Synthetic Studies on Quassinoids: Total Synthesis and Biological Evaluation of (+)-Des-D-chaparrinone

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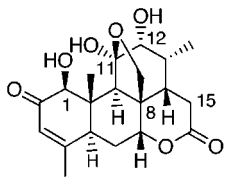
A total synthesis of des-D-chaparrinone (**2**), which lacks the ring D δ-lactone of (−)-chaparrinone (**1**) has been developed. The synthesis commences with the known, readily available tricyclic ketone **3** (R = Me). Elaboration of the configuration at C(5) followed by resolution of **6** employing 2(*R*),3(*R*)-2,3-butanediol gave rise to **9**. Installation of the ring C functionality provided **15** which was transformed into tricyclic diketone **25**. Introduction of the ring A functional groups afforded **29**, which upon exposure to aluminum trichloride and sodium iodide gave rise directly to (+)-des-D-chaparrinone (**2**). Biological studies revealed that (+)-**2** was devoid of any solid tumor activity.

Our continued interest in quassinoids as potential anticancer drugs has been sparked by our finding that (−)-chaparrinone (**1**)[3] possesses outstanding solid tumor selectivity in vivo against a variety of murine solid tumors.[4] For example, in the case of colon adenocarcinoma C38, (−)-chaparrinone exhibited a % *T*/*C* value of 0 and a gross log cell kill of 3.9, indicative of potential clinical activity.[5] We were indeed surprised by this finding since previous work on quassinoids published in the literature had suggested that a requirement for anticancer activity is the presence of an acylated hydroxyl group at C(15).[6] In view of the fact that (−)-chaparrinone lacks any oxygenated substituent at C(15) and exhibits outstanding antitumor activity, we set out to probe the effect, if any, of the lactone ring on solid tumor selectivity. Thus, we prepared by total synthesis des-D-chaparrinone (**2**) which lacks the ring D δ-lactone functionality. Note that the absence of the δ-lactone unit in **2** does not alter the orientation of the C(1), C(11), and C(12) hydroxyl groups in space relative to chaparrinone because of the very rigid nature of the ABC carbocyclic ring system and the C(8), C(11) hemiketal bridge.

A logical starting material for the construction of des-D-chaparrinone was the known carboxylic acid **3** (R = H)[7] which, in principle, possesses the necessary functional



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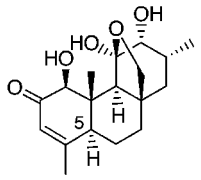
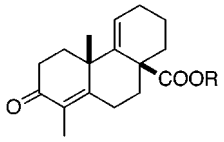


2

groups for installing both the ring A and ring C functionality. Our strategy called for initially establishing the configuration at C(5) followed by addressing the functional group and stereochemical issues presented by rings A and C. At the appropriate juncture in the synthesis, the matter of resolving a racemic intermediate would have to be confronted.



3

The stereogenic center at C(5) was realized via a dissolving metal reduction in liquid ammonia. Exposure of **3** (R = H) to excess lithium in liquid ammonia gave rise to the desired t*rans*-fused tricyclic keto acid **4** in 45% isolated yield along with 15% of the *cis*-fused compound **5**. The formation of the *cis*-fused product **5** can be avoided by employing methyl ester **3** (R = Me)[7] in the dissolving metal reduction. Thus, when **3** (R = Me) was exposed to excess lithium in liquid ammonia, a 55% yield of **6**, mp 135.0−136.5 °C, was obtained. In addition, ca. 25% of a 1:1 mixture of **7** and **8** was isolated, which, in principle, can be transformed into **6**. Note that *cis*-fused products could not be detected.

At this stage in the synthesis it was decided to attempt a resolution of tricyclic ketone **6** by preparing a diastereomeric mixture of ketals. After some experimentation, it was found that diastereomers **9** and **10**, resulting from ketalization of **6** with 2(*R*),3(*R*)-2,3-butanediol, were readily separable by column chromatography. The struc-

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(3) For the total synthesis of (−)-chaparrinone, see: Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

(4) Moher, E. D.; Reilly, M.; Grieco, P. A.; Corbett, T. H.; Valeriote, F. A. *J. Org. Chem.* **1998**, *63*, 3508.

(5) *T*/*C* values that are less than 42% are considered to be active by NCI standards; *T*/*C* values that are less than 10% are considered to have excellent activity and potential clinical activity by NCI standards. Similarly, gross log cell kill values of >2.8 are indicative of clinical activity. A gross log cell kill value between 2.0 and 2.8 is needed to effect partial or complete regression of 100−300 mg sized masses of most transplanted solid tumors of mice.

(6) Wall, M. E.; Wani, M. C.; *Annu. Rev. Pharmacol. Toxicol.* **1977**, *17*, 117. Kupchan, S. M.; Lacadie, J. A.; Howie, G. A.; Sickles, B. R. *J. Med. Chem.* **1976**, *19*, 1130.

(7) Snitman, D. L.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 187. Snitman, D. L.; Himmelsbach, R. J.; Watt, D. S. *J. Org. Chem.* **1978**, *43*, 4758.

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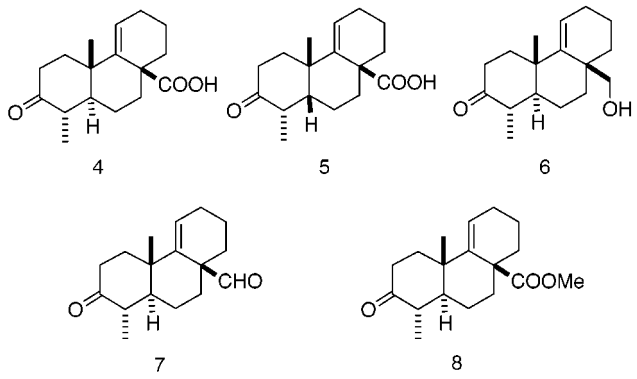
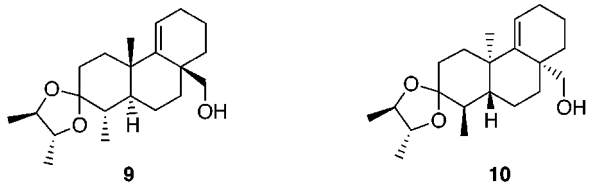


4 5 6 7 8

tures assigned to **9** and **10** were made possible by single-crystal X-ray analysis of the *p*-nitrobenzoate derived from **9**.[8]

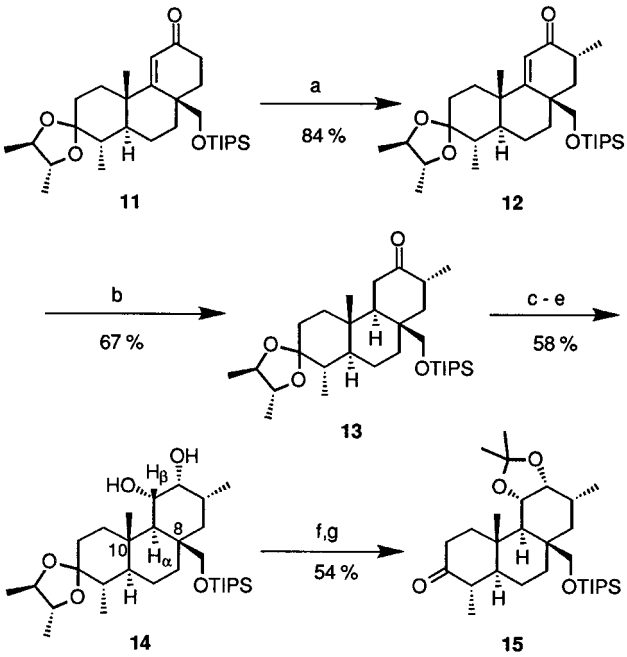


9 **10**

With chiral material material in hand (cf. **9**), in which the C(3) ketone is protected, efforts were directed toward installation of the ring C functionality (**Scheme 1**). After protection of the angular hydroxymethyl group in **9** as its triisopropylsilyl ether, allylic oxidation with Collins reagent provided enone **11** in 96% overall yield. Alkylation of **11** with methyl iodide from the less hindered face of the enolate afforded **12** in 83% yield, thus establishing the correct absolute configuration at C(13). The stereogenic center at C(9) was installed via a dissolving metal reduction providing **13** which was transformed via a three-step sequence into vicinal diol **14**. The observed stereochemistry follows from attack of the osmium tetraoxide from the less hindered face of the C(11)−C(12) olefin, away from the angular substituents at C(8) and C(10). Confirmation of the stereochemical assignment comes from the ^{1}H NMR spectrum of **14** which revealed a coupling constant of $J_{\alpha\beta} = 11.3$ Hz for the C(9) α proton and the C(11) β proton. Cleavage of the ketal and subsequent protection of the C(11)−C(12) diol as an acetonide afforded ketone **15**, possessing all the functionality needed to complete the elaboration of ring C.

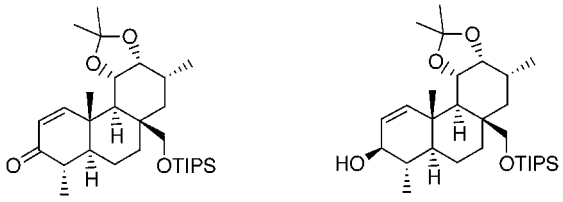
At this stage in the synthesis, attention was focused on incorporation of the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit present in ring A of **2**. Toward this end, we set out to transform **15** into enone **16**. α-Bromination/dehydrobromination of ketone **15** unfortunately gave rise to low yields of enone **16**. However, **16** was realized in 90% overall yield by α-selenenylation followed by oxidation and loss of benzeneselenenic acid. Reduction of enone **16** under Luche conditions at −78 °C gave rise to the β-allylic alcohol **17** in 89% yield.[9] Directed epoxidation of **17** with *tert*-butyl hydroperoxide in the presence of catalytic vanadyl acetylacetonate afforded the β-epoxide **18** exclusively, however, in low yield. The major product was enone **16** obtained by competing oxidation. In

Scheme 1



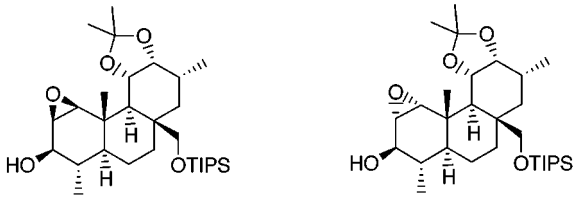
11 **12** **13** **14** **15**

a Reagents and conditions: (a) LDA, THF, HMPA, -78 °C→0 °C; MeI, -78 °C→0 °C; (b) Li, NH_3; (c) H_2NNHTs, $MgSO_4$, THF; (d) LDA,THF; (e)OsO_4, pyr; $NaHSO_3$; (f)1 N HCl, THF; (g) $Me_2C(OMe)_2$, CSA, THF.



16 **17**

retrospect, this result is not surprising since it is known that pseudo equatorial allylic alcohols undergo oxidation to enones in the presence of $VO(acac)_2$.[10] It has been shown that in hydroxyl-directed peracid oxidations, it is the pseudo equatorial hydroxyl that does the directing.[11] Thus, epoxidation of **17** with *m*-chloroperbenzoic acid in methylene chloride at 0 °C gave rise to β-epoxide **18** and α-epoxide **19** in a 3.5:1 ratio. However, addition of peracid at −78 °C followed by slow warming to −10 °C and allowing the reaction to stand overnight afforded a 97% yield of **18** and **19** in a ratio of 10:1.



18 19

Treatment of β-epoxy alcohol **18** with methanesulfonyl chloride in the presence of triethylamine gave the cor-

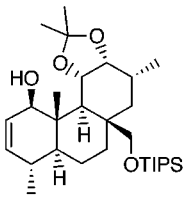
(8) The *p*-nitrobenzoate derived from **9** crystallizes in space group P1 with cell dimensions (at −174 °C) of $a = 14.203(4)$ Å, $b = 16.134(4)$ Å, $c = 11.976(3)$ Å, $\alpha = 90.20(1)°$, $\beta = 100.58(1)°$, and $\gamma = 110.71(1)°$; $D_{calc} = 1.276$ gm/cc for $Z = 4$.

(9) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(10) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(11) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. Chamberlain, P.; Roberts, M. L.; Whitman, G. H. *J. Chem. Soc. (B)* **1970**, 1374.

responding mesylate which upon exposure to lithium in liquid ammonia afforded (62%) the desired C(1) β-hydroxy $\Delta^{2,3}$ olefin **20**, along with recovered (19%) epoxy alcohol.



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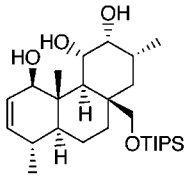
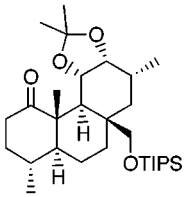


21

At this point in the synthesis there were several options available for completing the synthesis of **2**. All that remained was deprotection of the C(11)−C(12) diol, selective oxidation at C(11), and installation of the ring A functionality. In view of the numerous difficulties encountered with attempts to manipulate **20** so as to complete the installation of the ring A functionality and our inability to selectively protect the C(12) hydroxyl group in **21** [obtained from **20** upon exposure to hydrochloric acid in tetrahydrofuran (1:1)], it was determined to complete the synthesis employing the protocols developed in conjunction with the synthesis of (−)-chaparrinone.[3] Thus, the $\Delta^{2,3}$ olefin in **20** was reduced, and the resultant alcohol was oxidized giving rise to tricyclic ketone **22**. Cleavage of the acetonide in **22** afforded diol **23** which set the stage for the selective acetylation of the less hindered C(12) axial hydroxyl group. Exposure of diol **23** to acetic anhydride in pyridine provided a 55% yield of the C(12) monoacetate **24** along with 45% of the corresponding diacetate which was readily recycled back to **23** upon treatment with 1.0 N sodium hydroxide/tetrahydrofuran/methanol (1:1:3).



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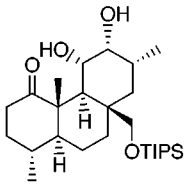

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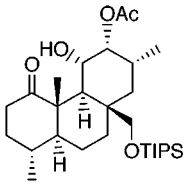
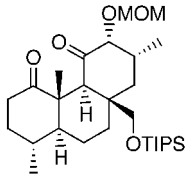


24

Prior to elaboration of ring A, keto alcohol **24** was transformed into diketone **25**. Oxidation of **24** with hydroxyiodinane oxide **26**,[12,13] followed by cleavage of the C(12) acetate and reprotection of the C(12) hydroxyl as a methoxymethyl ether, generated **25** in 92% overall yield.

With **25** in hand, the completion of the synthesis seemed to be all but assured. The methyl enol ether **27** was readily prepared from **25** under vigorously deoxygenated conditions using lithium diisopropylamide to



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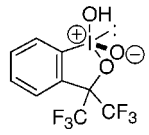
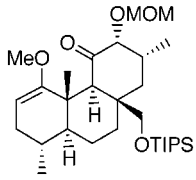


26

generate selectively the $\Delta^{1,2}$ enolate followed by quenching with dimethyl sulfate. Hydroboration and subsequent oxidation with pyridinium chlorochromate provided tricyclic diketone **28** in 67% overall yield.



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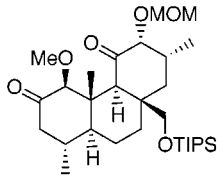
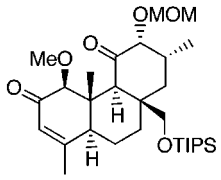


28

Conversion of **28** into the fully protected tricyclic enone **29** was realized via the three-step protocol established during the total synthesis of (−)-chaparrinone.[3] Treatment of **28** with lithium hexamethyldisilazide followed by trimethylsilyl chloride and *N*-bromosuccinimide yielded the corresponding α-bromoketone, which, upon heating to 120 °C in *N*,*N*-dimethylformamide with lithium carbonate and lithium bromide, afforded enone **29** in essentially quantitative yield.

Deprotection of the methyl and methoxymethyl ethers employing the boron tribromide conditions used in previous quassinoid work[3] was attempted first. Unfortunately, addition of boron tribromide in dichloromethane to **29** at −78 °C followed by slow warming to −23 °C gave, upon workup, a complex mixture of products from which the major product isolated was the C(1) deoxygenated ketone **30**. The formation of **30** most likely arises via the intermediacy of bromide **31**, followed by reduction, perhaps with loss of molecular bromine.



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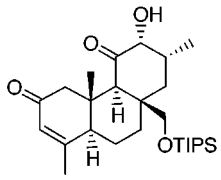

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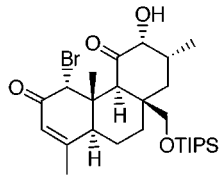

31

In conjunction with our total synthesis of simalikalactone D,[14] it had been found that prior removal of the methoxymethyl ether can facilitate methyl ether cleavage. Much to our surprise, exposure [0 °C(2.5 h) → rt (18 h)] of **29** to aluminum trichloride and sodium iodide in acetonitrile/dichloromethane (1:1) resulted in not only

(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(13) For the use of **26** as a mild oxidizing agent see: Grieco, P. A.; Piñeiro-Nuñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606 and references therein.

(14) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764.

cleavage of the methoxymethyl ether, but also the triisopropylsilyl ether and the C(1) methyl ether, thus giving rise to (+)-des-D-chaparrinone (**2**) in 47% yield. Biological studies[15] revealed that **2** was devoid of any solid tumor activity which suggests that the ring D δ-lactone is essential for solid tumor activity and selectivity.

Experimental Section[17]

(1α,4a*β*,8a*β*,10aα)-1,4a-Dimethyl-3,4,4a,6,7,8,8a,9,10,10a-dodecahydro-8a-(hydroxymethyl)phenanthren-2(1*H*)-one (6). To a solution of 2.6 g (62.0 mmol) of lithium in 1.2 L of anhydrous ammonia cooled to −78 °C was added dropwise via cannula over 50 min 18.0 g (62.0 mmol) of enone ester **3** (R = Me) in 450 mL of anhydrous tetrahydrofuran containing 5.8 mL (62.0 mmol) of *tert*-butyl alcohol. After 70 min, the reaction was quenched by the addition of 5.0 mL of isoprene followed by 25.0 g of ammonium chloride. The ammonia was evaporated with the aid of a stream of nitrogen. The residue was taken up in water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on silica gel with hexane/ethyl acetate (3:1) giving rise to 8.9 g (55%) of keto alcohol **6** as a crystalline compound: R_f 0.42 (hexane/ethyl acetate, 2:1); IR ($CHCl_3$) 3650−3400 (w), 1705 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (t, 1H, J = 3.7 Hz), 3.67 (m, 2H), 2.52 (td, 1H, J = 6.6, 14.0 Hz), 2.41 (ddd, 1H, J = 2.3, 5.3, 15.0 Hz), 2.30 (dq, 1H, J = 6.6, 13.7 Hz), 2.09−2.14 (m, 3H), 1.72−1.88 (m, 4H), 1.56−1.62 (m, 2H), 1.46 (brqd, 1H, J = 3.4, 13.6 Hz), 1.25−1.30 (m, 2H), 1.23 (s, 3H), 1.08−1.19 (m, 2H), 1.00 (d, 3H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.82, 145.87, 124.10, 67.38, 53.03, 52.14, 44.81, 39.21, 38.65, 38.43, 37.85, 37.59, 36.16, 26.00, 22.30, 20.06, 18.02, 11.57; high-resolution MS (CI) calcd for $C_{17}H_{27}O_2$ (M + 1) *m/e* 263.2012, found 263.2022. An analytical sample was prepared by recrystallization from hexane, mp 135.0−136.5 °C. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.98. Found: C, 77.83: H, 9.90.

(+)-(1*S*,4a*S*,8a*S*,10a*S*)-(1α,4a*β*,8a*β*,10aα)-1,4a-Dimethyl-2-[4′*R*,5′*R*-4′,5′-dimethyl-spiro-1′,3′-dioxolane]-1,3,4,4a,6,7,8,8a,9,10,10a-dodecahydro-8a-(hydroxymethyl)phenanthrene (9). To a solution of 12.2 g (46.8 mmol) of ketone **6** in 470 mL of benzene in a 1 L flask equipped with a Dean−Stark trap was added 2.7 g of *p*-toluenesulfonic acid monohydrate, followed by 5.0 g (55.5 mmol) of (−)-(*R*,*R*)-2,3-butanediol. The reaction was heated at reflux for 2.6 h. After cooling to ambient temperature, the solvent was removed in vacuo, and the residue was dissolved in ether and washed with 1.0 N sodium hydroxide. The aqueous layer was extracted with ether, and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate (8:1) afforded 6.5 g (42%) of enantiomerically pure ketal **9** as a colorless oil [R_f 0.58 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +33.7° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3620−3400 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (t, 1H, J = 3.7 Hz), 3.75 (dq, 1H, J = 6.0, 8.6 Hz), 3.67 (d, 1H, J = 10.9 Hz), 3.50−3.58 (m, 2H), 2.04−2.09 (m, 2H), 1.5−1.9 (m, 10H), 1.28−1.32 (m, 1H), 1.27 (d, 3H, J = 6.0 Hz), 1.21 (d, 3H, J = 6.0 Hz), 1.19−1.20 (m, 2H), 0.99 (s, 3H), 0.8−0.9 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.62, 123.37, 109.95, 80.08, 77.68, 68.07, 48.14, 39.20, 38.52, 38.30, 36.73, 35.18, 33.68, 26.03, 21.48, 19.65, 18.25, 18.16, 16.19, 10.97; high-resolution MS (EI) calcd for $C_{21}H_{34}O_3$ (*M*) *m/e* 334.2509, found 334.2510] and 9.0 g (57%) of a mixture of **9** and **10** as a colorless oil.

(+)-(1*S*,4a*S*,8a*S*,10a*S*)-(1α,4a*β*,8a*β*,10aα)-1,4a-Dimethyl-2-[4′*R*,5′*R*-4′,5′-dimethyl-spiro-1′,3′-dioxolane]-1,3,4,4a,8,8a,10,10a-dodecahydro-8a-[(triisopropylsilyloxy)methyl]-phenanthren-6(7*H*)-one (11). To a solution of 6.5 g (19.4 mmol) of alcohol **9** in 13 mL of *N*,*N*-dimethylformamide containing 4.0 g (58.0 mmol) of imidazole was added via syringe 6.2 mL (29.1 mmol) of triisopropylchlorosilane. After 72 h, the reaction was quenched by the addition of 10.0 mL of an aqueous saturated sodium bicarbonate solution. Upon dilution with water, the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, giving rise to 9.5 g (100%) of the corresponding silyl ether as a yellow oil. An analytical sample was prepared by preparative TLC: R_f 0.91 (hexane/ether, 4:1); $[\alpha]^{25}_D$ +26.4° (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.51 (t, 1H, J = 3.3 Hz), 3.95 (d, 1H, J = 9.6 Hz), 3.74 (dq, 1H, J = 6.0, 8.4 Hz), 3.45−3.55 (m, 2H), 2.08−2.14 (m, 2H), 2.02−2.07 (m, 2H), 1.52−1.81 (m, 8H), 1.45−1.51 (m, 1H), 1.22−1.30 (m, 1H), 1.26 (d, 3H, J = 5.9 Hz), 1.20−1.16 (m, 21H), 0.92−0.98 (m, 1H), 0.91 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz), 0.83−0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.85, 120.83, 110.08, 79.99, 77.61, 65.35, 48.32, 39.89, 38.97, 38.18, 35.48, 35.13, 34.00, 33.82, 26.29, 21.31, 19.93, 18,14, 18.09, 17.73, 16.20, 12.09, 10.96; high-resolution MS (CI) calcd for $C_{30}H_{55}O_3Si$ (M + 1) *m/e* 491.3923, found 491.3922.

In a dry 3.0 L, three-necked flask equipped with a mechanical stirrer was placed 650 mL of dichloromethane and 47.1 mL (582 mmol) of pyridine. To this stirred solution was added portionwise over 6 min 29.1 g (291 mmol) of chromium trioxide. After 30 min, 63 g of Celite was added. Upon stirring an additional 15 min, 9.5 g (19.4 mmol) of the above olefin in 300 mL of dichloromethane was added dropwise via a cannula. After 19.5 h, the reaction was quenched by the addition of 79 g of sodium bisulfate, and stirring was continued for an additional 30 min. The crude reaction mixture was filtered through flash silica gel, and the resulting solution was concentrated in vacuo leaving 9.4 g (96%) of enone **11** as a brown oil. An analytical sample was prepared by preparative TLC: R_f 0.32 (hexane/ether, 3:1); $[\alpha]^{25}_D$ +54.0° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 1640 (s), 1590 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 3.96 (d, 1H, J = 9.9 Hz), 3.75 (dq, 1H, J = 5.9, 8.5 Hz), 3.58 (d, 1H, J = 9.9 Hz), 3.53 (dq, 1H, J = 5.9, 8.5 Hz), 2.5 (ddd, 1H, J = 4.5, 5.1, 15.1 Hz), 2.22−2.32 (m, 2H), 2.17 (dt, 1H, J = 2.9, 13.7 Hz), 1.60−1.84 (m, 7H), 1.42−1.54 (m, 2H), 1.31 (qd, 1H, J = 3.1, 13.1 Hz), 1.26 (d, 3H, J = 5.9 Hz), 1.22−1.28 (m, 1H), 1.20 (d, 3H, J = 5.9 Hz), 1.03−1.18 (m, 19 H), 0.99 (s, 3H), 0.95−0.99 (m, 1H), 0.89 (d, 3H, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.38, 174.98, 125.01, 109.22, 80.11, 77.75, 65.39, 47.06, 41.49, 39.52, 38.80, 34.85, 34.64, 34.06, 33.87, 33.43, 20.83, 19.26, 18.03, 16.14, 12.00, 10.93; high-resolution MS (CI) calcd for $C_{30}H_{43}O_4Si$ (M + 1) *m/e* 505.3715, found 505.3663.

(+)-(1*S*,4a*S*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,7α,8a*β*,10aα)-2-[4′*R*,5′*R*-4′,5′-Di-methyl-spiro-1′,3′-dioxolane]-1,3,4,4a,8,8a,9,10a-dodecahydro-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthren-6(7*H*)-one (12). To 15.7 mL (15.7

(15) Des-D-chaparrinone (**2**) was examined in the soft agar colony formation disk diffusion assay.[16] This in vitro assay defines solid tumor selective compounds by quantitating differential cytotoxic activity between murine and human solid tumor cells and either murine leukemia or normal cells. Analogue **2** was tested against a murine leukemia (P388), two murine solid tumors (Colon 38 and Mam 17/Adr), and a human solid tumor (H-125 lung cancer).

(16) Corbett, T. H.; Valeriote, F. A.; Polin, L. et al. Discovery of Solid Tumor Active Agents Using a Soft-Agar-Colony-Formation Disk-Diffusion-Assay. In *Cytotoxic Anticancer Drugs: Models and Concepts for Drug Discovery and Development*; Valeriote, F. A., Corbett, T. H., Baker, L. H., Eds.; Kluwer Academic Publishers: Boston, 1992; p 35.

(17) Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on a Bruker AM-500 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer Model 298 spectrophotometer. Mass spectra were obtained on a Kratos MS 80/RFAQ spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and Robertson Microlit Laboratories, Inc., Madison, NJ. Melting points were obtained on a Fisher-Johns hot-stage instrument and are uncorrected. Reactions were monitored by thin-layer chromatography using E. Merck precoated silica gel 60 F-254 (0.25 mm) plates. The plates were visualized by immersion in a *p*-anisaldehyde solution and warming on a hot-plate. E. Merck silica gel 60 (230−400 mesh) was used for flash chromatography.

mmol) of a 1.0 M solution of freshly prepared lithium diisopropylamide at −78 °C was added dropwise via cannula a solution of 2.4 g (4.7 mmol) of enone **11** in 23.5 mL of tetrahydrofuran containing 3.3 mL (18.8 mmol) of hexamethylphosphoramide. After 25 min, the reaction was warmed to 0 °C and was kept at that temperature for 1 h, at which time the reaction was cooled to −78 °C. Methyl iodide (1.3 mL, 21.0 mmol) was added dropwise via syringe. After 15 min, the reaction was warmed to ambient temperature. The reaction was quenched after 4 h by the addition of a saturated aqueous ammonium chloride solution. The biphasic mixture was diluted with water and extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Chromatography of the crude product on flash silica gel with hexane/ether (3.5:1) gave rise to 2.1 g (84%) of ketone **12** as a yellow oil [R_f 0.36 (hexane/ether, 3:1); $[\alpha]^{25}_D$ +68.2° (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 1638 (s), 1594 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.00 (d, 1H, *J* = 9.7 Hz), 3.75 (dq, 1H, *J* = 5.9, 8.5 Hz), 3.63 (d, 1H, *J* = 9.7 Hz), 3.53 (dq, 1H, *J* = 5.9, 8.5 Hz), 2.51−2.58 (m, 1H), 2.27 (dd, 1H, *J* = 4.6, 12.9 Hz), 2.15 (brd, 1H, *J* = 13.7 Hz), 1.60−1.83 (m, 7H), 1.46 (td, 1H, *J* = 2.1, 12.2 Hz), 1.18−1.36 (m, 3H), 1.26 (d, 3H, *J* = 5.9 Hz), 1.20 (d, 3H, *J* = 5.9 Hz), 1.04−1.15 (m, 23H), 0.99 (s, 3H), 0.89 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.80, 174.16, 124.63, 109.25, 80.10, 77.76, 65.74, 47.20, 43.67, 42.25, 39.33, 38.81, 37.33, 35.03, 34.21, 33.45, 20.83, 19.01, 18.04, 18.01, 16.15, 15.46, 12.13, 12.01, 10.91; high-resolution MS (CI) calcd for $C_{31}H_{55}O_4Si$ (M + 1) *m/e* 519.3872, found 519.3852] along with 400 mg (16%) of recovered **11**.

(+)-(1*S*,4a*S*,4b*R*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,7α,8a*β*,10aα)-2-[4′R,5′R-4′,5′-Dimethyl-spiro-1′,3′-dioxolane]-1,3,4,4a,4b,5,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthren-6(7*H*)-one (13). To a stirred solution of 1.0 g (149.7 mmol) of lithium in 550 mL of anhydrous ammonia cooled to −78 °C was added dropwise via a cannula over 15 min 7.8 g (15.0 mmol) of enone **12** in 150 mL of anhydrous tetrahydrofuran. After 2.5 h, the reaction was quenched by the addition of 6.0 mL of isoprene followed by 10 g of ammonium chloride. The ammonia was evaporated with the aid of a stream of nitrogen. The residue was dissolved in water and extracted with ether. The combined organic extracts were dried over anhydrous magesnium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ether (6:1) gave 5.2 g (67%) of keto alcohol **13** [R_f 0.85 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +4.2° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1680 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 (ABq, 2H, *J* = 9.9 Hz), 3.72 (dq, 1H, *J* = 6.0, 8.4 Hz), 3.50 (dq, 1H, *J* = 5.8, 8.4 Hz), 2.47−2.52 (m, 1H), 2.27−2.39 (m, 3H), 2.08 (brd, 1H, *J* = 13.6 Hz), 1.57−1.71 (m, 4H), 1.46−1.51 (m, 2H), 1.24 (d, 3H, *J* = 5.9 Hz), 1.22 (m, 1H), 1.18 (d, 3H, *J* = 5.9 Hz), 1.13−1.65 (m, 2H), 1.04−1.12 (m, 21H), 0.96 (d, 3H, *J* = 6.4 Hz), 0.85−0.93 (m, 1H), 0.85 (d, 3H, *J* = 6.5 Hz), 0.76 (t, 1H, *J* = 13.0 Hz), 0.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.68, 109.80, 79.97, 77.68, 61.62, 56.14, 49.34, 45.68, 41.32, 39.92, 38.51, 37.99, 36.55, 35.51, 35.44, 33.22, 21.11, 18.06, 16.17, 14.36, 12.96, 12.01, 10.74; high-resolution MS (CI) calcd for $C_{31}H_{55}O_4Si$ (M + 1) *m/e* 521.4028, found 521.4032] along with 2.3 g (30%) of recovered **12**.

(−)-(1*S*,4a*S*,4b*R*,5*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-5,6-Dihydroxy-2-[4′R,5′R-4′,5′-dimethyl-spiro-1′,3′-dioxolane]-1,3,4,4a,4b,5,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene (14). To a solution of 4.8 g (9.1 mmol) of ketone **13** in 50 mL of tetrahydrofuran was added 2.8 g (23.7 mmol) of anhydrous magnesium sulfate and 2.0 g (11.0 mmol) of *p*-toluenesulfonyl hydrazide. After 6 h, an additional 680 mg of *p*-toluenesulfonyl hydrazide was added to drive the reaction to completion. After 14 h, the reaction was filtered and concentrtated in vacuo. The residue was chromatographed on silica gel with hexane/ether (3:1) giving rise to pure hydrazone which was used directly in the next reaction.

A solution of freshly prepared lithium diisopropylamide (137.1 mmol) in 18.3 mL of tetrahydrofuran cooled to −78 °C was treated dropwise over 15 min via cannula with a solution of the above hydrazone in 118 mL of tetrahydrofuran. The reaction was stirred for 25 min and was slowly warmed to ambient temperature. After 5 h, the reaction was cooled to 0 °C and quenched by the addition of a saturated ammonium chloride solution. The resulting bright yellow solution was diluted with 1.0 N hydrochloric acid, and the product was isolated by extraction with ether, giving rise to 4.6 g (100%) of the corresponding olefin. An anayltical sample was obtained by preparative TLC: R_f 0.92 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +34.6° (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (ABq, 2H, *J* = 10.3 Hz), 3.79 (d, 1H, *J* = 9.4 Hz), 3.75 (dq, 1H, *J* = 6.0, 8.4 Hz), 3.67(d, 1H, *J* = 9.4 Hz), 3.53 (dq, 1H, *J* = 6.0, 8.4 Hz), 2.30−2.34 (m, 1H), 2.13 (dd, 1H, *J* = 5.9, 12.3 Hz), 2.02 (brd, 1H, *J* = 13.3 Hz), 1.93 (brs, 1H), 1.66−1.75 (m, 3H), 1.53−1.60 (m, 3H), 1.25 (d, 3H, *J* = 6.0 Hz), 1.24 (m, 1H), 1.21 (d, 3H, *J* = 6.0 Hz), 1.12−1.21 (m, 4H), 1.04−1.10 (m, 18H), 0.94 (d, 3H, *J* = 7.0 Hz), 0.91 (td, 1H, *J* = 3.1, 13.1 Hz), 0.85 (d, 3H, *J* = 6.6 Hz), 0.71 (brt, 1H, *J* = 11.6 Hz), 0.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.84, 124.48, 110.17, 79.94, 77.78, 61.98, 55.27, 49.45, 43.77, 40.07, 38.70, 35.61, 35.35, 35.07, 33.31, 29.14, 21.62, 21.23, 18.15, 18.09, 16.22, 13.47, 12.11, 10.66; high-resolution MS (CI) calcd for $C_{31}H_{57}O_3Si$ (M + 1) *m/e* 505.4079, found 505.4052.

To a stirred solution of 4.6 g (9.1 mmol) of the above olefin in 91 mL of pyridine at ambient temperature was added over a 5 min period 2.7 g (10.5 mmol) of osmium tetraoxide in small portions. After 3 h, an additional 300 mg of osmium tetraoxide was added, and the reaction was allowed to continue for 1 h. The reaction was diluted with 70 mL of pyridine and was treated with a solution of 16.5 g of sodium bisulfite in water (65 mL)/pyridine (7.6 mL). After stirring for 12 h, the reaction was filtered through a pad of flash silica gel, and the resulting solution was concentrated in vacuo. The residue was dissolved in water and treated with sodium bicarbonate. The product was isolated by extraction with ether. The combined organic extracts were washed with 1.0 N hydrochloric acid solution to remove traces of pyridine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resuting yellow oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate (6:1) afforded 2.8 g (58%) of diol **14** as a clear oil: R_f 0.42 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ −11.6 ° (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3700−3300 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.95 (brdd, 1H, *J* = 2.1, 11.3 Hz), 3.87 (d, 1H, *J* = 9.8 Hz), 3.71−3.75 (m 2H), 3.68 (d, 1H, *J* = 9.8 Hz), 3.49−3.55 (m, 1H), 2.61 Idt, 1H, *J* = 3.6, 13.4 Hz), 1.97 (brd, 1H, *J* = 13.3 Hz), 1.84−1.88 (m, 1H), 1.60−1.73 (m, 4H), 1.51 (brd, 2H, *J* = 11.7 Hz), 1.27−1.35 (m, 2H), 1.24 (d, 3H, *J* = 6.0 Hz), 1.20 (d, 3H, *J* = 6.0 Hz), 0.98−1.14 (m, 22H), 0.93 (d, 3H, *J* = 6.8 Hz), 0.79−0.89 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 109.81, 79.85, 77.58, 76.56, 71.85, 61.62, 53.04, 50.16, 41.26, 38.71, 38.44, 37.71, 37.43, 36.12, 33.58, 30.72, 20.95, 18.18, 18.10, 17.43, 16.20, 13.60, 12.01, 10.96; high-resolution MS (CI) calcd for $C_{31}H_{59}O_5Si$ (M + 1) *m/e* 539.4134, found 539.4140.

(−)-(1*S*,4a*S*,4b*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-5,6-*O*-Isopropylidine-3,4,4a,5,6,7,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)-methyl]-1,4a,7-trimethylphenanthren-2(1*H*)-one (15). To a solution of 726 mg (1.35 mmol) of ketal **14** in 12 mL of tetrahydrofuran at ambient temperature was added 12 mL of 1.0 N hydrochloric acid. The reaction was allowed to stir for 48 h, at which time the reaction was diluted with water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ether (6:1) afforded 450 mg (72%) of the corresponding keto diol: R_f 0.20 (hexane/ethyl acetate, 2:1); $[\alpha]^{25}_D$ +1.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3580 (m), 3500−3300 (m), 1700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (brd, 1H, *J* = 8.3 Hz), 3.91 (d, 1H, *J* = 9.8 Hz), 3.80 (brs, 1H), 3.72 (d, 1H, *J* = 9.8 Hz), 2.96−3.00 (m, 1H), 2.38−2.44 (m, 1H), 2.28−2.33 (m, 2H), 2.10−2.18 (m, 1H), 2.03 (brd, 1H, *J* = 13.7 Hz), 1.83−1.93 (m, 2H), 1.75 (brd, 1H, *J* = 13.0 Hz), 1.54 (brd, 1H, *J* = 11.0 Hz), 1.49 (d, 1H, *J* = 11.4 Hz), 1.42 (td, 1H, *J* = 6.1, 13.1

Hz), 1.19−1.32 (m, 4H), 1.01−1.12 (m, 23H), 1.00 (d, 3H, J = 6.5 Hz), 0.95 (d, 3H, J = 6.7 Hz), 0.80−0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.84, 76.36, 71.56, 61.28, 54.31, 53.06, 45.04, 41.44, 41.30, 38.20, 37.52, 37.47, 35.69, 30.63, 21.89, 18.05, 17.34, 14.20, 12.07, 12.01; high-resolution MS (CI) calcd for $C_{27}H_{50}O_4Si$ (M + 1) *m/e* 467.3558, found 467.3548.

To a solution of 1.1 g (2.3 mmol) of the above keto diol in 25 mL of tetrahydrofuran was added 1.4 mL (11.3 mmol) of 2,2-dimethoxypropane followed by 158 mg (0.68 mmol) of camphorsulfonic acid. After 4.5 h, the reaction was diluted with water and treated with sodium bicarbonate. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ether (3:1) gave 873 mg (76%) of acetonide **15**: R_f 0.90 (hexane/ethyl acetate, 2:1); $[\alpha]^{25}_D$ −22.8° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 1705 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, 1H, J = 4.9, 10.5 Hz), 4.16 (dd, 1H, J = 4.3, 4.9 Hz), 3.85 (d, 1H, J = 9.9 Hz), 3.52 (d, 1H, J = 9.9 Hz), 2.45−2.50 (m, 1H), 2.40 (dd, 1H, J = 6.6, 13.8 Hz), 2.26−2.32 (m, 2H), 2.07−2.13 (m, 1H), 1.96 (dt, 1H, J = 3.2, 13.8 Hz), 1.72 (dd, 1H, J = 3.8, 12.7 Hz), 1.56−1.59 (m, 1H), 1.48 (td, 1H, J = 5.6, 13.5 Hz), 1.42 (s, 3H), 1.29 (s, 3H), 1.28 (d, 1H, J = 10.5 Hz), 1.19−1.26 (m, 2H), 1.02−1.16 (m, 27H), 0.98 (d, 3H, J = 6.6 Hz), 0.94 (t, 1H, J = 13.1 Hz), 0.82−0.87 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.32, 106.88, 78.34, 75.54, 61.69, 55.51, 54.82, 44.99, 41.60, 41.20, 39.19, 37.83, 37.50, 35.50, 28.73, 27.93, 26.48, 22.28, 18.06, 17.69, 14.00, 12.05, 11.60; high-resolution MS (CI) calcd for $C_{30}H_{55}O_4Si$ (M + 1) *m/e* 507.3872, found 507.3890. An analytical sample was prepared by crystallization from hexane, mp 129.5−130.0 °C. Anal. Calcd for $C_{30}H_{54}O_4Si$: C, 71.10; H, 10.73. Found: C, 70.72; H, 11.06.

(−)-(1*S*,4a*R*,4b*R*,5*S*,6*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-4a,4b,5,6,7,8,8a,9,10,10a-Dodecahydro-5,6-*O*-isopropylidine-8a-[(triisopropylsilyloxy)-methyl]-1,4a,7-trimethylphenanthren-2(1*H*)-one (16). To a solution of 8.6 mL (8.6 mmol) of a 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran cooled to −78 °C was added dropwise over 5 min via cannula 873 mg (1.72 mmol) of ketone **15** in 17 mL of anhydrous tetrahydrofuran. The reaction was allowed to stir for 1 h, at which time 1.3 mL (10.3 mmol) of chlorotrimethylsilane was added. After 10 min, the reaction was warmed to 0 °C and was kept at that temperature for an additional 10 min prior to the addition of 1.7 g (8.6 mmol) of phenylselenenyl chloride. After 15 min the reaction was warmed to ambient temperature. The reaction was quenched after 15 min by the addition of a saturated solution of ammonium chloride. The mixture was diluted with water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude α-phenylselenenylated ketone was filtered through flash silica gel and used directly in the next reaction.

The above selenenylated ketone was dissolved in 35 mL of dichloromethane and was treated with 427 μL of pyridine and 3.2 mL of a solution of 30% hydrogen peroxide/water (1:1). The biphasic reaction was stirred for 20 min and was quenched by the addition of a saturated solution of sodium bicarbonate. The solution was diluted with water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, affording 870 mg (100%) of crude enone **16**. An analytical sample of **16** was prepared by preparative TLC: R_f 0.50 (hexane/ether, 3:1); $[\alpha]^{25}_D$ −42.5° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 1665 (s), 1450 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, 1H, J = 10.4 Hz), 5.71 (d, 1H, J = 10.4 Hz), 4.41 (dd, 1H, J = 4.7, 10.7 Hz), 4.18 (t, 1H, J = 4.4 Hz), 3.83 (d, 1H, J = 9.8 Hz), 3.55 (d, 1H, J = 9.8 Hz), 2.30−2.36 (m, 1H), 2.10−2.17 (m, 1H), 2.00 (dt, 1H, J = 3.0, 13.7 Hz), 1.75 (brdd, 1H, J = 4.0, 12.8 Hz), 1.59−1.69 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 1.29−1.38 (m, 1H), 1.13 (d, 3H, J = 6.8 Hz), 1.10 (s, 3H), 1.03−1.12 (m, 23H), 0.99 (brt, 1H, J = 12.9 Hz), 0.91 (brdd, 1H, J = 11.1, 13.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.88, 161.47, 124.00, 107.37, 78.53, 75.71, 61.80, 51.60, 51.50, 42.21, 41.81, 40.56, 40.16, 35.21, 28.66, 28.04, 26.50, 21.31, 18.06, 17.60, 16.59, 12.10, 12.04; high-resolution MS (CI) calcd for $C_{30}H_{53}O_4Si$ (M + 1) *m/e* 505.3715, found 505.3706.

(−)-(1*S*,2*R*,4a*R*,4b*R*,5*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,2*β*,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-1,2,4a,4b,5,6,7,8,8a,9,10,10a-Dodecahydro-2-hydroxy-5,6-*O*-isopropylidine-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene (17). To a solution of 873 mg (1.72 mmol) of enone **16** in 30 mL of ethanol/tetrahydrofuran (2:1) was added 965 mg (2.58 mmol) of cerium chloride heptahydrate. After 10 min, the solution was cooled to −78 °C, and 98 mg (2.58 mmol) of sodium borohydride was added. The reaction was quenched after 1.5 h by the addition of 500 μL of a saturated solution of sodium bicarbonate. Upon warming to ambient temperature, the mixture was diluted with brine and water. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate (4:1) afforded 695 mg (89%) of allylic alcohol **17** as an oil: R_f 0.60 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ −14.9° (*c* 0.9, $CHCl_3$) 3600 (w), 3550−3300 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (dd, 1H, J = 1.4, 10.4 Hz), 5.26 (dd, 1H, J = 2.0, 10.4 Hz), 4.34 (dd, 1H, J = 4.7, 10.7 Hz), 4.13 (t, 1H, J = 4.3 Hz), 3.78 (d, 1H, J = 9.8 Hz), 3.68 (d, 1H, J = 8.8 Hz), 3.49 (d, 1H, J = 9.8 Hz), 2.03−2.13 (m, 1H), 1.98 (brd, 1H, J = 13.6 Hz), 1.71 (dd, 1H, J = 4.0, 12.7 Hz), 1.64 (brs, 1H), 1.51−1.59 (m, 3H), 1.48 (d, 1H, J = 10.8 Hz), 1.43 (s, 3H), 1.36−1.43 (m, 1H), 1.32 (s, 3H), 1.14−1.25 (m, 3H), 1.00−1.11 (m, 24H), 0.97 (s, 3H), 0.94 (t, 1H, J = 12.8 Hz), 0.82−0.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.12, 124.28, 107.05, 78.57, 76.02, 75.18, 61.91, 52.26, 49.99, 41.63, 40.21, 39.69, 37.21, 35.86, 28.70, 28.11, 26.67, 20.23, 19.08, 18.06, 17.70, 15.67, 12.04; high-resolution MS (CI) calcd for $C_{30}H_{55}O_4Si$ (M + 1) *m/e* 507.3872, found 507.3872.

(−)-(1*S*,2*R*,3*R*,4*S*,4a*R*,4b*R*,5*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,2*β*,3*β*,4*β*,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-3,4-Epoxy-2-hydroxy-5,6-*O*-isopropylidine-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)-methyl]-1,4a,7-trimethylphenanthrene (18). To a solution of 180 mg (0.36 mmol) of allylic alcohol **17** in 5.0 mL of dichloromethane cooled to −78 °C was added 125 mg (0.7 mmol) of *m*-chloroperbenzoic acid. The reaction was warmed to −20 °C and was kept at that temperature for 16 h. Upon warming to 0 °C, the reaction was quenched by the addition of a saturated solution of sodium bicarbonate. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate (3:1) gave 164 mg (88%) of β-epoxide **18** [R_f 0.28 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ −5.0° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3585 (w), 3560−3300 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, 1H, J = 4.0 Hz), 4.42 (dd, 1H, J = 4.8, 10.6 Hz), 4.18 (t, 1H, J = 4.5 Hz), 3.77 (d, 1H, J = 9.8 Hz), 3.51 (d, 1H, J = 9.8 Hz), 3.36 (brd, 1H, J = 8.1 Hz), 3.19 (dd, 1H, J = 2.7, 3.5 Hz), 2.06−2.17 (m, 1H), 1.96 (dt, 1H, J = 2.8, 13.5 Hz), 1.73 (dd, 1H, J = 4.0, 12.7 Hz), 1.65 (s, 1H), 1.59 (d, 1H, J = 9.7 Hz), 1.47 (s, 3H), 1.40 (brd, 1H, J = 13.7 Hz), 1.31 (s, 3H), 1.25−1.31 (m, 2H), 1.02−1.16 (m, 28H), 0.97 (s, 3H), 0.94−0.98 (m, 1H), 0.93 (d, 3H, J = 8.8 Hz), 0.76−0.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.02, 78.50, 76.69, 75.99, 75.19, 63.12, 62.05, 57.35, 52.09, 51.31, 41.77, 40.35, 39.50, 37.37, 35.90, 33.62, 28.53, 28.07, 26.59, 26.34, 19.62, 18.05, 17.59, 16.56, 14.66, 13.11, 12.03; high-resolution MS (CI) calcd for $C_{30}H_{55}O_5Si$ (M + 1) *m/e* 523.3821, found 523.3821] and 16 mg (9%) of the α-epoxide **19** which was not characterized.

(−)-(1*R*,4a*S*,4b*S*,5*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4*β*,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-1,4,4a,4b,5,6,7,8,8a,9,10,10a-Dodecahydro-4-hydroxy-5,6-*O*-isopropylidine-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene (20). To a solution of 390 mg (0.75 mmol) of epoxy alcohol **18** in 5.0 mL of dichloromethane cooled to 0 °C was added 315 μL (2.3 mmol) of triethylamine followed by 87 μL (1.1 mmol) of methane-

sulfonyl chloride. After 15 min, the reaction was quenched with water, and the product was isolated by extraction with ether. The combined organic extracts were washed with 1.0 N hydrochloric acid, dried over anhydrous magnesiun sulfate, filtered, and concentrated in vacuo. The crude mesylate was used directly in the next reaction.

To a solution of 54 mg (7.8 mmol) of lithium in 35 mL of anhydrous ammonia at −78 °C was added dropwise via cannula over 15 min the above mesylate in 19 mL of anhydrous tetrahydrofuran. After 1 h, the reaction was quenched by the addition of ammonium chloride. The ammonia was evaporated with the aid of a stream of nitrogen, and the residue was dissolved in water. The product was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting oil was chromatographed on flash silica gel. Elution with hexane/ether (4:1) afforded 192 mg (51%) of allylic alcohol **20** [R_f 0.90 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ −53° (*c* 1.8, $CHCl_3$); IR ($CHCl_3$) 3600−3200 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (d, 1H, J = 4.2 Hz), 5.50 (dt, 1H, J = 1.9, 10.1 Hz), 5.35 (dt, 1H, J = 2.1, 10.1 Hz), 4.32 (dd, 1H, J = 5.0, 10.3 Hz), 4.24 (t, 1H, J = 4.3 Hz), 4.02 (brs, 1H), 3.86 (d, 1H, J = 10.1 Hz), 3.42 (dd, 1H, J = 0.9, 10.1 Hz), 2.06−2.14 (m, 1H), 1.90 (dt, 1H, J = 3.2, 13.5 Hz), 1.80−1.87 (m, 1H), 1.65−1.73 (m, 2H), 1.54 (s, 3H), 1.36 (d, 1H, J = 10.3 Hz), 1.34 (s, 3H), 1.20−1.30 (m, 2H), 0.96−1.15 (m, 28H), 0.84−0.93 (m, 1H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.23, 129.50, 107.15, 78.37, 75.25, 74.69, 61.32, 55.36, 49.25, 41.85, 41.52, 39.50, 34.97, 32.46, 28.57, 27.55, 26.19, 21.25, 19.74, 18.04, 17.60, 12.02, 10.52; high-resolution MS (CI) calcd for $C_{30}H_{54}O_4Si$ (M + 1) *m/e* 507.3872, found 507.3864] along with 78 mg (20%) of **18**.

(+)-(1*R*,4a*S*,4b*S*,5*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,5α,6α,7α,8a*β*,10aα)-5,6-Dihydroxy-1,2,4a,4b,5,6,7,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)-methyl]-1,4a,7-trimethylphenanthren-4(3*H*)-one (23). To a solution of 170 mg (0.34 mmol) of allylic alcohol **20** in 4.0 mL of methanol at ambient temperature under an atmosphere of hydrogen was added 37 mg (0.04 mmol) of 10% palladium on activated carbon. After 2 h, the reaction was filtered through flash silica gel. The resulting yellow oil was chromatographed on flash silica gel. Elution with hexane/ether (3:1) gave 153 mg (90%) of the corresponding C(1) alcohol: R_f 0.40 (hexane/ether, 3:1); $[\alpha]^{25}_D$ −26.2° (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) 3600−3100 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (d, 1H, J = 3.5 Hz), 4.31 (dd, 1H, J = 5.0, 10.1 Hz), 4.22 (t, 1H, J = 4.2 Hz), 3.81 (d, 1H, J = 10.0 Hz), 3.43 (d, 1H, J = 10.0 Hz), 3.35−3.42 (m, 1H), 2.06−2.13 (m, 1H), 1.89 (dt, 1H, J = 2.9, 13.5 Hz), 1.65−1.74 (m, 3H), 1.49−1.64 (m, 3H), 1.53 (s, 3H), 1.35 (d, 1H, J = 10.1 Hz), 1.33 (s, 3H), 1.16−1.28 (m, 4H), 0.96−1.14 (m, 22H), 0.82−0.90 (m, 2H), 0.80 (d, 3H, J = 6.5 Hz), 0.79 (s, 3H), 0.65 (brt, 1H, J = 11.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.87, 78.44, 76.07, 75.02, 62.06, 56.85, 52.69, 44.01, 41.74, 39.73, 35.97, 34.45, 30.62, 30.55, 28.61, 27.51, 21.02, 20.49, 18.05, 17.63, 12.02, 11.01; high-resolution MS (CI) calcd for $C_{30}H_{57}O_4Si$ (M + 1) *m/e* 509.4028, found 509.4014.

To a solution of 195 mg (0.38 mmol) of the above alcohol in 4.0 mL of dichloromethane containing 1.0 mL of pyridine was added 630 mg (1.48 mmol) of hydroxyiodinane oxide **26**. After 48 h, the reaction was quenched with 1.0 N sodium hydroxide solution. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude ketone **23** was used directly in the next reaction.

The above crude ketone **23** was treated with 8.0 mL of a 3:1 mixture of tetrahydrofuran/1.0 N hydrochloric acid solution. After 30 min, the reaction was diluted with water and the product extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, leaving 179 mg (100%) of keto diol **23** as an oil. An analytical sample was prepared by preparative TLC: R_f 0.26 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +76.1° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3700−3100 (s), 1680 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (brs, 1H), 3.81 (ABq, 2H, J = 9.6 Hz), 3.65 (brt, 1H, J = 8.5 Hz), 3.15 (brd, 1H, J = 9.1 Hz), 2.98 (td, 1H, J = 7.2, 13.4 Hz), 2.58 (d, 1H, J = 11.6 Hz), 2.17 (brdd, 1H, J = 5.6, 12.3 Hz), 1.96−2.10 (m, 3H), 1.88−1.96 (m, 1H), 1.80−1.87 (m, 1H), 1.76 (brdd, 1H, J = 3.7, 13.0 Hz), 1.57 (brdd, 1H, J = 3.4, 13.9 Hz), 1.24−1.42 (m, 3H), 1.27 (s, 3H), 1.00−1.16 (m, 21H), 0.98 (d, 3H, J = 6.8 Hz), 0.92 (t, 1H, J = 13.1 Hz), 0.87 (d, 3H, J = 6.4 Hz), 0.78 (brt, 1H, J = 13.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.36, 75.50, 70.83, 61.02, 56.59, 51.48, 43.14, 40.60, 38.42, 37.79, 37.66, 34.65, 30.81, 30.26, 21.24, 19.06, 18.02, 17.51, 14.79, 11.97; high-resolution MS (CI) calcd for $C_{27}H_{50}O_4Si$ (M + 1) *m/e* 467.3558, found 467.3569.

(+)-(1*R*,4a*S*,4b*S*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4a*β*,4bα,6α,7α,8a*β*,10aα)-6-(Methoxymethoxy)-1,2,4a,6,7,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene-4(3*H*),5(4b*H*)-dione (25). To a solution of 178 mg (0.38 mmol) of diol **23** in 7.7 mL of pyridine at 50 °C was added 480 μL (15.0 mmol) of acetic anhydride. After 18 h, the reaction was cooled to ambient temperature and quenched by the addition of 1.0 N hydrochloric acid. The mixture was extracted with ether, and the combined ether extracts were washed with a saturated solution of sodium bicarbonate. The aqueous wash was extracted with ether, and the combined organic extracts were dried over anydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting yellow oil was chromatographed on flash silica gel with hexane/ethyl acetate (4:1) giving rise to 107 mg (55%) of monoacetate **24** which was used directly in the next reaction.

The above acetate was dissolved in 2.0 mL of dichloromethane and 2.0 mL of pyridine followed by the addition of 370 mg (0.92 mmol) of hydroxyiodinane oxide **26**. After 48 h, an additional 370 mg of **26** was added. After an additional 72 h, the reaction mixture was chromatographed directly on flash silica gel. Elution with hexane/ethyl acetate, 4:1, afforded 105 mg (100%) of the corresponding diketone: R_f 0.85 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +23.0° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 1740 (s), 1700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.92 (d, 1H, J = 2.7 Hz), 3.82 (d, 1H, J = 10.2 Hz), 3.35 (dd, 1H, J = 1.4, 10.2 Hz), 3.08 (s, 1H), 2.90 (td, 1H, J = 7.0, 13.8 Hz), 2.21 (s, 3H), 2.15−2.21 (m, 1H), 2.03−2.14 (m, 4H), 1.97−2.02 (m, 1H), 1.82−1.91 (m, 1H), 1.59−1.65 (m, 3H), 1.34 (s, 3H), 1.23−1.39 (m, 5H), 0.98−1.15 (m, 18H), 0.97 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.69, 206.92, 169.99, 80.36, 61.82, 55.40, 53.83, 49.89, 44.62, 39.28, 36.15, 34.98, 32.91, 29.09, 20.94, 20.86, 18.82, 18.00, 16.58, 15.76, 11.94; high-resolution MS (CI) calcd for $C_{29}H_{51}O_5Si$ (M + 1) *m/e* 507.3507, found 507.3498.

To a solution of 104 mg (0.2 mmol) of the above diketo acetate in 2.1 mL of deoxygenated methanol was added 27.5 mg (0.2 mmol) of potassium carbonate. After 3 h, the reaction was quenched by the addition of water followed by 1.0 N hydrochloric acid solution. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting diketo alcohol was used directly in the next reaction.

To a solution of the above diketo alcohol in 3.0 mL of 1,2-dichloroethane was added 435 μL (2.5 mmol) of diisopropylethylamine followed by 158 μL (2.1 mmol) of chloromethyl−methyl ether. After 18 h, the reaction was diluted with water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate (4:1) gave 98 mg (92%) of diketone **25**: R_f 0.70 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +38.0° (*c* 0.81, $CHCl_3$); IR ($CHCl_3$) 1700 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97 (d, 1H, J = 6.8 Hz), 4.76 (d, 1H, J = 6.8 Hz), 3.80 (d, 1H, J = 10.1 Hz), 3.78 (d, 1H, J = 2.8 Hz), 3.42 (s, 3H), 3.33 (dd, 1H, J = 1.1, 10.1 Hz), 3.24 (s, 1H), 2.94 (td, 1H, J = 7.0, 13.8 Hz), 1.95−2.14 (m, 5H), 1.81−1.90 (m, 1H), 1.58−1.65 (m, 2H), 1.41 (s, 3H), 1.21−1.39 (m, 4H), 0.95−1.13 (m, 24H), 0.88 (d, 3H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.93, 211.41, 95.32, 83.03, 62.07, 55.81, 55.25, 53.06, 49.88, 44.60, 38.74, 36.79, 36.42, 34.88, 33.43, 29.19, 20.96, 18.87, 18.01,

17.00, 15.92, 11.95; high-resolution MS (CI) calcd for $C_{29}H_{53}O_5Si$ (M + 1) *m/e* 509.3664, found 509.3662.

(−)-(1*S*,4*S*,4a*S*,4b*R*,6*R*,7*R*,8a*R*,10a*S*)-(1α,4*β*,4aβ,4bα,6α,7α,8a*β*,10aα)-4-Methoxy-6-(methoxymethoxy)-1,2,4a,6,7,8,8a,9,10,10a-tetradecahydro-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene-3(4*H*),5(4b*H*)-dione (28). To a solution of 72 mg (0.14 mmol) of diketone **25** in 2.0 mL of tetrahydrofuran cooled to −78 °C was added dropwise via cannula over 5 min 610 μL (0.61 mmol) of a 1.0 M solution of lithium diisopropylamide (prepared at 0 °C by the dropwise addition via syringe of 305 μL of a 2.5 M solution of *n*-butyllithium in hexane to 110 μL of diisopopylamine in 600 μL of anhydrous tetrahydrofuran). After 45 min, 87 μL (0.92 mmol) of dimethyl sulfate was added. The reaction was warmed to 0 °C after 15 min, and stirring was contined for an additional 20 min. The reaction was quenched with a saturated solution of ammonium chloride, diluted with water, and extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude methyl enol ether was used directly in the next reaction.

To a solution of the above methyl enol ether in 5.0 mL of tetrahydrofuran cooled to −78 °C was added 1.0 mL (1.0 mmol) of a 1.0 M solution of borane/tetrahydrofuran complex. After 30 min, the reaction was warmed to 0 °C. After an additional 3 h, the reaction was treated with 1.0 mL of 30% sodium hydroxide solution followed by 2.0 mL of 30% hydrogen peroxide.The reaction was quenched after 2.5 h with water, and the product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude alcohol was used immediately in the next reaction.

The above crude alcohol was dissolved in 5.0 mL of dichloromethane and was treated with 515 mg of Celite, 69 mg (0.84 mmol) of sodium acetate and 205 mg (0.95 mmol) of pyridinium chlorochromate. After 16 h, the contents of the reaction flask were filtered through flash silica gel, and the resulting solution was concentrated in vacuo. The yellow oil was chromatographed on flash silica gel. Elution with hexane/ethyl acetate, 3:1, afforded 52 mg (67%) of ketone **28**: R_f 0.31 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ −7.1° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 1720 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 4.62 (brs, 2H), 3.78 (d, 1H, *J* = 2.7 Hz), 3.75 (d, 1H, *J* = 10.4 Hz), 3.43 (s, 1H), 3.40 (s, 3H), 3.40 (d, 1H, *J* = 10.4 Hz), 3.28 (s, 3H), 3.24 (s, 1H), 2.39 (dd, 1H, *J* = 4.7, 13.8 Hz), 2.22 (brd, 1H, *J* = 13.2 Hz), 2.03−2.08 (m, 1H), 1.92−1.99 (m, 2H), 1.77−1.85 (m, 1H), 1.65 (brd, 1H, *J* = 2.7, 13.5 Hz), 1.16−1.32 (m, 5H), 1.11 (s, 3H), 0.97−1.08 (m, 26H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.73, 207.43, 95.64, 95.50, 86.02, 60.58, 58.57, 56.36, 55.94, 52.82, 49.14, 45.90, 45.34, 39.15, 35.17, 34.93, 32.14, 20.14, 20.00, 17.99, 17.13, 12.00, 11.94; high-resolution MS (CI) calcd for $C_{30}H_{55}O_6Si$ (M + 1) *m/e* 539.3770, found 539.3777.

(+)-(4*S*,4a*S*,4b*R*,6*R*,7*R*,8a*R*,10a*S*)-(4*β*,4aβ,4bα,6α,7α,8a*β*,10aα)-4a,6,7,8,8a,9,10,10a-Dodecahydro-4-methoxy-6-(methoxymethoxy)-8a-[(triisopropylsilyloxy)methyl]-1,4a,7-trimethylphenanthrene-3(4*H*),5(4b*H*)-dione (29). To a solution of 45 mg (0.084 mmol) of dione **28** in 1.7 mL of anhydrous tetrahydrofuran cooled to −78 °C was added via syringe over 5 min 835 μL (0.835 mmol) of a 1.0 M solution of lithium hexamethyldisilazide in tetrahydrofuran. After 1 h, 118 μL (0.93 mmol) of chlorotrimethylsilane was added. After 10 min, the reaction was warmed to 0 °C. After 15 min, the reaction was treated with 59 mg (0.33 mmol) of *N*-bromosuccinimide. The reaction was warmed (10 min) to ambient temperature and was filtered through silica gel. The solvent was removed in vacuo, and the crude bromo ketone was used directly in the next reaction.

A solution of the above crude bromo ketone in 2.0 mL of *N*,*N*-dimethylformamide containing 36 mg (0.42 mmol) of lithium bromide and 62 mg (0.84 mmol) of lithium carbonate was heated at 120 °C for 30 min. Upon cooling to ambient temperature and concentration of the solvent in vacuo, the crude product was chromatographed on flash silica gel. Elution with hexane/ethyl acetate, 3:1, afforded 45 mg (100%) of enone **29** as a solid: R_f 0.85 (hexane/ethyl acetate, 3:1); $[\alpha]^{25}_D$ +42.7° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) 1720 (s), 1680 (s), 1630 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (brs, 1H), 4.66 (ABq, 2H, *J* = 6.4 Hz), 3.81 (d, 1H, *J* = 2.9 Hz), 3.78 (d, 1H, *J* = 10.4 Hz), 3.48 (s, 3H), 3.44 (s, 1H), 3.41 (s, 3H), 3.38 (d, 1H, *J* = 10.4 Hz), 3.31 (s, 1H), 2.38 (brd, 1H, *J* = 12.1 Hz), 2.28 (dt, 1H, *J* = 3.0, 13.5 Hz), 2.01−2.12 (m, 1H), 1.99 (dd, 1H, *J* = 4.0, 13.2 Hz), 1.91 (s, 3H), 1.80 (brdd, 1H, *J* = 3.1, 13.9 Hz), 1.61 (brs, 1H), 1.45 (brqd, 1H, *J* = 2.8, 13.1 Hz), 1.16−1.28 (m, 4H), 1.15 (s, 3H), 1.00−1.09 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.01, 198.32, 160.30, 126.64, 95.63, 94.71, 85.73, 60.97, 59.69, 56.29, 56.00, 52.15, 46.24, 45.28, 39.24, 35.36, 34.58, 21.97, 19.30, 18.00, 17.09, 11.92, 11.36; high-resolution MS (CI) calcd for $C_{30}H_{52}O_6Si$ (*M*) *m/e* 536.3535, found 536.3564. An analytical sample was prepared by recrystallization from ether/hexane, mp 135−137 °C. Anal. Calcd for $C_{30}H_{52}O_6Si$: C, 67.12; H, 9.75. Found: C, 66.99; H, 9.70.

(+)-Des-D-chaparrinone (2). To a solution of 10 mg (0.019 mmol) of **29** in 930 μL of acetonitrile and 373 μL of dichloromethane cooled to 0 °C was added 49.6 mg (0.37 mmol) of aluminum trichloride followed by 56 mg (0.37 mmol) of sodium iodide. The reaction was allowed to stir for 2.5 h at 0 °C, at which time the reaction was warmed to ambient temperature where stirring was continued for 18 h. The reaction mixture was directly applied to a preparative TLC plate. Elution with 10% methanol in chloroform afforded 2.8 mg (47%) of des-D-chaparrinone (**2**) as a solid: R_f 0.47 (10% methanol/chloroform); $[\alpha]^{25}_D$ +65.3° (*c* 0.19, $CHCl_3$); IR ($CHCl_3$) 3590 (w), 3500−3100 (s), 1670 (s), 1625 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (brs, 1H), 6.11 (d, 1H, *J* = 1.3 Hz), 5.14 (brs, 1H), 4.02 (s, 1H), 3.85 (dd, 1H, *J* = 1.7, 8.4 Hz), 3.52 (d, 1H, *J* = 8.4 Hz), 3.52 (brs, 1H), 2.41 (brd, 1H, *J* = 12.2 Hz), 2.33 (s, 1H), 2.08−2.15 (m, 2H), 2.01 (s, 3H), 1.92 (brd, 1H, *J* = 13.4 Hz), 1.67 (dt, 1H, *J* = 2.9, 13.8 Hz), 1.53−1.62 (m, 3H), 1.40−1.48 (m, 2H), 1.12 (s, 3H), 1.01 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.86, 165.42, 123.67, 108.95, 83.66, 78.40, 71.43, 52.67, 49.51, 46.57, 46.00, 43.34, 32.37, 29.25, 23.23, 19.00, 15.96, 9.51; high-resolution MS (EI) calcd for $C_{18}H_{26}O_5$ (*M*) *m/e* 322.1781, found 322.1769. An analytical sample was prepared by recrystalization from ethyl acetate, mp 130.0−132.5 °C. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.99; H, 8.02.

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Supporting Information Available: Photocopies of the ^{1}H NMR and ^{13}C NMR spectra for compounds **2**, **9**, **11**−**18**, **20**, **23**, **25**, **28**, and **29** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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