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Prodigiosenes conjugated to tamoxifen and estradiol†

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We report the synthesis of the first click-appended prodigiosene conjugates. Four prodigiosene conjugates of estradiol functionalised at the 7α-position were prepared, as were three prodigiosene conjugates of tamoxifen. The coupling between a prodigiosene and an 11-hydroxy estradiol derivative *via* an ether linkage was investigated, as was the 11- and 7-functionalisation of the estradiol core. The robustness of estradiol protecting groups was severely challenged by reactions typically used to equip such frameworks for 11- and 7-functionalisation. Specifically, and important to synthesis involving estradiol, TBS, TMS and THP are not useful protecting groups for the functionalisation of this core. When the chemical features of the therapeutic agent limit the choice of protecting group (in this case, prodigiosenes bearing aryl, NH, alkenyl and ester groups), click chemistry becomes an attractive synthetic strategy. The anti-cancer activity of the seven click prodigiosene conjugates was evaluated.

Introduction

The conjugation of potent drugs to bioactive molecules (*e.g.* proteins,[1–3] lipids,[4] antibodies[5–7] and biological polymers[8]) represents an effective and proven strategy for the treatment of cancer.[9–11] Conjugation allows specific tissues to be targeted to result in reduced toxicity towards healthy cells.[12] We herein report conjugation of prodigiosenes to moieties that target estrogen receptors. En route to synthesising these conjugates, we discovered the surprising frailty of estradiol protecting groups. We thus used click chemistry to ensure robust connectivity between the prodigiosene and the estradiol. The first click-appended prodigiosene conjugates are reported herein, as are some tamoxifen–prodigiosene conjugates, alongside methodology that will be of use in the conjugation of either prodigiosenes or estradiols to other complex moieties.

Prodigiosin is a tripyrrolic, red pigmented natural product produced by certain strains of *Serratia* and *Streptomyces* bacteria (Fig. 1).[13,14] Prodigiosin exhibits a multitude of biological responses including immunosuppressive,[15] antimicrobial[16–19] and anti-cancer properties[20,21] through several modes of action, *e.g.* H^+/Cl^- exchange,[22–25] Cu-mediated DNA cleavage[26,27] and signal-transduction interference.[28–30] However, clinical applications have been limited due to poor selectivity. Derivatives of prodigiosin, named prodigiosenes,[31] featuring various modifications on the pyrrolyldipyrrin core of the natural product, have been shown to maintain the anticancer activity of the parent compound, as well as result in a reduced toxicity profile.[32–41]

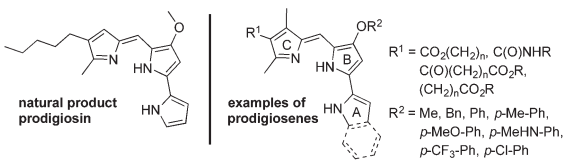

Fig. 1 Structure of prodigiosin and some prodigiosene analogs.

We previously reported prodigiosenes **1a–c** (Fig. 2, top) conjugated to estrone, estradiol and 4-hydroxytamoxifen.[33,36] These prodigiosene conjugates were designed to be delivered to cancerous tissues that express estrogen receptors (ERs), thereby increasing the selectivity of these drugs towards ER-positive breast cancer cells.[12,42–45] As a proof of principle, these first conjugates were linked through the readily accessible functionalities of the targeting moieties, even though those groups play a fundamental role in binding the ER pocket (Fig. 2, top).[46,47] Nevertheless, the conjugates exhibited growth inhibition against breast cancer cells and some selectivity for ER-positive breast cancer cell lines.[33,36]

Herein, we report our investigations towards the synthesis of prodigiosenes conjugated to estradiol derivatives at the 11- and 7-positions (Fig. 2, bottom). Linkage at these positions would allow the free hydroxyl moieties at the 3- and 17β-positions of estradiol to bind ERs. Indeed, chemical substitution at the 11β- and 7α-positions of estrogens, although more synthetically challenging than the 3- and 17β-positions,

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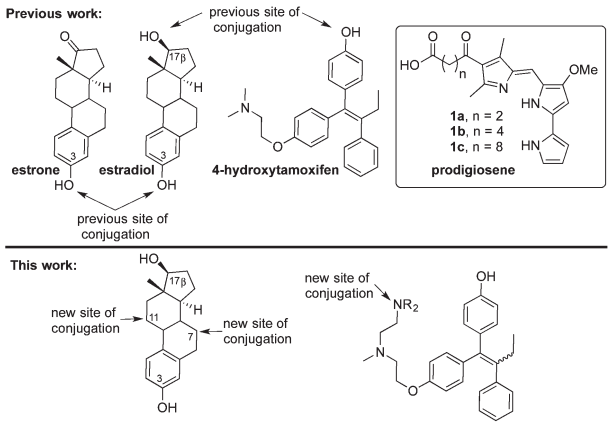


Fig. 2 Conjugation strategy for prodigiosene–estradiol and tamoxifen conjugates.

has given drugs with high binding affinities and potent estrogenic or anti-estrogenic activities.[46–49] Adhering to this approach, 4-hydroxytamoxifen will be conjugated through the amino side chain,[50] thereby situating the free phenolic group suitable for binding to ERs.[46,47]

Results and discussion

Synthesis

Cognisant that ethers are less reactive than esters,[36] we targeted the synthesis of estradiol–prodigiosene conjugates joined *via* an ether-linkage: a prodigiosene featuring a pendant alcohol on the C-ring would be conjugated with an estradiol substituted with a hydroxyl group at 11α-position (Fig. 3).

In order to synthesise a prodigiosene bearing a pendant hydroxy group, the direct reduction of **2** was attempted. However, the use of $LiAlH_4$ gave a complex mixture of prodigiosene derivatives, and the use of BH_3·THF afforded the reduced product in only very poor yields. Therefore, prodigiosene **2** was first protected as its Zn(II) dimer (**3** in Scheme 1), whereupon reduction of the ketone, using BH_3·THF, was followed by an acidic work-up that also effected decomplexation. It is significant, particularly for those interested in the functional group manipulation of dipyrrins, that reduction of this conjugated carbonyl group is feasible following N–N protection with Zn(II).

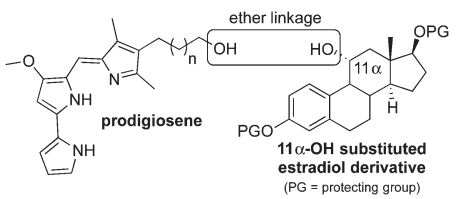
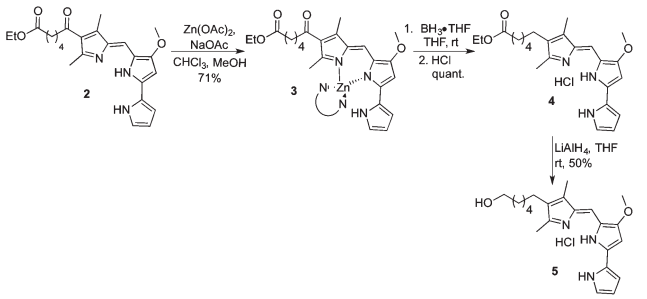


Fig. 3 Moieties required for the synthesis of ether-linked estradiol–prodigiosene conjugates.

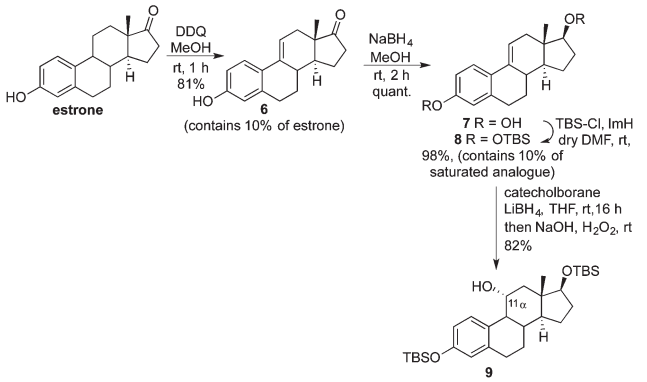


Scheme 1 Synthesis of prodigiosene **5**.

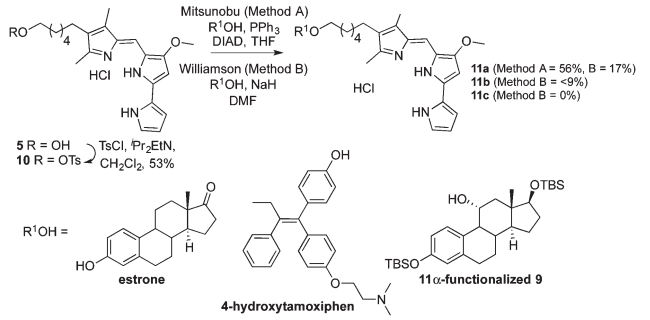
Reduction of the ester (**4**), using $LiAlH_4$, provided **5** (Scheme 1).

The synthesis of the requisite estradiol, functionalised with a hydroxyl substituent at the 11α-position, began with the oxidation of estrone to give **6**, alongside 10% recovery of the starting material within an inseparable mixture (Scheme 2).[51,52] Reduction of **6** gave the alcohol **7**, which was protected with TBS to give **8**.[53] This protecting group was chosen to be stable to reaction conditions suitable for the formation of esters involving prodigiosenes:[36] choices for suitable protecting groups are severely limited by the presence of the various functionality embedded within the prodigiosene skeleton. Hydroboration–oxidation of **8** gave the desired 11α-hydroxylated estradiol derivative **9** (Scheme 2).

The formation of the ether linkage was first attempted using prodigiosene **5** and estrone and 4-hydroxytamoxifen. Using Mitsunobu conditions,[54] estrone was coupled with **5** to give **11a** in reasonable yield (Scheme 3). However, the use of these conditions gave rise to neither **11b** (upon reaction with 4-hydroxytamoxiphen) nor **11c** (upon reaction with **9**). The primary alcohol of prodigiosene **5** was thus activated to give the tosylate **10**, which was then reacted with estrone and 4-hydroxytamoxifen under Williamson ether conditions. However, conjugate **11a** was obtained in only 17% yield, while **11b** could not be adequately purified despite chromatography over both silica and alumina. Use of the TBS-protected 11α-functionalised alcohol **9** was also unfruitful despite the



Scheme 2 Synthesis of estradiol derivative **9**.

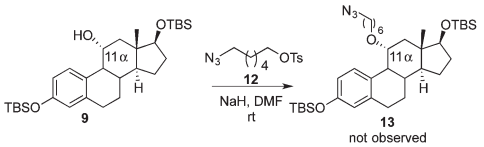


Scheme 3 Attempts to synthesise ether-linked prodigiosene conjugates **11a–c**.

fact that, upon treatment with NaH in DMF, **9** was quantitatively recovered. Under the Williamson ether synthesis conditions in the presence of tosylate **10**, conjugate **11c** was formed but could not be extracted from DMF. Furthermore, the use of high temperatures, in order to remove DMF, led to decomposition. The reaction was repeated in THF, but the desired product did not form. It is significant that such robust reactions to form ethers fail with these bulky alcohols.

Considering the challenges encountered in forming ether linkages (Scheme 3), we focused on the introduction of a linker at the 11α-position of estradiol (Scheme 4) with the plan to subsequently couple with prodigiosenes *via* either amide or ester linkages that had previous shown to be forthcoming. However, Williamson synthesis using linker **12**,[55] whose azide could lead to an amine or hydroxyl group later in the sequence, did not occur at the desired 11α-position (**13**) but instead at the phenolic position, *i.e.* TBS-deprotection at the phenolic position occurred. The TBS-protected alcohol **9** and tosylate **10** thus seemed unable to tolerate clean reactivity at the 11α-hydroxy position (Schemes 3 and 4).

Clearly, TBS is not a suitable protecting group for estradiol derivatives of this type. In contrast, the TMS group survives the conjugation of prodigiosenes with estradiols functionalised in other positions,[33,35,36] and has been demonstrated to be compatible with the coupling conditions required to form such esters, in contrast to the many protecting groups we evaluated. Furthermore, TMS can be removed without hydrolysis of the ester bond. As such, we targeted estradiol derivative **15** (Scheme 5, top and middle) protected with TMS groups at 3- and 17β-positions. Alcohol **7** [51–53] was protected with TMS to afford **14**. However, the TMS groups in **7** did not survive the hydroboration conditions (Scheme 5, top). Evidently, the robustness of estradiol protecting groups is far from established.

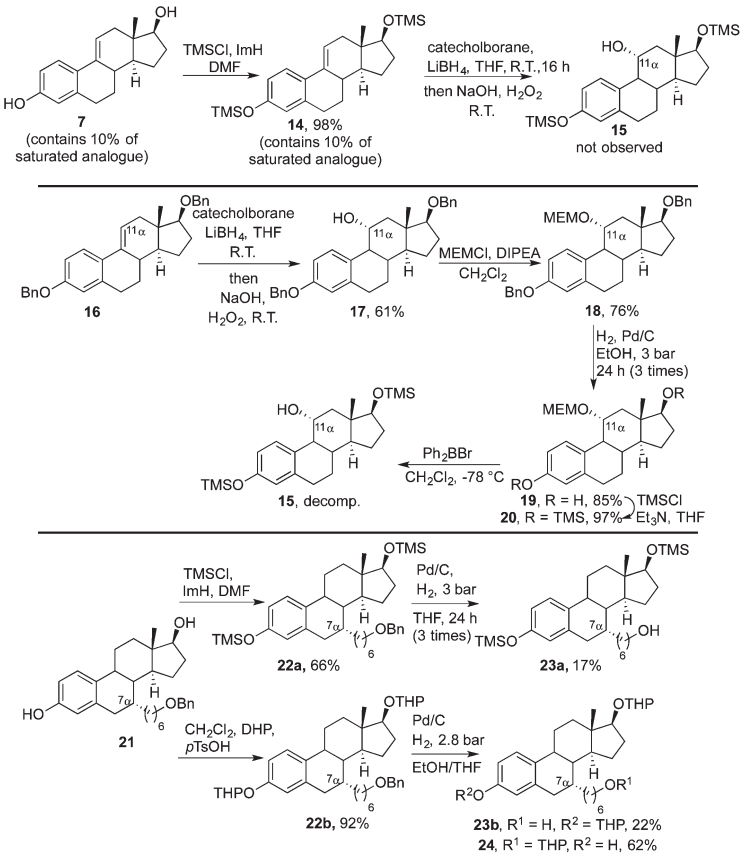


Scheme 4 Attempt to synthesise estradiol derivative **13**.

Consequently, we protected the hydroxyl groups at the 3- and 17β-positions as benzyl ethers, and planned to exchange with TMS groups later in the sequence. We thus focused on the 2-methoxyethoxymethyl ether (MEM) protecting group as it is stable to hydrogenolysis[56] and it has been removed, using Ph_2BBr, in the presence of a TMS group on a beta-lactam.[57,58] We evaluated the protecting group orthogonality using readily available **20** (Scheme 5, middle). Benzyl protection of **7** gave the protected estradiol **16**, along with ~10% of the saturated analogue that is carried from incomplete oxidation of estrone (Scheme 2). Subsequent hydroboration–oxidation gave the 11α-hydroxy derivative **17**, and enabled separation of the saturated analogue.[53] MEM protection, followed by hydrogenolysis and installation of TMS at the 3- and 17β-positions yielded estradiol **20**. Although removal of MEM in the presence of a TMS protecting group was previously reported,[57,58] attempted deprotection of estradiol **20** using Ph_2BBr resulted only in the decomposition of our material. Yet again, a successful protection/deprotection strategy *en route* to estradiol–prodigiosene conjugates defied the supporting evidence gained with model systems.

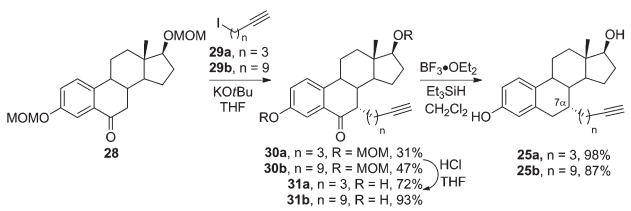
We turned our attention to the 7α-position of the estradiol backbone, given the challenging issues with the synthesis of the required 11-substituted TMS and TBS derivatives. Conjugation at the 7α-position has been shown to provide structures with high binding affinity to ERs,[48] and potential antagonist activity.[59] Cognisant that the TMS protecting group is stable to our planned esterification involving prodigiosenes,[36] we focused on the preparation of **23a** (Scheme 5, bottom). The free hydroxyl groups of estradiol **21** [59] were TMS-protected to give **22a**. However, debenzylation of **22a** using Pd/C at 1 atmosphere of hydrogen in ethanol occurred with the removal of the TMS groups, and we attributed this phenomenon to the ready migration of silyl groups in protic solvents.[60–62] Furthermore, the use of THF at 3 bar of hydrogen for 24 h afforded only a small amount of the desired alcohol. After repeating these conditions three times using the same material, **23a** was isolated in moderate purity and just 17% yield. As such, this route to TMS-protected functionalised estradiols was also jettisoned. The THP-protected **22b** was thus targeted (Scheme 3). However, when attempting the hydrogenolysis of **22b**, unexpected migration of the THP group at the phenolic position to the deprotected primary alcohol was observed, with undesired **24** isolated as the major product. Again, the fickleness of estradiol protecting groups is surprising.

As attempts to synthesise TBS-, TMS- and THP-protected estradiols were unyielding *en route* to 11- and 7-functionalised derivatives, we turned our focus towards estradiols suited to Cu(I)-catalyzed click chemistry with the goal of preparing the first click-appended conjugates of prodigiosenes. Using this approach, we anticipated being able to use protecting groups not based on silicon, as we would no longer be bound by the need to use esterification or etherification as a means of joining the requisite halves of each conjugate. The methoxymethyl acetal (MOM) protecting group thus became available



Scheme 5 Synthesis towards TMS-protected functionalised estradiols.

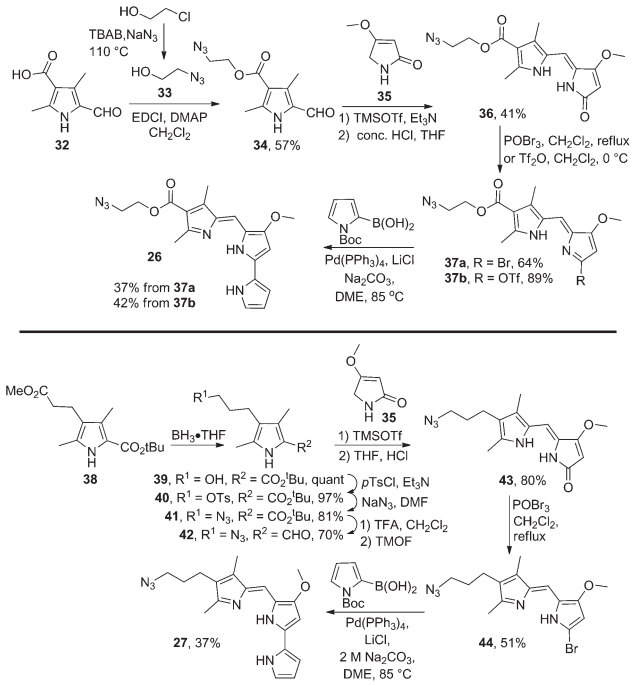
to us for this work. Our conjugates were designed to enable the bioevaluation of the effect of linker chain lengths between the estradiol (**25**) and the prodigiosene moiety (**26** and **27**, Scheme 7). Furthermore, in order to appreciate the influence of the pK_a of the prodigiosene moiety upon the biological properties of the final conjugates,[38] prodigiosenes were designed to feature an azido group linked *via* an ester (**26**, Scheme 7, top) or an alkyl group (**27**, Scheme 7, bottom) on the β-position of the C-ring. Prodigiosenes bearing these two functionalities have been shown to exhibit quite different properties in terms of acidity.[38] Estradiol **28**[59] was thus substituted with linkers **29a–b**[62] to give **30a–b**. Deprotection of the MOM ethers, followed by reduction of the ketone, afforded the desired estradiol coupling partners **25a–b** (Scheme 6).



Scheme 6 Synthesis of protected estradiols bearing alkyne at 7α-position.

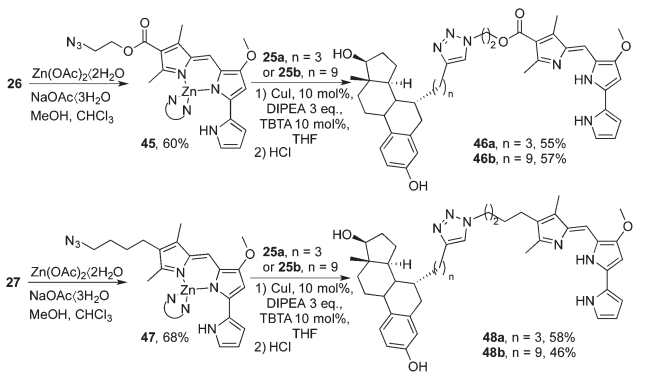
Prodigiosene **26** was synthesised as shown in Scheme 7 (top). Coupling of pyrrole **32**[38] with the linker **33**[63] yielded **34**, which was subsequently condensed with pyrrolinone **35**[64] to give the dipyrrinone **36**. The activated bromo (**37a**) and triflate (**37b**) dipyrrins were obtained in 64% and 89% yield, respectively. Both were subsequently subjected to Suzuki–Miyaura coupling conditions and (1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-yl)boronic acid to generate the key prodigiosene **26**, the first of its kind, bearing an ester-linked azide. Preparation of the prodigiosene **27**, bearing an alkyl-linked azide, commenced with the reduction of the methyl ester of pyrrole **38**[65] to provide the alcohol **39** (Scheme 5, bottom). Subsequent tosylation, followed by treatment with NaN_3, gave **41**. Decarboxylation and formylation provided **42**. Mukaiyama-aldol type condensation between **42** and **35** gave the dipyrrinone **43**,[41] which was brominated in preparation for Suzuki–Miyaura coupling to provide prodigiosene **27**.

The Cu(I)-catalyzed azide–alkyne cycloaddition (CuACC)[66] was then attempted using ester-linked azido prodigiosene **26** and the estradiol derivative **25b** as coupling partners. Although several sets of conditions were used,[67,68] decomposition of the prodigiosene moiety was observed during the reaction, presumably due to the complexation between the dipyrrinato and pyrrolic nitrogen atoms and the copper species.[27] The necessity to protect chelating ligands to enable



Scheme 7 Synthesis of ester- and alkyl linked prodigiosenes bearing azide.

CuACC has been previously noted.[69] Consequently, we protected prodigiosene **26** as a zinc complex (**45**, Scheme 8). Gratifyingly, the use of CuI, tris(benzyltriazolylmethyl)amine (TBTA) and diisopropylamine in THF successfully promoted the CuACC reaction between the prodigiosene zinc complex **45** and estradiols **25a–b**, which, after zinc decomplexation using aqueous HCl, afforded the prodigiosene–estradiol conjugates **46a–b**. Similarly, coupling estradiols **25a–b** and the alkyl-linked azido prodigiosene zinc complex **47** returned the desired prodigiosene–estradiol conjugates **48a–b** (Scheme 8). In general terms, it is significant that the dipyrrinato moiety was shown to undergo CuACC only when the N–N feature was protected. This discovery will be of use in the synthesis of



Scheme 8 Synthesis of 1,2,3-triazole-linked prodigiosene–estradiol conjugates.

functionalised dipyrrins and their complexes such as those used as probes or in optical devices.[70–75]

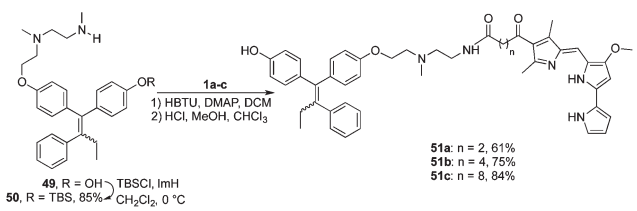
Preparation of tamoxifen conjugates

With four prodigiosene–estradiol conjugates in hand, we expanded the series through synthesis of three prodigiosenes conjugated to 4-hydroxytamoxifen. (*Z*)-4-Hydroxytamoxifen metabolite accounts for the anti-cancer activity of tamoxifen through its high binding affinity to ERs and antagonist activity. The *E* isomer is, instead, weakly estrogenic with a low binding affinity for the receptor.[76] However, the fact that the *E*/*Z* mixture of 4-hydroxytamoxifen analogue **49** [77] exhibits potencies similar to tamoxifen itself, as regards to ER affinity assays and ER antagonist activity,[27] prompted us to use that substrate to build 4-hydroxytamoxifen conjugated to prodigiosenes **1a–c**. The tamoxifen derivative **49** was thus selectively protected with TBS at the phenolic position to give **50** (Scheme 8). Coupling of **50** with prodigiosenes **1a–c**[33] (Fig. 2), followed by deprotection, successfully afforded conjugates **51a–c** (Scheme 9).

Anti-cancer activity

The seven conjugates **46a–b**, **48a–b** and **51a–c** were evaluated by the National Cancer Institute (NCI) across sixty cell lines (NCI-60) representing nine types of cancer,[78] and the activities were found to be moderate. Growth inhibition results at 10 μM of prodigiosene–hydroxytamoxifen conjugates **51a–c** against six human breast cancer cell lines, including MCF7 and T-47D (ER-positive cell lines) and MDA-MB-231/ATCC, HS 578 T, BT-549, MDA-MB 468 (ER-negative cell lines) are shown in the ESI.† Focusing on our goal to target breast cancer with conjugates that are designed to target ER receptors, the results are compared to the previously synthesised conjugates,[33] where the prodigiosene moiety is attached *via* the phenolic position of 4-hydroxytamoxifen that is considered essential for binding. The chain length of the linker of conjugates **51a–c** proved not to influence the extent of growth inhibition, nor did the presence of the conjugated carbonyl moiety. Unexpectedly, conjugates **51a–c**, exhibiting the free phenolic group of tamoxifen are less efficient at inhibiting breast cancer cell growth than those conjugates wherein the phenolic group is engaged in the conjugation with the prodigiosene unit. In contrast, high activity is observed for conjugate **51a** against the ER-negative MDA-MB-231/ATCC cell line.

The anticancer activity of 1,2,3-triazole prodigiosene–estradiol conjugates **46a–b** and **48a–b** are also provided in the ESI.† The alkyl-containing **48a–b** (higher pK_a) displayed enhanced growth inhibition compared to the ester-containing conjugates



Scheme 9 Synthesis of prodigiosene-4-hydroxytamoxifen conjugates.

46a–b (lower pK_a), suggesting that the pK_a of the prodigiosene skeleton plays a role on the anti-cancer activity as a function of enhanced transmembrane anion exchange rates, in line with previous work.[36] Akin to the conjugates to tamoxifen, the linker length is not significant upon growth inhibition suggesting that for prodigiosene conjugates of this genre, alkyl linkers of any length are equally valid. However, compound **48b** also displayed unexpectedly high growth inhibition against the MDA-MB-231/ATCC cell line. The unusual activity against MDA-MB-231/ATCC line for both **48b** and **51a** is intriguing, particularly in light of the fact that this metastatic human mammary carcinoma cell line has been shown to display higher TEA domain (TEAD) transcriptional activity than non-metastatic mammary carcinoma cell lines such as MCF7.[79] TEAD plays a critical role in the function of YAP (yes-associated protein), a protein that aids in cell proliferation and the suppression of apoptosis, and so the YAP/TEAD complex has been suggested as a useful pharmacological target for the treatment of proliferative diseases.[80–84] Of relevance to the results described herein, protoporphyrin IX, hematoporphyrin and verteporfin have been shown to inhibit the YAP/TEAD interaction, and thus suppress the oncogenic effects of YAP.[85] Given the structural similarity of these three porphyrins to the tripyrrolic nature of the prodigiosenes reported herein, the activity of **48b** and **51a** against MDA-MB-231/ATCC warrants further investigation, including the potential for photodynamic therapy effects, now that a reliable synthetic route is available for conjugates of this type.

Conclusions

In summary, the synthesis of estradiol–prodigiosene conjugates *via* an ether linkage, as a more stable alternative than ester, has been attempted. The robustness of estradiol protecting groups has been challenged by reactions typically used to equip such frameworks for 11- and 7-functionalisation. Specifically, TBS, TMS and THP are not useful protecting groups for the functionalisation of estradiol. When the chemical features of the therapeutic agent limit the choice of protecting group (in our case, prodigiosenes bearing aryl, NH, alkenyl and ester groups), click chemistry becomes an attractive synthetic strategy. We herein report the first click-appended prodigiosene conjugates: four prodigiosene conjugates of estradiol, functionalised at the 7α-position, were prepared, as were three prodigiosene conjugates of tamoxifen. The critical features of the targeting moieties were available for binding to ERs, and the influence of such groups was assessed through evaluation of anti-cancer activity. Unexpected growth inhibition activity was observed against the MDA-MB-231/ATCC cell line, which evidently cannot be ascribed to targeting *via* the ER.

Experimental procedures

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 ultrapure silica (230–400 mm) or 150 mesh Brockmann III activated neutral or basic alumina oxide as indicated. An automated system was employed for some chromatography, using prepacked KP-Sil Silica SNAP cartridges. NMR spectra were recorded using 500 MHz or 300 MHz spectrometer instruments. Chemical shifts (δ) are reported in parts per million (ppm) using the solvent signals as reference ($CDCl_3$ 7.26 ppm for ^{1}H, 77.16 ppm for ^{13}C while; MeOD 3.31 ppm for ^{1}H, 49.00 ppm for ^{13}C; DMSO 2.50 ppm for ^{1}H, 39.51 ppm for ^{13}C). Coupling constants, J, are reported in hertz. Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI^+ or ESI^- mode. Compounds **1a–c**,[33] **2**,[39] **6–9**,[51–53] **12**,[55] **16**,[53] **17**,[53] **21**,[59] **28**,[63] **29a**,[62] **32**,[38] **33**,[63] **35**,[64] **38**,[65] **49**[77] were prepared following literature procedures.

Zinc complex of (*Z*)-ethyl 3-(2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-3-oxopropanoate (3)

To a solution of prodigiosene **2** (0.80 g, 1.88 mmol) in $CHCl_3$ (200 mL) was added a solution of $Zn(OAc)_2{\cdot}2H_2O$ (1.03 g, 4.79 mmol) and NaOAc (0.42 g, 5.07 mmol) in MeOH (55 mL). After stirring for 6 hours at room temperature, water (150 mL) was added and the crude mixture then extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with brine (150 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude solid was purified using flash chromatography on Al_2O_3 neutral Brockman III (EtOAc/hexanes 30/70, 40/60, 50/50 then 60/40) to give the title compound as a green-red solid (0.61 g, 71%). R_f = 0.5 Al_2O_3 (EtOAc/hexane 70/30). Mp = 73 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 1.22 (t, J = 7.5 Hz, 3H), 1.65–1.67 (m, 8H), 2.16 (s, 6H), 2.31 (t, J = 7.0 Hz, 4H), 2.54 (s, 3H), 2.68–2.71 (m, 4H), 3.99 (s, 6H), 4.05 (q, J = 7.5 Hz, 4H), 6.06 (s, 1H), 6.10–6.11 (m, 1H), 6.49–6.50 (m, 1H), 6.61–6.62 (m, 1H), 7.35 (s, 1H), 9.22 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 13.1, 14.4, 18.1, 23.8, 24.9, 34.4, 42.3, 58.5, 60.3, 96.1, 110.7, 114.4, 117.9, 123.1, 126.5, 126.9, 131.9, 133.1, 138.7, 155.5, 155.8, 167.0, 173.8, 197.3. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{48}H_{56}N_6NaO_8Zn$: 931.3343; found 931.3320.

(*Z*)-Ethyl 6-(2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)hexanoate hydrochloride (4)

To a solution of prodigiosene **3** (0.17 g, 0.18 mmol) in anhydrous THF (35 mL) was added $BH_3{\cdot}$THF (1 M, 0.75 mL, 0.75 mmol), under inert atmosphere. After stirring for 3 hours at room temperature, the reaction was quenched through the addition of HCl (1 M, 35 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound as a red solid (0.17 g, quant.), which was used in the next step without

further purification. R_f = 0.40 Al_2O_3 (EtOAc/hexane 50/50). ^{1}H NMR ($CDCl_3$, 500 MHz) 1.24 (t, J = 7.5 Hz, 3H), 1.31–1.35 (m, 2H), 1.40–1.45 (m, 2H), 1.63 (quint., J = 7.5 Hz, 2H), 2.19 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 2.51 (s, 3H), 3.98 (s, 3H), 4.11 (q, J = 7.5 Hz, 2H), 6.06 (s, 1H), 6.30–6.32 (m, 1H), 6.85–6.86 (m, 1H), 6.99 (s, 1H), 7.17–7.18 (m, 1H), 12.48 (bs, 1H), 12.51 (bs, 1H), 12.57 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.1, 12.6, 14.4, 24.0, 29.0, 30.0, 34.4, 58.7, 60.4, 92.7, 111.5, 113.1, 116.3, 119.7, 122.5, 124.4, 126.3, 126.6, 137.8, 146.7, 147.5, 165.3, 173.8. HRMS-ESI (m/z): $[M + H - HCl]^+$ calcd for $C_{24}H_{32}N_3O_3$: 410.2438; found 410.2431.

(*Z*)-3-(2-((4-Methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)propan-1-ol hydrochloride (5)

To a suspension of $LiAlH_4$ (0.085 g, 2.24 mmol) in anhydrous THF (10 mL) was added a solution of prodigiosene **4** (0.50 g, 1.12 mmol) in anhydrous THF (40 mL) under inert atmosphere. After stirring for 2 hours at room temperature, the reaction was quenched through the addition of a saturated solution of Na_2SO_4 (10 mL) and HCl 5% (50 mL). The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified using flash chromatography on Al_2O_3 Brockman III neutral (EtOAc/hexane, 50/05 then 70/30) to give through the addition of as a red solid (0.26 g, 50%). R_f = 0.30 Al_2O_3 (EtOAc/hexane, 50/50). ^{1}H NMR ($CDCl_3$, 500 MHz) 1.29–1.38 (m, 4H), 1.39–1.45 (m, 2H), 1.55 (quint., J = 6.5 Hz, 2H), 2.19 (s, 3H), 2.36 (t, J = 6.5 Hz, 2H), 2.51 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 3.97 (s, 3H), 6.05 (s, 1H), 6.29–6.30 (m, 1H), 6.84–6.85 (m, 1H), 6.99 (s, 1H), 7.16–7.18 (m, 1H), 12.45 (bs, 1H), 12.47 (bs, 1H), 12.51 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.1, 12.6, 24.1, 25.7, 29.3, 30.3, 32.8, 58.7, 62.9, 92.7, 111.5, 113.1, 116.2, 119.7, 122.5, 124.4, 126.3, 126.9, 137.9, 146.6, 147.6, 165.2. HRMS-ESI (m/z): $[M + H - HCl]^+$ calcd for $C_{22}H_{30}N_3O_2$: 368.233; found 368.2314.

(*Z*)-6-(2-((4-Methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)hexyl 4-methylbenzenesulfonate (10)

TsCl (0.62 g, 1.63 mmol) and $(iPr)_2EtN$ (1.13 mL, 3.26 mmol) were added to a solution of prodigiosene **5** (0.60 g, 0.82 mmol) in anhydrous CH_2Cl_2 (120 mL) at room temperature and under inert atmosphere. The reaction mixture was stirred for 19 h, quenched through the addition of a saturated aqueous solution of NH_4Cl (80 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified using flash chromatography on Al_2O_3 Brockman III neutral, (EtOAc/hexane, 40/60, 50/50 then 80/20) to give the title compound as a red solid (0.45 g, 53%). R_f: 0.37 (Al_2O_3, EtOAc/hexane 50/50). ^{1}H NMR ($CDCl_3$, 500 MHz) 1.14–1.19 (m, 2H), 1.22–1.27 (m, 4H), 1.57 (t, J = 7.5 Hz, 2H), 1.71 (bs, 3H), 2.07 (s, 3H), 2.15 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 3.97 (s, 3H), 3.98 (t, J = 7.0 Hz, 2H), 6.07 (s, 1H), 6.11 (s, 1H), 6.60 (s, 1H), 6.63 (s, 1H), 6.88 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) 9.7, 10.6, 21.7, 24.1, 25.3, 28.9, 28.9, 30.5, 58.5, 70.8, 95.2, 109.9, 111.8, 113.4, 122.3, 122.7, 125.8, 128.0, 128.9, 129.5, 129.9, 133.3, 136.6, 144.7, 158.5, 168.6. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{29}H_{36}N_3O_4S$: 522.2421; found 522.2412.

(13*S*,14*S*)-3-((6-((*Z*)-2-((4-Methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)hexyl)oxy)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one (11a)

To a solution of estrone (0.031 g, 0.11 mmol) in anhydrous DMF (3 mL) was added NaH (5.0 g, 0.11 mmol) at 0 °C and under inert atmosphere. The reaction mixture was stirred for 40 min at room temperature then cooled down to 0 °C and a solution of prodigiosene **10** (0.05 g, 0.095 mmol) in anhydrous DMF (1 mL) was added. The reaction was stirred overnight at room temperature, then quenched with 1% HCl. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers washed with water (2 × 30 mL) and brine (1 × 30 mL), then dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified using flash chromatography (Al_2O_3 neutral type III, EtOAc/hexane, 40/60) then (SiO_2, EtOAc/hexane, 40/60) to give the title compound as a red film (17 mg, 17%). R_f = 0.50 (Al_2O_3, EtOAc/hexane, 40/60). ^{1}H NMR ($CDCl_3$, 500 MHz) 0.90 (s, 3H), 1.35–1.39 (m, 3H), 1.44–1.52 (m, 8H), 1.57–1.66 (m, 4H), 1.76 (quint., J = 6.5 Hz, 2H), 1.92–2.04 (m, 3H), 2.10–2.15 (m, 1H), 2.22 (s, 3H), 2.38–2.41 (m, 3H), 2.48–2.51 (m, 1H), 2.54 (s, 3H), 2.87–2.88 (m, 2H), 3.92 (t, J = 6.5 Hz, 2H), 4.00 (s, 3H), 6.08 (d, J = 1.5 Hz, 1H), 6.33–6.34 (m, 1H), 6.63 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.5 and 2.5 Hz, 1H), 6.88 (bs, 1H), 7.03 (s, 1H), 7.17–7.20 (m, 2H), 12.51 (bs, 1H), 12.56 (bs, 1H), 12.62 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 10.2, 12.7, 14.0, 21.7, 24.1, 26.0, 26.1, 26.7, 29.2, 29.4, 29.8 (2C), 30.3, 31.7, 36.0, 38.5, 44.1, 48.1, 50.5, 58.7, 67.8, 92.7, 111.5, 112.2, 113.2, 114.6, 116.2, 119.7, 122.5, 124.4, 126.3, 126.4, 126.9, 132.0, 137.8, 137.9, 146.6, 147.7, 157.2, 165.2, 221.1. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{40}H_{50}N_3O_3$: 620.3847; found 620.3847.

(11*R*,13*S*,14*S*,17*S*)-3,17-Bis(trimethylsilyloxy)-11-((2-methoxyethoxy)methoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (14)

To a solution of **7** [53] (400 mg, 1.48 mmol) in DMF (40 mL) was added imidazole (2.00 g, 29.6 mmol) followed by TMSCl (1.80 mL, 14.8 mmol). After stirring at room temperature for 16 h, water (150 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexane 1/9) to give a colorless oil (604 mg, 98% that contained 10% of the saturated analogue). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.12 (s, 9H), 0.27 (s, 9H), 0.78 (s, 3H), 1.29–1.45 (m, 3H), 1.53–1.60 (m, 1H), 1.77–1.84 (m, 1H), 1.92–2.09 (m, 4H), 2.15–2.19 (m, 1H), 2.75–2.89 (m, 2H), 3.73 (t, J = 5.1 Hz, 1H), 6.12–6.13 (m, 1H), 6.56 (d, J = 2.5 Hz, 1H),

6.64 (dd, J = 8.7, 2.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 0.4, 11.4, 24.2, 28.4, 30.1, 31.1, 39.1, 39.6, 41.8, 47.3, 81.9, 118.2, 118.3, 120.1, 125.1, 128.4, 135.2, 137.6, 153.9. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{24}H_{39}O_2Si_2$, 415.2483; found, 415.32483.

(11*R*,13*S*,14*S*,17*S*)-3,17-Bis(benzyloxy)-11-((2-methoxyethoxy) methoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (18)

To a solution of **17** [53] (370 mg, 0.79 mmol) in CH_2Cl_2 (8.0 mL) was added DIPEA (0.69 mL, 3.95 mmol) followed by MEMCl (0.23 mL, 1.97 mmol). After stirring at room temperature for16 h, a saturated solution of NH_4Cl (30 mL) was added. The mixture was stirred for 15 min, and then extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude was purified using flash chromatography (SiO_2, EtOAc/hexane 2/8) to give the title compound as a white solid (335 mg, 76%). Mp 70 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.84 (s, 3H), 1.27–1.33 (m, 3H), 1.35–1.46 (m, 2H), 1.57–1.69 (m, 2H), 1.83–1.87 (m, 1H), 2.04–2.11 (m, 1H), 2.32 (t, J = 10.0 Hz, 1H), 2.64 (dd, J = 12.2, 5.2 Hz, 1H), 2.78 (t, J = 6.7 Hz, 2H), 3.40 (s, 3H), 3.52 (t, J = 8.2 Hz, 1H), 3.56–3.62 (m, 2H), 3.75–3.82 (m, 2H), 4.14–4.19 (m, 1H), 4.57 (s, 2H), 4.90 (d, J = 6.7 Hz, 1H), 5.03–5.04 (m, 3H), 6.73 (d, J = 2.5 H, 1H), 6.77 (dd, J = 8.7, 2.5 Hz, 1H), 7.27–7.40 (m, 8H), 7.43 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 9.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.7, 23.2, 27.0, 28.1, 28.9, 37.4, 44.0, 44.3, 47.8, 49.9, 59.2, 68.0, 70.0, 71.8, 71.9, 77.8, 87.7, 94.7, 112.0, 114.5, 127.0, 127.5, 127.6, 127.9, 128.4, 128.7, 133.0, 137.5, 139.2, 139.5, 157.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{36}H_{44}Na_1O_5$, 579.3081; found, 579.3073.

(11*R*,13*S*,14*S*,17*S*)-11-((2-Methoxyethoxy)methoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*] phenanthrene-3,17-diol (19)

To a degassed (bubbling with nitrogen for 3 min) solution of **18** (450 mg, 0.81 mmol) in a mixture of THF/EtOH (15/20 mL) was added Pd/C 10% (50 mg) and 2 drops of triethylamine. The mixture was then purged 3 times with 1 bar of hydrogen, then stirred at 3 bar of hydrogen for 18 h. The reaction mixture was degassed using nitrogen, then filtered through a pad of Celite® washing with MeOH. After evaporation of the solvent under reduced pressure, the same procedure was repeated to obtain the title compound as a colorless oil (260 mg, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.73 (s, 3H), 1.21–1.26 (m, 3H), 1.35–1.42 (m, 2H), 1.46–1.53 (m, 1H), 1.63–1.67 (m, 1H), 1.79–1.84 (m, 1H), 2.07–2.13 (m, 1H), 2.28 (t, J = 10.0 Hz, 1H), 2.51 (dd, J = 12.0, 5.0 Hz, 1H), 2.70–2.72 (m, 2H), 3.41 (s, 3H), 3.57–3.64 (m, 2H), 3.73–3.77 (m, 2H), 3.79–3.83 (m, 1H), 4.12 (dt, J = 10.0, 5.0 Hz, 1H), 4.87 (d, J = 7.0 Hz, 1H), 5.00 (d, J = 7.0 Hz, 1H), 6.39 (s, 1H), 6.56 (d, J = 2.8 Hz, 1H), 6.59 (dd, J = 8.5, 2.8 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.9, 23.1, 26.9, 28.6, 30.3, 37.8, 43.2, 43.9, 47.6, 49.6, 59.1, 67.9, 71.9, 78.0, 81.3, 94.8, 112.5, 115.0, 126.9, 132.2, 139.6, 154.0. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{22}H_{32}Na_1O_5$, 399.2142; found, 399.2131.

(11*R*,13*S*,14*S*,17*S*)-3,17-Bis(trimethylsililoxy)-11-((2-methoxyethoxy)methoxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (20)

To a solution of **19** (260 mg, 0.69 mmol) in THF (10 mL) was added Et_3N (0.58 mL, 3.46 mmol) followed by TMSCl (0.44 mL, 2.76 mmol). After stirring at room temperature for 16 h, water (30 mL) was added and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4). After evaporation of the solvent the title compound was obtained as a colorless oil (350 mg, 97%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 9H), 0.25 (s, 9H), 0.72 (s, 3H), 1.17–1.61 (m, 6H), 1.61–1.69 (m, 1H), 1.79–2.01 (m, 2H), 2.29 (t, J = 10.0 Hz, 1H), 2.47 (dd, J = 12.0, 5.1 Hz, 1H), 2.74 (t, J = 6.6 Hz, 2H), 3.41 (s, 3H), 3.58 (t, J = 4.7 Hz, 2H), 3.65 (t, J = 8.2 Hz, 1H), 3.74–3.82 (m, 2H), 4.14 (dt, J = 10.2, 5.1 Hz, 1H), 4.91 (d, J = 7.0 Hz, 1H), 5.03 (d, J = 7.0 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 6.61 (dd, J = 8.5, 2.5 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 0.3, 0.4, 12.2, 23.3, 27.1, 28.7, 31.0, 37.7, 43.6, 44.0, 47.9, 49.4, 59.1, 67.9, 71.9, 78.1, 81.2, 94.8, 117.0, 119.6, 126.7, 133.4, 139.4, 153.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{28}H_{48}Na_1O_5Si_2$, 543.2932; found, 543.2907.

(((7*R*,13*S*,14*S*,17*S*)-7-(6-(Benzyloxy)hexyl)-17-((trimethylsilyl) oxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)trimethylsilane (22a)

To a solution of **21** [59] (480 mg, 1.04 mmol) in DMF (25 mL) was added imidazole (2.94 g, 43.2 mmol), followed by TMSCl (2.74 mL, 21.6 mmol). After stirring at room temperature for 16 h, water (100 mL) was added and the mixture was extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with water (2 × 40 mL), then brine (50 mL). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography (SiO_2, EtOAc/hexane 1/9) to give the title compound as a colorless oil (415 mg, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.10 (s, 9H), 0.26 (s, 9H), 0.75 (s, 3H), 0.98–1.05 (m, 1H), 1.14–1.20 (m, 3H), 1.26–1.35 (m, 6H), 1.44–1.50 (m, 2H), 1.56–1.62 (m, 4H), 1.71–1.73 (m, 1H), 1.81–1.85 (m, 1H), 1.89–1.96 (m, 1H), 2.26–2.30 (m, 2H), 2.68 (d, J = 16.5 Hz, 1H), 2.84 (dd, J = 16.5, 5.2 Hz, 1H), 3.44 (t, J = 6.2 Hz, 2H), 3.65 (t, J = 8.5 Hz, 1H), 4.49 (s, 2H), 6.54 (d, J = 2.5 Hz, 1H), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 7.25–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 0.4, 0.5, 11.5, 22.9, 25.7, 26.4, 27.4, 28.3, 29.9, 30.0, 30.5, 31.0, 33.4, 34.7, 37.4, 38.4, 42.1, 43.6, 46.3, 70.6, 73.0, 81.9, 117.2, 120.9, 126.8, 127.6, 127.7, 128.5, 132.8, 137.0, 138.8, 152.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{37}H_{58}Na_1O_3Si_2$, 629.3817; found, 629.3798.

6-((7*R*,13*S*,14*S*,17*S*)-13-Methyl-3,17-bis((trimethylsilyl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*] phenanthren-7-yl)hexan-1-ol (23a)

To a degassed (bubbled with nitrogen for 3 min) solution of estradiol **22a** (425 mg, 0.7 mmol) in THF (25 mL) was added

Pd/C 10% (300 mg) and 2 drops of triethylamine. The mixture was purged 3 times with 1 bar of hydrogen, then stirred at 3 bar of hydrogen for 24 h. The reaction mixture was degassed using nitrogen, then filtered through a pad of Celite® washing with CH_2Cl_2. This procedure was repeated 3 times. After evaporation of the solvent under reduced pressure, the crude was purified using column chromatography (SiO_2, EtOAc/hexane 1/9 then 2/8) to give estradiol **23a** (63 mg, 17%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.10 (s, 9H), 0.25 (s, 9H), 0.75 (s, 3H), 0.97–1.06 (m, 1H), 1.14–1.34 (m, 10H), 1.40–1.63 (m, 6H), 1.71–1.73 (m, 1H), 1.82–1.84 (m, 1H), 1.90–1.97 (m, 1H), 2.27–2.30 (m, 2H), 2.68 (d, J = 16.5 Hz, 1H), 2.84 (dd, J = 16.5, 5.5 Hz, 1H), 3.62–3.66 (m, 3H), 6.54 (d, J = 2.5 Hz, 1H), 6.61–6.63 (m, 1H), 7.12 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 0.4, 0.5, 11.5, 22.9, 25.7, 25.9, 27.4, 28.3, 29.9, 31.0, 32.9, 33.4, 34.8, 37.4, 38.4, 42.1, 43.6, 46.3, 63.2, 81.9, 117.3, 121.0, 126.8, 132.8, 137.0, 152.9. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{30}H_{52}Na_1O_3Si_2$, 539.3347; found, 539.3330.

2-(((7*R*,13*S*,14*S*,17*S*)-7-(6-(Benzyloxy)hexyl)-17-(cyclohexyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)tetrahydro-2*H*-pyran (22b)

To a solution of **21** [59] (475 mg, 1.03 mmol) in CH_2Cl_2 (47 mL) was added DHP (470 μL, 5.13 mmol) under nitrogen, followed by a catalytic amount of *para*-toluene sulfonic acid (2.0 mg, 1 mol%). The solution was stirred at room temperature for 2 hours, then water (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). After evaporation of the solvent, the residual oil was purified using flash column chromatography (SiO_2, EtOAc/hexane 1/9 then 2/8) to give the title compound as a colorless oil (600 mg, 92%) as a 1 : 1 mixture of 2 diastereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79 (s, 3H), 0.81 (s, 3H), 0.97–1.06 (m, 2H), 1.14–1.21 (m, 4H), 1.26–1.78 (m, 44H), 1.83–1.92 (m, 8H), 1.97–2.10 (m, 4H), 2.27–2.33 (m, 4H), 2.73 (dd, J = 16.5, 6.5 Hz, 2H), 2.85–2.89 (m, 2H), 3.44 (t, J = 6.5 Hz, 4H), 3.48–3.54 (m, 4H), 3.58–3.60 (m, 2H), 3.72–3.75 (m, 2H), 3.86–3.94 (m, 6H), 4.49 (s, 4H), 4.64–4.68 (m, 2H), 4.95–4.96 (m, 2H), 5.38 (dt, J = 14.0, 3.0 Hz, 2H), 6.76 (d, J = 2.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.7 Hz, 2H), 7.27–7.28 (m, 2H), 7.33–7.34 (m, 8H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.8, 11.9, 19.0 (2C), 19.5, 19.9, 20.1, 22.7, 22.8, 25.4, 25.6, 25.7, 25.8, 26.4, 27.0, 27.3, 27.4 (2C), 28.3, 28.9, 29.8, 29.9, 30.6 (2C), 30.8, 31.2, 33.3, 33.4, 34.8, 37.5, 38.1, 38.2 (2C), 38.3 (2C), 41.8 (2C), 43.0, 43.6, 46.6 (2C), 61.9, 62.1, 62.2, 62.9, 63.1, 70.6, 72.9, 84.4, 86.7, 94.8, 96.3, 96.6, 96.7, 99.5, 113.9, 114.0, 117.4, 117.5, 126.8, 126.9, 127.6, 127.7, 128.4, 133.1 (2C), 133.2, 133.3, 137.0 (2C), 138.8, 155.0, 155.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{41}H_{58}Na_1O_5$, 653.4176; found, 653.4163.

6-((7*R*,13*S*,14*S*,17*S*)-13-Methyl-3,17-bis((tetrahydro-2*H*-pyran-2-yl)oxy)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)hexan-1-ol (23b)

To a degassed (bubbled with nitrogen for 3 min) solution of estradiol **22b** (400 mg, 0.63 mmol) in a mixture of THF/EtOH (15/10 mL) was added Pd/C 10% (300 mg) and 2 drops of triethylamine. The mixture was then purged 3 times with 1 bar of hydrogen, then stirred at 2.8 bar of hydrogen for 18 h. The reaction mixture was then degassed using nitrogen, then filtered through a pad of Celite® washing with CH_2Cl_2. After evaporation of the solvent under reduced pressure, the crude material was purified using column chromatography (SiO_2, EtOAc/hexane 4/6) to give estradiol **23b** (75 mg, 22%) and estradiol **24** (210 mg, 62%). Estradiol **23b**: R_f = 0.44 (SiO_2, EtOAc/hexane 4/6), 1 : 1 mixture of two diastereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79 (s, 3H), 0.81 (s, 3H), 1.00–1.03 (m, 2H), 1.18–1.74 (m, 54H), 1.83–1.91 (m, 6H), 1.96–2.10 (m, 4H), 2.27–2.31 (m, 4H), 2.73 (dd, J = 16.5, 7.0 Hz, 2H), 2.85–2.89 (m, 2H), 3.48–3.50 (m, 2H), 3.58–3.62 (m, 6H), 3.72–3.76 (m, 2H), 3.89–3.97 (m, 4H), 4.65–4.68 (m, 2H), 5.38 (dt, J = 11.8, 3.2 Hz, 2H), 6.75 (d, J = 2.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 7.18 (t, J = 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.8, 19.0 (2C), 19.5, 20.1, 22.7, 22.8, 25.4, 25.7, 25.8, 25.9, 27.3, 27.4, 28.3, 28.9, 29.9, 30.6, 31.2, 32.9, 33.3, 33.4, 34.8, 37.5, 38.1, 38.2, 38.3 (2C), 41.8 (2C), 43.0, 43.6, 46.6 (2C), 61.9, 62.2 (2C), 62.9, 63.1, 65.5, 84.3, 86.7, 96.4, 96.6, 96.7, 99.5, 114.0 (2C), 117.5, 126.9 (2C), 133.1 (2C), 133.2 (2C), 136.9, 155.0, 155.1. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{34}H_{52}Na_1O_5$, 563.3707; found, 563.3685.

(7*R*,13*S*,14*S*,17*S*)-13-Methyl-17-((tetrahydro-2*H*-pyran-2-yl)oxy)-7-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-ol (24)

See procedure for compound **23b**. 1 : 1 mixture of two diastereoisomers. R_f = 0.24 (SiO_2, EtOAc/hexane 4/6). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (s, 3H), 0.82 (s, 3H), 0.99–1.06 (m, 2H), 1.20–1.73 (m, 60H), 1.84–1.92 (m, 4H), 1.98–2.08 (m, 4H), 2.25–2.28 (m, 4H), 2.67 (d, J = 16.5 Hz, 2H), 2.84 (d, J = 16.5, 2H), 3.49–3.53 (m, 2H), 3.61 (t, J = 6.6 Hz, 4H), 3.74 (t, J = 8.0 Hz, 2H), 3.90–3.96 (m, 2H), 4.68–4.71 (m, 2H), 6.54 (d, J = 2.2 Hz, 2H), 6.62 (dd, J = 8.4, 2.2 Hz, 2H), 7.11 (dd, J = 8.4, 3.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.8, 11.9, 19.3, 19.9, 22.7, 22.8, 25.6 (2C), 25.7, 25.9, 27.3, 27.4, 27.5, 28.2, 28.8, 29.8, 31.1, 32.7, 33.3, 33.4, 34.7, 37.5, 38.1, 38.3, 41.9 (2C), 43.0, 43.5, 46.5, 46.6, 61.9, 62.8, 63.0, 84.5, 86.9, 96.7, 99.5, 113.0, 116.3, 127.0, 131.6, 131.7, 137.0, 153.9 (2C). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{34}H_{52}Na_1O_5$, 563.3707; found, 563.3712.

11-Iodoundec-1-yne (29b)

According to the literature procedure,[62] to a solution of undec-10-yn-1-ol (1.00 g, 5.90 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added imidazole (483 mg, 7.10 mmol) and PPh_3 (1.87 g, 7.10 mmol). Then, solid I_2 (1.8 g, 7.1 mmol) was added in portions. After stirring at room temperature for 4 h, the reaction was quenched through the addition of a saturated solution of $Na_2S_2O_3$ (100 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash chrom-

atography (SiO_2 EtOAc/hexane 0.5/99.5) to give the title compound as a colorless oil (1.54 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30 (s, 6H), 1.37–1.40 (m, 4H), 1.52 (quint., J = 7.0 Hz, 2H), 1.82 (quint., J = 7.0 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 2.18 (dt, J = 7.0, 2.5 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 7.5, 18.5, 28.6 (2C), 28.8, 29.1, 29.4, 30.6, 33.7, 68.2, 84.9.

(7*S*,13*S*,14*S*,17*S*)-3,17-Bis(methoxymethoxy)-13-methyl-7-(pent-4-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (30a)

According to the literature procedure,[59] to a cold (0 °C) solution of estradiol **28** (500 mg, 1.33 mmol) in dry THF (15 mL) was added a solution of *t*BuOK in THF (1 M, 2.0 mL, 1.99 mmol) to give a yellow solution. After stirring at 0 °C for 1 h, the reaction mixture was cooled to −78 °C and a solution of 5-iodopent-1-yne **29a** (300 μL, 2.67 mmol) in anhydrous THF (5 mL), was added drop-wise. The reaction mixture was stirred at 0 °C for 2 h, and then for a further 16 h at room temperature. The reaction was quenched through the addition of an aqueous saturated solution of NH_4Cl (20 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using an automated chromatography system (SiO_2, EtOAc/hexane 5/95 for 5 min then EtOAc/hexane 5/95 to 40/60 for 40 min) to provide the title compound as a colorless oil (183 mg, 31%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79 (s, 3H), 1.31–1.39 (m, 2H), 1.45–1.61 (m, 6H), 1.65–1.69 (m, 1H), 1.76–1.89 (m, 1H), 1.90 (t, J = 2.5 Hz, 1H), 1.98–2.02 (m, 1H), 2.05–2.10 (m, 2H), 2.14–2.24 (m, 2H), 2.35–2.38 (m, 1H), 2.45–2.48 (m, 1H), 2.70 (dt, J = 11.5, 4.5 Hz, 1H), 3.36 (s, 3H), 3.46 (s, 3H), 3.64 (t, J = 8.5 Hz, 1H), 4.64 (dd, J_{AB} = 10.0, 6.5 Hz, 2H), 5.18 (s, 2H), 7.18 (dd, J = 8.5, 2.7 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.6, 18.1, 22.3, 22.4, 25.9, 26.7, 28.0, 37.1, 37.5, 42.3, 43.1, 45.4, 48.0, 55.3, 56.2, 68.8, 84.1, 86.4, 94.6, 96.2, 114.2, 122.5, 127.3, 132.3, 139.8, 155.9, 200.4. (ESI): $[M + Na]^+$ calcd for $C_{27}H_{36}Na_1O_5$, 463.2455; found, 463.2440.

(7*S*,13*S*,14*S*,17*S*)-3,17-Bis(methoxymethoxy)-13-methyl-7-(undec-10-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (30b)

According to the literature procedure,[59] to a cold (0 °C) solution of estradiol **28** (520 mg, 1.38 mmol) in dry THF (15 mL) was added a solution of *t*BuOK in THF (1 M, 2.1 mL, 2.10 mmol) to give a yellow solution. After stirring at 0 °C for 1 h the reaction mixture was cooled to −78 °C, and a solution of 11-iodoundec-1-yne **29b** (770 mg, 2.76 mmol) in anhydrous THF (5.0 mL), was added drop-wise. The reaction was stirred at 0 °C for 2 h, and then stirred for a further 16 h at room temperature. The reaction was quenched through the addition of an aqueous saturated solution of NH_4Cl (20 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using an automated chromatography system (SiO_2, EtOAc/hexane 7/93 for 5 min then EtOAc/hexane 7/93 to 60/40 for 40 min) to give the title compound as a colorless oil (338 mg, 47%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.80 (s, 3H), 1.16–1.42 (m, 16H), 1.47–1.63 (m, 6H), 1.93 (t, J = 2.7 Hz, 1H), 2.00 (dt, J = 12.0, 3.0 Hz, 1H), 2.10–2.12 (m, 2H), 2.17 (dt, J = 7.0, 3.0 Hz, 2H), 2.35–2.39 (m, 1H), 2.45 (dt, J = 11.5, 3.0 Hz, 1H), 2.70 (dt, J = 11.0, 5.0 Hz, 1H), 3.37 (s, 3H), 3.48 (s, 3H), 3.65 (t, J = 8.5 Hz, 1H), 4.66 (dd, J_{AB} = 10.0, 6.5 Hz, 2H), 5.20 (s, 2H), 7.19 (dd, J = 8.5, 3.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.7, 18.5, 22.4, 23.8, 26.7, 27.4, 28.0, 28.6, 28.8, 29.2, 29.6, 29.8, 37.1, 37.5, 42.4, 43.1, 45.4, 48.8, 55.3, 56.3, 68.2, 84.9, 86.5, 94.6, 96.2, 114.2, 122.4, 127.3, 132.5, 139.8, 155.8, 200.9 (1 carbon unaccounted for). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{33}H_{48}Na_1O_5$, 547.3394; found, 547.3400.

(7*S*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7-(pent-4-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (31a)

According to the literature procedure,[59] to a solution of **30a** (180 mg, 0.41 mmol) in THF (2.6 mL) at 0 °C was added 6 M HCl (2.6 mL). The resulting solution was stirred at room temperature for 20 h, and then water (50 mL) was added. The reaction mixture was then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash chromatography (SiO_2 EtOAc/hexane 5/5). The obtained solid contained 5% of the epimer, according to analysis using NMR spectroscopy, and was dissolved in hot Et_2O (15 mL). A solid was precipitated through the addition of pentane. Isolation of the solid *via* filtration, followed by washing with pentane gave the title compound as a white solid (104 mg, 72%, single isomer according ^{1}H and ^{13}C NMR spectroscopic analysis). Mp 174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79 (s, 3H), 1.32–1.39 (m, 3H), 1.47–1.61 (m, 5H), 1.64–1.79 (m, 1H), 1.79–1.84 (m, 1H), 1.91 (t, J = 2.5 Hz, 1H), 1.97 (dt, J = 12.5, 3.5 Hz, 1H), 2.08–2.25 (m, 5H), 2.38–2.47 (m, 1H), 2.46–2.49 (m, 1H), 2.71 (dt, J = 11.5, 4.7 Hz, 1H), 3.73–3.80 (m, 1H), 5.67 (s, 1H), 7.04 (dd, J = 8.2, 2.7 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.0, 18.2, 22.4, 22.6, 26.0, 26.8, 30.6, 36.6, 37.5, 42.7, 43.5, 45.5, 48.1, 68.9, 81.8, 84.1, 113.6, 121.6, 127.6, 132.3, 138.7, 154.7, 201.2. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{23}H_{29}O_3$, 353.2111; found, 353.2103.

(7*S*,13*S*,17*S*)-3,17-Dihydroxy-13-methyl-7-(undec-10-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-one (31b)

According to the literature procedure,[59] to a solution of compound **30b** (340 mg, 0.77 mmol) in THF (5.0 mL) at 0 °C was added 6 M HCl (5.0 mL). The solution was stirred at room temperature for 20 h, then water (50 mL) was added. The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine and then dried

(Na_2SO_4). After evaporation of the solvent under reduced pressure a white solid was obtained (260 mg, 93%) that was engaged in the next step without purification. Mp 170 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.78 (s, 3H), 1.14–1.39 (m, 16H), 1.43–1.61 (s, 6H), 1.84 (br s, 1H), 1.93 (t, J = 2.5 Hz, 1H), 1.96–1.98 (m, 1H), 2.08 (dt, J = 11.0, 3.5 Hz, 1H), 2.13–2.17 (m, 3H), 2.37–2.40 (m, 1H), 2.44–2.47 (m, 1H), 2.69 (dt, J = 11.5, 4.5 Hz, 1H), 3.79 (t, J = 8.5 Hz, 1H), 6.76 (s, 1H), 7.07 (dd, J = 8.5, 2.7 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.0, 18.5, 22.4, 23.9, 26.7, 27.4, 28.6, 28.8, 29.2, 29.5, 29.8, 30.4, 36.6, 37.4, 42.8, 43.4, 45.4, 48.9, 68.2, 81.8, 85.0, 113.6, 121.7, 127.5, 132.2, 138.5, 154.9, 202.2 (1 carbon unaccounted for). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{29}H_{40}Na_1O_3$, 459.2870; found, 459.2854.

(7*R*,13*S*,17*S*)-13-Methyl-7-(pent-4-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (25a)

According to the literature procedure,[59] to a suspension of **31a** (100 mg, 0.28 mmol) in dry CH_2Cl_2 (8.0 mL) at 0 °C was added $HSiEt_3$ (1.30 mL) followed by $BF_3{\cdot}OEt_2$ (8.0 mL). The reaction mixture was stirred at room temperature for 12 h, and then for a further 4 h at 40 °C. The reaction mixture was then carefully quenched at 0 °C through the addition of a 10% solution of potassium carbonate (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash chromatography (SiO_2, EtOAc/hexane 4/6) to give the title compound as a white solid (93 mg, 98%). Mp 78 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79 (s, 3H), 1.10–1.13 (m, 1H), 1.24–1.39 (m, 4H), 1.42–1.52 (m, 4H), 1.56–1.72 (m, 3H), 1.76–1.79 (m, 1H), 1.89–1.93 (m, 2H), 2.10–2.16 (m, 3H), 2.28–2.34 (m, 2H), 2.68 (d, J = 17.0 Hz, 1H), 2.89 (dd, J = 17.0, 5.5 Hz, 1H), 3.76 (t, J = 8.5 Hz, 1H), 4.77 (br s, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.63 (dd, J = 8.5, 2.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.2, 18.8, 22.8, 25.0, 27.3, 27.4, 30.7, 33.0, 34.6, 37.0, 38.2, 42.1, 43.6, 46.6, 68.4, 82.2, 84.7, 113.1, 116.3, 127.3, 132.0, 136.9, 153.6. HRMS-APCI (m/z): $[M + H]^+$ calcd for $C_{23}H_{31}O_2$, 339.2319; found, 339.2314.

(7*R*,13*S*,17*S*)-13-Methyl-7-(undec-10-yn-1-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (25b)

According to the literature procedure,[59] to a suspension of **31b** (50 mg, 0.11 mmol) in dry CH_2Cl_2 (3.0 mL) at 0 °C was added $HSiEt_3$ (0.5 mL) and $BF_3{\cdot}OEt_2$ (2.0 mL). The reaction mixture was stirred at room temperature for 5 h and then carefully quenched at 0 °C through the addition of a 10% solution of potassium carbonate (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash chromatography (SiO_2, EtOAc/hexane 4/6) to give the title compound as a white solid (40 mg, 87%). Mp 119 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.78 (s, 3H), 0.98–1.05 (m, 1H), 1.17–1.54 (m, 20H), 1.58–1.64 (m, 3H), 1.72–1.74 (m, 1H), 1.89–1.92 (m, 1H), 1.94 (t, J = 3.0 Hz, 1H), 2.10–2.19 (m, 3H), 2.28–2.33 (m, 2H), 2.71 (d, J = 16.5 Hz, 1H), 2.86 (dd, J = 16.5, 5.5 Hz, 1H), 3.75 (t, J = 8.5 Hz, 1H), 4.77 (s, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.63 (dd, J = 8.5, 2.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.2, 18.5, 22.8, 25.7, 27.4, 28.3, 28.6, 28.9, 29.2, 29.6, 29.8, 30.1, 30.7, 33.3, 34.7, 37.0, 38.2, 42.1, 43.5, 46.6, 68.2, 82.2, 85.0, 112.9, 116.3, 127.2, 132.1, 137.3, 153.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{29}H_{42}Na_1O_2$, 445.3077; found, 445.3080.

2-Azidoethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (34)

To a stirred solution of 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**32**,[38] 1.60 g, 9.60 mmol) in dry CH_2Cl_2 (35 mL) was added DMAP (1.30 g, 10.6 mmol) and EDCI (1.64 g, 10.6 mmol), followed by 2-azidoethanol (**33**, 925 mg, 10.6 mmol) and the resulting solution was heated at reflux temperature for 2 days. The reaction mixture was then cooled to room temperature and water (50 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (50 mL), then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude product was purified using flash chromatography (SiO_2, EtOAc/hexane 4/6) to give the title compound as a white solid (1.29 g, 57%). Mp 98 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.57 (s, 3H), 2.59 (s, 3H), 3.61 (t, J = 5.0 Hz, 2H), 4.41 (t, J = 5.0 Hz, 2H), 9.63 (s, 1H), 9.82 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.8, 14.6, 50.3, 62.1, 113.5, 128.5, 136.0, 143.7, 164.6, 177.5. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{10}H_{12}N_4Na_1O_3$, 259.0802; found, 259.0802.

(*Z*)-2-Azidoethyl 5-((3-methoxy-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (36)

To a solution of **35**[64] (659 mg, 5.83 mmol) in dry CH_2Cl_2 (190 mL) was added triethylamine (2.2 mL, 15.9 mmol) followed by TMSOTf (1.45 mL, 7.95 mmol) at 0 °C. After 20 min, a solution of **34** (600 mg, 2.65 mmol) in dry CH_2Cl_2 (40 mL) was added at 0 °C. The reaction mixture was stirred at this temperature for 4 hours. The reaction was quenched through the addition of phosphate buffer (pH = 7, 100 mL). The solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine, then dried (Na_2SO_4). After evaporation of the solvent, the resulting brown oil was dissolved in THF (230 mL) and concentrated aqueous HCl (580 µL, 6.89 mmol) was added. After a few minutes the reaction was quenched through the addition of saturated aqueous $NaHCO_3$ (200 mL), then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL). After concentration of the organic fraction under vacuum, the resulting suspension was washed with water and hexane, then hot methanol using filtration, to give a yellow solid (360 mg, 41%). Mp 229 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 2.64 (s, 3H), 3.60 (t, J = 5.0 Hz, 2H), 3.84 (s, 3H), 4.39 (t, J = 5.0 Hz, 2H), 5.02 (s, 1H), 6.32 (s, 1H), 10.64 (s, 1H), 11.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.5, 14.3, 50.5, 58.4, 61.7, 90.3, 99.6, 111.8, 122.7, 123.8, 128.3, 142.2, 165.3,

168.2, 173.6. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{17}N_5Na_1O_4$, 354.1173; found, 354.1175.

(*Z*)-2-Azidoethyl 2-((5-bromo-3-methoxy-1*H*-pyrrol-2-yl) methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (37a)

To a stirred solution of **36** (390 mg, 1.18 mmol) in dry CH_2Cl_2 (20 mL) was added $POBr_3$ (670 mg, 2.35 mmol). The resulting solution was heated at reflux temperature under nitrogen for 17 h, then more $POBr_3$ (200 mg, 0.70 mmol) was added. The resulting solution was heated at reflux temperature under nitrogen for 6 h, then was cooled to room temperature. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine, then dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified using flash chromatography (Al_2O_3 basic, Brockman III, CH_2Cl_2 100%) to give the title compound as a yellow solid (300 mg, 64%). Mp 116 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 2.41 (s, 3H), 2.61 (s, 3H), 3.59 (t, *J* = 5.0 Hz, 2H), 3.85 (s, 3H), 4.39 (t, *J* = 5.0 Hz, 2H), 5.59 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) 11.7, 15.2, 50.4, 58.7, 61.9, 100.2, 113.2, 115.7, 126.6, 133.9, 139.5, 144.4, 147.6, 164.9, 167.5. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{16}Br_1N_5O_3$, 394.0509; found, 394.0490.

(*Z*)-2-Azidoethyl 2-((3-methoxy-5-(((trifluoromethyl)sulfonyl) oxy)-1*H*-pyrrol-2-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (37b)

To a suspension of **36** (280 mg, 0.84 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added, drop-wise, Tf_2O (400 μL, 2.38 mmol). After stirring at this temperature for 4 h, the reaction was quenched through the addition of a saturated solution of $NaHCO_3$ (70 mL), then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash column chromatography (SiO_2, EtOAc/hexane 2/8 then 3/7) to give the title compound as a yellow solid (348 mg, 89%). Mp 117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (s, 3H), 2.59 (s, 3H), 3.60 (t, *J* = 5.0 Hz, 2H), 3.90 (s, 3H), 4.40 (t, *J* = 5.0 Hz, 2H), 5.43 (s, 1H), 7.12 (s, 1H), 11.03 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.7, 15.1, 50.3, 59.0, 62.0, 87.7, 113.4, 118.8 (q, J^1_{C-F} = 319 Hz), 119.0, 126.2, 133.7, 135.2, 145.0, 162.1, 164.7, 168.3. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{16}H_{16}F_3N_5\ Na_1O_6S_1$, 486.0666; found, 486.0678.

(*Z*)-2-Azidoethyl 2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl) methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (26)

37b (117 mg, 0.25 mmol) was dissolved in DME (4.0 mL), then LiCl (31 mg, 0.75 mmol) and boronic acid (63 mg, 0.30 mmol) were added. The solution was degassed by bubbling with N_2. $Pd(PPh_3)_4$ (29 mg, 10 mol/%) was then added. A degassed 2 M solution of Na_2CO_3 was added (0.5 mL, 1.00 mmol) and the suspension was stirred at 85 °C for 18 h. After cooling to room temperature, the solution was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL) and then dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, the crude material was purified using flash chromatography (Al_2O_3 basic Brockman III, EtOAc/hexane 1/9 then 2/8) to give the title compound as a red film (40 mg, 42%). Following the same procedure and starting from **37a**, prodigiosene **26** was isolated in 37% yield. Mp 77 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.22 (br s, 3H), 2.40 (s, 3H), 3.55 (t, *J* = 4.7 Hz, 2H), 3.98 (s, 3H), 4.33 (t, *J* = 4.7 Hz, 2H), 6.06 (s, 1H), 6.21 (s, 1H), 6.73 (d, *J* = 4.0 Hz, 1H), 6.76 (br s, 1H), 6.93 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.7, 13.3, 50.4, 58.7, 61.6, 96.2, 110.8, 112.3, 112.8, 113.8, 123.3, 126.3, 128.3, 131.6, 140.5, 143.7, 161.0, 165.0, 169.2. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{21}N_6O_3$, 381.1670; found, 381.1674.

tert-Butyl 4-(3-hydroxypropyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (39)

To a solution of **38** [65] (2.00 g, 7.11 mmol) in anhydrous THF (70 mL) was added BH_3·THF (1 M in THF, 15.6 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h, then was quenched through addition of 1 M HCl (50 mL) at 0 °C. The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (40 mL) and then dried (Na_2SO_4). After evaporation of the solvents under reduced pressure, a white solid was obtained (1.80 g, quant). It was used without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.55 (s, 9H), 1.70 (quint., *J* = 6.9 Hz, 2H), 2.20 (s, 3H), 2.24 (s, 3H), 2.45 (t, *J* = 6.9 Hz, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 8.62 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.8, 11.6, 20.4, 28.7, 33.7, 62.6, 80.3, 118.3, 121.2, 126.3, 129.0, 161.4. (ESI): $[M + Na]^+$ calcd for $C_{14}H_{23}N_1Na_1O_3$, 276.1570; found, 276.1557.

tert-Butyl 3,5-dimethyl-4-(3-(tosyloxy)propyl)-1*H*-pyrrole-2-carboxylate (40)

To a solution of **39** (1.80 g, 7.10 mmol) in anhydrous CH_2Cl_2 (70 mL) was added triethylamine (2.5 mL, 17.7 mmol) and then *p*TsCl (1.50 g, 7.80 mmol). The resulting solution was stirred at room temperature for 16 h and then quenched with water (50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers washed with brine (40 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude product was purified using flash column chromatography (SiO_2, EtOAc/hexanes 2/8 then 3/7) to give the title compound as a white solid (2.80 g, 97%). Mp 101 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.54 (s, 9H), 1.75 (quint., *J* = 6.8 Hz, 2H), 2.13 (s, 3H), 2.16 (s, 3H), 2.40 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 4.00 (t, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 8.58 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.7, 11.5, 19.9, 21.7, 28.7, 29.9, 70.0, 80.3, 118.4, 119.8, 126.1, 128.0, 129.1, 129.9, 133.4, 144.8, 161.3. (ESI): $[M + Na]^+$ calcd for $C_{21}H_{29}N_1Na_1O_5S_1$, 430.1659; found, 430.1652.

tert-Butyl 4-(3-azidopropyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (41)

To a solution of **40** (2.80 g, 6.90 mmol) in anhydrous DMF (50 mL) was added triethylamine (10 drops) and then NaN_3 (3.90 g, 20 mmol). The resulting solution was stirred at room temperature for 16 h, and then quenched with water (150 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers washed with water (40 mL), brine (40 mL) and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a white solid (1.6 g, 84%) that was used without further purification. Mp 68 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.56 (s, 9H), 1.71 (quint., J = 7.1 Hz, 2H), 2.19 (s, 3H), 2.24 (s, 3H), 2.45 (t, J = 7.1 Hz, 2H), 3.25 (t, J = 7.1 Hz, 2H), 8.46 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.7, 11.6, 21.1, 28.7, 29.7, 50.8, 80.4, 118.5, 120.3, 126.2, 128.9, 161.3. (ESI): $[M + Na]^+$ calcd for $C_{14}H_{22}N_4Na_1O_2$, 301.1635; found, 301.1637.

4-(3-Azidopropyl)-3,5-dimethyl-1*H*-pyrrole-2-carbaldehyde (42)

To a stirred solution of **41** (540 mg, 1.90 mmol) in CH_2Cl_2 (25 mL), was added TFA (3.8 mL, 52.0 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then TMOF (1.9 mL, 17.1 mmol) was added at 0 °C. After stirring for a further 20 min at room temperature, the reaction was quenched through the addition of water (10 mL) and $NaHCO_3$ solid until gassing stopped. The reaction mixture was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers washed with brine (30 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash column chromatography (SiO_2, EtOAc/hexanes 2/8 then 3/7) to give the title compound as a white solid (270 mg, 70%). Mp 50 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.73 (quint., J = 7.2 Hz, 2H), 2.26 (s, 3H), 2.27 (s, 3H), 2.47 (t, J = 7.2 Hz, 2H), 3.27 (t, J = 6.5 Hz, 2H), 9.48 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.9, 11.8, 20.8, 29.5, 50.8, 121.5, 128.2, 132.1, 135.5, 176.0. (ESI): $[M + Na]^+$ calcd for $C_{10}H_{14}N_4NaO_1$, 229.1060; found, 229.1062.

(*Z*)-5-((4-(3-Azidopropyl)-3,5-dimethyl-1*H*-pyrrol-2-yl)methylene)-4-methoxy-1*H*-pyrrol-2(5*H*)-one (43)

To a solution of **35**[64] (1.00 g, 9.07 mmol) in dry CH_2Cl_2 (300 mL) was added triethylamine (3.4 mL, 24.7 mmol) and TMSOTf (2.25 mL, 12.4 mmol) at 0 °C. After 20 min, a solution of **42** (850 mg, 4.12 mmol) in dry CH_2Cl_2 (60 mL) was added at 0 °C. The reaction mixture was stirred at this temperature for 4 hours and then quenched through the addition of phosphate buffer (pH = 7, 100 mL). The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic fractions were washed with brine and then dried (Na_2SO_4). After evaporation of the solvent the resulting brown oil was dissolved in THF (230 mL) and concentrated aqueous HCl (900 μL, 10.7 mmol) was added. After a few minutes the reaction was quenched through the addition of saturated aqueous $NaHCO_3$ (200 mL), then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL). After concentration of the combined organic fractions under vacuum, the resulting suspension was washed with water and hexane to give the title compound as a yellow solid (1.00 g, 80%). Mp 202 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.74 (quint., J = 7.1 Hz, 2H), 2.12 (s, 3H), 2.35 (s, 3H), 2.48 (t, J = 7.1 Hz, 2H), 3.27 (t, J = 7.1 Hz, 2H), 3.90 (s, 3H), 5.10 (d, J = 1.0 Hz, 1H), 6.36 (s, 1H), 10.20 (br s, 1H), 10.86 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.7, 11.5, 21.3, 29.7, 50.9, 58.3, 89.8, 100.6, 119.6, 121.9, 122.0, 125.6, 132.4, 168.0, 173.3. (ESI): $[M + Na]^+$ calcd for $C_{15}H_{19}N_5Na_1O_2$, 324.1431; found, 324.1441.

(*Z*)-2-((4-(3-Azidopropyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-5-bromo-3-methoxy-1*H*-pyrrole (44)

To a stirred solution of dipyrrinone **43** (500 mg, 1.66 mmol) in dry CH_2Cl_2 (30 mL) was added $POBr_3$ (950 mg, 3.32 mmol). The resulting solution was heated at reflux temperature under nitrogen for 17 h, and then more $POBr_3$ (950 mg, 3.32 mmol) was added. The resulting solution was heated at reflux temperature under nitrogen for an additional 20 h, and then was cooled to room temperature. A saturated aqueous solution of $NaHCO_3$ (30 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine, dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The crude product was purified using flash chromatography (Al_2O_3 basic, Brockman III, EtOAc/hexanes 1/9) to give the title compound as an orange solid (310 mg, 51%). Mp 72 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.72 (q, J = 7.0 Hz, 2H), 2.14 (s, 3H), 2.29 (s, 3H), 2.46 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H), 3.83 (s, 3H), 5.58 (s, 1H), 6.88 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.6, 12.4, 21.1, 29.5, 50.8, 58.5, 99.4, 116.3, 121.9, 126.5, 131.4, 137.0, 137.4, 144.1, 166.9. (ESI): $[M + H]^+$ calcd for $C_{15}H_{19}BrN_5O_1$, 364.0767; found, 364.0.757.

(*Z*)-5-((4-(3-Azidopropyl)-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-4-methoxy-1*H*,1′*H*-2,2′-bipyrrole (27)

The bromo-dipyrrin **43** (310 mg, 0.85 mmol) was dissolved in DME (14 mL). LiCl (107 mg, 2.55 mmol) and boronic acid (215 mg, 1.02 mmol) were added. The solution was degassed by bubbling with N_2. Pd $(PPh_3)_4$ (98 mg, 10 mol/%) was then added. A degassed 2 M solution of Na_2CO_3 was added (1.7 mL, 3.40 mmol) and the suspension was stirred at 85 °C for 18 h. After cooling to room temperature, the mixture was poured into water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (40 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude material was purified using flash chromatography (Al_2O_3 basic Brockman III, EtOAc/hexane 0.5/9.5, 1/9 then 2/8) to give the title compound as a red film (110 mg, 37%). Mp 70 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.62 (quint., J = 7.0 Hz, 2H), 1.69 (s, 3H), 2.13 (s, 3H), 2.32 (t, J = 7.0 Hz, 2H), 3.16 (t, J = 7.0 Hz, 2H), 3.99 (s, 3H), 6.11–6.13 (m, 2H), 6.59 (s, 1H), 6.67 (d, J = 3.0 Hz, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.7, 10.1, 21.1, 29.5, 50.8, 58.5, 95.5, 109.8, 112.2, 113.2, 121.0, 122.7, 125.6, 128.8, 129.5, 136.8,

137.3, 159.2, 168.9. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{19}H_{23}N_6O_1$, 351.1928; found, 351.1924.

Zinc complex 45

To a solution of prodigiosene **26** (195 mg, 0.51 mmol) in $CHCl_3$ (55 mL) was added a solution of $Zn(OAc)_2{\cdot}2\ H_2O$ (280 mg, 1.28 mmol) and $NaOAc{\cdot}3H_2O$ (188 mg, 1.38 mmol) in MeOH (14 mL). After stirring at room temperature for 16 h, water (50 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), and then dried (Na_2SO_4). After concentration of the solvent under reduced pressure, the residue was triturated in MeOH, the solid isolated *via* filtration (Millipore®), and the solid then washed three times with MeOH to produce the desired compound as a dark red solid (127 mg, 60%). Mp 238 °C with decomposition. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.18 (s, 6H), 2.56 (s, 6H), 3.54 (t, J = 5.0 Hz, 4H), 3.98 (s, 6H), 4.31 (t, J = 5.0 Hz, 4H), 6.05 (s, 2H), 6.10–6.11 (m, 2H), 6.50 (s, 2H), 6.61 (s, 2H), 7.34 (s, 2H), 9.21 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.3, 17.1, 50.4, 58.5, 61.5, 96.1, 110.7, 114.4, 116.1, 118.0, 123.1, 126.4, 132.0, 133.0, 141.0, 155.7, 156.6, 165.3, 167.1. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{38}H_{39}N_{12}O_6Zn_1$, 823.2402; found, 823.2398.

Zinc complex 47

This compound was obtained following the procedure above, using prodigiosene **27**. After concentration of the solvent under reduced pressure the residue was dissolved in Et_2O. The desired compound was precipitated by the addition of hexanes and then isolated, as a red solid, *via* filtration (Millipore®) (81 mg, 68%). Mp 102 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.64 (quint., J = 7.0 Hz, 4H), 1.87 (s, 6H), 2.23 (s, 6H), 2.39 (t, J = 7.0 Hz, 4H), 3.12 (t, J = 7.0 Hz, 4H), 3.95 (s, 6H), 6.04–6.05 (m, 4H), 6.39 (s, 2H), 6.48 (s, 2H), 7.20 (s, 2H), 9.25 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 10.1, 14.5, 21.7, 29.3, 50.8, 58.2, 95.0, 109.7, 111.4, 117.5, 121.2, 126.4, 127.5, 128.5, 134.2, 136.8, 151.2, 154.4, 165.0. HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{38}H_{42}N_{12}Na_1O_2Zn_1$, 785.2737; found, 785.2743.

General procedure 1 (GP1) for the CuACC reaction[86]

To a solution of estradiol **25a** or **25b** (0.028 mmol) in a mixture of a CH_2Cl_2/MeOH (1/0.4 mL) was added sodium ascorbate (0.028 mmol), prodigiosene complex **45** or **47** (0.028 mmol) and TBTA (10 mol%), followed by $CuSO_4{\cdot}5\ H_2O$ (0.028 mmol). After stirring at room temperature for 2 days, water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with HCl 1 M (50 mL) and brine, and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure the crude material was purified using flash chromatography.

(*Z*)-3-(4-(3-((7*R*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)propyl)-1*H*-1,2,3-triazol-1-yl)propyl 2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (46a)

Obtained using GP1, estradiol **25a** and prodigiosene complex **45** (27 mg, 0.032 mmol). The crude material was purified using flash chromatography (Al_2O_3 neutral Brockman III, EtOAc/hexane 5/5, then CH_2Cl_2/MeOH 99/1 to 90/10) to give the title compound as a red glass (26 mg, 55%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (s, 3H), 1.09–1.32 (m, 9H), 1.47–1.63 (m, 4H), 1.67–1.79 (m, 1H), 1.86 (d, J = 13.0 Hz, 1H), 2.10–2.17 (m, 4H), 2.24–2.28 (m, 2H), 2.34 (s, 3H), 2.50–2.56 (m, 1H), 2.61 (d, J = 16.0 Hz, 1H), 2.74–2.84 (m, 2H), 3.72 (t, J = 8.5 Hz, 1H), 3.97 (s, 3H), 4.57–4.63 (m, 4H), 6.01 (s, 1H), 6.26–6.27 (m, 1H), 6.53 (br s, 1H), 6.58 (d, J = 5.0 Hz, 1H), 6.79 (br s, 1H), 6.90 (s, 1H), 6.94 (br s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.19 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.3, 11.6, 14.2, 22.8, 25.6, 26.2, 27.4, 28.3, 29.8, 30.7, 33.5, 34.8, 37.1, 38.7, 42.3, 43.6, 46.7, 49.4, 58.8, 61.7, 82.1, 95.4, 111.3, 112.0, 112.8, 114.0, 115.4, 117.1, 121.2, 125.0, 125.8, 125.9, 127.3, 130.6, 136.7, 148.6, 155.3, 164.7, 168.4 (3 carbons unaccounted for). HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{42}H_{51}N_6O_5$, 719.3915; found, 719.3908.

(*Z*)-3-(4-(9-((7*R*,13*S*,14*S*,17*S*)-3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-7-yl)nonyl)-1*H*-1,2,3-triazol-1-yl)propyl 2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrole-4-carboxylate (46b)

Obtained using GP1, estradiol **25b** and prodigiosene complex **45** (27 mg, 0.032 mmol). The crude material was purified using flash chromatography (Al_2O_3 neutral Brockman III, EtOAc/hexane 5/5, then CH_2Cl_2/MeOH 99/1 to 90/10) to give the title compound as a red glass (30 mg, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.76 (s, 3H), 0.84–0.92 (m, 1H), 0.97–1.02 (m, 1H), 1.14–1.47 (m, 22H), 1.56–1.63 (m, 4H), 1.68–1.70 (m, 1H), 1.88 (d, J = 12.5 Hz, 1H), 2.08–2.12 (m, 1H), 2.26–2.27 (m, 3H), 2.30 (s, 3H), 2.64–2.70 (m, 3H), 2.81 (dd, J = 16.5, 5.0 Hz, 1H), 3.72 (t, J = 8.5 Hz, 1H), 3.96 (s, 3H), 4.62–4.66 (m, 4H), 6.02 (s, 1H), 6.26 (br s, 1H), 6.54 (d, J = 2.5 Hz, 1H), 6.63 (dd, J = 8.5, 2.5 Hz, 1H), 6.75 (br s, 1H), 6.88 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 11.2, 11.7, 13.8, 22.8, 25.4, 25.6, 27.4, 27.8, 29.1, 29.2 (2C), 29.5, 29.6, 29.8, 30.7, 32.1, 33.5, 34.9, 37.1, 38.4, 42.2, 43.5, 46.7, 49.4, 58.7, 61.7, 82.1, 95.9, 111.0, 111.1, 112.0, 112.5, 113.3, 114.4, 116.4, 121.3, 123.9, 126.3, 127.1, 127.7, 128.1, 129.2, 131.3, 137.0, 148.7, 154.4, 164.8, 168.8. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{48}H_{63}N_6O_5$, 803.4854; found, 803.4818.

(7*R*,13*S*,14*S*,17*S*)-7-(3-(1-(3-((*Z*)-2-((4-Methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)propyl)-1*H*-1,2,3-triazol-4-yl)propyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (48a)

Obtained using GP1, estradiol **25a** and prodigiosene complex **47** (25 mg, 0.032 mmol). The crude material was purified

using flash chromatography (Al_2O_3 basic Brockman III, EtOAc/hexane 3/7 up to 100% EtOAc with increments of 10%, then CH_2Cl_2/MeOH 98/2 up to 95/5) to give the title compound as a red glass (26 mg, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.75 (s, 3H), 0.83–0.94 (m, 1H), 1.04–1.12 (m, 1H), 1.18–1.32 (m, 4H), 1.39–1.48 (m, 2H), 1.54–1.62 (m, 2H), 1.74 (s, 4H), 1.85–1.94 (m, 3H), 2.04–2.07 (m, 4H), 2.17 (s, 3H), 2.26–2.27 (m, 4H), 2.55–2.64 (m, 2H), 2.72–2.78 (m, 1H), 2.83 (dd, J = 16.7, 4.2 Hz, 1H), 3.69 (t, J = 8.5 Hz, 1H), 3.97 (s, 3H), 4.14–4.15 (m, 2H), 6.05 (s, 1H), 6.18 (br s, 1H), 6.52–6.54 (m, 2H), 6.69 (br s, 1H), 6.74 (br s, 1H), 6.89 (s, 1H), 7.01–7.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.8, 11.3, 14.3, 21.0, 22.8, 25.3, 26.0, 27.4, 28.0, 30.6, 30.8, 31.0, 33.5, 34.8, 37.0, 38.4, 42.2, 43.6, 46.6, 49.6, 58.6, 82.1, 95.1, 110.3, 112.9, 113.1, 113.7, 116.8, 120.6, 120.9, 123.1, 125.8, 127.1, 128.1, 130.7, 136.6, 148.3, 155.1, 168.3, 207.0 (3 carbons unaccounted for). HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{42}H_{53}N_6O_3$, 689.4174; found, 689.4164.

(7*R*,13*S*,14*S*,17*S*)-7-(9-(1-(3-((*Z*)-2-((4-Methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)propyl)-1*H*-1,2,3-triazol-4-yl)nonyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol (48b)

Obtained using GP1, estradiol **25b** and prodigiosene complex **47** (25 mg, 0.032 mmol). The crude material was purified using flash chromatography (Al_2O_3 basic Brockman III, EtOAc/hexane 2/8 up to 100% EtOAc with increments of 5%, then CH_2Cl_2/IPA 99/1 up to 90/10) to give a red glass (23 mg, 46%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.77 (s, 3H), 0.85–0.90 (m, 1H), 0.98–1.04 (m, 1H), 1.16–1.40 (m, 18H), 1.43–1.50 (m, 2H), 1.56–1.65 (m, 4H), 1.68–1.71 (m, 1H), 1.83–1.90 (m, 3H), 1.94–1.98 (m, 2H), 2.09 (s, 4H), 2.26–2.30 (m, 4H), 2.64–2.69 (m, 3H), 2.82 (dd, J = 16.7, 4.7 Hz, 1H), 3.73 (t, J = 8.5 Hz, 1H), 3.96 (s, 3H), 4.22 (t, J = 6.7 Hz, 2H), 6.05 (s, 1H), 6.17 (br s, 1H), 6.57 (s, 1H), 6.62–6.72 (m, 3H), 6.89 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.8, 11.0, 11.3, 21.2, 22.8, 25.4, 25.6, 27.4, 27.8, 29.1, 29.2, 29.3, 29.4, 29.6, 29.8, 30.7, 31.0, 33.5, 34.9, 37.1, 38.4, 42.3, 43.6, 46.7, 49.8, 58.5, 82.2, 95.1, 110.3, 112.7, 113.2, 113.6, 116.7, 120.7, 120.9, 123.0, 125.9, 127.0, 128.1, 129.2, 130.9, 136.9, 148.4, 155.0, 168.4 (3 carbons unaccounted for). HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{48}H_{65}N_6O_3$, 773.5113; found, 773.5108.

N^1-(2-(4-(1-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)-N^1,N^2-dimethylethane-1,2-diamine (50)

Compound **49** [77] (500 mg, 1.16 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL). TBSCl (440 mg, 2.8 mmol) and imidazole (340 mg, 5.6 mmol) were added and the reaction mixture was then stirred at room temperature for 24 h, before being quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and then dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the crude mixture was purified using flash chromatography (SiO_2, CH_2Cl_2/MeOH 9/1 + 2% Et_3N) to give the title compound as a yellow oil (540 mg, 85%) of two diastereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.10 (s, 6H), 0.22 (s, 6H), 0.91–0.94 (m, 15H), 1.00 (s, 9H), 2.30 (s, 3H), 2.37 (s, 3H), 2.42 (s, 3H), 2.46–2.50 (s, 6H), 2.58 (t, J = 5.5 Hz, 2H), 2.63–2.67 (m, 4H), 2.73 (q, J = 5.5 Hz, 4H), 2.83 (t, J = 5.5 Hz, 2H), 3.92 (t, J = 6.0 Hz, 2H), 4.08 (t, J = 6.0 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 7.08–7.18 (m, 14H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ −4.3, −4.2, 13.8, 18.3, 25.8, 29.0, 29.2, 36.3, 36.4, 43.2, 49.3, 49.4, 56.4, 56.5, 57.0, 57.1, 65.9, 66.2, 113.4, 114.1, 119.1, 119.6, 126.0 (2C), 127.8, 127.9, 129.8, 130.7 (2C), 132.0, 132.1, 136.1, 136.5, 136.6, 136.9, 138.0, 138.1, 141.1, 141.2, 142.7, 142.8, 153.6, 154.4, 156.7, 157.5. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{34}H_{49}N_2O_2Si_1$, 545.3558; found, 545.3539.

General procedure 2 (GP2) for amide coupling

Compound **50** (75 mg, 0.14 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL). DMAP (16 mg, 0.14 mmol), HBTU (50 mg, 0.14 mmol) and prodigiosene **1a–c** (0.11 mmol) were added. After stirring at room temperature for 18 h, water (30 mL) was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). The crude mixture was concentrated and purified using column chromatography on Brockman III neutral alumina (EtOAc/hexane 6/4). The orange film obtained was dissolved in a mixture of MeOH/$CHCl_3$ (3/3 mL) and concentrated HCl (15 eq.) was added. The reaction mixture was stirred for 8 h and then a saturated solution of $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (50 mL), and then dried (Na_2SO_4). The crude mixture was concentrated and purified using column chromatography on Brockman III neutral alumina (EtOAc/hexane 6/4, then CH_2Cl_2/MeOH 9/1).

N-(2-((2-(4-(1-(4-Hydroxyphenyl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)(methyl)amino)ethyl)-4-(2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-*N*-methyl-4-oxobutanamide (51a)

Obtained using GP2 and prodigiosene **1a**. Orange glass (32 mg, 61%). Formed as 1 : 1 mixture of *E* and *Z* isomers: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.87–0.92 (m, 6H), 2.21–2.25 (m, 4H), 2.31 (s, 2H), 2.34 (s, 2H), 2.38–2.40 (m, 8H), 2.44–2.48 (m, 4H), 2.55–2.76 (m, 10H), 2.81–2.86 (m, 4H), 2.89 (s, 1H), 2.93 (s, 1H), 2.97–3.02 (m, 6H), 3.05 (s, 2H), 3.43 (t, J = 6.2 Hz, 2H), 3.47 (t, J = 7.0 Hz, 2H), 3.87 (t, J = 5.7 Hz, 2H), 3.91 (t, J = 7.0 Hz, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.03 (t, J = 5.7 Hz, 1H), 4.06 (t, J = 5.7 Hz, 1H), 6.03–6.05 (m, 2H), 6.23–6.25 (m, 2H), 6.42 (t, J = 8.5 Hz, 2H), 6.47–6.50 (m, 2H), 6.62–6.65 (m, 2H), 6.69 (t, J = 8.5 Hz, 2H), 6.75–6.77 (m, 4H), 6.80–6.83 (m, 4H), 6.92 (d, J = 9.5 Hz, 2H), 7.00 (t, J = 8.5 Hz, 2H), 7.06–7.10 (m, 8H), 7.12–7.15 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.6, 13.7, 13.8, 14.9 (2C), 26.8, 26.9, 27.4, 29.0, 29.1, 29.2, 29.8, 34.3, 34.4, 36.2, 37.7, 37.8, 38.8, 43.2, 43.5, 43.6, 46.0, 46.1, 48.4, 54.9 (2C), 55.6, 55.7, 56.3, 56.4, 56.7, 56.8, 58.7, 65.7,

65.9, 66.2, 95.7, 111.0 (2C), 112.2, 112.3, 113.4, 114.1, 114.7, 115.5, 115.6, 125.9, 127.9 (3C), 129.8, 130.7 (2C), 130.8, 132.0, 132.1, 132.2, 135.3, 135.5, 136.1, 136.2, 136.6, 136.7, 138.1 (2C), 140.6, 140.7, 142.8, 142.9, 154.5, 154.6, 155.6, 155.7, 156.7, 157.4, 157.5, 168.6, 172.3, 172.5, 172.6, 196.1. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{48}H_{54}N_5O_5$, 780.4119; found, 780.4124.

_N_-(2-((2-(4-(1-(4-Hydroxyphenyl)-2-phenylbut-1-en-1-yl) phenoxy)ethyl)(methyl)amino)ethyl)-6-(2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-*N*-methyl-6-oxohexanamide (51b)

Obtained using GP2 and **1b**. Orange glass (70 mg, 75%). Formed as 1 : 1 mixture of *E* and *Z* isomers: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88–0.93 (m, 6H), 1.64–1.69 (m, 8H), 2.25–2.28 (m, 8H), 2.31–2.44 (m, 14H), 2.49–2.54 (m, 4H), 2.69–2.75 (m, 8H), 2.83–2.85 (m, 2H), 2.89–2.99 (m, 6H), 3.31–3.50 (m, 4H), 3.85–3.88 (m, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 4.01–4.04 (m, 2H), 6.04 (d, J = 7.5 Hz, 2H), 6.26 (br s, 2H), 6.42–6.49 (m, 4H), 6.64–6.94 (m, 14H), 7.02 (t, J = 8.0 Hz, 2H), 7.07–7.15 (m, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.5, 13.8, 14.4, 24.0, 24.1, 25.0, 25.3, 29.1, 29.2, 32.9, 33.0, 33.6, 34.1, 34.2, 36.3, 36.4, 42.6, 43.1 (2C), 43.3, 45.7, 45.8, 48.4, 55.1, 56.0, 56.1, 56.4, 56.5, 56.7, 56.8, 58.7, 65.7, 65.8, 66.0, 66.1, 95.9, 110.9, 112.2, 113.3, 114.0, 114.7 (2C), 115.5, 123.4, 123.5, 123.6, 125.9, 126.3 127.9, 129.8, 130.6, 130.7, 130.8, 132.0, 132.1, 135.1, 135.5, 136.1, 136.3, 136.6, 136.8, 138.1 (2C), 140.6, 140.7, 140.8, 142.8, 142.9, 154.6, 154.7, 155.7, 156.5, 156.7, 157.3, 157.5, 168.8, 173.1, 173.2 (2C), 173.3, 197.6, 197.8. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{50}H_{58}N_5O_5$, 808.4432; found, 808.4422.

_N_-(2-((2-(4-(1-(4-Hydroxyphenyl)-2-phenylbut-1-en-1-yl) phenoxy)ethyl)(methyl)amino)ethyl)-10-(2-((4-methoxy-1*H*,1′*H*-[2,2′-bipyrrol]-5-yl)methylene)-3,5-dimethyl-2*H*-pyrrol-4-yl)-*N*-methyl-10-oxodecanamide 51c

Obtained using GP2 and **1c**. Orange glass (70 mg, 84%). Formed as 1 : 1 mixture of *E* and *Z* isomers: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.89–0.93 (m, 6H), 1.26–1.27 (m, 16H), 156–1.63 (m, 8H), 2.19–2.28 (m, 10H), 2.32–2.33 (m, 4H), 2.39–2.41 (m, 8H), 2.47 (quint., J = 7.4 Hz, 4H), 2.56–2.61 (m, 2H), 2.62–2.68 (m, 6H), 2.73–2.76 (m, 2H), 2.83–2.87 (m, 2H), 2.89–3.01 (m, 6H), 3.34–3.51 (m, 4H), 3.71 (s, 1H), 3.86–3.91 (m, 2H), 3.97 (s, 3H), 4.02–4.07 (m, 2H), 6.03–6.04 (d, J = 5 Hz, 2H), 6.24 (br s, 2H), 6.45–6.50 (m, 4H), 6.56–6.68 (m, 2H), 6.72–6.75 (m, 4H), 6.79–6.84 (m, 6H), 6.92–7.03 (m, 2H), 7.12–7.15 (m, 14H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.5, 13.8, 14.4, 24.4 (2C), 25.1 (2C), 25.6, 29.1, 29.2, 29.4, 29.5 (2C), 33.0, 33.1, 33.6, 33.7, 34.1 (2C), 36.4 (2C), 36.5, 42.8, 43.1 (2C), 43.4, 45.8 (2C), 48.5 (2C), 55.1, 56.0, 56.1, 56.5, 56.6, 56.8, 56.9, 58.7, 65.5, 65.8, 65.9, 66.0, 66.1, 67.2, 96.0, 110.9, 112.2, 113.3, 114.0, 114.7 (2C), 115.4, 115.5, 123.5, 125.9, 126.1, 127.9, 129.8, 130.7, 130.8, 132.0, 132.1 (2C), 132.2, 135.1, 135.2, 135.4, 135.5, 136.1, 136.4, 136.6, 136.8, 138.1 (2C), 140.7, 140.8 (2C), 140.9, 142.5, 142.8, 142.9 (2C), 154.6, 154.7, 155.6, 155.7, 156.5, 156.7, 157.3, 157.5, 168.9, 173.4, 173.5, 173.6 (2C), 198.5 (2C). HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{54}H_{66}N_5O_5$, 864.5058; found, 864.5046.

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References

1 D. Boehme and A. G. Beck-Sickinger, *J. Pept. Sci*, 2015, **21**, 186–200.
2 L. Fiume, M. Manerba and G. Di Stefano, *Expert. Opin. Drug Del.*, 2014, **11**, 1203–1217.
3 E. E. Ramsay and P. J. Dilda, *Front. Pharmacol.*, 2014, **5**, 181.
4 A. A. Radwan and F. K. Alanazi, *Saudi Pharm. J.*, 2014, **22**, 3–16.
5 H.-P. Gerber, F. E. Koehn and R. T. Abraham, *Nat. Prod. Rep.*, 2013, **30**, 625–639.
6 C. Peters and S. Brown, *Biosci. Rep.*, 2015, **35**, e00225.
7 A. M. Sochaj, K. W. Swiderska and J. Otlewski, *Biotechnol. Adv.*, 2015, **33**, 775–784.
8 M. A. Ghaz-Jahanian, F. Abbaspour-Aghdam, N. Anarjan, A. Berenjian and H. Jafarizadeh-Malmiri, *Mol. Biotechnol.*, 2015, **57**, 201–218.
9 C. M. Dawidczyk, C. Kim, J. H. Park, L. M. Russell, K. H. Lee, M. G. Pomper and P. C. Searson, *J. Controlled Release*, 2014, **187**, 133–144.
10 C. Ferrario and G. Batist, *Expert Opin. Drug Discovery*, 2014, **9**, 647–668.
11 R. Morphy and Z. Rankovic, *J. Med. Chem.*, 2005, **48**, 6523–6543.
12 M. Morioka, A. Kamizono, H. Takikawa, A. Mori, H. Ueno, S.-i. Kadowaki, Y. Nakao, K. Kato and K. Umezawa, *Bioorg. Med. Chem.*, 2010, **18**, 1143–1148.
13 A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582–3603.
14 N. R. Williamson, P. C. Fineran, F. J. Leeper and G. P. Salmond, *Nat. Rev. Microbiol.*, 2006, **4**, 887–899.
15 R. D'Alessio, A. Bargiotti, O. Carlini, F. Colotta, M. Ferrari, P. Gnocchi, A. M. Isetta, N. Mongelli, P. Motta, A. Rossi,

M. Rossi, M. Tibolla and E. Vanotti, *J. Med. Chem.*, 2000, **43**, 2557–2565.
16 F. Alihosseini, K.-S. Ju, J. Lango, B. D. Hammock and G. Sun, *Biotechnol. Prog.*, 2008, **24**, 742–747.
17 J.-M. Lehn, *Chem. – Eur. J.*, 2000, **6**, 2097–2102.
18 T. Nakashima, M. Kurachi, Y. Kato, K. Yamaguchi and T. Oda, *Microbiol. Immunol.*, 2005, **49**, 407–415.
19 K. Papireddy, M. Smilkstein, J. X. Kelly, S. M. Salem, M. Alhamadsheh, S. W. Haynes, G. L. Challis and K. A. Reynolds, *J. Med. Chem.*, 2011, **54**, 5296–5306.
20 B. Montaner and R. Pérez-Tomás, *Life Sci.*, 2001, **68**, 2025–2036.
21 R. Pérez-Tomás, B. Montaner, E. Llagostera and V. Soto-Cerrato, *Biochem. Pharmacol.*, 2003, **66**, 1447–1452.
22 M. S. Melvin, J. T. Tomlinson, G. Park, C. S. Day, G. R. Saluta, G. L. Kucera and R. A. Manderville, *Chem. Res. Toxicol.*, 2002, **15**, 734–741.
23 S. Ohkuma, T. Sato, M. Okamoto, H. Matsuya, K. Arai, T. Kataoka, K. Nagai and H. H. Wasserman, *Biochem. J.*, 1998, **334**, 731–741.
24 T. Sato, H. Konno, Y. Tanaka, T. Kataoka, K. Nagai, H. H. Wasserman and S. Ohkuma, *J. Biol. Chem.*, 1998, **273**, 21455–21462.
25 J. L. Seganish and J. T. Davis, *Chem. Commun.*, 2005, 5781–5783.
26 M. S. Melvin, J. T. Tomlinson, G. R. Saluta, G. L. Kucera, N. Lindquist and R. A. Manderville, *J. Am. Chem. Soc.*, 2000, **122**, 6333–6334.
27 G. Park, J. T. Tomlinson, M. S. Melvin, M. W. Wright, C. S. Day and R. A. Manderville, *Org. Lett.*, 2003, **5**, 113–116.
28 R. I. S. Diaz, J. Regourd, P. V. Santacroce, J. T. Davis, D. L. Jakeman and A. Thompson, *Chem. Commun.*, 2007, 2701–2703.
29 A. Fürstner, K. Reinecke, H. Prinz and H. Waldmann, *ChemBioChem*, 2004, **5**, 1575–1579.
30 B. Montaner, W. Castillo-Avila, M. Martinell, R. Oellinger, J. Aymami, E. Giralt and R. Perez-Tomas, *Toxicol. Sci.*, 2005, **85**, 870–879.
31 W. R. Hearn, M. K. Elson, R. H. Williams and J. Medina-Castro, *J. Org. Chem.*, 1970, **35**, 142–146.
32 S. M. Crawford, A. Al-Sheikh Ali, T. S. Cameron and A. Thompson, *Inorg. Chem.*, 2011, **50**, 8207–8213.
33 C. L. A. Hawco, E. Marchal, M. I. Uddin, A. E. G. Baker, D. P. Corkery, G. Dellaire and A. Thompson, *Bioorg. Med. Chem.*, 2013, **21**, 5995–6002.
34 E. Marchal, S. Rastogi, A. Thompson and J. T. Davis, *Org. Biomol. Chem.*, 2014, **12**, 7515–7522.
35 E. Marchal, D. A. Smithen, I. M. Uddin, A. W. Robertson, D. L. Jakeman, V. Mollard, C. D. Goodman, K. S. MacDougall, S. A. McFarland, G. I. McFadden and A. Thompson, *Org. Biomol. Chem.*, 2014, **12**, 4132–4142.
36 E. Marchal, M. I. Uddin, C. L. A. Hawco and A. Thompson, *Can. J. Chem.*, 2015, **93**, 526–535.
37 E. Marchal, M. I. Uddin, D. A. Smithen, L. A. Hawco, M. Lanteigne, D. P. Overy, R. G. Kerr and A. Thompson, *RSC Adv.*, 2013, **3**, 22967–22971.
38 S. Rastogi, E. Marchal, I. Uddin, B. Groves, J. Colpitts, S. A. McFarland, J. T. Davis and A. Thompson, *Org. Biomol. Chem.*, 2013, **11**, 3834–3845.
39 J. Regourd, A. Al-Sheikh Ali and A. Thompson, *J. Med. Chem.*, 2007, **50**, 1528–1536.
40 D. A. Smithen, A. M. Forrester, D. P. Corkery, G. Dellaire, J. Colpitts, S. A. McFarland, J. N. Berman and A. Thompson, *Org. Biomol. Chem.*, 2013, **11**, 62–68.
41 M. I. Uddin, S. Thirumalairajan, S. M. Crawford, T. S. Cameron and A. Thompson, *Synlett*, 2010, 2561–2564.
42 P. M. Levine, M. J. Garabedian and K. Kirshenbaum, *J. Med. Chem.*, 2014, **57**, 8224–8237.
43 J. Provencher-Mandeville, C. Debnath, S. K. Mandal, V. Leblanc, S. Parent, É. Asselin and G. Bérubé, *Steroids*, 2011, **76**, 94–103.
44 R. Schobert, G. Bernhardt, B. Biersack, S. Bollwein, M. Fallahi, A. Grotemeier and G. L. Hammond, *ChemMedChem*, 2007, **2**, 333–342.
45 C. Van Themsche, S. Parent, V. Leblanc, C. Descôteaux, A.-M. Simard, G. Bérubé and E. Asselin, *Endocr. – Relat. Cancer*, 2009, **16**, 1185–1195.
46 V. C. Jordan, *J. Med. Chem.*, 2003, **46**, 1081–1111.
47 V. C. Jordan, *J. Med. Chem.*, 2003, **46**, 883–908.
48 K. Cyrus, M. Wehenkel, E.-Y. Choi, H. Lee, H. Swanson and K.-B. Kim, *ChemMedChem*, 2010, **5**, 979–985.
49 D. Spera, G. Cabrera, R. Fiaschi, K. E. Carlson, J. A. Katzenellenbogen and E. Napolitano, *Bioorg. Med. Chem.*, 2004, **12**, 4393–4401.
50 J. P. Trebley, E. L. Rickert, P. T. Reyes and R. V. Weatherman, *Ernst Schering Res. Found. Workshop*, 2006, **58**, 75–87.
51 D. C. Labaree, J.-x. Zhang, H. A. Harris, C. O'Connor, T. Y. Reynolds and R. B. Hochberg, *J. Med. Chem.*, 2003, **46**, 1886–1904.
52 J.-x. Zhang, D. C. Labaree and R. B. Hochberg, *J. Med. Chem.*, 2005, **48**, 1428–1447.
53 R. Tedesco, R. Fiaschi and E. Napolitano, *J. Org. Chem.*, 1995, **60**, 5316–5318.
54 S. D. Lepore and Y. He, *J. Org. Chem.*, 2003, **68**, 8261–8263.
55 S. M. Goldup, D. A. Leigh, T. Long, P. R. McGonigal, M. D. Symes and J. Wu, *J. Am. Chem. Soc.*, 2009, **131**, 15924–15929.
56 T. W. Greene and P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., 2002, pp. 17–245.
57 D. L. Reger, J. D. Elgin, M. D. Smith, F. Grandjean, L. Rebbouh and G. J. Long, *Polyhedron*, 2006, **25**, 2616–2622.
58 M. Shibasaki, Y. Ishida and N. Okabe, *Tetrahedron Lett.*, 1985, **26**, 2217–2220.
59 X.-R. Jiang, J. Walter Sowell and B. T. Zhu, *Steroids*, 2006, **71**, 334–342.
60 J. Mulzer and B. Schöllhorn, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 431–432.
61 K. K. Olgivie and D. W. Entwistle, *Carbohydr. Res.*, 1981, **89**, 203–210.

62 A. T. Placzek, J. L. Hougland and R. A. Gibbs, *Org. Lett.*, 2012, **14**, 4038–4041.
63 O. Norberg, L. Deng, T. Aastrup, M. Yan and O. Ramström, *Anal. Chem.*, 2010, **83**, 1000–1007.
64 L. Duc, J. F. McGarrity, T. Meul and A. Warm, *Synthesis*, 1992, 391–394.
65 C. Schmuck, D. Rupprecht, C. Urban and N. Walden, *Synthesis*, 2006, 89–96.
66 M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015.
67 J. Kühhorn, A. Götz, H. Hübner, D. Thompson, J. Whistler and P. Gmeiner, *J. Med. Chem.*, 2011, **54**, 7911–7919.
68 Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless and M. G. Finn, *J. Am. Chem. Soc.*, 2003, **125**, 3192–3193.
69 J. Notni and H.-J. Wester, *Chem. – Eur. J.*, 2016, **22**, 11500–11508.
70 T. Kowada, H. Maeda and K. Kikuchi, *Chem. Soc. Rev.*, 2015, **44**, 4953–4972.
71 N. Boens, V. Leen and W. Dehaen, *Chem. Soc. Rev.*, 2012, **41**, 1130–1172.
72 M. Benstead, G. H. Mehl and R. W. Boyle, *Tetrahedron*, 2011, **67**, 3573–3601.
73 G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184–1201.
74 R. Ziessel, G. Ulrich and A. Harriman, *New J. Chem.*, 2007, **31**, 496–501.
75 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891–4932.
76 B. S. Katzenellenbogen, I. Choi, R. Delage-Mourroux, T. R. Ediger, P. G. V. Martini, M. Montano, J. Sun, K. Weis and J. A. Katzenellenbogen, *J. Steroid Biochem.*, 2000, **74**, 279–285.
77 J. P. Trebley, E. L. Rickert, P. T. Reyes and R. V. Weatherman, in *Chem. Genomics*, ed. S. Jaroch and H. Weinmann, Springer, Berlin Heidelberg, 2006, vol. 58, ch. 6, pp. 75–87.
78 https://dtp.cancer.gov/discovery_development/nci-60/methodology.htm.
79 J. M. Lamar, P. Stern, H. Liu, J. W. Schindler, Z. G. Jiang and R. O. Hynes, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, E2441–E2450.
80 J. Feng, J. Gou, J. Jia, T. Yi, T. Cui and Z. Li, *OncoTargets Ther.*, 2016, **29**, 5371–5381.
81 C. Wang, X. Zhu, W. Feng, Y. Yu, K. Jeong, W. Guo, Y. Lu and G. B. Mills, *Am. J. Cancer Res.*, 2016, **6**, 27–37.
82 W. Pan, Q. Wang, Y. Zhang, N. Zhang, J. Qin, W. Li, J. Wang, F. Wu, L. Cao and G. Xu, *Cell. Physiol. Biochem.*, 2016, **39**, 481–490.
83 K. Brodowska, A. Al-Moujahed, A. Marmalidou, M. Meyer Zu Horste, J. Cichy, J. W. Miller, E. Gragoudas and D. G. Vavvas, *Exp. Eye Res.*, 2014, **124**, 67–73.
84 W. Chen, Z. Cao, C. Krishnan and N. Panjwani, *Biochem. Biophys. Res. Commun.*, 2015, **466**, 221–225.
85 Y. Liu-Chittenden, B. Huang, J. S. Shim, Q. Chen, S. J. Lee, R. A. Anders, J. O. Liu and D. Pan, *Genes Dev.*, 2012, **26**, 1300–1305.
86 R. J. Detz, S. A. Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek and J. H. van Maarseveen, *Org. Lett.*, 2006, **8**, 3227–3230.

