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TETRAHEDRON

Synthesis of 18,18-Difluoro- or 18,18,18-Trifluoro-3-methoxy-12-oxaestra-1,3,5(10)-trienes

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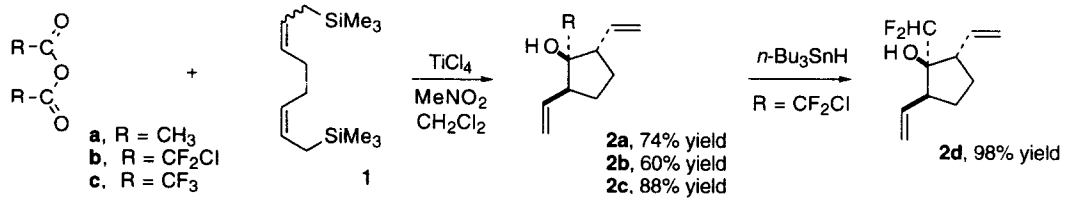
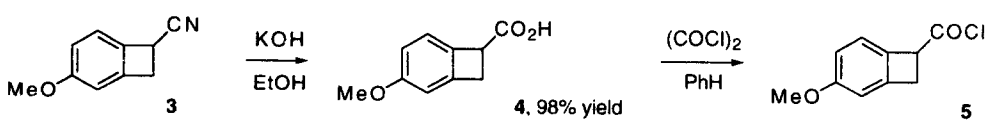
Abstract: Titanium tetrachloride mediated dialkylation of acetic anhydride, trifluoroacetic anhydride or difluorochloroacetic anhydride by 1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) leads, respectively, to *dl*-1-methyl-2,5-divinylcyclopentan-1-ol, *dl*-1-difluoromethyl-2,5-divinylcyclopentan-1-ol or *dl*-1-trifluoromethyl-2,5-divinylcyclopentan-1-ol. Esterification of these compounds with 4-methoxybenzocyclobutene-1-carboxylic acid and then pyrolysis led to 3-methoxy-12-oxa-17-vinylestra-1,3,5(10)-trien-11-one and to corresponding 18,18-difluoro or 18,18,18-trifluoro derivatives. Further transformations give rise to 3-methoxy-12-oxa-17-(2-oxoethyl)-18,18-difluoroestra-1,3,5(10)-trien-11-one and to the corresponding 18,18,18-trifluoro derivative.

Since the first synthesis of equilein and estrone in 1939[1,2] many steroids have been obtained, but curiously, only few oxasteroids have been elaborated. To the best of our knowledge, no 12-oxasteroid has been described.

In connection with our interest in steroid synthesis according to the orthoquinodimethane approach,[3,4] we have recently reported on a new strategy for the synthesis of 1,1-disubstituted-2,5-divinylcyclopentanes. These latter arise from the addition of 1,8-bis(trimethylsilyl)-2,6-octadiene **1** (BISTRO) to various electrophilic reagents.[5] Especially, we have shown that anhydrides react with BISTRO leading to divinylcyclopentanols **2**.[5b] **2b** can be reduced to the corresponding difluoro-compound **2d** by treatment with tributyltin hydride.



On the other hand, alcohols **2a,c,d** are esterified with 4-methoxybenzo-cyclobutene-1-carboxylic acid arising from nitrile **3** using the Kametani procedure.[6]



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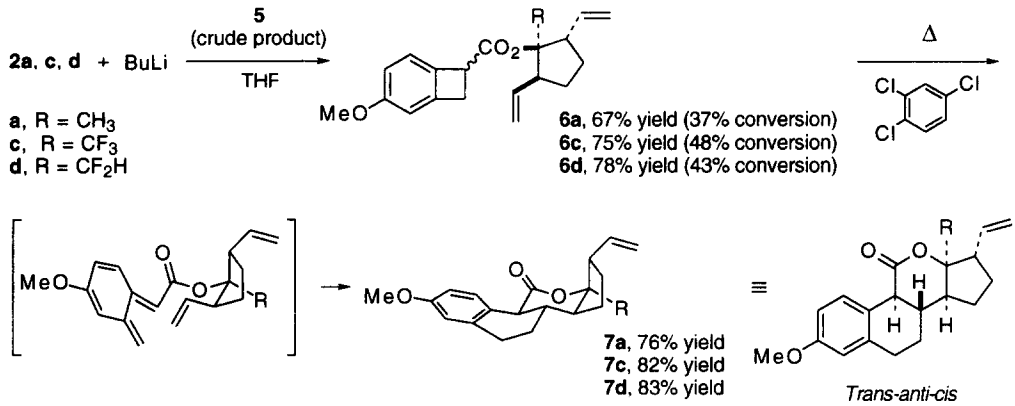
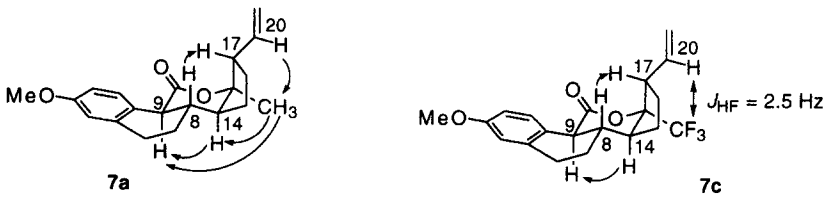
Preparation of esters **6** performed by acylation of **2** with acyl chloride **5** is unfortunately incomplete. Unchanged carboxylic acid **4** and alcohol **2** are partially recovered.

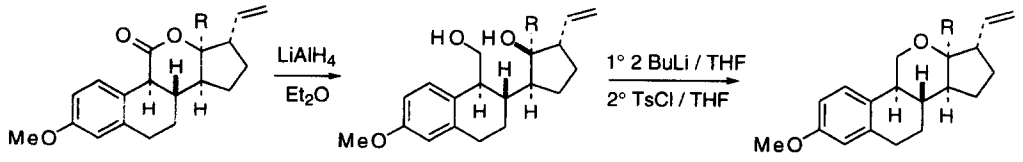


Thermolysis of **6a,c,d** affords *trans-anti-cis* steroids **7a,c,d**, respectively, in excellent yields and high stereoselectivity (>95%). We assume that only the vinyl group *syn* to the ester group is involved in the cycloaddition process according to an *exo* transition state.

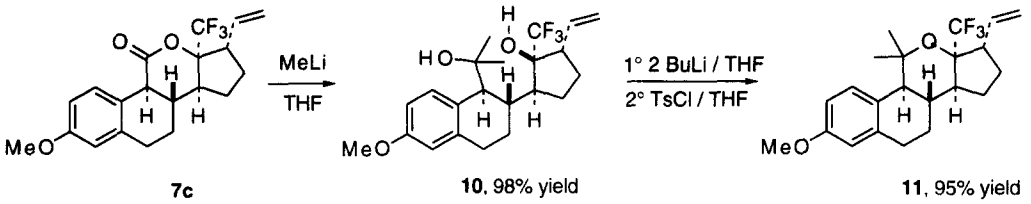
The relative stereochemistry of the steroids **7a,c,d** is determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz). In particular, for **7a**, phase mode NOESY experiments confirm the vicinal relationship between $H^{(8)}$ and $H^{(17)}$ and also between $H^{(20)}$, $Me^{(18)}$, $H^{(14)}$ and $H^{(9)}$. In contrast, no cross peak is observed between $H^{(8)}$ and $H^{(14)}$. On the other hand, the *trans* relationship between $H^{(9)}$ and $H^{(8)}$ is confirmed by the vicinal coupling constant (J = 12.5 Hz). In the case of **7c**, the proximal position of the trifluoromethyl group and the proton $H^{(20)}$ is established by the existence of a long-range coupling constant (J_{HF} = 2.5 Hz).



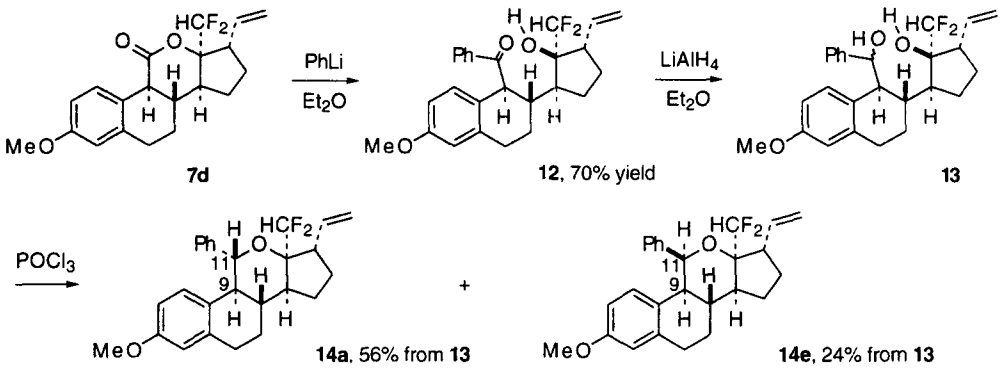
In order to prepare 12-oxasteroids, lactones **7a,c,d** are first reduced into the corresponding diols **8a,c,d**. Then, 12-oxasteroids **9c,d** are obtained in good yields by treatment of diols **8c,d**, respectively, with 2 equiv. of BuLi followed by addition of TsCl.



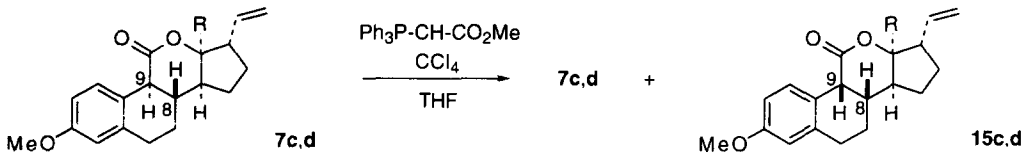
Treatment of ester **7c** by methylithium affords diol **10** which is then cyclized into 11,11-dimethyl-12-oxa steroid **11** by reaction with TsCl in presence of BuLi.



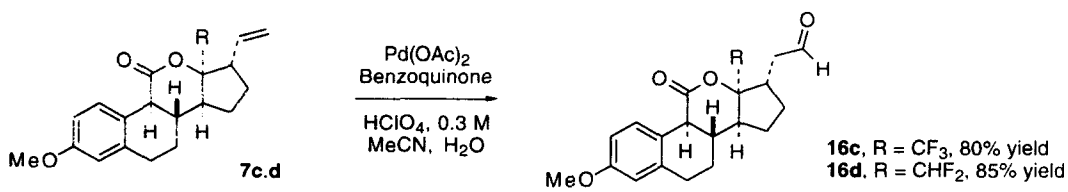
Diol **13** is easily prepared from lactone **7d** through a two step-sequence. Afterwards, **13** can be easily converted into 11-phenyl-steroid as a mixture of epimers (**14a** : **14e** = 2.33 : 1). The relationship between $H^{(9)}$ and $H^{(11)}$ is confirmed by the vicinal coupling constant (for **14a**, $H^{(11)}$ δ = 4.70 ppm, J = 10.0 Hz; for **14e**, $H^{(11)}$ δ = 4.31 ppm, J = 7.0 Hz). It is well established that 11-phenyl-estrone derivatives possess antiestrogenic or antiglucocorticoid properties.[7] Thus oxygenated compound **14** could be of great interest as an analog in biological test.



In order to convert the carbonyl function into an enol ether through a Wittig reaction, steroids **7c,d** are treated with (methoxycarbonylmethylene)triphenylphosphorane.[8] Unfortunately, the only reaction observed is a partial epimerisation of C-9 (**15c** : **7c** = 1.22 : 1). The stereochemistry at $C^{(9)}$ is revealed by the $H^{(8)}$–$H^{(9)}$ vicinal coupling constant (for **7c** or **7d**, J = 12.7 Hz; for **15c**, J = 4.5 Hz, for **15d**, J = 4.4 Hz).



The Wacker-type oxidation of the vinyl group of **7c,d** leads to the corresponding aldehydes **16c,d**, respectively, resulting from an anti-Markovnikov hydroxypalladation. These results have been rationalized by an intramolecular coordination of the palladium with oxygen of the lactonic or ether functions.[9]



Conclusion: We have described a short and efficient synthesis of 18-fluoro-3-methoxy-12-oxaestra-1,3,5(10)-trien-11-ones from 1,3-butadiene and 4-methoxybenzo-cyclobutene-1-carboxylic acid. The possibility of oxidizing the vinyl group by a Wacker-type oxidation enhances the synthetic versatility of this methodology.

EXPERIMENTAL SECTION

General. All reactions were run under argon in oven-dried glassware. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AC 400 spectrometer in $CDCl_3$ (or C_6D_6) solutions. Chemical shift (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 GF_{254} 230-400 mesh) and TLC on silica gel (Merck 60 F_{254}).

Material. All solvents were distilled before used. CH_2Cl_2 and $CHCl_3$ from P_2O_5, MeOH under $Mg(OMe)_2$, THF over sodium/benzophenone. **1,8-Bis(trimethylsilyl)-2,6-octadiene (BISTRO) 1** was prepared according to the previously described procedure.[10]

General procedure for the preparation of 2a,b,c.

Two-necked flask equipped with a magnetic stirring bar, a condenser and an argon outlet is charged with anhydrous CH_2Cl_2 (20 mL), $TiCl_4$ (2.3 mL, 20 mmol) and $MeNO_2$ (2.17 mL, 40 mmol). The solution is cooled at -60°C and then anhydride (10 mmol) is added. The mixture is cooled to -90°C and BISTRO (3.04 g, 12 mmol) is added in 15 mn. After 2 h, the solution is warmed to -60°C for 12 h., then mixture is pourred into a saturated solution of NH_4Cl. After usual work-up, the crude product is purified by chromatography on silica gel (petroleum ether - diethylether 5 : 1). ***(dl)*-1-Methyl-2,5-divinylcyclopentanol (2a).**[5a]

***(dl)*-1-Chlorodifluoromethyl-2,5-divinylcyclopentanol (2b).** IR (neat) 3530, 1640, 1120, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.86 (m, 2H), 5.17 (m, 4H), 3.03 (q, J = 8.1 Hz, 1H), 2.77 (q, J = 8.0 Hz, 1H), 2.30-1.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 136.4 (d), 135.2 (d), 131.1 (t, J_{CF} = 302 Hz), 118.9 (t), 116.2 (t), 86.6 (t, J_{CF} = 22 Hz), 55.0 (d), 47.3 (d), 29.3 (t), 28.4 (t). HRMS calcd for $C_{10}H_{13}ClF_2O$ 222.0623, found 222.0629.

***(dl)*-1-Trifluoromethyl-2,5-divinylcyclopentanol (2c).**[5e]

***(dl)*-1-Difluoromethyl-2,5-divinyl-cyclopentanol (2d).** Two-necked flask equipped with a magnetic stirring bar, a condenser and an argon outlet is charged with anhydrous benzene (2 mL), 82 mg (0.5 mmol) of AIBN and 250 mg (1 mmol) of alcohol **2b**. The mixture is brought to reflux until complete dissolution. Then 0.3 mL (1.1 mmol) of Bu_3SnH is added. The solution is refluxed for 5 h and then poured into 15 mL of water and extracted with ether. The organic layer is washed with water, dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue is chromatographed on silica gel (Et_2O-petroleum ether). Compound **2d** is isolated in 98% yield (184 mg). IR (neat) 3450, 1637, 1061, 1002, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.76 (m, 2H), 5.61 (dd, J_{HF}= 56.4, 55.7 Hz, 1H), 5.13 (m, 4H), 2.80 (t, J = 9.3 Hz, 1H), 2.66 (q, J = 9.3 Hz, 1H), 2.00-1.40 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 136.2 (d), 136.0 (d), 118.5 (t), 117.2 (t), 116.9 (t, J_{CF} = 245 Hz), 82.0 (t, J_{CF} = 20 Hz), 54.2 (d), 46.1 (d), 29.4 (t), 28.9 (t). HRMS calcd for $C_{10}H_{14}F_2O$ 188.10127, found 188.1018.

1-Cyano-4-methoxybenzocyclobutene (3).[6b] IR (neat) 2246, 1243, 1164, 1021, 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, J = 8.2 Hz, 1H), 6.81 (dd, J = 8.2, 1.7 Hz, 1H), 6.68 (d, J = 1.7 Hz, 1H), 4.14 (dd, J = 5.3, 2.8 Hz, 1H), 3.76 (s, 3H), 3.60 (dd, J = 14.2, 5.3 Hz, 1H), 3.45 (dd, J = 14.2, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 160.8 (s), 143.5 (s), 130.1 (s), 123.4 (d), 119.7 (s), 114.9 (d), 108.5 (d), 55.2 (q), 35.3 (d), 27.7 (t).

4-Methoxybenzocyclobutene-1-carboxylic acid (4).[6a] IR ($HCCl_3$) 3500-2500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (d, J = 8.1 Hz, 1H), 6.77 (dd, J = 8.2, 2.3 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 4.23 (t, J = 4.1

Hz, 1H), 3.75 (s, 3H), 3.74 (d, J = 4.0 Hz, 1H), 3.40 (d, J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 179.2 (s), 160.3 (s), 144.6 (s), 133.6 (s), 123.6 (d), 114.1 (d), 108.6 (d), 55.3 (q), 44.6 (d), 33.2 (t).

General procedure for the preparation of 6. Two-necked flask equipped with a magnetic stirring bar, an argon outlet is charged with 1.66 g (10 mmol) of **4** and 35 mL of anhydrous benzene. Oxalyl chloride (1.71 mL, 20 mmol) is added and the mixture is stirred at 20 °C for 3 h. Then, the solution is concentrated under vacuum. The residue is dissolved into 10 mL of anhydrous benzene and concentrated under vacuum again. This last operation is repeated three more times. The crude acyl chloride **5** is used without any purification in the next step. In a two-necked flask equipped with a magnetic stirring bar, an argon outlet, 10 mmol of alcohol **2** are dissolved in 30 mL of anhydrous THF. The solution is cooled at –50°C, n-BuLi is added (1.6M, 6.8 mL, 11 mmol) and then acylchloride **5** (11 mmol). The mixture is vigorously stirred for 6 h at 20 °C. The reaction is quenched by addition of brine and then extracted with Et_2O. The extracts are washed with water, dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue is purified by chromatography on silica gel.

***(dl)*-1-Methyl-2,5-divinylcyclopentyl 4-Methoxybenzocyclobutene-1-carboxylate (6a).** IR (CCl_4) 1752, 1609, 1275, 1167, 919 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.03 (d, J = 8.1 Hz, 1H), 6.75 (dd, J = 8.1, 2.2 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 5.86 (m, 2H), 5.13 (m, 4H), 4.10 (t, J = 6.6 Hz, 1H), 3.75 (s, 3H), 3.37 (d, J = 6.5 Hz, 2H), 2.18 (m, 2H), 1.65 (m, 4H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.5 (s), 160.1 (s), 144.8 (s), 137.6 (d), 137.5 (d), 134.4 (s), 123.5 (d), 116.7 (t), 114.0 (t), 108.6 (d), 108.4 (d), 81.6 (s), 64.6 (q), 55.3 (d), 54.3 (d), 44.9 (d), 33.2 (t), 30.6 (t), 27.3 (t), 19.0 (q).

***(dl)*-1-Trifluoromethyl-2,5-divinylcyclopentyl 4-Methoxybenzocyclobutene-1-carboxylate (6c).** IR (CCl_4) 1751, 1605, 1273, 1167, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.01 (d, J = 8.1 Hz, 1H), 6.74 (dd, J = 8.2, 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 5.82 (m, 2H), 5.08 (m, 4H), 4.21 (t, J = 4.1 Hz, 1H), 3.75 (s, 3H), 3.36 (d, J = 4.1 Hz, 2H), 3.01 (m, 2H), 1.95 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 160.4 (s), 144.8 (s), 135.4 (d), 134.8 (d), 133.9 (s), 124.9 (q, J_{CF} = 286 Hz), 123.7 (d), 117.9 (t), 117.2 (t), 114.2 (d), 108.6 (d), 91.3 (q, J_{CF} = 29.0 Hz), 55.3 (q), 48.9 (d), 45.6 (d), 33.0 (t), 30.1 (t), 29.1 (t).

***(dl)*-1-Difluoromethyl-2,5-divinylcyclopentyl 4-Methoxybenzocyclobutene-1-carboxylate (6d).** IR (CCl_4) 1750, 1605, 1275, 1166, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.03 (d, J = 8.0 Hz, 1H), 6.77 (dd, J = 8.2, 2.1 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.43 (t, J_{HF} = 54.6 Hz, 1H), 5.89 (m, 2H), 5.09 (m, 4H), 4.21 (t, J = 4.2 Hz, 1H), 3.75 (s, 3H), 3.37 (d, J = 4.1 Hz, 2H), 3.03 (m, 2H), 1.95 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.4 (s), 160.4 (s), 144.9 (s), 136.3 (d), 135.9 (d), 134.0 (s), 123.5 (d), 118.7 (t, J_{CF} = 245 Hz), 117.6 (t), 116.5 (d), 114.2 (d), 108.9 (t), 90.1 (t, J_{CF} = 20.2 Hz), 55.4 (q), 51.5 (d), 46.7 (d), 45.4 (d), 33.1 (t), 30.1 (t), 29.3 (t).

General procedure for the preparation of 7. A two-necked flask equipped with a magnetic stirring bar, an argon outlet, and a condenser is charged with **6** (10 mmol), 100 mL of 1,2,4-trichlorobenzene and boiled under argon for 12 hours. The mixture is then concentrated under vacuum. The residue is purified either by cristallisation (**7c**: Et_2O-petroleum ether: 1-1, **7d**: ethyl acetate-petroleum ether: 1-10) or by chromatography on silica gel (Et_2O-petroleum ether).

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-17-vinylestra-1,3,5(10)-trien-11-one (7a). 76% yield; mp 142 °C; IR ($CHCl_3$) 1756, 1643, 1242, 1113, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.6, 3.0 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 5.92 (ddd, J = 17.2, 10.9, 6.4 Hz, 1H), 5.13 (m, 2H), 3.76 (s, 3H), 3.37 (d, J = 12.3 Hz, 1H), 2.74 (m, 3H), 2.17 (dm, J = 11.1 Hz, 1H), 2.16 (m, 1H), 1.89 (m, 2H), 1.71 (td, J = 12.1, 2.8 Hz, 1H), 1.48 (m, 1H), 1.40 (m, 1H), 1.33 (s, 3H), 1.03 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.4 (s), 158.2 (s), 138.5 (s), 135.9 (d), 132.6 (s), 122.1 (d), 116.8 (t), 113.5 (d), 112.0

(d), 89.7 (s), 55.2 (d), 54.5 (q), 51.7 (d), 43.6 (d), 42.2 (d), 29.9 (t), 29.7 (t), 28.0 (q), 27.8 (t), 27.0 (t); Anal. calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found : C, 76.92; H, 7.69.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-trien-11-one (7c). 82% yield; mp 181 °C; IR ($CHCl_3$) 1758, 1611, 1263, 1185, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 8.7 Hz, 1H), 6.79 (dd, J = 8.6, 2.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.04 (ddd, J = 17.4, 10.6, 7.6 Hz, q, J_{HF} = 2.7 Hz, 1H), 5.10 (m, 2H), 3.39 (s, 3H), 3.29 (d, J = 12.7 Hz, 1H), 2.58 (td, J = 12.2, 5.5 Hz, 1H), 2.42 (m, 2H), 1.93 (td, J = 11.1, 7.9 Hz, 1H), 1.53 (m, 1H), 1.40 (m, 3H), 1.17 (q, J = 11.4 Hz, 1H), 0.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 158.9 (s), 137.9 (s), 133.9 (d), 133.4 (s), 125.5 (q, J_{CF} = 284 Hz), 122.1 (d), 117.1 (t), 114.0 (d), 111.9 (d), 89.1 (q, J_{CF} = 27 Hz), 54.7 (d), 54.3 (q), 46.2 (d), 44.2 (d), 40.8 (d), 29.7 (t), 28.9 (t), 27.6 (t), 26.9 (t); Anal. calcd. for $C_{20}H_{21}F_3O_3$: C, 65.57; H, 5.78. Found : C, 65.52; H, 5.82.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-vinylestra-1,3,5(10)-trien-11-one (7d). 83% yield; mp 156 °C; IR ($CHCl_3$) 1753, 1611, 1258, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.6, 2.8 Hz, 1H), 6.59 (d, J = 2.6 Hz, 1H), 5.93 (m, 1H), 5.81 (dd, J_{HF} = 58.2, 55.6 Hz, 1H), 5.27 (m, 2H), 3.77 (s, 3H), 3.48 (d, J = 12.7 Hz, 1H), 2.90 (m, 1H), 2.79 (m, 2H), 2.48 (q, J = 9.2 Hz, 1H), 2.28 (dt, J = 12.6, 7.5, 1H), 2.11 (m, 1H), 1.73 (q, J = 11.7 Hz, 1H), 1.72 (m, 1H), 1.60 (m, 1H), 1.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 171.2 (s), 158.1 (s), 138.0 (s), 132.9 (d), 132.3 (s), 121.7 (d), 118.9 (t), 114.9 (t, J_{CF} = 246 Hz), 113.1 (d), 111.8 (d), 88.6 (t, J_{CF} = 24 Hz), 54.9 (d), 53.5 (q), 42.9 (d), 41.4 (d), 40.8 (d), 29.6 (t), 28.9 (t), 27.2 (t), 27.1 (t); Anal. calcd. for $C_{20}H_{22}F_2O_3$: C, 68.95; H, 6.36. Found : C, 68.91; H, 6.29.

General procedure for the preparation of 8. In a two-necked flask equipped with a magnetic stirring bar, and an argon outlet the steroids **7** (1 mmol) are dissolved in 100 mL of anhydrous Et_2O. $AlLiH_4$ (1 mmol) is added and the mixture is refluxed for 6 hours. After cooling at room temperature, the solution is poured in 15 mL of cold water and extracted with CH_2Cl_2. The organic layer is washed with water, dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue is chromatographed on silica gel (Et_2O-petroleum ether).

(8β, 9α, 13α, 14α, 17α)-11,12-Seco-12-nor-11,13-dihydroxy-3-methoxy-17-vinylestra-1,3,5(10)-triene (8a). 98% yield; IR (CCl_4) 3409, 1611, 1180, 917 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (d, J = 8.2 Hz, 1H), 6.70 (dd, J = 8.2, 2.7 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 5.74 (m, 1H), 5.03 (m, 2H), 3.74 (s, 3H), 3.65 (m, 2H), 2.97 (m, 2H), 2.62 (m, 2H), 2.22 (m, 2H), 1.91-1.24 (m, 6H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.6 (s), 139.1 (s), 138.5 (d), 131.4 (s), 127.8 (d), 115.4 (t), 113.2 (d), 112.2 (d), 81.2 (s), 68.1 (t), 58.4 (q), 55.1 (d), 48.3 (d), 43.7 (d), 33.4 (d), 29.3 (t), 28.6 (t), 28.2 (t), 25.8 (q), 21.5 (t). Anal. calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found : C, 75.93; H, 8.95.

(8β, 9α, 13α, 14α, 17α)-11,12-Seco-12-nor-11,13-dihydroxy-3-methoxy-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-triene (8c). 98% yield; mp 135 °C; IR (CCl_4) 3406, 1609, 1171, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.4, 2.6 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 5.84 (m, 1H), 5.09 (m, 2H), 3.74 (s, 3H), 3.69 (d, J = 7.5 Hz, 2H), 3.12 (t, J = 6.9 Hz, 1H), 2.61 (m, 3H), 2.22 (m, 3H), 1.98 (m, 2H), 1.63 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.7 (s), 138.9 (s), 135.4 (d), 131.3 (s), 127.4 (d), 123.1 (q, J_{CF} = 289 Hz), 117.1 (t), 113.2 (d), 112.4 (d), 83.5 (q, J_{CF} = 27 Hz), 67.8 (t), 58.0 (q), 55.2 (d), 43.3 (d), 43.2 (d), 33.5 (d), 29.3 (t), 29.0 (t), 26.2 (t), 21.8 (t). Anal. calcd. for $C_{20}H_{25}F_3O_3$: C, 64.85; H, 6.80. Found : C, 64.82; H, 6.82.

(8β, 9α, 13α, 14α, 17α)-11,12-Seco-12-nor-11,13-dihydroxy-3-methoxy-18,18-difluoro-17-vinylestra-1,3,5(10)-triene (8d). 98% yield; mp 139 °C; IR (CCl_4) 3412, 1608, 1173, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06 (d, J = 8.4 Hz, 1H), 6.69 (dd, J = 8.4, 2.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 5.71 (m, 1H), 5.23 (dd, J_{HF} = 57.1, 55.3 Hz, 1H), 5.09 (m, 2H), 3.75 (s, 3H), 3.71 (d, J = 5.5 Hz, 2H), 3.07 (t, J = 6.8 Hz, 1H), 2.58 (m, 3H), 2.17 (m, 3H), 1.78 (m, 2H), 1.62 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 157.7 (s), 139.1 (s), 135.7 (d), 131.3 (s), 127.4 (d), 114.4 (t, J_{CF} = 247 Hz), 117.5 (t), 113.2 (d), 112.4 (d), 82.5 (t, J_{CF} = 25 Hz), 67.9 (t), 57.3 (q), 55.2 (d), 43.7 (d), 41.4 (d), 33.2 (d), 29.3 (t), 28.8 (t), 26.2 (t), 21.9 (t). Anal. calcd. for $C_{20}H_{26}F_2O_3$: C, 68.16; H, 7.44. Found : C, 68.21; H, 7.37.

General procedure for the preparation of 9. A two-necked flask equipped with a magnetic stirring bar and an argon outlet is charged with diol **8** (0.12 mmol) and 2 mL of anhydrous THF. The solution is cooled at -60°C and n-BuLi (1.6 M, 0.24 mmol) is slowly added. The mixture is vigorously stirred until -30°C and then a solution of tosyl chloride (0.12 mmol) in 1 mL of THF is added. When TLC shows the appearance of transient compound **9**, the reaction is quenched by addition of aqueous saturated NH_4Cl and extracted with ether. The extracts are dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue is chromatographed on silica gel (Et_2O-petroleum ether) leading to **9**.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-triene (9c). 80% yield; IR (CCl_4) 1608, 1263, 1052, 911 cm^{-1}; ^1H NMR (C_6D_6) δ 6.86 (d, J = 8.2 Hz, 1H), 6.75 (dd, J = 8.5, 2.9 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H), 5.88 (ddd, J = 17.7, 10.9, 8.2 Hz, q J_{HF} = 2.8 Hz, 1H), 5.06 (m, 2H), 3.85 (q, J = 9.2 Hz, 1H), 3.23 (dd, J = 11.7, 3.4 Hz, 1H), 3.09 (dd, J = 10.9, 8.7 Hz, 1H), 2.64 (t, J = 8.4 Hz, 1H), 2.36 (m, 3H), 2.04-1.32 (m, 7H); ^{13}C NMR (C_6D_6) δ 159.1 (s), 141.1 (s), 137.1 (d), 130.8 (s), 129.5 (d), 129.2 (q, J_{CF} = 292 Hz), 116.5 (t), 114.2 (d), 113.1 (d), 84.3 (q, J_{CF} = 27 Hz), 69.2 (t), 56.3 (q), 55.2 (d), 47.8 (d), 42.4 (d), 33.1 (d), 30.9 (t), 29.8 (t), 28.6 (t), 26.4 (t); Anal. calcd. for $C_{20}H_{23}F_3O_2$: C, 68.17; H, 6.58. Found : C, 68.04; H, 6.72.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-vinylestra-1,3,5(10)-triene (9d). 80% yield; mp 138 °C; IR (CCl_4) 1608, 1264, 1056, 926 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 8.6, 2.7 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 5.86 (m, 1H), 5.56 (dd, J_{HF} = 57.2, 55.1, 1H), 5.13 (m, 2H), 3.74 (s, 3H), 3.70 (m, 2H), 3.07 (br. d, J = 6.4 Hz, 1H), 2.61 (m, 3H), 2.24 (m, 1H), 2.19 (td, J = 10.0, 8.8 Hz, 1H), 1.95 (m, 2H), 1.71 (m, 2H), 1.58 (m, 1H), 1.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 157.9 (s), 139.3 (s), 135.9 (d), 131.3 (s), 127.5 (d), 117.7 (t), 117.2 (t, J_{CF} = 247 Hz), 113.4 (d), 112.6 (d), 82.4 (t, J_{CF} = 21 Hz), 68.0 (t), 57.5 (q), 55.3 (d), 43.8 (d), 41.8 (d), 33.5 (d), 29.3 (t), 29.0 (t), 26.5 (t), 22.3 (t); Anal. calcd. for $C_{20}H_{24}F_2O_2$: C, 71.83; H, 7.23. Found : C, 71.84; H, 7.18.

(8β, 9α, 13α, 14α, 17α)-11,12-Seco-12-nor-11,13-dihydroxy-11,11-dimethyl-3-methoxy-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-triene (10). A two-necked flask equipped with a magnetic stirring bar and an argon outlet is charged with **7c** (74 mg, 0.2 mmol) and 5 mL of anhydrous CH_2Cl_2. The solution is cooled at -60°C and then methyllithium (0.4 mmol) is added. The mixture is stirred until room temperature and then poured into a 1N aqueous solution of HCl. The extraction is performed with CH_2Cl_2. The organic layer is washed with water, filtered and dried over $MgSO_4$. After concentration under vacuum, the crude product is purified by chromatography on silica gel (Et_2O-petroleum ether) to give pure **10**. 98% yield; IR (CCl_4) 3406, 1609, 1262, 1168, 739 cm^{-1}; ^1H NMR (C_6D_6) δ 7.08 (d, J = 9.0 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 9.0, 2.7 Hz, 1H), 5.92 (m, 1H), 4.99 (m, 2H), 4.31 (s, 3H), 2.89 (t, J = 2.6 Hz, 1H), 2.63 (m, 2H), 2.45 (q, J = 5.6 Hz, 1H), 2.37 (m, 3H), 1.40 (m, 5H), 1.21 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (C_6D_6)

δ 158.0 (s), 141.3 (s), 135.9 (d), 132.8 (s), 127.9 (d), 126.8 (q, J_{CF} = 292 Hz), 116.9 (t), 113.2 (d), 111.1 (d), 83.5 (q, J_{CF} = 26 Hz), 74.7 (s), 57.3 (d), 55.1 (q), 46.9 (d), 34.1 (d), 28.7 (t), 28.7 (t), 28.5 (q), 28.2 (t), 28.0 (q), 26.6 (t), 24.0 (t); Anal. calcd. for $C_{22}H_{29}F_3O_3$: C, 66.31; H, 7.34. Found : C, 66.34; H, 7.32.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-11,11-dimethyl-12-oxa-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-triene (11). A two-necked flask equipped with a magnetic stirring bar and an argon outlet is charged with **10** (40 mg, 0.1 mmol) and 2 mL of anhydrous THF. The solution is cooled at -60°C and then n-BuLi (0.2 mmol) are slowly added. The mixture is vigorously stirred until -30°C, and then a solution of tosyl chloride (0.1 mmol) in 1 mL of THF is added. After completion of the reaction (TLC), it is quenched by addition of 2 mL of aqueous saturated NH_4Cl and extracted with ether. The extracts are dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue is chromatographed on silica gel (Et_2O-petroleum ether) leading to **11**. 95% yield; IR (CCl_4) 1634, 1232, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, J = 8.6 Hz, 1H), 6.58 (dd, J = 8.7, 2.5 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.10 (m, 1H), 5.08 (m, 2H), 3.46 (s, 3H), 2.87 (d, J = 10.1 Hz, 1H), 2.52 (q, J = 5.6 Hz, 1H), 2.37 (t, J = 5.3 Hz, 2H), 2.17 (m, 1H), 1.90-1.25 (m, 7H), 1.69 (m, 1H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.6 (s), 139.7 (s), 135.9 (d), 131.6 (s), 128.0 (d), 126.3 (q, J_{CF} = 292 Hz), 115.6 (t), 113.9 (d), 112.1 (d), 84.6 (q, J_{CF} = 27 Hz), 80.3 (s), 57.8 (d), 54.6 (q), 47.5 (d), 46.2 (d), 40.2 (d), 31.3 (t), 30.5 (t), 27.7 (t), 26.4 (t), 26.2 (q), 25.8 (q); Anal. calcd. for $C_{22}H_{27}F_3O_2$: C, 69.46; H, 7.15. Found : C, 69.44; H, 7.12.

(8β, 9α, 13α, 14α, 17α)-11,12-Seco-12-nor-13-hydroxy-3-methoxy-11-phenyl-18,18-difluoro-17-vinylestra-1,3,5(10)-trien-11-one (12). A two-necked flask equipped with a magnetic stirring bar and an argon outlet is charged with **7d** (52 mg, 0.15 mmol) and 4 mL of anhydrous CH_2Cl_2. Then phenyllithium (0.15 mmol) is slowly added and the solution is stirred for three hours. The reaction is quenched by addition of aqueous 1N HCl solution and extracted with CH_2Cl_2. The organic layer is washed with water, filtered and dried over $MgSO_4$. After concentration under vacuum, the crude product is purified by chromatography on silica gel (Et_2O-petroleum ether) to give pure **12**. 70% yield; IR (CCl_4) 3416, 1697, 1262, 923, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 1H), 7.42 (m, 3H), 6.81 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 2.6 Hz, 1H), 6.57 (dd, J = 8.4, 2.7 Hz, 1H), 5.79 (m, 1H), 5.40 (dd, J_{HF} = 55.9, 55.8 Hz, 1H), 5.11 (m, 2H), 4.67 (d, J = 7.0 Hz, 1H), 3.74 (s, 3H), 2.89 (dd, J = 8.7, 5.7 Hz, 1H), 2.80 (t, J = 5.6 Hz, 1H), 2.56 (m, 2H), 2.21-1.24 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 203.6 (s), 158.1 (s), 138.9 (s), 137.5 (s), 135.6 (d), 132.7 (d), 130.2 (d), 129.2 (d)(2C), 128.5 (d)(2C), 126.6 (s), 121.8 (q, J_{CF} = 247 Hz), 117.5 (t), 113.9 (d), 112.3 (d), 82.3 (q, J_{CF} = 20 Hz), 57.0 (d), 55.2 (q), 53.4 (d), 52.7 (d), 42.7 (d), 37.2 (t), 28.3 (t), 26.7 (t), 24.4 (t); Anal. calcd. for $C_{26}H_{28}F_2O_3$: C, 73.22; H, 6.62. Found : C, 73.19; H, 6.62.

(8β, 9α, 11α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-vinylestra-1,3,5(10)-triene (14a). In a flask equipped with a magnetic stirring bar, a condenser and an argon outlet, crude diol **13** (arising from reduction of **12** (44 mg, 0.1 mmol) performed with $LiAlH_4$ in ether) is dissolved in 2 mL of $POCl_3$ and the mixture is refluxed until complete disappearance of **13** by TLC. The solution is concentrated under vacuum and then purified by chromatography on silica gel (Et_2O-petroleum ether) to provide a mixture of epimers (**14a** : **14e** = 2.33 : 1). **14a**, 56% yield; IR (neat) 1608, 1260, 1059, 920, 803, 737, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (m, 4H), 7.25 (t, J = 7.1 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 6.28 (dd, J = 8.8, 2.9 Hz, 1H), 6.12 (d, J = 8.8 Hz, 1H), 5.86 (m, 1H), 5.57 (dd, J_{HF} = 57.2, 54.6, 1H), 5.09 (m, 2H), 4.70 (d, J = 10.0 Hz, 1H), 3.67 (s, 3H), 3.19 (m, 1H), 2.92 (t, J = 10.3 Hz, 1H), 2.83 (m, 2H), 2.59 (m, 1H), 2.10-1.20 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 157.7 (s), 142.6 (s), 140.3 (s), 136.0 (d), 132.0 (d), 130.0-128.0 (d)(6C),

117.5 (t), 116.8 (t, J_{CF} = 247 Hz), 114.0 (d), 110.7 (d), 85.3 (t, J_{CF} = 21 Hz), 79.0 (d), 68.0 (t), 55.2 (q), 53.3 (d), 49.6 (d), 43.6 (d), 42.1 (d), 33.8 (t), 30.6 (t), 27.7 (t), 26.9 (t); Anal. calcd. for $C_{26}H_{28}F_2O_2$: C, 76.07; H, 6.88. Found : C, 76.04; H, 6.87.

(8β, 9α, 11β, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-vinylestra-1,3,5(10)-triene (14e). 24% yield; IR (neat) 1608, 1260, 1059, 920, 803, 737, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39 (m, 4H), 7.09 (t, J = 7.1 Hz, 1H), 6.71 (d, J = 2.8 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.65 (dd, J = 8.3, 2.8 Hz, 1H), 5.83 (m, 1H), 5.74 (dd, J_{HF} = 57.2, 54.6, 1H), 5.11 (m, 2H), 4.31 (d, J = 7.0 Hz, 1H), 4.19 (dd, J = 9.9, 7.1 Hz, 1H), 3.77 (s, 3H), 2.76 (m, 1H), 2.62 (m, 2H), 2.2-1.2 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 158.5 (s), 144.0 (s), 141.0 (s), 135.8 (d), 132.7 (d), 130.0-128.0 (d)(6C), 117.0 (t), 116.9 (t, J_{CF} = 247 Hz), 115.8 (d), 111.3 (d), 89.2 (d), 85.3 (t, J_{CF} = 21 Hz), 55.3 (q), 53.3 (d), 52.2 (d), 45.6 (d), 40.5 (d), 31.6 (t), 30.0 (t), 29.9 (t), 25.5 (t).

Procedure for the preparation of 15. A flask equipped with a magnetic stirring bar, a condenser and an argon outlet, is charged with steroids **7c,d** (0.1 mmol), triphenylphosphorane (0.2 mmol) and 2 mL of CCl_4. The mixture is refluxed 48 hours, cooled until room temperature and then concentrated under vacuum. The residue is taken up in CH_2Cl_2 purified by chromatography on silica gel (Et_2O-petroleum ether) to provide a mixture (**7** : **15** = 1 : 1.22).

(8β, 9β, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18,18-trifluoro-17-vinylestra-1,3,5(10)-trien-11-one (15c). 55% yield; IR (neat) 1753, 1610, 1254, 1162, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 1H), 6.75 (dd, J = 8.5, 2.6 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 5.94 (m, 1H), 5.21 (m, 2H), 3.76 (s, 3H), 3.70 (d, J = 4.5 Hz, 1H), 2.81 (m, 3H), 2.56 (m, 1H), 2.81 (m, 3H), 1.53 (m, 1H), 2.56 (m, 1H), 1.73 (m, 4H), 1.23 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.6 (s), 158.9 (s), 136.5 (s), 133.2 (d), 131.5 (s), 124.4 (q, J_{CF} = 284 Hz), 123.2 (d), 117.6 (t), 113.9 (d), 112.2 (d), 90.3 (q, J_{CF} = 27 Hz), 56.5 (d), 55.2 (q), 41.5 (d), 39.4 (d), 37.6 (d), 29.7 (t), 28.2 (t), 27.7 (d), 26.1 (d).

(8β, 9β, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-vinylestra-1,3,5(10)-trien-11-one (15d). 55% yield; IR (neat) 1753, 1611, 1258, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 1H), 6.75 (dd, J = 8.6, 2.6 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H), 5.87 (m, 1H), 5.72 (t, J_{HF} = 55.9 Hz, 1H), 5.26 (m, 2H), 3.76 (s, 3H), 3.66 (d, J = 4.4 Hz, 1H), 2.82 (m, 3H), 2.58 (t, J = 7.2 Hz, 1H), 2.15 (m, 2H), 1.95-1.15 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 158.8 (s), 136.7 (s), 132.9 (d), 131.7 (s), 123.7 (d), 119.5 (t), 114.3 (t, J_{CF} = 247 Hz), 113.8 (d), 112.1 (d), 90.0 (t, J_{CF} = 24 Hz), 56.0 (d), 55.2 (q), 41.9 (d), 37.7 (d), 36.9 (d), 30.2 (t), 29.7 (t), 28.5 (t), 27.5 (t).

General procedure for the preparation of 16. A two-necked flask equipped with a magnetic stirring bar and an argon outlet is charged with $Pd(OAc)_2$ (0.1M), benzoquinone (0.9 M) and CH_3CN (12 mL / mmol of starting material). Water (CH_3CN / H_2O = 7 / 1) and then $HClO_4$ (0.3 M) are successively added. The solution is vigorously stirred for 1 hour at 20°C and then steroid **7** is added. When the reaction is over (TLC), the mixture is poured into a 30% aqueous solution of NaOH. After decantation, the aqueous layer is diluted with water and extracted with ether. The extracts are filtered and then concentrated under vacuum. The crude product is purified by chromatography on silica gel (Et_2O-petroleum ether).

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18,18-trifluoro-17-(2-oxoethyl)-estra-1,3,5(10)-trien-11-one (16c). 80% yield; IR (CCl_4) 1763, 1723, 1612, 1259, 1169 cm^{-1}; ^1H NMR (C_6D_6) δ 9.21 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 8.5, 2.5 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 3.44 (s, 3H), 3.26 (d, J = 12.4 Hz, 1H), 2.59 (1/2 AB, J = 18.0 Hz, 1H), 2.42 (m, 3H), 2.03 (dd, J = 11.1,

7.9 Hz, 1H), 1.81 (dd, J = 16.1, 8.1 Hz, 1H), 1.42 (m, 2H), 1.12 (q, J = 12.5 Hz, 1H), 0.93 (m, 4H); ^{13}C NMR (C_6D_6) δ 199.8 (d), 170.0 (s), 158.4 (s), 138.1 (s), 132.4 (s), 125.2 (q, J_{CF} = 284 Hz), 121.1 (d), 113.5 (d), 112.2 (d), 88.7 (q, J_{CF} = 28.0 Hz), 55.2 (q), 44.3 (d), 43.7 (t), 42.8 (d), 42.6 (d), 41.0 (d), 29.7 (t), 29.2 (t), 28.1 (t), 27.0 (t); Anal. calcd. for $C_{20}H_{21}F_3O_4$: C, 62.82; H, 5.54. Found : C, 62.73; H, 5.71.

(8β, 9α, 13α, 14α, 17α)-3-Methoxy-12-oxa-18,18-difluoro-17-(2-oxoethyl)-estra-1,3,5(10)-trien-11-one (16d). 85% yield; IR (CCl_4) 1765, 1725, 1611, 1258, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.79 (t, J = 1.5 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.7, 2.7 Hz, 1H), 6.59 (d, J = 2.7 Hz, 1H), 5.82 (dd, J_{HF} = 56.9, 54.8, 1H), 3.76 (s, 3H), 3.47 (d, J = 12.4 Hz, 1H), 2.97 (1/2 AB, d, J = 16.8, 3.0 Hz, 1H), 2.78 (m, 2H), 2.53 (1/2 AB, d, J = 16.8, 11.1 Hz, 1H), 2.42 (dt, J = 8.8, 8.3 Hz, 1H), 2.24 (m, 1H), 2.09 (m, 2H), 1.76 (q, J = 11.9 Hz, 1H), 1.66 (m, 1H), 1.41 (m, 2H), 0.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 199.5 (d), 171.1 (s), 158.4 (s), 138.2 (s), 132.5 (s), 125.0 (t, J_{CF} = 248 Hz), 121.7 (d), 113.5 (d), 112.1 (d), 88.3 (t, J_{CF} = 1.0 Hz), 55.3 (q), 44.2 (d), 43.2 (t), 42.2 (d), 41.3 (d), 41.0 (d), 29.9 (t), 29.8 (t), 28.4 (t), 27.3 (t). Anal. calcd. for $C_{20}H_{22}F_2O_4$: C, 65.92; H, 6.09. Found : C, 65.89; H, 6.11.

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