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New progesterone receptor antagonists: Phosphorus-containing 11β-aryl-substituted steroids

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Abstract—A new series of phosphorus-containing 11β-aryl-substituted steroids have been synthesized in an eight-step sequence involving a palladium-catalyzed coupling reaction to introduce a phosphorus group onto the aromatic ring. The compounds were evaluated for progesterone receptor (PR) antagonist activity in a T47D cell-based assay and for glucocorticoid receptor (GR) antagonist activity in an A549 cell-based assay. The structure–activity relationships of these compounds are discussed. Selected compounds were tested in vivo in a rat complement C3 assay.

1. Introduction

The progesterone receptor (PR) is a member of the steroid receptor sub-family of the nuclear hormone receptor superfamily, a group of nuclear transcription factors.[1] Progesterone, the endogenous ligand for the PR, is involved in the control of ovulation and preparation of the uterus to support pregnancy. A PR antagonist therefore has potential utility as a contraceptive. In addition, PR antagonists have potential applications in the treatment of reproductive disorders such as uterine leiomyomas and endometriosis, as well as hormone dependent tumors.[1]

The discovery of the first competitive progesterone antagonist, mifepristone (Fig. 1, RU-486, **1**), has stimulated an intense search for more potent and more selective antiprogestins.[2] Although various attempts to differentiate the antiprogestin activity of mifepristone and other analogues from their antiglucocorticoid activity have identified some selective progesterone receptor modulators (PRMs), new compounds having antiprogestational activity devoid of antiglucocorticoid activity remain highly desirable, both in terms of clinical applications and basic endocrine research.[2a,2c]

Steroid receptors are closely related structurally and in their mechanism of action. Slight modifications of the steroidal structure have been found to induce important affinity and specificity variations for the corresponding receptors. The most prominent structural feature of mifepristone is the 4-(dimethylamino)phenyl group at the 11β-position of the 19-nor steroid. Without this substituent, the molecule would be expected to act as a progestin. Replacement of the 4-(dimethylamino)phenyl group with a 4-acetylphenyl (ZK112993, **2**)[3] leads to equally potent or more potent antiprogestins. Both compounds **1** and **2** are known for their overt antiglucocorticoid activity, which prevents their long-term clinical usage. Minor changes at the C-17 position produce antiprogestins with dramatically reduced antiglucocorticoid activity.[4] For example, Org-33628 (compound **3**) with a spiral cyclic chain at the C-17 position exhibits higher PR antagonist potency with significantly lower GR activity,[2a,2b] when compared with mifepristone (**1**) and ZK112993 (**2**). This led us to use Org-33628 as a template to make a chemically novel steroidal series with similar PR potency and higher selectivity against GR, when compared to mifepristone (compound **1**).

There have been literature reports on using phosphinic acids as bioisosteres of the carboxylic acid group.[5] We envisioned that phosphonyl groups can serve as bioisosteres for the carbonyl group on the 11-β-aryl group of Org-33628. In the present article, we describe the synthesis and biological properties of these derivatives.

Keywords: Phosphorus-containing steroids; Progesterone receptor antagonist.
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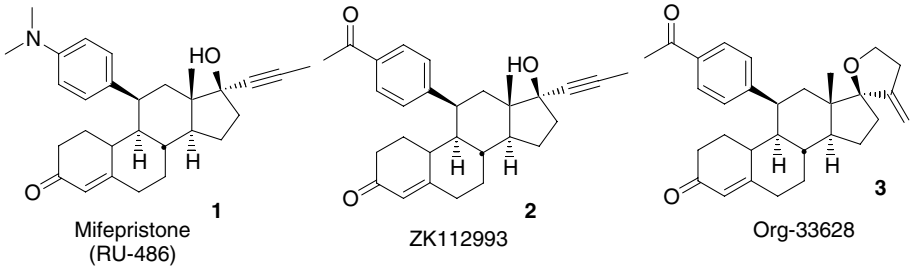
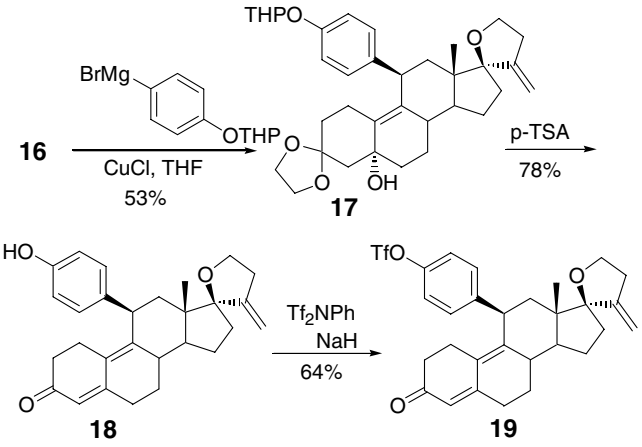


Figure 1. Some known steroidal progesterone receptor antagonists.

2. Chemistry

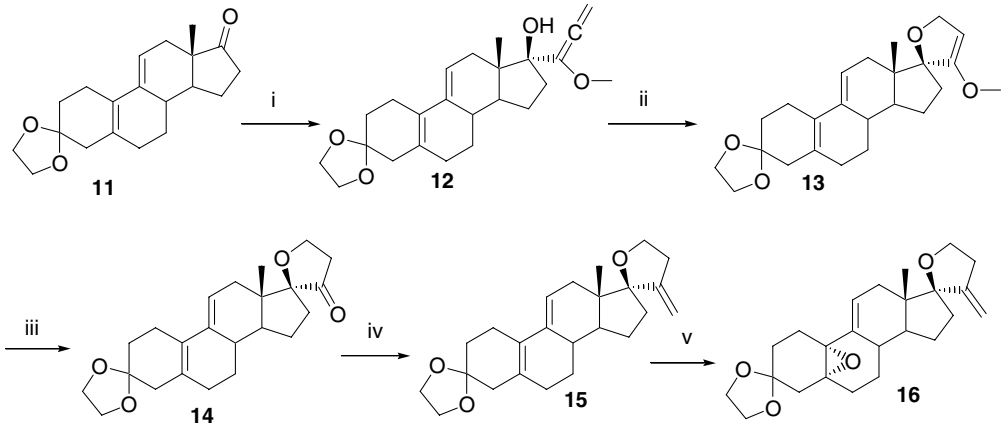
The backbone of the steroid was assembled according to the route described in Scheme 1.[6a] Thus, lithiated methoxy allenamide was captured by commercially available ethylene deltanone **11**, to generate compound **12**. Base-assisted cyclization was accomplished using a catalytic amount of crown ether (di-cyclohexyl-18-crown-6) to generate compound **13**. The selected deprotection of the methoxy group was accomplished by carefully monitoring the reaction time and the amount of acid used for the reaction. The resulting compound **14** was subjected to Wittig reaction condition to furnish compound **15**. At this point, the C-17 side chain for Org-33628 is fully installed.

Epoxidation using *m*CPBA under basic conditions provided epoxide intermediate **16**, with α:β ratio of 3:1, which is in consistency with the literature.[6b] The remaining products resulted from epoxidation of either one or both of the double bonds between C9 to C11 and the double bond on the C-17 spiral side chain. These side products are separable from the desirable product. In Scheme 2, epoxide **16** was subjected to the cuprate reaction conditions to provide the intermediate **17**.[6b] Free phenol **18** was obtained upon acidic deprotection conditions and then was reacted with a triflating reagent (Tf_2NPh) to furnish aryl triflate **19**.[7] For the conversion of compound **17** to **18**, both strong acid *p*-TSA and mild acid, such as, oxalic acid or acetic acid work the same.



Scheme 2. Installation of C11 side chain and preparation of triflate precursor **19**.

In the literature, aryl bromides, iodides and triflates can react with dialkyl phosphites or dialkyl phosphine oxide catalyzed by palladium/phosphine ligand.[8a,b,c] Since an iodide or bromide group cannot remain intact in the Grignard precursor for the cuprate reaction, we chose to use triflate **19** as the precursor for the phosphination reaction. There are several examples in the literature on converting the triflate group to a phosphonyl group. We first examined $Pd(PPh_3)_4$/4-methyl-morpholine using conventional synthesis (100 °C, 16 h) as well as with



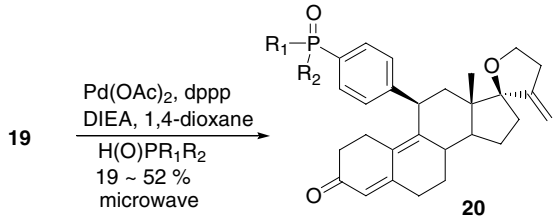
Scheme 1. Installation of C-17 side chain. Reagents: (i) *n*-BuLi, 1-methoxy-propa-1,2-diene **5**, −78 °C; (ii) KO-*t*-Bu, Di-Cy-18-C-6 **7**, *t*-BuOH; (iii) HCl/acetone; 43% for last 3 steps; (iv) $CH_3(PPh_3)Br$, KO-*t*-Bu, toluene, 67%; (v) *m*CPBA, sodium bicarbonate, CH_2Cl_2, 38%.

microwave irradiation (30 min, 150 °C). The product was formed with low conversion. The second catalyst system, $Pd(OAc)_2$/dppp/DIEA, turned out to be practical in generating clean product with a facile purification. Due to the switch from a monodentate ligand PPh_3 to a bidentate ligand 1,4-bis(diphenylphosphino)butane (dppp), the reductive elimination step in the catalytical cycle is probably accelerated due to the faster dissociation of the bidentate phosphine ligand, dppp, than that of the monodentate ligand PPh_3, in a dissociative mechanism in catalytical cycle.[9] Despite the abundant literatures on the thermal reaction of phosphination from aryl or vinyl triflate,[8] the reaction involving irradiation by microwaves has not been reported before. We found that microwave irradiated conditions constantly provided the desired coupling product **20** with higher yield and purity. It is observed that THF, 1,4-dioxane, and DMF are all suitable solvents, while DMSO tends to be unstable under microwave conditions Scheme 3.

By using LiOH/tBuOH/water,[10a] compounds **20c** and **20e** were converted to mono-hydroxyl phosphoryl 11-β-phenyl-substituted steroids **20d** and **20f**. We also attempted the same conversion by using $KOSiMe_3$,[10b] only to recover starting material. The most commonly used acidic reagent TMSBr[10c] led to an A-ring aromatized compound without any formation of desired product (Scheme 4).

3. Results and discussion

The compounds were evaluated for PR antagonist activity based on their ability to block progesterone induction of alkaline phosphatase activity in the human breast cancer cell line T47D (Table 1). The compounds were also tested for their GR antagonist activity based on their ability to inhibit corticoid-induced transcription from a glucocorticoid response element (GRE)-linked luciferase reporter gene in the human lung carcinoma cell line A549. The IC_{50}s of the compounds from the T47D and A549 assays are listed in Table 1. The ratio of the A549 IC_{50} to the T47D IC_{50} was calculated and is listed in the column 'Ratio', as a measure of the separation of PR and GR antagonist activities. Mifepristone (RU-486), a commercial drug, was tested as a control.



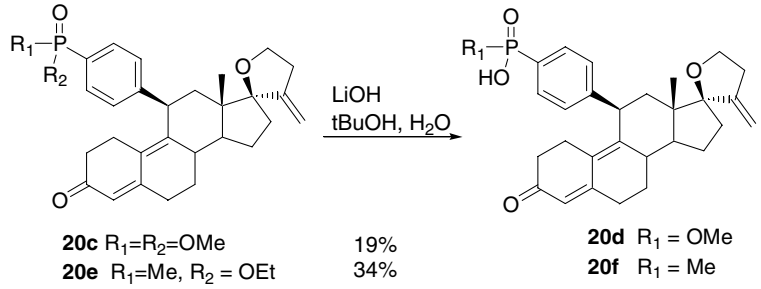
Scheme 3. Pd-catalyzed phosphination reaction under microwave irradiation.

The progesterone antagonist activities in the T47D assay were first examined. A wide range of substitutions at R_1 and R_2 are tolerated, except for acidic functional groups such as OH. When R_1 and R_2 are alkoxy groups, the size change did not affect potencies, as shown in **20a** and **20c**. Yet, a change in the electronics reduced potency slightly, as shown in **20a** and **20 g**, where **20g** bears a more electron-withdrawing group. Substitution of the phenyl group did not significantly change the potency (**20 h** vs **20i**). Replacing the methyl with phenyl group decreased the potency (**20b** vs **20h**). When R_1 and R_2 are tied into a cyclic structure, such as in **20k**, the potency remained unchanged in comparison with **20a**. Finally, replacing MeO with OH (**20c** vs **20d**) or EtO with OH (**20e** vs **20f**) abolished T47D activity. The poor antagonistic activities of **20d** and **20f** might be caused by the negative charge of these compounds which prevents them from penetrating the membrane and getting into the cell. Although our compounds were less potent than mifepristone, representative compounds demonstrated better selectivity (~13-fold), such as **20b** and **20e**. In terms of potency, more modification of this series of compounds needs to be done in order for them to be of value for further drug development.

Compounds **20a**, **20b**, and **20e** were further evaluated in vivo in the rat uterus complement C3 assay.[11] In this assay, ethinyl estradiol (EE) stimulates C3 expression and progestins inhibit this expression. In turn, antiprogestins counteract inhibition by the progestin. The results was shown in Table 2. The in vivo activities of three selected compounds **20a**, **20b**, and **20e** showed similar trends as in the T47D assay.

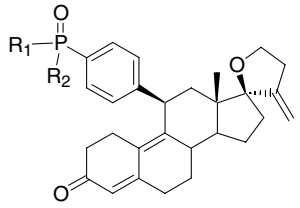
4. Conclusion

In summary, a novel series of phosphorus-containing C11 aryl-substituted steroids were synthesized by utilizing Pd-catalyzed phosphination reaction of triflate.



Scheme 4. Synthesis of **20d** and **20f** via hydrolysis reaction.

Table 1. Potencies of compounds **20a**–**20k** in T47D and A549 assays



Compound	R_1	R_2	T47D IC_{50} (nM)	A549 IC_{50} (nM)	Ratio = IC_{50} (A549)/IC_{50} (T47D)
1	Mifepristone	—	0.2	2.6	13
20a	OCH_2CH_3	OCH_2CH_3	9.9	237.7	24
20b	Me	Me	3.58	660.15	184
20c	OCH_3	OCH_3	8.27	230.1	28
20d	OCH_3	OH	>1000	>3000	—
20e	Me	OCH_2CH_3	1.6	270.86	169
20f	Me	OH	>1000	>3000	—
20g	OCH_2CF_3	OCH_2CF_3	28	140.81	5
20h	Ph	Ph	44	163.45	4
20i	4-Cl-Ph	4-Cl-Ph	20	143.11	7
20j	PhO	PhO	3.4	34.33	10
20k	$–OCH_2CMe_2CH_2O–$	—	7.2	286.53	40

Table 2. Potencies of compounds **20a**, **20b**, and **20e** tested in the rat uterine C3 model by oral administration

Compound	% inh	ID_{50} (mg/kg)
Mifepristone[11]		3.0
20a	16% inh at 30 mpk	>30
20b	38% inh at 20 mpk	>30
20e	18% inh at 10 mpk 78% inh at 30 mpk	10–30

These compounds were tested in cell-based in vitro assays for progestin and glucocorticoid antagonist activities. Most of the compounds were potent PR antagonists (nanomolar range), with some showing better selectivity than mifepristone. Selected compounds showed modest oral progestin antagonist activity in rat uterus.

5. Experimental

5.1. Biological assay

5.1.1. T47D alkaline phosphatase assay. T47D human breast cancer cells were plated in 96-well tissue culture plates at 10,000 cells per well in assay medium [RPMI medium without phenol red (Invitrogen) containing 5% (v/v) charcoal-treated FBS (Hyclone) and 1% (v/v) penicillin–streptomycin (Invitrogen)]. Two days later, the medium was decanted and test compound or control was added at a final concentration of 0.1% (v/v) dimethylsulfoxide in fresh assay medium. Twenty-four hours later, an alkaline phosphatase assay was performed using a SEAP kit (BD Biosciences Clontech, Palo Alto, CA). Briefly, the medium was decanted and the cells were fixed for 30 min at room temperature with 5% (v/v) formalin (Sigma). The cells were washed once at room temperature with Hanks' buffered saline solution (Invitrogen). Equal volumes (0.05 mL) of 1× dilution buffer, assay buffer, and 1:20 substrate/enhancer mixture were then added. After a 1-h incubation at room temperature in the dark, the lysate was transferred to a white 96-well plate (Dynex) and luminescence was read using a LuminoSkan Ascent (Thermo Electron, Woburn, MA).

5.1.2. A549 reporter assay. A549 human lung carcinoma cells were washed with OPTI-MEM I (Gibco). The medium was removed and lipid–DNA complex solution (1.5 μg/mL of GRE-luciferase reporter DNA in 8.5 mL OPTI-MEM I plus 6 μL/mL DMRIE-C reagent in 8.5 mL OPTI-MEM I, combined and mixed, then incubated at room temperature for 40 min) was overlayed onto the cells in a T160 flask. The cells were incubated for 16 h at 37 °C in a CO_2 incubator. The DNA-containing medium was removed and 30 mL of growth medium containing 5% (v/v) charcoal-treated fetal bovine serum was added. After 5–6 h, the cells were seeded in 96-well plates and incubated overnight at 37 °C. To each well were then added test compounds followed by dexamethasone as a corticoid challenge. The cells were incubated for 24 h. Luciferase assay buffer (Promega) was added to each well and the cells were incubated for 30 min at room temperature. Luciferase activity was measured in a DYNEX Microlite plate on a TopCount (Packard).

5.1.3. Rat complement C3 assay. Ovariectomized two-month-old Sprague–Dawley rats were purchased from Harlan (Indianapolis, IN). Five to seven days after surgery, the rats were dosed once with test compound or control. All of the animals received ethinyl estradiol at a dose of 0.3 mg/kg, administered orally as a suspension in sesame oil. In addition, the animals received a dose of 3 mg/kg medroxyprogesterone acetate (progestin agonist), given orally in 20% (w/v) hydroxyl-propyl-β-D-cyclodextrin. Test compounds were dosed orally in cyclodextrin, while this vehicle was used as the negative

control (no progestin antagonism). Mifepristone was given as a positive control for antagonism. About 24 h later, the rats were euthanized by carbon dioxide asphyxiation. Whole uteri were removed, trimmed of fat, and frozen on dry ice prior to storage at −80 °C. The uteri were homogenized in 1–2 mL each of TRIzol (Invitrogen Life Technologies, Carlsbad, CA); and the homogenates were processed for RNA preparation according to the manufacturer's directions. Quantitative PCR was performed using rat complement C3 primers and TaqMan probe from Applied Biosystems (Foster City, CA) and an ABI PRISM 7000 Sequence Detection System (Applied Biosystems). The level of 28S ribosomal RNA in each sample was determined for normalization, and a dilution series of one of the estrogen-treated samples was used to generate a standard curve. In Table 2, percent inhibition and ID_{50} data are shown. This is a measure of the extent of inhibition of the progestin effect by the antagonist. To calculate these values, uterus weight in the presence of estradiol plus the agonist was set at 0% inhibition (baseline for an antagonist), and uterus weight in the presence of estradiol alone was set at 100% inhibition.

5.2. General information for chemistry

^{1}H NMR spectra were obtained at 400 MHz and 300 MHz on Brucker AVANCE300 and AVANCE400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Thin-layer chromatography was carried out using 2.5 × 7.5-cm silica gel 60 (250 μM layer) plates with UV detection. Magnesium sulfate was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM science silical gel 60 (230–400 mesh). Standard solvents from J. T. Baker were used as received. Anhydrous solvents from J. T. Baker or Aldrich and all other commercially available reagents were used without further purification. Mass spectra were obtained on a Hewlett-Packard 5989A quadrupole mass spectrometer. Silica gel (E. Merck, 230–400 mesh) was used for all flash chromatography. Thin-layer chromatography was performed on Analtech silica gel GF prescored plates (250 μm). HPLC analysis was carried out on Agilent 1100 Series LC/MSD equipment.

5.2.1. Spiro[estra-5(10),9(11)-diene-17,2′(3′H)-furan]-3,3′-dione,4′,5′-dihydro-, cyclic 3-(1,2-ethanediyl acetal), (17β)-(9CI) (14). Compound **14** was prepared from ethylene deltanone (**11**) in 3 steps according to the procedure reported in Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, 7746–7747.

5.2.2. 19,24-Dinorchola-5(10),9(11),20-trien-3-one, 17,23-epoxy-, cyclic 1,2-ethanediyl acetal, (17α)-(9CI) (15). This compound was prepared according to the procedure reported in Hamersma, J. A.; Orlemans, E. O. M.; Rewinkel, J. B. M. EP0582338A2.

5.2.3. 19,24-Dinorchola-9(11),20-dien-3-one, 5,10:17,23-diepoxy-, cyclic 1,2-ethanediyl acetal, (5α,10α,17α)-(9CI) (16). A solution of compound **15** (4.0 g, 10.85 mmol) in dichloromethane (40 mL) was prepared in a 500-mL round-bottomed flask. To this solution was added sodium bicarbonate (5.38 g, 64.0 mmol) and the mixture was cooled to less than −40 °C under nitrogen using a dry ice-acetone bath. A solution of *m*CPBA (75%, 2.87 g, 12.48 mmol) in dichloromethane (40 mL) was prepared and added to the reaction mixture in portions via syringe. The reaction mixture was stirred at less than −40 °C for half an hour, then stirred in an ice bath for half an hour. The reaction mixture was partitioned in a mixture of ice water/dichloromethane (1:1). After stirring, the layers were separated upon melting of the ice and the aqueous layer was extracted twice with dichloromethane. The organic layers were washed with saturated sodium bicarbonate, water, brine, dried, filtered, and evaporated to provide a clear oil that later solidified. The material was purified by column chromatography (5–30% ethyl acetate/hexane) to provide desired product as a white solid (1.6 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (br s, 1H), 5.03 (s, 1H), 4.79 (s, 1H), 3.96–3.75 (m, 6H), 2.64–2.60 (m, 2H), 2.43 (m, 1H), 2.17–1.12 (m, 17H), 0.87 (s, 3H); MS (*m*/*e*): 385 (MH^+).

5.2.4. 19,24-Dinorchola-9,20-dien-3-one, 11-[4-(2-tetrahydro-2-*H*-pyranoxy)phenyl]-17,23-epoxy-5-hydroxy-, cyclic 1,2-ethanediyl acetal, (5α,11β,17α)-(9CI) (17). Copper (I) chloride (257 mg, 2.60 mmol) was weighed into a 100-mL round-bottomed flask. After flushed with dry nitrogen and capped with septum, 4-(2-tetrahydro-2-*H*-pyranoxy)-phenylmagnesium bromide (0.5 M in THF) (10.4 mL, 5.20 mmol) was added via syringe under nitrogen. Solution was stirred vigorously for 1–3 min until a cloudy, white solution resulted. Immediately, a solution of compound **16** (1.0 g, 2.60 mmol) in THF (15 mL) was added. The mixture was stirred for 1 h and then was quenched by adding aqueous saturated ammonium chloride solution and was extracted twice with ethyl acetate. The organic extracts were washed with water, brine, dried, filtered, and evaporated to a residue. The residue was purified by column chromatography (5–40% ethyl acetate/hexane) to afford desired product as a white solid (0.77 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.34 (m, 1H), 5.08 (s, 1H), 4.82 (s, 1H), 4.35 (s, 1H), 4.15 (s, 1H), 4.0–3.89 (m, 5H), 3.81–3.76 (m, 2H), 3.60 (m, 1H), 2.63 (m, 2H), 2.40–1.24 (m, 24H), 0.53 (s, 3H); MS (*m*/*e*): 585 (MNa^+), 545$(M-H_2O)^+$.

5.2.5. 19, 24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-hydroxyphenyl)-, (11β,17α)-(9CI) (18). A solution of compound **17** (100 mg, 0.178 mmol) in acetone (10 mL) was prepared. Oxalic acid (22 mg, 0.178 mmol) was added. The reaction mixture was heated to reflux. After 1 h, an additional amount of oxalic acid (17 mg) was added and refluxed for one more hour. Water was added and the solution was extracted twice with ethyl acetate. The organic extracts were dried, filtered, and evaporated to yield a white solid. The crude material was purified by column chromatography (5–50% ethyl acetate/hexane) to afford a white solid (58 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.5 Hz, 2H), 6.73 (dd, J = 1.9 and 6.7 Hz, 2H), 5.77 (s, 1H), 5.44 (s, 1H), 5.13 (s, 1H), 4.84 (s, 1H), 4.23 (d, J = 7.1

Hz, 1H), 3.87–3.80 (m, 2H), 2.69–1.24 (m, 18H), 0.59 (s, 3H); MS (*m/e*): 439 (MNa^+), 417 (MH^+).

5.2.6. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-trifluoromethanesulfonyloxyphenyl)-, (11β,17α)-(9CI) (19). To a dry flask containing NaH (35 mg, 60% in mineral oil, 0.864 mmol) was added a solution of compound **18** (0.24 g, 0.576 mmol) in THF (20 mL) slowly. The solution was cooled in a dry-ice acetone bath under nitrogen. After 30 min, *N*-phenyl-trifluoromethane-sulfonimide (309 mg, 0.864 mmol) in THF (3 mL) was added. After 35 min, the mixture was slowly warmed to room temperature. This was stirred until reaction was completed, monitored by TLC and HPLC. Brine was added followed by ethyl acetate. The aqueous layer was extracted with ethyl acetate and the organic layers were washed with brine, dried, filtered, and evaporated. The crude material was purified by column chromatography (5–30% ethyl acetate/hexane) to afford a white solid (250 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 4H), 5.79 (s, 1H), 5.15 (t, J = 1.8 Hz, 1H), 4.86 (s, 1H), 4.32 (d, J = 7.1, 1H), 3.87–3.77 (m, 2H), 2.72–2.56 (m, 5H), 2.48–1.24 (m, 13H), 0.54 (s, 3H); MS (*m/e*): 549 (MH^+), 571 (MNa^+).

5.2.7. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-(diethoxy-phosphorylphenyl)-, (11β,17α)-(9CI) (20a). The title compound was prepared as a white solid (20 mg, 41%) according to the procedure for compound **20b**, starting from compound **19** (50 mg, 0.091 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.2 and 12.0 Hz, 2H), 7.28–7.26 (m, 2H), 5.78 (s, 1H), 5.14 (s, 1H), 4.86 (s, 1H), 4.34 (d, J = 7.3 Hz, 1H), 4.17–4.05 (m, 4H), 3.85–3.79 (m, 2H), 2.70–2.58 (m, 5H), 2.49–1.24 (m, 19H), 0.53 (s, 3H); MS (*m/e*): 536 (MH^+), 559 (MNa^+).

5.2.8. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-(dimethyl-phosphorylphenyl)-, (11β,17α)-(9CI) (20b). A mixture was prepared consisting of compound **19** (150 mg, 0.273 mmol), dimethylphosphine oxide (43 mg, 0.547 mmol), palladium (II) acetate (6.1 mg, 0.0273 mmol), 1,4-bis(diphenylphosphino)butane (17 mg, 0.041 mmol), diisopropylethylamine (0.19 mL, 1.092 mmol), and dioxane (3.5 mL). The mixture was reacted using a CEM microwave utilizing the P150 program at 150 °C for 30 min. The reaction was completed by LC-MS. The orange solution was poured onto water and extracted twice with ethyl acetate. The organic extracts were washed with brine, dried, filtered, and evaporated. The residue was purified by column chromatography (5–40% methanol/ethyl acetate) to afford a white solid (65.6 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (dd, J = 8.5 and 11.4 Hz, 2H), 7.31–7.26 (dd, J = 2.0 and 8.3 Hz, 2H), 5.78 (s, 1H), 5.15 (t, J = 1.8 Hz, 1H), 4.86 (s, 1H), 4.34 (d, J = 7.0 Hz, 1H), 3.85–3.79 (m, 2H), 3.49 (m, 1H), 2.73–2.53 (m, 5H), 2.49–0.80 (m, 18H), 0.55 (s, 3H); MS (*m/e*): 477 (MH^+), 500 (MNa^+).

5.2.9. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-(dimethoxy-phosphorylphenyl)-, (11β,17α)-(9CI) (20c). The title compound was prepared as a white solid according to the procedure for compound **20b** in 63.4% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H), 7.21 (m, 2H), 5.71 (s, 1H), 5.12 (s, 1H), 4.81 (s, 1H), 4.31 (d, 1H, J = 5.9 Hz), 3.75 (m, 8H), 3.5 (s, 1H), 2.68–1.38 (m, 17H), 0.52 (s, 3H); MS (*m/e*): 509(MH^+), 531 (MNa^+), 1017 ($2MH^+$).

5.2.10. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-(hydroxy-methoxy-phosphorylphenyl)-, (11β,17α)-(9CI) (20d). Compound **20c** (80 mg, 0.157 mmol) in *t*-BuOH (2.4 mL) and water (1.2 mL) with LiOH (8 mg, 0.314 mmol) was stirred at 80 °C for 2.5 h. The resulted solution was partitioned between ethyl acetate/water (50 mL:50 mL). The organic layer was dried and concentrated. The resulted crude material was purified by preparative TLC (30% methanol/dichloromethane) to provide desired product (14 mg, 19%). ^{1}H NMR δ (CD_3OD) 7.70 (m, 2H), 7.21 (m, 2H), 5.70 (s, 1H), 5.18 (s, 1H), 4.42 (d, 1H, J = 5.8 Hz), 3.80 (m, 3H), 3.42 (m, 4H), 2.78–1.08 (m, 17H), 0.58 (s, 3H); MS (*m/e*): 495(MH^+), 517 (MNa^+), 1011 ($2MNa^+$).

5.2.11. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-(ethoxy-methyl-phosphinoyl)phenyl]-, (11β,17α)-(9CI) (20e). The title compound was prepared as a white solid according to the procedure for compound **20b** in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.29 (m, 2H), 5.79 (s, 1H), 5.18 (s, 1H), 4.86 (s, 1H), 4.36 (d, 1H, J = 5.7 Hz), 4.08 (m, 2H), 3.82 (m, 2H), 3.4 (s, 1H), 2.71–1.22 (m, 23H), 0.52 (s, 3H); MS (*m/e*): 507 (MH^+), 529 (MNa^+); HRMS: calcd MH^+ for $C_{31}H_{39}O_4P$ 507.2664; found 507.2666.

5.2.12. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-(hydroxy-methyl-phosphinoyl)phenyl]-, (11β,17α)-(9CI) (20f). The title compound was prepared as a white solid according to the procedure for compound **20d** in 34% yield. ^{1}H NMR (CD_3OD) 7.68 (m, 2H), 7.21 (m, 2H), 5.72 (s, 1H), 5.68 (s, 1H), 4.42 (d, 1H), 3.80 (m, 2H), 2.78–1.29 (m, 22H), 0.56 (s, 3H); MS (*m/e*): 477 (MH^-), 501 (MNa^+); HRMS: calcd MH^+ for $C_{29}H_{35}O_4P$ 479.2351; found 479.2361.

5.2.13. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-[bis-(2,2,2-trifluoro-ethoxy)-phosphoryl]-phenyl]-, (11β,17α)-(9CI) (20 g). The title compound was prepared as a white solid (107 mg, 30%) according to the procedure for compound **20b**, starting from compound **19** (300 mg, 0.547 mmol). ^{1}H NMR ($CDCl_3$) δ 7.72 (m, 2H), 7.32 (m, 2H), 5.75 (s, 1H), 5.13 (s, 1H), 4.83 (s, 1H), 4.45 (m, 5H), 3.81 (m, 2H), 2.71–1.34 (m, 18H), 0.52 (s, 3H); MS (*m/e*): 645 (MH^+), 667 (MNa^+); HRMS: calcd MH^+ for $C_{32}H_{35}F_6O_5P$ 645.2205; found 645.2171.

5.2.14. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-(diphenyl-phosphinoyl)-phenyl]-, (11β,17α)-(9CI) (20h). The title compound was prepared as a white solid product (104 mg, 47%), according to the procedure for compound **20b**, starting from compound **19** (200 mg, 0.365 mmol). ^{1}H NMR ($CDCl_3$) δ 8.02 (m, 2H), 7.62–7.42 (m, 12H), 5.72 (s, 1H), 5.12 (s, 1H), 4.82 (s, 1H), 4.33 (d, 1H, J = 5.9 Hz), 3.81 (m, 2H), 2.71–1.42 (m, 18H), 0.52 (s, 3H); MS (*m/e*): 601 (MH^+), 623 (MNa^+); HRMS: calcd MH^+ for $C_{40}H_{41}O_3P$ 601.2872; found 601.2855.

5.2.15. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-[bis-(4-chloro-phenyl)-phosphinoyl]-phenyl]-, (11β,17α)-(9CI) (20i). The title compound was prepared as a white solid (155 mg, 42%) according to the procedure for compound **20b**, starting from compound **19** (300 mg, 0.547 mmol). ^{1}H NMR δ ($CDCl_3$) 7.62–7.28 (m, 12H), 5.72 (s, 1H), 5.13 (s, 1H), 4.83 (s, 1H), 4.32 (d, 1H, J = 6.2 Hz), 3.53 (m, 2H), 2.68–1.38 (m, 18H), 0.52 (s, 3H); MS (*m*/*e*): 669 (MH^+), 691 (MNa^+); HRMS: calcd MH^+ for $C_{40}H_{39}Cl_2O_3P$ 669.2092; found 669.2085.

5.2.16. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-(4-(diphenoxy-phosphorylphenyl)-, (11β,17α)-(9CI) (20j). The title compound was prepared as a white solid (160 mg, 46%), according to the procedure for compound **20b**, starting from compound **19** (300 mg, 0.547 mmol). ^{1}H NMR ($CDCl_3$) δ 7.82 (m, 2H), 7.28–7.08 (m, 12H), 5.72 (s, 1H), 5.14 (s, 1H), 4.82 (s, 1H), 4.32 (d, 1H, J = 5.8 Hz), 3.82 (m, 2H), 2.71–1.41 (m, 18H), 0.51 (s, 3H); MS (*m*/*e*): 633 (MH^+), 655 (MNa^+); HRMS: calcd MH^+ for $C_{40}H_{41}O_5P$ 633.2770; found 633.2744.

5.2.17. 19,24-Dinorchola-4,9,20-trien-3-one, 17,23-epoxy-11-[4-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-phenyl]-, (11β,17α)-(9CI) (20k). The title compound was prepared as a white solid (100 mg, 33%), according to the procedure for compound **20b**, starting from compound **19** (300 mg, 0.547 mmol). ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 2H), 7.28 (m, 2H), 5.78 (s, 1H), 5.12 (s, 1H), 4.82 (s, 1H), 4.32 (m, 3H), 3.85 (m, 5H), 2.72–1.35 (m, 17H), 1.18 (s, 3H), 1.02 (s, 3H), 0.55 (s, 3H); MS (*m*/*e*): 549 (MH^+), 571 (MNa^+); HRMS: calcd MH^+ for $C_{33}H_{41}O_5P$ 549.2770; found 549.2745.

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