Octahydrophenanthrene-2,7-diol Analogues as Dissociated Glucocorticoid Receptor Agonists: Discovery and Lead Exploration

Ralph P. Robinson,* Leonard Buckbinder, Amber I. Haugeto, Patricia A. McNiff, Michele L. Millham, Matthew R. Reese, Jean F. Schaefer, Yuriy A. Abramov, Jon Bordner, Yves A. Chantigny, Edward F. Kleinman, Ellen R. Laird, Bradley P. Morgan, John C. Murray, Eben D. Salter, Matthew D. Wessel, and Sue A. Yocum

Pfizer Global Research & Development, Groton Laboratories, Eastern Point Road, Groton, Connecticut 06340

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As exemplified by the lead compound **2**, octahydrophenanthrene-2,7-diol analogues exhibit the profile of a pathway-selective or "dissociated" agonist of the glucocorticoid receptor (GR), retaining the potent activity that glucocorticoids have for transrepression (as measured by inhibition of IL-1 induced MMP-13 expression) but showing an attenuated capacity for transactivation (as measured in an MMTV luciferase reporter assay). With the guidance of a homology model of the GR ligand binding domain, structural modifications to **2** were carried out that were successful in replacing the allyl and propynyl side chains with groups likely to be more chemically stable and less likely to produce toxic metabolites. Key to success was the introduction of an additional hydroxyl group onto the tricyclic carbon framework of the series.

Introduction

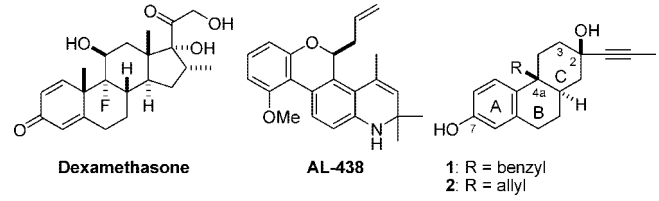
Synthetic glucocorticoid agonists (glucocorticoids) are the most effective anti-inflammatory drugs available. The biological effects of this drug class, and the endogenous adrenal hormone cortisol, are mediated by the glucocorticoid receptor (GR[a]), a member of the nuclear hormone receptor gene family. Despite being highly efficacious, long-term glucocorticoid therapy is severely limited by debilitating side effects including diabetes and osteoporosis.

Inhaled administration of rapidly inactivated glucocorticoids (e.g., fluticasone propionate) has led to improvements in therapeutic index by minimizing systemic exposure. Unfortunately, this strategy is limited to use in topical indications and is not applicable to arthritis and other systemic inflammatory conditions. An exciting and potentially more general approach to attenuating the side effects associated with GR-based therapy has arisen from new understanding regarding pathways involved in glucocorticoid signaling.

As is the case with agonists of other nuclear hormone receptors, glucocorticoids activate transcription of some genes while concurrently repressing transcription of others. In the transrepression pathway, gene transcription is down-regulated via protein−protein binding interactions of monomeric GR/ligand complexes with various transcription factors (e.g., NFκB and AP1). In the transactivation pathway, gene transcription is stimulated by binding of dimeric GR/ligand complexes directly to DNA.

The beneficial effects of glucocorticoids are, for the most part, mediated via transrepression of pro-inflammatory cytokines and metalloproteinases, whereas the undesirable effects are mediated through transactivation of genes linked to gluconeogenesis and metabolism. Therefore, to identify anti-inflammatory agents that will have glucocorticoid-like efficacy with reduced side effects, new GR ligands are sought that, via induction of appropriate receptor conformations, favor pathways for transrepression over those for transactivation.[1−3]

Chart 1



Several classes of compounds have been reported in the literature to possess the profile of such a pathway-selective or "dissociated" agonist of GR.[1,4] The best characterized is a series of benzopyrano[3,4-*f*]quinoline derivatives, for example, (*S*)-2,5-dihydro-10-methoxy-2,2,4-trimethyl-5-(2-propen-1-yl)-1*H*-[1]benzopyrano[3,4-f]quinoline (AL-438), that exhibit anti-inflammatory efficacy in vivo with decreased GR mediated side effects.[3,5] Confidence in the approach has been further strengthened by studies with a mouse expressing a GR mutant that selectively abolishes GR DNA-mediated activity.[6]

Screening our collection of analogues of the previously reported GR antagonist **1**[7] led to the identification of **2** (Chart 1), a high affinity nonsteroidal ligand of GR (IC_{50} = 6.2 nM) exhibiting potent transrepression activity as measured by inhibition of IL-1 stimulated expression of endogenous pro-inflammatory genes in human chondrosarcoma cells (SW-1353). In these assays, **2** suppressed induction of IL-8 (controlled in part by the transcription factor NFκB) with an IC_{50} = 34 nM, achieving 75% the maximal effect of dexamethasone (75% max dex). Similarly, MMP-13 expression (controlled in part by AP1) was inhibited with an IC_{50} of 14 nM (79% max dex). In both cases, the functional activity of **2** could be reversed by co-incubation with mifepristone (RU-486), a potent GR antagonist.

At this stage, the ability of **2** and analogues to signal via transactivation was assayed in SW1353 cells stably transfected with the glucocorticoid-responsive mouse mammary tumor virus (MMTV) promotor[8] and the luciferase reporter. In this well-established system, **2** showed appreciably reduced maximal transactivation activity (8.5%) relative to dexamethasone (100%).

* To whom correspondence should be addressed. Phone: 860-441-4923. Fax: 860-715-4706. E-mail: ralph.p.robinson@pfizer.com.

[a] Abbreviations: AR, androgen receptor; ER, estrogen receptor; GR, glucocorticoid receptor; IL, interleukin; LBD, ligand binding domain; MMP, matrix metalloproteinase; MMTV, mouse mammary tumor virus; PR, progesterone receptor.

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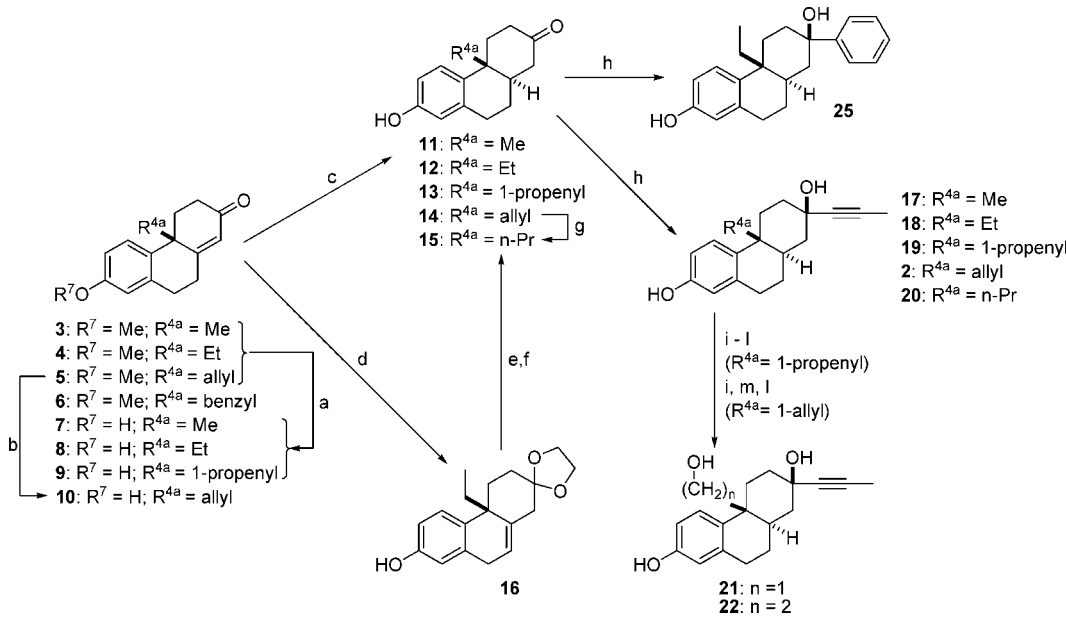
Scheme 1[a]



[a] (a) D,L-methionine, $MeSO_3H$, room temp, ~18 h; (b) BBr_3, CH_2Cl_2, −78 to 0 °C, 5 h; (c) Li, NH_3, THF, −78°; (d) $(CH_2OH)_2$, *p*-TsOH (cat.), toluene, Δ; (e) H_2 (3 atm), $Pd(OH)_2$, toluene, 70°C, 16 h; (f) aqueous HCl, THF, room temp, 4.5 h; (g) H_2 (3 atm), 10% Pd/C, MeOH, 2 h; (h) PhLi or lithiopropyne, THF; (i) 4-$O_2N(C_6H_4)COCl$, aqueous NaOH, acetone, 0°C; (j) O_3, MeOH, CH_2Cl_2, −78°C, ~1 min, then DMS; (k) aqueous NaOH, THF, room temp; (l) $NaBH_4$, MeOH, room temp, 20 min; (m) O_3, MeOH, CH_2Cl_2, −78°C, ~1 min, then DMS, then $NaBH_4$.

Selectivity for GR versus other nuclear hormone receptors was assessed in binding assays for the estrogen (ER), progesterone (PR), and androgen (AR) receptors. Although **2** bound to PR and AR with low affinity (IC_{50} > 1000 nM), binding to ERα and ERβ was quite significant (IC_{50} of 93 and 250 nM, respectively).

Herein we describe aspects of our work aimed at defining the in vitro structure−activity relationships around **2**. Our efforts were guided by a desire to improve the attractiveness of this compound as a lead for discovery of an orally administered pathway-selective GR modulator. At the outset, we were especially interested in finding acceptable replacements for the C4a allyl, C2 propynyl, and C7 phenolic hydroxyl groups. The first two were viewed as being potentially susceptible to oxidative metabolism leading to reactive metabolites. Also, the reactivity of these functional groups under a variety of oxidizing and reducing reaction conditions would likely limit the scope of chemistry that could be carried out to prepare analogues. Replacing the C7 phenolic hydroxyl group would likely reduce affinity for ER, a receptor that binds phenolic steroids as endogenous ligands.[9] Since **2** is relatively lipophilic (clogP = 4.6), we also sought to lower its lipophilicity by introducing additional polar functionality.[10]

Chemistry

All compounds were prepared starting from the enones **3**−**5** (Scheme 1), prepared in high enantiomeric purity from 6-methoxy-2-tetralone according to procedures analogous to those described previously for the synthesis of **6**.[7] In the cases of **3** and **4** cleavage of the 7-methoxy group took place in a straightforward manner using D,L-methionine in methanesulphonic acid,[11] giving **7** and **8**. However, in the case of the allyl enone **5**, these conditions yielded enone **9** through double bond isomerization. This side reaction was not observed when BBr_3/CH_2Cl_2 was employed, which allowed the preparation of **10**.

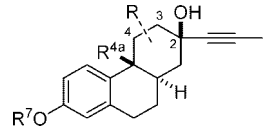
Reduction of enones **7**−**10** to the corresponding ketones **11**−**14** was carried out using lithium metal in liquid ammonia at −78 °C. These conditions invariably led to formation of ~30% of the corresponding cis B/C ring fused diastereoisomer, which was removed by fractional crystallization or chromatography. Because of our particular interest in compounds bearing an ethyl group at C4a and the difficulty in carrying out dissolving metal reductions on large scale, an alternative procedure was developed for the preparation of **12** from **8**.[12] Thus, reaction of **8** with ethylene glycol and catalytic TsOH in refluxing toluene gave **16**, the product of ketal formation and migration of the double bond into the B-ring. Subsequent catalytic hydrogenation of **16** (H_2, $Pd(OH)_2$, toluene, 70 °C) followed by ketal hydrolysis afforded a 3:1 mixture of **12** and the corresponding cis ring-fused diastereomer. Catalytic hydrogenation of the allyl group of **14** yielded ketone **15**.

Addition of lithiopropyne to **14** afforded **2** with good diastereoselectivity. Likewise, lithiopropyne additions to **11**−**13** and **15** provided **17**−**20**, respectively (Table 1). Exemplified by the addition of phenyllithium to provide **25** (Table 2), alternative C2 substituents in the C4a ethyl series could be obtained by addition of other organometallic reagents to ketone **12**.[13] For compounds **18** and **25**, as well as for compounds **32** and **42** described below, structural assignments were confirmed by X-ray crystallography.

Several analogues were obtained by modification of the C4a or C7 side chains (R^{4a} and R^7) of initial targets. The C4a hydroxymethyl analogue **21** was obtained from **19** in four steps including selective ozonolysis of the corresponding C7 4-nitrobenzoyl derivative (Scheme 1).[14] The C4a 2-hydroxyethyl analogue **22** was obtained in a similar manner from **2**. Selective alkylation (R^7Cl, NaH, THF/DMF) provided the C7 4-pyridylmethyl ether **23** and the C7 (2-methyl-2-pyridyl)methyl ethers **24**, **26**, **31**, and **33** from the corresponding phenols (Tables 1 and 2).

Analogues of **18** and **25** bearing an α-OH group at C3 or C4 (**30**, **32**, **36**, and **42**) were prepared as shown in Schemes 2 and 3. Bromination of **12** using phenyltrimethylammonium perbromide (THF, −78 to 0 °C) regio- and stereoselectively gave the

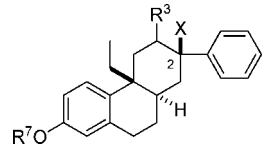
Table 1. C2 Propynyl Analogues



	R^7	R^{4a}	R	binding IC_{50} (nM)[a] GR	ERα	ERβ	AR	PR	transrepression MMP-13[a,b] IC_{50} nM (% max dex)	transactivation MMTV[a] (% max dex)
2	H	allyl	H	6.2	93	250	$>10^3$	1100	14 (79)[c]	8.5
17	H	Me	H	17					>5000	0.3
18	H	Et	H	5.6	89	580	420	2600	14 (86)[c]	6.4
19	H	CH=CHMe	H	3.5					>5000	1.6
20	H	n-Pr	H	1.5					>5000	0.8
21	H	CH_2OH	H	$>10^3$						
22	H	$(CH_2)_2OH$	H	$>10^3$						
23	CH_2-(4-py)	Et	H	3	670	3500			31 (88)	14.6
24	CH_2-(2-Me-3-py)	Et	H	2.3	$>10^4$	$>10^4$	880		6.3 (90)	18.4
30	H	Et	3-α-OH	35	$>10^4$	$>10^4$	$>10^4$	$>10^4$	63 (79)	12.7
31	CH_2-(2-Me-3-py)	Et	3-α-OH	3.3[d]	$>10^4$	$>10^4$	$>10^4$	$>10^4$	15 (84)[c,e]	18
36	H	Et	4-α-OH	360	$>10^4$	$>10^4$	$>10^4$			

[a] $n = 1$ (dose response curves run in triplicate) except where otherwise noted. [b] IC_{50}: concentration of test compound that inhibits IL-1-induced MMP-13 production by 50%. [c] Inhibition reversed by coincubation with RU-486. [d] $n = 2$ (IC_{50} values of 3.0 and 3.5 nM). [e] $n = 2$ (IC_{50} values of 13 and 16 nM).

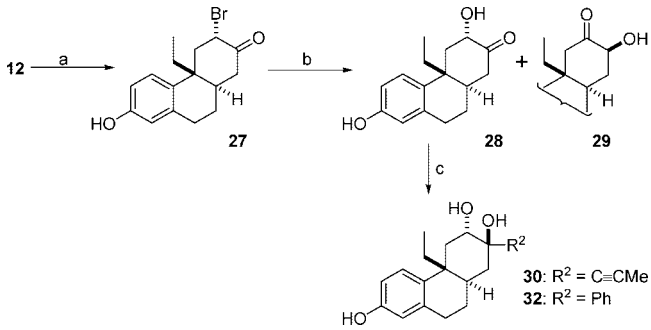
Table 2. C2 Phenyl Analogues



	R^7	R^3	X	binding IC_{50} (nM)[a] GR	ERα	ERβ	AR	PR	transrepression MMP-13[a,b] IC_{50} nM (% max dex)	transactivation MMTV[a] (% max dex)
25	H	H	OH	21					>5000	0.9
26	CH_2-(2-Me-3-py)	H	OH	6					1500	0
32	H	α-OH	OH	2.5	3400	660	$>10^4$	750	140 ± 60 (67)[c,d]	6.2
33	CH_2-(2-Me-3-py)	α-OH	OH	1.5	$>10^4$	$>10^4$	$>10^4$	$>10^3$	38 (78)[c,e]	6.3
42	H	β-OH	OH	3.8					5000[f]	2.3
48	H	α-OH	H	1.3					1100	5.8

[a] $n = 1$ (dose response curves run in triplicate) except where otherwise noted. [b] IC_{50}: concentration of test compound that inhibits IL-1-induced MMP-13 production by 50%. [c] Inhibition reversed by co-incubation with RU-486. [d] $n = 7$. [e] $n = 2$ (IC_{50} values of 25 and 50 nM). [f] $n = 2$ (47% and 58% inhibition at 5000 nM).

Scheme 2[a]



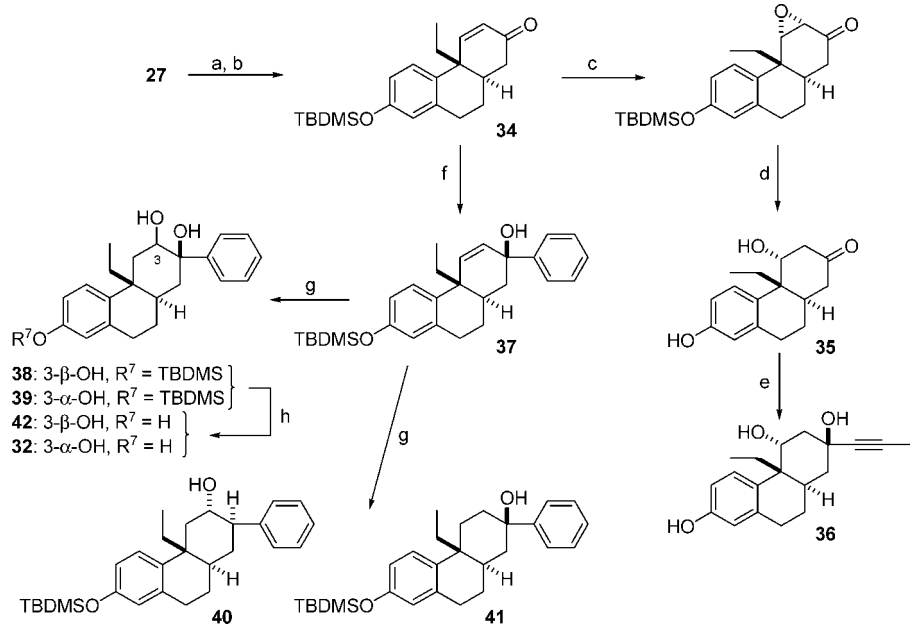
[a] (a) PTAB, THF, −78°C to 0°C, 2.5 h; (b) aqueous K_2CO_2, acetone, 50°C, 1 h; (c) R^2M, THF.

3*S* bromoketone **27**.[15] Hydrolysis of **27** (K_2CO_3/aqueous acetone)[16] provided the 3*S* hydroxyketone **28**[17] along with small amounts of the isomeric hydroxyketone **29**. Treatment of the mixture of hydroxyketones with lithiopropyne under the usual conditions provided a ∼3:2 mixture diastereomeric C2 adducts as well a small amount of an adduct arising from addition to **29**. The desired analogue **30** was easily isolated by flash chromatography. Similarly, addition of phenyllithium to **28** provided triol **32**.

Installation of a 4*S*-hydroxyl group to obtain **36** was carried out in a manner similar to that published for the synthesis of 1α,25-dihydoxycholesterol.[18] Elimination of HBr from **27** ($CaCO_3$, DMA, 170 °C)[19] yielded the Δ^3-enone, which was protected as the *tert*-butyldimethylsilyl ether **34** (Scheme 3). Epoxidation (aqueous H_2O_2, NaOH, MeOH) followed by reductive epoxide opening (Hg, Al, EtOH, aqueous $NaHCO_3$) gave the 4*S*-hydroxyketone **35**, which was converted to **36** under the usual conditions.

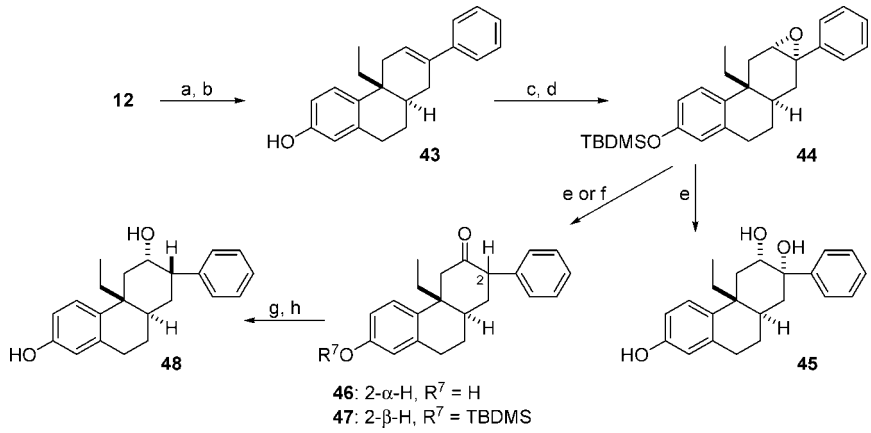
As a result of the promising biological profile of compounds **32** and **33** (Table 2), an alternative synthesis of **32** was sought in order to improve the overall yield and control stereochemistry at C2. Although an improved overall yield of **32** was not attained, an alternative synthesis permitted isolation of **42**, the C3 epimer of **32** (Scheme 3). Addition of phenylmagnesium bromide to **34** led to stereoselective formation of the allylic alcohol **37**. In agreement with literature reports on the regiochemistry of the hydroboration of allylic alcohols,[20] treatment of **37** with BH_3·THF followed by oxidative workup favored formation of the corresponding 2,3-diols **38** and **39** as opposed to the 2,4 diols, which were not detected in the product mixture. Unfortunately, significant over-reduction also occurred, which gave rise to the unwanted products **40** and **41**. Deprotection of **38** and **39** gave **42** and **32**, respectively.

Scheme 3[a]



[a] (a) $CaCO_3$, DMA, reflux, 2 h; (b) TBDMSCl, imidazole, CH_2Cl_2, room temp, ~18 h; (c) 30% aqueous H_2O_2, NaOH, MeOH, −10°C, ~18 h; (d) Al/Hg, aqueous $NaHCO_3$, EtOH, 4 h; (e) LiC≡CMe, −78°C to room temp, ~18 h; (f) PhMgCl, THF, −78°C to room temp, ~2 h; (g) BH_3·THF, THF, 0 °C to room temp, 4 days; (h) TBAF, AcOH, THF, room temp, 4 h.

Scheme 4[a]



[a] (a) PhMgBr, THF, −78°C to room temp, 2 h; (b) $KHSO_4$, toluene, Δ, ~18 h; (c) TBDMSCl, imidazole, CH_2Cl_2, room temp, ~18 h; (d) mCPBA, $CHCl_3$, room temp, ~18 h; (e) aqueous H_2SO_4, DMSO, room temp, ~18 h, then 60°C, ~24 h; (f) BF_3·OEt_2, CH_2Cl_2, −78°C, 20 min; (g) $NaBH_4$, MeOH, −78° to room temp; (h) TBAF, AcOH, THF, 2 h.

Similarly, in the course of further exploration of routes to **32**, a synthesis of **48** (the analogue of **32** in which the C2 OH is replaced with H) was developed (Scheme 4). Addition of phenylmagnesium bromide to **12** followed by elimination using $KHSO_4$ in hot toluene provided olefin **43**.[21] Epoxidation of **43** using mCPBA took place exclusively from the α face, giving **44**. Compound **32** was not detected following exposure of **44** to aqueous acid in DMSO, which instead yielded the diol **45** and ketone **46**, both having an equatorial (*β*) phenyl substituent. In contrast, treatment of **44** with BF_3·OEt_2 in CH_2Cl_2 at −78 °C cleanly provided ketone **47**, which was treated with $NaBH_4$ and deprotected to give **48**. We attribute the formation of **46** under aqueous conditions to acid-catalyzed enolization of **47** initially formed by stereospecific 1,2-hydride shift.

Discussion

To help guide target design and understand structure−activity relationships with respect to GR binding, **2** was docked into a homology model of the GR ligand binding domain (LBD) based on the crystal structure of PR with bound dexamethasone.[22] In the most favorable orientation (Figure 1), the A, B, and C rings of **2** align well with the corresponding rings of dexamethasone (not shown). Interestingly, the C4a allyl substituent projects toward helix 5 and there is no direct interaction with helix 12, the conformation of which is important in determining GR agonism versus antagonism.[23] The homology model suggests that the C7 hydroxyl group plays a role similar to that of the A ring carbonyl function of dexamethasone, forming hydrogen bonds with Arg611 and Gln570. Considering that large groups at C7 (as in **23** and **24**, vide infra) are often well tolerated, we postulate that such groups may protrude into a surface cleft formed by reorientation of the polar and solvent-accessible Gln570 and Arg611 side chains.

The C4a allyl substituent of **2** was expected to be reactive under various reductive and oxidative conditions and is installed early in the synthesis. Thus, before commitment of resource to

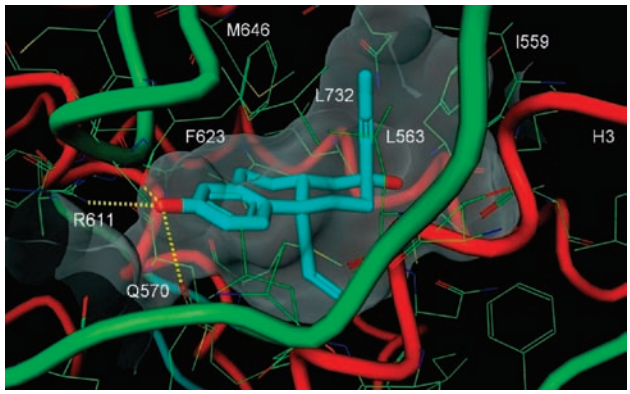


Figure 1. Compound **2** docked into the GR ligand binding domain (homology model).

producing bulk intermediates for exploration of other structural modifications, identifying a more chemically stable replacement for the allyl group was our first priority in exploring structure−activity relationships around **2**.

The most easily obtained C4a variant of **2** was the corresponding *n*-propyl analogue (**20**). Unfortunately, despite having potent binding to GR, this compound lacked activity in the IL-1 induced MMP-13 assay (Table 1). This was also the case for the C4a methyl and 1-propenyl analogues (**17** and **19**, respectively), indicating that transrepression activity within the series is very sensitive to minor structural changes at the C4a position. In contrast, the C4a ethyl analogue **18** showed a profile quite similar to that of **2**.[24] On the basis of this favorable result and the relative chemical inertness of the ethyl group, subsequent exploration of the series focused predominantly on analogues bearing ethyl at the C4a position.

Similar to **2**, **18** showed appreciable affinity for ERα and ERβ (IC_{50} of 89 and 580 nM, respectively). Fortunately, conversion of the C7 hydroxyl to ether derivatives provided compounds with significantly improved selectivity for GR. Pyridylmethyl ether derivatives such as **23** and **24** had especially attractive profiles (e.g., **24**, ERα IC_{50} > 10000 nM; ERβ IC_{50} > 10000 nM; GR IC_{50} = 2.3 nM).

Having established that ethyl is an acceptable substituent at the C4a position, we next concentrated on finding suitable replacements for the 1-propynyl group at C2. A particular concern with alkyne functionality was the potential for formation of reactive species arising from epoxidation of the C−C triple bond. Inspection of the **2**-ligated GR LBD homology model showed that the propyne group projects into a hydrophobic pocket formed by residues M560, M639, M646, I559, I629, L563, L732, and F623 (Figure 1, select residues shown). For this reason, we prepared numerous analogues with lipophilic C2 groups varying in both size and rigidity (e.g., alkyl, alkenyl, arylmethyl, aryl, heteroaryl). Exemplified by **25** and its ether derivative **26** (Table 2), relatively small changes in structure at C2 resulted in loss of transrepression and, in many cases, significant attenuation of GR binding affinity as well.

In parallel with our efforts to find an acceptable substitute for the C2 propynyl group, we began an investigation into the possibility of introducing additional polar functionality in order to lower the overall lipophilicity of the series. This was driven in large part by the observation that poor aqueous solubility often resulted from derivatization of the C7 hydroxyl group (necessary to increase selectivity over ER) and the high clogP values for compounds such as **24** (clogP = 5.9). The GR LBD homology model with bound **2** suggested that polar functionality on the C4a side chain would not be favored because of the hydrophobic nature of the surrounding area of the binding pocket. Nevertheless, since functionalization of the C4a group was relatively straightforward, we prepared the C4a hydroxymethyl and 2-hydroxyethyl analogues **21** and **22**, respectively. Neither compound showed appreciable GR binding at 5 μM (Table 1).

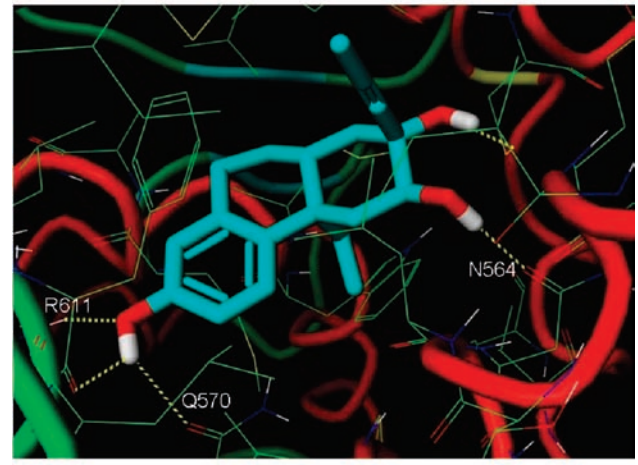


Figure 2. Compound **30** docked into the GR ligand binding domain (homology model).

We next explored the possibility of introducing polarity into the C-ring by preparing the C3α hydroxyl and C4α hydroxyl analogues **30** and **36**, respectively. This effort was inspired by the structural analogy to corticosteroids, which require a hydroxyl group at position 11β in the C-ring (corresponding to C4α in our series), as well as the GR LBD homology model, which revealed possibilities for a C3 or C4 hydroxyl substituent to form hydrogen bond interactions with the polar amino acid side chain of Asn564 (Figure 2). The C4α hydroxyl analogue **36** bound GR weakly (IC_{50} = 360 nM). However, the C3α hydroxyl isomer (**30**) retained much of the GR-related activity of the parent compound **18** (Table 1), and despite an unmasked hydroxyl group at C7, the compound showed no appreciable affinity for ER. Compound **31**, the (3-methyl-2-pyridyl)methyl derivative of **30**, displayed improved activity with respect to GR binding and transrepression. Its activity profile resembled closely that of **24**, the corresponding analogue unfunctionalized at C3. Thus, we achieved our objective of introducing additional polar functionality onto the tricyclic skeleton to reduce lipophilicity (e.g., **30**, clogP = 3.7 versus **18**, clogP = 4.6; **31**, clogP = 5.0 versus **24**, clogP = 5.9) without negatively impacting the biological profile.

Although the route to **30** was low-yielding, it nonetheless allowed the preparation of additional C3α hydroxyl analogues such as C2 phenyl analogue **32** (Table 2). Strikingly, in contrast to all other non-alkyne C2 analogues yet prepared, **32** unexpectedly inhibited IL-1 induced MMP-13 expression (IC_{50} = 140 nM, 67% max dex), albeit somewhat attenuated relative to **18** and **30**. Again, activity in the transrepression assay was increased through preparation of the corresponding (3-methyl-2-pyridyl)-methyl derivative **33** (IC_{50} = 38 nM, 78% max dex), which retained a low propensity for transactivation in the MMTV assay (6% dex). Additionally, **33** showed high selectivity for GR over the other nuclear hormone receptors assayed (binding IC_{50} of >1000 nM). In contrast to **32**, the C3β epimer **42** failed to show transrepression activity despite having high affinity for GR. Compound **48**, lacking the C2β hydroxyl, bound GR potently but showed only very weak activity in the transrepression assay.

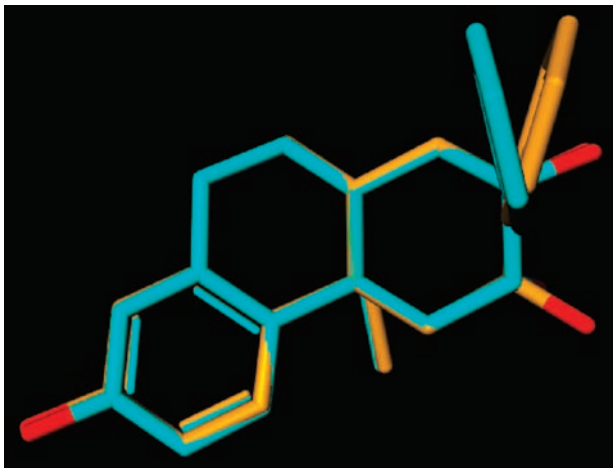


Figure 3. Overlaid X-ray crystal structures of compounds **32** (blue) and **42** (orange).

With the discovery of compounds **32** and **33**, we achieved our initial goal of finding replacements for the C4a allyl and C2 propynyl groups of **2**, at the same time improving GR selectivity and maintaining specificity for transrepression over transactivation. Furthermore, the introduction of additional polar functionality allowed the C7 hydroxyl to be derivatized, thus counteracting the potential for increased lipophilicity and decreased aqueous solubility when doing so.

On the basis of the GR LBD homology model, the ability of the C3α hydroxyl to hydrogen-bond to Asn564 may be a factor in promoting the unexpected transrepression activity elicited by compounds **32** and **33**. However, this does not explain why, in the C2 propyne series, agonist activity is independent of the presence of a C3α hydroxyl. Alternatively, the role of the C3 hydroxyl may be to help populate conformations that are preferred for transrepression. X-ray crystallography and quantum mechanical calculations indicate that differences in conformational preference do arise upon introduction of the C3α hydroxyl group, although the changes are relatively minor. Thus, in the X-ray crystal structures of **25** and **42**, the orientations of the C2 phenyl group are identical, the C2−C3 single bond nearly lying in the plane described by the C2 phenyl ring. However, in the X-ray structure of **32**, the phenyl ring is tilted about 30° relative to that of **42** (Figure 3). Quantum mechanical calculations indicate that the barrier to free phenyl ring rotation (E^R) is about 1 kcal/mol for compounds **25** and **42**. In contrast, the phenyl ring in **32** is less free to rotate ($E^R = 4$ kcal/mol) as a result of interaction with the C3 hydroxyl substituent.

Conclusion

Compounds derived from the nonsteroidal octahydrophenanthrene template (e.g., **1**) have been previously described as potent, selective GR receptor antagonists. As exemplified by **2**, close-in analogues of **1** exhibit the profile of a pathway-selective or "dissociated" agonist of GR, retaining the potent activity that glucocorticoids have for transrepression (as measured by inhibition of IL-1 induced MMP-13 expression) but showing an attenuated capacity for transactivation (as measured in the MMTV luciferase reporter assay).

To guide design of compounds having improved structural and physicochemical characteristics, a GR ligand binding domain homology model was developed on the basis of a crystal structure of the progesterone receptor. This model proved to be very useful, especially in the design of analogues bearing an additional hydroxyl group to lower overall lipophilicity.

Binding to GR is quite tolerant of C2 and C4a side chain variation, in contrast to transrepression activity, which is much less so. Introduction of a C3α hydroxyl group restored transrepression activity to C2 phenyl analogues, obviating the requirement for a 1-propynyl group at this position. Thus, as demonstrated by our discovery of compounds **32** and **33**, we were successful in preparing analogues of **2** in which the allyl and propynyl side chains are replaced with groups likely to be more chemically stable and less likely to produce toxic metabolites. At the same time, selectivity for binding GR versus binding ER was increased. Although their follow-up is beyond the scope of this paper, these analogues have proven key to identification of drug-candidate-quality GR modulators for the treatment of inflammation.[25]

Experimental Section

Chemistry. Reagents were purchased commercially and used without further purification unless otherwise indicated. Reactions were performed under a nitrogen atmosphere, magnetically stirred, and run at room temperature except where otherwise indicated. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F_{254} plates on which compounds were visualized using ultraviolet (UV) light and ceric ammonium molybdate stain. Chromatography was performed on Biotage Flash 25 or Flash 40 columns (Cyax Corp.) under low pressure. Preparative HPLC was carried out on a Shimadzu Discovery VP instrument using a Waters Xterra Prep MS C18, 5 μm, 30 mm × 50 mm column and eluting with a 5−100% gradient of 0.1% formic acid in acetonitrile and 0.1% formic acid in water.

Enantiomeric excess (ee) determinations were carried out by chiral HPLC on a Chiralcel OJ column, eluting with 2-propanol/hexane (1% diethylamine) and detecting by UV at 214 nm. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Varian Unity 400 or 500 MHz spectometer. Chemical shifts are reported in parts per million (δ) relative to residual $CHCl_3$ (7.24 ppm) or DMSO (2.49 ppm) as internal reference. Coupling constants (J) are reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Low resolution mass spectra (LCMS) were recorded by positive and negative electrospray ionization (ESI) using a Waters/Micromass ESI/MS model ZMD/LCZ mass spectrometer equipped with Gilson 215 liquid handling system and Hewlett-Packard 1100 diode array detector. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ, and are within ±0.4% of the calculated values unless stated otherwise. X-ray crystal structures were collected on a Bruker APEX or a Siemens P4 diffractometer.

1-Ethyl-6-methoxy-3,4-dihydro-1*H*-naphthalen-2-one. A solution of 6-methoxy-2-tetralone (120.55 g, 0.684 mol) and pyrrolidine (61 mL, 0.685 mol) in toluene (1.7 L) was heated to reflux using a Dean−Stark trap for 3 h. The reaction mixture was cooled to room temperature and concentrated to a solid. Ethyl iodide (121 mL, 1.51 mol) and MeOH (1.2 L) were added. The resulting solution was heated at reflux overnight and then concentrated. A solution of AcOH (120 mL) and NaOAc (120 g) in H_2O (240 mL) was added to the residue, and the resulting mixture was heated at reflux for 2 h. The mixture was cooled and extracted several times with Et_2O. The combined organic layers were washed twice with aqueous 1 M HCl, twice with aqueous 1 M NaOH, and once with brine. After the solution was dried ($MgSO_4$), the solvent was evaporated to afford the title compound as an oil, 121.8 g. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, $J = 8.3$ Hz, 1 H), 6.81−6.78 (m, 2 H), 3.83 (s, 3 H), 3.30 (apparent t, $J = 6.7$ Hz, 1 H), 3.18−3.12 (m, 1 H), 3.00−2.94 (m, 1 H), 2.68−2.62 (m, 1 H), 2.58−2.49 (m, 1 H), 1.92−1.86 (m, 2 H), 0.91 (t, $J = 7.3$ Hz, 3 H). LCMS: m/z 204 $[M]^+$.

(1*S*,9*S*)-Ethyl-10-hydroxy-5-methoxy-10-methyl-tricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-trien-13-one. A solution of 1-ethyl-6-methoxy-3,4-dihydro-1*H*-naphthalen-2-one (121.8 g, 0.592 mol) and freshly distilled (*S*)-(−)-α-methylbenzylamine (72 g, 0.592 mol) in toluene

(600 mL) was heated at reflux overnight using a Dean−Stark trap to collect water. Roughly half of the toluene was then distilled off, and freshly distilled methylvinylketone (4.39 g, 0.626 mol) was added dropwise. The solution was stirred at room temperature for 2 h and then heated in an oil bath at 45 °C overnight. The mixture was cooled in an ice bath, and aqueous 10% H_2SO_4 was added. After it was stirred at room temperature for 2 days, the solution was extracted three times with EtOAc. The combined organic layers were washed with H_2O, washed with brine, dried ($MgSO_4$), and concentrated to afford an oil. The title compound (59.6 g) was isolated by chromatography, eluting with 15% EtOAc/hexanes followed by 21% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.04 (d, J = 8.7 Hz, 1 H), 6.80 (dd, J = 2.5, 8.7 Hz, 1 H), 6.61 (d, J = 2.5 Hz, 1 H), 3.79 (s, 3 H), 3.32 (dd, J = 7.1, 17.8 Hz, 1 H), 3.08 (d, J = 17.8 Hz, 1 H), 2.50 (d, J = 7.1 Hz, 1 H), 2.20−2.05 (m, 2 H), 1.77−1.68 (m, 1 H), 1.59 (br s, 1 H), 1.52−1.35 (m, 3 H), 1.34 (s, 3 H), 0.82 (t, J = 7.3 Hz, 3 H). LCMS: m/z 275 $[MH]^+$.

(4a*R*)-4a-Ethyl-7-methoxy-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (4). A solution of 59.6 g (0.217 mol) of (1*S*,9*S*)-ethyl-10-hydroxy-5-methoxy-10-methyl-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-13-one in MeOH (300 mL) was added dropwise to 1 M NaOMe in MeOH (250 mL). The mixture was heated at reflux for 3 h and then cooled to room temperature. The mixture was neutralized with AcOH and concentrated. The residue was dissolved in EtOAc and washed sequentially with aqueous saturated $NaHCO_3$, H_2O, and brine. After the solution was dried ($MgSO_4$), the solvent was evaporated to afford **4** as a tan solid, 55 g, ee = 98.9%. ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J = 8.7 Hz, 1 H), 6.77 (dd, J = 2.9, 8.7 Hz, 1 H), 6.62 (d, J = 2.9 Hz, 1 H), 5.91 (s, 1H), 3.77 (s, 3 H), 2.99−2.93 (m, 1 H), 2.85−2.34 (overlapping m, 6 H), 2.04−1.87 (m, 3 H), 0.79 (t, J = 7.6 Hz, 3 H). LCMS: m/z 257 $[MH]^+$.

(4a*R*)-4a-Ethyl-7-hydroxy-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (8). To a well-stirred solution of **4** (55 g, 0.214 mol) in methanesulfonic acid (890 mL) was added, in portions, D,L-methionine (106.7 g, 0.715 mol). The mixture was stirred overnight, poured into ice, and stirred for an additional 30 min. The precipitated solid was collected by filtration and then dissolved in EtOAc. The resulting solution was washed with aqueous saturated $NaHCO_3$ and brine. After the solution was dried ($MgSO_4$), the solvent was evaporated to afford a red semisolid. This was triturated with Et_2O and filtered to collect **8** as a yellow solid (34 g, 66%). ^{1}H NMR ($CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 1 H), 6.76 (dd, J = 2.6, 8.3 Hz, 1 H), 6.62 (d, J = 2.6 Hz, 1 H), 5.97 (s, 1H), 3.00−2.95 (m, 1 H), 2.86−2.38 (overlapping m, 6 H), 2.08−1.90 (m, 3 H), 0.84 (t, J = 7.3 Hz, 3 H). LCMS: m/z 243 $[MH]^+$. Anal. ($C_{16}H_{18}O_2$) C, H.

4a-(*R*)-Ethyl-7-hydroxy-3,4,4a,9-tetrahydro-1*H*-phenanthren-2-one Ethylene Ketal (16). A mixture of **8** (156 g, 0.644 mol), ethylene glycol (180 mL, 3.22 mol), *p*-TsOH·H_2O (10 mg), and toluene (10 L) was heated to reflux for 16 h using a Dean−Stark apparatus. The mixture was cooled to room temperature, concentrated, and dissolved in EtOAc. The resulting solution was washed with H_2O, washed with brine, dried (K_2CO_3), and concentrated. Compound **16** (154 g, 84%) was isolated as a low melting solid by chromatography, eluting with 30% EtOAc/hexanes. LCMS: m/z 287 $[MH]^+$.

(4a*R*,10a*R*)-4a-Ethyl-7-hydroxy-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (12). To a suspension of 20% $Pd(OH)_2$/C (25.3 g) in toluene (2.53 L) was added **16** (253 g, 0.883 mol). The resulting mixture was hydrogenated at 3 atm for 48 h at 65 °C. It was then cooled to room temperature, filtered, and concentrated. The residue was chromatographed, eluting with 30% EtOAc/hexanes. Fractions containing the intermediate hydrogenation product were concentrated and dissolved in THF (1 L). Aqueous 1 M HCl (1 L) was added, and the resulting mixture was stirred at room temperature for 2 h. The mixture was extracted with Et_2O, and the extracts were washed with brine, dried ($MgSO_4$), and concentrated. The title compound (115 g, 54%) was isolated by chromatography (30% EtOAc/hexanes as eluant) and subsequent recrystallization from 50% EtOAc/hexanes. Mp 169−171 °C. ^{1}H NMR ($CDCl_3$): δ 7.11 (d, J = 8.3 Hz, 1 H), 6.65−6.60 (m, 2H), 2.93−2.90 (m, 2 H), 2.71−2.70 (m, 1 H), 2.50−1.50 (m, 10 H), 0.81 (t, J = 7.8 Hz, 3 H). LCMS: m/z 245 $[MH]^+$. Anal. ($C_{16}H_{20}O_2$) C, H.

(4a*S*)-4a-Allyl-7-methoxy-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (5). This intermediate was prepared in a manner analogous to the preparation of **4** starting from 6-methoxy-2-tetralone and allyl bromide, ee = 97.9%. ^{1}H NMR ($CDCl_3$): 7.12 (d, J = 8.5 Hz, 1 H), 6.80 (dd, J = 2.7, 8.5 Hz, 1 H), 6.63 (d, J = 2.7 Hz, 1 H), 5.95 (s, 1 H), 5.67−5.55 (m, 1 H), 5.03−4.96 (m, 2 H), 3.80 (s, 3 H), 3.02−2.95 (m, 1 H), 2.90−2.60 (m, 5 H), 2.58−2.40 (m, 3 H), 2.08−1.99 (m, 1 H). LCMS: 269 $[MH]^+$. Anal. ($C_{18}H_{20}O_2$) C, H.

(4a*S*)-4a-Allyl-7-hydroxy-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (10). Boron tribromide (10.6 mL, 112 mmol) was added dropwise to a solution of **5** (15.0 g, 55.9 mmol) in CH_2Cl_2 (350 mL) at −78°. The mixture was allowed to warm to 0 °C over 5 h and was then poured into ice−water. Solid $NaHCO_3$ was carefully added to neutralize the mixture, which was then extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated. Compound **10** (11.0 g, 53%) was isolated by chromatography, eluting with 5−10% EtOAc/CH_2Cl_2. ^{1}H NMR ($CDCl_3$): δ 7.14 (d, J = 8.5 Hz, 1 H), 6.72 (dd, J = 2.7, 8.5 Hz, 1 H), 6.58 (d, J = 2.7 Hz, 1 H), 5.94 (s, 1 H), 5.62−5.54 (m, 1 H), 5.03−4.98 (m, 2 H), 4.85 (br s, 1 H), 2.95−2.91 (m, 1 H), 2.85−2.63 (m, 5 H), 2.53−2.40 (m, 3 H), 2.08−1.99 (m, 1 H). LCMS: 255 $[MH]^+$. Anal. ($C_{17}H_{18}O_2$·0.25 H_2O) C, H.

(4a*S*,10a*R*)-4a-Allyl-7-hydroxy-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (14). A three-neck round-bottom flask was equipped a dry ice reflux condenser and a mechanical stirrer. Ammonia (400 mL) was condensed into the flask at −78 °C. To this flask was added approximately 0.08 g (11.5 mmol) of Li wire to obtain a dark-blue solution. A solution of **10** (10.5 g, 41.3 mmol) in THF (100 mL) was slowly added to the mixture, keeping the mixture dark-blue. Just before dissipation of the blue color was anticipated, more Li (about 0.08 g, 11.5 mmol) was added to maintain the blue color. The process was repeated until a total amount of 0.6 g (86.5 mmol) Li had been added. The mixture was stirred an additional 30 min after addition of the enone was complete and was quenched by dropwise addition of excess aqueous saturated NH_4Cl. The mixture was allowed to warm to room temperature, and the NH_3 was allowed to evaporate. The residue was taken up in H_2O and extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was triturated with Et_2O and filtered to collect **14** as a tan solid (5.22 g, 49%). ^{1}H NMR ($CDCl_3$): δ 7.05 (d, J = 8.3 Hz, 1 H), 6.62−6.58 (m, 2H), 5.72−5.62 (m, 1 H), 5.08−5.01 (m, 2 H), 4.73 (br s, 1 H), 2.91−2.88 (m, 2 H), 2.63−2.28 (m, 7 H), 2.11−2.03 (m, 1 H), 1.95−1.84 (m, 1 H), 1.66−1.56 (m, 2 H).

(4a*R*)-4a-Methyl-7-methoxy-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (3). This intermediate was prepared in a manner analogous to the preparation of **4** starting from 6-methoxy-2-tetralone and methyl iodide. ^{1}H NMR ($CDCl_3$): δ 7.20 (d, J = 8.7 Hz, 1 H), 6.80 (dd, J = 2.5, 8.7 Hz, 1 H), 6.60 (d, J = 2.5 Hz, 1 H), 5.88 (s, 1 H), 3.78 (s, 3 H), 2.96−2.94 (m, 1 H), 2.89−2.82 (m, 1 H), 2.75−2.65 (m, 2 H), 2.54−2.47 (m, 2 H), 2.36−2.31 (m, 1 H), 2.03 (td, J = 4.4, 14.5 Hz, 1 H), 1.54 (s, 3 H). LCMS: m/z 243 $[MH]^+$. Anal. ($C_{16}H_{18}O_2$) C, H.

(4a*R*)-7-Hydroxy-4a-methyl-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (7). This intermediate was obtained by demethylation of **3** using a procedure analogous to the preparation of **8**. Recrystallization was from hot EtOAc with a trace of MeOH, ee = 97.2%. ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J = 8.3 Hz, 1 H), 6.73 (dd, J = 2.9, 8.3 Hz, 1 H), 6.56 (d, J = 2.9 Hz, 1 H), 5.89 (s, 1 H), 2.96−2.90 (m, 1 H), 2.87−2.79 (m, 1 H), 2.74−2.65 (m, 2 H), 2.53−2.47 (m, 2 H), 2.35−2.30 (m, 1 H), 2.03 (td, J = 4.9, 14.3 Hz, 1 H), 1.53 (s, 3 H). LCMS: m/z 229 $[MH]^+$. Anal. ($C_{15}H_{16}O_2$) C, H.

(4a*R*,10a*R*)-7-Hydroxy-4a-methyl-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (11). This intermediate was obtained by dissolving metal reduction of **7** using a procedure analogous to the preparation of **14** from enone **10**. Recrystallization was from hot EtOAc/hexane. ^{1}H NMR ($CDCl_3$): δ 7.16 (d, J = 8.7 Hz, 1 H),

6.65 (dd, $J = 2.5, 8.7$ Hz, 1 H), 6.58 (d, $J = 2.5$ Hz, 1 H), 4.90 (br s, 1 H), 2.88−2.78 (m, 2 H), 2.61−2.27 (m, 5 H), 2.02−1.93 (m, 1 H), 1.82−1.71 (m, 2 H), 1.61−1.55 (m, 1 H), 1.26 (s, 3 H). LCMS: *m*/*z* 231 $[MH]^+$. Anal. ($C_{15}H_{18}O_2$) C, H.

(4a*S*)-7-Hydroxy-4a-(1-propenyl)-4,4a,9,10-tetrahydro-3*H*-phenanthren-2-one (9). This intermediate was prepared by treatment of **5** with D,L-methionine and methansulfonic acid using a procedure analogous to the demethylation of **4** to provide **8**. The title compound was purified by chromatography, eluting with 10% EtOAc/CH_2Cl_2. ^{1}H NMR ($CDCl_3$): δ 7.13 (d, $J = 8.3$ Hz, 1 H), 6.73 (dd, $J = 2.5, 8.3$ Hz, 1 H), 6.56 (d, $J = 2.5$ Hz, 1 H), 6.00 (s, 1 H), 5.54 (d, $J = 15.4$ Hz, 1 H), 5.27 (dq, $J = 6.6, 15.4$ Hz, 1 H), 2.90−2.35 (overlapping m, 8 H), 2.07−2.00 (m, 1 H), 1.62 (d, $J = 6.6$ Hz, 3 H).

(4a*S*,10a*R*)-7-Hydroxy-4a-(1-propenyl)-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (13). This intermediate was obtained by dissolving metal reduction of **9** using a procedure analogous to the preparation of **14** from enone **10**. Recrystallization was from hot EtOAc. ^{1}H NMR ($CDCl_3$): δ 7.10 (d, $J = 8.3$ Hz, 1 H), 6.63 (dd, $J = 2.5, 8.3$ Hz, 1 H), 6.54 (d, $J = 2.5$ Hz, 1 H), 5.87 (d, $J = 15.4$ Hz, 1 H), 5.18 (dq, $J = 6.6, 15.4$ Hz, 1 H), 4.95 (br s, 1 H), 2.84−2.64 (overlapping m, 4 H), 2.48−2.43 (m, 1 H), 2.39 (d, $J = 14.5$ Hz, 1 H), 2.27 (apparent d, $J = 14.9$ Hz, 1 H), 1.99−1.95 (m, 1 H), 1.87−1.77 (m, 2 H), 1.67 (d, $J = 6.6$ Hz, 3 H), 1.54−1.49 (m, 1 H). Anal. ($C_{17}H_{20}O_2$) C, H.

(4a*R*,10a*R*)-7-Hydroxy-4a-(1-propyl)-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (15). A solution of **14** (500 mg, 1.95 mmol) in MeOH (20 mL) was hydrogenated at 3 atm for 2 h. The mixture was passed through a 0.45 μm nylon filter, and the filtrate was concentrated to afford **15** (492 mg, 98%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.07 (d, $J = 8.3$ Hz, 1 H), 6.62−6.57 (m, 2 H), 2.90−2.86 (m, 2 H), 2.66 (dt, $J = 4.2, 13.3$ Hz, 1 H), 2.48 (d, $J = 13.7$ Hz, 1 H), 2.46−2.40 (m, 2 H), 2.30 (dd, $J = 4.2, 15.4$ Hz, 1 H), 2.03−1.85 (overlapping m, 2 H), 1.78−1.71 (m, 1 H), 1.63−1.54 (m, 2 H), 1.43−1.16 (overlapping m, 3 H), 0.85 (t, $J = 7.1$ Hz, 3 H).

(3*S*,4a*R*,10a*R*)-3-Bromo-4a-ethyl-7-hydroxy-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (27). To a solution of **12** (1.0 g, 4.1 mmol) in THF (100 mL) at −78 °C was added phenyltrimethylammonium bromide tribromide (1.57 g, 4.2 mmol) in portions. The mixture was allowed to stir at −78 °C for 20 min and then allowed to slowly warm to about room temperature over 0.5 h. Brine was added, and the resulting mixture was extracted twice with EtOAc. The combined extracts were dried ($MgSO_4$) and concentrated to give an orange oil. Compound **27** (647 mg, 49%) was isolated as a white foam by chromatography, eluting with a gradient of 15−50% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.08 (d, $J = 8.3$ Hz, 1 H), 6.64 (apparent d, $J = 8.3$ Hz, 1 H), 6.62 (apparent s, 1 H), 4.79 (dd, $J = 5.7, 13.5$ Hz, 1 H), 3.28 (dd, $J = 5.7, 13.5$ Hz, 1 H), 2.94−2.91 (m, 2 H), 2.63−2.61 (m, 2 H), 2.19−2.13 (m, 1 H), 2.08 (t, $J = 13.5$ Hz, 1 H), 1.95−1.85 (m, 2 H), 1.72−1.66 (m, 1 H), 1.58−1.52 (m, 1 H), 0.92 (t, $J = 7.8$ Hz, 3 H).

Mixture of (3*S*,4a*R*,10aR)-4a-Ethyl-3,7-dihydroxy-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (28) and (2*S*,4a*R*,10a*R*)-4a-Ethyl-2,7-dihydroxy-1,4,4a,9,10,10a-hexahydro-2*H*-phenanthren-3-one (29). A mixture of **27**, H_2O (25 mL), and acetone was warmed to 50 °C, and K_2CO_3 (270 mg, 1.95 mmol) was added. The mixture was stirred for 1.5 h at 50 °C and then poured into excess aqueous 1 M HCl. The mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a white foam. The mixture (containing some starting material) was chromatographed using a gradient of 20−40% EtOAc/hexanes to afford a 2:1 mixture of **28** and **29** (358 mg, 69%). Compound **28**: ^{1}H NMR ($CDCl_3$), selected signals, δ 7.10 (d, $J = 8.3$ Hz, 1 H), 4.30 (ddd, $J = 1.0, 6.7, 12.7$ Hz, 1 H), 3.10 (dd, $J = 6.7, 13.0$ Hz, 1 H), 2.93−2.90 (m, 2 H), 2.60 (apparent t, $J = 14.5$ Hz, 1 H), 2.51 (dd, $J = 4.4, 14.5$ Hz, 1 H). Compound **29**: ^{1}H NMR ($CDCl_3$), selected signals, δ 6.95 (d, $J = 8.3$ Hz, 1 H), 4.25−4.21 (m, 1 H), 3.29 (d, $J = 13.0$ Hz, 1 H).

(4a*S*,10a*R*)-7-(*tert*-Butyldimethylsilanyloxy)-4a-ethyl-4a,9,10,10a-tetrahydro-1*H*-phenanthren-2-one (34). A solution of **27**(4.0 g, 12.3 mmol) in dimethylacetamide (150 mL) was added slowly to a refluxing mixture of $CaCO_3$ in dimethylacetamide (100 mL). Heating to reflux was continued for 2 h. The mixture was cooled, aqueous 1 M HCl was added, and the mixture was extracted twice with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The corresponding Δ^3-enone (1.22 g, 41%) was isolated by chromatography, eluting with 5% EtOAc/CH_2Cl_2. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, $J = 10.4$ Hz, 1 H), 7.29 (d, $J = 8.8$ Hz, 1 H), 6.72 (dd, $J = 3.1, 8.8$ Hz, 1 H), 6.67 (d, $J = 3.1$ Hz, 1 H), 6.10 (d, $J = 10$. Four Hz, 1 H), 5.90 (br s, 1 H), 2.99−2.91 (m, 2 H), 2.61 (dd, $J = 14.3, 17.9$ Hz, 1 H), 2.48−2.39 (m, 2 H), 2.01−1.92 (m, 1 H), 1.85−1.78 (m, 1 H), 1.75−1.70 (m, 1 H), 1.67−1.60 (m, 1 H), 0.88 (t, $J = 7.8$ Hz, 3 H).

The Δ^3-enone (245 mg, 1.01 mmol) was dissolved in CH_2Cl_2 (20 mL). Imidazole (85 mg, 1.25 mmol) and *tert*-butyldimethylsilylchloride (175 mg, 1.16 mmol) were added, and the mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 and then washed with aqueous 0.5 M citric acid, water, and brine. The solution was dried ($MgSO_4$) and concentrated to afford **34** as an oil, 322 mg (89%). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, $J = 10.4$ Hz, 1 H), 7.28 (d, $J = 8.3$ Hz, 1 H), 6.68 (dd, $J = 2.6, 8.3$ Hz, 1 H), 6.64 (d, $J = 2.6$ Hz, 1 H), 6.08 (d, $J = 10$. Four Hz, 1 H), 2.95−2.90 (m, 2 H), 2.60 (dd, $J = 15.0, 18.6$ Hz, 1 H), 2.47−2.41 (m, 2 H), 2.01−1.94 (m, 1 H), 1.84−1.78 (m, 1 H), 1.76−1.70 (m, 1 H), 1.68−1.62 (m, 1 H), 1.00 (s, 9 H), 0.87 (t, $J = 7.8$ Hz, 3 H), 0.21 (s, 6 H).

(4*R*,4a*R*,10a*R*)-4a-Ethyl-4,7-dihydroxy-3,4,4a,9,10,10a-hexahydro-1*H*-phenanthren-2-one (35). A solution of **34** (570 mg, 1.60 mmol) in MeOH (100 mL) was cooled to −10 °C in an ice/salt bath. Aqueous 5% NaOH (6.4 mL) and then aqueous 30% H_2O_2 (0.11 mL, 8.0 mmol) were added. The reaction mixture was allowed to stand in a freezer (−10 °C) overnight. The reaction was quenched by addition of aqueous 0.5 M citric acid and then partially concentrated to remove MeOH. The mixture was extracted three times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford the corresponding 3,4-epoxide (452 mg, 76%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.31 (d, $J = 8.3$ Hz, 1 H), 6.69 (dd, $J = 2.6, 8.3$ Hz, 1 H) 6.63 (d, $J = 2.6$ Hz, 1 H), 4.19 (d, $J = 4.2$ Hz, 1 H), 3.43 (d, $J = 4.2$ Hz, 1 H), 2.92−2.86 (m, 2 H), 2.64−2.57 (m, 1 H), 2.50 (dd, $J = 6.2, 19.2$ Hz, 1 H), 2.17 (dd, $J = 11.9, 19.2$ Hz, 1 H), 1.76−1.48 (series of m, 4 H), 1.00 (s, 9 H), 0.90 (t, $J = 7.8$ Hz, 3 H), 0.21 (s, 6 H).

Strips of Al foil (3.38 g total) were separately dipped in aqueous 2% $HgCl_2$ for 20 s, rinsed with EtOAc and Et_2O, and added to a stirred mixture of the 3,4-epoxide, aqueous NaOH (10 w/v, 5 mL), and EtOH (50 mL) cooled in an ice/salt bath at −10 °C. The mixture was stirred at −10 °C for 4 h and then filtered through a pad of Celite, washing with $CHCl_3$. Brine was added to the filtrate. The aqueous layer was separated and extracted three times with $CHCl_3$. The combined $CHCl_3$ layers were dried ($MgSO_4$) and concentrated to give a yellow oil. Compound **35** (62 mg, 20%) was isolated by chromatography, eluting with a gradient of 25−50% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$), selected signals: δ 7.18 (d, $J = 8.3$ Hz, 1 H), 6.70 (dd, $J = 2.6, 8.3$ Hz, 1 H), 6.66 (d, $J = 2.6$ Hz, 1 H), 5.22 (br s, 1 H), 4.83 (apparent t, $J = 3.1$ Hz, 1 H), 2.94−2.84 (m, 2 H), 2.73−2.61 (m, 3 H), 2.48 (apparent t, $J = 15.6$ Hz, 1 H), 2.38 (ddd, $J = 1.8, 4.4, 15.6$ Hz, 1 H), 1.99−1.90 (m, 1 H), 1.86−1.78 (m, 1 H), 0.87 (t, $J = 7.8$ H, 3 H).

General Procedure for Additions of Lithiopropyne to Ketones 11−15, 28, and 35. (2*R*,4a*R*,10a*R*)-4a-Ethyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (18). Propyne gas was bubbled for 6 min into THF (140 mL) at 0 °C. The solution was cooled to −78 °C, and 2.5 M *n*-BuLi in hexane (100 mL, 250 mmol) was slowly added to produce a thick white precipitate. When addition of *n*-BuLi was complete, the mixture was stirred in an ice bath for 15 min. A solution of **12** (3.5 g, 14 mmol) in THF (80 mL) was added dropwise. The mixture was allowed to warm to room temperature overnight and then cooled

in an ice bath. Aqueous saturated NH_4Cl was added to quench the reaction. The resulting mixture was extracted twice with EtOAc, and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed, eluting successively with CH_2Cl_2 and 5% EtOAc/CH_2Cl_2. Clean fractions containing **18** were combined and concentrated to afford a pale-yellow solid (1.78 g, 45%). A sample for testing and elemental analysis was obtained by subsequent trituration of some of the material with CH_2Cl_2. ^{1}H NMR (DMSO-d_6): δ 9.00 (s, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 6.48 (dd, J = 2.1, 8.3 Hz, 1 H), 6.45 (apparent s, 1H), 5.26 (s, 1 H), 2.77−2.74 (m, 2 H), 2.28−2.25 (m, 1 H), 1.73 (s, 3 H, overlapped), 1.75−1.24 (overlapping m, 9 H), 1.14−1.10 (m, 1 H), 0.62 (t, J = 7.3 Hz, 3H). LCMS: m/z 267 [M − OH]$^+$. Anal. ($C_{19}H_{24}O_2 \cdot 0.5H_2O$) C, H. The assigned structure of **18** was confirmed by single crystal X-ray analysis.

The following compounds (**2**, **17**, **19**, **20**, **30**, and **36**) were prepared using the same reaction conditions.

(2*R*,4a*R*,10a*R*)-4a-Methyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (17). 17 was prepared from **11**. ^{1}H NMR ($CDCl_3$): δ 7.17 (d, J = 8.3 Hz, 1 H), 6.66 (dd, J = 3.1, 8.3 Hz, 1 H), 6.58 (d, J = 3.1 Hz, 1 H), 4.59 (s, 1 H), 2.98−2.82 (m, 2 H), 2.18 (dt, J = 3.4, 13.0 Hz, 1 H), 2.08 (br s, 1 H), 2.00−1.57 (series of m, 8 H), 1.80 (s, 3 H, overlapped), 1.07 (s, 3 H). LCMS: m/z 253 [M − OH]$^+$. Anal. ($C_{18}H_{22}O_2$) C, H.

(2*R*,4a*S*,10a*R*)-4a-Propenyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (19). 19 was prepared from **13**. ^{1}H NMR ($CDCl_3$): δ 7.07 (d, J = 8.7 Hz, 1 H), 6.61 (dd, J = 2.5, 8.7 Hz, 1 H), 6.53 (d, J = 2.5 Hz, 1 H), 5.79 (apparent d, J = 15.5 Hz, 1 H), 4.89−4.79 (m, 1 H), 2.87−2.70 (m, 2 H), 2.31 (dt, J = 3.3, 13.3 Hz, 1 H), 2.00−1.44 (series of m, 8 H), 1.75 (s, 3 H, overlapped), 1.56 (dd, J = 1.2, 6.6 Hz, 3 H, overlapped). LCMS: m/z 279 [M − OH]$^+$. Anal. ($C_{20}H_{24}O_2 \cdot 0.25H_2O$) C, H.

(2*R*,4a*R*,10a*R*)-4a-Allyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthrene-2,7-diol (2). 2 was prepared from **14**. ^{1}H NMR ($CDCl_3$): δ 7.05 (d, J = 8.3 Hz, 1 H), 6.63−6.61 (m, 2 H), 5.62−5.53 (m, 1 H), 5.01 (apparent d, J = 9.8 Hz, 1 H), 4.95 (apparent d, J = 16.6 Hz, 1 H), 2.99−2.85 (m, 2 H), 2.43 (dd, J = 8.8, 13.5 Hz, 1 H), 2.32 (dt, J = 3.6, 13.5 Hz, 1 H), 2.10−1.55 (series of m, 9 H), 1.79 (s, 3 H, overlapped). LCMS: m/z 295 [M − H]$^-$. Anal. ($C_{20}H_{24}O_2 \cdot 0.2H_2O$) C, H.

(2*R*,4a*R*,10a*R*)-4a-Propyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthrene-2,7-diol (20). 20 was prepared from **15**. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, J = 7.9 Hz, 1 H), 6.60−6.57 (m, 2 H), 4.55 (br s, 1 H), 2.90−2.82 (m, 2 H), 2.34 (dt, J = 3.3, 13.3 Hz, 1 H), 1.84 (s, 3 H, overlapped), 1.92−1.49 (overlapping m, 9 H), 1.24−1.10 (m, 2 H), 1.03−0.97 (m, 1 H), 0.77 (t, J = 7.1 Hz, 3 H). LCMS: m/z 281 [M − OH]$^+$. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.04; H 8.78.

(2*R*,3*S*,4a*R*,10a*R*)-4a-Ethyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,3,7-triol (30). 30 was prepared from a 3:1 mixture of **28** and **29** (32% from **28**). Recrystallized from hot EtOAc. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, J = 8.3 Hz, 1 H), 6.63−6.61 (m, 2 H), 3.63−3.58 (m, 1 H), 2.93−2.83 (m, 2 H), 2.59 (dd, J = 4.1, 13 Hz, 1 H), 2.03−1.98 (m, 1 H), 1.94−1.88 (m, 2 H), 1.84 (s, 3 H), 1.82−1.74 (m, 2 H), 1.69−1.63 (m, 2 H), 1.43 (t, J = 12.4 Hz, 1 H), 1.35−1.26 (m, 1 H), 0.78 (t, J = 7.3 Hz, 3 H). Anal. ($C_{19}H_{24}O_3 \cdot 0.25H_2O$) C, H.

(2*S*,4*R*,4a*R*,10a*R*)-4a-Ethyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthrene-2,4,7-triol (36). 36 was prepared from **35**. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, J = 8.3 Hz, 1 H), 6.65 (dd, J = 2.6, 8.3 Hz, 1 H), 6.62 (d, J = 2.6 Hz, 1 H), 4.59 (apparent t, J = 3.1 Hz, 1 H), 2.93−2.80 (m, 2 H), 2.39−2.34 (m, 2 H), 2.09−2.05 (m, 1 H), 1.99−1.92 (m, 2 H), 1.90−1.80 (m, 1 H), 1.86 (s, 3 H, overlapped), 1.65−1.57 (m, 2 H), 1.50−1.45 (m, 1 H), 0.74 (t, J = 7.8 Hz, 3 H). Anal. ($C_{19}H_{24}O_3$) C, H.

(4a*S*,10a*R*)-4a-Hydroxymethyl-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (21). A solution of **19** (150 mg, 0.5 mmol) in acetone (20 mL) was cooled to 0 °C in an ice bath and treated with aqueous 1 M NaOH (0.5 mL, 0.5 mmol). The mixture was stirred in the ice bath for 15 min, 4-nitrobenzoyl chloride (111 mg, 0.6 mmol) was added, and the resulting mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by addition of excess aqueous saturated $NaHCO_3$. It was then extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to provide the corresponding C7 4-nitrobenzoyl ester derivative as a clear oil (223 mg, 100%).

The 4-nitrobenzoyl ester was dissolved in a mixture of MeOH (8 mL) and CH_2Cl_2 (4 mL). The resulting solution was cooled to −78 °C and treated with a stream of O_3 for 1 min. The mixture was purged with a stream of O_2. Excess Me_2S (1.5 mL) was added. The resulting mixture was then allowed to warm to room temperature overnight. Evaporation afforded the corresponding C4a carbaldehyde as a yellow solid.

To cleave the 4-nitrobenzoyl ester, the solid was dissolved in THF (20 mL) and treated with aqueous 1 M NaOH (10 mL, 10 mmol) for 3 h. Excess aqueous 1 M HCl was added, and the resulting mixture was extracted with EtOAc. The organic layer was washed with aqueous saturated $NaHCO_3$, washed with brine, dried ($MgSO_4$), and concentrated. The corresponding C7 hydroxy-C4a-carbaldehyde (24 mg, 14%) was isolated by chromatography, eluting with a gradient of 10−40% EtOAc/hexanes.

The aldehyde was dissolved in MeOH (5 mL), treated with $NaBH_4$ (20 mg, 0.53 mmol), and stirred for 20 min. The reaction was quenched by addition of excess AcOH and concentrated. The residue was taken up in EtOAc, washed with aqueous saturated $NaHCO_3$, washed with brine, dried ($MgSO_4$), and concentrated. Compound **21** (a white solid, 5 mg, 3.5% overall) was isolated by chromatography, eluting with a gradient of 20−50% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$), selected signals: δ 7.15 (d, J = 8.3 Hz, 1 H), 6.62 (dd, J = 2.5 Hz, 1 H), 6.58 (d, J = 2.5 Hz, 1 H), 3.78 (d, J = 11.2 Hz, 1 H), 3.64 (d, J 11.2 Hz, 1 H), 2.91−2.80 (m, 2 H), 2.33 (dt, J = 3.3, 10.0 Hz, 1 H), 2.17−2.07 (m, 1 H), 1.83 (s, 3 H, overlapped).

(4a*S*,10a*R*)-4a-(2-Hydroxyethyl)-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (22). A solution of **2** (300 mg, 1.0 mmol) in acetone (40 mL) was cooled to 0 °C in an ice bath and treated with aqueous 1 M NaOH (1 mL, 1 mmol). The mixture was stirred in the ice bath for 15 min, 4-nitrobenzoyl chloride (223 mg, 1.2 mmol) was added, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched by addition of excess aqueous saturated $NaHCO_3$ and extracted twice with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to provide the corresponding 4-nitrobenzoyl ester derivative as a clear oil (447 mg, 100%).

A portion of the 4-nitrophenyl ester (75 mg, 0.17 mmol) was dissolved in a mixture of MeOH (4 mL) and CH_2Cl_2 (2 mL). The solution was cooled to −78 °C and treated with a stream of O_3 for 20 s. The mixture was purged with a stream of O_2, and excess Me_2S (0.5 mL) was added. The mixture was stirred at −78 °C for 25 min, and then $NaBH_4$ (29 mg, 0.77 mmol) was added. The cooling bath was removed, and the mixture was allowed to warm to room temperature. Excess aqueous saturated NH_4Cl was added. The resulting mixture was diluted with H_2O and extracted twice with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated to afford the corresponding 2-hydroxyethyl product as a clear oil.

To cleave the 4-nitrobenzoyl ester, the oil was dissolved in THF (10 mL) and treated with aqueous 1 M NaOH (5 mL, 5 mmol) for 3 h. Excess aqueous 1 M HCl was added, and the resulting mixture was extracted twice with EtOAc. The combined organic layers were washed with aqueous saturated $NaHCO_3$, washed with brine, dried ($MgSO_4$), and concentrated. Compound **22** (24 mg, 51%) was isolated by crystallization of the residue from hot EtOAc/hexanes. ^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 6.47 (apparent d, J = 8.3 Hz, 1 H), 6.45 (apparent s, 1 H), 3.40−3.30 (m, 1 H), 3.15−3.07 (m, 1 H), 2.78−2.72 (m, 2 H), 2.25 (apparent d, J = 13.7 Hz, 1 H), 1.85−1.45 (overlapping m, 7 H), 1.73 (s, 3 H, overlapped), 1.39−1.22 (m, 3 H). LCMS: m/z 299 [M − H]$^-$. Anal. ($C_{19}H_{24}O_3 \cdot 0.5H_2O$) C, H.

(2*R*,4a*R*,10a*R*)-4a-Ethyl-2-prop-1-ynyl-7-(pyridin-4-ylmethoxy)-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (23). To a solution of **18** (97 mg, 0.34 mmol) in DMF (10 mL) was added 60% NaH

in oil (50 mg, 1.3 mmol). The mixture was stirred for 1 h, and then 4-picolylchloride hydrochloride (67 mg, 0.41 mmol) was added. After it was stirred overnight, the reaction mixture was quenched (aqueous saturated NH_4Cl), diluted with water, and extracted twice with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford a yellow oil. During removal of residual DMF under high vacuum, crystallization of product was evident. The title compound (65 mg, 51%) was triturated with Et_2O/hexanes and collected by filtration. ^{1}H NMR ($CDCl_3$): δ 8.69 (d, J = 5.7 Hz, 2 H), 7.64 (d, J = 5.7 Hz, 2 H), 7.17 (d, J = 8.3 Hz, 1 H), 6.76−6.73 (m, 2 H), 5.18 (s, 2 H), 2.97−2.89 (m, 2 H), 2.38 (dt, J = 3.4, 13.5 Hz, 1 H), 2.10 (br s, 1 H), 1.99−1.91 (m, 2 H), 1.88−1.60 (overlapping m, 6 H), 1.79 (s, 3 H, overlapped), 1.58−1.52 (m, 1 H), 1.29−1.24 (m, 1 H), 0.71 (t, J = 7.8 Hz, 3 H). LCMS: m/z 376 $[MH]^+$. The hydrochloride salt was prepared by precipitation from EtOAc with HCl gas. Anal. Calcd for $C_{25}H_{29}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 71.33; N, 7.42; N, 3.33. Found: C, 71.54, H, 6.95; N, 3.06.

(2*R*,4a*R*,10a*R*)-4a-Ethyl-7-(2-methylpyridin-3-ylmethoxy)-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (24). **24** was prepared from **18** and 3-chloromethyl-2-methylpyridine hydrochloride under the same conditions used in the synthesis of **23**. ^{1}H NMR ($CDCl_3$): δ 8.50 (d, J = 5.2 Hz, 1 H), 7.81 (d, J = 7.3 Hz, 1 H), 7.24 (dd, J = 5.2, 7.3 Hz, 1 H), 7.17 (d, J = 8.3 Hz, 1 H), 6.79−6.75 (m, 2 H), 5.03 (s, 2 H), 2.98−2.93 (m, 2 H), 2.65 (s, 3 H), 2.39 (dt, J = 3.4, 13.5 Hz, 1 H), 2.13 (br s, 1 H), 1.99−1.92 (m, 2 H), 1.87−1.63 (overlapping m, 6 H), 1.79 (s, 3 H, overlapped), 1.61−1.56 (m, 1 H), 1.30−1.26 (m, 1 H), 0.72 (t, J = 7.3 Hz, 3 H). LCMS: m/z 390 $[MH]^+$. Anal. ($C_{26}H_{31}NO_2 \cdot 0.25H_2O$) C, H, N.

(2*R*,4a*R*,10a*R*)-4a-Ethyl-2-phenyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,7-diol (25). A solution of **12** (200 mg, 0.82 mmol) in THF (6 mL) was cooled to −78 °C and treated with 1.8 M PhLi in cyclohexane (1.8 mL, 3.2 mmol). The reaction mixture was allowed to warm to room temperature slowly overnight. It was then quenched by addition of aqueous saturated NH_4Cl and extracted with EtOAc. The extract solution was washed with brine, dried (Na_2SO_4), and concentrated to afford an oil containing **25** and its C2 diastereomer. Compound **25** (61 mg, 23%) was isolated by chromatography, eluting with 18% EtOAc/hexanes. Slow evaporation from EtOAc/hexanes provided crystalline material. ^{1}H NMR ($CDCl_3$): δ 7.57 (d, J = 7.3 Hz, 2 H), 7.34 (apparent t, J = 7.8 Hz, 2 H), 7.28−7.26 (m, 1 H, overlapped by $CHCl_3$), 6.98 (d, J = 8.3 Hz, 1 H), 6.56−6.52 (m, 2 H), 4.50 (s, 1 H), 2.86−2.79 (m, 2 H), 2.50 (dq, J = 3.1, 13.5 Hz, 1 H), 2.40 (dt, J = 3.6, 14.0 Hz, 1 H), 2.31 (dt, J = 3.1, 13.5 Hz, 1 H), 2.03−1.84 (series of m, 4 H), 1.80 (br s, 1 H), 1.66−1.56 (m, 2 H), 1.38−1.30 (m, 1 H), 1.25−1.19 (m, 1 H), 0.77 (t, J = 7.3 Hz, 3 H). LCMS: m/z 305 $[M - OH]^+$. Anal. ($C_{22}H_{26}O_2 \cdot 0.25H_2O$) C, H. The assigned structure of **25** was confirmed by single crystal X-ray analysis.

(2*R*,3*S*,4a*R*,10a*R*)-4a-Ethyl-2-phenyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,3,7-triol (32). 32 was prepared by addition of PhLi to ketone **28** according to a procedure similar to that used for the preparation of **25**. Mp 191−192 °C. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, J = 7.3 Hz, 2 H), 7.31−7.28 (m, 2 H), 7.24−7.21 (m, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 6.57 (dd, J = 2.6, 8.3 Hz, 1 H), 6.52 (apparent s, 1 H), 4.50 (br s, 1 H), 4.12 (dd, J = 4.1, 13.0 Hz, 1 H), 2.85−2.75 (m, 2 H), 2.65 (dd, J = 4.1, 13.0 Hz, 1 H), 2.17 (dd, J = 2.9, 13.7 Hz, 1 H), 1.96 (apparent t, J = 13.5, Hz, 1 H), 1.88−1.82 (m, 1 H), 1.80−1.74 (m, 2 H), 1.68−1.63 (m, 1 H), 1.38−1.31 (m, 1 H), 0.80 (t, J = 7.3 Hz, 3 H). LCMS: m/z 321 $[M - OH]^+$. Anal. ($C_{22}H_{26}O_3 \cdot 0.2H_2O$) C, H. The assigned structure of **32** was confirmed by single crystal X-ray analysis.

The corresponding 2*S* epimer (**45**) exhibited a similar ^{1}H NMR spectrum to **32** with methine signals at δ 4.24 (dd, J = 4.1, 11.7 Hz, 1 H) and 2.57 (dd, J = 4.1, 13.0 Hz, 1 H) in $CDCl_3$. This spectrum matched exactly that obtained from a sample of the compound obtained by acid hydrolysis of epoxide **44** (vide infra).

(2*R*,4a*R*,10a*R*)-4a-Ethyl-7-(2-methylpyridin-3-ylmethoxy)-2-phenyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (26). 26 was prepared from **25** and 3-chloromethyl-2-methylpyridine hydrochloride under the same conditions used in the synthesis of **23**. ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J = 4.2 Hz, 1 H), 7.80 (d, J = 7.8 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 2 H), 7.34 (apparent t, J = 7.8 Hz, 2 H), 7.27−7.22 (m, 2 H), 7.06 (d, J = 8.3 Hz, 1 H), 6.70−6.67 (m, 2 H), 4.98 (s, 2 H), 2.90−2.85 (m, 2 H), 2.63 (s, 3 H), 2.52−2.49 (m, 1 H), 2.42 (dt, J = 3.6, 13.5 Hz, 1 H), 2.31 (dt, J = 3.1, 13.5 Hz, 1 H), 2.05−1.86 (overlapping m, 4 H), 1.66−1.60 (m, 2 H), 1.38−1.33 (m, 1 H), 1.27−1.23 (m, 1 H), 0.77 (t, J = 7.3 Hz, 3 H). LCMS: m/z 428 $[MH]^+$. Anal. ($C_{29}H_{33}NO_2 \cdot 0.5H_2O$) C, H, N.

(2*R*,3*S*,4a*R*,10a*R*)-4a-Ethyl-7-(2-methylpyridin-3-ylmethoxy)-2-prop-1-ynyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,3-diol (31). 31 was prepared from **30** and 3-chloromethyl-2-methylpyridine hydrochloride under the same conditions used in the synthesis of **23**. ^{1}H NMR ($CDCl_3$): δ 8.49 (dd, J = 1.3, 5.2 Hz, 1 H), 7.76 (dd, J = 1.3, 7.8 Hz, 1 H), 7.19 (dd, J = 5.2, 7.8 Hz, 1 H), 7.14 (d, J = 8.3 Hz, 1 H), 6.80−6.76 (m, 2 H), 5.02 (s, 2 H), 3.62 (dd, J = 3.6, 11.9 Hz, 1 H), 2.98−2.92 (m, 2 H), 2.62 (s, 3 H), 2.62−2.59 (m, 1 H, overlapped), 2.06−1.99 (m, 1 H), 1.96−1.75 (overlapping m, 4 H), 1.83 (s, 3 H, overlapped), 1.72−1.65 (m, 2 H), 1.46 (t, J = 12.4 Hz, 1 H), 1.35−1.26 (m, 1 H), 0.79 (t, J = 7.8 Hz, 3 H). LCMS: m/z 406 $[MH]^+$.

(2*R*,3*S*,4a*R*,10a*R*)-4a-Ethyl-7-(2-methylpyridin-3-ylmethoxy)-2-phenyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,3-diol (33). 33 was prepared from **32** and 3-chloromethyl-2-methylpyridine hydrochloride under the same conditions used in the synthesis of **23**. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, J = 3.6 Hz, 1 H), 7.79 (d, J = 7.3 Hz, 2 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.34−7.31 (m, 2 H), 7.26−7.24 (m, 1 H, overlapped by $CHCl_3$), 7.19−7.17 (m, 1 H), 7.11 (d, J = 8.3 Hz, 1 H), 6.75 (dd, J = 2.6, 8.3 Hz, 1 H), 6.70 (d, J = 2.6 Hz, 1 H), 4.99 (s, 2 H), 4.18 (apparent d, J = 13.5 Hz, 1 H), 2.89−2.82 (m, 2 H), 2.69 (dd, J = 4.1, 13.5 Hz, 1 H), 2.24 (dd, J = 3.1, 14.0 Hz, 1 H), 1.99 (apparent t, J = 13.0, Hz, 1 H), 1.93−1.88 (m, 1 H), 1.85−1.77 (m, 2 H), 1.74−1.68 (m, 1 H), 1.40−1.36 (m, 1 H), 0.83 (t, J = 7.8 Hz, 3 H). LCMS: m/z 444 $[MH]^+$. Anal. ($C_{29}H_{33}NO_3 \cdot 0.25H_2O$) C, H, N.

(2*S*,4a*S*,10a*R*)-7-(*tert*-Butyldimethylsilanyloxy)-4a-ethyl-2-phenyl-1,2,4a,9,10,10a-hexahydrophenanthren-2-ol (37). To a solution of enone **34** (500 mg, 1.4 mmol) in THF (50 mL) at −78 °C was added dropwise 2 M PhMgBr in THF (2 mL, 4.0 mmol). The reaction mixture was stirred at −78 °C for 1 h and subsequently allowed to warm to room temperature over about 1 h. Aqueous saturated NH_4Cl was added to quench the reaction, which was then diluted with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The title compound, an oil (482 mg, 79%), was isolated by chromatography, eluting with 8% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.51−7.49 (m, 2 H), 7.32−7.23 (m, 4 H), 6.73 (d, J = 10.4 Hz, 1 H), 6.64 (dd, J = 2.6, 8.3 Hz, 1 H), 6.57 (d, J = 2.6 Hz, 1 H), 5.78 (dd, J = 1.6, 10.4 Hz, 1 H), 2.85−2.75 (m, 2 H), 2.23 (apparent t, J = 13.0 Hz, 1 H), 1.97 (d, J = 13.5 Hz, 1 H), 1.88−1.82 (m, 2 H), 1.81−1.74 (m, 1 H), 1.61 (br s, 1 H), 1.55−1.48 (m, 2 H), 0.99 (s, 9 H), 0.85 (t, J = 7.3 Hz, 3 H), 0.21 (s, 6 H).

Hydroboration of Compound 37. A solution of **37** (370 mg, 0.83 mmol) in THF (10 mL) was cooled to 0 °C and treated dropwise with 1 M $BH_3 \cdot$THF in THF (8.3 mL, 8.3 mmol). The mixture was allowed to stir at room temperature overnight. By TLC analysis, starting material remained. Thus, additional 1 M $BH_3 \cdot$THF in THF (5 mL, 5 mmol) was added. After it was stirred for an additional 2 days, the mixture was cooled in an ice bath. Water (22 mL), aqueous 10% NaOH (35 mL), and aqueous 30% H_2O_2 were sequentially added, and the resulting mixture was allowed to stir at room temperature overnight. Excess peroxide was quenched by addition of solid sodium thiosulfate. The mixture was neutralized by sequential addition of AcOH and aqueous 1 N HCl. It was extracted twice with EtOAc. The combined organic extracts were washed with water, washed with brine, dried ($MgSO_4$), and concentrated. The crude product mixture was chromatographed, eluting with 10% EtOAc/hexanes to afford **38** (oil, 44 mg, 12%), **39** (oil, 45 mg, 12%) as well as the over-reduction products **40** and **41**. The ^{1}H NMR spectra of **38**, **39**, and **41** closely resemble

those reported for **42**, **32**, and **25**, respectively, except for *tert*-butyldimethylsilyl (TBDMS) singlets at about δ 1.0 and 0.2. Compound **40**: ^{1}H NMR ($CDCl_3$), selected signals, δ 7.44−7.26 (m, 5 H), 7.10 (d, J = 8.3 Hz, 1 H), 6.63 (dd, J = 2.6, 8.3 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1 H), 3.95 (td, J = 3.6, 10.9, Hz, 1 H), 2.91−2.88 (m, 2 H), 2.83 (dd, J = 4.2, 12.4 Hz, 1 H), 2.60−2.55 (m, 1 H), 1.00 (s, 9 H), 0.21 (s, 6 H).

(2*R*,3*R*,4a*R*,10a*R*)-4a-Ethyl-2-phenyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,3,7-triol (42). Compound **38** (44 mg, 0.097 mmol) was dissolved in THF (4 mL). Acetic acid (0.12 mL, 2.0 mmol) and 1.0 M tetrabutylammonium fluoride in THF (0.6 mL, 0.6 mmol) were added. The mixture was stirred for 4 h and then concentrated. The title compound (a white solid, 25 mg, 76%) was isolated by chromatography, eluting with 15% EtOAc/hexanes. Mp 207−209 °C. ^{1}H NMR ($CDCl_3$): δ 7.67−7.65 (m, 2 H), 7.38−7.35 (m, 2 H), 7.28−7.26 (m, 1 H), 7.04 (d, J = 8.3 Hz, 1 H), 6.61−6.57 (m, 2 H), 4.57 (apparent t, J = 3.1 Hz, 1 H), 2.92−2.82 (overlapping m, 3 H), 2.41 (dt, J = 2.6, 13.5 Hz, 1 H), 2.33−2.26 (m, 2 H), 2.14−2.08 (m, 1 H), 2.02−1.85 (overlapping m, 2 H), 1.78−1.73 (m, 1 H), 1.63−1.58 (m, 1 H), 0.79 (t, J = 7.3 Hz, 3 H). LCMS: m/z 321 $[M - OH]^+$. Anal. ($C_{22}H_{26}O_3 \cdot 0.33H_2O$) C, H. The assigned structure of **42** was confirmed by single crystal X-ray analysis.

(4b*R*,8a*R*)-4b-Ethyl-7-phenyl-4b,5,8,8a,9,10-hexahydrophenanthren-2-ol (43). A solution of **12** (500 mg, 2.0 mmol) in THF (20 mL) was cooled to −78 °C and treated with 1 M PhMgBr in THF (15 mL, 15 mmol). The reaction mixture was allowed to warm to room temperature over 2 h. It was then quenched by addition of aqueous saturated NH_4Cl and extracted with EtOAc. The extract solution was washed with brine, dried ($MgSO_4$), and concentrated to afford an oil containing **25** and its C2 diastereomer. The oil was dissolved in toluene, treated with $KHSO_4$ (340 mg, 2.5 mmol), and heated to reflux overnight. The toluene was evaporated, and the title compound (a white solid, 420 mg, 67%) was isolated by chromatography, eluting with a gradient of 5−20% EtOAc/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 7.8 Hz, 2 H), 7.34 (apparent t, J = 7.3 Hz, 2 H), 7.26−7.23 (m, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 6.66 (dd, J = 2.6, 8.3 Hz, 1 H), 6.59 (d, J = 2.6 Hz, 1 H), 6.19−6.18 (m, 1 H), 2.94−2.86 (m, 3 H), 2.51−2.48 (m, 1 H), 2.41−2.35 (m, 1 H), 2.16 (apparent d, J = 18.1 Hz, 1 H), 2.08−2.02 (m, 1 H), 1.96−1.87 (m, 1 H), 1.79−1.74 (m, 1 H), 1.64−1.58 (m, 1 H), 1.48−1.43 (m, 1 H), 1.23 (t, J = 7.3 Hz, 3 H). Anal. ($C_{22}H_{24}O$) C, H.

(6a*R*,7a*S*,8a*S*,9a*R*)-*tert*-Butyl-(9a-ethyl-7a-phenyl-5,6,6a,7,7a,8a,9,9a-octahydro-8-oxacyclopropa[*b*]phenanthren-3-yloxy)dimethylsilane (44). To a solution of **43** (409 mg, 1.3 mmol) and imidazole (137 mg, 2.0 mmol) in CH_2Cl_2 was added *tert*-butyldimethylsilyl chloride (226 mg, 1.5 mmol). The mixture was stirred overnight. Analysis by TLC indicated that some starting material remained. Thus, additional imidazole (44 mg, 0.65 mmol) and *tert*-butyldimethylsilyl chloride (98 mg, 0.65 mmol) were added. After 5 h of additional stirring, aqueous 0.5 M citric acid was added. The organic layer was washed with aqueous saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed, eluting with 50% CH_2Cl_2/hexanes to afford the TBDMS ether derivative of 43 (505 mg, 93%). A portion of this (100 mg, 0.24 mmol) was dissolved in $CHCl_3$ (15 mL), treated with 57% *m*-chloroperbenzoic acid (75 mg, 0.25 mmol), and stirred overnight. The mixture was diluted with $CHCl_3$ and sequentially washed with aqueous saturated $NaHCO_3$, aqueous NaI, aqueous Na_2CO_3, and brine. The resulting solution was dried ($MgSO_4$) and concentrated. The title compound, an oil (76 mg, 73%), was isolated by chromatography, eluting with 10% CH_2Cl_2/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.46−7.45 (m, 2 H), 7.38 (apparent t, J = 7.3, 2 H), 7.33−7.30 (m, 1 H), 7.01 (d, J = 8.8 Hz, 1 H), 6.63 (dd, J = 2.6, 8.8 Hz, 1 H), 6.56 (d, J = 2.6 Hz, 1 H), 3.20 (d, J = 5.7 Hz, 1 H), 2.90−2.75 (m, 3 H), 2.72 (dd, J = 5.7, 15.0 Hz, 1 H), 2.36 (dd, J = 11.9, 15.0 Hz, 1 H), 2.16 (dd, J = 4.4, 14.8 Hz, 1 H), 2.01−1.98 (m, 2 H), 1.90−1.82 (m, 2 H), 1.65−1.61 (m, 3 H), 1.47−1.40 (m, 1 H), 0.99 (s, 9 H), 0.21 (s, 6 H).

Hydrolysis of 44 in Aqueous H_2SO_4/DMSO. To a solution of **44** (76 mg, 0.17 mmol) in water (1 mL) and DMSO (3 mL) were added 2 drops of concentrated H_2SO_4. The resulting mixture was stirred overnight, then heated at 60 °C for a second night. The mixture was cooled, diluted with water, and filtered to collect a solid. The solid was dissolved in Et_2O, and the resulting solution was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed, eluting with 20% EtOAc/hexanes to afford clean samples of compounds **45** and **46**. The ^{1}H NMR of compound **45** matched exactly that obtained from a sample of the compound prepared by addition of PhMgBr to ketone **28** (vide supra). Compound **46** ^{1}H NMR ($CDCl_3$): δ 7.39−7.36 (m, 2 H), 7.31−7.27 (m, 1 H), 7.16 (d, J = 7.3 Hz, 2 H), 7.00 (d, J = 8.8 Hz, 1 H), 6.67−6.65 (m, 2 H), 4.69 (br s, 1 H), 3.68 (dd, J = 7.0, 12.7 Hz, 1 H), 3.28 (d, J = 13.0 Hz, 1 H), 3.03−2.92 (m, 2 H), 2.46 (d, J = 13.0 Hz, 1 H), 2.37−2.32 (m, 1 H), 2.25−2.11 (overlapping m, 2 H), 1.93−1.80 (overlapping m, 3 H), 0.82 (t, J = 7.3 Hz, 3 H). LCMS: m/z 321 $[MH]^+$.

(2*S*,4b*R*,8a*R*)-4b-Ethyl-7-phenyl-4b,5,6,7,8,8a,9,10-octahydrophenanthrene-2,6-diol (48). A solution of **44** (100 mg, 0.23 mmol) in CH_2Cl_2 (10 mL) was cooled to −78 °C and treated with $BF_3 \cdot OEt_2$ (0.15 mL, 1.2 mmol). After 10 min at −78 °C, the reaction was quenched by addition of excess aqueous saturated $NaHCO_3$ and allowed to warm to room temperature. The mixture was then diluted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated to afford crude **47** as an oil (91 mg, ∼90%). ^{1}H NMR ($CDCl_3$), selected signals: δ 3.82 (d, J = 6.2 Hz, 1 H), 3.03 (d, J = 13.0 Hz, 1 H), 2.94−2.10 (m, 2 H), 2.45−2.43 (m, 1 H), 2.37 (d, J = 13.0 Hz, 1 H), 2.30−2.24 (m, 1 H). A portion of crude **47** (50 mg, ∼0.12 mmol) was dissolved in MeOH (5 mL), cooled to −78 °C, and treated with $NaBH_4$ (20 mg, 0.5 mmol). After being stirred at −78 °C for 10 min, the mixture was allowed to gradually warm to room temperature over 1.5 h. Aqueous saturated $NaHCO_3$ was added to quench the reaction, which was then extracted with EtOAc. The extract solution was washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in THF (90 mL). Acetic acid (70 μL, 1.2 mmol) and 1.0 M tetrabutylammonium fluoride in THF (0.25 mL, 0.25 mmol) were added. After 1.5 h, the mixture was concentrated and chromatographed, eluting with 30% EtOAc/hexanes to afford the title compound as a white solid (19 mg, 49% from **47**). ^{1}H NMR ($CDCl_3$): δ 7.42−7.40 (m, 2 H), 7.28−7.18 (overlapping m, 3 H), 7.06 (d, 7.9 Hz, 1 H), 6.61−6.58 (m, 2 H), 4.19−4.15 (m, 1 H), 3.44−3.41 (m, 1 H), 2.88−2.85 (m, 2 H), 2.51 (dd, J = 4.2, 13.1 Hz, 1 H), 2.12−1.98 (m, 2 H), 1.89−1.56 (overlapping m, 6 H), 1.35−1.25 (m, 1 H), 0.78 (t, J = 7.5 Hz, 3 H).

Receptor Binding Assays. Compound affinities for human GR and AR were assessed as previously described.[7] Human PR, ERα and ERβ were obtained from PanVera (Invitrogen). The ERα and ERβ binding assays were run in a manner similar to that described for AR.[7] The PR assay was run according to the protocol supplied by PanVera (Invitrogen).

Whole Cell Functional Assay: IL-1 Stimulated MMP-13 Production. SW1353 human chondrosarcoma cells were plated at confluence into 96-well plates in Dulbecco's modified Eagle medium (DMEM) with 10% fetal bovine serum. After 24 h, medium was removed and replaced with 200 μL/well serum-free DMEM containing 1 mg/L insulin, 2 g/L lactalbumin hydrosylate, and 0.5 mg/L ascorbate. The medium was removed 16 h later and replaced with 150 μL/well fresh serum-free medium containing ±20 ng/mL IL-1β, ±5 nM dexamethasone, ±test compound. After 24 h of incubation at 37 °C and 5% CO_2, 125 μL sample from each well was removed under asceptic conditions for MMP-13 production analysis (Amersham Bio-Trak MMP-13 ELISA) using the manufacturer's protocol.

Whole Cell Functional Assay: MMTV. Clonal SW1353 human chondrosarcoma cells stably transfected with pMAM-neo-luciferase mouse mammary tumor virus (MMTV) reporter construct were plated near confluence into 96-well plates in DMEM media with 10% fetal bovine serum. After 24 h, medium was removed and replaced with phenol red-free, serum-free DMEM medium supple-

mented with 2 mM L-glutamine, 1 mg/L insulin, 0.5 mg/L ascorbate, and 2 g/L lactalbumin hydrosylate. Treatments were ±dexamethasone or compound. After 16 h of incubation at 37 °C and 5% CO_2, 100 μL of LucLite reagent (Packard) was added to each well. After 5 min of incubation in the dark, luminescence was detected in a TopCount microplate scintillation counter.

Computational Details. A homology model of the GR LBD was built using the Sybyl 6.8 suite of programs (Tripos, Inc., St. Louis, MO), specifically, the Composer module, used to develop homology models. The GR model was based on the crystal structure of the progesterone receptor[22] (PDB code 1A28), which had 53.2% identity to the GR 1D amino acid sequence (Swissprot code P04150). From the sequence alignment (done using the PAM360 matrix), there was one residue missing from the GR sequence, and this monomer (SER898) was excised from the PR structure. Composer was then used to develop a crude homology model, which was then further optimized with the Sybyl geometry optimization engine, using Sybyl force field, and a conjugate gradient decent method, until convergence was reached. The final rmsd between the PR crystal structure and the GR homology (α carbons only) model was 0.92 Å. This model was considered suitable for SAR explorations around GR.

The conformational search of **25**, **32**, and **42** started from full geometry optimization in gas phase at the B3LYP/6-31G(d,p) level of theory,[26] adopting the Gaussian 98 software package (Gaussian, Inc., Pittsburgh, PA). A relaxed scan of the potential energy surface was then performed at the AM1 level[27] by the rotation of the C2 phenyl ring around the C2−C1′ axis.

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Supporting Information Available: Elemental analytical data for compounds **2**, **3**, **5**, **7**, **8**, **10**−**13**, **17**−**20**, **22**−**26**, **30**, **32**−**33**, **36**, **42**, and **43**; X-ray crystallographic information and data for compounds **18**, **25**, **32**, and **42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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