Synthesis of Prodigiosene-Estrogen Conjugates: optimization of protecting group strategies and anticancer properties

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Abstract

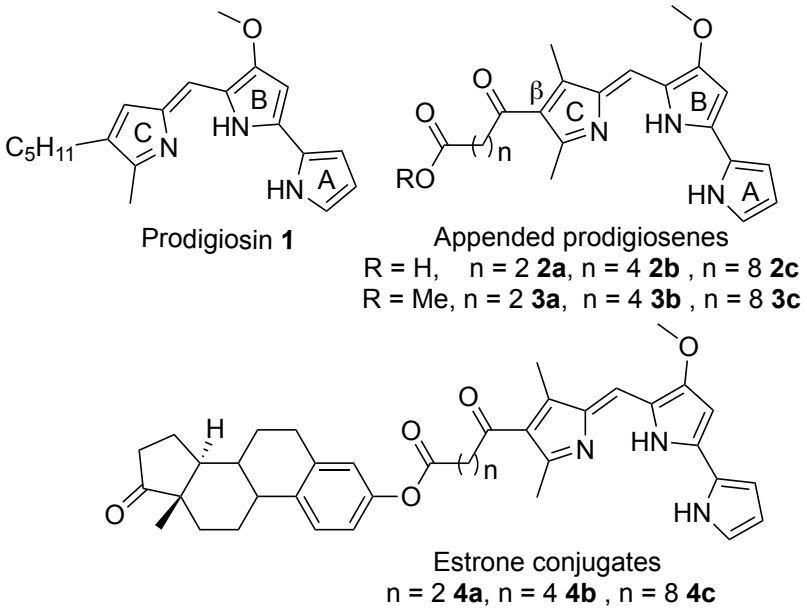
The tripyrrolic prodigiosene skeleton was conjugated to several estrogen ligands. The conjugation was achieved via an ester linker that proved to be unusually sensitive to hydrolysis during synthesis. This work describes the determination of an appropriate protecting group for the hydroxy groups of the estrogen linker. The anticancer properties of the target prodigiosene-estrogen conjugates were evaluated against breast cancer cells and some show selectivity for ER+ breast cancer cell lines.

Introduction

The conjugation of two biologically active molecules is a useful way to increase therapeutic efficacy, in some cases giving rise to a somewhat additive effect of the two drug moieties.[1,2] This strategy has also been used to increase drug selectivity. Undesired off-target toxicity is thus decreased since the relevant pharmacophore is conjugated to, and thereby hauled with, an appended structural unit that targets a specific tissue,[3] antigen[4,5] or receptor[6-12] of interest. Prodigiosin (**1**, Figure 2) is a red tripyrrolic natural product isolated from bacteria of the *Serratia* and *Streptomyces* genus, and it exhibits anti-cancer activity[13-16] as well as antimicrobial,[14,17] antimalarial,[18-20] and immunosuppressive activity.[21] However, *in vivo*

studies showed that prodigiosin exhibits a therapeutic window too narrow for use as an anticancer-drug (i.e., toxic dose too close to therapeutic dose).[22] We hypothesized that the conjugation of prodigiosin analogues (named prodigiosenes)[23] to targeting moieties could be used to target cancerous cells: in particular, conjugation to an estrogen derivative could allow increased selectivity of prodigiosenes for estrogen receptor-positive (ER+) breast cancers by acting as a carrier drug.[24]

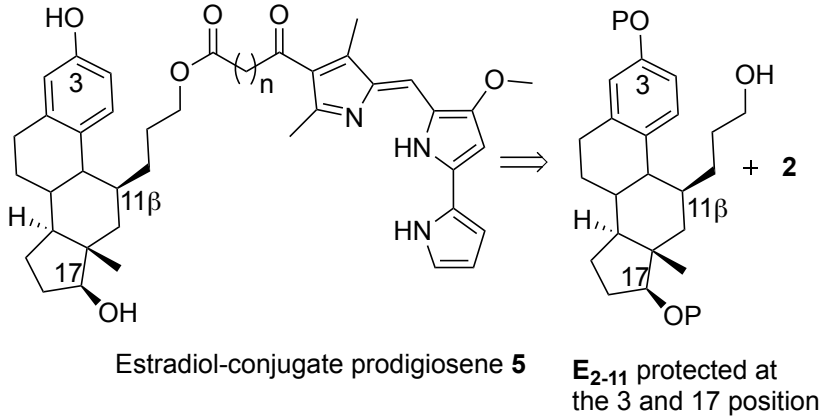
Figure 1. Natural product prodigiosin 1 and derivatives 2, 3 and 4.



In previous work, we developed the synthesis of appended prodigiosenes with a carboxylic acid linker attached via the beta position of the C-ring (**2**, Figure 1).[25] We also showed that the methyl esters (**3**) of these appended prodigiosienes maintain their anti-cancer activity.[26] Recently we developed a synthesis of prodigiosene conjugates and were able to obtain a series of estrone-appended prodigiosenes (**4**).[27] With these tools in hand, we decided to undertake the preparation of prodigiosenes conjugated to an estrogen derivative. For optimal binding to the estrogen receptor (ER) we envisioned the use of an estradiol (E_2) derivative with the two hydroxyl groups at the 3- and 17-positions remaining unprotected/uncapped. The fact that E_2 substituted with a propyl ester group at the 11β-

position maintains good binding affinity for both ERα and ERβ[28] guided our choice to link prodigiosenes via this position (**5**, Figure 3).

Figure 2. Estradiol conjugate prodigiosene 5.



Results and Discussion

Prodigiosene derivatives (**2a**, n = 2; **2b**, n = 4; and **2c**, n = 8, Figure 4) were prepared[27] ready for conjugation using estradiol (E_2), with a propanolic chain at the 11β-position as a targeting group (**E_{2-11}**, Figure 3). However, because of the presence of three hydroxy functionalities on **E_{2-11}**, careful choices of protecting groups were essential for successful coupling of the two partners, as well as subsequent deprotection. Our initial protecting group strategy involved benzyl ethers, as benzyl protected **E_{2-11}** (**9**, Figure 4).[28-30] Cognizant that hydrogenolysis using H_2/Pd/C would likely reduce the double bond of the dipyrrin moiety, we turned to the use of BCl_3 as it had been used for the deprotection of a benzyl-protected estradiol.[29] Indeed, we hoped that the benzyl ether might be selectively deprotected in the presence of an aliphatic ester,[31] as the deprotection of alkyl esters requires higher loadings of BCl_3, longer reaction times or higher temperatures.[32,33] We thus evaluated the utility of this deprotection strategy by using **8** as a model compound. As a control, treatment of estradiol **6** with BCl_3 in DCM at 0 °C (Figure 4a) gave complete conversion to the deprotected estradiol **7** after only 40 minutes. Pleasingly, under the same conditions, the ethyl ester prodigiosene **8** remained untouched (Figure 4b).

Figure 3. Attempt to synthesize a prodigiosene conjugated to E2-11.

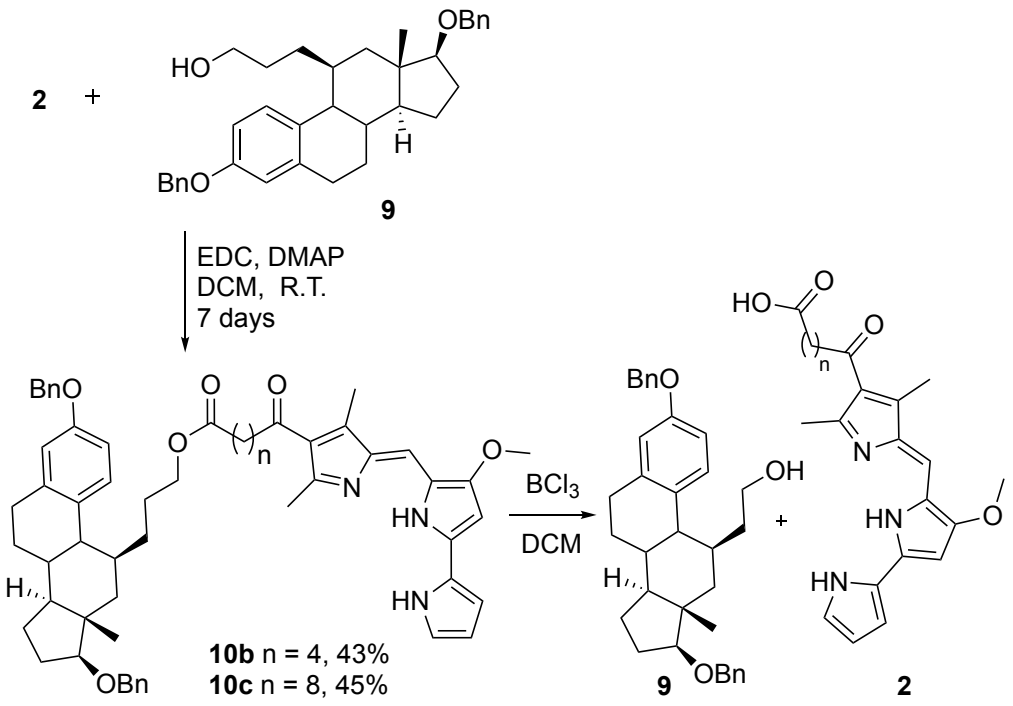
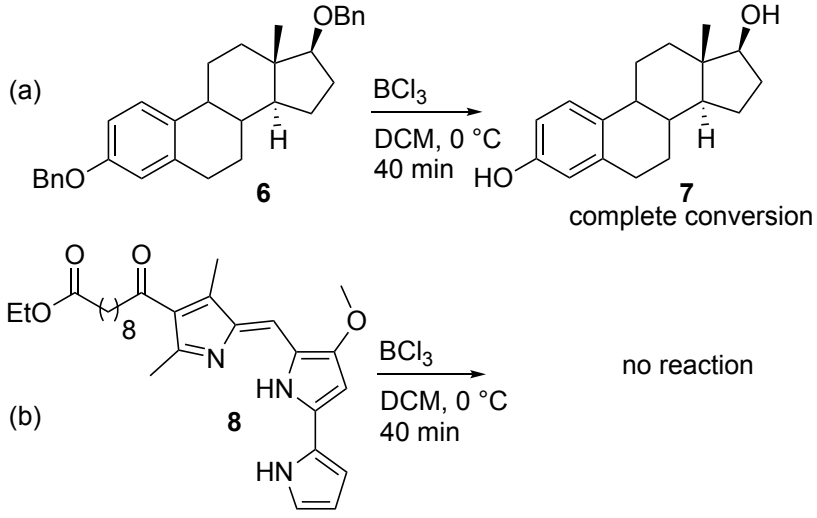


Figure 4. Evaluation of the use of BCl3 as a deprotecting agent.

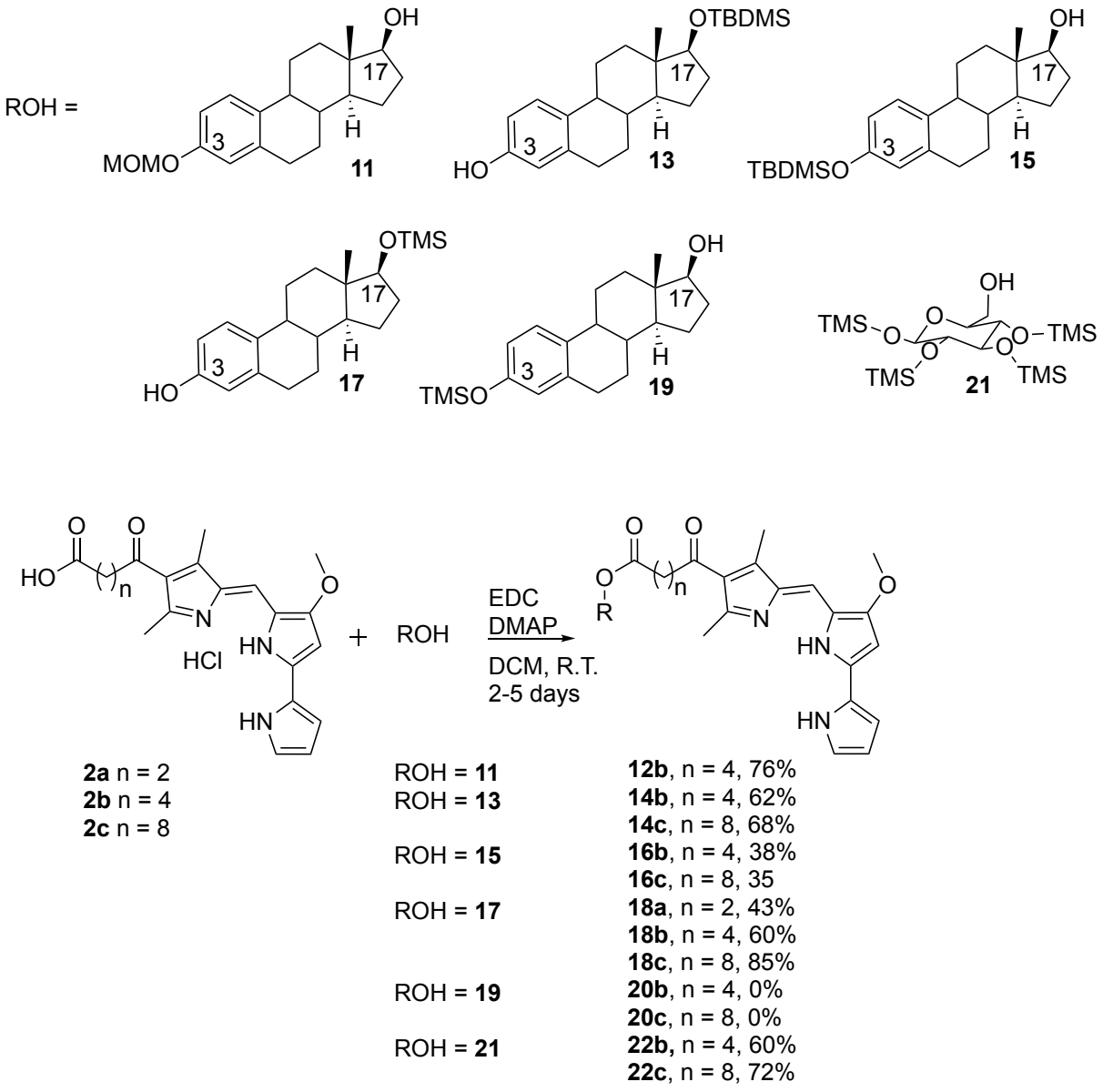


These results prompted us to prepare prodigiosenes conjugated to the benzyl-protected estradiol (**9**). We thus attempted the benzyl deprotection of conjugates **10b** and **10c** using the successful conditions shown in Figure 4. Unfortunately, the desired deprotection of the benzyl ether was accompanied by hydrolysis of the ester linker, with only traces of the desired conjugate observed. This unexpected result, given the robustness of **8** under these conditions,

implied that to find a suitable protecting group we would have to assess deprotection conditions using a prodigiosene conjugated to an estrogen derivative, or a bulkier group than the simple alkyl group of **8**. To find deprotection conditions that were compatible with an ester linkage, we worked with the readily available E_2. Each E_2 hydroxyl group can be independently protected, leaving the other alcohol amenable to coupling.[34-36] Consequently, deprotection conditions for each hydroxyl group (phenol at the 3-position and secondary alcohol at the 17-position) could be evaluated within the corresponding conjugate. Glucose was also chosen as a functional model: courtesy of the higher glucose metabolic rate of cancer cells compared to healthy cells,[37] glucose may also be used as a targeting moiety for improved drug selectivity for cancer cells.[38,39]

Esterification occurred in moderate-good yield, both at the phenolic and 17-OH positions when a MOM or TBDMS protecting group was used (**12b**, **14b**, **14c**, **16b** and **16c**, Figure 6). E_2 protected with a TMS group at the 17-position (**17**) underwent esterification to give conjugates **18a-c** in good yield. However, attempted esterification of **19**, featuring a TMS-protected phenol, was incomplete after five days and only traces of an albeit impure product was isolated (**20b** and **20c**). Presumably the sterically encumbered environment of the hydroxyl group at the 17-position results in reduced reactivity of **19**.

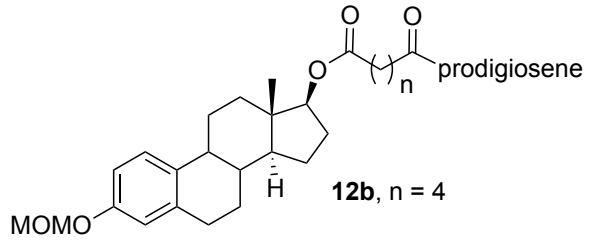
Figure 5. Synthesis of protected prodigiosene conjugates.



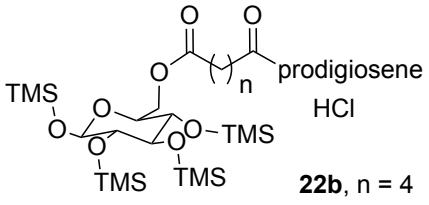
We then turned our attention to the deprotection of the prodigiosene conjugates **12**, **14**, **16**, **18** and **22** (**Figure 6** and **Table 1**). Deprotection of the MOM protecting group is often achieved using harsh acidic conditions.[40] Such exposure in this case led to complete and unwanted hydrolysis of the ester linkage **12b** (Entry 1, **Table 1**). We consequently investigated the use of the more labile TBDMS protecting group. Deprotection of a TBDMS group at the phenolic position of an estradiol derivative was previously reported using a high loading of TFA in DCM for 8 h.[10] Fearing that these harsh condition would cleave the ester linker of our conjugates, we investigated the use of weaker acids such as formic acid[41] (Entry

2) and citric acid (Entry 3), yet no reaction occurred. We thus attempted the use of a strong acid in slight excess (Entry 5 and 6). Pleasingly, in the presence of 3 equivalents of HCl in MeOH/$CHCl_3$ deprotection of the alcohol at the phenolic position of **16c** occurred in 20 hours to give **24c** in 27% isolated yield (Entry 5). Using the same conditions, only 3 hours were required for the deprotection of the alcohol at the 17-position of **14b** (Entry 6). The formation of the methyl ester of prodigiosene **2b** and **2c** was also observed (20% and 10% yield, respectively). It seems that even slightly acidic reaction conditions induce ester hydrolysis or direct transesterification with methanol to form the methyl ester of prodigiosenes (**3b** and **3c**).

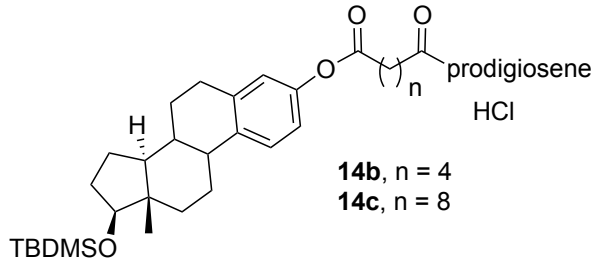
Figure 1. Structure of protected conjugates 12, 14, 16, 18 and 22 and deprotected conjugates 23, 24 and 25.



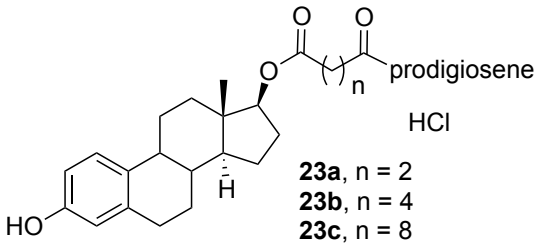
12b, n = 4



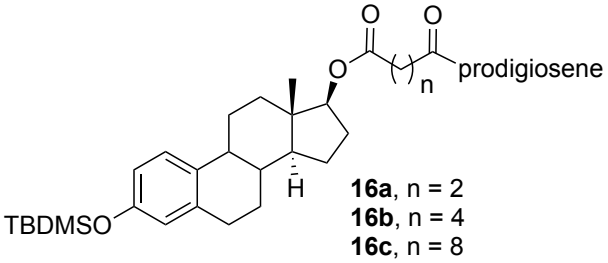
22b, n = 4



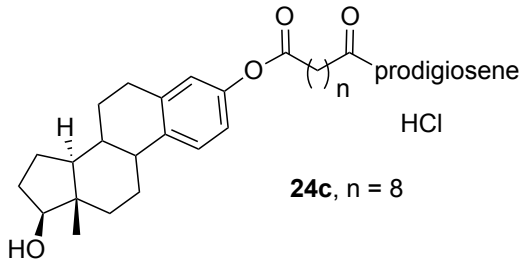
14b, n = 4
14c, n = 8



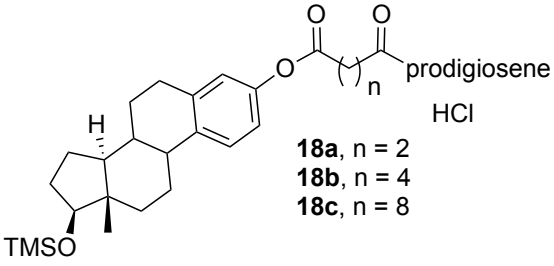
23a, n = 2
23b, n = 4
23c, n = 8



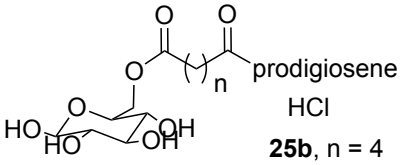
16a, n = 2
16b, n = 4
16c, n = 8



24c, n = 8



18a, n = 2
18b, n = 4
18c, n = 8



25b, n = 4

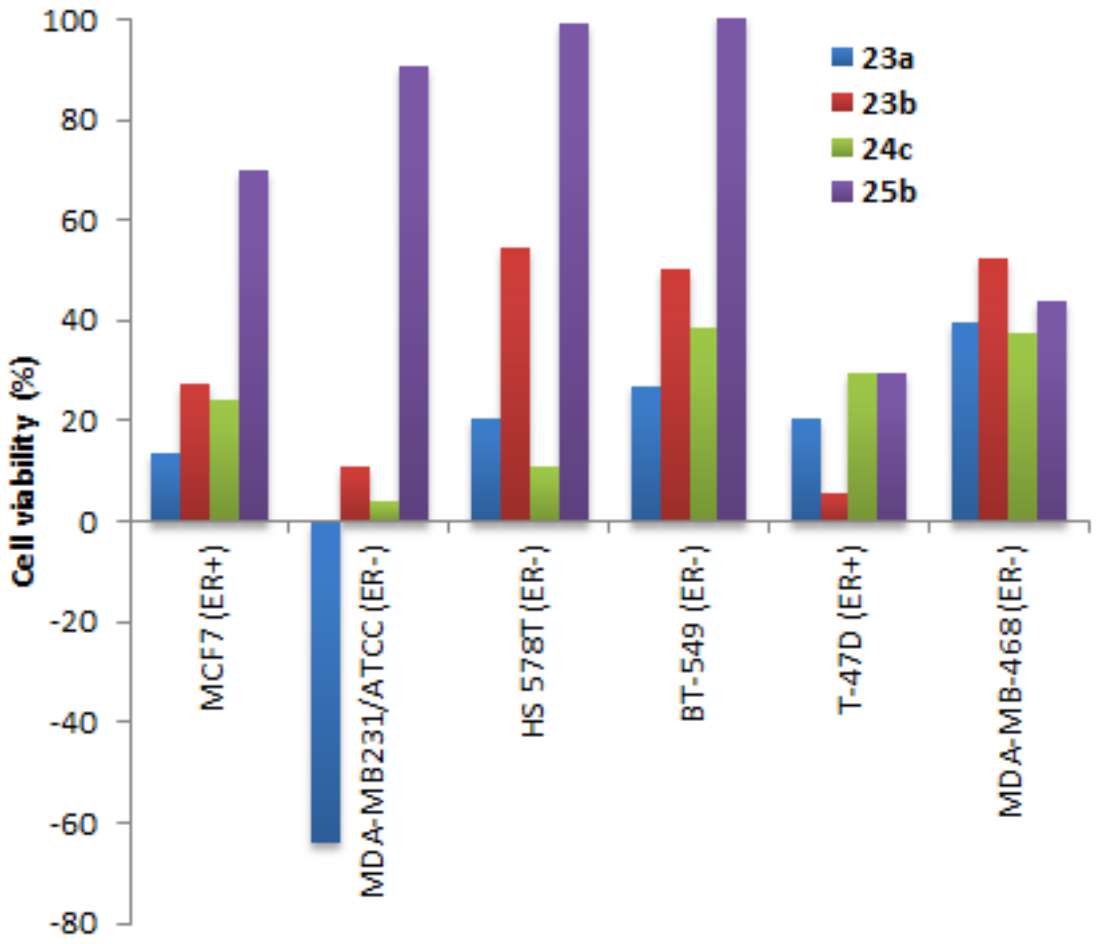
The use of various fluoride anion sources was also investigated as a strategy by which to cleave the TBDMS group in a controlled manner. However, the use of acidic HF-pyridine complex[42,43] quickly led to hydrolysis (Entry 4), as did TBAF (Entry 7).[44,45] Furthermore, our ester linkage was found to be sensitive to basic conditions, as confirmed when attempting the TMS deprotection of **22b** using a catalytic amount of K_2CO_3 (Entry 8).

As mildly acidic conditions may be more suited to the presence of a labile ester linkage we then investigated the use of 3 equivalents of HCl in $MeOH/CHCl_3$ for the TMS deprotection of the glucose conjugate **22b (**Entry 9). After a few minutes, complete deprotection occurred and the conjugate **25b** was isolated in 88% yield with no evidence of hydrolysis or transesterification by methanol. The same procedure was successfully applied for the TMS deprotection of compounds **18a-c** (Entry 10-12). This procedure was preferred to the use of TFA (Entry 13) as it was quicker and allowed the facile isolation of the prodigiosene conjugates as their HCl salts, which were stable to hydrolysis during the work-up conditions and following isolation. Having identified a protecting group compatible with the ester coupling conditions and that could be easily removed without ester cleavage, we undertook the preparation of an $\mathbf{E_2}$-11 O-protected at the 3- and 17-positions with TMS groups. However, due to the lability of the TMS group the expected estradiol remained elusive.

Using these strategies, five new prodigiosene-conjugates were obtained. The fact that the estrone-conjugate **4a** exhibited a GI_{50} value of 1.91 ±0.04 μM against the breast cancer cell line MCF-7,[27] prompted us to investigate the anticancer activity of some of these new conjugates. Thus the cell viability of six breast cancer cell lines was evaluated after treatment at 10 μM with estradiol-prodigiosene conjugates **23a**, **23b** and **24c** as well as the glucose-prodigiosene conjugate **25b** (**Figure 7**). The screening was conducted by the National Cancer Institute (NCI) and the panel contains estrogen receptor positive (ER+: MCF-7 and T-47D)

and estrogen receptor negative (ER-: MDA-MB231/ATCC, HS 578T, BT-549, MDA-MB-468) cell lines.

Figure 7. Cell Viability. Cell viability following treatment of breast cancer cells (MCF-7, MDA-MB231/ATCC, HS 578T, BT-549, T-47D, MDA-MB-468) with 10 μM of prodigiosene conjugates **23a**, **23b**, **24c** and **25b** (http://dtp.cancer.gov).



The estradiol prodigiosene conjugates **23a**,**b** and **24c** proved to be efficient at reducing the growth of breast cancer cells, with cell viability below 54% across the panel (**Figure 7**). Surprisingly high activity was observed against the MDA-MB231/ATCC cell line. This activity parallels that of the estrone-conjugate **4a**.[27] When looking at the five other breast cancer cell lines, the highest levels of activities for compounds **23a**,**b** were against MCF7 and T-47D cells. The glucose conjugate **25b** seems active only against two cell lines: T-47D and MDA-MB-468. Considering the promising results obtained for the estradiol conjugates tested

at 10 μM, the GI_{50} (half maximal growth inhibition) for **23a**,**b** and **24c** was also determined against the same breast cancer cell lines (Table 2). A lack of selectivity between the cancer cell lines was observed for compound **24c** (estradiol conjugated at the 17-OH position) with GI_{50} between 0.3 and 0.5 μM. However, compounds **23a** and **b** (estradiol conjugated at the phenolic position) exhibited some selectivity for the MCF-7 estrogen receptor positive cell line with a GI_{50} value of 0.9 μM. Again, a surprisingly high activity is observed for conjugate **23a** against the triple negative cell line MDA-MB231. The linker chain length seems to play a minor role in the activity of the conjugate as **23a** (two carbon linker) and **23b** (four carbon linker) present close GI_{50} values. However, the use of a four carbon linker for the next generation of estrogen-derived conjugates shows promise, considering that the conjugate **23b** exhibits the most promising GI_{50} values for all ER+ cell lines in the panel (MCF-7: 0.9 μM and T-47D: 1.4 μM).

Conclusions

In conclusion, we report the design and synthesis of prodigiosenes conjugated to an estradiol derivative ($E_{2\text{-}11}$) to increase the affinity of prodigiosene for ER+ breast cancer cells. This synthesis required careful choice of protecting groups for the alcohol functionality of the estradiol. Using E_2 as a model, we found that the ester linker was extremely sensitive to basic conditions and Lewis acids, and moderately sensitive to Brønsted acidic conditions. The use of Bn, MOM and TBDMS protecting groups would appear to be compatible with the esterification reaction, yet their deprotection in the presence of the sensitive ester and dipyrrinato moieties resulted in cleavage of the ester linker. We found that TMS ethers could be deprotected upon rapid exposure to 3 equivalents of HCl, thereby minimizing hydrolysis and favoring the formation of the HCl salt of the prodigiosene conjugate. We were pleased to see that estradiol-prodigiosene conjugates inhibit the growth of breast cancer cells with some

selectivity for ER+ lines, even though the position of the linker was not optimal, i.e. conjugation to the phenoxy group involved in the binding of the estrogen with its receptor. These observations regarding the robustness and manipulation of protecting groups will be applied to the synthesis of prodigiosenes bearing conjugates optimized for interaction with ER+.

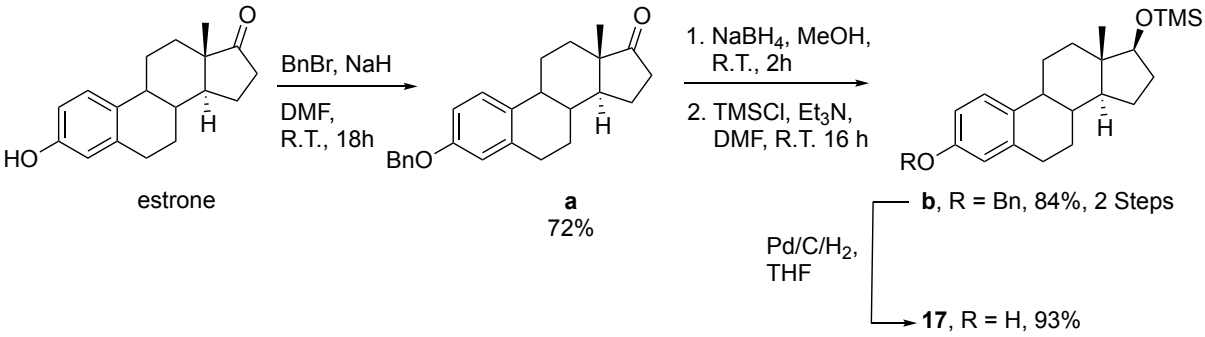
Experimental Section

General methods

All chemicals were purchased and used as received unless otherwise indicated. Moisture sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Flash chromatography was performed using Silicycle ultra pure silica (230-400 mm) or 150 mesh Brockmann III activated neutral alumina oxide as indicated. The NMR spectra were recorded using 500 MHz and 300 MHz spectrometers using $CDCl_3$, DMSO-d_6, MeOD or D_2O as solvent and are reported in part per million (δ) using the solvent signals at: 7.26 ppm for ^1H and at 71.16 ppm for ^{13}C while $CDCl_3$ was used; at 2.50 ppm for ^1H and at 39.52 ppm for ^{13}C while DMSO-d_6 was used; at 3.31 ppm for ^1H and at 49.00 ppm for ^{13}C while MeOD was used; and at 4.79 ppm for ^1H while D_2O was used. *J* values are given in Hertz. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI+ mode. Melting points are uncorrected. Compounds **2**,[25,26] **9**,[28-30] **11**,[34] **13**,[35] **15**[36] and **21**[46,47] were prepared using literature procedures.

(8*S*,9*S*,13*S*,14*S*)-3-(Benzyloxy)-9,13-dimethyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[a]phenanthren-17(14*H*)-one a (Figure 8)

Figure 8. Preparation of estradiol 17.



Sodium hydride (160 mg, 60% suspension in mineral oil, 8.0 mmol) was washed with hexane under nitrogen and then suspended in dry DMF (20 mL). A solution of estrone (1.1 g, 4.0 mmol) in dry THF (10 mL) was then added cautiously. Benzyl bromide (0.7 mL, 6.0 mmol) was then added and the mixture was stirred at room temperature for 18 h. Water (2 mL) was added drop-wise to decompose the excess sodium hydride (H_2 evolution) and the resulting mixture was partitioned between EtOAc (15 mL) and water (20 mL). The organic phase was washed with water (3 x 15 mL), dried, and evaporated to leave a residue that was purified on silica-gel column chromatography using 5-15% EtOAc in hexane to give the product as a bright white solid (1.1 g, 72 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.92 (s, 3H), 1.42-1.67 (m, 6H), 1.95-1.97 (m, 1H), 1.99-2.08 (m, 2H), 2.11-2.18 (m, 1H), 2.24-2.29 (m, 1H), 2.38-2.42 (1H), 2.48-2.53 (m, 1H), 2.89-2.92 (m, 2H), 5.04 (s, 2H), 6.74 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.5, 2.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.32 (tt, J = 7.5, 1.5 Hz, 1H), 7.37-7.40 (m, 2H), 7.43-7.44 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 14.0, 21.7, 26.0, 26.7, 29.8, 31.7, 36.0, 38.5, 44.1, 48.2, 50.5, 70.1, 112.5, 115.0, 126.5, 127.6, 128.0, 128.7, 132.4, 137.3, 137.9, 157.0, 221.1. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{28}NaO_2$, 383.1982; found, 383.1974.

((8*S*,9*S*,13*S*,14*S*,17*S*)-3-(Benzyloxy)-9,13-dimethyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yloxy)trimethylsilane b (Figure 8)

To an ice-cooled solution of **a** (360 mg, 1.0 mmol) in dry methanol (10 mL) was added sodium borohydride (84 mg, 2.2 mmol), and the mixture was stirred at room temperature for 2 h. Most of the solvent was evaporated, and the crude intermediate was precipitated by the addition of 10% aqueous acetic acid (50 mL). The solid that formed was collected using filtration, dried *in vacuo*, and carried to the next step without further purification. To a stirred solution of the crude product from the previous step (362 mg, 1.0 mmol) in dry THF (10 mL) was added Et_3N (0.3 mL, 2.0 mmol) followed by TMSCl (0.2 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with water (50 mL) and extracted using EtOAc (3 x 20 mL). The combined organic phases were washed with water (3 x 20 mL), dried on Na_2SO_4, filtered and evaporated to leave a residue that was purified on silica-gel column chromatography using 5-10% EtOAc in hexane to give **b** (407 mg**,** 84% yield) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) 0.10 (s, 9H), 0.75 (s, 3H), 0.87-0.94 (m, 2H), 1.12-1.29 (m, 6H), 1.53-1.69 (m, 1H), 1.86-1.97 (m, 2H), 2.15-2.20 (m, 1H), 2.27-2.30 (m, 1H), 2.82-2.85 (m, 2H), 3.64 (t, J = 8.5 Hz, 1H), 5.03 (s, 2H), 6.72 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 8.5, 2.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.31-7.45 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.4, 23.3, 26.5, 27.4, 30.0, 31.0, 37.2, 39.0, 43.5, 44.2, 49.9, 70.1, 81.8, 112.4, 114.9, 126.5, 127.6, 128.0, 128.7, 133.2, 137.5, 138.2, 156.8. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{28}H_{38}NaO_2Si$, 457.2533; found, 457.2526.

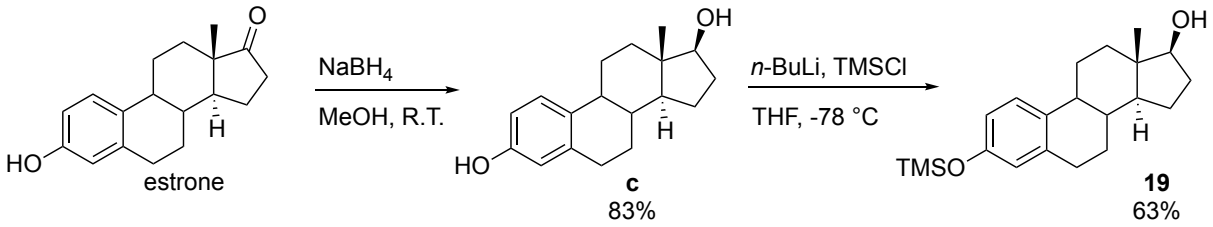
(8*S*,9*S*,13*S*,14*S*,17*S*)-9,13-Dimethyl-17-(trimethylsilyloxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-ol 17 (Figure 8)

To a mixture of **b** (407 mg, 0.9 mmol) and a catalytic amount of palladium on activated carbon (10 mol%) in a 50 mL round bottom flask was added dry THF (15 mL) followed by a trace of triethylamine (1 drop). After the mixture was purged with hydrogen gas, the mixture

was stirred for 18 h under one atmosphere of hydrogen. The mixture was then filtered through a plug of Celite to remove the catalyst which was then rinsed with EtOAc (3 x 10 mL). Evaporation of the solvent from the combined organic fractions gave **16** (300 mg, 93% yield) as a bright white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) 0.10 (s, 9H), 0.74 (s, 3H), 1.09-1.54 (m, 7H), 1.60-1.71 (m, 1H), 1.84-1.99 (m, 3H), 2.11-2.30 (m, 2H), 2.77-2.83 (m, 2H), 3.66 (t, J = 8.5 Hz, 1H),4.54 (s, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.5, 23.3, 26.5, 27.3, 29.8, 30.9, 37.2, 39.0, 43.4, 44.2, 49.8, 81.9, 112.8, 115.4, 126.7, 133.0, 138.4, 153.3. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_2Si$, 367.2064; found, 367.2045.

17β-Estradiol c (Figure 9)

Figure 9. Preparation of estradiol 19.



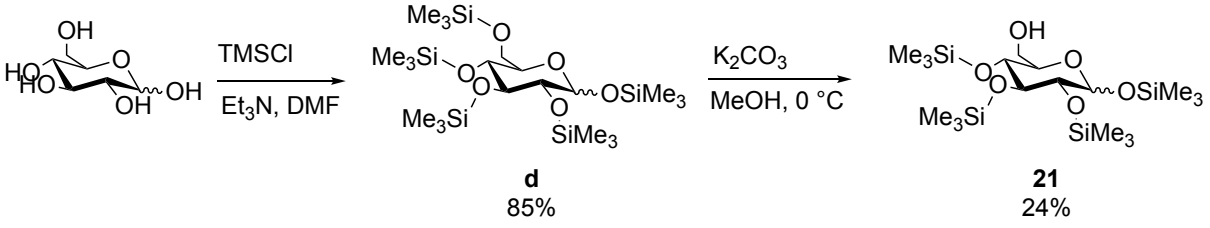
To an ice-cooled solution of sodium borohydride (311 mg, 8.2 mmol) in dry methanol (50 mL) was added estrone (1.4 g, 5.2 mmol), and the mixture was stirred at room temperature for 2 h. Most of the solvent was evaporated, and the crude product was precipitated by the addition of 10% aqueous acetic acid (20 mL). The solid was collected on a sintered glass crucible and washed thoroughly with water (250 mL), dried *in vacuo*, and carried to the next step without further purification (1.2 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz, selected peaks) 0.78 (s, 3H), 2.759-2.85 (m, 2H), 3.74 (t, J = 7.5 Hz, 1H), 4.53 (br s, 1H), 6.56 (d, J = 2.5 Hz, 1H), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H). Spectral data for compound **c** are consistent with the literature.[48]

(8*S*,9*S*,13*S*,14*S*,17*S*)-9,13-Dimethyl-3-(trimethylsilyloxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-ol 19 (Figure 9)

To a solution of estradiol **c** (640 mg, 2.4 mmol) in dry THF (112 mL) under N_2 at -78 °C was added drop-wise *n*-BuLi 1.6 M in hexane (3.0 mL, 4.7 mmol) and the solution was stirred for 10 min. Then at -78 °C TMSCl (0.6 mL, 4.7 mmol) was added slowly and the reaction mixture was stirred at -78 °C for 5 min under N_2. Water (15 mL) was added to the solution and the organic layer was separated. Then product was extracted into EtOAc (3 x 15 mL), and removal of the solvent gave a crude product which was purified on silica-gel column chromatography using 0-15% EtOAc in hexane to give the pure product as bright white solid (511 mg, 63 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.26 (s, 9H), 0.78 (s, 3H), 1.16-1.54 (m, 8H), 1.67-1.73 (m, 1H), 1.84-1.89 (m, 1H), 1.94 (dt, *J* = 12.5, 3.2 Hz, 1H), 2.08-2.21 (m, 2H), 2.28-2.33 (m, 1H), 2.76-2.87 (m, 2H), 3.71-3.75 (m, 1H), 6.56 (d, *J* = 3.0 Hz, 1H), 6.63 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.2, 23.3, 26.4, 27.4, 29.8, 30.7, 36.9, 38.9, 43.4, 44.1, 50.2, 82.1, 117.3, 120.1, 126.3, 133.4, 138.0, 153.0. HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{32}NaO_2Si$, 367.2064; found, 367.2045.

1,2,3,4,6-Penta-O-trimethylsilyl-α,β-D-glucopyranose d (Figure 10)[46]

Figure 10. Preparation of compound 21.



d 85%

21 24%

To a suspension of D-glucose (2 g, 11.1 mmol) in triethylamine (8.5 mL, 61.05 mmol) was added dry DMF (35 mL). TMSCl (7.7 mL, 61.05 mmol) was then slowly added at 0 °C. After 18 h stirring at room temperature the reaction mixture was poured into a mixture of ice and hexane. The mixture was extracted with hexane (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine (2 × 50 mL) and then dried (Na_2SO_4). Purification

via chromatography on silica gel with a graduated elution from petroleum ether 100% to petroleum ether/EtOAc 94/0.6 gave a colourless oil (5.2 g, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) α/β, 1/0.15 : 0.10 (s, 9H), 0.12 (s, 9H), 0.14 (s, 9H), 0.17 (s, 9H), 3.19-3.24 (m, 0.4Hβ), 3.33 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.31-3.34 (m, 1H), 3.58-3.61 (m, 0.19Hβ), 3.64-3.73 (m, 3H), 3.77 (t, *J* = 9.0 Hz, 1H), 4.45 (d, *J* = 7.5 Hz, 0.15Hβ), 5.00 (d, *J* = 3.0 Hz, 1Hα). ^{13}C NMR ($CDCl_3$, 125 MHz) β + α: 0.1, 0.3, 0.6, 1.1, 1.4, 62.5, 72.1 (β), 72.4, 72.6, 74.2, 74.3, 78.6 (β), 94.0, 98.3 (β).

1,2,3,4-Tetra-O-trimethylsilyl-a-D-glucopyranose 21 (Figure 10)[47,49]

Compound **d** (3.7 g, 6.83 mmol) was dissolved in MeOH, (11 mL), K_2CO_3 (7 mg, 0.051 mmol) was added at 0 °C. After 1 h the reaction was stopped by adding a drop of acetic acid and the solvent was then removed under reduced pressure. The crude product was purified using flash chromatography through silica with a graduated elution from hexane 100% to EtOAc/hexane 0.4/9.6) to give a white solid (744 mg, 24%). Mp 45 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 0.13 (s, 9H), 0.14 (s, 9H), 0.15 (s, 9H), 0.18 (s, 9H), 1.73-1.75 (m, 1H), 3.33 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.44 (t, *J* = 9.0 Hz, 1H), 3.67-3.74 (m, 3H), 3.79 (t, *J* = 9.0 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.3, 0.5, 1.0, 1.4, 62.0, 71.9, 72.0, 73.7, 74.2, 94.1.

General procedure for the synthesis of conjugates

Prodigiosene **2** (0.11 mmol), the alcohol (0.11 mmol, 1.0 eq.), EDC (0.12 mmol, 1.1 eq.) and DMAP (0.12 mmol, 1.1 eq.) were dissolved in CH_2Cl_2 (12 mL) under nitrogen. After stirring at room temperature, water was added and the crude mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude solid was purified using column chromatography.

3-((11*S*,13*S*,14*S*,17*S*)-3,17-Bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-11-yl)propyl 6-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-6-oxohexanoate 10b

This compound was obtained according to the general procedure using prodigiosene **2b** (50 mg, 0.11 mmol) and the alcohol **9** (56 mg, 0.11 mmol) after seven days of reaction. It was purified using column chromatography (Al_2O_3 type III, EtOAc/hexane 3/7, then SiO_2 EtOAc/hexane 5/5) to give a red glass (42 mg, 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (s, 3H), 1.04-1.10 (m, 1H), 1.13-1.49 (m, 4H), 1.54-1.57 (m, 7H), 1.74-1.78 (m, 2H), 1.88-1.95 (m, 1H), 2.9-2.10 (m, 3H), 2.17-2.20 (m, 3H), 2.29-2.32 (s, 4H), 2.42-2.44 (m, 1H), 2.53-2.62 (m, 3H), 2.67-2.74 (m, 1H), 3.37 (t, *J* = 7.7 Hz, 1H), 3.81-3.86 (m, 1H), 3.89 (s, 3H), 3.91-3.96 (m, 1H), 4.47 (s, 3H), 4.91 (s, 3H), 5.97 (s, 1H), 6.12-6.13 (m, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.66-6.68 (m, 2H), 6.73 (br s, 1H), 6.83 (br s, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 7.16-7.33 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.5, 14.6, 15.3, 23.2, 23.7, 24.7, 24.8, 27.1, 27, 5, 28.1, 30.5, 34.3, 34.4, 36.2, 39.6, 42.4, 43.8, 49.6, 52.2, 58.7, 64.5, 70.0, 71.7, 89.6, 95.9, 110.9, 112.1, 113.0, 114.2, 114.8, 123.7, 126.2, 127.5, 127.6, 128.0, 128.4, 128.6, 130.4, 137.4, 139.1, 139.4, 142.4, 156.4, 168.8, 173.7, 197.2, 210.9, five ^{13}C signals missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{57}H_{66}N_3O_6$, 888.4946; found, 888.4927.

3-((8*S*,9*S*,11*S*,13*S*,14*S*,17*S*)-3,17-Bis(benzyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-11-yl)propyl-10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate 10c

This compound was obtained according to the general procedure using prodigiosene **2c** (58 mg, 0.12 mmol) and the alcohol **9** (60.5 mg, 0.12 mmol) after seven days of reaction. It was purified using column chromatography (SiO_2 EtOAc/hexane 5/95 to 20/80) to give a red glass (51 mg, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) 1.00 (s, 3H), 1.26-1.33 (m, 11H), 1.51-1.64 (m, 7H), 1.79-1.89 (m, 2H), 1.96-2.05 (m, 1H), 2.17-2.26 (m, 3H), 2.33 (s, 3H), 2.41 (s, 3H),

2.51-2.56 (m, 1H), 2.63-2.87 (m, 3H), 3.46 (t, *J* = 7.8 Hz, 1H), 3.96-4.02 (m, 5H), 4.57 (s, 2H), 5.01 (s, 2H), 6.04 (s, 1H), 6.26 (bs, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.75-6.78 (m, 2H), 6.88 (br s, 1H), 6.94 (br s, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.28-7.43 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.6, 14.3, 15.3, 15.5, 23.2, 24.2, 24.7, 25.0, 27.1, 27.5, 28.0, 29.2, 29.3, 29.5, 29.6, 30.5, 34.2, 34.5, 36.1, 39.6, 43.0, 43.8, 49.6, 52.2, 58.8, 64.4, 69.9, 71.7, 89.6, 94.4, 111.9, 112.2, 112.9, 114.7, 117.9, 124.8, 127.4, 127.5, 127.6, 127.9, 128.4, 128.6, 130.4, 137.4, 139.1, 139.3, 145.4, 156.4, 167.3, 171.3, 173.9, 179.2, 197.8, four ^{13}C signals missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{61}H_{74}N_3O_6$, 944.5572; found, 944.5561.

(13*S*,14*S*,17*S*)-3-(Methoxymethoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl 6-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-6-oxohexanoate 12b

This compound was obtained according to in the general procedure using prodigiosene **2b** (50 mg, 0.11 mmol) and the alcohol **11** (35 mg, 0.11 mmol) after three days of reaction. The crude solid was purified using column chromatography (Al_2O_3 type III, EtOAc/hexane 6/4) to give a red glass (38 mg, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.80, (s, 3H), 1.23-1.46 (m, 6H), 1.68-1.73 (m, 4H), 1.85 (m, 2H), 2.16-2.21 (m, 2H), 2.24-2.25 (m, 4H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.83-2.86 (m, 2H), 3.47 (s, 3H), 3.97 (s, 3H), 4.68 (t, *J* = 8.5 Hz, 2H), 5.14 (s, 3H), 6.02 (s, 1H), 6.24 (t, *J* = 2.5 Hz, 1H), 6.73 (d, *J* = 3.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 6.80-6.82 (m, 2H), 6.91 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.2, 12.5, 23.4, 23.8, 25.0, 26.3, 27.3, 27.7, 29.9, 34.6, 37.0, 38.6, 42.4, 43.0, 44.0, 49.9, 56.0, 58.6, 82.7, 94.6, 96.0, 110.9, 112.1, 113.6, 113.9, 116.3, 123.0, 123.3, 126.5, 128.4, 134.0, 138.1, 155.2, 168.9, 173.8, 197.4, six ^{13}C signals missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{42}H_{52}N_3O_6$, 694.3851; found, 694.3846.

(13*S*,14*S*,17*S*)-17-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl 6-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-6-oxohexanoate 14b

This compound was obtained according to general procedure using prodigiosene **2b** (50 mg, 0.11 mmol) and the alcohol **13** (67 mg, 0.17 mmol) after two days of reaction. The crude solid was purified using column chromatography (Al_2O_3 type III, EtOAc/hexane 3/7) to give a red glass (52 mg, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.02 (s, 3H), 0.04 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 1.10-1.53 (m, 7H), 1.61-1.67 (m, 1H), 1.77-1.78 (m, 4H), 1.84-1.96 (m, 3H), 2.15-2.28 (m, 5H), 2.41 (s, 3H), 2.54-2.57 (m, 2H), 2.71-2.73 (m, 2H), 2.82-2.85 (m, 2H), 3.63 (t, *J* = 7.5 Hz, 1H), 3.98 (s, 3H), 6.06 (s, 1H), 6.22 (t, *J* = 3.5 Hz, 1H), 6.74-6.75 (m, 2H), 6.78-6.81 (m, 2H), 6.94 (s, 1H), 7.26 (t, *J* = 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) -4.6, -4.3, 11.5, 12.5, 14.4, 18.3, 23.4, 23.7, 24.9, 26, 0, 26.4, 27.2, 29.7, 31.1, 34.5, 37.2, 38.6, 42.4, 43.7, 44.4, 49.8, 58.7, 81.8, 96.0, 110.9, 112.5, 114.2, 118.6, 121.6, 123.4, 123.7, 126.2, 126.5, 127.9, 130.1, 138.2, 138.4, 142.5, 148.4, 160.4, 168.9, 172.5, 197.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{46}H_{62}N_3O_5Si$, 764.4453; found, 764.4474.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(*tert*-Butyldimethylsilyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl-10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate 14c

This compound was obtained according to general procedure using prodigiosene **2c** (40 mg, 0.08 mmol) and the alcohol **13** (48 mg, 0.12 mmol) after three days of reaction. The crude solid was purified using column chromatography (Al_2O_3 type III, EtOAc/hexane 5/95 to 15/85) to give a red glass (46 mg, 68%). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.02 (s, 3H), 0.03 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 1.10-1.28 (m, 2H), 1.36-1.41 (m, 12H), 1.66-1.74 (m, 6H), 1.86-1.95 (m, 3H), 2.15-2.31 (m, 4H), 2.46-2.56 (m, 6H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.82-2.86

(m, 2H), 3.64 (t, J = 8.5 Hz, 1H), 3.99 (s, 3H), 6.05 (s, 1H), 6.33-6.34 (m, 1H), 6.76-6.77 (m, 1H), 6.81 (dd, J = 8.5, 2.5 Hz, 1H), 6.88 (d, J = 2.5 Hz, 1H), 6.99 (br s, 1H), 7.13 (br s, 1H), 7.27 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) -4.7, -4.3, 11.5, 12.6, 18.2, 23.4, 24.2, 25.1, 26.0, 26.4, 27.2, 29.2, 29.3, 29.5 (2 C), 29.7, 31.1, 34.5, 37.2, 38.6, 41.4, 43.1, 43.6, 44.4, 49.8, 58.8, 81.8, 94.5, 111.9, 112.2, 117.8, 118.6, 121.6, 124.5, 124.9, 126.5, 127.8, 138.2, 138.4, 148.5, 172.8, 179.2, 197.8, five ^{13}C signals missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{50}H_{70}N_3O_5Si$, 820.5079; found, 820.5070.

(13*S*,14*S*,17*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahy-dro-6*H*-cyclopenta[a]phenanthren-17-yl 3-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-3-oxopropanoate 16b

This compound was synthesised according to the general procedure using prodigiosene **2b** (50 mg, 0.11 mmol) and the alcohol **15** (63 mg, 0.16 mmol) with 2 days of reaction. It was obtained after purification using chromatography (SiO_2, EtOAc/hexane 2/8 then 3/7) as a red glass (32 mg, 38%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.18 (s, 6H), 0.81 (s, 3H), 0.97 (s, 9H), 1.22-1.55 (m, 8H), 1.69-1.75 (m, 4H), 1.83-1.85 (m, 2H), 2.15-2.34 (m, 8H), 2.42 (s, 3H), 2.70 (br s, 2H), 2.79-2.82 (m, 2H), 3.99 (s, 3H), 4.68 (t, J = 8.5 Hz, 1H), 6.06 (s, 1H), 6.25 (br s, 1H), 6.55 (s, 1H), 6.60 (dd, J = 8.5, 2.5 Hz, 1H), 6.79 (br s, 1H), 6.89 (br s, 1H), 6.96 (br s, 1H), 7.10 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) -4.2, 12.3, 12.5, 18.3, 23.4, 23.7, 24.9, 25.8, 25.8, 26.2, 27.4, 27.7, 29.7, 34.6, 37.0, 38.6, 42.5, 43.1, 43.9, 49.9, 58.7, 82.7, 95.6, 111.2, 112.2, 115.1, 117.3, 120.0, 123.8, 124.7, 126.2, 127.0, 133.0, 137.9, 143.3, 153.4, 168.5, 173.7, 179.4, 197.2, three ^{13}C signals missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{46}H_{62}N_3O_5Si$, 764.4453; found, 764.4432.

(13*S*,14*S*,17*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl 10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate 16c

This compound was synthesised according to general procedure using prodigiosene **2c** (50 mg, 0.10 mmol) and estradiol **15** (59 mg, 0.15 mmol) with 2 days of reaction. It was obtained after purification using chromatography (Al_2O_3 type III neutral, CH_2Cl_2 100% then, EtOAc/hexane 2/8 to 5/5) as an orange glass (29 mg, 35%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.18 (s, 6H), 0.82 (s, 3H), 0.97 (s, 9H), 1.22-1.55 (m, 11H), 1.59-1.64 (m, 6H), 1.69-1.75 (m, 2H), 1.83-1.91 (m, 3H), 2.15-2.21 (m, 2H), 2.23-2.31 (m, 5H), 2.40 (s, 3H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.79-2.82 (m, 2H), 3.96 (s, 3H), 4.68 (t, *J* = 8.5 Hz, 1H), 6.03 (s, 1H), 6.24 (t, *J* = 3.2 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.72 (d, *J* = 3.2 H, 1H), 6.81 (br s, 1H), 6.91 (s, 1H), 7.10 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) -4.2, 12.3, 12.5, 18.3, 23.4, 23.5, 24.3, 24.8, 25.3, 25.9, 26.3, 27.4, 27.7, 29.3, 29.6, 29.7, 34.8, 36.8, 37.1, 38.7, 42.9, 43.1, 44.0, 49.9, 58.6, 82.6, 92.4, 95.9, 110.8, 112.2, 113.6, 117.3, 120.1, 123.0, 123.5, 126.3, 126.5, 128.4, 129.4, 133.1, 137.9, 141.9, 153.4, 160.6, 168.9, 174.1, 198.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{50}H_{70}N_3O_5Si$, 820.5079; found, 820.5042.

(13*S*,14*S*,17*S*)-13-Methyl-17-((trimethylsilyl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl 4-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-4-oxobutanoate 18a

This compound was obtained according to the general procedure using prodigiosene **2a** (50 mg, 0.12 mmol) with two days of reaction. The crude solid was purified using column chromatography (Al_2O_3 neutral type III, EtOAc/hexane 3/7 then 4/6) to give a dark-red film (36 mg, 43%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.11 (s, 9H), 0.75 (s, 3H), 1.12-1.52 (m, 7H), 1.63-1.69 (m, 1H), 1.83-1.96 (m, 3H), 2.17-2.22 (m, 1H), 2.26-2.30 (m, 4H), 2.44 (s, 3H), 2.83-2.86 (m, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 3.64-3.65 (t, *J* = 8.5 Hz,

1H) , 3.99 (s, 3H), 6.05-6.06 (m, 1H), 6.22-6.23 (m, 1H), 6.74-6.75 (m, 1H), 6.79-6.81 (m, 2H), 6.86 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.94 (s, 1H), 7.27 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.4, 12.6, 14.5, 23.4, 24.8, 26.4, 27.2, 28.7, 29.7, 31.0, 37.1, 37.5, 38.6, 43.4, 44.4, 49.9, 58.7, 81.8, 96.1, 110.9, 112.1, 113.9, 118.6, 121.6, 122.8, 123.3, 126.4, 128.2, 129.7, 138.1, 138.3, 142.5, 148.6, 160.9, 169.0, 172.4, 194.9, one ^{13}C missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{41}H_{52}N_3O_5Si$, 694.3676; found, 694.3671.

(13*S*,14*S*,17*S*)-13-m-17-((Trimethylsilyl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl 6-(5-((*Z*)-(4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5(2*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)-6-oxohexanoate 18b

This compound was obtained according to the general procedure using prodigiosene **2b** (100 mg, 0.23 mmol) and the alcohol **17** (95 mg, 0.27 mmol) with two days of reaction. The crude solid was purified using column chromatography (SiO_2, EtOAc/hexane 5/5) to give a red glass (100 mg, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.09 (s, 9H), 0.74 (s, 3H), 1.11-1.53 (m, 7H), 1.62-1.68 (m, 1H), 1.76-1.77 (m, 4H), 1.84-1.89 (m, 2H), 1.91-1.97 (m, 1H), 2.18-2.21 (m, 4H), 2.26-2.30 (m, 1H), 2.41 (s, 3H), 2.54-2.56 (m, 2H), 2.71-2.72 (m, 2H), 2.82-2.84 (m, 2H), 3.63 (t, *J* = 8.5 Hz, 1H), 3.99 (s, 3H), 6.07 (s, 1H), 6.20-6.21 (m, 1H), 6.73-6.76 (m, 3H), 6.80 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.94 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.4, 12.5, 14.2, 23.3, 23.7, 24.9, 26.3, 27.2, 29.7, 31.0, 34.5, 37.1, 38.6, 42.4, 43.4, 44.4, 49.9, 58.7, 81.8, 96.1, 110.8, 112.1, 113.9, 118.6, 121.6, 123.4, 126.2, 126.5, 128.1, 129.8, 138.2, 138.4, 140.3, 142.4, 148.5, 160.9, 169.1, 172.5, 197.2, one ^{13}C missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{43}H_{56}N_3O_5Si$, 722.3984; found, 722.3976.

(8*R*,9*S*,13*S*,14*S*,17*S*)-13-Methyl-17-(trimethylsilyloxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl-10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate 18c

This compound was obtained according to the general procedure using prodigiosene **2c** (63 mg, 0.10 mmol) and the alcohol **17** (63 mg, 0.18 mmol) after two days of reaction. The crude solid was purified using column chromatography (Al_2O_3 neutral type III, EtOAc/hexane 5/95 to 15/85) to give a deep red glass (85 mg, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.10 (s, 9H), 0.74 (s, 3H), 1.11-1.55 (m, 14H), 1.61-1.75 (m, 6H), 1.85-1.96 (m, 3H), 2.14 (s, 3H), 2.17-2.22 (m, 1H), 2.26-2.31 (m, 1H), 2.40 (s, 3H), 2.51 (t, *J* = 7.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.80-2.90 (m, 2H), 3.63 (t, *J* = 8.5 Hz, 1H), 3.99 (s, 3H), 6.08 (s, 1H), 6.19-6.20 (m, 1H), 6.72-6.73 (m, 2H), 6.76 (d, *J* = 2.5 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.94 (s, 1H), 7.27 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.4, 11.4, 12.4, 14.0, 23.3, 24.3, 25.1, 26.3, 27.2, 29.2, 29.3, 29.5, 29.7, 31.0, 31.7, 34.5, 37.1, 38.6, 42.8, 43.4, 44.4, 49.9, 58.7, 81.8, 96.2, 110.7, 112.2, 113.8, 118.7, 121.6, 123.4, 123.6, 126.2, 126.5, 128.3, 129.8, 138.1, 138.4, 140.4, 142.3, 148.5, 161.0, 169.2, 172.8, 198.2. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{47}H_{64}N_3O_5Si$, 778.4610; found, 778.4585.

((2S,3S,4R,5S,6R)-3,4,5,6-Tetrakis((trimethylsilyl)oxy)tetrahydro-2H-pyran-2-yl)methyl 6-((Z)-2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)-6-oxohexanoate 22b

This compound was obtained according to general procedure using prodigiosene **2b** (50 mg, 0.11 mmol) and the alcohol **21** (54 mg, 0.11 mmol) with three days of reaction. The crude was purified using column chromatography (Al_2O_3 type III, EtOAc/hexane 3/7) to give a red glass (56 mg, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.13 (s, 9H), 0.14 (s, 18H), 0.15 (s, 9H), 1.69-1.70 (m, 4H), 2.36 (br s, 3H),2.38-2.40 (m, 2H), 2.41 (s, 3H), 2.71 (t, *J* = 7.0 Hz, 2H), 3.36 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.43 (t, *J* = 9.0 Hz, 1H), 3.78 (t, *J* = 9.0 Hz, 1H), 3.89-3.92

(m, 1H), 3.96 (s, 3H), 4.02 (dd, J = 12.0, 5.5 Hz, 1H), 4.34 (dd, J = 12.0, 2.5 Hz, 1H), 5.01 (s, 1H), 6.01 (s, 1H), 6.27 (t, J = 3.5 Hz, 1H), 6.74 (dd, J = 4.0, 1.5 Hz, 1H), 6.87 (br s, 1H), 6.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.28, 0.58, 1.08, 1.38, 12.5, 14.2, 23.7, 24.7, 29.8, 34.2, 42.4, 58.7, 63.9, 70.0, 72.5, 73.9, 74.0, 94.0, 96.1, 110.8, 112.2, 114.1, 123.5, 126.1, 128.0, 130.0, 139.9, 142.5, 160.7, 169.0, 173.5, 197.2, one ^{13}C missing. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{40}H_{68}N_3O_9Si_4$: 846.4027; found 846.4021.

((3*R*,4*S*,5*S*,6*S*)-3,4,5,6-Tetrakis(trimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl)methyl-10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate 22c

This compound was obtained according to general procedure using prodigiosene **2c** (30 mg, 0.06 mmol) and the alcohol **21** (29 mg, 0.06 mmol) with three days of reaction. The crude was purified using column chromatography (SiO_2, EtOAc/hexane 5/95 to 20/80) to give a red glass (40 mg, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) 0.13 (s, 9H), 0.14 (s, 9H), 0.15 (s, 9H), 0.16 (s, 9H), 1.26-1.39 (m, 6H), 1.53-1.74 (m, 4H), 2.19 (br s, 2H), 2.34 (dt, J = 7.5, 3.3 Hz, 2H), 2.45 (s, 3H), 2.54 (s, 3H), 2.70 (t, J = 7.5 Hz, 2H), 3.36 (dd, J = 9.0, 3.0 Hz, 1H), 3.43 (t, J = 9.0 Hz, 1H), 3.79 (t, J = 9.0 Hz, 1H), 3.89-3.93 (m, 1H), 3.99-4.04 (m, 4H), 4.35 (dd, J = 12.0, 2.5 Hz, 1H), 5.01 (d, J = 3.0 Hz, 1H), 6.05 (s, 1H), 6.30-6.35 (m, 1H), 6.88 (d, J = 3.0, Hz, 1H), 6.99 (br s, 1H), 7.11 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 0.3, 0.6, 1.0, 1.4, 12.6, 15.2, 24.3, 24.9, 25.1, 29.3, 29.4, 29.6, 34.3, 43.0, 58.8, 63.8, 70.0, 72.5, 73.9, 74.0, 94.0, 95.0, 111.6, 112.2, 116.4, 116.6, 124.2, 125.4, 126.3, 132.8, 144.2, 167.9, 173.8, 179.3, 197.9. HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{44}H_{76}N_3O_9Si_4$, 902.4653; found, 902.4666.

General procedure for the TMS deprotection

The prodigiosene conjugate (1.0 eq.) was dissolved in a mixture of MeOH/$CHCl_3$ then HCl conc. (3 eq.) in MeOH (1 mL) was added. After 5 min the reaction mixture was concentrated

in vacuo. The resulting solid was triturated with ether and then isolated using a sintered glass filter. The desired compound was obtained as a red solid following a wash using diethyl ether.

(13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-((*Z*)-2-((4-methoxy-1H,1'H-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2H-pyrrol-4-yl)-4-oxobutanoate hydrochloride 23a

Obtained as a red solid (20 mg, 59%) following the general procedure using **18a** (36 mg, 0.052 mmol) in a mixture of MeOH/$CHCl_3$ (2/4 mL). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.77 (s, 3H), 1.15-1.21 (m, 1H), 1.26-1.60 (m, 5H), 1.67-1.72 (m, 1H), 1.86-1.88 (m, 1H), 1.93-1.96 (m, 1H), 2.07-2.15 (m, 1H), 2.18-2.23 (m, 1H), 2.29-2.32 (m, 1H), 2.52 (s, 3H), 2.84-2.86 (m, 2H), 2.87 (s, 3H), 2.95 (t, *J* = 6.2 Hz, 2H), 3.16 (t, *J* = 6.2 Hz, 2H), 3.72 (t, *J* = 8.5 Hz, 1H), 4.04 (s, 3H), 6.10 (s, 1H), 6.39 (s, 1H), 6.82 (s, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.01 (br s, 1H), 7.10 (s, 1H), 7.28-7.30 (m, 2H), 12.67 (br s, 1H), 12.72 (br s, 1H), 12.96 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.2, 12.8, 15.8, 23.3, 26.3, 27.2, 28.6, 29.6, 30.7, 36.8, 37.8, 38.6, 43.3, 44.3, 50.2, 59.2, 82.0, 93.6, 112.7, 118.7, 119.6, 121.6, 122.1, 123.2, 123.5, 124.5, 126.4 (2 C), 128.9, 138.0, 138.3, 138.6, 148.6, 148.9, 150.6, 166.9, 172.1, 194.5, 3 ^{13}C signals missing. HRMS-ESI (*m/z*): $[M-Cl]^+$ calcd for $C_{38}H_{43}N_3O_5$, 622.3281; found, 622.3275.

(13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl 6-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-6-oxohexanoate hydrochloride 23b

Obtained as a red solid (39 mg, 68%) following the general procedure using **18b** (39 mg, 0.056 mmol) in a mixture of MeOH/$CHCl_3$ (2/4 mL). Mp 138 °C. Rf = 0.55 (EtOAc/hexane, 6/4, Al_2O_3). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.77 (s, 3H), 1.15-1.21 (m, 1H), 1.25-1.53 (m, 8H), 1.66-1.72 (m, 1H), 1.82-1.86 (m, 4H), 1.87-1.89 (m, 1H), 1.94 (dt, *J* = 13.5, 3.0 Hz, 1H), 2.09-2.14 (m, 1H), 2.18-2.23 (m, 1H), 2.29-2.32 (m, 1H), 2.52 (s, 3H), 2.60-2.61 (m, 2H), 2.81-2.84 (m, 2H), 2.86 (s, 3H), 3.73 (t, *J* = 8.5 Hz, 1H), 4.07 (s, 3H), 6.12 (d, *J* = 2.0 Hz,

1H), 6.40-6.42 (m, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.03-7.04 (m, 1H), 7.13 (s, 1H), 7.28 (s, 1H), 7.31-7.32 (m, 1H), 12.69 (br s, 1H), 12.73 (s, 1H), 13.02 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.2, 12.7, 15.8, 23.2, 23.6, 24.8, 26.2, 27.1, 29.6, 30.7, 34.4, 36.8, 38.6, 42.7, 43.3, 44.2, 50.2, 59.2, 65.6, 82.0, 93.5, 112.7, 118.7, 119.4, 121.6, 122.1, 123.0, 123.5, 125.0, 126.5, 128.8, 138.0, 138.3, 138.6, 148.5, 148.7, 150.4, 166.8, 172.4, 196.7. HRMS-ESI (*m/z*): $[M\text{-}Cl]^+$ calcd for $C_{40}H_{48}N_3O_5$, 650.3588; found, 650.3599.

(13*S*,14*S*,17*S*)-3-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl 10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate hydrochloride 23c

Obtained as a red solid (30 mg, 38%) following the general procedure using **18c** (84 mg, 0.108 mmol) in a mixture of MeOH/$CHCl_3$ (1/4 mL). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.76 (s, 3H), 1.14-1.54 (m, 14H), 1.65-1.75 (m, 6H), 1.85-1.87 (m, 1H), 1.93-1.95 (m, 1H), 2.06-2.14 (m, 1H), 2.17-2.22 (m, 1H), 2.27-2.34 (m, 1H), 2.49 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.80-2.84 (m, 5H), 3.71 (t, *J* = 8.5 Hz, 1H), 4.04 (s, 3H), 6.09 (br s, 1H), 6.38 (br s, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.00 (br s, 1H), 7.10 (s, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.29 (br s, 1H), 12.66 (br s, 2H), 12.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.2, 12.7, 15.7, 23.2, 24.2, 25.1, 26.3, 27.1, 29.1, 29.2, 29.4, 29.5, 29.6, 30.7, 34.5, 36.8, 38.6, 43.2, 43.3, 44.2, 50.2, 59.2, 82.0, 93.5, 112.6, 112.8, 118.7, 119.3, 121.6, 122.1, 122.9, 123.5, 125.2, 126.5, 128.7, 138.0, 138.3, 138.7, 148.5, 148.7, 150.3, 166.8, 172.7, 197.5. HRMS-ESI (*m/z*): $[M\text{-}Cl]^+$ calcd for $C_{44}H_{56}N_3O_5$, 706.4214; found, 706.4199.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-Hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl-10-((*Z*)-2-((4-methoxy-1*H*,1'*H*-2,2'-bipyrrol-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-10-oxodecanoate hydrochloride 24c

The prodigiosene **16c** (29 mg, 0.035 mmol) was dissolved in a mixture of MeOH/$CHCl_3$ (0.5/1 mL) then HCl conc. (9 µL, 0.10 mmol) in MeOH (0.5 mL) was added. After 24 h the reaction mixture was concentrated in *vacuum*, the resulting solid was triturated in ether and filtered using a sintered filter and then washed with ether to give a red solid (7 mg, 27 %). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.82 (s, 3H), 1.25-1.45 (m, 12H), 1.50-1.73 (m, 9H), 1.84-1.86 (m, 2H), 2.14-2.26 (m, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 2.50 (s, 3H), 2.73 (t, *J* = 7.5 Hz, 2H), 2.79-2.80 (m, 1H), 2.84 (s, 3H), 4.06 (s, 3H), 4.70 (t, *J* = 8.2 Hz, 1H), 4.90 (s, 1H), 6.11 (br s, 1H), 6.40 (s, 1H), 6.55 (s, 1H), 6.63 (d, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 7.10-1.12 (m, 2H), 7.30 (s, 1H), 12.65 (br s, 2H), 12.94 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 12.3, 12.7, 15.8, 23.4, 24.2, 25.3, 26.4, 27.3, 27.7, 29.2, 29.3, 29.5, 29.6, 29.7, 34.8, 37.0, 38.7, 43.1, 43.2, 43.9, 49.9, 59.3, 82.5, 93.6, 112.7, 112.9, 115.4, 119.4, 122.1, 122.9, 123.5, 125.2, 126.6, 128.8, 132.6, 138.3, 138.8, 148.6, 150.4, 153.5, 166.8, 174.1, 197.6, (1 ^{13}C signal non accounted for). HRMS-ESI (*m/z*): $[M-Cl]^+$ calcd for $C_{44}H_{56}N_3O_5$, 706.4214; found, 706.4189.

((2S,3*R*,4*R*,5*S*,6*S*)-3,4,5,6-Tetrahydroxytetrahydro-2*H*-pyran-2-yl)methyl 6-((*Z*)-2-((4-methoxy-1*H*,1'*H*-[2,2'-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-6-oxohexanoate hydrochloride 25b

Obtained as a red solid (50 mg, 88%) following the general procedure using **22b** (82 mg, 0.097 mmol) in a mixture of MeOH/$CHCl_3$ (2/4 mL). Mp 171 °C dec. ^{1}H NMR (D_2O, 500 MHz) described as a α/β (1/5) mixture: 1.26-1.33 (m, 2Hα,β), 1.45-1.49 (m, 2Hα,β), 1.90 (s, 3Hα,β), 2.17-2.18 (m, 2Hα,β), 2.22 (s, 3Hα,β), 2.36-2.38 (s, 2Hα,β), 3.24 (t, *J* = 8.5 Hz, 1Hβ), 3.41-3.55 (m, 2Hα and 2Hβ), 3.60-3.64 (m, 1Hβ), 3.64-3.66 (m, 1Hα), 3.73 (t, *J* = 8.5 Hz, 1Hα), 3.82 (s, 3Hα,β), 4.23-4.31 (m, 1Hα and 1Hβ), 4.35-4.42 (m, 1Hα and 1Hβ), 4.64

(d, J = 8.0 Hz, 1Hβ), 5.20 (d, J = 3.5 Hz, 1Hα), 5.90 (br s, 1Hβ), 6.03 (br s, 1Hα), 6.15 (br s, 1Hβ), 6.18 (br s, 1Hα), 6.28 (br s, 1Hβ), 6.42 (br s, 1Hα), 6.58 (br s, 1Hα), 6.82 (bs, 1Hβ), 6.99 (br s, 1Hα and 1Hβ). ^{13}C NMR (DMSO, 125 MHz) described as a α/β mixture: 12.1, 15.0, 22.9, 24.1, 33.5, 41.8, 59.6, 64.0, 69.1, 70.2, 70.6, 72.2, 72.8, 73.5, 74.7, 76.4, 92.3, 94.9, 96.9, 111.7, 112.9, 120.1, 121.8 122.6, 122.8, 124.3, 129.2, 137.4, 147.5, 150.8, 170.0, 172.9, 196.2. HRMS-ESI (*m/z*): $[M\text{-}Cl]^+$ calcd for $C_{28}H_{36}N_3O_9$, 558.2446; found, 558.2419.

NCI Evaluation

The Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) employs the NCI60 cell line screen as an early stage of drug discovery and development. The NCI60 cell line screen consists of 60 human tumor cell lines, each chosen for their ability to perform consistently and provided appropriate representation of a variety of tumor types: 59 cell lines were available for screening when this work was performed.[50] Each cell line used has been extensively characterized.[50] The multi-dose drug screen involves treatment of each cell line with compounds over a 5-log mol/L concentration range for 2 days.[50,51] The cells are then fixed and stained with sulphorhodamine B and optical densities are measured.[50,51] Growth inhibition is calculated relative to cells at the time zero control and those without drug treatment.[50,51] http://dtp.cancer.gov.

Tables

Table 1. Deprotection conditions for prodigiosene conjugates.

Entry	Compounds	Reaction conditions	Yield
1	**12b**	HCl (200 eq), THF, 16 h	(hydrolysis)
2	**16c**	HCO_2H, THF 3 days	n.r.[a]
3	**16b**	citric acid (0.3 eq), 24 h	n.r.[a]
4	**16c**	HF-pyridine, DCM, 6 h	(hydrolysis)
5	**16c**	HCl (3 eq), MeOH, $CHCl_3$, 20 h	27% (**24c**)
6	**14b**	HCl (3 eq), MeOH, $CHCl_3$, 3 h	57% (**23b**)
7	**14b**, **14c**	TBAF (4 eq), THF, 16 h	(hydrolysis)
8	**22b**	K_2CO_3 cat, MeOH, 1.5 h	(hydrolysis)
9	**22b**	HCl (3 eq), MeOH, $CHCl_3$, 3 min	88% (**25b**)
10	**18a**	HCl (3 eq), MeOH, $CHCl_3$, 3 min	59% (**23a**)
11	**18b**	HCl (3 eq), MeOH, $CHCl_3$, 3 min	68% (**23b**)
12	**18c**	HCl (3 eq), MeOH, $CHCl_3$, 3 min	38% (**23c**)
13	**18b**	TFA (3 eq), DCM 2 h	57% (**23b**)

[a] n.r.: no reaction

Table 2. GI_{50} (half maximal growth inhibition) in μM of prodigiosene conjugates 23a, 23b and 24c against 6 breast cancer cell lines. (http://dtp.cancer.gov).

	23a	**23b**	**24c**
MCF-7 (ER+)	0.9	0.9	0.4
MDA-MB231 (ER-)	0.5	2.0	n.d.[a]
HS 578T (ER-)	3.2	n.d. [a]	0.5
BT 549 (ER-)	3.5	4.4	0.3
T-47D (ER+)	2.2	1.4	n.d. [a]
MDA-MB-468 (ER-)	2.5	4.9	0.5

[a] n.d.: not determined

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ASSOCIATED CONTENT

Supporting Information. NMR spectra for new compounds. This material is available free-of-charge via the Internet at http://pubs.acs.org.

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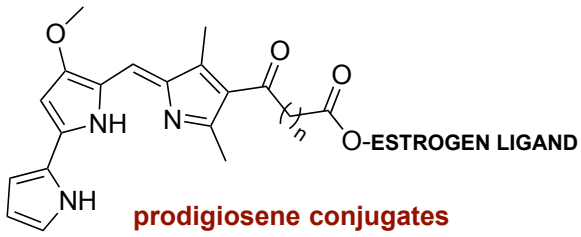

prodigiosene conjugates

Figure Legends

Figure 2. Natural product prodigiosin 1 and derivatives 2, 3 and 4.

Figure 3. Estradiol conjugate prodigiosene 5.

Figure 4. Attempt to synthesize a prodigiosene conjugated to E2-11.

Figure 5. Evaluation of the use of BCl3 as a deprotecting agent.

Figure 6. Synthesis of protected prodigiosene conjugates.

Figure 7. Structure of protected conjugates 12, 14, 16, 18 and 22 and deprotected conjugates 23, 24 and 25.

Figure 7. Cell Viability. Cell viability following treatment of breast cancer cells (MCF-7, MDA-MB231/ATCC, HS 578T, BT-549, T-47D, MDA-MB-468) with 10 μM of prodigiosene conjugates **23a**, **23b**, **24c** and **25b** (http://dtp.cancer.gov).

Figure 8. Preparation of estradiol 17.

Figure 9. Preparation of estradiol 19.

Figure 10. **Preparation of compound 21.**

Table Legends

Table 3. Deprotection conditions for prodigiosene conjugates.

Table 4. GI_{50} (half maximal growth inhibition) in μM of prodigiosene conjugates 23a, 23b and 24c against 6 breast cancer cell lines. (http://dtp.cancer.gov).