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Novel Elongated Phosphoranes by Heck-Reaction and Pd(0)-Catalysed Alkynylation and their Use in C-7 Group Functionalisation in Estrones

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Halobenzoylmethylidenephosphoranes 3 are reacted under C-C bond formation to give a number of novel elongated phosphoranes 5 and 6. The C-C bond formation could be achieved both under Heck conditions and by metal-catalyzed ethynylation reaction. The products, desactivated phosphoranes, can be reacted in Wittig-olefinations with aldehydes. Exemplary use of the phosphoranes is shown in the C-7 chain functionalisation in synthetic estrones, which may be valuable precursors for radioligands in early breast cancer diagnosis.

Introduction

In our quest for suitable radioligands for the estrogen receptor ER_α as radiodiagnostica for estrogen-positive breast cancer,[1] 7-substituted 6,7-dehydroestra-3,17β-diols have been found to be interesting target compounds. In order to study the influence of the nature of the C-7 substitution on the biological activity of the molecules, a number of these structures are to be synthesised. While a polar terminus of the substituent has been deemed to be beneficial,[2] a number of building blocks have been found to be compatible with the estrogen receptor, among them aromatic units.[3] An expedient synthetic strategy[4] is based on the conjugate addition of a suitably functionalised alkyl iodide to a protected 6-oxoestrone with subsequent functional group transformation. In a similar effort to introduce various C-16 functionalities in the estrone via a C-17 keto group, a protocol of aldehyde formation and Wittig-olefination with desactivated phosphoranes was used successfully.[5] In the following, the preparation of novel phosphoranes, partly with polar functionalities, via C-C bond formation of halobenzoylmethylidenetriphenylphosphoranes, either by Heck-reaction or by alkynylation, is described. Furthermore, the synthesis of C-7 substituted estrones by aldehyde-formation and subsequent Wittig-olefination is exemplified.
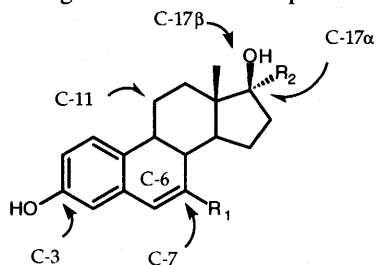
Results and Discussion

Halobenzoylmethylidenetriphenylphosphoranes 3 are air stable and also stable towards moisture. They are easily acquired by reaction of dihaloacetophenones with triphenylphosphine to the corresponding phosphonium salts and subsequent dehydrohalogenation (Scheme 1). In a number of cases the phosphonium salts are both hygroscopic and moisture sensitive, so that the phosphonium salts are best transformed immediately to the phosphoranes in an aqueous solution of sodium carbonate.[6] These desactivated phosphoranes 3 are reactive enough to undergo Wittig-olefination with carbaldehydes, but do not react with ketones.[7] Exception to this rule are highly strained molecules such as cyclopropanone or cyclopropanone hemiacetal.[8]
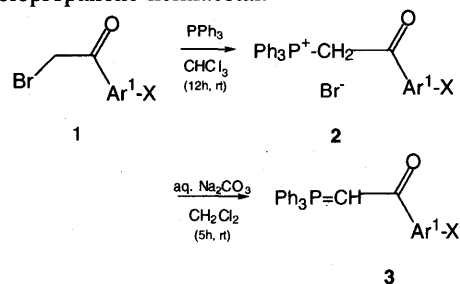
Ar^1-Br: p-Br-Ph (3a); m-Br-Ph (3b); p-I-Ph (3c); o-Br-Ph (3d); 2-Thienyl (3e)

(see also ref. 6,9)

Scheme 1

The authors have found that halobenzoylmethylidenetriphenylphosphoranes 3 are stable enough to undergo C-C bond formation via Suzuki-Kumada coupling.[9] As the conditions for the Suzuki-Kumada coupling reaction are similar to those typically found in Heck reactions, it was deemed possible that these
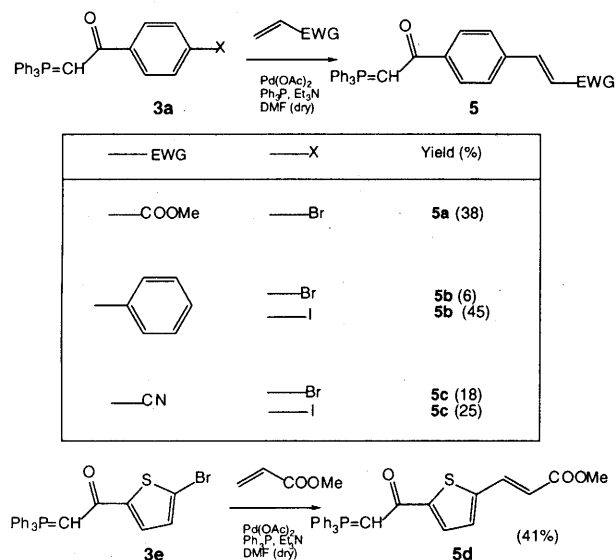
phosphoranes could also be derivatised by Heck reaction or related reactions.

The Heck reaction is a well-studied transformation and has been applied among others to the synthesis of a large number of vinylarenes and hetarenes.[10] Nevertheless, thus far no example of a Heck reaction with a phosphorane-ylid had been described. The authors have found that the halobenzoylmethylidenphosphoranes 3 indeed undergo Heck reactions with a number of alkenes (see Table 1). p-Iodobenzoylmethylidenetriphenyl-phosphorane 3c gives higher yields than the corresponding bromo-substituted compounds. Olefins with basic functionalities such as vinylpyridines or free NH-groups such as acrylic amide did not give the desired products. Whether this is an issue of the work-up or an inherent problem of the reaction has to be studied more closely.

The p-iodobenzoylmethylidenephosphorane 3c also underwent ethynylation reactions with ease.[11] Here, the typical catalyst system Pd(PPh$_3$)$_4$/CuI[12] with diisopropylamine as xx was used. It must be pointed out that in some cases (e.g., in the case of p-cyanophenylacetylene) the yields of the reaction are very dependent on reaction times. The substituents (nitro-, cyano- and amido-) on the phenyl acetylene substrates were chosen in such a way that a number of subsequent transformations would enable the generation of a plethora of further terminal polar functional groups (e.g., carboxylic acid, amino, alkylamido-, dialkylamido-, or carbaldhyde). The p-functionalised phenylacetylenes were prepared by Pd(0) mediated ethynylation of the corresponding p-functionalised bromobenzenes and

| —— EWG	—— X	Yield (%)
——COOMe	——Br	5a (38)
(phenyl ring)	——Br	5b (6)
	——I	5b (45)
——C N	——Br	5c (18)
	——I	5c (25)

(41%)

3e   5d

Scheme 2 and Table 1
subsequent treatment of the trimethylsilylphenylacetylenes with 1N methanolic KOH (see Scheme 3 and Table 1). The p-amidophenylacetylene could not be prepared directly by coupling of p-

bromobenzonitrile with trimethylsilylacetylene with subsequent desilylation. Rather, p-cyanophenylacetylene 7a had to be subjected to a partial hydrolysis to 7d, using aq. H$_2$O$_2$ under PTC conditions.[13]

The desactivated phosphoranes prepared above are useful in directly elongating a C-7 chain in estrones with concomitant introduction of a polar terminus. As a Wittig-olefination, hydrogenation procedure was envisaged (see below, Scheme 7), a two-step process with an olefination reaction by the iodo-benzoylmethylidene-
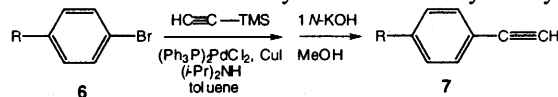
——R	Yield (%)	Time (h)
-CN	7a 55	4
-NO$_2$	7b 57	5
-CON(Bn)$_2$	7c —	5

7a   7d 78%
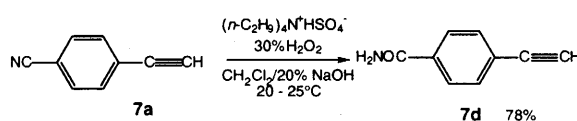
Scheme 3 and Table 2
triphenylphosphorane itself and a subsequent C-C bond formation by either Heck-reaction or alkynylation proved to be disadvantageous because of the poor yield in the Wittig reaction. Moreover, a hydrogenolysis of the newly formed enone moiety in the C-7 iodobenzoylethenyl substituted estrones leads to partial deiodination in the product.

The synthesis of 7-formylalkyl-6,7-dehydroestrones can be carried out via the estra-1,3,5(10)trien-6,17-dione 17,17-acetal 12. C-7 substitution is known to proceed

Ar^1-X = p-Ph-I

——Ar^2	Yield (%)	Time (h)
(cyclohexyl/phenyl)	8a 44	13
-CN	8b 50 / 98	13 / 3

Ar^1-X = p-Ph-I

——Ar^2	Yield (%)	Time (h)
-NO$_2$	8c 99	13
-CONH$_2$	8d 13	13

Ar^1-X = (thienyl)-Br

——Ar^2	Yield (%)	Time (h)
-CN	8e 46	4
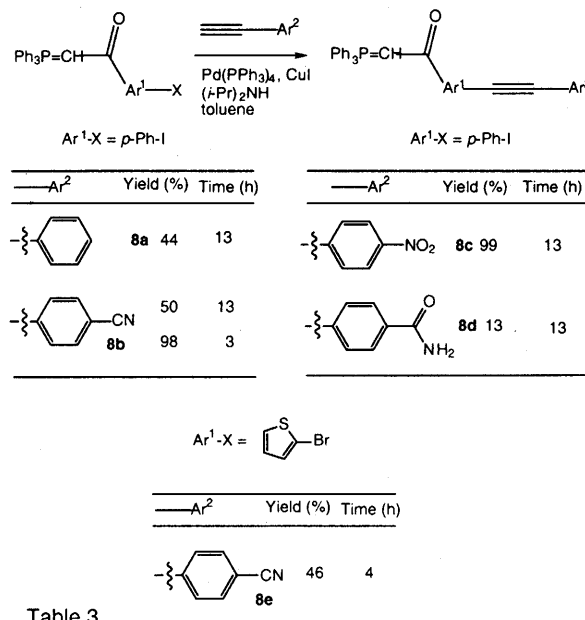
Table 3

directly by reaction of the C-nucleophile to the enolate of

for n = 5, 10
for n = 5
9   10

for n = 5, 10
R = SiMe₃, SiMe₂Buᵗ
11
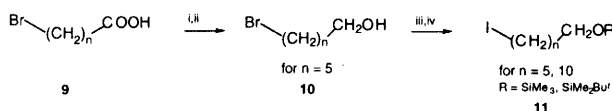
i. CH₂N₂, Et₂O; ii. LiBH₄, Et₂O, MeOH; iii. NaI, acetone; iv. R₃SiCl, Me-Im, Et₂O

Scheme 4

1 2. The only matters of choice are the oxidation state and the nature of the protective group with which the aldehyde functionality equivalent at the terminus will be introduced with the alkyl chain at C-7. Trimethylsiloxyalkyl iodides, tert-butyldimethyl-siloxyalkyl iodides and iodoalkanone acetals could all be reacted with **12**. However, it was found that after the addition, at the stage of the C-17

i.) KOBuᵗ, THF, Me₂BuᵗSiOC₁₂H₂₂I;
ii.) KOBuᵗ, THF, Me₃SiOC₁₂H₂₂I; iii.)
Bu₄NF; THF; iv.) PDC, CH₂Cl₂, US;
v.) NaBH₄, MeOH, Et₂O; vi.
p-TsOH, benzene, Δ; vii. PDC,
CH₂Cl₂

Scheme 5

deprotected 6,7-dehydroestrone, it was not possible to deprotect the terminus, irrelevant of whether the carbaldehyde was protected as a dioxolane or a 5,5-dimethyl-1,3-dioxane.[15] Thus, the trialkylsiloxy group proved the protective group of choice and the terminus was introduced at the oxidation state of an alcohol. While the trimethylsiloxy group cleaved during the work-up to give the alcohol **14**, the tert-butyldimethylsiloxy group was inert to these conditions and was cleaved in a second, fluoride induced step to **14**. Nevertheless, the one-step addition-PG cleavage proved to give the better yield. The alcohol was oxidized with pyridinium dichromate. Here ultrasonication proved to be very beneficial.

In the case of **21a-SiMe₂Buᵗ**, which is substituted at C7α with a trialkylsilyloxyhexyl group, the desilylation, acid catalysed dehydration-deacetalisation sequence presents a problem, as here the deprotected alcohol functionality reacts with the keto group at C-17

and a number of products are created. Moreover, the first formed cation may also react with the siloxy-moiety at the C-7 terminus. This is indicated in the fact that 7-(ω-cyanoalkyl)-6-hydroxy-3-methxoyestra-1,3,5(10)-trien-17-one 17,17- acetals give progressively more side products upon acid catalysed elimination with shortening
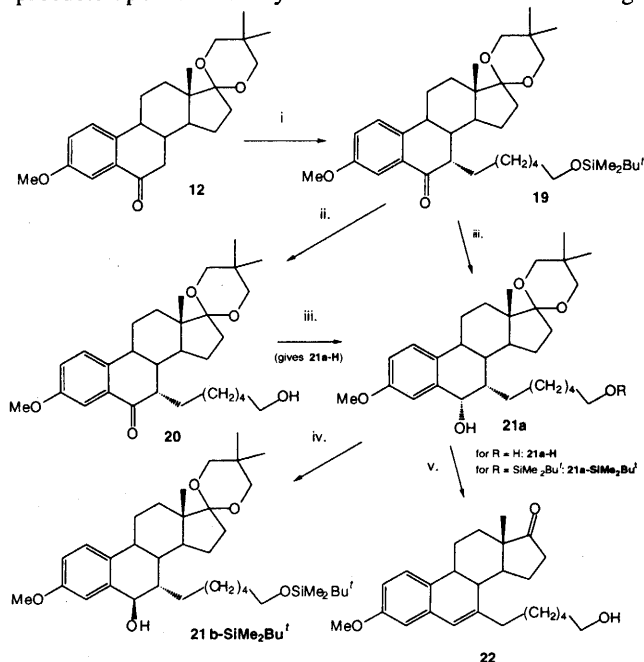
i.) KOBuᵗ, THF, Me₂BuᵗSiOC₆H₁₂I;
ii.) Bu₄NF; THF; iii.) NaBH₄, MeOH,
Et₂O; iv.) POCl₃, Py; v.) p-TsOH,
benzene, Δ.

Scheme 6

of the side chain at C-7α (i.e., C₆-CN (32%); C₄-CN (19%), while C₂-CN virtually only gives oligomeric products). In the case of **19**, **22** is formed in only 4% yield. The same yield of **22** is found, when **21a-H** is treated with p-TsOH under analogous conditions. It was deemed possible to circumvent this sequence by reduction of **19** to **21a-H**, mesylation and base catalysed dehydration of the secondary mesylate. De facto, mesylation and dehydration should have been possible to be run in a one-pot procedure; in fact, however, in this case the pyridinium salt **23** (not shown) is formed, most probably by mesylation of the 6-hydroxy group and subsequent nucleophilic substitution. Furthermore, subjecting **21a-SiMe₂Buᵗ** to either BF₃·Et₂O in CH₂Cl₂, BF₃·Et₂O in THF[16] or to Burgess' reagent (ClSO₂NHCOOMe)[17] resulted in mixtures of products. The reaction of POCl₃ with pyridine[18] as base, a reaction well known to yield alkenes from sec.-alkanols, leads to **21b-SiMe₂Buᵗ**, the C6-epimer of **21a-SiMe₂Buᵗ**. In the reduction of **21a-SiMe₂Buᵗ** with NaBH₄ it is believed that NaBH₄ approaches **21a-SiMe₂Buᵗ** from the less hindered face, namely from the β-face, as the substituent at C-7α effectively covers the α-face, and forces the hydroxy group into the α-position. The 6α-hydroxy **21a-SiMe₂Buᵗ** is calculated to be less stable than its 6β-epimer. In the reaction of **21a-SiMe₂Buᵗ** with POCl₃ it is believed that an S$_N$2 type reaction occurs

with water as the attacking nucleophile upon hydrolysis of the phosphoric ester.

When looking at the spectroscopic data of **21b-SiMe₂Buʹ**, it is interesting to note that not only the H-6 undergoes a chemical shift in the proton NMR but also H-4 experiences a high-field shift by 0.35 – 0.40 ppm (6β-hydroxy-**21b-SiMe₂Buʹ** vs. 6α-hydroxy **21a-SiMe₂Buʹ**). A similar shift of H-4 has been noted in steroidal 4-en-3-one series.[19]
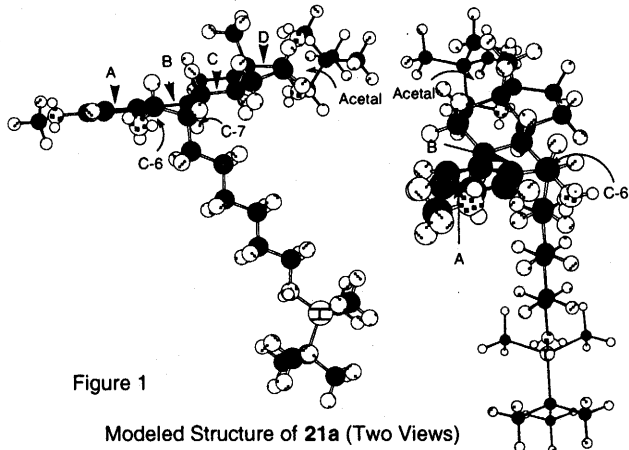

Figure 1

Modeled Structure of **21a** (Two Views)

While proton catalysed elimination (i.e. *E*1-type elimination) of C-7 substituted 6-hydroxyestra-1,3,5(10)-trienes of type **21** with small to medium sized, terminally substituted C-7 alkyl chains seems inadvisable, a base catalysed, synchronous elimination (i.e. *E*2-type elimination) seems equally difficult. The reason for this may lie in the fact that the conformational rigidity of the B-ring is such that the two leaving groups do not come to lie in *anti*periplanar or *syn*periplanar positions. In fact, when C-7 unsubstituted 6-hydroxyestra-1,3,5(10)-trien-17-one is compared with **21a** in MM2-based molecular dynamics calculations[20] it can be seen that the C-7α substituent renders the B-ring conformationally more rigid. At this point, a route to the C-7α hydroxyhexylestra-1,3,5,(10),6-tetraene is envisaged via transformation of **19** to the corresponding 6-tosylhydrazone followed by base catalysed elimination.[21]
When the 7α-formylalkylestra-1,3,5(10)-trienes were reacted with the stabilized phosphoranes, the
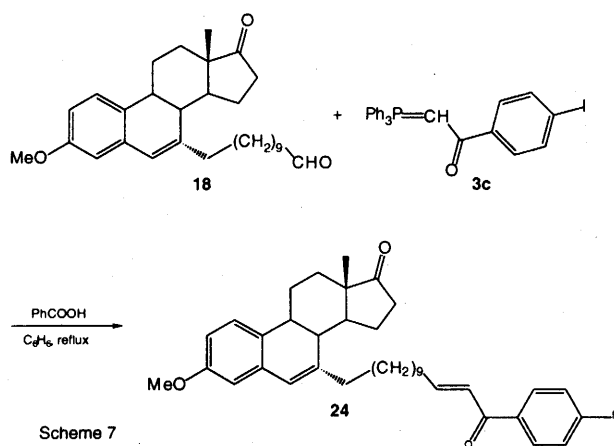
Scheme 7

corresponding Wittig products could be isolated. With these stabilized phosphoranes benzoic acid has to be used
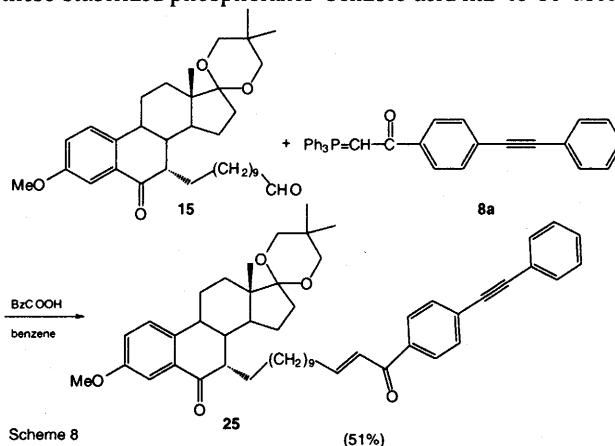
Scheme 8

as a catalyst.[22] That the Wittig-olefination of ketoaldehydes such as **15** proceeds very selectively on the aldehyde-functionality can be seen in the fact that **15** only gave *E*-**25**. The keto functionality was left unchanged. The mediocre yield in case of phosphorane **3c** may be due to the relative instability of the iodo-moiety under the reaction conditions. The stabilized phosphoranes can be kept in pure form for some weeks when in the solid state. Exposure to light should be avoided.

Experimental

Phenylacetylene and estrone (estra-1,3,5(10)-trien-3-ol-17-one) were obtained commercially. 3-Methoxy-6-oxoestrone-17,17-(2ʹ-[5ʹ,5ʹ-dimethyl-1ʹ,3ʹ-dioxane])[14] (**12**), *p*-bromobenzoylmethylidenetriphenylphosphorane (**3a**) and *p*-iodobenzoylmethylidenetriphenylphosphorane (**3c**) were prepared analogous to literature procedures.[6] *p*-Cyanophenylacetylene (**7a**),[23] *p*-nitrophenylacetylene

ω-trimethylsiloxy- and ω-tert-butyldimethylsiloxyalkyl iodides **11**[25] were prepared analogous to literature procedures; for these preparations, the experimental procedures are listed below.

6-*tert.*-Butyldimethylsiloxyhexane iodide (11a). – Typical procedure for preparation of α,ω-trialkylsiloxyalkane iodides.

– To LiBH$_4$[24] (163 mg, 7.5 mmol) in dry ether (15 mL) was slowly added methyl bromohexanoate (**9a-OMe**) (1.04 g, 5.0 mmol) and subsequently dropwise MeOH (280 mg, 355 μl, 8.75 mmol). After the gas evolution had ceased the solution was held at reflux for 1h. After the solution was cooled, 2N HCl (1 mL) was added carefully. The phases were separated, the aqueous phase was extracted with ether (2 X 10 mL) and the combined organic phase was dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (ether/hexane 1:1) to give 6-bromohexanol (**10a**) (905 mg, quant.) as a colorless oil. A mixture of bromohexanol (**10a**) (905 mg, 5.0 mmol) and NaI (2.5 g, 16.7 mmol)[17] in acetone (19 mL) was held at reflux for 8h. The cooled solution was concentrated *in vacuo*. Then water (15 mL) was added, the phases separated and the aq. phase extracted with ether (2 X 15 mL). The combined organic phase was dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. Column chromatography on silica gel (ether/hexane 1:1) gave 6-iodohexanol (**11a-OH**) (978 mg, 86%) as a colorless oil. To iodohexanol (**11a-OH**) (830 mg, 3.6 mmol) in dry ether (5 mL) were added at 0°C 2-methylimidazole (364 mg, 4.4 mmol) and then in 6 portions *tert.*-butyldimethylchlorosilane (657 mg, 4.4 mmol) as a solid. The mixture was stirred for 1h at 0°C and for 2h at rt. The suspension was poured into ice-water (15 mL) and quickly extracted with ether (2 X 15 mL). The combined organic phase was dried diligently over anhydrous MgSO$_4$ and concentrated *in vacuo*. Column chromatography on silica gel (hexane/ether 2:1) gave **11a** (748 mg, 60%) as a colorless oil; IR (neat) 2930, 2892, 2856, 1462, 1254, 1103, 835, 775 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.01 (s, 6H, 2 CH$_3$), 0.86 (s, 9H, C(CH$_3$)$_3$), 1.34 (m, 4H), 1.48 (m, 2H), 1.79 (m, 2H), 3.15 (t, 2H, *J* 6.9 Hz), 3.57 (t, 2H, *J* 6.3 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 0.00 (+, 2 CH$_3$), 7.15 (-), 18.35 (C$_{quat}$), 24.76 (-), 25.95 (+, 3C, C(CH$_3$)$_3$), 30.28 (-), 32.56 (-), 33.50 (-), 63.00 (-); MS (70 eV) m/z (%) 285 (100, M$^+$-Bu').

p-(*E*-Phenylethenyl)benzoylmethylidene-phosphorane (5b).

– Method A: A mixture of **3a** (500 mg, 1.09 mmol), styrene (0.19 mL, 170 mg, 1.64 mmol), triethylamine (0.18 mL, 132 mg, 1.31 mmol), palladium acetate (24 mg, 0.11 mmol) and triphenylphosphine (71 mg, 0.27 mmol) in N,N-dimethylformamide (2 mL) was heated at 100°C for 24h. Thereafter the cooled solution was diluted with water and extracted with dichloromethane. The organic phase was washed with water, dried over

anhydrous MgSO$_4$ and concentrated *in vacuo*. Chromatography on silica gel (eluant: ether) yielded **5b** (32 mg, 6%) as a pale yellow powder (ether), mp 208 – 210°C (ether); R$_f$ 0.43 (ether/ethyl acetate 1:1); IR (KBr) ν 3050, 1519, 1481, 1437, 1410, 1387, 1103, 880, 746, 715, 693 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.43 (brs, 1H), 7.14 – 7.77 (m, 24H), 7.97 (d, 2H, ^3J 8.2 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 50.87 (CH, $^1J_{C=P}$ 112.1 Hz), 125.95 (+,CH), 126.52 (+, CH), 127.05 (C$_{quat}$, J_{C-P} 91.3 Hz), 127.35 (+, CH), 127.58 (+, CH), 128.55 (+, CH), 128.64 (+, CH), 128.84 (+, CH), 128.87 (+, CH J_{C-P} 12.1 Hz), 132.06 (+, CH, J_{C-P} 2.4 Hz), 133.16 (CH, J_{C-P} 10.9 Hz), 137.37 (C$_{quat}$), 138.27 (C$_{quat}$), 140.39 (C$_{quat}$, J_{C-P} 14.6 Hz), 184.28 (C$_{quat}$, $^2J_{C-P}$ 2.4 Hz, C=O). MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 483 (MH$^+$, 51). HRMS Found: 483.1877; Calcd. for C$_{34}$H$_{28}$OP: 483.1878.

Method B: A mixture of **3c** (273 mg, 0.54 mmol), styrene (0.1 mL, 84 mg, 0.81 mmol), triethylamine (0.09 mL, 65 mg, 0.65 mmol), palladium acetate (12 mg, 0.054 mmol) and triphenylphosphine (35 mg, 0.135 mmol) in N,N-dimethylformamide (1 mL) was heated at 100°C for 2h. Thereafter the cooled solution was diluted with water, dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. Chromatography on silica gel (eluant ether/ethyl acetate 1:1) yielded **5b** (117 mg, 45%).

p-(Methoxycarbonylethenyl)benzoyl-methylidenephosphorane (5a).

– A mixture of **3a** (500 mg, 1.09 mmol), methyl acrylate (0.15 mL, 141 mg, 1.64 mmol), triethylamine (0.18 mL, 132 mg, 1.31 mmol), palladium acetate (24 mg, 0.11 mmol) and triphenylphosphine (71 mg, 0.27 mmol) in N,N-dimethylformamide (2 mL) was heated at 100°C for 24h. Thereafter the cooled solution was diluted with water and extracted with dichloromethane. The organic phase was washed with water, dried over anhydrous MgSO$_4$ and concentrated *in vacuo*. Chromatography on silica gel (eluant: chloroform / ethyl acetate 5 : 1 - 3 : 1) yielded **5a** (193 mg, 38%) as an orange powder (ether); mp 198 – 199°C (ether); R$_f$ 0.41 (ether/ethyl acetate 1:1); IR (KBr) 3042, 1712, 1633, 1574, 1518, 1480, 1437, 1408, 1388, 1312, 1203, 1171, 1104, 881, 840, 747, 716, 694 cm-1; ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.80 (s, 3H, OCH$_3$), 4.45 (d, 1H, $^1J_{H-P}$ 24.1 Hz), 6.46 (d, 1H, ^3J 16.2 Hz, olef. H), 7.46 - 7.58 (m, 11H), 7.60 - 7.75 (m, 7H), 7.98 (d, 2H, Ar-H); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 51.65 (+, COOCH$_3$), 51.70 (+, CH, $^1J_{C=P}$ 112.1 Hz), 117.79 (+, CH), 126.79 (C$_{quat}$, $^1J_{C-P}$ 90.1 Hz), 127.46 (+, CH), 127.64 (+, CH), 128.91 (+, CH, J_{C-P} 12.2 Hz), 132.15 (+, CH, J_{C-P} 2.4Hz), 133.14 (+, CH, J_{C-P} 9.9 Hz), 135.11 (C$_{quat}$), 143.07 (C$_{quat}$, J_{C-P} 14.6 Hz), 144.69 (+, CH), 167.49 (C$_{quat}$, C=O, COOCH$_3$), MS (70 eV) m/z (%) 464 (M$^+$, 100), 435 (M$^+$-CHO, 22), 303 (M$^+$-CH$_3$COOCH=CHPh, 73). HRMS Found: 464.1539; Calcd. for C$_{30}$H$_{25}$O$_3$P: 464.1541.

5-(Methoxycarbonylethenyl)thien-2-oyl-methylidenephosphorane (5d). - A mixture of **3e** (90 mg, 0.19 mmol), methyl acrylate (0.15 mL, 141 mg, 1.64 mmol), triethylamine (0.10 mL, 73 mg, 0.73 mmol), palladium acetate (24 mg, 0.11 mmol) and triphenylphosphine (71 mg, 0.27 mmol) in N,N-dimethylformamide (2 mL) was heated at $100°C$ for 10h. Thereafter the cooled solution was diluted with water and extracted with ether (2 X 5 mL) and chloroform (10 mL). The organic phase was washed with water, dried over anhydrous $MgSO_4$ and concentrated and dried *in vacuo*. (It is advantageous to remove as much as possible of the residual DMF at this stage). Chromatography on silica gel (ether) gave **5d** (38 mg, 41%) as a slowly crystallizing yellow oil; IR (neat) v 3058, 2954, 1708, 1621, 1530, 1511, 1438, 1387, 1195, 1118, 747, 720, 693 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.77 (s, 3H, COOCH$_3$), 4.34 (bs, 1H), 6.22 (d, 1H, ^3J 15.5 Hz), 7.15 (d, 1H, ^3J 4.0 Hz), 7.26 – 7.73 (m, 17H); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 51.61 (+, COOCH$_3$), 51.80 (+, CH, $^1J_{C=P}$ 113.3 Hz), 116.37 (+, CH), 126.41 (C$_{quat}$, $^1J_{C-P}$ 91.4 Hz), 126.61 (+, CH), 128.48 (+, CH, J_{C-P} 12.2 Hz), 131.28 (+, CH), 131.77 (C$_{quat}$), 131.91 (+, CH, J_{C-P} 2.5 Hz), 133.14 (+, CH, J_{C-P} 11.0 Hz), 137.90 (+, CH), 140.38 (C$_{quat}$), 167.37 (C$_{quat}$, C=O, COOMe), 186.40 (C$_{quat}$, C=O); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 471 (MH$^+$, 6). HRMS Found: 471.1182; Calcd. for C$_{28}$H$_{24}$O$_3$PS: 471.1184.

p-Cyanophenylacetylene (7a). – To a mixture of trimethylsilylacetylene (1.18 g, 1.7 mL, 12.0 mmol) and 4-bromobenzonitrile (**6a**) (1.82 g, 10.0 mmol) in triethylamine (40 mL) was added bis[triphenylphosphine]palladium dichloride (140 mg, 0.2 mmol) and copper(I) iodide (20 mg, 0.1 mmol). The reaction mixture was stirred for 4h at rt under argon. Then the solvent was removed under reduced pressure. To a solution of the residue in methanol (20 mL), a 1N aqueous KOH solution (10 mL) was added and the mixture was stirred at rt for 1h. After removal of the methanol, the product was extracted with ether and purified by column chromatography on silica gel (benzene) to afford a yellow solid. Recrystallisation from ethanol gave **7a** as pale yellow needles (703 mg, 55%); R$_f$ 0.59; mp 152 - 153°C; IR (KBr) v 3234, 2226, 2100, 1602, 1498, 1407, 1271, 839, 731, 687 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.31 (s, 1H), 7.57 (d, 2H, J 8.6 Hz), 7.63 (d, 2H, J 8.6 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 81.85 (CH), 82.16 (C$_{quat}$), 112.62 (C$_{quat}$), 118.58 (C$_{quat}$, CN), 127.28 (C$_{quat}$), 132.33 (CH), 132.97 (CH); MS (70 eV) m/z (%) 127 (M$^+$, 100).

p-Amidophenylacetylene (7d). – At 0°C hydrogen peroxide (35w% aq., 0.8 mL), tetrabutylammonium hydrogen sulfate (107 mg, 0.31 mmol) and a 20w% aq. NaOH solution (0.6 mL) were added to a solution of p-cyanophenylacetylene (**7a**) (200 mg, 1.57 mmol) in

CH$_2$Cl$_2$ (0.6 mL). The reaction mixture was allowed to warm to rt. After 0.5h, ethyl acetate (5 mL) was added. The organic layer was separated, washed with sat. aq. NaCl solution (5 mL) and dried over anhydrous MgSO$_4$. The solvent was evaporated to leave a pure colorless powder of **7d** (177 mg, 78%); mp 176 – 177°C (ethyl acetate); R$_f$ 0.17 (ether); IR (KBr) v 3394, 3280, 3176, 1658, 1622, 1557, 1411, 1393, 1280, 1143, 1119, 1016, 853, 800, 623 cm^{-1}; ^{1}H NMR (270MHz, CDCl$_3$) δ 3.22 (s, 1H), 5.98 (br, 2H, NH$_2$), 7.57 (dd, 2H, J 6.6 Hz, J 2.0 Hz), 7.77 (dd, 2H, J 6.6 Hz, J 2.0 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 135, DEPT 90) δ 79.78 (CH), 82.64 (C$_{quat}$), 125.96 (C$_{quat}$), 127.33 (CH), 132.36 (C$_{quat}$), 133.28 (CH), 168.44 (C$_{quat}$, C=O); MS (70 eV) m/z (%) 145 (M$^+$, 79), 129 (M$^+$-NH$_2$, 100), 101 (M$^+$-CONH$_2$, 53). HRMS: 145.0528. Calcd. for C$_9$H$_7$ON: 145.0528.

p-Nitrophenylacetylene (7b). – Trimethylsilylacetylene (1.18 g, 1.7 mL, 12.0 mmol), 4-bromonitrobenzene (**6b**) (2.02 g, 10.0 mmol), and (Ph$_3$P)$_2$PdCl$_2$ in triethylamine (40 mL) was reacted as described above (5h). After treating the crude material dissolved in methanol (20 mL) with 1N aq. KOH (10 mL), the product is worked up as above. Column chromatography on silica gel (hexane/benzene 4:1) afforded a yellow solid, which was crystallised from ethanol to give **7b** as pale yellow needles (840 mg, 57%); R$_f$ 0.28; 151 - 152°C; IR (KBr) v 3250, 3102, 1594, 1512, 1344, 1288, 1105, 854, 750, 678 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.37 (s, 1H), 7.64 (d, 2H, ^3J 8.9 Hz), 8.20 (d, 2H, ^3J 8.9 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 81.62 (C$_{quat}$), 82.35 (CH), 123.57 (CH), 128.93 (C$_{quat}$), 132.97 (C$_{quat}$), 147.56 (C$_{quat}$); MS (70 eV) m/z (%) 147 (M$^+$, 100), 117 (M$^+$-NO, 40), 101 (M$^+$-NO$_2$, 73).

p-(E-Cyanoethenyl)benzoylmethylidenetri-phenylphosphorane (5c). – (Method 1): A mixture of p-bromobenzoylmethylidenetriphenylphosphorane (**3a**) (250 mg, 0.54 mmol), acrylonitrile (0.05 mL, 43 mg, 0.82 mmol), triethylamine (0.09 mL, 65 mg, 0.65 mmol), palladium acetate (12 mg, 0.054 mmol) and triphenylphosphine (35 mg, 0.135 mmol) in N,N-dimethylformamide (1 mL) was heated at 90°C for 15h. Thereafter the cooled solution was diluted with water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. Chromatography on silica gel (eluant ether / ethyl acetate 1:0 – 1:1) yielded **5c** (42 mg, 18%) as an orange powder (ether), mp 209 – 210°C (ether); R$_f$ 0.39 (ether/ethyl acetate 1:1); IR (KBr) 3008, 2212, 1614, 1573, 1495, 1478, 1436, 1412, 1394, 1310, 1211, 1179, 1105, 1071, 1014, 997, 972, 883, 824, 752, 715, 693 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.38 (d, 1H, $^2J_{H-P}$ 23.1 Hz), 5.81 (d, 1H, J 16.7 Hz), 7.29 - 7.68 (m, 18H), 7.91 (d, 2H, ^3J 7.3 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 52.09 (CH, $^1J_{C=P}$ 110.9 Hz), 96.10 (CH), 118.29 (CN), 126.59 (C$_{quat}$, $^1J_{C-P}$ 91.4 Hz), 126.92

(CH), 127.60 (CH), 128.93 (CH, J_{C-P} 12.2 Hz), 132.20 (CH, J_{C-P} 2.4 Hz), 133.08 (CH, J_{C-P} 9.8 Hz), 134.07 (C_{quat}), 143.92 (C_{quat}, J_{C-P} 14.6 Hz), 150.37 (CH), 183.12 (C=O, $^2J_{C-P}$ 3.7 Hz); MS (EI, 70 eV) m/z (%) 431 (M^+, 100), 402 (M^+-CHO, 21), 303 ([M^+-NC-CH=CH-Ph], 70); HRMS Found: 432.1521; Calcd. for $C_{29}H_{23}NOP$: 432.1517.

(Method 2): A mixture of p-iodobenzoylmethylidenetriphenylphosphorane (3c) (273 mg, 0.54 mmol), acrylonitrile (0.05 ml, 43 mg, 0.82 mmol), triethylamine (0.09 ml, 65 mg, 0.65 mmol), palladium acetate (12 mg, 0.054 mmol) and triphenylphosphine (35 mg, 0.135 mmol) in N,N-dimethylformamide (1 ml) was heated at 90°C for 15h. Thereafter the cooled solution was diluted with water and extracted with dichloromethane. The organic phase was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. Chromatography on silica gel (eluant ether / ethyl acetate 1:1) yielded 5c (58 mg, 25%) as an orange powder (ether).

p-(Phenylethynyl)benzoylmethylidenetriphenylphosphorane (8a).

– In an oven-dried flask held under argon was placed p-iodobenzoylmethylidenetriphenylphosphorane (3c) (500 mg, 0.99 mmol), dry diisopropylamine (3 mL), dry toluene (1.9 mL) and $Pd(PPh_3)_4$ (34 mg, $2.72\,10^{-2}$ mmol). The reaction mixture was heated to 60°C, and phenylacetylene (0.11 mL, 101 mg, 0.99 mmol) and CuI (4 mg, $2.13\,10^{-2}$ mmol) were added. The reaction was stirred under argon at 60°C for 13 h. The flask was allowed to cool to room temperature, and diethylether (25 mL) was added. The mixture was washed with water, and saturated aqueous NaCl and dried over magnesium sulfate. The solvent was concentrated *in vacuo*. Chromatography on silica gel (eluant ether / ethyl acetate 1:1) yielded 8a (209 mg, 44%) as yellow powder (ether), mp 222 – 223°C (ether); R_f 0.54 (ether/ethyl acetate 1:1); IR (KBr) 3056, 1565, 1516, 1482, 1438, 1403, 1387, 1188, 1104, 1079, 1015, 998, 876, 853, 753, 718, 689 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.44 (d, 1H, 2JH-P 24.1 Hz), 7.28 - 7.83 (m, 22H), 7.95 (2H, 3J 8.3 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 51.38 (CH, $^1J_{C=P}$ 110.9 Hz), 89.77 (C_{quat}), 90.19 (C_{quat}), 123.32 (C_{quat}), 123.97 (C_{quat}), 126.85 (C_{quat}, $^1J_{C-P}$ 91.4 Hz), 126.92 (CH), 128.19 (CH), 128.30 (CH), 128.91 (CH, J_{C-P} 12.1 Hz), 131.07 (CH), 131.59 (C_{quat}), 132.13 (CH, J_{C-P} 2.4 Hz), 133.13 (CH, J_{C-P} 9.8 Hz), 140.95 (C_{quat}, J_{C-P} 14.6 Hz), 183.79 (C=O, $^2J_{C-P}$ 2.4 Hz); MS (EI, 70 eV) m/z (%) 480 (M^+, 100), 451 (M^+-CHO, 25), 303 ([M^+-Ph-C≡C-Ph], 74). HRMS (FAB, 3-nitrobenzyl alcohol): 481.1714 (MH^+); Calcd. for $C_{34}H_{26}OP$: 481.1721. Anal. Calcd. for $C_{34}H_{25}OP$ (480.55) C, 85.21; H, 5.27. Found C, 84.98; H, 5.24.

p-(4'-Cyanophenylethynyl)benzoylmethylidenetriphenylphosphorane (8b).

– p-Iodobenzoylmethylidenetriphenylphosphorane (40 mg, 0.08 mmol), p-cyanophenylacetylene (7a) (10 mg, 0.08

mmol), $Pd(PPh_3)_4$ (3 mg, $2.4\,10^{-6}$ mol, 3 mol%) and CuI (0.3 mg, $1.6\,10^{-6}$ mol, 2 mol%) in dry diisopropylamine (0.24 mL) and dry toluene (0.15 mL) were reacted (13h, 60°C, argon) and worked up as described above. The reaction mixture was purified by TLC chromatography (ether – ether/ethyl acetate 1:1) to give 8b (20 mg, 50%) as a pale yellow solid; mp 277 - 278°C (ether); R_f 0.54 (ether/ethyl acetate 1:1); IR (KBr) 3050, 2220, 1603, 1565, 1507, 1436, 1404, 1385, 1107, 886, 690 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.46 (d, 1H, $^2J_{P-H}$ 23.1 Hz), 7.45 – 7.76 (m, 21H), 7.97 (d, 2H, ^3J 8.2 Hz); ^{13}C NMR (67.8 MHz, DEPT 90, DEPT 135) δ 51.93 (CH, $^1J_{C=P}$ 88.52 (C_{quat}), 94.23 (C_{quat}), 111.32 (C_{quat}), 118.60 (C_{quat}), 122.84 (C_{quat}), 126.69 (C_{quat}, $^1J_{C-P}$ 91.4 Hz), 127.06 (CH), 128.33 (C_{quat}), 128.96 (CH, J_{C-P} 12.1 Hz), 131.34 (CH), 132.14 (CH, J_{C-P} 13.5 Hz), 132.19 (CH), 133.13 (CH, J_{C-P} 9.8 Hz), 141.78 (C_{quat}, J_{C-P} 14.6 Hz), 183.50 (C_{quat}, $^2J_{C-P}$ 2.4 Hz, C=O); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 506 (MH^+, 100), 303 (29). HRMS (FAB. 3-nitrobenzyl alcohol): 506.1672 (MH^+); Calcd. for $C_{35}H_{25}ONP$: 506.1674.

p-(4'-Nitrophenylethynyl)benzoylmethylidenetriphenylphosphorane (8c).

– p-Iodobenzoylmethylidenetriphenylphosphorane (3c) (500 mg, 0.99 mmol), p-nitrophenylacetylene (7b) (146 mg, 0.99 mmol), $Pd(PPh_3)_4$ (34 mg, $2.72\,10^{-2}$ mmol, 3 mol%), CuI (4 mg, $2.13\,10^{-2}$ mmol, 2 mol%) in dry diisoproylamine (3.0 mL) and dry toluene (1.9 mL) were reacted (13h, 60°C, argon). After the reaction was cooled to rt, chloroform (25 mL) was added, the mixture was washed with water (2 X 15 mL) and sat. aq. NaCl (1 X 15 mL). The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was washed with ether (20 mL) and yielded 8c (518 mg, 99%) as a pale yellow powder; mp 258 - 259°C (ether); R_f 0.18 (ether); IR (KBr) 3058, 2216, 1592, 1569, 1515, 1482, 1437, 1406, 1387, 1344, 1187, 1107, 1015, 877, 854, 824, 748, 718, 692 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.46 (d, 1H, $^2J_{H-P}$ 23.8 Hz), 7.45 – 7.76 (m, 19H), 7.98 (d, 2H, ^3J 8.6 Hz), 8.21 (d, 2H, ^3J 8.6 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 51.83 (CH, $^1J_{C=P}$ 110.9 Hz), 88.30 (C_{quat}), 95.17 (C_{quat}), 122.66 (C_{quat}), 123.59 (CH), 126.69 (C_{quat}, $^1J_{C-P}$ 91.3 Hz), 127.04 (CH), 128.91 (CH, J_{C-P} 12.2 Hz), 130.35 (C_{quat}), 131.36 (CH), 132.20 (CH), 132.78 (CH), 133.10 (CH, J_{C-P} 9.7 Hz), 141.97 (C_{quat}, J_{C-P} 15.8 Hz), 146.86 (C_{quat}), 183.43 (C_{quat}, C=O, $^2J_{C-P}$ 2.4 Hz); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 526 (MH^+, 46). HRMS (FAB, 3-nitrobenzyl alcohol) Found: 526.1577. Calcd. for $C_{34}H_{25}O_3NP$: 526.1572 (MH^+).

4-(p-Amidophenylethynyl)benzoylmethylidenetriphenylphosphorane (8d).

– A mixture of p-iodobenzoylmethylidenetriphenylphosphorane (3c) (100 mg, 0.2 mmol), dry isopropylamine (0.6 mL) and $Pd(PPh_3)_4$ (7 mg, 3mol%, 6.3 μmol) in dry

toluene (0.4 mL) was heated at 60°C under argon, and *p*-amidophenylacetylene (**7d**) (29 mg, 0.2 mmol) and CuI (0.3 mg, 2 mol%, 1.5 μmol) were added. The reaction mixture was stirred at 60°C for 13h. Then it was cooled to rt and ether (10 mL) was added. The mixture was washed with water (5 mL), sat. aq. NaCl solution (5 mL) and dried over anhydrous MgSO$_4$. The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography on silica gel (ethyl acetate) to give **8d** (49 mg, 47%) as a pale yellow powder, mp 295 – 296°C (ethyl acetate); R$_f$ 0.11 (ethyl acetate); IR (KBr) v 3300, 3166, 1737, 1680, 1609, 1564, 1437, 1238, 1108, 875, 750, 716, 691 cm^{-1}; ^{1}H NMR (270 MHz, DMSO-d$_6$) δ 4.59 (d, 1H, $^2J_{H-P}$ 24.1 Hz), 7.47 – 8.07 (m, 25H); ^{13}C NMR (67.8 MHz, DMSO-d$_6$, DEPT 135, DEPT 90) δ 49.68 (CH, $^1J_{C=P}$ 111.3 Hz), 89.72 (C$_{quat}$), 91.25 (C$_{quat}$), 122.51 (C$_{quat}$), 124.90 (C$_{quat}$), 126.40 (C$_{quat}$, J_{C-P} 91.4 Hz), 126.88 (CH), 127.74 (CH), 128.96 (CH, J_{C-P} 12.2 Hz), 130.91 (CH), 131.14 (CH), 132.27 (CH), 132.69 (CH, J_{C-P} 11.0 Hz), 134.00 (C$_{quat}$), 140.91 (C$_{quat}$, J_{C-P} 14.6 Hz), 166.97 (C$_{quat}$, C=O), 181.47 (C$_{quat}$, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 524 (MH$^+$, 64); HRMS Found: 524.1779; Calcd. for C$_{35}$H$_{27}$NO$_2$P: 524.1777 (MH$^+$).

5-(4'-Cyanophenylethynyl)thien-2-oyl-methylidenetriphenylphosphorane (8e).

– A mixture of 5-bromothien-2-oylmethylidenetriphenylphosphorane (**3e**) (70 mg, 0.15 mmol), dry isopropylamine (0.5 mL) and Pd(PPh$_3$)$_4$ (5 mg, 4.5 μmol) was heated at 60°C under argon, and *p*-cyanophenylacetylene (**7a**) (19 mg, 0.15 mmol) and CuI (0.6 mg, 3.0 μmol) were added. The reaction mixture was stirred at 60°C for 4h. Then it was cooled to rt and ether (10 mL) was added. Water (5 mL) was added and the phases were separated. The organic phase was washed with sat. aq. NaCl (5 mL) and dried over anhydrous MgSO$_4$. The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography on silica gel (ether) to give **8e** (35 mg, 46%) as yellow needles, mp 240 - 242°C; R$_f$ 0.18 (ether); IR (KBr) v 3054, 2224, 2194, 1601, 1519, 1436, 1385, 1104, 867, 838, 744, 729 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 4.30 (d, 1H, $^2J_{H-P}$ 22.4 Hz), 7.22 (d, 1H, ^3J 3.6 Hz), 7.41 (d, 1H, ^3J 3.6 Hz), 7.45 – 7.74 (m, 19H); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 51.52 (+, CH, $^1J_{C=P}$ 112.1 Hz), 88.16 (C$_{quat}$), 91.75 (C$_{quat}$), 111.32 (C$_{quat}$), 118.54 (C$_{quat}$), 123.02 (C$_{quat}$), 125.95 (+, CH), 126.52 (C$_{quat}$, $^1J_{C=P}$ 91.6 Hz), 128.05 (C$_{quat}$), 129.00 (+, CH, J_{C-P} 12.2 Hz), 131.73 (+, CH), 132.00 (+, CH), 132.32 (+, CH, J_{C-P} 2.4 Hz), 133.13 (+, CH, J_{C-P} 9.7 Hz), 133.40 (+, CH), 151.45 (C$_{quat}$, J 16.0 Hz), 176.70 (C$_{quat}$, C=O); MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 512 (18). HRMS Found: 512.1240; Calcd. for C$_{33}$H$_{23}$ONPS: 512.1238.

7α-(11'-*tert*-Butyldimethylsiloxyundecyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6,17-dione-

17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane])

(**13**) – To 3-*O*-Methyl-estra-1,3,5(10)-trien-6,17-one-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12**) (250 mg, 0.65 mmol) in dry DME (8 mL) was added at 0°C dry THF (0.75 mL) and KOBu^t (84 mg, 0.75 mmol). The mixture was stirred at rt for 1h under an inert atmosphere. Then the mixture was cooled to –78°C and 11-*tert*-butyldimethylsiloxyundecane iodide (**11b**) (309 mg, 0.75 mmol) was added. The mixture was stirred for 22h under gradual warming to rt. Water (10 mL) was added and the mixture was extracted with ethyl acetate (20 mL). The organic phase was washed with aq. sat. NaCl (20 mL) and dried over anhydrous MgSO$_4$. It was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (toluene/ethyl acetate 30:1) to give **13** (94 mg, 22%) as an oil. R$_f$ 0.52; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.00 (s, 6H, 2 CH$_3$), 0.69 (s, 3H, CH$_3$), 0.79 (s, 3H, CH$_3$), 0.84 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 1.18 – 1.80 (m, 24H), 1.93 – 2.07 (m, 3H), 2.25 – 2.43 (m, 4H), 2.66 – 2.71 (m, 1H), 3.34 – 3.56 (m, 4H), 3.54 (t, 2H, J 3.5 Hz), 3.79 (s, 3H, OCH$_3$), 7.03 (dd, 1H, J 2.7, 8.7 Hz), 7.27 (1H, d, J 8.7 Hz), 7.48 (d, 1H, J 2.7 Hz); ^{13}C NMR (100.4 MHz, CDCl$_3$) δ –5.28 (2C), 13.75, 18.33, 21.98, 22.24, 22/49, 23.79, 25.76, 25.96 (6C), 26.54, 26.91, 27.38, 29.40, 29.54, 29.58, 29.69, 30.33, 32.85, 37.30, 42.80, 42.89, 47.34, 48.82, 55.38, 63.28, 70.72, 108.33, 109.95, 121.32, 127.16, 132.20, 138.97, 158.06, 201.30; MS (FAB, 3-nitrobenzyl alcohol) *m/z* (%) 669 (MH$^+$). HRMS (FAB) Found 669.4910. Calcd for C$_{41}$H$_{69}$O$_5$Si: 669.4914 (MH$^+$).

7α-(11'-*tert*-Butyldimethylsiloxyhexyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6,17-dione-

17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane])

(**19**) – To 3-*O*-Methyl-estra-1,3,5(10)-trien-6,17-dione-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (**12**) (580 mg, 1.51 mmol) in dry DME (13 mL) was added at 0°C dry THF (1.74 mL) and KOBu^t (195 mg, 1.74 mmol). The mixture was stirred at rt for 1h under an inert atmosphere. Then the mixture was cooled to –78°C and 11-*tert*-butyldimethylsiloxyhexane iodide (**11a**) (775 mg, 2.27 mmol) was added. The mixture was stirred for 16h under gradual warming to rt. Water (10 mL) was added and the mixture was extracted with ethyl acetate (20 mL). The organic phase was washed with aq. sat. NaCl (20 mL) and dried over anhydrous MgSO$_4$. It was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (toluene/ethyl acetate 30:1) to give **19** (294 mg, 33%) as an oil; R$_f$ 0.49; IR (neat) 3014, 2932, 2858, 1678, 1609, 1495, 1464, 1283, 1257, 1216, 1105, 1036, 836, 770 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.00 (s, 6H, 2 CH$_3$), 0.71 (s, 3H, CH$_3$), 0.80 (s, 3H, CH$_3$), 0.85 (s, 9H, C(CH$_3$)$_3$), 0.86 – 2.87 (m, 21H), 1.14 (s, 3H, CH$_3$), 3.34- 3.47 (m, 3H), 3.53 (2H, t, J 6.6 Hz), 3.65 (d, 2H, J 11.5 Hz), 3.81 (s, 3H, OCH$_3$), 7.05 (dd, 1H, J 3.0, 8.6 Hz), 7.30 (d, 1H, J 8.6 Hz), 7.50 (d, 1H, J 3.0 Hz); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 13.77

(+, CH₃), 18.35 (C_quat), 22.00 (+, CH₃), 22.23 (-), 22.50 (+, CH₃), 23.78 (-), 25.75 (-), 25.97 (+, 5 X CH₃), 26.51 (-), 26.87 (-), 27.39 (-), 29.31 (-), 29.54 (-), 30.35 (C_quat), 32.83 (-), 37.29 (+, CH), 42.77 (+, CH), 42.88 (+, CH), 47.33 (C_quat), 48.83 (+, CH), 55.42 (+, OCH₃), 63.29 (-), 70.71 (-), 72.58 (-), 108.34 (C_quat), 109.87 (+, CH), 121.40 (+, CH), 127.04 (+, CH), 127.21 (C_quat), 138.99 (C_quat), 158.04 (C_quat), 201.38 (C_quat, C=O); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 599 (MH⁺). HRMS (FAB) Found 599.4128. Calcd. for $C_{36}H_{58}O_5Si$: 599.4132 (MH⁺).

7α-(11'-Hydroxyundecyl)-3-*O*-methyl-estra-(1,3,5(10)-trien-6,17-dione-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (14) –

Method A: To 3-*O*-Methyl-estra-1,3,5(10)-trien-6,17-dione-17,17-(2'-[5',5'-dimethyl-1',3'-dioxane]) (12) (828 mg, 2.16 mmol) in dry DME (30 mL) was added at 0°C dry THF (2.48 mL) and KOBuᵗ (242 mg, 2.48 mmol). The mixture was stirred at rt for 1h under an inert atmosphere. Then the mixture was cooled to –78°C and 11-trimethylsiloxyundecane iodide (11c) (800 mg, 2.48 mmol) was added. The mixture was stirred for 14h under gradual warming to rt. Water (20 mL) was added and the mixture was extracted with ethyl acetate (30 mL). The organic phase was washed with aq. sat. NaCl (30 mL) and dried over anhydrous MgSO₄. It was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (toluene/ethyl acetate 15:1) to give 14 (422 mg, 35%) as an oil. R_f 0.25; IR (neat) 3458, 3016, 2928, 1676, 1494, 1464, 1215, 1105, 1035, 758 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.74 (s, 3H, CH₃), 0.83 (s, 3H, CH₃), 1.17 (s, 3H, CH₃), 1.18 – 2.10 (m, 27H), 2.21 – 2.47 (m, 5H), 2.73 (dt, 1H, J 4.4, 11.1 Hz), 3.40 (t, 2H, J 9.7 Hz), 3.62 – 3.69 (m, 4H), 3.84 (s, 3H, OCH₃), 7.08 (dd, 1H, J 2.9, 8.6 Hz), 7.32 (d, 1H, J 8.6 Hz), 7.53 (d, 1H, J 2.9 Hz); ¹³C NMR (150.8 MHz, CDCl₃) δ 13.74, 21.96, 22.20, 22.46, 23.76, 25.66, 26.50, 26.88, 27.33, 29.29, 29.33, 29.45, 29.47 (3C), 29.63, 30.31, 32.73, 37.27, 42.77, 42.86, 47.31, 48.80, 55.38, 62.95, 70.69, 72.55, 108.32, 109.93, 121.32, 127.16, 132.14, 138.99, 158.02, 201.41; MS (FAB, 3-nitrobenzyl alcohol) m/z (%) (555, MH⁺). HRMS (FAB) Found 555.4058. Calcd for $C_{35}H_{54}O_5$: 555.4050 (MH⁺).

Method B: To 13 (75 mg, 0.11 mmol) in THF (10 mL) was added dropwise via syringe tetrabutylammonium fluoride (41 mg, 0.13 mmol) in THF (0.13 mL). The reaction solution was stirred for 3h at rt. Then the mixture was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel (toluene/ethyl acetate 15:1) to give 14 (61 mg, 92%).

7α-(6'-Hydroxyhexyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6,17-dione-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (20) – To 19 (293 mg, 0.49 mmol) in THF (30 mL) was added dropwise via syringe tetrabutylammonium fluoride (179 mg, 0.57

mmol) in THF (0.57 mL). The reaction solution was stirred for 4h at rt. The reaction mixture was concentrated *in vacuo* and the residue was subjected directly to column chromatography on silica gel (ether) to give 20 (208 mg, 88%) as colorless needles; mp 76 – 79°C; R_f 0.63 (ether); IR (KBr) 3438, 2930, 2858, 1677, 1608, 1493, 1105 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.74 (s, 3H, CH₃), 0.83 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 1.18 – 2.48 (m, 21H), 2.72 (m, 1H), 3.33 – 3.67 (m, 5H), 3.46 (t, 2H, ^3J 8.6 Hz), 3.84 (s, 3H, OCH₃), 7.08 (dd, 1H, ^3J 2.9, 8.6 Hz), 7.33 (d, 1H, ^3J 8.6 Hz), 7.52 (d, 1H, ^3J 2.9 Hz); ¹³C NMR (67.8 MHz, CDCl₃, DEPT 90, DEPT 135) δ 13.78 (+, CH₃), 22.01 (+, CH₃), 22.26 (-), 22.51 (+, CH₃), 23.72 (-), 25.61 (-), 26.52 (-), 26.88 (-), 27.31 (-), 29.33 (-), 29.38 (-), 30.39 (C_quat), 32.68 (-), 37.28 (+, CH), 42.77 (+, CH), 42.89 (+, CH), 47.33 (C_quat), 48.79 (+, CH), 55.45 (+, OCH₃), 62.98 (-), 70.73 (-), 72.59 (-), 108.35 (C_quat), 109.88 (+, CH), 121.45 (+, CH), 127.24 (+, CH), 132.13 (C_quat), 139.03 (C_quat), 158.06 (C_quat), 201.42 (C_quat, C=O); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 485 (MH⁺, 27), 307 (34), 154 (100). HRMS (FAB) Found 485.3266. Calcd. for $C_{30}H_{45}O_5$: 485.3267.

7α-(11'-Hydroxyundecyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6α-ol-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (16) – To 14 (400 mg, 0.72 mmol) in a solvent mixture of MeOH (2 mL) and ether (1 mL) was added at 0°C NaBH₄ (100 mg, 2.64 mmol). The resulting reaction mixture was stirred at rt for 2h. Then aq. 10w% NH₄Cl (5 mL) was added. The mixture was extracted with ether (5 mL). The organic phase was washed with water (5 mL) and dried over anhydrous MgSO₄. It was concentrated *in vacuo* to give 16 (333 mg, 83%) as a colorless solid; R_f 0.23; IR (neat) 3428, 3008, 2926, 2854, 1610, 1496, 1466, 1215, 1106, 1037, 757 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.74 (s, 3H, CH₃), 0.83 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 1.18 – 2.40 (m, 34H), 3.37 – 3.75 (m, 6H), 3.81 (s, 3H, OCH₃), 4.90 (br., 1H), 6.77 (dd, 1H, J 2.6, 8.6 Hz), 7.18 (d, 1H, J 8.6 Hz), 7.21 (d, 1H, J 2.6 Hz); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 556 (M⁺); HRMS Found 556.4124. Calcd. for $C_{35}H_{56}O_5$: 556.4128.

7α-(6'-Hydroxyhexyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6α-ol-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (21a-H) – To 20 (208 mg, 0.43 mmol) in a solvent mixture of MeOH (2 mL) and ether (1 mL) was added at 0°C NaBH₄ (70 mg, 1.85 mmol). The resulting reaction mixture was stirred at rt for 3.5h. Then aq. 10w% NH₄Cl (5 mL) was added. The mixture was extracted with ether (3 X 5 mL). The organic phase was washed with water (5 mL) and dried over anhydrous MgSO₄. Concentration of the solution *in vacuo* gave xx (198 mg, 95%) as a colorless solid, R_f 0.47 (ether); IR (neat) 3408, 2936, 2862, 1609, 1495, 1468, 1105, 1037, 909 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.73 (s, 3H, CH₃), 0.83 (s, 3H, CH₃), 1.16 (s, 3H, CH₃),

1.18 – 1.96 (m, 20H), 2.25 – 2.40 (m, 3H), 3.38 – 3.70 (m, 7H), 3.80 (s, 3H, OCH$_3$), 4.90 (m, 1H), 6.76 (dd, 1H, J 2.6, 8.6 Hz), 7.18 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 14.00 (+, CH$_3$), 22.03 (+, CH$_3$), 22.50 (+, CH$_3$), 22.91 (-), 23.05 (-), 25.53 (-), 27.04 (-), 29.56 (-), 30.12 (-), 30.39 (C$_{quat}$), 31.32 (-), 32.67 (-), 38.31 (+, CH), 40.79 (+, CH), 41.45 (+, CH), 43.75 (+, CH), 47.55 (C$_{quat}$), 55.24 (+, OCH$_3$), 62.95 (-), 70.73 (-), 72.59 (-), 74.34 (+, CH), 108.55 (C$_{quat}$), 111.14 (+, CH), 113.17 (+, CH), 126.86 (+, CH), 131.89 (C$_{quat}$), 140.14 (C$_{quat}$), 158.00 (C$_{quat}$); MS (70 eV) m/z (%) 486 (M$^+$, 12), 468 (M+-H20, 2), 385 (57), 141 (100). HRMS Found 486.3343. Calcd. for C$_{30}$H$_{46}$O$_5$: 486.3345.

7-(11'-Hydroxyundecyl)-3-O-methyl-estra-1,3,5(10),6-tetraen-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (17)

– To 16 (300 mg, 0.54 mmol) in benzene (7 mL) was added p-toluenesulfonic acid monohydrate (100 mg, 0.57 mmol) and the resulting mixture was held at reflux for 2h. Then the solution was concentrated in $vacuo$ and acetone (7 mL) was added. The solution was stirred at rt for 12h. The reaction mixture was concentrated in $vacuo$ and ether (10 mL) was added. The solution was washed with aq. 5w% Na$_2$CO$_3$ (5 mL). The organic phase was dried over anhydrous MgSO$_4$ and concentrated in $vacuo$. The residue was subjected to column chromatography on silica gel (ether/hexane 2:1) to give 17 (78 mg, 32%) as a colorless oil; R$_f$ 0.23; IR (neat) 3416, 3014, 2926, 1736, 1605, 1500, 1465, 1267, 1215, 1156, 756 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.92 (s, 3H, CH$_3$), 1.20 – 2.63 (m, 32H), 3.64 (t, 2H, J 6.6 Hz), 3.80 (s, 3H, OCH$_3$), 6.25 (s, 1H), 6.71 (d, 1H, J 2.8 Hz), 6.71 (dd, 1H, J 2.8, 8.4 Hz), 7.17 (d, 1H, J 8.4 Hz); ^{13}C NMR (150.8 MHz, CDCl$_3$) δ 14.05, 24.16, 25.49, 25.76, 28.85, 29.27, 29.45, 29.56, 29.61, 29.64, 29.68, 30.81, 32.80, 35.52, 36.32, 41.70, 41.83, 47.49, 49.63, 55.30, 63.04, 110.75, 111.24, 124.42, 124.49, 130.82, 135.67, 146.28, 158.33, 220.29; MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 452 (M$^+$); HRMS Found 452.3288; Calcd. for C$_{30}$H$_{44}$O$_3$: 452.3290.

7-(11'-Formyldecyl)-3-O-methyl-estra-1,3,5(10),6-tetraen-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (18)

– To 17 (75 mg, 0.16 mmol) in CH$_2$Cl$_2$ (2 mL) was added pyridinium dichromate (PDC) (93 mg, 0.24 mmol) and the resulting solution was stirred for 24h. The reaction mixture was directly subjected to column chromatography on silica gel (ether/hexane 2:1) to give slightly impure 18 (43 mg, 57%) as a colorless oil; R$_f$ 0.44; IR (neat) 3018, 2928, 2854, 2724, 1734, 1500, 1464, 1373, 1267, 1215, 1034, 756 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.85 (s, 3H, CH$_3$), 1.23 – 2.52 (m, 31H), 3.73 (s, 3H, OCH$_3$), 6.18 (s, 1H), 6.54 (d, 1H, J 2.6 Hz), 6.64 (dd, 1H, J 2.6, 8.6 Hz), 7.11 (d, 1H, J 8.6 Hz), 9.69 (s, 1H, CHO); ^{13}C NMR (67.8 MHz, CDCl$_3$) δ 14.05, 22.07, 24.15, 25.50, 28.82,

29.16, 29.36, 29.40, 29.56, 29.63, 29.69, 30.80, 35.53, 36.32, 41.67, 41.81, 43.92, 47.46, 49.63, 55.29, 77.23, 110.73, 111.21, 124/45, 130.80, 135.65, 146.29, 158.33, 202.96; MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 450 (M$^+$), HRMS Found 450.3137. Calcd. for C$_{30}$H$_{42}$O$_3$: 450.3134.

7α-(11'-Formyldecyl)-3-O-methyl-estra-1,3,5(10)-trien-6,17-dione-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (15)

– To 14 (55 mg, 0.10 mmol) in CH$_2$Cl$_2$ (2 mL) was added PDC (58 mg, 0.15 mmol) and the reaction mixture was sonicated at rt for 4h. Then the mixture was directly subjected to column chromatography on silca gel (toluene/ethyl acetate 7:1) to give 15 (39 mg, 71%) as a colorless oil; R$_f$ 0.60; IR (neat) 3018, 2928, 2856, 1712, 1677, 1608, 1494, 1215, 1105, 1034, 754 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.48 (s, 3H, CH$_3$), 0.50 - 1.92 (m, 21H), 2.24 - 2.49 (m, 2H), 2.86 - 2.96 (m, 6H), 3.09 (d, 1H, J 11.2 Hz), 6.64 - 6.72 (m, 2H), 7.58 (d, 1H, J 2.3 Hz), 8.96 (1H, t, J 1.6 Hz, CHO); ^{13}C NMR (67.8 MHz, DEPT 90, DEPT 135) δ 14.09 (CH$_3$), 21.70 (CH$_3$), 22.22 (-), 22.45 (-), 22.67 (CH$_3$), 24.17 (-), 26.91 (-), 27.09 (-), 27.89 (-), 29.37 (-), 29.64 (-), 29.73 (-), 29.82 (-), 29.89 (-, 2C), 29.98 (-), 30.28 (C$_{quat}$), 37.76 (+, CH), 42.97 (+, CH), 43.26 (+, CH), 43.80 (-), 47.80 (C$_{quat}$), 48.95 (+, CH), 54.83 (+, OCH$_3$), 70.84 (-), 72.60 (-), 108.50 (C$_{quat}$), 110.16 (+, CH), 121.73 (+, CH), 127.86 (+, CH), 133.00 (C$_{quat}$), 138.94 (C$_{quat}$), 158.87 (C$_{quat}$), 199.93 (C$_{quat}$), 200.76 (+, CH, CHO); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 553 (MH$^+$). HRMS Found: 553.3894 (MH$^+$). Calcd. for C$_{35}$H$_{53}$O$_5$: 553.3893.

7α-(6'-$tert$-Butyldimethylsiloxyhexyl)-3-O-methyl-estra-1,3,5(10)-trien-6α-ol-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (21a-SiMe$_2$Bu^t)

– To 19 (400 mg, 0.67 mmol) in a solvent mixture of MeOH (2 mL) and ether (1 mL) was added at 0°C NaBH$_4$ (100 mg, 2.64 mmol). The resulting reaction mixture was stirred at rt for 1h. Then aq. 10w% NH$_4$Cl (5 mL) was added. The mixture was extracted with ether (3 X 5 mL). The organic phase was washed with water (5 mL) and dried over anhydrous MgSO$_4$. Concentration of the solution in $vacuo$ and column chromatography (toluene/ethyl acetate 30:1) gave 21a-SiMe$_2$Bu^t (322 mg, 80%) as a colorless solid; R$_f$ 0.32; IR (neat) v 3470, 3006, 2928, 2858, 1610, 1496, 1466, 1257, 1215, 1105, 1038, 837, 758, 667 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.03 (s, 6H, 2 CH$_3$), 0.73 (s, 3H, CH$_3$), 0.83 (s, 3H, CH$_3$), 0.88 (s, 9H, 3 CH$_3$), 1.10 – 2.43 (m, 22H), 1.16 (s, 3H, CH$_3$), 3.39 – 3.65 (m, 4H), 3.55 (t, 2H, ^3J 6.6 Hz), 3.82 (s, 3H, OCH$_3$), 4.88 (m, 1H, OH), 6.77 (dd, 1H, J 8.6, 2.6 Hz), 7.15 – 7.19 (m, 2H); ^{13}C NMR (67.8 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 0.00 (+, 2 CH$_3$), 13.98 (+, CH$_3$), 18.40 (C$_{quat}$), 22.03 (+, CH$_3$), 22.51 (+, CH$_3$), 23.04 (-), 23.09 (-), 25.82 (-), 26.00 (+, 3 CH$_3$), 26.99 (-), 27.08 (-), 29.56 (-), 30.33 (-),

30.39 (-), 31.55 (-), 32.90 (-), 38.31 (+, CH), 40.79 (+, CH), 41.47 (+, CH), 43.74 (+, CH), 47.53 (C_{quat}), 55.24 (+, OCH_3), 63.34 (-), 70.73 (-), 72.60 (-), 74.41 (+, CH), 108.53 (C_{quat}), 111.10 (+, CH), 113.21 (+, CH), 126.84 (+, CH), 131.91 (C_{quat}), 140.16 (C_{quat}), 158.02 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 601 (MH^+, 7), 600 (M^+, 12), 599 (M^+-1, 14), 583 (MH^+-H_2O, 26), 385 (34). HRMS Found: 600.4214 (MH^+, FAB). Calcd. for $C_{36}H_{60}O_5Si$: 600.4210.

7α-(6'-*tert*-Butyldimethylsiloxyhexyl)-3-*O*-methyl-6-pyridyl-estra-1,3,5,(10)-triene 17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) hydrochloride (23) – Attempted One Step Mesylation – Dehydromesylation of 21a-SiMe₂Buⁱ.

To 21a-SiMe₂Buⁱ (300 mg, 0.50 mmol) in pyridine (3 mL) was added methanesulfonyl chloride (69 mg, 0.60 mmol) at 0°C. The resulting reaction mixture was stirred for 3h. Then aq. 10w% NH_4Cl (5 mL) was added. The mixture was extracted with ether (3 X 10 mL). The organic phase was washed with water (10 mL) and dried over anhydrous $MgSO_4$. Concentration of the solution *in vacuo* and column chromatography (toluene/ethyl acetate 30:1) gave 23 (170 mg, 52%) as a colorless solid; IR (neat) ν 3346, 3018, 2932, 2858, 2398, 1613, 1505, 1475, 1246, 1215, 1105, 1034, 836, 761, 668 cm⁻¹; ¹H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6H, 2 CH_3), 0.64 (s, 3H, CH_3), 0.89 (s, 9H, 3 CH_3), 1.14 – 2.48 (m, 25H), 3.37 – 3.61 (m, 6H), 3.76 (s, 3H, OCH_3), 6.59 (s, 1H), 7.03 (dd, 1H, ^4J 2.8, ^3J 8.6 Hz), 7.29 (d, 1H, ^4J 2.8 Hz), 7.41 (d, 1H, J 8.6 Hz), 8.18 (dd, 2H), 8.59 (t, 1H, J 7.6 Hz), 8.86 (d, 2H, J 6.0 Hz); ¹³C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135), δ 13.80 (+, CH_3), 18.38 (C_{quat}), 21.96 (+, CH_3), 22.35 (+, CH_3), 22.48 (-), 25.64 (-), 25.70 (-), 26.02 (+, CH_3), 26.76 (-), 26.86 (-), 28.18 (-), 29.24 (-), 29.87 (C_{quat}), 30.33 (-), 32.97 (-), 35.56 (+, CH), 37.77 (+, CH), 42.84 (+, CH), 44.15 (+, CH), 47.62 (C_{quat}), 55.85 (+, OCH_3), 63.32 (-), 70.73 (-), 72.61 (-), 73.26 (+, CH), 107.92 (C_{quat}), 115.83 (+, CH), 118.58 (+, CH), 127.24 (C_{quat}), 127.87 (+, 2 CH), 128.05 (+, CH), 133.96 (C_{quat}), 144.35 (+, 2 CH), 145.77 (+, CH), 159.19 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 662 (MH^+-Cl, 5.8); HRMS Found: 662.4604 (MH^+-Cl). Calcd. for $C_{41}H_{64}O_4NSi$: 662.4605.

Attempted Dehydration of 21a-SiMe₂Buⁱ with *p*-TsOH - 7-(6'-hydroxyhexyl)-3-*O*-methyl-estra-1,3,5(10),6-tetraen-17-one (22) –

To 21a-SiMe₂Buⁱ (196 mg, 0.40 mmol) in benzene (5 mL) was added *p*-toluenesulfonic acid monohydrate (70 mg, 0.40 mmol) and the resulting mixture was held at reflux for 3h. Then the solution was concentrated *in vacuo* and acetone (5 mL) was added. The solution was stirred at rt for 12h. The reaction mixture was concentrated *in vacuo* and ether (10 mL) was added. The solution was washed with 5w% aq. Na_2CO_3 (5 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue

was subjected to column chromatography on silica gel (toluene/ethyl acetate 15:1 – 9:1) to give 22 (6 mg, 4%) as a colorless oil; IR (neat) ν 3446, 3018, 2934, 2858, 1736, 1500, 1215, 1037, 756, 668 cm⁻¹; ¹H NMR (270 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 0.99 – 2.59 (m, 22H), 3.67 (t, 2H, J 6.6 Hz), 3.80 (s, 3H, OCH_3), 6.25 (s, 1H), 6.71 (d, 1H, ^4J 2.6 Hz), 6.71 (dd, 1H, ^4J 2.6 Hz, ^3J 8.4 Hz), 7.18 (d, 1H, ^3J 8.4 Hz); ¹³C NMR (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) δ 14.02 (+, CH_3), 18.40 (C_{quat}), 24.12 (-), 25.46 (-), 25.79 (-), 28.72 (-), 29.45 (-), 30.73 (-), 32.70 (-), 35.49 (-), 36.19 (-), 41.62 (+, CH), 41.76 (+, CH), 47.05 (+, CH), 49.62 (C_{quat}), 55.28 (+, OCH_3), 62.95 (-), 110.67 (+, CH), 111.23 (+, CH), 124.42 (+, CH), 124.47 (+, CH), 130.75 (C_{quat}), 135.56 (C_{quat}), 146.07 (C_{quat}), 158.27 (C_{quat}), 220.00 (C_{quat}, C=O); MS (70 eV) m/z 382 (M^+). HRMS Found: 382.2507. Calcd. for $C_{25}H_{34}O3$: 382.2508.

Reaction of 21a-SiMe₂Buⁱ with POCl₃/Py – Formation of 7α-(6'-Hydroxyhexyl)-3-*O*-methyl-estra-1,3,5(10)-trien-6β-ol-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (21b-SiMe₂Buⁱ) –

21a-SiMe₂Buⁱ (50 mg, 0.08 mmol) in dry pyridine (0.03 mL) was treated with phosphorus oxychloride (POCl₃) (18 mg, 0.01 mL, 0.12 mmol) at 0°C and left for 20h under stirring at rt. Then the reaction mixture was poured into ice water (5 mL) and extracted with ether (3 X 15 mL). The organic phase is dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is subjected to column chromatography on silica gel (ether/hexane 1:2) and subsequently to TLC plate separation (ether/hexane 1:2) to yield 21b-SiMe₂Buⁱ as a colorless solid (10 mg, 20%, non-opitimized); R_f (ether/hexane 1:2) 0.79; IR (neat) ν 3446, 2926, 2854, 1613, 1501, 1463, 1257, 1107, 1039, 836, 777 cm⁻¹; 1H NMR (CD_2Cl_2) δ –0.02 (s, 6H, 2 CH_3), 0.70 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.85 (s, 9H, OC($\underline{C}H_3$)), 1.11 (s, 3H, CH_3), 1.15 – 2.33 (m, 22H), 3.31 – 3.68 (m, 4H), 3.54 (t, 2H, J 6.6 Hz), 3.75 (s, 3H, OCH_3), 4.52 (m, 1H), 6.76 – 6.80 (m, 2H), 7.22 (d, 1H, ^3J 8.2 Hz); ¹³C NMR (67.8 MHz, CD_2Cl_2, DEPT 90, DEPT 135) δ 1.19 (+, 2 CH_3), 14.29 (+, CH_3), 18.62 (C_{quat}), 22.10 (+, CH_3), 22.68 (+, CH_3), 23.00 (-), 24.73 (-), 26.13 (+, $\underline{C}(CH_3)_3$), 26.33 (-), 27.21 (-), 27.40 (-), 28.79 (-), 30.10 (-), 30.30 (-), 30.49 (C_{quat}), 30.64 (+, CH), 33.28 (-), 36.06 (+, CH), 38.22 (+, CH), 41.78 (+, CH), 43.86 (+, CH), 48.14 (C_{quat}), 55.60 (+, OCH_3), 63.59 (-), 71.01 (-), 71.73 (+, CH), 72.90 (-), 108.95 (C_{quat}), 114.59 (+, CH), 116.03 (+, CH), 127.47 (+, CH), 132.97 (C_{quat}), 138.51 (C_{quat}), 158.34 (C_{quat}); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) 601 (MH^+, 5), 600 (M^+, 7, 583 (MH^+-H_2O, 43). HRMS Found: 600.4206 (MH^+, FAB); Calcd. for $C_{36}H_{60}O5Si$: 600.4210.

7-(12'-[*p*-Iodobenzoyl]dodec-11'-enyl)-3-*O*-methyl-estra-1,3,5(10),6-tetraen-17-dione-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane])

(24) – To 18 (20 mg, 0.04 mmol) in benzene (1 mL) was added benzoic acid (10 mg, 0.08 mmol) and the phosphorane 3c (61 mg, 0.12 mmol). The resulting reaction mixture was held at reflux for 2h. Then the solution was concentrated *in vacuo* and subjected to column chromatography on silica gel (toluene/ethyl acetate 9:1) to give 24 (7 mg, 25%) as a colorless oil; R_f 0.56; IR (neat) 3018, 2928, 2854, 1736, 1581, 1215, 1005, 758 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 0.92 (s, 3H, CH$_3$), 0.96 – 1.99 (m, 20H), 2.14 – 3.03 (m, 11H), 3.80 (s, 3H, OCH$_3$), 6.25 (s, 1H), 6.71 (dd, 1H, J 2.4, 8.4 Hz), 6.81 (d, 1H J 15.0 Hz), 7.05 – 7.11 (m, 1H), 7.18 (d, 1H, J 8.4 Hz), 7.63 (d, 2H, J 8.1 Hz), 7.82 (d, 2H, J 8.1 Hz); MS (70 eV) m/z (%) 678 (M$^+$); HRMS Found: 678.2569. Calcd. for C$_{38}$H$_{47}$O$_3$I: 678.2570.

7α-(12'-[Tolanylcarbonyl]dodec-11'-enyl)-3-*O*-methyl-estra-1,3,5(10)-trien-17-one-17,17-(2''-[5'',5''-dimethyl-1'',3''-dioxane]) (25) - General Procedure C.

– To 15 (35 mg, 0.06 mmol) in benzene (1.5 mL) was added benzoic acid (20 mg, 0.16 mmol) and the phosphorane 8a (91 mg, 0.18 mmol). The resulting reaction mixture was held at reflux for 15h. Then the solution was concentrated *in vacuo* and subjected to column chromatography on silica gel (toluene/ethyl acetate 15:1) to give 25 (24 mg, 51%) as a pale yellow oil; R_f 0.68; IR (KBr) 3014, 2926, 2854, 1674, 1606, 1493, 1464, 1288, 1215, 1105, 1035, 756 cm^{-1}; ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.74 (s, 3H, CH$_3$), 0.83 (s, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$), 1.23 - 1.74 (m, 22H), 1.93 – 2.12 (m, 3H), 2.25 – 2.48 (m, 6H), 2.68 – 2.76 (m, 1H), 3.37 – 3.50 (m, 3H), 3.67 (d, 1H, J 11.2 Hz), 3.84 (s, 3H, OCH$_3$); 6.88 (1H, d, J 15.5 Hz), 7.04 – 7.38 (m, 6H), 7.52 – 7.57 (m, 3H), 7.62 (d, 2H, J 8.2 Hz), 7.92 (d, 2H, J 8.2 Hz); ^{13}C NMR (67.9 MHz, CDCl$_3$, DEPT 90, DEPT 135) δ 17.80 (CH$_3$), 22.02 (CH$_3$), 22.27 (-), 22.52 (CH$_3$), 23.83 (-), 26.55 (-), 26.93 (-), 27.42 (-), 28.17 (-), 29.25 (-), 29.35 (-), 29.37 (-), 29.48 (-), 29.55 (-), 29.72 (-), 30.38 (-), 32.92 (-), 37.32 (+, CH), 42.81 (+, CH), 42.92 (+, CH), 47.36 (C$_{quat}$), 48.86 (+, CH), 55.45 (+, OCH$_3$), 70.75 (-), 72.61 (-), 88.75 (C$_{quat}$), 92.45 (C$_{quat}$), 108.38 (C$_{quat}$), 110.00 (+, CH), 121.38 (+, CH), 122.73 (C$_{quat}$), 125.55 (+, CH), 127.23 (+, CH), 127.66 (C$_{quat}$), 128.43 (+, CH), 128.51 (+, CH), 128.75 (+, CH), 131.65 (+, CH), 131.74 (CH), 132.31 (C$_{quat}$), 137.20 (C$_{quat}$t), 139.03 (C$_{quat}$), 150.52 (+, CH), 158.07 (C$_{quat}$), 189.97 (C$_{quat}$), 201.42 (C$_{quat}$t); MS (FAB, 3-nitrobenzyl alcohol) m/z (754, M$^+$); HRMS (FAB) Found 755.4672 (MH$^+$). Calcd for C$_{51}$H$_{63}$O$_5$: 755.4676.

Acknowledgement

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