# Synthesis of 1,10-Seco-5α-estr-1-ynes: Potential Mechanism-based Inhibitors of 3α- and 3β-Hydroxysteroid Dehydrogenases

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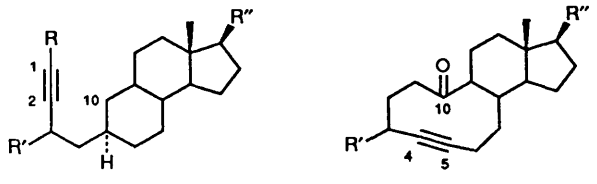
Oxido-reductase reactions mediated by 3α- and 3β-hydroxysteroid dehydrogenases alter the biological effects of steroid hormones. A novel and practical synthetic route from 19-nortestosterone **1** to (3*R*,*S*)-1,10-seco-5α-estr-1-yne-3,17β-diol **13a** and structurally related analogues has been developed so that the potential of these 1,10-secosteroids as mechanism-based inhibitors of 3α- and 3β-hydroxysteroid dehydrogenases can be evaluated. Following double-bond reduction and acetylation of steroid **1**, the $\Delta^2$-enol *tert*-butyldimethylsilyl ether derivative **4** is formed with high regioselectivity, then cleaved by ozonolysis, reduced with $NaBH_4$, and methylated with $CH_2N_2$ to give 2,3-secosteroid **6**. Carbons $C^1$ and $C^2$ are then sequentially removed to yield the (dodecahydro-1*H*-benz[*e*]inden-7-yl)acetic acid derivative **10**. Partial reduction and deacetylation of compound **10** by DIBALH yields the (dodecahydro-1*H*-benz[*e*]inden-7-yl)acetaldehyde derivative **11**. The addition of HC≡CMgBr, LiC≡CCl and LiC≡CCF$_3$ to aldehyde **11** yields 1,10-seco-5α-estr-1-yne **13a**, and the chloro- and trifluoro-methylacetylenic analogues **13b** and **13c**, respectively. Selective oxidation by DDQ of **13a**, and **13b**, but not **13c**, yields the corresponding 3-keto-1,10-secosteroids **14a** and **14b**.

Michael acceptors and compounds that can be enzymatically converted into Michael acceptors have been used to investigate the mechanism of action of hydroxysteroid dehydrogenases.‡ These electrophilic compounds covalently modify enzymes causing an irreversible loss of enzyme activity. We have reported previously the synthesis of 5,10-secoestr-4-ynes[2] and 14,15-secoestr-15-ynes[3] and their use as irreversible enzyme inhibitors.[4-9] We report here the synthesis of a group of 1,10-seco-5α-estr-1-ynes. These novel secosteroids are potential mechanism-based irreversible inhibitors of 3α- and 3β-hydroxysteroid dehydrogenases. Accounts of the important physiological roles of these enzymes can be found elsewhere.[10-13]

The 1,10-seco-5α-estr-1-ynes described here differ from the earlier described 5,10-secoestr-4-ynes as potential inhibitors of 3α- and 3β-hydroxysteroid dehydrogenases in several ways.




One difference is the location of the acetylenic moiety on the opposite side of the $C^3$ hydroxy group. The different location of the sp hybridized carbons in the two types of secosteroids makes possible after enzymic (or chemical) oxidation the affinity alkylation of nucleophilic groups in the enzymes that are located on either side of $C^3$ of the steroid. Thus, information about two neighbouring areas in the catalytic region of these enzyme active site environments is potentially available with the two classes of secosteroids.

Other important differences between these 1,10- and 5,10-secosteroids arise from the different synthetic routes used in their preparation. For the 5,10-secosteroids, the acetylenic carbons are those originally present at $C^4$ and $C^5$ in the steroid from which the 5,10-secosteroids are derived. Thus, if one wants to prepare these 5,10-secosteroids enriched in $^{13}C$ at $C^4$ and $C^5$, for use in $^{13}C$ NMR studies to probe the structure of the covalent adducts formed between these 5,10-secosteroids and the enzymes they irreversibly inhibit, one confronts a formidable synthetic task. By contrast, the 1,10-secosteroids can be easily prepared with $^{13}C$ enrichment at $C^1$ and $C^2$ for analogous NMR studies. Synthesis of the 1,10-secosteroids proceeds by cleavage of the steroid A-ring between $C^2$ and $C^3$, and then removal of $C^2$ and $C^1$. Subsequently, a two-carbon acetylenic fragment is then added to $C^3$ from the original steroid to give the 1,10-seco-5α-estr-1-yne. Use of a $^{13}C$-labelled acetylenic fragment conveniently leads to the desired $^{13}C$-labelled compounds.

Finally, because of the route of synthesis of the 1,10-seco-5α-estr-1-ynes, and the fact that these compounds contain a terminal acetylenic group, their reactivity as enzyme inhibitors can be readily altered. This is accomplished by the addition of an acetylenic fragment containing an electron withdrawing or donating group to $C^3$ from the original steroid. Some consequences of altering the reactivity of acetylenic alcohols and ketones used as enzyme inactivators have been established previously.[14,15] The synthesis of 1,10-seco-5α-estr-1-ynes where R = H, Cl and $CF_3$, for use in future enzymatic studies to explore reactivity effects, are reported in this paper.§

## Results and Discussion

The side-chain on $C^5$ containing the acetylenic alcohol group of 1,10-seco-5α-estr-1-ynes may assume many different conformations. Among these conformations are those in which the side-chain remains in the plane of the remaining steroid rings

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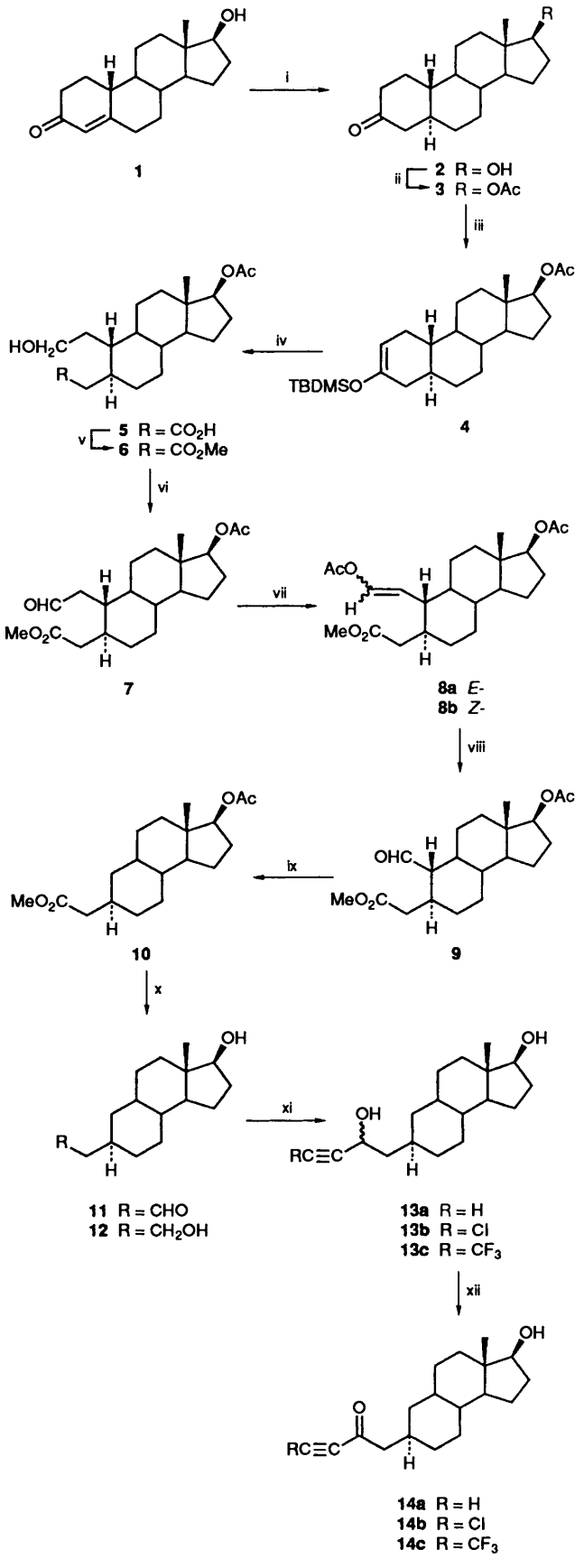
‡ A comprehensive review of Michael acceptors and other classes of compounds used as hydroxysteroid dehydrogenase inhibitors has appeared recently.[1]

§ Dodecahydrobenz[*e*]inden-7-yl)acetic acid derivative **10** is also a key intermediate for the preparation of additional benz[*e*]indene derivatives that are of interest because of their potent modulatory effects on $GABA_A$ receptor function.[16]




**Scheme 1** *Reagents and yields:* i, Li–$NH_3$, 80%; ii, AcOAc–$C_6H_5N$, 96%; iii, TBDMS–OTf, 87%; iv, $O_3$–$NaBH_4$, 70%; v, $CH_2N_2$, 100%; vi, PCC, 97%; vii, $CH_3CO_2C(CH_3)=CH_2$–$H^+$, 62%; viii, $O_3$–$Me_2S$, 92%; ix, Wilkinson's catalyst, 91%; x, DIBALH, 87%; xi, HC≡CMgBr, or LiC≡CCl, or LiC≡$CCF_3$, 36–95%; xii, DDQ–dioxane, 30–32%

such that $C^2$, $C^3$ and $C^4$ are displaced as little as possible from the positions they would occupy in a steroid A-ring. In these conformations, the acetylenic group would be aligned along the axis of the $C^2$–$C^3$ bond of a steroid. These 1,10-secosteroid conformations are most like those of steroid substrates and therefore most likely to be the ones leading to productive binding and enzymatic oxidation of the acetylenic alcohol group. Molecular models indicate that these preferred conformations are best obtained when there are no substituents present on $C^{10}$. Accordingly, the synthetic route chosen yields 1,10-seco-5α-estr-1-ynes without $C^{10}$ substituents.

The starting material is commercially available 19-nortestosterone (**1**, Scheme 1). Reduction of this compound with lithium in liquid ammonia as reported in the literature[17] gave 17β-hydroxy-5α-estran-3-one (**2**, 80% yield) which was then acetylated to give the corresponding known acetate **3**[18] (96% yield). The next step in the synthesis requires the selective formation of a $\Delta^2$-enol derivative of steroid **3**. Although 3-keto-5α-androstanes are known to be selectively converted into $\Delta^2$-enol acetates using isopropenyl acetate and an acid catalyst,[18–21] this is not the case for 3-keto-5α-estranes. Villotti *et al.* reported[18] that steroid **3** was converted into a chromatographically pure, sharp melting solid initially thought to be the $\Delta^2$-enol acetate derivative. However, further chemical transformations carried out on this product by the investigators indicated that it was actually a mixture of $\Delta^2$- and $\Delta^3$-enol acetates. The ratio of the two isomeric enol acetates was not specified. We repeated this reaction using *p*-TsOH as the catalyst and obtained identical results. The NMR spectrum of the purified product indicated (by integration of the peak area of the vinyl protons) that the product was a 3:2 mixture of the $\Delta^2$-and $\Delta^3$-enol acetates, respectively. Thus, the selectivity of the reaction is poor and a more selective approach to the synthesis of $\Delta^2$-enol derivatives was developed.

Treatment of steroid **3** with TBDMS–OTf according to the procedure of Mander and Sethi[22] gave an excellent yield (87%) of the desired $\Delta^2$-enol silyl ether **4**. The reaction was completed within 5 min and was conveniently monitored by IR. HPLC analysis on the total reaction product indicated that the reaction was highly selective. The ratio of $\Delta^2$- and $\Delta^3$-enol silyl ethers was routinely found to be minimally 19:1.

Cleavage of the A-ring was then effected by ozonolysis of steroid **4** in dichloromethane and MeOH (1:1) at −78 °C, followed by $NaBH_4$ reduction (without product isolation), and an acidic work-up. A mixture of two products, the acid **5** and its corresponding silyl ester, in the ratio of ~1:3, respectively, generally was obtained by this procedure. The silyl ester subsequently was converted without isolation into acid **5** by hydrolysis with 10% potassium carbonate[23] in THF and MeOH (overall yield 70%). Treatment with diazomethane quantitatively converted acid **5** into methyl ester **6**. On a small scale (0.1–3.0 g) the reaction was carried out in EtOEt, on a larger scale the reaction is more conveniently carried out in a solution of 20% EtOH in EtOAc because of the low solubility of acid **5**. Oxidation of methyl ester **6** with PCC[24] buffered with anhydrous sodium acetate in dichloromethane gave secosteroid **7** as a stable white crystalline solid (97% yield). It is worthwhile to note that the aldehyde group present after the ozonolysis reaction was reduced to a hydroxy group and later regenerated by PCC oxidation to minimize side reactions encountered in trying to work with the original ozonolysis product.

The next steps in the synthesis were designed to sequentially remove carbons $C^1$ and $C^2$. Secosteroid **7** was converted in 62% yield into a mixture of *E*- and *Z*-enol acetates **8a** and **8b** using isopropenyl acetate and *p*-TsOH as catalyst. HPLC analysis showed the ratio of **8a**:**8b** to be 19:1. It was possible to separate these enol acetates chromatographically for product characterization, but they were used routinely as a mixture for the next

reaction. Ozonolysis in dichloromethane followed by reduction with $Me_2S$ gave aldehyde **9** as a stable, white crystalline solid (92% yield). To remove the formyl group from aldehyde **9**, this compound was decarbonylated with Wilkinson's catalyst in benzonitrile[3,25,26] at 160 °C for 14 h to yield (91%) compound **10**.

The two-carbon fragment remaining from the steroid A-ring was next modified in preparation for the introduction of the various acetylenic moieties. Reduction of compound **10** with DIBALH[27-29] in dichloromethane at −78 °C gave cleanly the deacetylated aldehyde **11** (83% yield). The yield of undesired diol **12**, which can arise by further reduction of aldehyde **11**, was minimized to < 10% of the total products by carefully controlling the temperature and rate of addition of the DIBALH.

Conversion of compound **11** into acetylenic diol **13a** was achieved in 55% yield using ethynylmagnesium bromide. Compound **11** was converted into the chloroacetylenic diol **13b** in 95% yield using lithium chloroacetylide (generated *in situ* from *E*-1,2-dichloroethylene and BuLi in THF[30]), and into trifluoromethylacetylenic diol **13c** in 36% yield using 1,1,1-trifluoropropynyllithium (generated from 1,1,1-trifluoropropyne and BuLi in THF[15,31]). There is clear evidence from the $^{13}C$ NMR spectra of acetylenic diols **13a** and **13b** that these compounds are a ~1:1 mixture of diastereoisomers. For compound **13a**, both the accetylenic carbon ($C^2$) and the prop-2-ynylic carbon ($C^3$) are observed as pairs (each peak is of comparable intensity) showing resonance signals at $\delta$ 72.55, 72.51 and $\delta$ 59.98, 59.93, respectively. For compound **13b**, the same pairs of carbon resonance signals, again of comparable intensity in each case, are observed at $\delta$ 62.63, 62.58 and $\delta$ 60.24, 60.18, respectively. For compound **13c**, neither the $^{19}F$ NMR nor the $^{13}C$ NMR spectra provided any evidence for concluding that the product is a mixture of diastereoisomers. The $^{19}F$ NMR spectrum of compound **13c** shows only one singlet at $\delta$ −50.92 (referenced to $CFCl_3$, $\delta$ 0.00) for the $CF_3$ group. The $^{13}C$ NMR spectrum contains only quartet for the carbon of the $CF_3$ group at $\delta$ 114.15 ($^1J_{C,F}$ = 258.5 Hz), and a single quartet for each of the acetylenic carbons at $\delta$ 71.60 ($^2J_{C,F}$ = 51.8 Hz) and $\delta$ 88.69 ($^3J_{C,F}$ = 6.5 Hz). Nevertheless, considering the similarities in the reactions used to prepare compounds **13a–c**, it is likely that compound **13c** is also a ~1:1 mixture of diastereoisomers. It has not been possible yet to separate compounds **13a–c** into their respective diastereoisomeric components.

Because we have found previously[6,14,32] that understanding the biochemical details of enzyme inactivation caused by enzymic oxidation of acetylenic alcohols is greatly facilitated when the corresponding acetylenic ketones are also available for study, we investigated the selective oxidation of the prop-2-ynylic hydroxy groups of compounds **13a–c**. DDQ has been widely used for many years for the selective oxidation of allylic alcohols to allylic ketones. There are a few examples reported for the oxidation of prop-2-ynylic alcohols by DDQ.[14,33] We found that compounds **13a–c** were not oxidized by DDQ in dioxane at room temp. However, by refluxing the dioxane we were able to convert compounds **13a** and **13b** into their corresponding acetylenic ketones **14a** and **14b** in moderate yields (30 and 32%, respectively). Unfortunately, this oxidation method failed to convert compound **13c** into compound **14c**. In this case, the secondary alcohol at the other end of the molecule was selectively oxidized in preference to the trifluoromethylacetylenic alcohol.*

In summary, the synthetic route reported here is an efficient route for the preparation of 1,10-seco-5α-estr-1-ynes. The route is also of general use for the preparation of (dodecahydrobenz[*e*]inden-7-yl)acetic acid derivatives with defined stereochemistry at all chiral centres. Preliminary studies have shown that compounds **13a–c** cause a time-dependent loss of enzyme activity of purified, homogeneous rat liver 3α-hydroxysteroid dehydrogenase.† A detailed analysis of the inactivation of this enzyme by these inhibitors will be the subject of future studies.

## Experimental

All melting points were determined with a capillary melting point apparatus and were uncorrected. NMR spectra were recorded at ambient temperature in $CDCl_3$ (unless noted otherwise) with a 5 mm probe on either a Varian Gemini-300 operating at 300 MHz ($^1H$) or 75 MHz ($^{13}C$), or a Varian XL-300 operating at 282.45 MHz ($^{19}F$). For $^1H$ NMR, $^{13}C$ NMR and $^{19}F$ NMR spectra; the internal references were $(CH_3)_4Si$ ($\delta$ 0.00), $CDCl_3$ ($\delta$ 77.00) and $CFCl_3$ ($\delta$ 0.00), respectively. *J* Values are given in Hz. IR spectra were recorded as films on a NaCl plate with a Perkin-Elmer 1710 FT-IR spectrophotometer. Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ. Solvents were used either as purchased or dried and purified by standard methodology. Flash chromatography was performed using silica gel (32–63 microns) purchased from Scientific Adsorbants, Atlanta, GA. The 19-nortestosterone was purchased from Steraloids, Wilton, NH. The 1,1,1-trifluoropropyne was purchased from Farchan Labs., Gainsville, FL.

3-(tert-*Butyldimethylsilyloxy*)-5α-*estr*-2-*en*-17β-*yl Acetate* **4**.—To a stirred solution of 17β-acetoxy-5α-estran-3-one **3** (1.60 g, 5 mmol) in dry dichloromethane (DCM) (30 $cm^3$) was added triethylamine (2 $cm^3$) followed by TBDMS–OTf (2.64 g, 10 mmol) at 0 °C. After 25 min, the mixture was diluted with DCM (20 $cm^3$) and washed with a saturated aq. $NaHCO_3$ (30 $cm^3$), then brine (30 $cm^3$), and dried over $Na_2SO_4$. The solvent was removed to yield a solid which was purified by chromatography (silica gel, DCM, pre-treated with 1% triethylamine in hexane) yielding 1.9 g (87%) of product as white crystals: m.p. 89–90 °C (Found: C, 72.5; H, 10.1. $C_{26}H_{44}O_3Si$ requires C, 72.2; H, 10.25%); $\nu_{max}/cm^{-1}$ 2927, 2858, 1739, 1676, 1472, 1371 and 1246; $\delta_H$ 4.80 (1 H, m, HC=C), 4.59 (1 H, t, *J* 8.5, CHOAc), 2.04 (3 H, s, $COCH_3$), 0.91 (9 H, s, $Me_3C$), 0.80 (3 H, s, $CH_3$) and 0.11 (6 H, s, $Me_2Si$); $\delta_C$ 171.58 (OCOMe), 149.88 ($C^3$), 103.48 ($C^2$), 82.97 ($C^{17}$), 25.51 ($Me_3C$), 11.81 ($C^{18}$), 4.62 ($Me_3C$), 4.78 ($Me_2Si$), 49.71, 48.65, 42.58, 40.52, 38.43, 37.70, 36.76, 33.19, 29.97, 29.27, 27.31, 25.51, 25.45, 25.26, 23.15 and 20.98.

[3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-{3-*Acetoxy*-6-(2-*hydroxyethyl*)-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*}*acetic Acid* **5**.—A solution of silyl ether **4** (0.87 g, 2 mmol) in DCM (10 $cm^3$) and MeOH (10 $cm^3$) was treated with $O_3$ at −78 °C until a blue colour persisted. After the excess of $O_3$ had been discharged by an $O_2$ stream, $NaBH_4$ (1.0 g) was added with

* There is no resonance in the $^1H$ NMR spectrum of the product for the proton on $C^{17}$. The IR spectrum contains an absorbance peak at 1729 $cm^{-1}$ consistent with the presence of a cyclopentanone group in the product. Elemental analysis was not performed. We also attempted to non-selectively oxidize both hydroxy groups of compound **13c** to ketone groups with Jones reagent[34] in acetone. In this case, oxidation of the trifluoromethylacetylenic alcohol group occurred, but the spectra recorded on the product were inconsistent with those expected for the desired diketone and the structure of the product could not be assigned from the data available. We suspect that the trifluoromethylacetylenic ketone group was formed and that it underwent a secondary reaction. No further work has been done to characterize the product of this reaction.

† The half lives of inactivation of rat liver 3α-hydroxysteroid dehydrogenase by **13a** (250 μm), **13b** (250 μm) and **13c** (250 μm) in the presence of 2.3 mM $NAD^+$ are 3.8, 4.2 and 21.5 min, respectively. Enzyme inactivation in the absence of $NAD^+$ also occurs with compounds **13b** (250 μm, $t_{\frac{1}{2}}$ = 12.3 min) and **13c** (250 μm, $t_{\frac{1}{2}}$ = 72 min). The latter results indicate that **13b** and **13c** may be sufficiently electrophilic to directly react with the enzyme.[35]

stirring. The mixture was allowed to react at −78 °C for 1 h and at room temp. for a further 1 h. The mixture then was diluted with EtOEt (25 $cm^3$) and poured into cooled 10% aq. HCl (250 $cm^3$). The organic phase was washed with water (25 $cm^3$), then brine (25 $cm^3$), and dried over $Na_2SO_4$. The solvent was removed on a rotary evaporator to give a viscous liquid which solidified to a white solid upon the addition of hexane. After removal of the solid, the solution of hexane containing the silyl ester of acid **5** was evaporated and the residue was hydrolysed with a mixture consisting of 10% aq. $K_2CO_3$ (10 $cm^3$), THF (15 $cm^3$), and MeOH (30 $cm^3$) for 1.5 h at room temp. to yield a further portion of acid **5**. The crude compound was recrystallized from MeOH to give 0.49 (70%) of product as white crystals: m.p. 139.5–141.5 °C (Found: C, 68.0; H, 9.3. $C_{20}H_{32}O_5$ requires C, 68.15; H, 9.15%); $\nu_{max}/cm^{-1}$ 3328, 2918, 2850, 1732, 1705, 1444 and 1246; $\delta_H$ 4.59 (1 H, t, *J* 8.4, C*H*OAc), 2.62 (1 H, dd, *J* 15.8, *J* 2.6, C$H_2CO_2H$), 2.05 (3 H, s, $OCOCH_3$) and 0.80 (3 H, s, $CH_3$); $\delta_C$ 178.54 ($CO_2H$), 171.78 (OCOMe), 82.83 (CHOAc), 59.79 ($CH_2OH$), 11.75 ($CH_3$), 49.61, 46.85, 43.24, 42.39, 40.59, 39.20, 38.10, 36.68, 32.22, 31.95, 29.75, 27.21, 25.73, 22.97 and 20.89.

*Methyl* [3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-{3-*Acetoxy*-6-(2-*hydroxyethyl*)-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*}-*acetate* **6**.—To a solution of compound **5** (3.52 g, 10 mmol) in EtOEt (350 $cm^3$), diazomethane in EtOEt was added until a yellow colour persisted at 0 °C. The solution was allowed to stir for an additional 15 min. The excess of diazomethane was destroyed by the addition of several drops of formic acid. The mixture was washed with 10% aq. $NaHCO_3$ (100 $cm^3$), water (100 $cm^3$) and brine (100 $cm^3$), and dried over $Na_2SO_4$. Solvent removal gave a quantitative yield of product as white crystals: m.p. 72–73.5 °C (Found: C, 68.8; H, 9.65. $C_{21}H_{34}O_5$ requires C, 68.8; H, 9.35%); $\nu_{max}/cm^{-1}$ 3455, 2921, 2873, 1737, 1437, 1373 and 1246; $\delta_H$ 4.59 (1 H, t, *J* 7.7, C*H*OAc), 3.68 (3 H, s, $CO_2CH_3$), 3.68–3.61 (2 H, m, C$H_2$OH), 2.59 (2 H, dd, *J* 15, *J* 4.1, C$H_2CO_2CH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.80 (3 H, s, $CH_3$); $\delta_C$ 174.47 ($CO_2Me$), 171.55 (OCOMe), 82.75 (CHOAc), 60.02 ($CH_2OH$), 51.3 ($MeO_2C$), 11.75 ($CH_3$), 49.62, 46.98, 43.20, 42.38, 40.62, 39.07, 38.36, 36.69, 32.53, 32.18, 29.74, 27.23, 25.78, 22.97 and 20.89.

*Methyl* [3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-(3-*Acetoxy*-6-*formylmethyl*-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*)-*acetate* **7**.—To a stirring suspension of PCC (pyridinium chlorochromate) (0.65 g, 3.0 mmol) and anhydrous NaOAc (0.25 g, 3.0 mmol) in dry DCM (50 $cm^3$) was added a solution of compound **6** (0.73 g, 2.0 mmol) in dry DCM (10 $cm^3$) at room temp. under $N_2$. After the mixture had been stirred for 2 h, EtOEt (40 $cm^3$) was added. The mixture was filtered with a Buchner funnel filled with silica gel and washed with DCM. The solvent was removed to give a solid, which was recrystallized from EtOEt to give 0.70 g (96.5%) of product as white crystalline needles: m.p. 105–107 °C (Found: C, 69.05; H, 8.8. $C_{21}H_{32}O_5$ requires C, 69.2; H, 8.85%); $\nu_{max}/cm^{-1}$ 2923, 2854, 2721, 1737, 1734, 1437, 1374 and 1246; $\delta_H$ 9.82 (1 H, t, *J* 1.6, CHO), 4.59 (1 H, t, *J* 8.0, C*H*OAc), 3.67 (3 H, s, $CO_2CH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.80 (3 H, s, $CH_3$); $\delta_C$ 202.48 (CHO), 173.60 ($CO_2Me$), 171.40 (OCOMe), 82.53 (CHOAc), 11.69 ($CH_3$), 51.32, 49.50, 47.83, 45.60, 42.37, 40.68, 40.43, 39.19, 38.95, 36.56, 32.09, 29.58, 27.22, 26.34, 22.90 and 20.83.

*Methyl* [3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-{3-*Acetoxy*-6-[(2E)-*acetoxyvinyl*]-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*}-*acetate* **8a**.—A solution of compound **7** (20 g, 55 mmol) and *p*-TsOH (1.0 g, 5% w/w) in isopropenyl acetate (500 $cm^3$) was gently distilled for 2.0 h and ~25 $cm^3$ of distillate was collected. After refluxing for 14 h, the mixture was gently distilled for another 2.0 h and ~25 $cm^3$ of distillate was collected. The reaction mixture was cooled to room temp. and poured into DCM (500 $cm^3$), and washed with water (100 $cm^3$), saturated aq. $NaHCO_3$ (100 $cm^3$) and water (100 $cm^3$). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated to give a yellow oil, which was chromatographed (silica gel, 20% EtOAc in hexane) to give 14 g (62%) of product as colourless crystals: m.p. 122–123 °C (Found: C, 68.2; H. 8.5. $C_{23}H_{34}O_6$ requires C, 67.9; H, 8.4%); $\nu_{max}/cm^{-1}$ 2920, 2850, 1750, 1738, 1737, 1673, 1436, 1372 and 1226; $\delta_H$ 7.01 (1 H, d, *J* 12.5, AcOC*H*=CH), 5.01 (1 H, dd, *J* 12.5, *J* 10.7, AcOCH=C*H*), 4.59 (1 H, t, *J* 7.8, C*H*OAc), 3.63 (3 H, s, $CO_2CH_3$), 2.11 (3 H, s, $OCOCH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.79 (3 H, s, $CH_3$); $\delta_C$ 174.09 ($CO_2Me$), 171.50 (OCOMe), 168.32 (C=COCOMe), 136.35 (=C), 117.35 (=C), 82.67 (CHOAc), 11.80 ($CH_3$), 51.21, 49.73, 47.39, 47.04, 42.60, 40.23, 39.74, 38.81, 36.48, 31.45, 29.61, 27.32, 27.13, 22.95, 20.94 and 20.45.

*Methyl* [3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-{3-*Acetoxy*-6-[(2Z)-*acetoxyvinyl*]-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*}*acetate* **8b**.—This compound was separated chromatographically from enol acetate **8a** by the above described procedure and isolated in 3.3% yield as a white crystalline solid: m.p. 93–94 °C (Found: C, 68.2; H, 8.6. $C_{23}H_{34}O_6$ requires C, 67.9; H, 8.4%); $\nu_{max}/cm^{-1}$ 2922, 2851, 1757, 1737, 1672, 1438, 1370, 1213 and 768; $\delta_H$ 7.14 (1 H, d, *J* 6.6, AcOC*H*=CH), 4.59 (1 H, t, *J* 7.7, C*H*OAc), 4.53 (1 H, dd, *J* 10.5, *J* 6.6, AcOCH=C*H*), 3.64 (3 H, s, $CO_2CH_3$), 2.16 (3 H, s, $OCOCH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.82 (3 H, s, $CH_3$).

*Methyl*[3S-(3α,3aα,5aβ,6β,7α,9aα,9bβ)]-(3-*Acetoxy*-6-*formyl*-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*)*acetate* **9**.—A solution of compounds **8a** and **8b** (0.81 g, 2.0 mmol) in DCM (50 $cm^3$) and AcOH (0.5 $cm^3$) was cooled to −78 °C in an acetone–dry ice bath and treated with $O_3$ until the blue colour persisted. The excess of $O_3$ was removed with a stream of $O_2$, then $Me_2S$ (4 drops, *ca.* 4.0 mmol) was added and the mixture was stirred for 1.0 h at −78 °C, and then for 1.0 h at room temp. The mixture was diluted with DCM (50 $cm^3$) and the organic layer was washed with water (50 $cm^3$), saturated aq. $NaHCO_3$ (50 $cm^3$), water (2 × 50 $cm^3$) again, and dried over $Na_2SO_4$. The organic solvent was removed to give a solid, which was recrystallized from EtOEt to give 0.64 g (92%) of product as white crystals: m.p. 123–124 °C (Found: C, 68.7; H, 8.8. $C_{20}H_{30}O_5$ requires C, 68.55; H, 8.6%); $\nu_{max}/cm^{-1}$ 2924, 2870, 2805, 2707, 1738, 1735, 1721, 1436, 1372 and 1244; $\delta_H$ 9.44 (1 H, d, *J* 5.4, CHO), 4.62 (1 H, t, *J* 8.5, C*H*OAc), 3.66 (3 H, s, $CO_2CH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.80 (3 H, s, $CH_3$); $\delta_C$ 205.44 (CHO), 172.88 ($CO_2Me$), 171.38 (OCOMe), 82.41 (CHOAc), 11.71 ($CH_3$), 60.58, 51.41, 49.30, 42.61, 42.36, 38.88, 38.83, 36.16, 33.30, 30.70, 29.19, 26.96, 26.57, 22.88 and 20.84.

*Methyl* [3S-(3α,3aα,5aβ,7α,9aα,9bβ)]-(3-*Acetoxy*-3a-*methyldodecahydro*-1H-*benz*[e]*inden*-7-*yl*)*acetate* **10**.—A mixture of compound **9** (0.70 g, 2.0 mmol) and Wilkinson's catalyst (1.85 g, 2.0 mmol) in benzonitrile (30 $cm^3$) was heated to 160 °C for 20 h under $N_2$. Most of the benzonitrile was removed by distillation and a mixture of EtOAc and hexane (1 : 1 v/v, 50 $cm^3$) was added to precipitate the yellow organometallic by-product. The yellow solid was filtered off and washed with cold EtOAc (2 × 20 $cm^3$). The combined organic layer was evaporated to give a viscous liquid, which was chromatographed (silica gel, 1% MeCN in DCM) to give 0.59 g (91%) of product as slightly yellow crystals: m.p. 61–62 °C (Found: C, 70.95; H, 9.3. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%); $\nu_{max}/cm^{-1}$ 2918, 2851, 1741, 1738, 1446, 1373 and 1246; $\delta_H$ 4.61 (1 H, t, *J* 8.5, C*H*OAc), 3.67 (3 H, s, $CO_2CH_3$), 2.04 (3 H, s, $OCOCH_3$) and 0.80 (3 H, s, $CH_3$); $\delta_C$ 173.74 ($CO_2Me$), 171.44 (OCOMe), 82.72 (CHOAc), 11.85 ($CH_3$), 51.20, 49.43,

43.30, 43.12, 41.70, 40.58, 39.19, 36.58, 34.70, 32.49, 29.97, 28.95, 27.20, 22.86 and 20.90.

[3S-(3α,3aα,5aβ,7α,9aα,9bβ)]-(3-*Hydroxy*-3a-*methyl-dodecahydro*-1H-*benz*[e]*inden*-7-*yl*)*acetaldehyde* **11**.—To a stirred solution of compound **10** (0.48 g, 1.5 mmol) in dry DCM (30 $cm^3$) was added slowly a solution of DIBALH in toluene (1.0 mol $dm^{-3}$ solution; 3.5 $cm^3$, 3.5 mmol) at −78 °C under $N_2$. After 2 h, $Pr^iOH$ (2 $cm^3$) was added, followed by addition of saturated aq. $NH_4Cl$ (20 $cm^3$). The temperature was allowed to rise to room temp. and 10% aq. HCl (20 $cm^3$) was added. The mixture was stirred until all the inorganic salts dissolved, and extracted with DCM (2 × 50 $cm^3$). The organic layer was washed with water (50 $cm^3$), saturated aq. ($NaHCO_3$ (50 $cm^3$), then brine (50 $cm^3$), and dried over $Na_2SO_4$. The solvent was evaporated to give an oil, which was purified by chromatography (silica gel, 30% EtOAc in hexane) to give 323 mg (87%) of product as an oil (Found: C, 76.5; H, 10.2. $C_{16}H_{28}O_2$ requires C, 76.75; H, 10.5%); $\nu_{max}/cm^{-1}$ 3420, 2914, 2852, 2720, 1723, 1446, 1381, 1064 and 1051; $\delta_H$ 9.77 (1 H, t, *J* 2.2, CHO), 3.66 (1 H, t, *J* 8.6, C*H*OH), 2.31 (2 H, dd, *J* 2.2, *J* 4.4, $CH_2$CHO) and 0.75 (3 H, s, $CH_3$); $\delta_C$ 203.38 (CHO), 81.85 (CHOH), 10.89 ($CH_3$), 51.25, 49.71, 43.59, 40.88, 39.50, 36.40, 32.74, 32.61, 30.21, 30.08, 29.10 and 22.75.

[3S-(3α,3aα,5aβ,7α,9aα,9bβ)]-2-(3-*Hydroxy*-3a-*methyl-dodecahydro*-1H-*benz*[e]*inden*-7-*yl*)*ethanol* **12**.—This compound was isolated chromatographically in 9% yield from product **11** in the procedure described above and had: m.p. 145–147 °C (Found: C, 76.0; H, 11.3. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%); $\nu_{max}/cm^{-1}$ 3279, 2914, 2870, 2858, 2841, 1469, 1443, 1381, 1348, 1067 and 1056; $\delta_H$ 3.73–3.65 (3 H, m, $CH_2$OH and C*H*OH) and 0.76 (3 H, s, $CH_3$); $\delta_C$ ($CD_3OD$), 82.63 (CHOH), 60.78 ($CH_2OH$), 11.71 ($CH_3$), 51.36, 49.59, 49.30, 49.02, 48.74, 48.45, 45.36, 44.84, 42.91, 41.29, 41.23, 37.98, 35.64, 34.28, 31.72, 30.74, 30.56 and 23.93.

(3R,S)-1,10-*Seco*-5α-*estr*-1-*yne*-3,17β-*diol* **13a**.—To a stirring solution of ethynylmagnesium bromide in THF (0.5 mol $dm^{-3}$ solution in THF; 6 $cm^3$, 3.0 mmol) was added in 5 min a solution of compound **11** (0.125 g, 0.5 mmol) in THF (5 $cm^3$) at 0 °C under $N_2$. After the mixture had been stirred for 5 h at room temp., saturated aq. $NH_4Cl$ (50 $cm^3$) was added to hydrolyse the organometallic complex. The mixture was extracted with EtOAc (2 × 50 $cm^3$). The organic layer was washed with water (50 $cm^3$), then brine (50 $cm^3$), and dried over $Na_2SO_4$. The solvent was removed to give an oil, which was purified by chromatography (silica gel, 30% EtOAc in hexane) to give 76 mg (55%) of product as a white amorphous solid: m.p. 92–97 °C (Found: C, 78.1; H, 10.35. $C_{18}H_{28}O_2$ requires C, 78.2; H, 10.2%); $\nu_{max}/cm^{-1}$ 3382, 3306, 2915, 2113, 1446, 1381, 1055 and 1024; $\delta_H$ 4.45 (1 H, t, *J* 6.2, C*H*OH), 3.65 (1 H, t, *J* 8.6, C*H*OH), 2.60 (1 H, s, C≡CH), 2.46 (2 H, d, *J* 2.1, side chain $CH_2$) and 0.75 (3 H, s, $CH_3$); $\delta_C$ 85.46 (HC≡C), 81.85 (CHOH), 72.55 (HC≡*C*), 72.51 (HC≡*C*), 59.98 (HC≡C*C*HOH), 59.93 (HC≡C*C*HOH), 10.89 ($CH_3$), 49.77, 45.16, 43.57, 43.50, 41.15, 39.59, 39.31, 36.43, 33.91, 32.79, 32.54, 30.13, 30.08, 29.22 and 22.74.

(3R,S)-1-*Chloro*-1,10-*seco*-5α-*estr*-1-*yne*-3,17β-*diol* **13b**.—To a stirred solution of BuLi (2.5 mol $dm^{-3}$ solution in hexane; 10 $cm^3$, 25 mmol) in dry THF (10 $cm^3$) was added slowly a solution of (*E*)-1,2-dichloroethylene (3.84 g, 40 mmol) in dry THF (10 $cm^3$) at below 0 °C under $N_2$. After addition was complete, the temperature was allowed to rise to room temp. for about 10 min, and then cooled to −10 °C prior to the addition of a solution of compound **11** (0.33 g, 1.0 mmol) in THF (10 $cm^3$ added over a 10 min period). The reaction mixture then was allowed to warm and stir at room temp. for a further 2.5 h, cooled to −60 °C, and quenched with saturated aq. $NH_4Cl$ (20 $cm^3$). It was again warmed to room temp. and EtOAc (100 $cm^3$) and water (100 $cm^3$) were added. The organic layer was washed with water (2 × 50 $cm^3$), then brine (50 $cm^3$), and filtered with a Buchner funnel containing silica gel. The solvent was evaporated to give an oil which was purified by chromatography (silica gel, 30% EtOAc in hexane) to yield 0.37 g (95%) of product as a white amorphous solid: m.p. 51–56 °C (Found: C, 69.6; H, 8.7; Cl, 11.3. $C_{18}H_{27}ClO_2$ requires C, 69.55; H, 8.75; Cl, 11.4%); $\nu_{max}/cm^{-1}$ 3350, 2914, 2847, 2233, 1446, 1381, 1347, 1265, 1139, 1111 and 1053; $\delta_H$ 4.43 (1 H, t, *J* 6.5, C*H*OH), 3.64 (1 H, t, *J* 8.5, C*H*OH) and 0.74 (3 H, s, $CH_3$); $\delta_C$ 81.73 (CHOH), 70.73 (HC≡C), 62.63 (HC≡*C*), 62.58 (HC≡*C*), 60.24 (C≡C*C*HOH), 60.18 (C≡C*C*HOH), 10.83 ($CH_3$), 49.70, 45.07, 43.40, 41.07, 39.49, 39.23, 36.38, 33.79, 32.69, 32.46, 30.08, 30.00, 29.94, 29.18 and 22.68.

(3R,S)-1-*Trifluoromethyl*-1,10-*seco*-5α-*estr*-2-*yne*-3,17β-*diol* **13c**.—To a solution of 1,1,1-trifluoropropyne (4.0 g, *ca.* 40 mmol) condensed in dry THF (10 $cm^3$) was added dropwise a solution of BuLi in hexane (2.5 mol $dm^{-3}$; 8.0 $cm^3$, 20 mmol) over a 10 min period at −78 °C under $N_2$. After 10 min, a solution of compound **11** (0.30 g, 1.2 mmol) in THF (5.0 $cm^3$) was added and the mixture was allowed to warm to room temp. within ~1.0 h. After a further 2.5 h, the mixture was cooled to −5 °C and saturated aq. $NH_4Cl$ solution was added. The mixture was extracted with DCM (2 × 50 $cm^3$) and the combined organic layer was washed with water (50 $cm^3$), then brine (50 $cm^3$), and dried over $Na_2SO_4$. The solvent was evaporated to give an oil, which was purified by chromatography (silica gel, 10% EtOAc in hexane) to give 0.15 g (36%) of product as an amorphous solid: m.p. 60–65 °C (Found: C, 66.1; H, 7.8; F, 16.7. $C_{19}H_{27}F_3O_2$ requires C, 66.3; H, 7.9; F, 16.55%); $\nu_{max}/cm^{-1}$ 3391, 2917, 2268, 1447, 1380, 1351, 1276, 1141 and 1051; $\delta_H$ 4.53 (1 H, m, C*H*OH), 3.64 (1 H, t, *J* 8.5, C*H*OH) and 0.74 (3 H, s, $CH_3$); $\delta_C$ 114.15 (q, $^1J_{C,F}$ 258.5, $CF_3$), 88.69 (q, $^3J_{C,F}$ 6.5, $CF_3C{\equiv}C$), 81.96 (CHOH), 71.60 (q, $^2J_{C,F}$ 51.8, $CF_3C{\equiv}C$), 59.40 (C≡C*C*HOH), 10.89 ($CH_3$), 49.72, 44.09, 43.51, 43.43, 41.11, 39.64, 39.04, 36.40, 33.73, 32.83, 32.29, 30.11, 29.98, 29.17 and 22.73; $\delta_F$ −50.92 ($CF_3$).

17β-*Hydroxy*-1,10-*seco*-5α-*estr*-1-*yn*-3-*one* **14a**.—A solution of compound **13a** (55 mg, 0.2 mmol) and DDQ (90 mg, 0.4 mmol) in dioxane (10 $cm^3$) was refluxed for 20 h. The mixture was cooled to room temp. and crystalline hydroquinone was removed by filtration. The solution was evaporated to give an oil which was purified by chromatography to give 16 mg (30%) of product as white crystals (from EtOEt–hexane): m.p. 63–65 °C (Found: C, 78.9; H, 9.4. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.55%); $\nu_{max}/cm^{-1}$ 3974, 3846, 3397, 3298, 2916, 2850, 2091, 1679, 1470, 1446, 1380 and 1056; $\delta_H$ 3.65 (1 H, m, C*H*OH), 3.22 (1 H, s, C≡CH), 2.47 (2 H, d, *J* 7.0, $CH_2CO$) and 0.75 (3 H, s, $CH_3$); $\delta_C$ 187.61 (C=O), 81.90 (CHOH), 78.23 (≡C), 77.22 (≡C), 10.91 ($CH_3$), 52.95, 49.37, 43.55, 40.90, 39.22, 36.42, 34.08, 32.83, 32.51, 30.25, 30.06, 29.11 and 22.77.

1-*Chloro*-17β-*hydroxy*-1,10-*seco*-5α-*estr*-1-*yn*-3-*one* **14b**.—A solution of compound **13b** (100 mg, 0.32 mmol) and DDQ (200 mg, 0.88 mmol) in dioxane (10 $cm^3$) was refluxed for 4 h. The mixture was cooled to room temp. and crystalline hydroquinone was removed by filtration. The solution was evaporated to give an oil which was purified by chromatography to give 32 mg (32%) of pure product as a colourless oil (Found: C, 69.9; H, 8.3; Cl, 11.2. $C_{18}H_{25}ClO_2$ requires C, 70.0; H, 8.2; Cl, 11.5%); $\nu_{max}/cm^{-1}$ 3402, 2915, 2860, 2195, 1677, 1446, 1399, 1226, 1119 and 1059; $\delta_H$ 3.64 (1 H, m, C*H*OH), 2.43 (2 H, d, *J* 6.9, $CH_2CO$) and 0.73 (3 H, s, $CH_3$); $\delta_C$ 186.48 (C=O), 81.85

(CHOH), 72.49 (≡C), 68.99 (≡C), 10.88 ($CH_3$), 52.95, 49.67, 43.48, 40.85, 39.16, 36.37, 34.08, 33.93, 32.46, 30.16, 30.00, 29.06 and 22.73.

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