a number of derivatives of 9-hydroxyellipticine have been carried out, with 9-hydroxy-*N*-methylellipticinium acetate (**2**) (Celiptium®, Figure 1, part a) having entered the market for the treatment of advanced breast cancer.[5,6]

9-Hydroxyellipticine (**1**) and derivatives exert their antitumour activity via a multi-faceted mechanism that includes DNA intercalation, the generation of DNA strand breaks and interference with the action of topoisomerase II.[7–10] DNA intercalation is believed to be a key interaction that is directly related to anticancer activity. However, in contrast to many other established DNA intercalators, there are no X-ray crystal structures or NMR solution structures of 9-hydroxyellipticine (**1**) or derivatives with DNA. Two recent studies have provided important information about the nature of the drug/DNA complex.[11,12] Spectroscopic studies[12] and theoretical calculations[11] have shown that the chromophore of **1** is oriented perpendicular to the helix axis, with the 9-OH group protruding into the minor groove and the pyridine nitrogen atom lying in the major groove.[11,12] The placement of these two functional groups in the DNA grooves allows for their use as chemical handles for the attachment of other DNA-targeting groups,

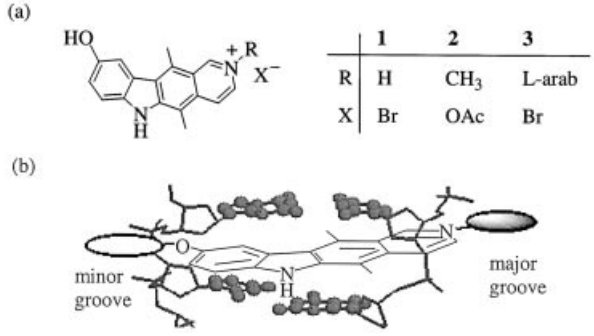

Figure 1. (a) 9-Hydroxyellipticine (**1**) and important clinical derivatives Celiptium® (**2**) and Ellipravin (**3**), where L-arab = α-L-arabinopyranosyl and (b) schematic drawing showing the relative orientation of the proposed major and minor groove binding groups at the 2- and 9-positions of ellipticines

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including groove binders, at these positions. Whilst a range of 2- and 9-substituted derivatives of **1** have been reported,[13] almost all derivatives contain simple alkyl and related substituents. One exception is the reported synthesis and in vitro screening of 40 *N*-glycosides of **1**.[14,15] Sugars were chosen for attachment to the ellipticine chromophore due to their prevalence in many antitumour drugs, and in order to improve aqueous solubility. 2-(α-L-Arabinopyranosyl)-9-hydroxyellipticinium bromide (**3**) (Ellipravin, Figure 1, part a) was selected from 40 glycosides for preclinical evaluation. Whilst no DNA-binding studies on **3** have been reported, modelling studies with oligonucleotides suggest that the sugar is located in the major groove.[16]

The establishment of the binding orientation of 9-hydroxyellipticine (**1**) with DNA provides the basis for the rational design of DNA threaders in which major and minor groove binding motifs are tethered to the ellipticine core (Figure 1, part b).[13] Carbohydrates are an attractive choice for the development of threaders of this type, due to the importance of sugars as groove binders in naturally occurring DNA-binding antitumour antibiotics,[17−19] and due to the significant improvements in aqueous solubility generally conferred by carbohydrates.[20] In addition, glycosylated phenols have been widely used in anticancer drug design.[21] While the exact mechanism and the mode of DNA binding of Ellipravin (**3**) are unknown, the high clinical activity of **3** has demonstrated that addition of carbohydrates to **1** has the potential to lead to novel antitumour derivatives. In this paper, we report the synthesis of six new carbohydrate derivatives of Celiptium (**2**) and Ellipravin (**3**) and preliminary DNA binding studies that confirm that these derivatives retain the ability to bind to DNA by intercalation. Of particular interest is the synthesis of a new ellipticine derivative containing two sugars, that is proposed to act as a DNA threading agent.

Results and Discussion

L-Arabinose was selected as the carbohydrate for synthetic studies, due to the demonstrated clinical activity of Ellipravin (**3**). Attachment of L-arabinose to the 9-hydroxy group of Celiptium (**2**) and Ellipravin (**3**)[15] by direct *O*-aryl glycosidation, and by the incorporation of both a short ester and a short ether linker between the sugar and the 9-position, were investigated.

Preparation of *O*-Aryl Glycosides

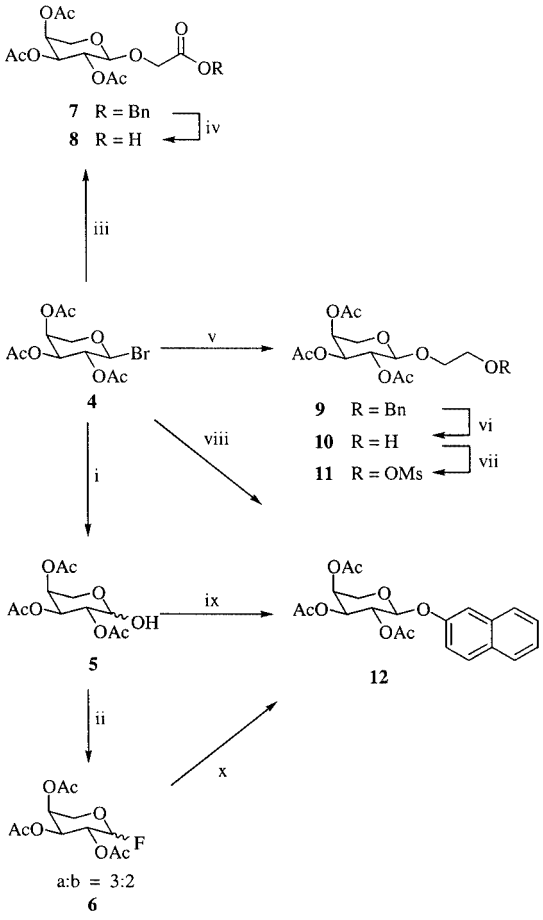
Given the limited availability of ellipticines **2** and **3**, the lack of solubility of these quaternised compounds in aprotic solvents that are generally favoured for glycosidations,[22] and the susceptibility of 9-hydroxyellipticines to oxidation, particularly under basic conditions,[8,10,13,23] glycosidation was initially investigated using 2-naphthol as a model system. The naphthyl *O*-glycoside **12** was prepared under Königs−Knorr conditions in low yield (9%) from the glycosyl bromide **4**[24] and 2-naphthol in the presence of silver carbonate (dichloromethane/diethyl ether, 1:1). Variation of the reaction conditions including the use of different solvents (toluene, acetone), the number of equivalents of reagents (1.2−5 equiv. of silver carbonate, 0.4−1.5 equiv. of sugar **4**) and the use of both silver carbonate and silver zeolite as insoluble promoters failed to significantly improve the yield of **12**. Celiptium (**2**) is insoluble in dichloromethane/diethyl ether, the most successful solvent system identified for the formation of the naphthyl-*O*-glycoside **12**. The reaction was nevertheless attempted with Celiptium (**2**) in dimethylformamide (DMF). However, there was no evidence for formation of the corresponding *O*-aryl glycoside using this solvent.

The low yields often observed in the synthesis of aryl glycosides are generally attributed to the poor nucleophilicity of the phenol functional group compared to alcohols in glycosidation reactions. This is a major contributing factor to the low observed yield in the synthesis of **12** using Königs−Knorr conditions. This limitation has been addressed recently by the application of the Mitsunobu protocol to the preparation of *O*-aryl glycosides of a number of naturally occurring DNA-binding antitumour antibiotics.[25] Using this procedure, the generation of the phenoxide ion under conditions that favoured an S_N2 pathway provided a highly efficient route for the stereoselective synthesis of aryl 2-deoxy-β-D-glycosides.

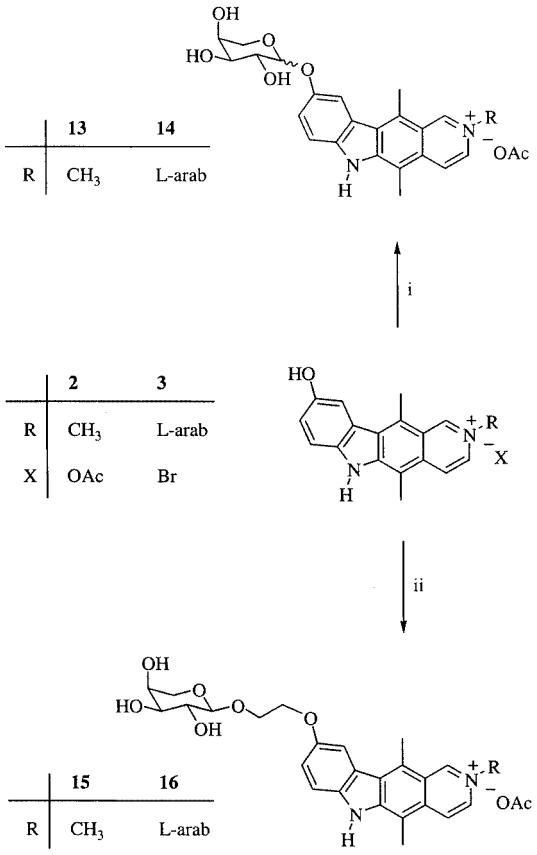
The Mitsunobu conditions[25] were first applied to the synthesis of the naphthyl *O*-glycoside **12** (Scheme 1). Treatment of hemiacetal **5**,[26] prepared by hydrolysis of the glycosyl bromide **4**, with 2-naphthol (diethyl azodicarboxylate, triphenylphosphane, 0 °C, tetrahydrofuran) afforded the desired aryl glycoside **12** in 39% yield. While this yield was higher than the yield of **12** prepared under Königs−Knorr conditions (9%), the reaction failed in DMF, the solvent of choice for the corresponding reaction with ellipticines **2** and **3**.

The third approach to form the *O*-aryl glycoside **12** involved the use of the glycosyl fluoride **6**. Glycosyl fluorides have attracted significant attention as they are readily prepared, stable to chromatography, and are excellent glycosyl donors in the presence of a range of activating agents.[22] The required glycosyl fluoride **6** was prepared as a mixture of anomers (α/β = 3:2) by treatment of hemiacetal **5** with (diethylamino)sulfur trifluoride at low temperatures (Scheme 1). Treatment of the fluoride **6** with boron trifluoride−diethyl ether followed by 2-naphthol afforded the *O*-aryl glycoside **12** in 10% estimated yield from analysis of the crude product. Due to the poor yield, this method was not investigated further.

The use of other glycosyl donors (trifluoroacetimidates,[27] thioglycosides[28]) was not investigated as glycosidations with these systems are not favoured in DMF or polar protic solvents, in which the quaternised ellipticines **2** and **3** are soluble. Similarly, initial formation of the *O*-aryl glycoside from the free-base 9-hydroxyelliptine (**1**) using the Schmidt procedure,[27] followed by *N*-glycosidation, is also problematic as **1** is also only soluble in DMF and polar protic solvents. Whilst the use of nucleophilic solvents is highly undesirable in glycosidation reactions, the single ex-



Scheme 1. (i) H_2O/acetone, Ag_2CO_3; (ii) (diethylamino)sulfur trifluoride, dichloromethane, −30 to 25 °C; (iii) $HOCH_2COOBn$, Ag zeolite, toluene, MS (4 Å); (iv) H_2, Pd/C, ethanol; (v) $HOCH_2$-CH_2OBn, Ag zeolite, toluene, MS (4 Å); (vi) H_2, Pd/C, ethanol; (vii) MsCl, NEt_3, tetrahydrofuran, 0 °C; (viii) $AgCO_3$, 2-naphthol, dichloromethane/diethyl ether (1:1); (ix) triphenylphosphane, diethyl azodicarboxylate, tetrahydrofuran, 2-naphthol; (x) boron trifluoride−diethyl ether, acetonitrile, 2-naphthol



Scheme 2. (i) **4**, sodium methoxide, methanol, 0 °C; (ii) **11**, sodium methoxide, methanol, 0 °C, where L-arab = α-L-arabinopyranosyl

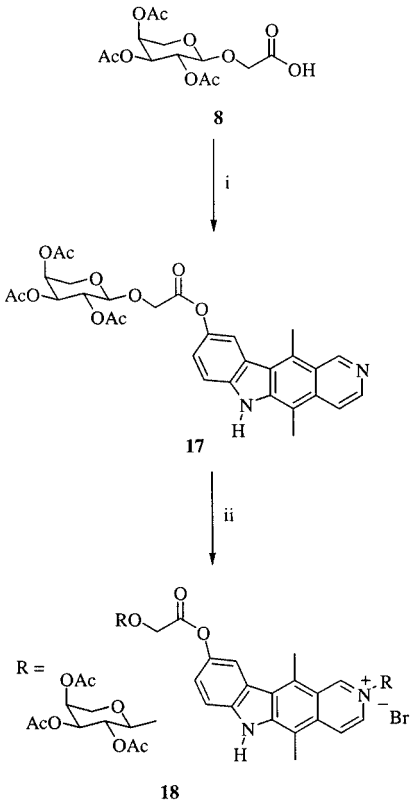
ample in the literature of *O*-glycosides of 9-hydroxyellipticine involved a low-yielding (20%) synthesis, which was accomplished by treatment of Celiptium (**2**) with a glycosyl bromide in sodium methoxide/methanol.[29] These conditions were originally reported for the *O*-glycosidation of 5-hydroxyindole[30] and were subsequently applied to the glycosidation of **2** to give *O*-aryl glycosides. Large excesses of the glycosyl bromides and short reaction times (< 5 min) were reported, presumably due to competing nucleophilic attack of the base and solvent on the sugar. Due to this literature precedent and the good solubility of Celiptium (**2**) and Ellipravin (**3**) in alcohols and water, these conditions were investigated for the synthesis of arabinosyl derivatives of 9-hydroxyellipticine.

The desired ellipticine *O*-aryl glycosides **13** and **14** were successfully prepared by treatment of Celiptium (**2**) and ellipravin (**3**), respectively, with sodium methoxide/methanol at 0 °C for 15 min in the presence of 5 equiv. of arabinosyl bromide **4** (Scheme 2). Rigorous exclusion of oxygen was required in all reactions in order to minimise oxidative degradation of ellipticine under these strongly basic conditions. In agreement with the literature,[29] a large excess of the glycosyl bromide **4**, short reaction times and low temperatures (0 °C) were essential in order to obtain the *O*-aryl glycosides **13** and **14**, which were identified by analysis of the NMR spectra and mass spectra of the crude products. However, insufficient material was obtained to allow these products to be fully characterised.

Preparation of Ester-Linked Glycosides

Given the difficulties in formation of the *O*-aryl glycosides outlined in Scheme 1, and the low overall yields of **13** and **14**, the synthesis of ester-linked derivatives of 9-hydroxyellipticine was investigated. The ester linkage was chosen as syntheses of numerous esters of 9-hydroxyellipticine (**1**) have been reported by reaction of **1** with a range of carboxylic acids in the presence of *N*,*N*′-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in DMF.[31] Hence, the carboxylic acid functional group was introduced into L-arabinose as shown in Scheme 1.

Reaction of benzyl glycolate with bromide **4** in the presence of silver zeolite afforded the protected glycoside **7** which was subjected to hydrogenolysis to give the carboxylic acid **8** in reasonable yield (Scheme 1). The acid **8** was treated with *N*,*N*′-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in DMF followed by 9-hydroxyellipticine (**1**), in the presence of a catalytic amount of (dimethylamino)pyridine to give the desired ester **17** in 17% isolated



Scheme 3. (i) (a) *N*,*N*′-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole, DMF, (b) **1**, (dimethylamino)pyridine or (a) thionyl chloride, (b) **1**, $CHCl_3$, NEt_3;(ii) **4**, $CdCO_3$, nitromethane

yield (Scheme 3). A slightly improved yield (23%) was obtained by initial conversion of the acid **8** to the corresponding acid chloride, which was immediately treated with 9-hydroxyellipticine in chloroform/triethylamine (3:1) to give the protected *O*-glycoside **17**. The isolated yield of ester **17** was lower than expected from analysis of the crude product by NMR spectroscopy, as significant hydrolysis of the ester to regenerate 9-hydroxyellipticine (**1**) occurred during purification by flash chromatography.

The protected *O*-glycoside **17** was treated with glycosyl bromide **4** under the literature conditions used for the preparation of **3**.[15] The crude product contained the peracetylated bis(glycoside) **18**, as evidenced by electrospray mass spectrometry (m/z = 837 [M^+]) and analysis of the product by NMR spectroscopy, but by-products resulting from cleavage of the glycolate ester were also observed. Analytically pure material could not be obtained, as attempted purification of **18** by HPLC in aqueous ammonium acetate and methanol resulted in quantitative hydrolysis of the ester bond. Attempted deacetylation of the *O*-glycoside **17** and the bis(glycoside) **18** by treatment with ammonia in methanol at low temperatures (−15 °C) also resulted in cleavage of the glycolic ester bond. This susceptibility of the glycolate ester bond to hydrolysis is presumed to arise from the increased electrophilicity of the carbonyl group due to the inductive, electron-withdrawing effect of the ether substituent on the α-carbon atom. Thus, while the protected esters **17** and **18** were prepared, the poor stability of the ester linker suggested that these compounds would hydrolyse in vivo and hence further chemistry on these compounds was not investigated.

Preparation of Ether-Linked Glycosides

Replacement of the ester linker with the hydrolytically stable ether functional group was achieved as shown in Scheme 2. Treatment of the arabinosyl bromide **4** with 2-(benzyloxy)ethanol afforded the protected arabinose derivative **9**, which was converted into the mesylate **11** under standard conditions via the alcohol **10** (Scheme 1). Initial attempts to synthesise **15** and **16** using mild bases (Cs_2CO_3, K_2CO_3) in DMF were unsuccessful. The ellipticine *O*-glycoside **15** and bis(glycoside) **16** were both successfully prepared by treatment of the 9-hydroxyellipticines **2** and **3**, respectively, with sodium methoxide in methanol at 0 °C for 15 min in the presence of 5 equiv. of mesylate **11** (Scheme 2).

The reaction conditions were optimised by monitoring the reaction of Celiptium (**2**) with mesylate **11** by electrospray mass spectrometry, as the positively charged ellipticines in the reaction mixture give strong positive molecular ions, allowing aliquots of the reaction to be rapidly analysed at short time intervals. The reaction time of 15 min, as well as the presence of at least 5 equiv. of the mesylate **4**, resulted in maximum formation of the glycoside **15**. With less than 5 equiv. of mesylate, unchanged and degraded starting materials were recovered, while prolonged reaction times (30 min to 2 h) resulted in the formation of a higher molecular weight peak by mass spectral analysis, corresponding to a bis(sugar) adduct of Celiptium (**2**) at the expense of the desired *O*-glycoside **15**; this by-product was not isolated or characterised. While the isolated yields of analytically pure **15** and **16** after HPLC were very low (< 5%), the small scale of the reactions and the purification of charged salts most likely contribute to this figure; the mass spectral analysis of the reaction with time suggest that the glycosides are formed in approximately 20% yield. Hence it is possible that on a larger scale an improved isolated yield could be obtained.

DNA-Binding Studies

The interactions of Celiptium (**2**), Ellipravin (**3**), *O*-glycoside **15** and bis(glycoside) **16** with calf thymus DNA (ct-DNA) were studied by flow linear dichroism (LD) spectroscopy. In this technique, the DNA is oriented with respect to the incident (linearly polarised) radiation allowing the interaction of the oriented DNA with a ligand that has absorption bands in the UV/Vis region to be monitored. Any ligand that becomes oriented as a result of becoming associated with the DNA will give rise to an LD signal in the chromophore absorption band of the ligand with an intensity that is usually proportional to the amount of bound ligand.[32,33]

LD has been used previously to study the interaction of the parent 9-hydroxyellipticine **1** with DNA.[12] Titration of a solution of **1** into a solution of ct-DNA at constant DNA

concentration showed that the binding mode is dependent on the ratio of the drug to the DNA base-pairs.[12] Initial titration studies with Celiptium (**2**) using LD and CD showed similar trends to those reported for 9-hydroxyellipticine (**1**) (data not shown). Hence, LD studies with ellipticines **2**, **3**, **15** and **16** were carried out at a drug/DNA ratio of 1:10. Under these conditions, all the potential intercalation sites are not saturated and a single binding mode is present.

Figure 2 shows the UV and LD spectra obtained on addition of each of the ellipticines **2**, **3**, **15** and **16** to ct-DNA. The UV spectra of the ellipticines (curve i, upper spectra) overlap with the DNA absorptions below 300 nm (data not shown). Upon addition of Celiptium (**2**) to DNA (Figure 2, part a, curve ii), the Celiptium (**2**) absorption maxima at 326, 371 and 465 nm shift to longer wavelengths, consistent with formation of a Celiptium/DNA complex. Similar trends are observed in the UV spectra of ellipticines **3**, **15** and **16** (Figure 2, parts b−d) in the presence of ct-DNA.

The lower curves in Figure 2 show the corresponding LD spectra of the ellipticine plus ct-DNA solutions (curve iii). In each case, the presence of an LD signal at wavelengths corresponding to the maxima in the absorbance spectrum of the ellipticine plus DNA solution is immediate evidence that all four ellipticines interact with DNA and become oriented. In addition, the negative LD signal for the aromatic transitions of the ellipticines above 300 nm, where there is no overlap with the DNA absorptions, necessitates that the ellipticine chromophore is more perpendicular than parallel to the DNA helical axis, consistent with intercalation between the base pairs. For comparison, groove binders typically exhibit strong variations of the LD signal with wavelength, giving both positive and negative signals.[32,33] Small increases in the LD signals of the four ellipticine/DNA complexes at 260 nm, compared with the LD of the DNA alone (data not shown), are also consistent with intercalation, which occurs due to lengthening or stiffening of the DNA about the intercalation site.

The LD^r spectra (the difference between the normal absorption spectrum and the linear dichroism spectrum), shown in the lower part of Figure 2 (curve iv) give further information about the binding mode. The relatively flat and negative LD^r spectra confirm the orientation of the ellipticine chromophores perpendicular to the long axis of the DNA. In addition, the increase in the LD^r signal at wavelengths corresponding to the ellipticines (i.e., > 300 nm in the region where there is no overlap with the DNA absorptions) in comparison to those due to the DNA, confirm lengthening and stiffening of the DNA, consistent with the intercalation of the compound. The strong similarity between the spectra in Figure 2, parts a−d indicates a similar mode of binding for all compounds.

From these data alone, the relative orientation of the ellipticine chromophores with respect to the DNA bases (i.e., whether the pyridine nitrogen atom projects into the major or the minor groove) cannot be determined. The characteristics of the DNA plus Celiptium (**2**) spectrum (Figure 2, part a) are almost identical to the published data for DNA plus 9-hydroxyellipticine **1**.[12] This is not surprising since the addition of a single methyl group at the 2-position, which converts **1** into **2**, would not be expected to alter the binding orientation of the compound with DNA. Further-

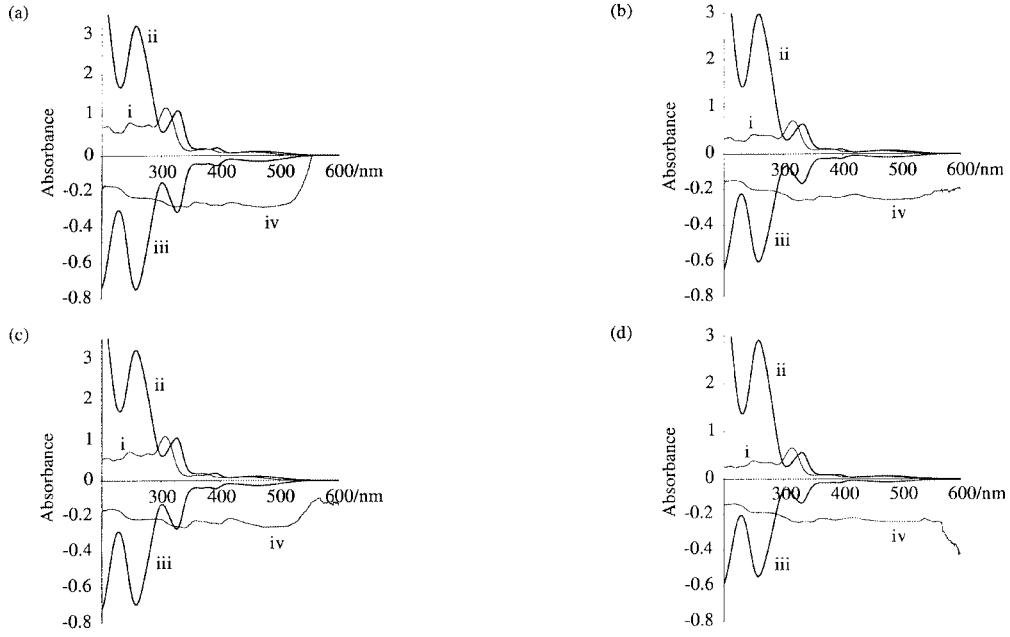


Figure 2. UV and LD spectra showing the binding of ellipticines **2** (a) **3** (b) **15** (c) and **16** (d) to calf thymus DNA at pH = 7; the UV spectra show the ellipticines (40 μM) (curve i) and the ellipticines (50 μM) in the presence of ct-DNA (500 μM) (curve ii); shown below are the corresponding LD spectra (curve iii) and LD^r spectra (curve iv) of the ellipticine plus DNA solutions; the LD spectra are multiplied by 10 to correct for different cell path lengths

more, the steric bulk of the additional glycosides in compounds **3**, **15** and **16** would be expected to strongly disfavour any orientation that does not allow these groups to project out into the grooves of the DNA.

The bis(glycoside) **16** is of particular interest as a new class of DNA-threading agent. Intercalation of the chromophore is only possible if the molecule threads through the DNA, positioning one sugar in the major groove and one sugar in the minor groove (see Figure 1, part b), with the potential to provide multiple sites of interaction between the DNA and the threader. Further structural characterisation of this complex, including the measurement of equilibrium association constants and dissociation rate constants would be informative in establishing whether the two sugars significantly increase the residence time of **16** on DNA compared with Celiptium (**2**).

Conclusion

The *O*-aryl ester- and ether-linked arabinosyl derivatives of Celiptium and ellipravin **13**−**18** represent a new class of derivatives of 9-hydroxyellipticine. While the limited stability of the ester derivatives **17** and **18** suggests that these compounds could function as pro-drugs in vivo, the stable bis(glycoside) **16** is of particular interest as a DNA threading agent; DNA intercalation of the ellipticine chromophore of **16** positions one sugar in the major groove and one sugar in the minor groove. While the impact on biological activity of the sugars at the 9-position in **13**−**16** cannot be predicted, the absence of the phenol functional group at the 9-position will prevent the formation of reactive quinone imines; formation and subsequent alkylation of these intermediates is a major pathway related to the cytoxicity of 9-hydroxyellipticines including **1** and **2**.[8,10] This change in chemical reactivity, as well as the effect of the new sugars on DNA binding, topoisomerase II poison activity and inhibition of p53 phosphorylation, should provide valuable information on the in vivo mechanism of action of the ellipticines and may identify new lead compounds with interesting biological activity profiles.

Experimental Section

General Remarks: Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried glassware using freshly distilled and purified solvents. Flash chromatography was performed on Merck silica gel (type 9385, 230−400 mesh). HPLC was performed using a Waters 600E Multisolvent Delivery System, a Rheodyne 7725i injector and a Waters 486 tuneable absorbance detector (254 nm analytical; 350 nm preparative), and Alltech Alltima C18 columns: analytical 5 micron column (250 mm × 4.6 mm i.d.), flow rate 0.8 mL min^{-1}; preparative 10 micron column (300 mm × 22 mm i.d.), flow rate 7 mL min^{-1}. The solvents used were 50 mM ammonium acetate buffer (solvent A) and methanol (solvent B). Melting points were determined using a Reichert heating stage and are uncorrected. Optical rotations were recorded at 25 °C with a Perkin−Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1}deg·cm^2·g^{-1}. Microanalyses were performed by the Microanalytical Unit at the University of Otago, New Zealand. Ultraviolet spectra were recorded with a Cary 4E UV/Vis/NIR spectrophotometer at 20 °C. Infrared spectra were recorded as thin films with a Perkin−Elmer 1600 Fourier transform spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker AC200 NMR spectrometer or a Bruker WM AMX 400 and referenced to the residual solvent peak. EI mass spectra were recorded with an AEI MS902 spectrometer, CI mass spectra were recorded with a ThermoQuest PolarisQ Ion Trap mass spectrometer and ES mass spectra were recorded with an LCQ Ion Trap mass spectrometer, using capillary voltages of +10 V (positive ion) and −10 V (negative ion). High-resolution mass spectra were recorded as follows. EI: 70 eV with a source temperature of 200 °C and a 5.3 kV accelerating voltage, using perfluorokerosene as the reference mass; ES: Kratos Analytical Concept ISQ mass spectrometer to a resolution of 7000 (10% valley definition); LSIMS: recorded using a 10 kV caesium ion primary beam, with *m*-nitrobenzoic acid as a liquid matrix and internal mass reference. 9-Acetoxyellipticine was a gift from Professor M. Ishiguro, Suntori Institute for Bioorganic Chemistry, Osaka and Celiptium (**3**) was provided by Sanofi Chimie, Sisteron.

2,3,4-Tri-*O*-acetyl-L-arabinose (5): Silver carbonate (54.5 mg, 0.198 mmol) was added to a stirred solution of bromide **4**[24] (44.0 mg, 0.130 mmol) in acetone (0.80 mL) and water (9.0 μL, 0.50 mmol) at 0 °C with minimum exposure to light. After 4 h, the insoluble silver salts were removed by filtration (0.45 μm Millipore filter) and the solvent removed to give hemiacetal **5**[26] (35.3 mg, 98%) as a cream-coloured oily solid; α/β = 1:2. ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.47 (d, $^3J_{1\beta,2}$ = 3.4 Hz, 1-H_β), 4.61 (d, $^3J_{1\alpha,2}$ = 7.5 Hz,1-H_α) ppm.

2,3,4-Tri-*O*-acetyl-L-arabinopyranosyl Fluoride (6): Hemiacetal **5** (390 mg, 1.4 mmol) was dissolved in dichloromethane (20 mL) and chilled to −30 °C with stirring under nitrogen. (Diethylamino)sulfur trifluoride (250 μL, 1.9 mmol) was added rapidly and the solution allowed to warm to room temperature. After 1 h, the solution was chilled to −30 °C and methanol (3 mL) added. The solvent was removed, the residue taken up in chloroform (60 mL), washed with water (5 × 40 mL), dried with anhydrous sodium sulfate and the solvent removed to give the crude product (370 mg). Purification by flash chromatography (dichloromethane) afforded sugar **6** (338 mg, 86%) as a clear oil; α/β = 3:2. $C_{11}H_{15}FO_7$ (278.2): calcd. C 47.48, H 5.43; found C 47.67, H 5.48. IR: $\tilde{\nu}_{max}$ = 1748 cm^{-1} (CO). ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 5.78 (dd, $^3J_{1\beta,2\beta}$ = 2.7, $^3J_{1\beta,F}$ = 54.5 Hz, 1-Hβ), 5.42 (m, 4-H), 5.37 (dd, $^3J_{3\beta,4\beta}$ = 3.4, $^3J_{3\beta,2\beta}$ = 10.7 Hz, 3-H_β), 5.30−5.22 (m), 5.16 (ddd, $^3J_{2\beta,1\beta}$ = 2.7, $^3J_{2\beta,3\beta}$ = 10.7, $^3J_{2\beta,F}$ = 29.8 Hz, 2-H_β), 4.12 (m), 3.88 (dd, $^3J_{5e,4}$ = 2.0, $^3J_{5e,5a}$ = 13.3 Hz, 5-H_e), 3.77 (ddd, $^3J_{5a,4}$ = 1.0, $^3J_{5a,5e}$ = 11.5 Hz, 5-H_a) 2.17−2.03 (m, 9 H, CH_3CO's) ppm. ^{19}F NMR (376 MHz, $CDCl_3$, 27 °C): δ = −133.7 (d, *J* = 49 Hz), −149.2 (dd, *J* = 23, *J* = 53 Hz) ppm. MS (EI): *m/z* (%) = 278 (3) [M^+], 259.0816 [M − F˙] {$C_{11}H_{15}O_7$ requires 259.0818}, 115 (100), 216 (5) [M − F − Ac].

2-(2′,3′,4′-Tri-*O*-acetyl-α-L-arabinopyranosyl)glycolic Acid (8): Silver zeolite (2 g) and activated 4-Å molecular sieves were added to a solution of benzyl glycolate (153 mg, 0.92 mmol) in toluene (12 mL) and the mixture stirred in the dark for 5 min at room temperature. A solution of bromide **4** (462 mg, 1.6 mmol) in toluene (30 mL) was added and the reaction mixture stirred at room temperature. Further portions of silver zeolite (1 g) were added after 11.5 h and 23 h. After 39 h, the reaction mixture was diluted with dichloromethane, filtered through silica, and the solvent was re-

moved to give the crude product (530 mg). Purification by flash chromatography (0.8 → 3% acetone in dichloromethane) afforded glycolate **7** as a white solid (342 mg, 87%). $[\alpha]_D^{20} = -14$ (c = 4.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 7.35 (s, 5 H, Ph), 5.3−5.2 (m, 2 H, 2′-H and 4′-H), 5.18 (s, 2 H, 2 × 2-H), 5.05 (dd, $^3J_{3',4'} = 3.5$, $^3J_{3',2'} = 9.3$ Hz, 1 H, 3′-H), 4.58 (d, $^3J_{1',2'} = 6.6$ Hz, 1 H, 1′-H_a), 4.32 (s, 2 H, PhCH_2), 4.02 (dd, $^3J_{5e',5a'} = 13$, $^3J_{5e',4'} = 3.5$ Hz, 1 H, 5′-H_e), 3.60 (dd, $^3J_{5a',5e'} = 12.8$, $^3J_{5a',4'} = 1.8$ Hz, 1 H, 5′-H_a), 2.12 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO) ppm. The glycolate **7** (328 mg, 770 μmol) was dissolved in ethanol (35 mL), Pd/C (10%, 320 mg) added and the mixture stirred under hydrogen for 15.5 h. The reaction mixture was filtered through Celite and the solvent removed to give the crude product (220 mg) which was dissolved in diethyl ether and extracted into saturated $NaHCO_3$. The combined aqueous extracts were acidified to pH = 3 with hydrochloric acid (10 M) and extracted into dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate and the solvent was removed to give sugar **8** (190 mg, 72%). $[\alpha]_D^{20} = -7.0$ (c = 6.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.30−5.20 (m, 2 H, 2′-H and 4′-H), 5.09 (dd, $^3J_{3',4'} = 3.5$, $^3J_{3',2'} = 9.3$ Hz, 1 H, 3′-H), 4.57 (d, $^3J_{1',2'} = 6.5$ Hz, 1 H, 1′-H), 4.34 (s, 2 H, 2 × 2-H), 4.06 (dd, $^3J_{5e',4'} = 3.3$, $^3J_{5e',5a'} = 13.1$ Hz, 1 H, 5′-H_e), 3.68 (d, $^3J_{5a',5e'} = 13.2$ Hz, 1 H, 5′-H_a), 2.15 (s, 3 H, CH_3CO), 2.11 (s, 3 H, CH_3CO) and 2.04 (s, 3 H, CH_3CO) ppm. MS (ES^-): m/z (%) = 668 (100) [M_2], 334 (72) [M]. MS (CI^-): m/z (%) = 334 (12) [M], 333 (100) [M − H], 291 (40) [M − Ac]. LSIMS: m/z = 335.0973 [M + H^+] {$C_{13}H_{19}O_{10}$ requires 335.0978}.

2′-(Benzyloxy)ethyl 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranoside (9): Silver zeolite (5.14 g) and molecular sieves (4 Å) were added to a solution of 2-(benzyloxy)ethanol (0.79 mL, 5.6 mmol) in toluene (50 mL). A solution of bromide **4** (3.20 g, 9.4 mmol) in distilled toluene (300 mL) was added and the mixture stirred at room temperature under nitrogen for 5 d, filtered through Celite and the solvent removed to give the crude product (3.46 g). Purification by flash chromatography (25 → 30% EtOAc in hexane) gave sugar **9** (2.05 g, 90%) as a clear oil. $[\alpha]_D^{20} = +5.8$ (c = 5.0, $CHCl_3$): IR: $\tilde{\nu}_{max}$ = 1742 (CO) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 7.28−7.21 (m, 5 H, Ph), 5.19−5.11 (m, 2 H, 2-H and 4-H), 4.97 (dd, ^3J = 3.5, 9.4 Hz, 1 H, 3-H), 4.48 (s, 2 H, PhCH_2), 4.46 (d, ^3J = 6.9 Hz, 1 H, 1-H), 4.00−3.86 (m, 3 H, 2 × 2′-H and 5-H_e), 3.73−3.52 (m, 3 H, 2 × 1′-H and 5-H_a), 2.06 (s, 3 H, CH_3CO), 1.95 (6 H, 2 × CH_3CO) ppm. MS (EI): m/z (%) = 410 (3) [M], 367.1389 [M − Ac] {$C_{18}H_{23}O_8$ requires 367.1393}, 91 (100).

2′-Hydroxyethyl 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranoside (10): Sugar **9** (1.54 g, 3.75 mmol) was dissolved in ethanol (150 mL), Pd/C (10%, 1.57 g) was added, and the mixture stirred under hydrogen for 22 h. The mixture was filtered through Celite and the solvent removed to give the crude product (1.23 g), which was purified by flash chromatography (0 → 2% methanol in dichloromethane) to give sugar **10** (1.15 g, 96%) as a cream-colored, crystalline solid; m.p. 90.5−91.5 °C. $[\alpha]_D^{20} = +53$ (c = 1.9, $CHCl_3$). $C_{13}H_{20}O_9$ (320.3): calcd. C 48.75, H 6.29; found C 49.03, H 6.44%. IR: $\tilde{\nu}_{max}$ = 1748 (CO) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.30−5.25 (m, 1 H, 4-H), 5.21 (dd, $^3J_{2,1} = 7.1$, $^3J_{2,3} = 9.6$ Hz, 1 H, 2-H), 5.05 (dd, $^3J_{3,4} = 3.5$, $^3J_{3,2} = 9.5$ Hz, 1 H, 3-H), 4.46 (d, $^3J_{1,2} = 6.9$ Hz, 1 H, 1-H), 4.05 (dd, $^3J_{5e,4} = 3.0$, $^3J_{5e,5a} = 13.1$ Hz, 1 H, 5-H_e), 3.92−3.73 (m, 4 H, 2 × CH_2), 3.66 (dd, $^3J_{5a,4} = 1.6$, $^3J_{5a,5e} = 13.2$ Hz, 1 H, 5-H_a), 2.15 (s, 3 H, CH_3CO), 2.08 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO) ppm. MS (EI): m/z (%) = 319.1030 [M − H] {$C_{13}H_{19}O_9$ requires 319.1029}, 73 (100).

2′-(Mesyloxy)ethyl 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranoside (11): Triethylamine (0.20 mL, 1.4 mmol) was added to a stirred solution of sugar **10** (41 mg, 0.13 mmol) in tetrahydrofuran (4 mL) at 0 °C under nitrogen, followed by dropwise addition of mesyl chloride (0.10 mL, 1.3 mmol) and the mixture was stirred at 0 °C for 2 d. The solvent was removed and the residue taken up in cold chloroform, washed with ice-cold water and dried with anhydrous sodium sulfate. Removal of the solvent afforded mesylate **11** as a clear oil in quantitative yield. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 5.30−5.25 (m, 1 H, 4-H), 5.19 (dd, $^3J_{2,1} = 6.8$, $^3J_{2,3} = 9.4$ Hz, 1 H, 2-H), 5.04 (dd, $^3J_{3,4} = 3.4$, $^3J_{3,2} = 9.3$ Hz, 1 H, 3-H), 4.48 (d, $^3J_{1,2} = 6.8$ Hz, 1 H, 1-H), 4.37 (t, $^3J = 4.5$ Hz, 4 H, 2 × 2′-H), 4.13−4.00 (m, 3 H, 5-H_e and 2 × 1′-H), 3.67−3.61 (m, 1 H, 5-H_a), 3.04 (s, 1 H, SO_2CH_3), 2.14 (s, 3 H, CH_3CO), 2.08 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO) ppm.

Naphth-2-yl 2′,3′,4′-Tri-*O*-acetyl-α-L-arabinopyranoside (12)

Mitsunobu Conditions: Triphenylphosphane (27.9 mg, 106 μmol) and diethyl azodicarboxylate (16.5 μL, 105 μmol) in tetrahydrofuran (0.15 mL) were added to a stirred solution of sugar **5** (23.8 mg, 86.2 μmol) and naphth-2-ol (10.1 mg, 70.1 μmol) in tetrahydrofuran (0.5 mL) at 0 °C, and the mixture was stirred at 0 °C for 2.75 h. Removal of the solvent afforded a cream-yellow oily solid which, upon purification by flash chromatography (dichloromethane), afforded glycoside **12** as a white solid (10.8 mg, 39%); m.p. > 300 °C. ^1H NMR (200 MHz, $CDCl_3$, 27 °C): δ = 7.77 (dd, ^3J = 1.5, 6.1 Hz, 2 H, aryl), 7.40 (m, 4 H, aryl), 7.20 (dd, ^3J = 2.4, 8.9 Hz, 1 H, aryl), 5.50 (dd, $^3J_{2',1'} = 6.2$, $^3J_{2',3'} = 8.7$ Hz, 1 H, 2′-H), 5.37 (m, 1 H, 4′-H), 5.25 (d, $^3J_{1',2'} = 6.1$ Hz, 1 H, 1′-H_a), 5.20 (dd, $^3J_{3',4'} = 3.3$, $^3J_{3',2'} = 8.7$ Hz, 1 H, 3′-H), 4.17 (dd, $^3J_{5e',4'} = 4.1$, $^3J_{5e',5a'} = 12.8$ Hz, 1 H, 5′-H_e), 3.81 (dd, $^3J_{5a',4'} = 2.1$, $^3J_{5a',5e'} = 12.8$ Hz, 1 H, 5′-H_a), 2.16 (s, 3 H, CH_3CO), 2.11 (s, 3 H, CH_3CO), 2.10 (s, 3 H, CH_3CO) ppm. MS(EI): m/z (%) = 402.1315 [M^+] {$C_{21}H_{22}O_8$ requires 402.1330}, 259 (13.8) [M − $OC_{10}H_7$], 144 (100) [$C_{10}H_7OH$], 43 (98.4) [CH_3CO].

Königs−Knorr Conditions: Silver carbonate (24.4 mg, 88 μmol) was added to a solution of sugar **4** (36.9 mg, 109 μmol) and naphth-2-ol (10.7 mg, 74 μmol) in diethyl ether/dichloromethane (1:1, 1.6 mL) over 4-Å molecular sieves. The mixture was stirred in the dark at room temperature for 25.5 h, passed through a layer of silica to remove the silver salts and the solvent removed to give the crude product (19.5 mg). Purification by flash chromatography twice (0 → 2% methanol in dichloromethane; 0 → 0.5% methanol in dichloromethane), gave compound **12** (2.7 mg, 9%), which showed similar spectral properties to that isolated using the Mitsunobu conditions.

Glycosyl Fluoride Route: Boron trifluoride−diethyl ether (50 μL, 400 μmol) was added to a solution of fluoride **6** (24 mg, 87 μmol) and naphth-2-ol (6.8 mg, 47 μmol) in acetonitrile (2 mL), and the mixture stirred under nitrogen for 7 d. The solvent was removed and the residue taken up in $CHCl_3$, washed with saturated $NaHCO_3$ and water, and dried with anhydrous sodium sulfate. Removal of the solvent gave the crude product (12.5 mg), which was purified by flash chromatography (0 → 1% methanol in dichloromethane) to afford impure **12** (3.1 mg) which was identified on comparison with authentic material prepared as described above.

9-(α-L-Arabinopyranosyl)-2-methyllipticinium Acetate (13): Ellipticinium (**2**) (20.0 mg, 59.5 μmol) was dissolved in distilled methanol (5.0 mL) and chilled to 0 °C with stirring under nitrogen. A solution of sodium methoxide in methanol (0.30 mL, 2.1 M, 630 μmol) was added, followed by glycosyl bromide **4** (105 mg, 310 μmol), and the reaction mixture stirred at 0 °C for 10 min. The solution

was diluted with diethyl ether (3.0 mL) and the precipitate retained. Mass spectral analysis of the crude product was consistent with the presence of glycoside **13**. ^{1}H NMR (400 MHz, CD_3OD, 27 °C): δ = 9.63 (1-H), 8.15 (3-H), 8.05 (4-H), 7.60 (10-H), 7.28 (7-H), 7.05 (8-H), 4.1−3.6 (m, H-sugars) ppm. MS (ES^+): *m*/*z* (%) = 409 (10) [M^+], 278 (100).

2-(α-L-Arabinopyranosyl)-9-(α-L-arabinopyranosyl)ellipticinium Acetate (14): Compound **3**[15] (14.5 mg, 24 μmol) was dissolved in methanol (8 mL) and chilled to 0 °C with stirring under nitrogen. A solution of sodium methoxide in methanol (0.255 mL, 0.94 M, 240 μmol) was added, followed by glycosyl bromide **4** (41.4 mg, 122 μmol), and the reaction mixture stirred at 0 °C for 15 min, then allowed to warm to room temperature for a further 10 min. The solvent was removed and the residue washed with dichloromethane to removed unchanged sugar starting material, yielding the crude product. This contained predominantly unchanged starting material **3**, with only trace amounts of the desired product **14** which could not be isolated in sufficient amounts to allow full characterisation. ^{1}H NMR (400 MHz, CD_3OD, 27 °C): δ = 9.66 (1-H), 8.22 (3-H), 7.90 (4-H), 7.90 (10-H), 7.50 (7-H), 7.30 (8-H) ppm. MS (ES^+): *m*/*z* (%) = 527 (11) [M^+], 395 (100) [M − arab$^+$].

9-(2′-[α-L-Arabinopyranosyl]ethyloxy)-2-methylellipticinium Acetate (15): Celiptium (**2**) (20.0 mg, 59.5 μmol) was dissolved in methanol (3.5 mL) and chilled to 0 °C with stirring under nitrogen. A solution of sodium methoxide in methanol (0.65 mL, 0.94 M, 610 μmol) was added, followed by a solution of mesylate **11** (119 mg, 297 μmol) in methanol (3.0 mL), and the solution stirred under nitrogen at 0 °C for 20 min. The solvent was removed, the residue washed with dichloromethane to remove unchanged sugar starting materials and the resultant crude product was purified by reverse phase HPLC (40−85% methanol in 25 mM ammonium acetate over 45 min). Integration of the analytical HPLC trace (254 nm) showed the *O*-glycoside **15** was the major product present (ca. 25%). Purification of a portion of the material gave a number of mixed fractions in addition to pure **15** which was isolated as an orange solid (1.8 mg, 6%). UV (H_2O): λ_{max} (ε) = 210 (14300), 247 (17900), 278 (16800), 307 (27300), 379 (3700), 439 (2300) nm (dm^3 mol^{-1} cm^{-1}). ^{1}H NMR (400 MHz, CD_3OD, 27 °C): δ = 9.85 (s, 1 H, 1-H), 8.40 (d, $^3J_{3,4}$ = 7.2 Hz, 1 H, 3-H), 8.26 (dd, $^3J_{4,1}$ = 1.2, $^3J_{4,3}$ = 7.2 Hz, 1 H, 4-H), 7.96 (d, $^3J_{10,8}$ = 2.3 Hz, 1 H, 10-H), 7.56 (d, $^3J_{7,8}$ = 8.8 Hz, 1 H, 7-H), 7.34 (dd, $^3J_{8,10}$ = 2.4, $^3J_{8,7}$ = 8.8 Hz, 1 H, 8-H), 4.49 (s, 3 H, 2-CH_3), 4.39 (d, $^3J_{1'',2''}$ = 6.9 Hz, 1 H, 1′′-H), 4.36 (t, $^3J_{2',1'}$ = 4.8 Hz, 2 H, −OCH_2CH$_2$OAr), 4.23 and 4.01 (2 dt, $^3J_{1',2'}$ = 4.8, $^3J_{1A',1B'}$ = 11.4 Hz, (2 × 1 H, −OCH$_2$CH_2OAr), 3.93 (dd, $^3J_{5e'',4''}$ = 3.1, $^3J_{5e'',5a''}$ = 12.5 Hz, 1 H, 5′′-H$_e$), 3.86−3.84 (m, 1 H, 4′′-H), 3.67 (dd, $^3J_{2'',1''}$ = 6.8, $^3J_{2'',3''}$ = 8.9 Hz, 1 H, 2′′-H), 3.61 (dd, $^3J_{5a'',4''}$ = 1.6, $^3J_{5a'',4''}$ = 12.5 Hz, 1 H, 5′′-H$_a$), 3.58 (dd, $^3J_{3'',4''}$ = 3.5, $^3J_{3'',2''}$ = 8.9 Hz, 1 H, 3′′-H), 3.33 (s, 3 H, 11-CH_3), 2.87 (s, 3 H, 5-CH_3), 1.90 (s, 3 H, $CH_3CO_2^-$) ppm. MS (ES^+): *m*/*z* = 453.2019 [M^+] {$C_{25}H_{29}N_2O_6$ requires 453.2026}.

9-[2′-(α-L-Arabinopyranosyl)ethyloxy]-2-(α-L-arabinopyranosyl)-ellipticinium Acetate (16): Compound **3** (70 mg, 0.12 mmol) was dissolved in methanol (25 mL) and chilled to 0 °C with stirring under nitrogen. A solution of sodium methoxide in methanol (1.1 mL, 1.075 M, 1.2 mmol) was added and the mixture stirred for 10 min. A solution of mesylate **11** (231 mg, 0.58 mmol) in methanol (20 mL) was added, and the solution stirred at 0 °C for 30 min. The solvent was removed and the residue washed with dichloromethane to remove unchanged sugar starting material. The crude product was dissolved in water and purified by reverse phase HPLC (40−85% methanol in 25 mM ammonium acetate over 45 min followed by 40−70% methanol in 25 mM ammonium acetate over 60 min) to give a number of impure samples containing **16**. Pure compound **16** was isolated from several fractions as an orange solid (2.0 mg, 3%). UV (H_2O): λ_{max} (ε) = 211 (6900), 211 (6900), 249 (9600), 314 (16500), 454 (1700) nm (dm^{3}mol^{-1}cm^{-1}). ^{1}H NMR (400 MHz, CD_3OD, 27 °C): δ = 9.87 (s, 1 H, 1-H), 8.48 (dd, $^3J_{3,1}$ = 1.2, $^3J_{3,4}$ = 7.5 Hz, 1 H, 3-H), 8.30 (d, $^3J_{4,3}$ = 7.5 Hz, 1 H, 4-H), 7.74 (s, 1 H, 10-H), 7.44 (d, $^3J_{7,8}$ = 8.6 Hz, 1 H, 7-H), 7.22 (dd, 1 H, $^3J_{8,10}$ = 2.0, $^3J_{8,7}$ = 8.5 Hz, 8-H), 5.69 (d, $^3J_{1''',2'''}$ = 8.7 Hz, 1 H, 1′′′-H), 4.42 (d, $^3J_{1'',2''}$ = 7.0 Hz, 1 H, 1′′-H), 4.34−4.24 (m, 4 H, 2 × 2′-H and 1′-H$_A$ and 5′′′-H$_e$), 4.12−4.09 (m, 2 H), 4.05−4.01 (m, 1 H, 1′-H$_B$), 3.99−3.97 (m, 1 H), 3.92 (dd, $^3J_{5e'',4''}$ = 3.0, $^3J_{5e'',5a''}$ = 17.7 Hz, 1 H, 5′′-H$_e$), 3.88−3.86 (m, 2 H, 4′′-H and 1 H), 3.70 (dd, $^3J_{2'',1''}$ = 7.0, $^3J_{2'',3''}$ = 8.9 Hz, 1 H, 2′′-H), 3.64 (dd, $^3J_{5a'',4''}$ = 1.6, $^3J_{5a'',5e''}$ = 14.4 Hz, 1 H, 5′′-H$_a$), 3.61 (dd, $^3J_{3'',4''}$ = 3.4, $^3J_{3'',2''}$ = 8.9 Hz, 1 H, 3′′-H), 3.21 (s, 3 H, 11-CH_3), 2.77 (s, 3 H, 5-CH_3), 1.92 (s, 3 H, $CH_3CO_2^-$) ppm. MS (ES^+): *m*/*z* = 571.2271 [M^+] {$C_{29}H_{35}N_2O_{10}$ requires 571.2292}.

Ellipticin-9-yl 2′-(2′′,3′′,4′′-Tri-*O*-acetyl-α-L-arabinopyranosyl)glycolate (17): Acid **8** (17.5 mg, 52 μmol), *N*,*N*′-dicyclohexylcarbodiimide (13.1 mg, 63 μmol) and 1-hydroxybenzotriazole (7.4 mg, 55 μmol) were dissolved in DMF (1.5 mL) and stirred at room temperature for 4.5 h. 9-Hydroxyellipticine (**1**) (11.6 mg, 44 μmol) and (dimethylamino)pyridine (0.5 mg, 4 μmol) were added and stirring was continued for 42.5 h. The solvent was removed and the residue taken up in dichloromethane. The organic soluble portions were combined and the solvent removed to give the crude product, which was purified by flash chromatography (0 → 20% methanol in dichloromethane) to give compound **17** as a yellow solid (4.3 mg, 17%). ^{1}H NMR (400 MHz, CD_3OD, 27 °C): δ = 9.58 (s, 1 H, 1-H), 8.34 (d, $^3J_{3,4}$ = 6.2 Hz, 1 H, 3-H), 8.11 (d, 1 H, $^3J_{10,8}$ = 2.0 Hz, 10-H), 7.98 (d, $^3J_{4,3}$ = 6.1 Hz, 1 H, 4-H), 7.54 (d, $^3J_{7,8}$ = 8.7 Hz, 1 H, 7-H), 7.32 (dd, 1 H, $^3J_{8,10}$ = 2.1, $^3J_{8,7}$ = 8.7 Hz, 8-H), 5.32 (d, ^3J = 1.3 Hz, 1 H, 3′′-H), 5.24−5.17 (m, 2 H, 2′′-H and 4′′-H), 4.83 (d, $^3J_{1'',2''}$ = 6.6 Hz, 1 H, 1′′-H), 4.67 (ABq, ^3J = 4.8 Hz, 2 H, 2 × 2′-H,), 4.08 (dd, $^3J_{5e'',4''}$ = 3.0, $^3J_{5e'',5a''}$ = 13.2 Hz, 1 H, 5′′-H$_e$), 3.86 (dd, $^3J_{5a'',4''}$ = 1.4, $^3J_{5a'',5e''}$ = 13.3 Hz, 1 H, 5′′-H$_a$), 3.18 (s, 3 H, 11-CH_3), 2.76 (s, 3 H, 5-CH_3), 2.16 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO) ppm. MS (EI): *m*/*z* (%) = 578.1893 [M^+] {$C_{30}H_{30}N_2O_{10}$ requires 578.1901}, 262 (100) [**1**]. MS (ES^+): *m*/*z* (%) = 579 (87) [M + H^+], 239 (100).

DNA-Binding Studies: Water was purified using a Millipore Alpha-Q system. Stock solutions of calf thymus DNA (ct-DNA) (1500 μM) and separate solutions of the ellipticines **2**, **3**, **15** and **16** (800 μM) were prepared in water. The DNA concentration in bases was determined spectroscopically using ε_{258} = 6600 mol^{-1} dm^3 cm^{-1}. UV and LD titrations were performed by preparing a solution of DNA (500 μM) and adding aliquots of both the DNA stock and ellipticine stock solutions to give solutions with a constant DNA concentration and the following ratios of ellipticine/DNA: 1:50, 1:40, 1:30, 1:20, 1:10 and 1:5. Titration solutions (pH = 7) contained NaCl (20 mM) and Na_2HPO_4 (1 mM).

UV Absorbance: UV spectra were recorded with a Cary 4E UV/Vis/NIR spectrophotometer at 20 °C in a 1-cm quartz cuvette. Blank spectra of the relevant solvent were collected and subtracted from the sample spectra. UV spectra of the ellipticines (40 μM) in water were also acquired.

Linear Dichroism (LD): LD spectra were measured with a Jasco J-710 spectropolarimeter, adapted for LD measurements. Orientation of the ellipticine/DNA samples was achieved in a flow Couette cell[34] with an inner rotating cylinder with a base plate adapted for the smaller compartment. The experimental path length was 1 mm

and the rotation speed was ca. 1000 rpm for all samples. A background spectrum of phosphate buffer, at the same rotation speeds as the samples, was collected and subtracted from all spectra. Data were collected with a response time of 0.5 s, at a speed of 1000 nm min^{-1} and a step resolution of 0.5 nm. Data were averaged over 16 acquisitions for all spectra. LD^r spectra were calculated using $LD^r(\lambda) = LD(\lambda)/A(\lambda)$, after adjustment of absorbance values due to different path lengths.

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