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Synthesis of bone-targeted oestrogenic compounds for the inhibition of bone resorption

Philip C. Bulman Page,[a,*] Jonathan P. G. Moore,[a] Ian Mansfield,[a] Michael J. McKenzie,[a] Wayne B. Bowler[b] and James A. Gallagher[b]

[a]*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*
[b]*Department of Human Anatomy and Cell Biology, University of Liverpool, Liverpool L69 3GE, UK*

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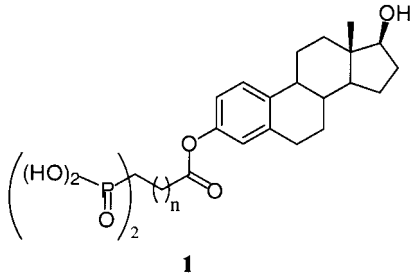
Abstract—Syntheses have been realised for several members of a new class of potential bone resorption inhibitors consisting of steroidal oestrogenic compounds linked at the 17 position to a geminal bis(phosphonic acid) moiety through an ester linkage. The approach used has the potential to allow other biologically active compounds to be coupled to the geminal bisphosphonate unit.

1. Introduction

Geminal bisphosphonates are stable pyrophosphate analogues that bind efficiently to bone surface.[1] They have been used in the clinic to inhibit bone resorption, in most cases with few side effects.[2] Some simple examples, for example etidronate and alendronate, are already marketed for the treatment of osteoporosis and Paget's disease.[3] It has been suggested that bisphosphonates are general metabolic inhibitors.[4] The low level of side effects has been attributed to the rapid absorption of the geminal bisphosphonate to the bone surface and incorporation within the bone matrix, thereby preventing undesired effects within other organs.[2] Other clinically used treatments for osteoporosis, such as hormone replacement threrapy, are effective, but can have effects on other tissues.[5] We are interested in using geminal bisphosphonates as bone-targeting moieties for the treatment of bone-related disease;[6] our aim is to use the bone tropism to deliver therapeutics at the desired site of action, thus reducing unwanted side effects in other tissues. We report here the synthesis of geminal bisphosphonic acids functionalized with derivatives of oestradiol, an osteoclast inhibitor known to regulate the circuitry of cytokine action that controls bone remodelling.[7]

In the design of such compounds it is vital to consider the linkage between the geminal bisphosphonate moiety and the oestrogenic unit. A conjugate with a linker not readily cleaved by hydrolysis or by enzyme action may not retain oestrogenic activity, while a conjugate with a linker too readily cleaved would not achieve targeting. Oestrogen–bisphosphonate conjugates are known with non-hydrolysable linkers,[8] and with ether,[9] carbonate,[10] and amide[11] linkers. Cortisone–bisphosphonate conjugates are known with ester linkers.[12] We reasoned that a carboxylic ester linkage might provide an appropriate balance between stability and ease of cleavage, and, further, that this balance might be adjusted by, for example altering the steric environment around the ester unit. In the case of oestradiol, such an ester linkage might readily be positioned at either the 3- or 17-hydroxylated positions as in **1** or **2**, and this design would in addition allow the incorporation of other hydroxyl functionalized biologically active compounds.



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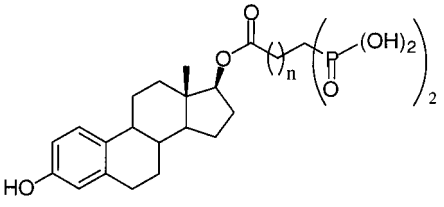

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Keywords: oestrogen; bisphosphonate; targeting.

* Corresponding author. Tel.: +1509-222581; fax: +1509-223926; e-mail: p.c.b.page@lboro.ac.uk

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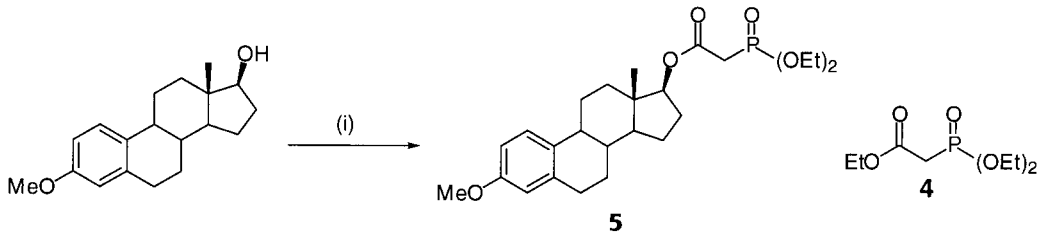
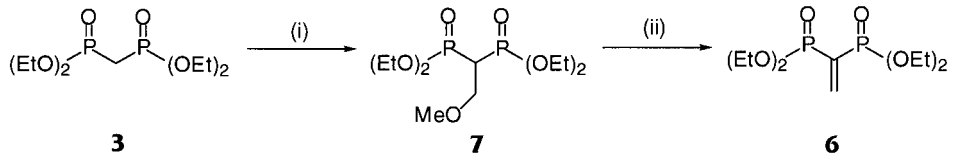


Scheme 1. (i) DMAP, toluene, Δ, 4 d; 63%.



Scheme 2. (i) Et_2NH, $(CH_2O)_n$, MeOH, Δ; (ii) cat. TsOH, toluene, Δ, 24 h; 88% overall.

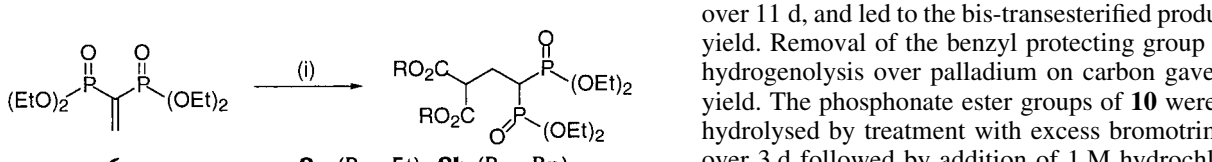
2. Results and discussion

The methylene unit of simple methylene bisphosphonates such as **3** is readily deprotonated,[13] but the anions are correspondingly poorly reactive in nucleophilic substitution,[14] and it was therefore necessary to add a functional group to the geminal bisphosphonate, which could be used in a subsequent coupling step. Our feasibility studies using triethyl phosphonoacetate **4** showed that it is possible to carry out a transesterification selectively at the carboxylic ester of **4** with the 17-hydroxy group of 3-*O*-methyl-17β-oestradiol to give **5** in 63% yield (Scheme 1). However, transesterification of **4** did not occur with the phenolic 3-hydroxy group of oestrone under similar conditions.

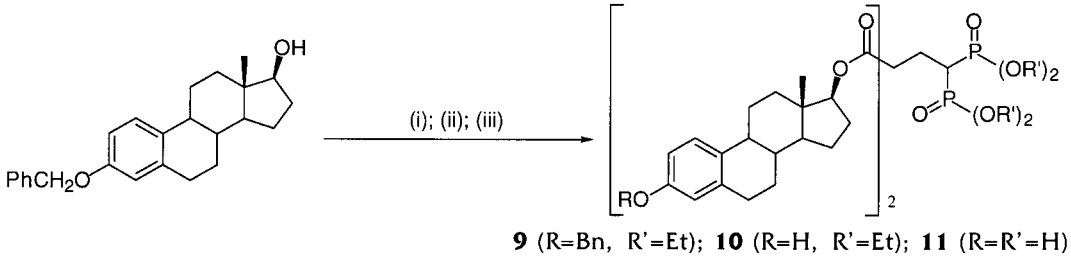
Ethylidene bisphosphonate **6** was identified as a key intermediate, and was prepared in multigramme quantities from tetraethyl methylene bisphosphonate **3** by the method of Degenhardt.[15] Treatment with paraformaldehyde and diethylamine in methanol produced β-methoxyethylene 1,1-bisphosphonate **7**, which was dehydrated under Dean–Stark conditions to give **6** in 88% overall yield (Scheme 2).

A tetraethyl geminal bisphosphonate containing a diethyl malonate unit **8a** was generated in 95% yield by Michael addition of the malonate anion to ethylidene bisphosphonate **6** induced by sodium ethoxide in ethanolic solution at room temperature (Scheme 3).[16,17] The dibenzyl analogue **8b** was prepared similarly, in 58% yield, from dibenzyl malonate.

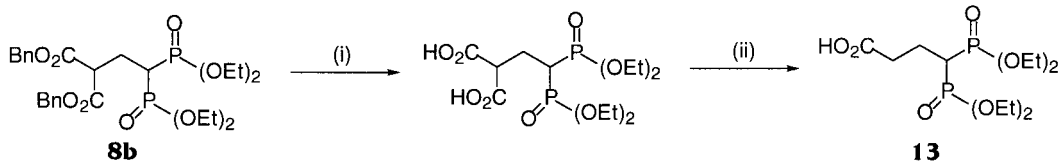
Benzyl ether protection of the 3-hydroxy group of 17β-oestradiol was chosen to allow for easy and selective removal at a later stage of the synthesis. Oestrone was converted into its methyl and benzyl ethers and the ketone groups reduced with sodium borohydride in methanol to give the protected 17β-oestradiols after separation from the 17α-isomer contaminants.[18] Chemoselective transesterification of both the carboxylic esters of intermediate **8a** with 3-*O*-benzyl-17β-oestradiol took place in toluene solution under reflux in the presence of 4,4-dimethylaminopyridine over 11 d, and led to the bis-transesterified product **9** in 67% yield. Removal of the benzyl protecting group by catalytic hydrogenolysis over palladium on carbon gave **10** in 96% yield. The phosphonate ester groups of **10** were selectively hydrolysed by treatment with excess bromotrimethylsilane over 3 d followed by addition of 1 M hydrochloric acid to the reaction mixture;[19] the product bis(phosphonic acid) **11** precipitated in excellent yield (Scheme 4). Intermediate **8a** was similarly bis-transesterified with testosterone (82%)



Scheme 3. (i) 0.1 equiv. NaOEt, diethyl or dibenzyl malonate, EtOH, rt, 15 min.

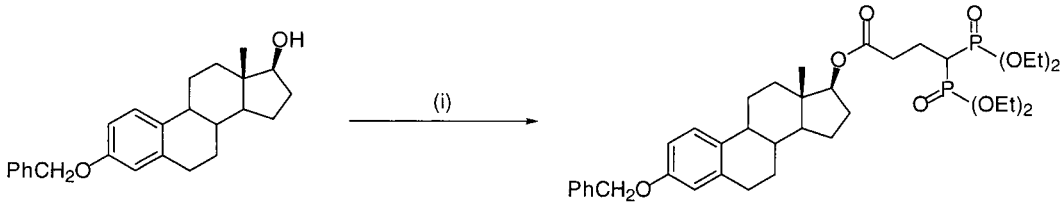


Scheme 4. (i) **8a**, 0.1 equiv. DMAP, toluene, Δ, 11 d, 67%; (ii) H_2, 10% Pd/C, THF–MeOH, 6 h, 96%; (iii) 35 equiv. TMSBr, $CHCl_3$–CCl_4, rt, 1–3 d; H_3O^+, 94%.



8b **13**

Scheme 5. (i) H_2, Pd/C; THF, overnight, 88%; (ii) Δ 130°C, 3 h, 99%.



15 **14**

Scheme 6. (i) **13**, 1.0 equiv. EDCI, 0.5 equiv. DMAP, DCM, 0°C, rt overnight, 33%.

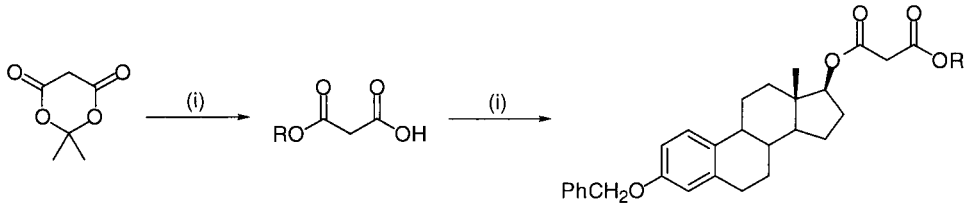
and the phosphonate ester groups hydrolysed (72%) to give the bis(phosphonic acid).

The analogous bis(phosphonic acid) **12**, containing a single carboxylic ester unit, is a less sterically hindered and so potentially more readily hydrolysable conjugate. The bisphosphonate mono-carboxylic acid **13** was produced from **8a** according to the method of Sturtz in 27% yield by basic hydrolysis and decarboxylation induced by heating.[17] In a superior procedure, hydrogenolysis of the benzyl esters of **8b** (88%) followed by decarboxylation induced by heating (99%) led to **13** as a much cleaner material (Scheme 5).

An alternative coupling procedure was next sought which would avoid the lengthy transesterification process, and which might also allow coupling at the 3-position of oestrone. Coupling of 3-*O*-benzyl-17β-oestradiol **15** to acid **13** to give ester **14** was successfully achieved using EDCI as dehydrating agent in 2 h at 0°C (Scheme 6).[20]

In order to provide a range of steroidal bisphosphonate conjugates with a spectrum of lability towards hydrolysis in vivo, we wished to prepare mixed malonyl derivatives of geminal bisphosphonic acids. The need for an efficient and general synthesis seemed to us to dictate an alternative strategy involving initial generation of mixed malonates followed by incorporation of the bisphosphonate unit (Scheme 6).

Attempted functionalization of 3-*O*-benzyl-17β-oestradiol **15** with malonyl dichloride or ethyl malonyl chloride proved unsuccessful. With a view to utilising a carbodiimide coupling, ethyl malonic half ester **16a** was prepared from



16 **17**

Scheme 7. (i) ROH, MeCN, Δ; (ii) **15**, DCC, DMAP, CH_2Cl_2 or MeCN, rt.

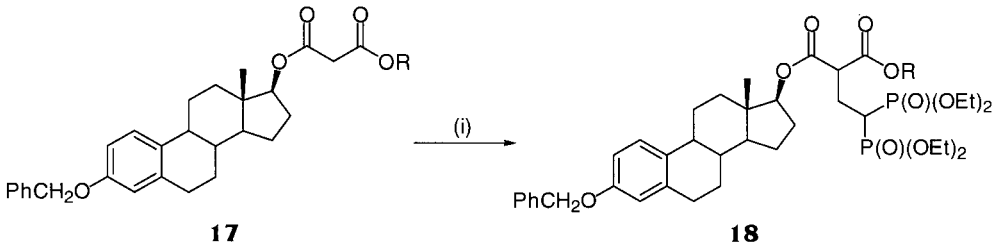
Table 1. Preparation and coupling of malonic half esters

Entry	ROH	Yield of **16** (%)	Yield of **17** (%)
a	EtOH	[a]	46
b	4-$NO_2C_6H_4OH$	97	69
c	MeOH	65	68
d	*i*-PrOH	100[b]	69
e	*t*-BuOH	54	15
f	PhOH	34	92
g	**15**	49	–

[a] Prepared by the method of Strube.[21]
[b] Crude yield.

diethyl malonate by the method of Strube,[21] and coupled to 3-*O*-benzyl-17β-oestradiol to give mixed malonate **17a** using DCC. A more efficient preparation of mixed malonates **17b–f** was realised through addition of a range of alcohols to Meldrum's acid in acetonitrile under reflux to give malonic half esters **16b–g** (Scheme 7, Table 1);[22] DCC-mediated coupling of 3-*O*-benzyl-17β-oestradiol to **16b–f** took place in dichloromethane solution, providing mixed malonates **17b–f**.

After some experimentation, deprotonation of **17a–d** and conjugate addition to tetraethyl ethylidene bisphosphonate



17 18

Scheme 8. (i) LHMDS, THF; **6**, 60°C, 18 h.

Table 2. Preparation of bisphosponate conjugates

Entry	ROH	Yield of **18** (%)
a	EtOH	30
b	4-$NO_2C_6H_4OH$	24
c	MeOH	57
d	*i*-PrOH	40

6 was achieved to produce **18a–d**, each as a ca 1:1 mixture of diastereoisomers, for example using lithium hexamethyldisilazide as base at 60°C in THF solution (Scheme 8, Table 2). Similar transformation could not be achieved for the other mixed malonates.

Selective hydrogenolysis of the benzyl ether of **18b** did not prove possible, but hydrogenolyses of the benzyl ethers of **18a** and **c** to give the phenols **19a** and **c** (80 and 79% yields, respectively), and subsequent phosphonate ester hydrolyses (100 and 70% yields, respectively), were carried out as described above for bis-carboxylic ester **9**, to provide the corresponding bisphosphonic acids **20a** and **c** (Scheme 9).

3. Conclusions

Several members of a new class of potential bone resorption inhibitors have been prepared, consisting of steroidal units linked at the **17** position to a geminal bis(phosphonic acid) moiety through ester linkages. The synthesis utilises chemoselective reactions at a carboxylic ester and selective phosphonate ester hydrolysis, and has the potential to allow many oestrogen derivatives as well as other biologically active compounds to be coupled to the geminal bisphosphonate unit. Investigation of the biological properties of the steroidal bis(phosphonic acid) conjugates is in progress.

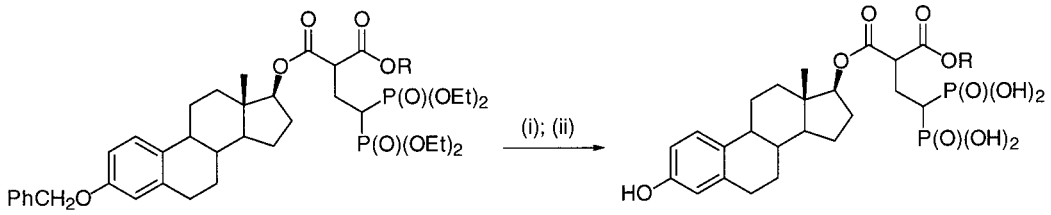
4. Experimental

4.1. General experimental detail

Light petroleum ether (bp 40–60°C) was distilled from calcium chloride. Ethyl acetate was distilled from phosphorus pentoxide or calcium chloride. Dichloromethane was distilled from phosphorus pentoxide or pentachloride. Tetrahydrofuran was distilled under a nitrogen atmosphere from the sodium/benzophenone ketyl radical or purchased from the Aldrich Chemical Company in sure seal containers. Toluene was distilled from calcium hydride. Ethanol was distilled from calcium hydride or stored over sodium ethoxide and distilled prior to use. Methanol was distilled from calcium hydride or stored over sodium methoxide and distilled prior to use. Triethylamine, pyridine and diethylamine were stored over potassium hydroxide pellets and distilled prior to use. *N*-Bromosuccinimide was recrystallized from water and dried under high vacuum. Commercially available reagents were used as supplied, without further purification, unless otherwise stated.

Microanalyses were performed on Carlo Erba Model 1106 or Perkin–Elmer 2400 instruments. Optical rotation values were measured with an Optical Activity-polAAar 2001 instrument, operating at 589 nm, at the temperatures indicated. Melting points were carried out on an Electrothermal-IA 9100 or a Kofler block apparatus and are uncorrected.

Infrared absorption spectra were recorded on a Perkin–Elmer Paragon 2001 or 883 LR, or Nicolet 205 FT-IR spectrophotometers in the range 4000–600 cm^{-1}, and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Liquids were run as thin films, and solids as Nujol mulls on sodium chloride plates, or as solutions in chloroform or methanol. Mass spectra were recorded using Kratos MS-80, VG Analytical 7070E, or Jeol-SX102 instruments using EI, CI, and FAB ionization techniques, a Fisons



18a (R = Et); **18c** (R = Me) **20a** (R = Et); **20c** (R = Me)

Scheme 9. (i) H_2, Pd/C, 60 psi, CH_2Cl_2; (ii) 8 equiv TMSBr, CH_2Cl_2, 2.5 d; MeOH, 30 min.

Instrument Trio 1000 quadrapole instrument, or by the EPSRC National Service. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on Bruker AC 200, AC 250, AMX 400 or DPX 400 instruments.

4.2. Procedures

4.2.1. 17β-(3-Methoxy-1,3,5-oestratrienyl) 2-(diethylphosphono)acetate 5. Triethyl phosphonoacetate (0.039 g, 0.175 mmol), 3-methoxy-17β-oestradiol (0.100 g, 0.349 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.006 g, 0.052 mmol), were heated under reflux in toluene (10 mL) for 4 d. The resulting mixture was washed with water (100 mL), and the product extracted into CH_2Cl_2 (100 mL). The organic layer was collected and concentrated under reduced pressure, and the crude product purified by column chromatography on silica gel, using 25–75% ethyl acetate–petroleum ether (40–60°C) as eluent to give **5** as a colourless oil (0.05 g, 63%); ν_{max} 2970, 1710, 1600, 1575, 1495, 1030 and 980 cm^{-1}; δ_H ($CDCl_3$) 0.79 (3H, s), 1.15–1.87 (11H, m), 1.29 (6H, t, J=7 Hz), 2.05–2.34 (3H, m), 2.74–2.86 (2H, m), 2.94 (2H, d, J_{P-H}=22 Hz), 3.70 (3H, s), 4.03–4.19 (4H, m), 4.68 (1H, t, J=9 Hz), 6.57 (1H, s), 6.64 (1H, dd, J=9, 3 Hz), and 7.13 (1H, d, J=9 Hz); *m/z* (EI) 464 (89) (M^+), 268 (24), 179 (100), and 160 (68); Found: 464.2324. $C_{25}H_{37}PO_6$ requires: 464.2328.

4.2.2. Tetraethyl ethylidene bisphosphonate 6. Tetraethyl methylene bisphosphonate (47.4 g, 0.165 mol), paraformaldehyde (24.75 g, 0.825 mol), and diethylamine (17.1 mL, 12.1 g, 0.165 mol) were added to methanol (470 mL). The reaction mixture was heated under reflux until it became a colourless solution (ca 30 min), and stirred for further 15 h at room temperature. The mixture was concentrated under reduced pressure, and toluene (150 mL) added. The solvent was removed under reduced pressure, and the concentration–evaporation process repeated a second time. This procedure was performed in order to remove any residual methanol from the crude viscous intermediate. The 2-methoxyethylene 1,1-bisphosphonate intermediate **7** was isolated as a viscous clear oil; purification at this stage was not required and the product was used in its crude form; δ_H ($CDCl_3$) 1.29 (12H, t, J=8 Hz), 2.67 (1H, tt, J_{P-H}=24 Hz, J_{H-H}=5 Hz), 3.32 (3H, s), 3.86 (2H, td, J_{P-H}=17 Hz, J_{H-H}=5 Hz), and 4.15 (8H, m).

Toluene-*p*-sulfonic acid (0.15 g) was added to a solution of the crude tetraethyl 2-methoxyethylene 1,1-bisphosphonate **7** in toluene (250 mL). The reaction mixture was heated under reflux overnight. The reaction mixture was washed with water (3×100 mL), the organic layer dried over $MgSO_4$, and the solvent removed under reduced pressure to yield **6** as an oil (43.16 g, 88% overall); ν_{max} 3020, 2960, 1485, 1452, 1402, 1270, and 1050 cm^{-1}; δ_H ($CDCl_3$) 1.30 (12H, t, J=8 Hz), 4.0–4.2 (8H, m), and 6.94 (2H, dd, *trans* J_{P-H}=40, *cis* J_{P-H}=36 Hz); δ_C ($CDCl_3$) 16.15 (t, J=3 Hz), 63.08 (d, J=3 Hz), 132.58 (t, J=127 Hz) and 149.11; δ_P ($CDCl_3$) 11.6; *m/z* (CI) 301.0970 $(M+H)^+$; $C_{10}H_{22}O_6P_2$ requires 301.0970.

4.2.3. Tetraethyl 3,3-bis(ethoxycarbonyl)propylene bisphosphonate 8a. Sodium (0.23 g, 10 mmol) was dissolved in ethanol (100 mL) and stirred at 0°C under a nitrogen atmosphere. The mixture was allowed to reach room temperature and stirred until all the sodium had dissolved. The sodium ethoxide solution so prepared was transferred via a cannula to a mixture of **6** (30.0 g, 100 mmol) and diethyl malonate (15.20 mL, 16.02 g, 100 mmol) in ethanol (50 mL). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 30 min, washed with aqueous HCl (1 M, 3×100 mL) and extracted with CH_2Cl_2 (200 mL). The organic layer was dried over $MgSO_4$, the solvent removed under reduced pressure, and final traces of solvent removed under high vacuum to give **8a** as a colourless oil (43.8 g, 95%). (Found: C, 43.97; H, 7.55; $C_{17}H_{34}O_{10}P_2$ requires: C, 44.35; H, 7.44); ν_{max} 3010, 1749, 1732, 1270, and 1045 cm^{-1}; δ_H ($CDCl_3$) 1.28 (6H, t, J=7 Hz), 1.35 (12H, t, J=7 Hz), 2.33–2.75 (3H, m), 3.97 (1H, t, J=8 Hz), and 4.12–4.27 (12H, m); δ_C ($CDCl_3$) 14.48, 16.71 (d, J_{C-P}=6 Hz), 25.29 (d, J_{C-P}=5 Hz), 34.71 (t, J_{C-P}=132 Hz), 50.51 (t, J_{C-P}=8 Hz), 61.97, 63.22 (t, J_{C-P}=8 Hz), and 169.31; δ_P ($CDCl_3$) 22.33; *m/z* (CI) 460.1632 (M^+); $C_{17}H_{34}O_{10}P_2$ requires 460.1627.

4.2.4. Oestrone methyl ether. Oestrone (1.00 g, 3.67 mmol) was dissolved in acetone (75 mL), and anhydrous K_2CO_3 (1.53 g, 11.1 mmol) and iodomethane (1.38 mL, 3.15 g, 22.2 mmol) were added. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 24 h. Aqueous HCl (1 M, 150 mL) was added and the reaction mixture extracted into CH_2Cl_2. The solvent was removed under reduced pressure and the crude product purified by flash column chromatography using 20% ethyl acetate–petroleum ether (40–60°C) as eluent. The product was obtained as a colourless powder (0.89 g, 85%); ν_{max} 2980, 1735, 1615, 1580, and 1510 cm^{-1}; δ_H ($CDCl_3$) 0.83 (3H, s), 1.26–1.68 (6H, m), 1.76–2.50 (7H, m), 2.77–2.88 (2H, m), 3.69 (3H, s), 6.57 (1H, d, J=3 Hz), 6.63 (1H, dd, J=8, 3 Hz), and 7.12 (1H, d, J=8 Hz); *m/z* (EI) 284 (100), 199 (75), 160 (81); Found: 284.1780. $C_{19}H_{24}O_2$ requires 284.1776.

4.2.5. 3-*O*-Methyl-17β-oestradiol. Oestrone methyl ether (0.50 g, 1.76 mmol) was dissolved in methanol (20 mL) and tetrahydrofuran (20 mL). Sodium borohydride (0.10 g, 2.64 mmol) was added. The reaction mixture was stirred for 2 h at room temperature under a nitrogen atmosphere. Water (100 mL) was added and the mixture extracted with CH_2Cl_2. The solvent was removed and the crude product purified by flash column chromatography, using 50% ethyl acetate–petroleum ether (40–60°C) as eluent. The product was obtained as a colourless powder (0.44 g, 87%); ν_{max} 3480, 2980, 1630, 1575, 1502, and 1470 cm^{-1}; δ_H ($CDCl_3$) 0.78 (3H, s), 1.10–2.55 (14H, m), 2.81–2.99 (2H, m), 3.73 (1H, t, J=8 Hz), 3.80 (3H, s), 6.63 (1H, m), 6.71 (1H, dd, J=8, 3 Hz), and 7.21 (1H, d, J=8 Hz); *m/z* (EI) 286 (41), 268 (23), 160 (72), and 147 (100); Found: 286.1938. $C_{19}H_{26}O_2$ requires: 286.1933.

4.2.6. Oestrone benzyl ether. Oestrone (10.0 g, 37.0 mmol and anhydrous K_2CO_3 (25.6 g, 185 mmol) were added to acetone (150 mL). Benzyl bromide (7.79 mL, 11.2 g, 65.4 mmol) was added slowly with stirring, the reaction mixture allowed to stir overnight at room temperature, filtered, and concentrated under reduced pressure. The

concentrate was dissolved in CH_2Cl_2 (200 mL) and washed with aqueous HCl (1 M, 3×100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was recrystallized from methanol and washed repeatedly with cold methanol to remove traces of benzyl bromide. The product was obtained as colourless crystals (9.47 g, 71%), mp 129–130°C; (Found: C, 83.2; H, 7.88. $C_{25}H_{28}O_2$ requires: C, 83.29; H 7.83%); ν_{max} 3012, 2936, 1730, 1606, and 1497 cm^{-1}; δ_H ($CDCl_3$) 0.92 (3H, s), 1.39–1.73 (6H m), 1.92–2.67 (7H, m), 2.85–2.95 (2H, m), 5.05 (2H, s), 6.75 (1H, d, *J*=2 Hz), 6.80 (1H, dd, *J*=6, 2 Hz), 7.22 (1H, d, *J*=6 Hz), and 7.33–7.46 (5H, m); δ_C ($CDCl_3$) 13.8, 21.6, 25.9, 26.5, 29.6, 31.7, 35.9, 38.3, 44.0, 48.0, 50.4, 69.9, 112.4, 114.9, 126.4, 127.4, 127.8, 128.5, 132.3, 137.2, 137.8, 156.8, and 221.0; *m/z* (EI) 360 (M^+) and 91 (100); Found: 360.2095, $C_{25}H_{28}O_2$ requires: 360.2089.

4.2.7. 3-*O*-Benzyl-17β-oestradiol 15. Sodium borohydride (2.36 g, 62.4 mmol) was added slowly at 0°C to a solution of oestrone benzyl ether **145** (7.50 g, 20.8 mmol) in CH_2Cl_2 (100 mL) and methanol (100 mL). The reaction mixture was stirred for 3 h under a nitrogen atmosphere and allowed to reach room temperature. Water (150 mL) was added and the mixture extracted with CH_2Cl_2 (200 mL) and washed with aqueous HCl (1 M, 3×100 mL). The organic layer was dried over $MgSO_4$. The solvent was removed and the crude product recrystallized from methanol to give colourless needles (6.70 g, 89%), mp 95°C; (Found: C, 82.97; H, 8.72. $C_{25}H_{30}O_2$ requires: C, 82.83; H, 8.34%); ν_{max} 3610, 2932, 1605, and 1453 cm^{-1}; δ_H ($CDCl_3$) 0.78 (3H, s), 1.10–2.38 (14H, m), 2.81–2.88 (2H, m), 3.32 (1H, dd, *J*=8, 9 Hz), 5.03 (2H, s), 6.71 (1H, d, *J*=3 Hz), 6.77 (1H, dd, *J*=7, 3 Hz), 7.20 (1H, d, *J*=8 Hz), and 7.28–7.46 (5H, m); δ_C ($CDCl_3$) 11.03, 23.10, 26.29, 27.20, 29.76, 30.54, 36.69, 38.82, 43.24, 43.95, 50.04, 69.96, 81.87, 112.28, 114.84, 126.32, 127.43, 127.80, 128.50, 132.95, 137.33, 138.02, and 156.72; *m/z* (FAB) 362.2240 (M^+); $C_{25}H_{30}O_2$ requires 362.2246.

4.2.8. Tetraethyl (3,3-bis(17β-(3-benzyloxyoestra-1,3,5-trienyl)oxycarbonyl)propylidene) bisphosphonate 9. 4-[(*N*,*N*-Dimethylamino)pyridine (0.013 g, 0.11 mmol) and 3-*O*-benzyl-17β-oestradiol (0.861 g, 2.39 mmol) were added to a solution of **8a** (0.50 g, 1.09 mmol) in toluene (10 mL). The reaction mixture was heated under reflux for 11 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the product purified by column chromatography on silica gel using 1–3% methanol–CH_2Cl_2 as eluent to give **9** as a colourless viscous oil (0.80 g, 67%); ν_{max} 3017, 2936, 1724, 1605, 1498, 1203, and 929 cm^{-1}; δ_H ($CDCl_3$) 0.84 (3H, s), 0.88 (3H, s),1.23–1.97 (21H, m), 1.35 (12H, t, *J*=7 Hz), 2.15–2.36 (13H, m), 4.72–4.81 (2H, m), 5.05 (4H, s), 6.74 (2H, s), 6.80 (d, 2H, *J*=9 Hz), 7.23 (d, 2H, *J*=9 Hz), and 7.30–7.47 (10H, m); δ_C ($CDCl_3$) 13.09, 13.20, 17.43, 17.51, 24.35, 26.19, 27.24, 28.29, 28.53, 30.82, 35.51 (t, J_{C-P}=132 Hz), 37.95, 44.15, 44.31, 44.84, 50.80, 51.38 (t, J_{C-P}=73 Hz), 63.83 (t, J_{C-P}=7 Hz), 71.00, 85.02 (d, J_{C-P}=10 Hz), 113.39, 115.92, 127.42, 128.49, 128.89, 129.59, 133.73, 138.39, 138.95, 157.84, and 169.96 (d, J_{C-P}=4 Hz); δ_P ($CDCl_3$) 20.4; *m/z* (FAB) 1092.5212 (M^+); $C_{63}H_{82}O_{12}P_2$ requires 1092.5282.

4.2.9. Tetraethyl (3,3-bis(17β-(3-hydroxyoestra-1,3,5-trienyl)oxycarbonyl)propylidene) bisphosphonate 10. 10% Pd–C (140 mg) was added to a solution of **9** (692 mg, 0.633 mmol) in 1:1 THF–MeOH (10 mL). The reaction mixture was shaken under an atmosphere of hydrogen (1 bar) for 6 h. The reaction mixture was filtered, CH_2Cl_2 added, and the solution washed with brine. The organic layer was collected, dried over $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using 3–5% MeOH–CH_2Cl_2 as eluent to give **10** as a foam (557 mg, 96%); (Found: C, 64.68; H, 7.76. $C_{49}H_{70}O_{12}P_2$ requires: C, 64.46; H, 7.73%); δ_H ($CDCl_3$) 0.775 (3H, s), 0.781 (3H, s), 1.15–1.87 (21H, m), 1.34 (12H, t, *J*=7 Hz), 2.09–2.33 (6H, m), 2.49 (2H, hept, *J*=8 Hz), 2.66 (1H, tt, J_{P-H}=24, J_{H-H}=7 Hz), 2.81 (4H, m), 4.05 (1H, t, *J*=8 Hz), 4.16–4.24 (8H, m) 4.71 (2H, q, *J*=9 Hz), 6.58 (2H, s), 6.66 (2H, d, *J*=8 Hz), and 7.08 (2H d, *J*=9 Hz); δ_C ($CDCl_3$) 11.93, 12.03, 16.29 (d, *J*=5 Hz), 23.22, 24.95, 26.16, 27.18, 27.37, 29.53, 34.17 (t, *J*=134 Hz), 36.81, 38.56, 42.98, 43.17, 43.68, 49.64, 50.23 (t, *J*=9 Hz), 63.06 (t, *J*=7 Hz), 83.95, 84.09, 112.77, 115.31, 126.22, 131.48, 131.53, 137.79, 154.23, and 168.84; δ_P ($CDCl_3$) 20.7 (s); *m/z* (FAB) 912.4743 (M^++H); $C_{49}H_{70}O_{12}P_2$ requires 912.4343.

4.2.10. 3,3-Bis-(17β-(3-hydroxy oestra-1,3,5-trienyl)oxycarbonyl)propylidene bis(phosphonic acid) 11. Trimethylsilyl bromide (1.24 mL, 1.47 g, 9.62 mmol) was added to a solution of **10** (250 mg, 0.275 mmol) in 1:1 CCl_4–$CHCl_3$ (3 mL) and the reaction mixture stirred for 24 h under a nitrogen atmosphere. Water (5 mL) was added. The off-white precipitate was removed by filtration, washed with cold water and CH_2Cl_2, and dried under high vacuum to give **11** as an off-white powder (206 mg, 94%); mp 180°C (dec); δ_H (CD_3OD) 0.85 (3H, s), 0.86 (3H, s), 1.20–2.05 (21H, m), 2.10–2.30 (5H, m), 2.38–2.50 (3H, m), 2.70–2.81 (4H, m), 4.08 (1H, t, *J*=7 Hz), 4.72 (2H, t, *J*=8 Hz), 6.47 (2H, d, *J*=2 Hz), 6.53 (2H, dd, *J*=9, 2 Hz), and 7.05 (2H, d, *J*=9 Hz); δ_C (CD_3OD) 12.64, 12.71, 24.22, 26.37, 27.44, 28.45, 28.52, 30.63, 36.79 (t, *J*=127 Hz), 38.16, 40.18, 44.28, 44.40, 45.10, 50.94, 52.04, 85.26, 85.34, 113.79, 116.08, 127.21, 132.36, 138.73, 155.94, and 170.49; δ_P (CD_3OD) 22.6; *m/z* (negative ion FAB) 799 (M^+-H, 100).

4.2.11. Tetraethyl (3,3-bis(17β-(androst-4-en-3-onyl)oxycarbonyl)propylidene)bisphosphonate. Testosterone (0.500 g, 1.73 mmol), **8a** (0.363 g, 0.788 mmol), and 4-(*N*,*N*-dimethylamino)pyridine were dissolved in toluene (7 mL) and heated under reflux under an atmosphere of nitrogen. After 10 d, further testosterone (0.250 g, 0.86 mmol) was added and the reaction mixture heated under reflux for 6 d, then washed with saturated aqueous ammonium chloride. The mixture was extracted with CH_2Cl_2, and the organic layer dried over $MgSO_4$. The solvent was removed under reduced pressure, and the product purified by column chromatography on silica gel using 3% methanol–CH_2Cl_2 as eluent. The product was isolated as a foam (0.61 g, 82%); δ_H ($CDCl_3$) 0.76 (3H, s), 0.78 (3H, s), 0.80–1.80 (20H, m), 1.12 (6H, s), 1.28 (12H, t, *J*=7 Hz), 1.94–1.98 (2H, m), 2.05–2.57 (13H, m), 3.94 (1H, t, *J*=8 Hz), 4.58 (2H, q, *J*=8 Hz), and 5.66 (2H, s); δ_C ($CDCl_3$) 11.91, 12.02, 16.31,

16.42, 17.39, 20.49, 23.45, 24.82–25.02 (m), 27.31, 31.43, 32.67, 33.88, 34.34 (t, J=133 Hz), 35.34, 35.69, 36.53, 38.57, 42.56–42.72 (m), 50.17, 53.61, 61.51, 62.61–62.92 (m), 83.50, 83.64, 123.97, 168.80, 168.88, 170.77, and 199.37; δ_P ($CDCl_3$) 22.98; *m/z* (positive ion FAB) (M^++H) 946 (14), 703 (87), and 461 (100).

4.2.12. 3,3-Bis(17β-(androst-4-en-3-only)oxycarbonyl)-propylidene bis(phosphonic acid). Tetraethyl (3,3-bis(17β-(androst-4-en-3-onyl)oxycarbonyl)propylidene)bis-phosphonate (0.129 g, 0.136 mmol) was dissolved in CH_2Cl_2 (2 mL) and CCl_4 (2 mL), and the mixture stirred under an atmosphere of nitrogen. Trimethylsilyl bromide (0.62 mL, 0.731 g, 4.77 mmol) was added slowly and the reaction mixture stirred for 24 h. Water (25 mL) was added and the reaction mixture stirred for 20 min, filtered, and the residue washed with water and CH_2Cl_2. The product was isolated by filtration, and dried under high vacuum (0.082 g, 72%); δ_H (CD_3OD) 0.87 (3H, s) 0.88 (3H, s), 0.91–2.47 (41H, m), 1.23 (6H, s), 4.03 (1H, t, J=6 Hz), 4.65 (2H, t, J=8 Hz), and 5.70 (2H, s); δ_P (CD_3OD) 20.59; *m/z* (negative ion FAB) (M^+-H) 831.5 (14), 589 (10), 152 (100).

4.2.13. 4,4-Bis(diethoxyphosphoryl)butanoic acid 13. A solution of potassium hydroxide (2.24 g, 40.0 mmol) in water (5 mL) was added to a solution of **8a** (9.25 g, 20.0 mmol) in THF (20 mL) at 15°C. The mixture was stirred for 15 h at room temperature and the solvent removed under reduced pressure. The residue was dissolved in saturated aqueous potassium hydrogen sulphate (10 mL) and extracted with ethyl acetate (3×15 mL). The organic layer was dried over $MgSO_4$, and the solvent removed to give the diacid as an oil. The acid was heated at 130°C for 3 h to afford the monoacid **13** (1.95 g, 27%); δ_H (MeOD) 1.35 (12H, t, J=8 Hz) 2.06–2.25 (2H, m), 2.63–2.69 (1H, m), 2.81 (1H, tt, J_{P-H}=24, J=7 Hz), and 4.11–4.25 (8H, m); δ_C (MeOD) 16.57, 16.71, 21.82–22.10 (m), 32.53–33.07 (m), 35.87 (t, J_{C-P}=133 Hz), 64.07–64.36 (m), and 175.85; δ_P (MeOD) 24.95; *m/z* (negative ion FAB) 361 (100) (M^+-H); Found: 363.1300. $C_{12}H_{25}D_2O_8P_2$ requires: 363.1307 (positive ion FAB).

4.2.14. Tetraethyl 3,3-bis(benzyloxycarbonyl)propylene bisphosphonate 8b. Tetraethyl ethylidene bisphosphonate **6** (1.00 g, 3.33 mmol), and dibenzyl malonate (0.83 mL, 0.946 g, 3.33 mmol) were dissolved in THF (15 mL). Lithium bis(trimethylsilyl)amide solution in THF (1 M, 0.33 mL, 0.33 mmol) was added to the reaction mixture and stirred for 1 h at room temperature. Saturated aqueous ammonium chloride (50 mL) was added, and the reaction mixture extracted with CH_2Cl_2 (100 mL). The organic layer was collected and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using 2–3% methanol–CH_2Cl_2 as eluent to give **8b** as a colourless oil (1.12 g, 58%); δ_H ($CDCl_3$) 1.30 (6H, t, J=7 Hz), 1.31 (6H, t, J=7 Hz), 2.37–2.74 (3H, m), 4.07–4.24 (9H, m), 5.14 (4H, s), and 7.24–7.35 (10H, m); δ_C ($CDCl_3$) 16.10, 16.24, 24.81, 34.11 (t, J_{C-P}=132 Hz), 49.93 (t, J_{C-P}=8 Hz), 62.66 (m), 67.11, 128.03, 128.22, 128.40, 135.12, and 168.41; δ_P ($CDCl_3$) 32.19; *m/z* (positive ion FAB) (M^++H) 585 (36), 369 (7), and 91 (100); (Found: 585.2018. $C_{27}H_{39}P_2O_{10}$ requires: 585.2019 (M^++H)).

4.2.15. 3,3-Bis(diethoxyphosphoryl)propylene bis(carboxylic acid). Tetraethyl 3,3-bis(benzyloxycarbonyl)propylene bisphosphonate **8b** (0.698 g, 1.19 mmol) was dissolved in THF (10 mL), and Pd/C (0.10 g) added. The reaction mixture was stirred under an atmosphere of hydrogen (1 bar) overnight at room temperature, filtered, and saturated aqueous ammonium chloride (50 mL) added. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$, the solvent removed under reduced pressure, and the product dried under high vacuum to give a colourless solid (0.42 g, 88%); δ_H (MeOD) 1.35 (12H, t, J=7 Hz), 1.74 (2H, hept, J=8 Hz), 2.08 (1H, tt, J_{P-H}=23, J=7 Hz), 3.18 (1H, t, J=7 Hz), and 3.48–3.63 (8H, m); δ_C (MeOD) 16.55, 16.68, 25.95 (t, J_{P-C}=4 Hz), 35.01 (t, J_{P-C}=133 Hz), 51.10 (m), 64.45 (dd, J=9.4, 6.7 Hz), and 171.84; δ_P (MeOD) 22.8; *m/z* (positive ion FAB) (M^++D) 406 (100), and (M^++H) 405 (90).

4.2.16. 4,4-Bis(diethoxyphosphoryl)butanoic acid 13. 3,3-Bis(diethoxyphosphoryl)propylene bis(carboxylic acid) (0.200 g, 0.495 mmol) was heated to 130°C for 3 h under a stream of nitrogen to give **13** as a colourless oil (0.174 g, 99%); data as described above.

4.2.17. Tetraethyl (3-(17β-(3-benzoyloxyoestra-1,3,5-trienyl)oxycarbonyl)propylene bisphosphonate 14. 4,4-Bis(diethoxyphosphoryl)butanoic acid **13** (0.071 g, 0.20 mmol), 3-*O*-benzoyl-17β-oestradiol (0.089 g, 0.24 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.005 g, 0.04 mmol) were dissolved in CH_2Cl_2 (5 mL), and stirred at 0°C under an atmosphere of nitrogen. EDCI (0.0455 g, 0.24 mmol) was added, and the reaction mixture, allowed to reach room temperature with stirring overnight, washed with water (30 mL), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel using 1–3% methanol–CH_2Cl_2 as eluent to give **14** as a colourless oil (0.048 g, 33%); ν_{max} 3053, 2983, 1729, 1601, 1243, and 1025 cm^{-1}; δ_H ($CDCl_3$) 0.84 (3H, s), 1.25–1.93 (11H, m), 1.35 (12H, t, J=7 Hz), 1.12–2.74 (7H, m), 2.87–2.92 (2H, m), 4.12–4.28 (8H, m), 4.70 (1H, dd, J=9, 7 Hz), 6.92–7.00 (2H, m), 7.33 (1H, d, J=8 Hz), 7.46–7.67 (3H, m), and 8.20 (2H, dt, J=8, 2 Hz); δ_C ($CDCl_3$) 12.06, 16.32, 16.43, 21.04, 23.25, 26.03, 27.00, 27.59, 29.50, 35.68 (t, J=132 Hz), 36.86, 38.18, 38.35, 42.87, 43.98, 49.80, 62.61 (t, J=7 Hz), 82.74, 118.67, 121.58, 126.43, 128.49, 129.70, 130.10, 133.45, 137.84, 138.19, 148.68, and 172.72; δ_P ($CDCl_3$) 23.2; *m/z* (positive ion FAB) 719 (M^++H).

4.2.18. Ethyl malonic half ester 16a. Diethyl malonate (10.0 g, 62.5 mmol) was dissolved in absolute ethanol (40 mL), and a solution of potassium hydroxide (3.5 g) in ethanol (40 mL) added dropwise over 1 h. The reaction mixture was stirred for 2 h. and left to stand overnight. The crude precipitated intermediate was recrystallized from the mother liquors and washed with ether to give the potassium salt as a colourless crystalline solid (5.0 g, 50%); $C_5H_7KO_4$ requires C=35.28, H=4.15; Found C=34.47, H=4.13%. The potassium salt (4.45 g, 26 mmol) was dissolved in water (3 mL) and conc. HCl (2.5 mL) added slowly over 30 min, maintaining the temperature below 10°C. The reaction mixture was filtered and the residue washed with diethyl ether (5 mL). The aqueous layer was

extracted with diethyl ether (3×10 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed under reduced pressure to give **16a** as a colourless liquid (1.9 g, 55%), ν_{max} 3486, 1743, and 1735 cm^{-1}; δ_H ($CDCl_3$) 1.29 (3H, t, J_{H-H}=7 Hz), 3.43 (2H, s), 4.23 (2H, q, J_{H-H}=7 Hz), and 8.21 (1H, br s).

4.2.19. *p*-Nitrobenzyl malonic half ester 16b. Meldrum's acid (1.00 g, 6.94 mmol) and *p*-nitrobenzyl alcohol (1.00 g, 6.53 mmol) were heated under reflux in acetonitrile (3.5 mL) for 22 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue subjected to high vacuum to give a yellow solid (1.5 g, 97%) which was recrystallized from *t*-butanol–hexane (2:1) to afford **16b** as a pale yellow solid (1.00 g, 64%), mp 95–98°C; ν_{max} 3500, 1747, 1727, 1605, 1522, and 1335 cm^{-1}; δ_H ($(CD_3)_2CO$) 3.50 (2H, s), 5.22 (2H, s), 7.58 (2H, d, J_{H-H}=3 Hz), and 8.11 (2H, d, J_{H-H}=4 Hz); δ_C ($(CD_3)_2CO$) 40.1, 64.6, 122.8, 128.1, 166.8, and 205.2.

4.2.20. Methyl malonic half ester 16c. Meldrum's acid (1.00 g, 6.94 mmol) and methanol (222 mg, 6.93 mmol) were heated under reflux in acetonitrile (3.5 mL) for 20 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5% MeOH–CH_2Cl_2 as eluent to give **16c** as a colourless oil (530 mg, 65%), ν_{max} 2600, 1736, and 1728 cm^{-1}; δ_H ($CDCl_3$) 3.48 (2H, s), 3.81 (3H, s), and 9.98 (1H, br s); δ_C ($CDCl_3$) 40.7, 52.7, 167.1, and 171.3.

4.2.21. *i*-Propyl malonic half ester 16d. Meldrum's acid (2.0 g, 13.9 mmol) and isopropanol (834 mg, 13.89 mmol) were heated under reflux in acetonitrile (7.0 mL) for 22 h. The solvent was removed under reduced pressure and **16d** collected as a colourless oil essentially pure by NMR spectroscopy (2.03 g, 100%, ν_{max} 1750 and 1720 cm^{-1}; δ_H ($CDCl_3$) 1.31 (6H, d, *J*=6 Hz), 3.41 (2H, s), and 5.10 (1H, hept, J_{H-H}=6 Hz).

4.2.22. Phenyl malonic half ester 16f. Meldrum's acid (1.84 g, 12.76 mmol) and phenol (1 g, 10.63 mmol) were heated under reflux in acetonitrile (3.5 mL) for 22 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the crude product purified by column chromatography on silica gel using 20–100% ethyl acetate–petroleum ether (40–60°C) as eluent to give **16f** as off-white crystals (648 mg, 34%), ν_{max} 1754 and 1698 cm^{-1}; δ_H ($CDCl_3$) 3.68 (2H, s), 7.08–7.17 (2H, m), 7.21–7.30 (1H, m), 7.33–7.44 (2H, m), and 9.51 (1H, br s); δ_C ($CDCl_3$) 41.1, 121.2, 126.3, 129.5, 150.4, 164.9, and 171.5; $C_9H_8O_4$ requires C, 59.99; H, 4.48. Found C, 59.98; H, 4.54%.

4.2.23. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) malonic half ester 16g. Meldrum's acid (79.6 mg, 0.552 mmol) and 3-*O*-benzyl-17β oestradiol (200 mg, 0.552 mmol) were heated under reflux in acetonitrile (1.75 mL) for 22 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5% MeOH–CH_2Cl_2 as eluent, affording **16g** as a colourless solid (120 mg, 49%), ν_{max} 3420, 2361, 1749, 1718, 1654 and 1462 cm^{-1}; δ_H ($CDCl_3$) 0.84 (3H, s), 1.25–2.26 (16H, m), 2.84–2.87 (2H, m), 3.45 (2H, s), 4.78 (1H, t, *J*=7 Hz), 5.03 (2H, s), 6.70 (1H, s), 6.77 (1H, d, J_{H-H}=12 Hz), 7.18 (1H, d, J_{H-H}=8 Hz), and 7.25–7.43 (5H, m); δ_C (400 MHz, $CDCl_3$) 12.4, 23.6, 26.6, 27.6, 27.8, 30.1, 37.2, 38.9, 41.2, 43.6, 44.2, 50.1, 70.4, 84.8, 112.7, 115.3, 126.8, 127.9, 128.3, 129.0, 133.1, 137.7, 138.3, 157.2, 167.7, and 170.9; $C_{28}H_{32}O_5$ requires C, 74.96; H, 7.20. Found C, 73.65; H, 7.20%.

4.2.24. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) ethyl malonate 17a. 3-*O*-Benzyl-17β oestradiol (1.0 g, 2.96 mmol), ethyl malonic half ester **16a** (391 mg, 2.96 mmol) and dicyclohexylcarbodiimide (672 mg, 3.26 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mol%) were stirred in diethyl ether (35 mL) for 18 h under an atmosphere of nitrogen. The mixture was filtered, the solid washed with ether, and the combined solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using 10% EtOAc–petroleum ether (40–60°C) as eluent to give **17a** as a colourless crystalline solid (640 mg, 46%), ν_{max} 1752, 1729, 1605 and 1498 cm^{-1}; δ_H ($CDCl_3$) 0.82 (3H, s), 1.28 (3H, t, J_{H-H}=8 Hz), 1.39–1.57 (9H, m), 1.8–1.9 (2H, m), 2.3–2.4 (2H, m), 2.84 (2H, m), 3.38 (2H, s), 4.17 (2H, q, J_{H-H}=8 Hz), 4.76 (1H, t, J_{H-H}=8 Hz), 5.03 (2H, s), 6.70 (1H, s), 6.77 (1H, d, J_{H-H}=8 Hz), 7.23 (1H, d, J_{H-H}=9 Hz), and 7.30–7.43 (6H, m); δ_C ($CDCl_3$) 12.4, 14.4, 23.6, 26.6, 27.6, 27.8, 30.1, 37.2, 39.0, 41.8, 43.6, 44.2, 50.2, 61.9, 70.4, 84.2, 112.7, 115.3, 126.7, 127.8, 128.2, 128.9, 133.2, 137.8, 138.3, 157.2, 167.0, and 167.1. $C_{32}H_{35}O_5$ requires C, 76.93; H, 7.06. Found C, 76.59; H, 7.43%.

4.2.25. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) *p*-nitrobenzyl malonate 17b. 3-*O*-Benzyl-17β oestradiol (608 mg, 1.68 mmol), *p*-nitrobenzyl malonic half ester **16b** (400 mg, 1.68 mmol), dicyclohexylcarbodiimide (382 mg, 84.8 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mol%) were stirred in CH_2Cl_2 (15 mL) for 4 d under an atmosphere of nitrogen. The mixture was filtered, the solvent removed under reduced pressure, and the residue purified by column chromatography on silica gel using 20% EtOAc–petroleum ether (40–60°C) as eluent to give **17b** as an off-white solid (700 mg, 69%), ν_{max} 1750, 1731, 1607, 1519 and 1533 cm^{-1}; δ_H ($CDCl_3$) 0.69 (3H, s), 1.16–1.20 (6H, m), 1.26–1.37 (1H, m), 1.71–1.74 (3H, m), 2.01–2.16 (3H, m), 3.39 (2H, s), 4.65 (1H, t, J_{H-H}=9 Hz), 4.93 (2H, s), 5.29 (2H, s), 6.6 (1H, s), 6.69 (1H, d, J_{H-H}=6 Hz), 7.09 (1H, d, J_{H-H}=8 Hz), 7.27–7.35 (5H, m), 7.44 (2H, d, J_{H-H}=8 Hz), and 8.13 (2H, d, J_{H-H}=8 Hz); δ_C ($CDCl_3$) 11.0, 22.2, 25.1, 26.3, 26.9, 28.7, 35.8, 37.5, 40.6, 42.1, 42.7, 48.7, 64.5, 68.9, 83.0, 111.3, 113.8, 122.8, 125.3, 126.4, 126.6, 126.8, 127.3, 131.6, 136.3, 141.5, 146.8, 155.8, 165.2, and 165.2.

4.2.26. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) methyl malonate 17c. 3-*O*-Benzyl-17β oestradiol (1.00 g, 2.76 mmol), methyl malonic half ester **16c** (323 mg, 2.76 mmol), dicyclohexylcarbodiimide (627 mg, 3.04 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mol%) were stirred in CH_2Cl_2 (25 mL) for 18 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 20% EtOAc–petroleum ether (40–60°C) as

eluent to give **17c** as a colourless crystalline solid (846 mg, 68%), ν_{max} 1741, 1726, 1461 and 1165 cm^{-1}; δ_H ($(CD_3)_2CO$) 0.83 (3H, s), 1.25–1.51 (6H, m), 1.55–1.65 (2H, m), 1.85–1.95 (2H, m), 2.18–2.22 (3H, m), 2.80–2.89 (2H, m), 3.40 (2H, s), 3.76 (3H, s), 4.77 (1H, t, J_{H-H}=8 Hz), 5.04 (2H, s), 6.72 (1H, s), 6.78 (1H, d, J_{H-H}=8 Hz), 7.20 (1H, d, J_{H-H}=8 Hz), and 7.30–7.44 (5H, m); δ_C (400 MHz, $CDCl_3$) 11.9, 23.1, 26.1, 27.1, 27.3, 29.6, 36.7, 38.4, 42.5, 43.0, 43.7, 49.6, 52.3, 69.9, 83.8, 112.2, 114.7, 126.3, 127.3, 127.7, 128.4, 132.6, 137.2, 137.8, 156.6, 166.4, and 167.7; *m/z* (FAB) 462.2412 (M^+); $C_{29}H_{34}O_5$ requires 462.2406.

4.2.27. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) isopropyl malonate 17d. 3-*O*-Benzyl-17β oestradiol (450 mg, 1.24 mmol), *i*-propyl malonic half ester **16d** (182 mg, 1.24 mmol), dicyclohexylcarbodiimide (308 mg, 1.5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mol%) were stirred in acetonitrile (4 mL) for 18 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5–10% EtOAc–petroleum ether (40–60°C) as eluent to give **17d** as a colourless crystalline solid (420 mg, 69%), ν_{max} 1747, 1498, 1458, 1722, and 1376 cm^{-1}; δ_H ($CDCl_3$) 0.82 (3H, s), 1.24 (6H, d, J_{H-H}=6 Hz), 1.30–1.95 (10H, m), 2.14–2.34 (3H, m), 2.78–2.89 (2H, m), 3.35 (2H, s), 4.76 (1H, t, J_{H-H}=8 Hz), 5.02 (2H, s), 5.06 (1H, hept, J_{H-H}=6 Hz), 6.70 (1H, s), 6.75 (1H, d, J_{H-H}=9 Hz), 7.17 (1H. d. J_{H-H}=9 Hz), and 7.35 (5H, m); δ_C ($CDCl_3$) 12.0, 21.7, 21.8, 23.3, 26.2, 27.2, 27.4, 29.8, 36.9, 38.6, 42.3, 43.2, 43.8, 49.8, 52.4, 70.0, 83.8, 112.3, 114.9, 126.4, 127.2, 127.9, 128.6, 132.8, 137.4, 137.9, 156.8, 166.3, and 166.8; *m/z* (FAB) 491.2791 ($M+H^+$); $C_{31}H_{39}O_5$ requires 491.2798.

4.2.28. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) phenyl malonate 17f. 3-*O*-Benzyl-17β oestradiol (500 mg, 1.39 mmol), phenyl malonic half ester **16f** (249 mg, 1.39 mmol), dicyclohexylcarbodiimide (429 mg, 2.08 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (10 mol%) were stirred in CH_2Cl_2 (5 mL) for 18 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 10% EtOAc–petroleum ether (40–60°C) as eluent to give **17f** as a colourless solid (670 mg, 92%), ν_{max} 1774 and 1723 cm^{-1}; δ_H ($CDCl_3$) 0.85 (3H, s), 1.19–1.50 (6H, m), 1.60–1.80 (4H, m), 2.15–2.33 (3H, m), 2.82–2.86 (2H, m), 3.61 (2H, s), 4.82 (1H, t, J_{H-H}=9 Hz), 5.01 (2H, s), 6.70 (1H, s), 6.77 (1H, d, J_{H-H}=9 Hz), and 7.11–7.42 (11H, m); δ_C ($CDCl_3$) 12.4, 23.5, 26.5, 27.5, 27.7, 30.0, 37.1, 38.8, 42.2, 43.5, 44.1, 50.0, 70.2, 84.4, 112.6, 115.1, 121.6, 126.5, 126.7, 127.7, 128.1, 128.8, 129.8, 133.0, 137.6, 138.2, 150.7, 157.1, 165.5, and 166.4; *m/z* (FAB) 524.2563 (M^+); $C_{34}H_{36}O_5$ requires 524.2563.

4.2.29. Tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (ethoxycarbonyl) propylene bisphosphonate 18a. 17β (3-Benzyloxyoestra-1,3,5(10)-trienyl) ethyl malonate **17a** (100 mg, 0.297 mmol) was dissolved in CH_2Cl_2 (2 mL). Triethylamine (120 mg, 1.186 mmol) and tetraethyl ethylidene bisphosphonate (89 mg, 0.297 mmol) were added and the reaction mixture stirred at room temperature overnight under an atmosphere of nitrogen. The solvent was removed in vacuo and the residue purified by column chromatography on silica gel using 1–2% MeOH–CH_2Cl_2 as eluent to give **18a** as a colourless oil (70 mg, 30%), ν_{max} 1755, 1731, 1608 and 1500, 1254, and 1163 cm^{-1}; δ_H ($CDCl_3$) 0.81 (3H, s), 0.82 (3H, s), 1.26–1.40 (15H, m), 1.80–2.85 (16H, m), 3.9–4.15 (1H, m), 4.19–4.24 (12H, m), 4.75–4.80 (1H, m), 5.02 (2H, s), 6.71 (1H, s), 6.74 (1H, d, J_{H-H}=9 Hz), and 7.20 (1H, d, J_{H-H}=8 Hz); δ_C ($CDCl_3$) 11.8, 11.9, 14.1, 16.3 (t, J_{C-P}=6 Hz), 23.2, 24.8, 26.1, 27.1, 27.2, 29.7, 34.2 (t, J_{C-P}=138 Hz), 36.7, 38.4, 41.4, 41.6, 49.6, 62.6 (t, J_{C-P}=6 Hz), 69.9, 83.6, 83.9, 112.2, 114.7, 126.3, 127.4, 127.8, 128.5, 132.4, 137.0, 137.8, 156.6, 167.1, 167.2, and 167.3; δ_P ($CDCl_3$) 24.15 and 24.20; *m/z* (FAB) 777.3797 (M^+); $C_{40}H_{59}O_{11}P_2$ requires 777.3533.

4.2.30. Tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (*p*-nitrobenzyloxycarbonyl) propylene bisphosphonate 18b. β (3-Benzyloxyoestra-1,3,5(10)-trienyl) *p*-nitrobenzyl malonate **17b** (200 mg, 0.33 mmol) was dissolved in CH_2Cl_2 (2 mL), diethylamine (49 mg, 70 μL, 0.66 mmol) added, and the solution stirred for 10 min. Tetraethyl ethylidene bisphosphonate (99 mg, 0.33 mmol) was added and the reaction mixture stirred at room temperature overnight under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5% MeOH–CH_2Cl_2 as eluent to give **18b** as a brown oil (70 mg, 24%), ν_{max} 1749, 1731, 1608, 1524, 1499, 1347, 1252, and 1163 cm^{-1}; δ_H ($CDCl_3$) 0.72 (3H, s), 0.75 (3H, s), 1.35 (12H, t, J_{H-H}=7 Hz), 1.74–1.78 (2H, m), 1.80–185 (1H, m), 2.00–2.10 (1H, m), 2.17–2.22 (3H, m), 2.48–2.55 (3H, m), 2.83–2.85 (2H, m), 3.39 (3H, s), 4.14–4.24 (8H, m), 5.03 (2H, s), 5.22–5.34 (2H, m), 6, 71 (1H, s), 6.78 (1H, d, J_{H-H}=8 Hz), 7.16 (1H, d, J_{H-H}=4 Hz), 7.31–7.44 (4H, m), 7.55 (2H, d, J_{H-H}=9 Hz), and 8.22 (2H, d, J_{H-H}=9 Hz); δ_C ($CDCl_3$) 13.0, 13.1, 17.5 (t, J_{H-H}=6 Hz), 24.4, 27.0, 28.2, 28.4, 30.8, 34.9 (t, J_{P-C}=143 Hz), 37.9, 39.5, 44.3, 44.7, 50.7, 63.9 (t, J_{H-H}=10 Hz), 66.7, 71.0, 85.0, 113.4, 115.87, 124.9, 127.4, 128.5, 128.9, 129.60, 129.61, 129.7, 133.6, 138.3, 143.2, 148.4, 157.8, 169.5, and 169.7; δ_P ($CDCl_3$) 23.49 and 23.51.

4.2.31. Tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (methyloxycarbonyl) propylene bisphosphonate 18c. LHMDS (0.133 mL, 0.119 g, 0.711 mmol) was added to 17β (3-benzyloxyoestra-1,3,5(10)-trienyl) methyl malonate **17c** (300 mg, 0.66 mmol) and tetraethyl ethylidene bisphosphonate (200 mg, 0.664 mmol) in THF (4.5 mL) solution and heated at 60°C for 18 h. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 1–2% MeOH–CH_2Cl_2 as eluent to give **18c** as a brown oil (289 mg, 57%), δ_H ($CDCl_3$) 0.80 (3H, s), 1.35 (12H, t, J_{H-H}=7 Hz), 1.85–2.05 (6H, m), 2.21–2.35 (4H, m), 2.40–2.71 (3H, m), 2.80–2.97 (2H, m), 3.75 (3H, s), 4.14–4.26 (8H, m), 4.67–4.82 (1H, m), 5.03 (2H, s), 6.72 (1H, s), 6.78 (1H, d, J_{H-H}=8 Hz), 7.20 (1H, d, J_{H-H}=8 Hz), and 7.30–7.45 (5H, m); δ_C ($CDCl_3$) 11.9, 16.4 (t, J=6 Hz), 23.3, 26.2, 27.2, 27.3, 29.8, 34.2 (t, J_{C-P}=134 Hz), 38.5, 43.1, 49.7, 52.6, 62.7 (t, J_{C-P}=7 Hz), 69.9, 84.0, 112.4, 114.9, 126.4, 127.4, 127.8, 128.5, 131.0, 137.2, 137.8, 156.7, 168.5, and 169.8; δ_P ($CDCl_3$), 24.09,

24.01; *m/z* (FAB) 762.3286 (M^+); $C_{39}H_{56}O_{11}P_2$ requires 762.3298.

4.2.32. Tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (*i*-propyloxycarbonyl) propylene bisphosphonate 18d. Sodium hydride (9.6 mg, 0.4 mmol) was added to a solution of 17β (3-benzyloxyoestra-1,3,5 (10)-trienyl) *i*-propyl malonate **17d** (100 mg, 0.2 mmol) and a solution of tetraethyl ethylidene bisphosphonate (60.2 mg, 0.2 mmol in THF (0.5 mL) added. The reaction mixture was stirred at room temperature for 1 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 1–2% MeOH–CH_2Cl_2 as eluent to give **18d** as a brown oil (82 mg, 40%), δ_H ($CDCl_3$) 0.81 (3H, s), 1.25 (6H, d, J_{H-H}=6 Hz), 1.33 (12H, t, J_{H-H}=8 Hz), 2.10–2.13 (13H, m), 2.81–2.90 (2H, m), 4.19 (8H, q, J_{H-H}=8 Hz), 5.03 (2H, s), 6.71 (1H, s), 6.75 (1H, d, J_{H-H}=8 Hz), 7.17 (1H, d, J_{H-H}=8 Hz), and 7.35 (4H, m); δ_C ($CDCl_3$) 11.9, 16.2 (t, J_{C-P}=6 Hz), 21.6, 23.2, 24.8, 26.0, 27.1, 27.2, 29.7, 34.2 (t, J_{C-P}=160 Hz), 38.4, 43.1, 43.7, 49.6, 52.4, 62.7 (4C, t, J_{C-P}=8 Hz), 83.6, 112.8, 115.3, 126.8, 127.9, 128.3, 129.0, 133.1, 137.7, 138.3, 157.2, 168.4, and 168.9; δ_P ($CDCl_3$) 24.10 and 24.25.

4.2.33. Tetraethyl (17β (3-hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (ethoxycarbonyl) propylene bisphosphonate 19a. 10% Palladium on activated charcoal (158 mg) was added to a solution of tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl)) (ethoxycarbonyl) propylene bisphosphonate **18a** (778 mg, 1 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred for 18 h under an atmosphere of hydrogen (60 psi). The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5% MeOH–CH_2Cl_2 as the eluent to give **19a** as a colourless foam (550 mg, 80%), ν_{max} 3276, 2982, 2930, 1745, 1731, 1611, 1503, 1246, and 1164 cm^{-1}; δ_H ($CDCl_3$) 0.79 (3H, s), 1.21–1.36 (18H, m), 1.59–2.75 (15H, m), 3.95–4.09 (1H, m), 4.20–4.25 (10H, m), 4.70–4.80 (1H, m), 6.62 (1H, s), 6.65 (1H, d, J_{H-H}=9 Hz), and 7.10 (1H, d, J_{H-H}=9 Hz); δ_C ($CDCl_3$) 13.1, 13.2, 15.28, 15.31 17.5 (t, J_{C-P}=5 Hz), 25.6, 27.0, 27.8, 28.8, 28.9, 35.8 (t, J_{C-P}=135 Hz), 38.5, 40.5, 45.4, 51.16, 51.18, 62.9, 63.1, 63.9, 64.2, 85.1, 85.3, 114.5, 116.8, 128.0, 133.9, 139.1, 156.9, 170.19, 170.21, 170.3, and 170.4; δ_P ($CDCl_3$) 24.14 and 24.08; *m/z* (FAB) 687.3071 ($M+H^+$); $C_{33}H_{52}O_{11}P_2$ requires 687.3063.

4.2.34. Tetraethyl (17β (3-hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (methyloxycarbonyl) propylene bisphosphonate 19c. 10% Palladium on activated charcoal (41 mg) was added to a solution of tetraethyl (17β (3-benzyloxyoestra-1,3,5(10)-trienyl)oxycarbonyl)) (methoxycarbonyl) propylene bisphosphonate **18c** (200 mg, 0.262 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred for 22 h under an atmosphere of hydrogen. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel using 5% MeOH–CH_2Cl_2 as the eluent to give **19c** as a colourless foam (140 mg, 79%), δ_H ($CDCl_3$) 0.79 (3H, s), 1.35 (12H, t, J_{H-H}=8 Hz), 1.50–1.98 (10H, m), 2.08–2.70 (4H, m), 2.77–2.86 (1H, m), 3.72 (3H, s), 3.96–4.09 (2H, m), 4.10–4.33 (8H, m), 4.65–4.82 (1H, m), 6.59 (1H, s), 6.65 (1H, d, J_{H-H}=8 Hz), and 7.10 (1H, d, J_{H-H}=8 Hz); δ_C ($CDCl_3$) 11.9, 12.1, 16.4, 23.3, 24.8, 26.2, 27.3, 29.6, 34.1 (t, J_{C-P}=134 Hz), 36.8, 38.6, 43.1, 43.2, 43.8, 49.9 (t, J_{C-P}=11 Hz), 52.6, 52.7, 63.0 (t, J_{P-C}=7 Hz), 83.9, 84.0, 112.87, 115.4, 126.3, 131.2, 137.8, 154.7, 168.8, and 169.5; δ_P ($CDCl_3$) 24.11 and 24.07; *m/z* (FAB) 673.2914 ($M+H^+$); $C_{32}H_{51}O_{11}P_2$ requires 673.2907. $C_{32}H_{50}P_2O_{11}$ requires C, 57.12; H, 7.50. Found C, 56.58; H, 7.34%.

4.2.35. (17β (3-Hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (ethoxycarbonyl) propylene bis(phosphonic acid) 20a. Tetraethyl (17β (3-hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (ethoxycarbonyl) propylene bisphosphonate **19a** (457 mg, 0, 666 mmol) was stirred with trimethylsilyl bromide (816 mg, 0.703 mL, 5.329 mmol) in CH_2Cl_2 (10 mL) for 2.5 d. The solvent was removed and the resulting concentrate stirred with MeOH (20 mL) for a further 30 min. The solvent was removed under reduced pressure to afford the product as an orange foam (450 mg, 100%), ν_{max} 2683, 1752, 1730, and 1182 cm^{-1}; δ_H ($(CD_3)_2CO$) 0.85 (3H, s), 1.11–2.83 (20H, m), 3.90–4.14 (1H, m), 4.19–4.36 (2H, m), 4.7 (1H, q, J_{H-H}=9 Hz), 6.52 (1H, s), 6.59 (1H, d, J_{H-H}=9 Hz), and 7.09 (1H, d, J_{H-H}=9 Hz); δ_C ($(CD_3)_2CO$) 11.5, 35.9, 24.9, 26.3, 27.2, 27.3, 29.8, 36.9, 44.0, 49.8, 84.0, 113.4, 115.7, 126.8, 131.5, 138.2, 156.0, 169.6, and 169.8; δ_P ($(CD_3)_2CO$) 28.16; *m/z* (FAB) 575 ($M+H^+$), 597 ($M+Na^+$).

4.2.36. (17β (3-Hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl) (methyloxycarbonyl) propylene bis(phosphonic acid) 20c. Trimethylsilyl bromide (0.102 mL, 118 mg, 0.773 mmol) was added slowly to a solution of tetraethyl (17β (3-hydroxyoestra-1,3,5(10)-trienyl)oxycarbonyl)) (methoxycarbonyl) propylene bisphosphonate **19c** (65 mg, 0.0967 mmol) in dichloromethane (1.5 mL). The reaction mixture was stirred at room temperature for 2.5 d. The solvent was removed under reduced pressure and the resulting concentrate stirred with methanol (2 mL) for 30 min. The solvent was removed under reduced pressure to afford the product as a creamy brown foam (38 mg, 70%), δ_H ($(CD_3)_2CO$) 0.84 (3H, s), 1.08–1.97 (10H, m), 2.36–2.82 (5H, m), 3.74 (3H, s), 3.87–4.06 (1H, m), 4.75 (1H, q, J_{H-H}=8 Hz), 6.53 (1H, s), 6.58 (1H, d, J_{H-H}=8 Hz), and 7.07 (1H, d, J_{H-H}=8 Hz); δ_C ($(CD_3)_2CO$) 16.6, 16 7, 28.2, 29.9, 31.4, 32.4, 42.0, 44.0, 48.2, 48.4, 49.0, 54.7, 55.4, 57.2, 57.3, 88.8, 88.9, 117.9, 120.2, 131.4, 136.1, 142.7, 160.2, 173.5, 173.6, 174.3, and 174.4; δ_P ($(CD_3)_2CO$) 28.13.

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