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Synthesis of 11β-Perfluorohexylestradiol

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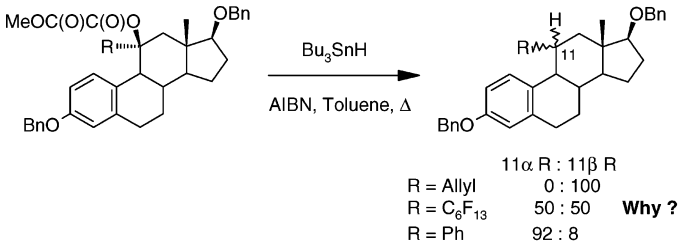
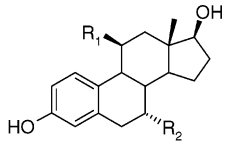


We report the synthesis of 11β-perfluorohexylestradiol **1e** using a perfluoroorganometallic reagent for the introduction of the fluorous part. This compound is useful for biological studies and for imaging the ERα estradiol receptor distribution in the whole cell by secondary ion mass spectrometry (SIMS). The key step of this synthesis involves the radical reduction of an 11β-oxalate derivative. The stereochemical outcome of this reaction was studied for a range of C11 substituents, and we attempted to rationalize the apparent abnormal behavior of the phenyl group.

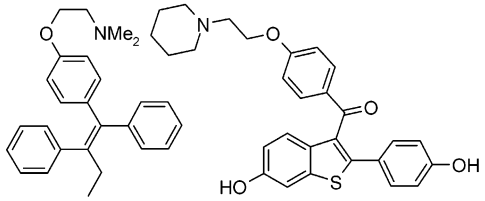
Estrogens play a critical role in the growth, development, and maintenance of a diverse range of tissues. They exert their physiological effects via activation of the estrogen receptor (ER), which functions as a ligand-activated transcriptional regulator.[1] The estrogen receptor, which is known to exist as two distinct subtypes, ERα and ERβ,[2] has become an enormously important target for chemotherapeutic drugs against certain reproductive cancers.

A wide repertoire of structurally distinct compounds bind to the ER with differing degrees of affinity and potency. Estrogens, such as estradiol **1a** (Chart 1), act solely as receptor agonists, whereas antiestrogens, such as fulvestrant **1b**, function as pure antagonists. A third category of compounds, termed selective ER modulators (SERMs) or partial antiestrogens, have the ability to act as agonists or antagonists, depending upon the exact cellular context and the ER isoform targeted.[3,4] The latter category includes some compounds that are in clinical use, such as tamoxifen **2** and raloxifene **3**, which are administered for the treatment of osteoporosis and hormone-dependent breast cancer. The widespread use

CHART 1. Estrogens and Antiestrogens



1a R_1 = H, R_2 = H estradiol
1b R_1 = H, R_2 = $(CH_2)_9S(O)(CH_2)_3C_2F_5$ fulvestrant
1c R_1 = $pC_6H_4O(CH_2)_5SO_2(CH_2)_3C_2F_5$, R_2 = H RU 58668
1d R_1 = H, R_2 = C_6F_{13}
1e R_1 = C_6F_{13}, R_2 = H



tamoxifen **2** raloxifene **3**

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of these drugs for the treatment of ER-positive breast cancer, both in the advanced disease and as an adjuvant therapy, has demonstrated the utility of partial antiestrogens. Unfortunately, following an initial period of effective clinical application, most breast cancers will begin to develop resistance to this therapy after a few months.[3] Consequently, the development of more effective pharmaceutical agents for the treatment of estrogen-receptor-positive breast cancer, and the elucidation of this inactivation process, remains essential.

The solution of the crystal structure of the ligand binding domain of ER complexes with various estrogens has helped illuminate the molecular basis for estrogenic or antiestrogenic activity.[5]

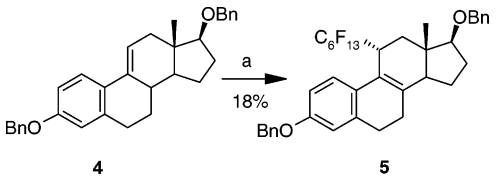
At the same time, ligand binding domain complexes with partial antiestrogens such as raloxifene **3** have also been crystallized.[5,6] The picture of antiestrogenic activity that has emerged suggests the key is the displacement of the 12 helix of the ligand binding domain by the "side chain" of the antiestrogens, which occupy what would be the 11β position in estradiol **1a**.[6]

Recently, the emergence of new pure antiestrogens, antagonists devoid of any estrogenic activity, has raised the hope for pharmaceuticals of increased effectiveness. Two such antiestrogens, RU 58668 **1c** (11β-substituted)[7] and ICI 182,780 **1b** (a 7α-substituted steroid, fulvestrant as generic name),[8] neatly encapsulate the findings of ER structure−activity relationships.[9]

Prior to the establishment of the exact mode of estradiol binding to the ER, a detailed pharmacophore had already emerged from the wealth of structure−binding affinity relationships that had been acumulated.[9] It has been repeatedly shown that the 11β and 7α positions of the steroid may be substituted by large, nonpolar groups without a loss of affinity.[9] In fact, certain compounds, such as RU 58668 **1c** and fulvestrant **1b** cited above, can show superior binding affinity. It is assumed, though unproven, that these pure antiestrogens demonstrate the ability to displace the same H12 helix as the partial antiestrogens tamoxifen **2** and raloxifene **3**.[6] The equivalency of positions 7α and 11β was further demonstrated in the case of fulvestrant **1b**; this derivative undergoes a complete rotation of its steroid core so that its 7α long chain can be accommodated inside the ligand binding cavity of ERβ.[10]

The introduction of highly fluorinated chains into the estradiol nucleus in the key 7α or 11β positions could give compounds useful for mapping the distribution of the receptor ERα−substrate complex in the cell by ionic microscopy (SIMS).[11] We have recently published our work in this area concerning the preparation of 7α-perfluorohexylestradiol **1d**.[12] On the basis of the new results described above, we report here the synthesis of 11β-perfluorohexylestradiol **1e**.

SCHEME 1[a]



[a] (a) $C_6F_{13}I$, CuCl, ethanolamine, *tert*-butyl alcohol, 80 °C, 8 h.

We initially chose to prepare the requisite compound **1e** by perfluoroalkylation of a readily available 9(11)-dehydroestradiol derivative **4**.[13] Not too unexpectedly for a sterically crowded double bond, attempts to introduce the perfluorohexyl moiety by a radical chain reaction with perfluorohexyliodide failed under a variety of conditions and initiators.[14]

Use of the conditions described by Burton[15] (CuCl, ethanolamine, *tert*-butyl alcohol) gave incomplete success. Although a fluorinated product was isolated (albeit in a modest 18% yield), its structure was determined to be that of an 11α-perfluorohexyl-8(9)-dehydroestradiol derivative **5** (Scheme 1), useless for our purpose.[16]

More gratifying results were obtained with FITS-6, tridecafluorohexylphenyliodonium trifluoromethanesulfonate ($PhI(C_6F_{13})(CF_3SO_3)$), as an electrophilic perfluoralkylating agent.[17] Using pyridine as a base,[18] we observed the formation of a mixture of the dibenzylated 11-perfluorohexyl-9(11)-dehydroestradiol **6** (46%)[19] and the 8(9)-dehydroestradiol derivative **5** (3.5%) already described in the previous experiment (Scheme 2).

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(16) The 11α structure of **5** was confirmed a posteriori when the stereochemistries of compounds **1e** and **12** were unambiguously determined. In this work, 11α-substituted estradiol derivatives showed consistently negative optical rotations, whereas those of 11β compounds are positive. Moreover, the angular methyl group appears as a sharp singlet in ^1H and ^{13}C NMR spectra of 11α derivatives, and as a broad line or a triplet in the 11β-perfluoroalkylated spectra.

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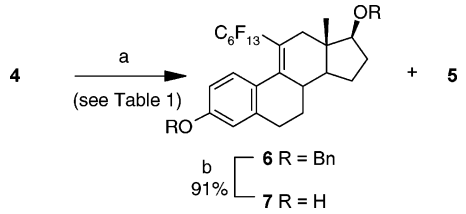
(19) The 9(11)-dehydro structure of **6** mainly relies on the presence of an isolated AB system for protons H12α and H12β (δ 2.31 and 2.35, respectively) identified by HCOR and DEPT (δ C12 = 40.8 ppm), and on the absence of coupling with other protons in a COSY experiment. The signals corresponding to these protons, although partially obscured, were more apparent in the debenzylated derivative **7** of **6** (δ 2.02 and 2.35 ppm, J = 14.6 Hz) and showed no further coupling.

SCHEME 2[a]



[a] (a) FITS-6, CH_2Cl_2, additive (see Table 1), rt, 2 h; (b) H_2, 10% Pd/C, MeOH, rt, 14 h.

TABLE 1. Perfluoroalkylation of 9(11)-Dehydroestradiol Dibenzyl Ether 4 with FITS-6

entry	additives (equiv)[a]	**6** (%)[b]	**5** (%)[b]	recovered **4** (%)[b]
1	pyridine (1)	46	3.5	18
2	$^nBu_4NI$ (1.1)	3.5	3.5	80
3	H_2O (1.1), $NaHCO_3$ (1.1)	4	34	24
4	Et_3SiH (5)	4	4	75[c]
5	Et_3SiH (2.5), dBMP[d] (2.5)	11	34	27

[a] One equivalent of **4** and 1.1 equiv of FITS-6 were used in all experiments, rt, 2 h. [b] Isolated yield. [c] **4** was reduced to estradiol dibenzyl ether. [d] 2,6-Di-*tert*-butyl-4-methylpyridine.

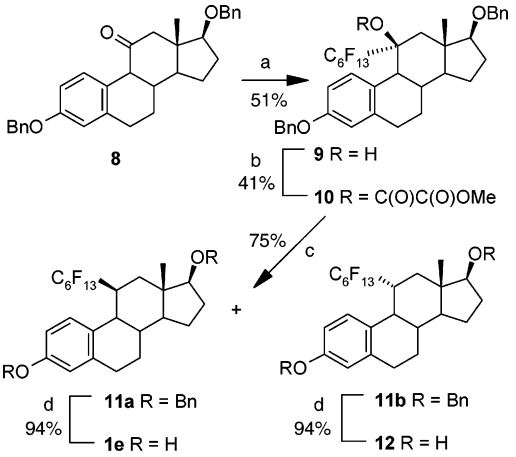
Attempts to capture the putative carbocationic intermediate with various nucleophiles were unsuccessful (Table 1) but showed interesting variations in the distribution of the elimination products. In particular, changing the base from pyridine (entry 1) to sodium bicarbonate (entry 3) or a non-nucleophilic amine (entry 5) inverted the relative proportions of **6** and **5**.

Unfortunately, the double bond in **6** proved to be unreactive under a variety of catalytic as well as ionic reduction conditions.

We next turned to a route devised by Napolitano et al.[20] involving the condensation of an organometallic derivative with a 11-ketoestradiol followed by deoxygenation of the resulting alcohol. In this way, reaction of perfluorohexylmagnesium bromide[21] with the 9α-ketone **8**[13,20] readily afforded the perfluoroalkylated tertiary alcohol **9** in 51% isolated yield (Scheme 3).

The next step, deoxygenation of alcohol **9**, proved to be troublesome. Not unexpectedly, in view of the destabilizing influence of a perfluoroalkylated chain on an adjacent incipient carbocation,[22] this reaction failed under the usual ionic protocol using boron trifluoride-diethyl etherate and triethylsilane even under forcing conditions.[20] The formation of a conventional alcohol derivative suitable for further reduction (xanthate[23] or pentafluorophenylthionocarbonate)[24] was impeded by the thermal instability of the intermediate alcoholate, and also by the sluggish reactivity of this encumbered and quite acidic alcohol at low temperature. We thus observed that the lithium or potassium alcoholate derived from **9** reverts

SCHEME 3[a]



[a] (a) $C_6F_{13}MgBr$, Et_2O, −60 °C, 2 h; (b) (i) ^{n}BuLi, THF/hexane, −60 °C, 10 min, (ii) methyl chlorooxoacetate, −60 °C to room temperature, 1 h; (c) Bu_3SnH, AIBN, toluene, reflux, 14 h; (d) H_2, 10% Pd/C, MeOH, rt, 14 h.

to a mixture of the 9α-ketone **8** and its 9β epimer,[25] by elimination of the perfluoroalkyl group, at temperatures above −20 °C.

Although we were able to prepare the corresponding trifluoroacetate (BuLi, $(CF_3CO)_2O$, −78 °C, 30% yield), no fluorinated product could be isolated after workup (aqueous HF) of the reduction mixture (Ph_2SiH_2, (t-BuO)$_2$, 120 °C, 20 h).[26] Recently, Stéphan et al. were faced with a cognate problem in the androstene series, and elegantly solved it by reduction of an oxalate derivative.[27] However, they observed that the reduction was accompanied by respectable amounts of elimination and/or rearrangement products.

In our case, the intermediate oxalate **10** was obtained with a modest (41%) isolated yield, but we were pleased to find that the ensuing reduction proceeded quite cleanly, giving a 50:50 mixture of the epimeric 11-perfluorohexylestradiols **11a** and **11b** in 75% isolated yield, the recovery of the starting alcohol **9** accounting for the remaining mass balance. No elimination product **5** or **6** could be detected in this reaction. The two isomers **11a** and **11b** could be easily separated by chromatography. Further deprotection of the benzyl ether groups by catalytic hydrogenation (10% Pd/C, H_2) proceeded uneventfully to give 11β-perfluorohexylestradiol **1e** (94% yield) as well as its 11α isomer **12**, thus achieving the projected synthesis. Assignment of the stereochemistry at center 11 by NMR with both isomers at hand was relatively straightforward. In compound **12**, the H9 proton could be located at δ 2.31, and appears as a triplet with a coupling constant of 10.2 Hz, pointing to a trans relationship with both H8 and H11. In compound **1e**, the H9 proton appears at δ 2.81 as a doublet of doublets (J = 10.5 and 4.2 Hz), as expected for a trans relationship with H8 and a cis relationship with H11. Moreover, in this later compound, the angular methyl group (δ 0.78)

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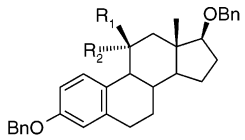
CHART 2[a]



13a R_1 = OH, R_2 = allyl
14a R_1 = OC(O)C(O)OMe, R_2 = allyl
15a R_1 = allyl, R_2 = H (100%)[a]

13b R_1 = OH, R_2 = Ph
14b R_1 = OC(O)C(O)OMe, R_2 = Ph
15b R_1 = H, R_2 = Ph (92%)[a]
15c R_1 = Ph, R_2 = H (8%)[a]

[a] Relative percentage of 11α and 11*β* isomers formed.

is broadened by space coupling with the fluorine atoms of the 11*β*-perfluorohexyl side chain.

We were intrigued by the lack of stereoselectivity observed during the reduction step of the fluorinated alcohol **9**. On the basis of ample evidence in the estradiol series,[20] attack of bulky reagents at the 11 position occurs mainly by the less hindered α face of the steroid nucleus, as exemplified here by the condensation of perfluorohexylmagnesium bromide with ketone **8** leading exclusively to the 11*β*-alcohol **9**. Moreover, it has been shown that, in the sugar series, the reduction of a related oxalate occurs with full inversion of the fluorinated center;[28] we thus expected the same behavior in our particular case. To gain some insight into the stereochemical outcome of this reaction in our system, we also investigated the reduction of oxalate derivatives of the 11α-allyl alcohol **13a**,[13] and of the 11α-phenyl alcohol **13b** (Chart 2).[20]

The reduction of oxalate **14a** was fully selective toward the 11*β*-allylestradiol derivative **15a**;[13] no 11α epimer could be detected within experimental error.[29] A contrasting result was obtained with the phenyl oxalate derivative **14b**. In this case, we observed a 92:8 ratio in favor of the α stereoisomer **15b** (Chart 2). It appears that, under the conditions used here, the behavior of a perfluorohexyl group is intermediate between that of an allyl and a phenyl group.

Two factors must be accounted for in order to explain the stereoselectivity observed during the reduction of oxalates **10**, **14a**, and **14b**: the steric bulk of the substituent on one hand and the rate of hydrogen abstraction by the intermediate radical on the other hand.

With regard to the first point, perfluoroalkyl chains may be considered bulky, rigid rods.[31] Insofar as it may be envisaged that the steric interactions involved here are confined to the beginning of the chain, it is noteworthy that a trifluoromethyl group has repeatedly been

16a R_1 = H, R_2 = CF_3
16b R_1 = alkyl, R_2 = CF_3
16c R_1 = H, R_2 = CH_2R_F
16d R_1 = alkyl, R_2 = C_6F_{13}

FIGURE 1. Partially fluorinated radicals.

claimed to be as large as an isopropyl group in 1,3-diaxial interactions in cyclohexane as well as in other systems.[32] The bulk of a longer fluorinated chain may be thought to be slightly larger and thus closer to that of a phenyl group in this context.[33]

As expected for a nonsterically demanding group, the reduction of the allyl compound **13a** was fully stereoselective. But at this stage, the only apparent factor that could explain the diverging behavior between the perfluorohexyl group and the phenyl group appears to be the difference in the rate of hydrogen abstraction from the hydrogen donor Bu_3SnH.

Thanks to their high electrophilic character, fully fluorinated radicals are widely used for the easy introduction of a perfluoralkyl chain onto aromatic or olefinic substrates.[14] For the same reason, these radicals are also strong hydrogen atom abstractors.[34] The behavior of partially fluorinated radicals **16a**−**d** (Figure 1) is less well understood.

Thus it was shown that the radical **16a** formed from 2,2,2-trifluoroethyliodide adds with difficulty to electron-rich olefins.[35] We have observed that tertiary trifluoromethylated radical **16b**, derived from xanthates, reacted sluggishly with allyltributyltin under atypical radical reaction conditions.[36] In a related example, it has been demonstrated that the radical **16c** is only 4.3 times more reactive for addition to olefins and 5.8 times more reactive for hydrogen abstraction than a conventional primary alkyl radical.[37] These observations point to a reduced electrophilicity of the radical center in these species compared to that of the perfluorinated series, and consequently a lower hydrogen abstraction rate.[38] However, these figures remain still higher than in the nonfluorinated case. In particular, the absolute hydrogen abstraction rate from tributyltin hydride by the benzyl radical was measured to be 3.6×10^4 M^{-1} s^{-1} at 298 K.[39] The value reported for **16c** is 1.4×10^7 M^{-1} s^{-1} at the same temperature,[37] pointing to a ca. 400-fold increased rate in favor of the partially fluorinated radical. For a more fluorinated (and thus more polar) radical like **16d**, this effect may be expected to be greater.[37]

One may thus be tempted to attribute the observed stereoselectivities to the reactivity−selectivity prin-

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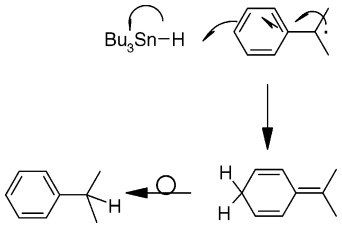
(39) Franz, J. A.; Suleman, N. K.; Alnajjar, M. S. *J. Org. Chem.* **1986**, *51*, 19−25.

SCHEME 4



ciple: the most reactive fluorinated radical is also the least selective.

To check this hypothesis, we also investigated the reduction of both compounds with a large excess of tributyltin hydride (80 equiv).[40] Under these conditions, we observed an increase of the selectivity in the reduction of the fluorinated oxalate **10** (**11a/11b** = 20/80 vs 50/50) and practically no change with the phenyl derivative **14b** (**15c/15b** = 10/90 vs 8/92). Thus, in the case of the fluorinated radical, hydrogen abstraction competes effectively with radical inversion.

However, this hardly explains the very strong preference of the phenyl group for the α position upon radical reduction. It should be recalled that, by contrast, upon ionic reduction (BF_3, Et_2O/Et_3SiH) of the benzyl alcohol **13b**, the 11α-phenyl group (like other common substituents) goes exclusively to the β position to give **15c** (Chart 2).[20] Although ionic reduction may not involve a true free carbocationic species, this shows that the phenyl group could be well-accommodated in the 11β position. On the other hand, Bu_3SnH may be considered bulkier than Et_3SiH, and thus should show a stronger tendency to deliver its hydrogen atom from the less hindered α face of the steroid nucleus. One possible clue to these observations could be that the delivery of the hydrogen atom from Bu_3SnH occurs directly to the nucleus of the phenyl group rather than to the crowded 11-benzylic center.[39] This hypothesis is consistent with the insensitivity of the selectivity to hydride concentration. The resulting semibenzene derivative thus obtained is then able to evolve to the more stable 11α-phenylestradiol by a hydrogen shift (Scheme 4).[41]

Contrary to the case of the phenyl oxalate, the stereochemical outcome of the radical reduction of the perfluoroalkylated oxalate **10** appears to be governed by a balance between kinetic and steric factors. With the proper choice of reaction conditions, we were able to form substantial amounts of the β isomer during the reduction, necessary for achieving the synthesis of the requisite 11β-perfluorohexylestradiol **1e**. Biological testing of this substance is currently underway.

Experimental Section

11α-Tridecafluorohexyl-3,17β-dibenzyloxyestra-1,3,5(10),8(9)-tetraene (5). A mixture of ethanolamine (0.11 mL, 1.82 mmol, 4.1 equiv), 9(11)-dehydroestradiol **4** (200 mg, 0.44 mmol), tBuOH (0.54 mL), CuCl (15 mg, 0.15 mmol, 0.35 equiv), and perfluorohexyliodide (490 μL, 2.20 mmol, 5 equiv) was stirred at 80 °C for 8 h. After dilution with saturated $NaHCO_3$ (5 mL), extraction with dichloromethane, and drying ($MgSO_4$), PTLC on silica gel (CH_2Cl_2:pentane 2:3) afforded pure **5** (62 mg, 18%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.62 (s, 3H), 1.43−1.77 (m, 4H), 2.04−2.23 (m, 4H), 2.42−2.72 (m, 3H), 3.58 (t, J = 7.8 Hz, 1H), 3.96 (dt, J = 27.0, 7.2 Hz, 1H), 4.42−4.51 (AB system, J_{AB} = 12.1 Hz, 2H), 4.95 (s, 2H), 6.69 (m, 2H), 6.99 (m, 1H), 7.17−7.36 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 21.4, 26.7, 28.4, 28.6, 35.3, 36.3 (dd, J_{CF} = 21, 17 Hz), 44.5, 46.3, 70.0, 71.8, 87.7, 111.5, 114.4, 121.7, 122.7, 127.4, 127.5, 127.6, 128.0, 128.4, 128.6, 129.2, 137.0, 137.2, 138.9, 141.8, 157.0. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.3 (t, J = 9 Hz, 3F), −107.0 and −116.7 (AB system, J = 276 Hz, 2F), −120.2 (m, 2F), −122.2 to −123.4 (m, 4F), −126.7 (m, 2F). MS pos. ESI (*m/z*): 791 [M + Na^+], 722 [M + Na^+ − CF_3]. $[\alpha]^{25}_D$ −86 (*c* 0.5, dichloromethane). HRMS: obsd 768.2280, calcd 768.2273 ($C_{38}H_{33}O_2F_{13}$).

11-Tridecafluorohexyl-3,17β-dibenzyloxyestra-1,3,5(10),9(11)-tetraene (6). FITS-6 (327 mg, 0.49 mmol, 1.1 equiv) was added in one portion to a solution of 9(11)-dehydroestradiol **4** (200 mg, 0.44 mmol) and pyridine (25 μL, 0.44 mmol, 1 equiv) in dichloromethane (12 mL). After the mixture had been stirred for 2 h at room temperature, the reaction was quenched by the addition of water (10 mL). The organic layer was washed with water (2 × 5 mL), and dried over $MgSO_4$. After removal of the solvent, the residue was purified by PTLC on silica gel (CH_2Cl_2:pentane 2:3) to afford **5** (12 mg, 3.5%) (vide supra) and **6** (155 mg, 46%) as glasses.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.30−1.89 (m, 6H), 2.02−2.19 (m, 3H), 2.55−2.70 (m, 3H), 3.64 (t, J = 8.3 Hz, 1H), 4.61 (s, 2H), 5.08 (s, 2H), 6.80 (m, 2H), 7.20−7.45 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 24.3, 26.8, 28.1, 28.2, 40.8, 41.6, 42.2, 47.7, 69.9, 71.7, 87.2, 111.2, 112.9, 118.8, 127.4, 127.47, 127.52, 127.9, 128.3, 128.5, 129.2, 129.7, 136.5, 138.5, 140.0, 146.2, 159.0. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.3 (t, J = 10 Hz, 3F), −100.5 and −103.2 (AB system, J = 269 Hz, 2F), −118.1 (m, 2F), −123.5 (m, 4F), −126.6 (m, 2F). MS pos. ESI (*m/z*): 791 [M + Na^+], 722 [M + Na^+ − CF_3]. HRMS: obsd 768.2264, calcd 768.2273 ($C_{38}H_{33}O_2F_{13}$).

11α-Tridecafluorohexyl-3,17β-dibenzyloxyestra-1,3,5(10)-trien-11β-ol (9). Freshly distilled perfluorohexyliodide (3.24 mL, 15 mmol) was slowly added, at −60 °C under an argon atmosphere, to a 3 M solution of methylmagnesium bromide in diethyl ether (5 mL, 15 mmol). After being stirred for 30 min at −60 °C, followed by careful addition of a solution of ketone **8** (1.12 g, 2.40 mmol) in THF (5 mL), the mixture was stirred again for 2 h at −60 °C and allowed to reach room temperature. After addition of a saturated solution of ammonium chloride (10 mL), we filtered the mixture on a pad of Celite, and washed it with CH_2Cl_2 (20 mL). The organic phase was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 10 mL) and water (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluant: CH_2Cl_2) to afford 962 mg of **9** as a white solid (51% yield). Mp: 126.2−126.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.13−1.37 (m, 3H), 1.43−1.78 (m, 7H), 1.94−2.06 (m, 1H), 2.13−2.25 (m, 2H), 2.55−2.58 (m, 3H), 3.40 (t, J = 7.8 Hz, 1H), 4.41−4.51 (AB system, J = 12 Hz, 2H), 4.96 (s, 2H), 6.69 − 6.73 (m, 2H), 7.17−7.37 (m, 10H), 7.83 (t, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 23.9, 26.0, 27.4, 28.2, 35.7, 42.0, 44.9, 46.1, 50.3, 69.9, 71.7, 81.2 (t, J_{CF} = 21 Hz), 88.5, 110.9, 113.8, 127.4, 127.5, 127.6, 127.9, 128.4, 128.6, 129.1, 129.2, 131.3, 137.4, 138.9, 141.5, 156.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.4 (t, J = 10 Hz, 3F), −111.3 and −115.7 (AB system, J = 286 Hz, 2F), −118.2 (m, 2F), −122.1 to −123.3 (m, 4F), −126.8 (m, 2F). IR (cm^{-1}, KBr): 3615, 3026, 2939, 2862, 1613, 1577, 1450, 1234. MS pos. ESI (*m/z*): 825 [M + K^+], 809 [M + Na^+], 787 [M + H^+]. $[\alpha]^{25}_D$ −15 (*c* 0.44, dichloromethane). Anal. Calcd for $C_{38}H_{37}F_{13}O_3$: C, 58.02; H, 4.48. Found: C, 57.92; H, 4.19.

(40) We greatly acknowledge one of the reviewers for this very interesting suggestion.

(41) Maeda, H.; Huang, Y.; Hino, N.; Yamauchi, Y.; Ohmori, H. *Chem. Commun.* **2000**, 2307−2308.

General Procedure for the Preparation of Oxalates. A solution of *n*-butyllithium (0.6 mL, 1.2 M in hexane, 1.2 equiv) was added to a solution of the steroidal alcohol (0.59 mmol) in THF (2 mL), and cooled to −60 °C under an argon atmosphere. After stirring the solution for 10 min at −60 °C, we added methyl chlorooxoacetate (144 mg, 2 equiv). The mixture was allowed to reach room temperature, and was then diluted with CH_2Cl_2 (5 mL) and water (2 mL). The organic phase was separated, washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography of the residue (eluant: CH_2Cl_2) afforded the oxalate derivative.

Oxalic Acid 11α-Tridecafluorohexyl-3,17β-dibenzyloxyestra-1,3,5(10)-triene-11β-yl Ester Methyl Ester (10). Yield of 41%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.29−1.79 (m, 10H), 1.93−2.15 (m, 2H), 2.57−2.73 (m, 3H), 3.54 (t, J = 7.2 Hz, 1H), 3.74 (dd, J = 15.7, 2.2 Hz, 1H), 3.93 (t, 3H), 4.58 (s, 2H), 5.07 (s, 2H), 6.81−6.83 (m, 2H), 7.30−7.48 (m, 10H), 7.68 (dd, J = 9.6, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.3, 23.9, 25.5, 27.5, 28.2, 34.7, 40.0, 42.4, 46.6, 50.5, 53.6, 69.8, 71.8, 88.5, 90.6, 111.2, 113.4, 127.4, 127.5, 127.6, 127.9, 128.3, 128.5, 129.5, 137.2, 138.7, 141.5, 155.4, 156.9, 157.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.3 (t, J = 10 Hz, 3F), −104.2 and −106.2 (AB system, J = 284 Hz, 2F), −117.2 to −128.7 (m, 8F).

General Procedure for the Radical Reduction of Oxalates. To a solution of the oxalate (0.15 mmol) in dry, degassed toluene (2 mL) were added Bu_3SnH (120 μL, 0.45 mmol, 3 equiv) and AIBN (5 mg, 0.03 mmol, 0.2 equiv). The mixture was refluxed overnight. The solution was cooled and partitioned between CH_2Cl_2 (5 mL) and water (5 mL). The aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC on silica gel (eluant: CH_2Cl_2/pentane 3/2).

11β-Tridecafluorohexyl-3,17β-dibenzyloxyestra-1,3,5(10)-triene (11a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (broad s, 3H), 1.05−1.26 (m, 3H), 1.37−1.64 (m, 5H), 1.79 (dd, J = 12.6, 2.1 Hz, 1H), 1.94−2.02 (m, 2H), 2.43 (d, J = 14.7 Hz, 1H), 2.57 (m, 1H), 2.71−2.83 (m, 2H), 3.30 (t, J_{HF} = 19.8 Hz, 1H), 3.40 (t, J = 6.9 Hz, 1H), 4.42−4.53 (AB system, J = 12.3 Hz, 2H), 4.94 (s, 2H), 6.59−6.70 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 7.18−7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 23.0, 27.3, 28.2, 30.6, 35.7, 38.1 (t, J = 19 Hz), 38.4, 42.6, 48.5, 53.0, 69.8, 71.6, 89.5, 112.3, 114.4, 127.4, 127.5, 127.6, 127.9, 128.3, 128.5, 137.2, 138.6, 139.0, 156.4. ^{19}F NMR (188 MHz, $CDCl_3$): δ −81.7 (t, J = 9 Hz, 3F), −102.1 (m, 2F), −119.1 (m, 2F), −120.6 to −122.7 (m, 4F), −125.9 (m, 2F). MS pos. ESI (*m/z*): 819 $[M + K]^+$, 793 $[M + Na]^+$. $[\alpha]^{25}_D$ 82.6 (*c* 0.38, dichloromethane). Anal. Calcd for $C_{38}H_{37}F_{13}O_2$: C, 59.22; H, 4.58. Found: C, 59.33; H, 4.53.

General Procedure for Catalytic Hydrogenations. To a solution of the steroid (0.045 mmol) in MeOH (2 mL) was added 10% Pd/C (6 mg). The substrate was hydrogenated overnight under 1 atm. The mixture was then filtered on Celite, and the filtrate was evaporated to afford the product.

11β-Tridecafluorohexyl-3,17β-dihydroxyestra-1,3,5(10)-triene (1e). Yield of 94%. Mp: 196.3−196.5 °C. ^{1}H NMR (300 MHz, methanol-d_4): δ 0.78 (broad s, 3H), 1.00−2.05 (m, 10H), 2.30 (d, J = 14.6 Hz, 1H), 2.45−2.69 (m, 2H), 2.81 (dd, J = 10.5, 4.5 Hz, 1H), 3.24 (s, 1H), 3.42 (broad t, J_{HF} = 21 Hz, 1H), 3.58 (t, J = 7.3 Hz, 1H), 6.36 (s, 1H), 6.43 (dd, J = 8.7, 2.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, methanol-d_4): δ 13.5, 24.0, 28.5, 31.0, 31.7, 37.6, 38.4, 39.6 (t, J_{CF} = 19 Hz), 43.7, 49.7, 53.8, 83.8, 113.7, 115.9, 128.3, 130.1, 139.7, 155.7. ^{19}F NMR (188 MHz, methanol-d_4): δ −80.0 (t, J = 9.1 Hz, 3F), −100.1 (m, 2F), −117.1 (m, 2F), −119.2 (m, 2F), −120.4 (m, 2F), −123.9 (m, 2F). IR (cm^{-1}, KBr): 3328, 2954, 2910, 1234. MS neg. ESI (*m/z*): 635 [M + formate], 625.2 [M + Cl^-], 589 [M − 1]. $[\alpha]^{25}_D$ 92.8 (*c* 0.54, methanol-d_4). HRMS: obsd 590.1483, calcd 590.1490 ($C_{24}H_{23}O_2F_{13}$).

Supporting Information Available: Experimental details and characterization data of compounds **7**, **11b**−**15b**. Copies of ^{1}H, ^{19}F (if relevant), and ^{13}C NMR spectra of compounds **1e**, **5**−**7**, **9**−**12**, **14**, **15b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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