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Palladium-Catalyzed *Ortho*-Arylation of Carbamate-Protected Estrogens

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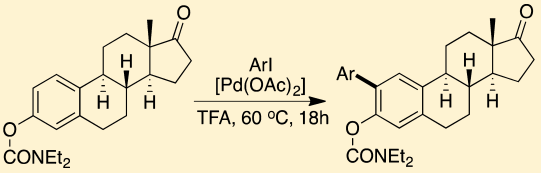
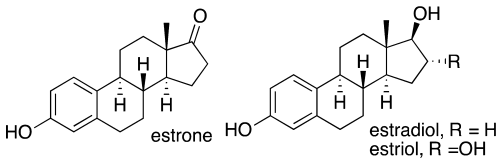
Supporting Information

ABSTRACT: The palladium-catalyzed *ortho*-arylation of diethyl carbamate-protected estrone and estriol with aryl iodides gives the 2-arylated analogues. Subsequent removal of the carbamate directing group furnishes 2-arylated estrone, estradiol, or estriol depending on the method used.



Estrone, estradiol, and estriol, collectively referred to as estrogens, are a set of endogenous C18 steroids that are the primary female sex hormones and are responsible for mediating a wide range of physiological functions.[1] Estrogens have also been found to play a role in the development of breast cancer through increased activation of the estrogen receptor ligand.[2]



Methodologies that allow late-stage modification of estrogens are therefore desirable tools in the synthesis of compounds with improved biological activity. In this regard, catalytic[3] C−H functionalization[4] of the phenolic A-ring is an attractive synthetic approach. Both Gaunt and Liu described the catalytic *ortho*-arylation of estrone, employing copper and palladium catalysts, respectively,[5] using diaryliodium salts as the arylating reagents. Larrosa recently showed that a chromium-arene adduct of the *O*,*O*′-dimethyl ester of estradiol is arylated in the 2-position with aryl iodides under palladium catalysis.[6] We were keen to see whether aryl halides could be exploited in the arylation of estrogens without the need to form chromium−arene adducts and report here the palladium-catalyzed *ortho*-arylation of carbamate-protected estrone and estriol with aryl iodides, which represents a compact route to functionalized estrones, estradiols, and estriols.

Initial attempts focused on rhodium-catalyzed arylation of estrone, using conditions developed previously,[7] however, this proved unsuccessful.[8] More recently, we developed the *ortho*-arylation of carbamate-protected phenols with aryl iodides;[9] gratifyingly, we find that, after appropriate optimization,[8] this methodology can be extended to the carbamate-protected estrone **1**.

With optimized conditions in hand, we next briefly explored the scope of the reaction with respect to the aryl iodide (Table 1). Aryl iodides with both electron-donating and electron-withdrawing groups in the 4-position were tolerated under the reaction conditions, and the corresponding arylated estrone carbamates **2a**−**f** were isolated in moderate to good yields. The site of arylation at the sterically less hindered 2-position was confirmed by a single-crystal X-ray analysis of **2f**, the results of which are shown. As can be seen, the bromide was tolerated under the reaction conditions, which opens the possibility of subsequent elaboration by, for instance, cross-coupling. A hydroxyl group was also tolerated on the aryl iodide substrate, giving the product **2g**. Pleasingly, the palladium-catalyzed arylation of **1** with iodobenzene was amenable to scale-up under the optimized reaction conditions, giving **2a** in 80% yield on a 1.5 g scale.

The reaction appears to be particularly sensitive to steric bulk, with 2-tolyl iodide giving a low yield of **2h** as an inseparable mixture with residual **1**, while none of the desired product was obtained with 2-chloroiodobenzene. Similarly no *ortho*-functionalization was observed with 2-iodopyridine, benzyl iodide, or cyclohexyl iodide acting as substrates. Further evidence that the reaction is sensitive to steric bulk is the complete absence of any observed arylation in the more hindered *ortho* site.[10]

We next turned our attention to deprotecting the representative product **2a**. Hydrolysis under basic conditions proved ineffective; however, the use of $LiAlH_4$ gave the 2-arylated estradiol **3** in excellent yield under mild conditions (Scheme 1). Conversely, the estrone **4** could be accessed by first protecting the ketone of **2a** as the corresponding acetal (**5**).

The catalytic methodology could be further extended to the *ortho*-arylation of protected estriol (Scheme 1). The reaction of

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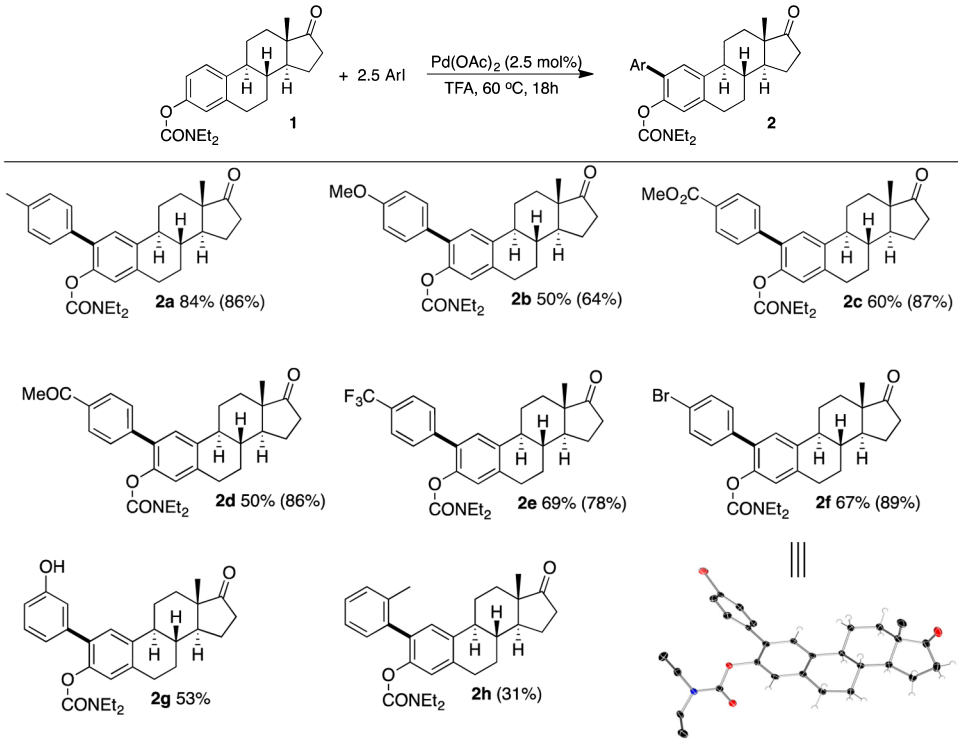
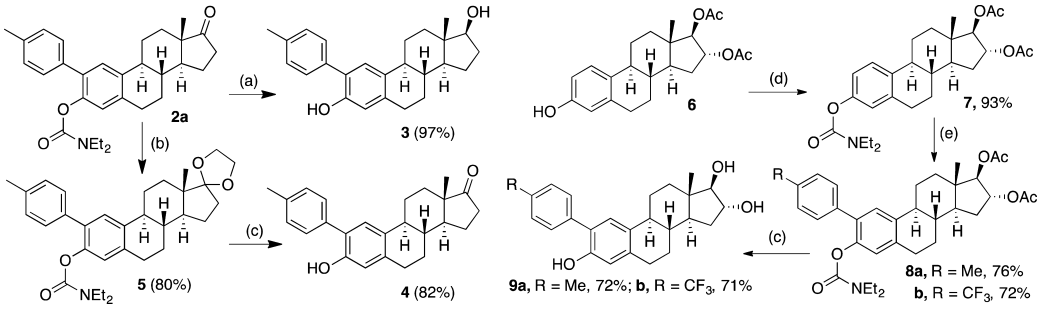
Table 1. *Ortho*-Arylation of 1[a]



[a]Using 0.135 mmol **1**. Isolated yields, ^{1}H NMR spectroscopic yields in parentheses (1,3,5-$C_6H_3OMe_3$ internal standard).

Scheme 1. *Ortho*-Arylated Estrogens[a]



[a]Conditions: (a) $LiAlH_4$, THF, rt, 2 h; (b) ethylene glycol, PTSA catalyst, benzene, reflux (Dean-Stark), 16 h; (c) (i) $LiAlH_4$, THF, reflux, 2 h, (ii) H_2O, 0 °C; (d) $ClCONEt_2$, NEt_3, Py, 80 °C, 18 h; (e) ArI (0.26 mmol) $Pd(OAc)_2$ (4.5 μmol), AgOAc (0.21 mmol), CF_3CO_2H, 60 °C, 18 h.

the diacetate-protected estriol **6** with diethylcarbamoyl chloride gave the carbamate-protected analogue **7** in excellent yield. The arylation of **7** with 4-iodotoluenes or 4-(trifluoromethyl)-iodobenzene under the optimized arylation conditions developed above gave the *ortho*-arylated diacetates **8a,b** in good yield, which were readily deprotected by $LiAlH_4$ followed by hydrolysis, yielding the desired functionalized estriols **9a** and **b**.

In summary, we have developed the catalytic *ortho*-arylation of carbamate-protected estrone and estriol, wherein the carbamate group directs arylation to the 2-position. Subsequent removal of the carbamate yields functionalized estrone, estradiol, and estriol products, allowing access to derivatives of all of the endogenous estrogens. We are currently exploring the scope of other C−H functionalizations of estrogens, and these results will be published in due course.

EXPERIMENTAL SECTION

General Experimental Information. Reagents were used as supplied from commercial sources. Anhydrous THF was obtained from a purification column composed of activated alumina and subsequently stored under nitrogen. All other anhydrous solvents were prepared by drying the corresponding reagent-grade solvent over molecular sieves. Microwave reactions were carried out with an Emrys Optimizer Microwave (0−20 bar pressure range, 15−300 W power range) in a 5 mL sealed microwave vial equipped with a stir bar under an atmosphere of air. The reactions were heated at a rate of 2 °C/s and then held at the desired temperature for the stated duration. Mass spectrometry: electron ionization (EI), triple sector analyzer, 2.0−5.0 mg/mL analyte concentration, m/z 50−850 mass range, approximately 4000 at m/z 500 resolution, <5 ppm internal calibration mass accuracy); electrospray (ESI), time-of-flight (TOF) analyzer, 1/s scan rate, 0.025 to 0.05 mg/mL analyte concentration, m/z 50−40000 mass range, approximately 15000 at m/z 1000 resolution, <2 ppm internal calibration and <5 ppm external calibration mass accuracy; MALDI

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ionization, TOF-TOF analyzer, <5 ppm nearest neighbor calibration mass accuracy).

Preparation of 3-Diethylcarbamate-Protected Estrone 1. To a flame-dried Schlenk tube, equipped with a magnetic stir bar, were added estrone (1.5 g, 5.5 mmol), anhydrous triethylamine (1.5 mL, 11 mmol), diethylcarbamoyl chloride (1.4 mL, 11 mmol), and anhydrous pyridine (30 mL) under nitrogen. The resulting solution was stirred at 80 °C for 18 h. The mixture was cooled to room temperature, diluted with dichloromethane, and washed with water (2 × 20 mL), 1 M HCl (5 × 20 mL), and brine (2 × 20 mL) before being dried over sodium sulfate and concentrated in vacuo to afford **1** as an off-white solid, 1.98 g (98%). The spectroscopic data are in agreement with the literature:[11] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 1H, 1-ArH), 6.89 (dd, J = 8.5, 2.6 Hz, 1H, 2-ArH), 6.85 (d, J = 2.6 Hz, 1H, 4−Ar-H), 3.47−3.33 (m, 4H, Et-CH_2), 2.90 (dd, J = 6.6, 2.6 Hz, 2H, 6-CH_2), 2.50 (dd, J = 18.9,[12] 8.9 Hz, 1H), 2.45−2.37 (m, 1H), 2.28 (m, 1H, 9-CH), 2.12 (dd, J = 18.9,[12] 8.9 Hz, 1H), 2.08−1.92 (m, 3H), 1.69−1.37 (m, 6H), 1.28−1.16 (m, 6H, Et-CH_3), 0.91 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.8 (17-C═O), 154.5 (OC(O)NEt_2), 149.4 (3-ArC), 137.7 (ArC), 136.5 (ArC), 126.1 (ArCH), 121.8 (ArCH), 119.0 (ArCH), 50.4 (14-CH), 48.0 (13-C), 44.1 (CH), 42.2 (NCH_2CH_3), 41.9 (NCH_2CH_3), 38.1 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.4 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 13.8 (18-CH_3), 13.7 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 3055, 2980, 2948, 2931, 2875, 2829, 1731, 1706, 1414, 1220, 1157, 754; mp 194.8−195.6 °C; HRMS (ESI) calcd for $C_{23}H_{32}NO_3$ $[M + H]^+$ 370.2377 and $C_{23}H_{31}NNaO_3$ $[M + Na]^+$ 392.2196, found 370.2371 and 392.2190.

General Procedure for the Palladium-Catalyzed Direct Arylation of 1 (Table 1). To a flame-dried Young's tube, equipped with a magnetic stir bar, were added **1** (50 mg, 0.135 mmol), palladium acetate (1 mg, 4.5 μmol), silver acetate (45 mg, 0.27 mmol), and trifluoroacetic acid (1 mL) under an atmosphere of nitrogen. The tube was wrapped in aluminum foil, and the appropriate aryl iodide was added (0.3375 mmol). The mixture was stirred at 60 °C for 18 h, cooled to room temperature, diluted with diethyl ether (5 mL), washed with water (2 × 5 mL), and dried over sodium sulfate, and then the volatiles were removed in vacuo. The crude material was purified by flash chromatography eluting with 3:1 petroleum ether/ethyl acetate.

Compound ***2a:*** off-white solid, 52 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.27 (m, 1H, 1-ArH), 7.26−7.23 (m, 2H, ArH), 7.15 (d, J = 7.6 Hz, 2H, ArH), 6.91 (s, 1H, 4-ArH), 3.23 (q, J = 7.5 Hz, 4H, Et-CH_2), 2.93 (dd, J = 9.1, 4.6 Hz, 2H, 6-CH_2), 2.50 (dd, J = 18.9,[12] 8.6 Hz, 1H), 2.44−2.36 (m, 1H), 2.35 (s, 3H, tolyl-CH_3), 2.30 (dd, J = 11.0, 4.6 Hz, 1H, 9-CH), 2.13 (dd, J = 18.9,[12] 8.6 Hz, 1H), 2.09−1.89 (m, 3H), 1.68−1.42 (m, 6H), 1.02 (m, 6H, Et-CH_3), 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0 (17-C═O), 154.4 (OC(O)NEt_2), 146.3 (ArC), 137.0 (ArC), 136.7 (ArC), 136.6 (ArC), 135.3 (ArC), 132.2 (ArC), 128.9 (ArCH), 128.7 (ArCH), 127.7 (1-ArCH), 123.1 (4-ArCH), 50.5 (CH), 48.0 (13-C), 44.2 (CH), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.1 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 21.1 (Ar−CH_3), 13.8 (18-CH_3), 13.1 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2962, 2934, 2916, 2878, 1733, 1715, 1266, 1150; mp 104.7−106.2 °C; HRMS (ESI) calcd for $C_{30}H_{38}NO_3$ $[M + H]^+$ 460.2846 and $C_{30}H_{37}NNaO_3$ $[M + Na]^+$ 482.2666, found 460.2834 and 482.2654.

Compound ***2b:*** orange gum, 32 mg (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 9.0 Hz, 2H, ArH), 7.25 (s, 1H, 1-ArH), 6.93 (s, 1H, 4-ArCH), 6.89 (d, J = 9.0 Hz, 2H, ArH), 3.83 (s, 3H, OCH_3), 3.25 (q, J = 7.9 Hz, 4H, Et-CH_2), 2.94 (dd, J = 5.0, 3.7 Hz, 2H, 6-CH_2), 2.51 (dd, J = 18.9,[12] 8.7 Hz, 1H), 2.45−2.39 (m, 1H), 2.37−2.29 (m, 1H, 9-CH), 2.13 (dd, J = 18.9,[12] 9.1 Hz, 1H), 2.09−1.92 (m, 3H), 1.70−1.43 (m, 6H), 1.08−1.00 (m, 6H, Et-CH_3), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.9 (17-C═O), 158.7 (ArC-OMe), 154.3 (OC(O)NEt_2), 146.3 (ArC), 136.9 (ArC), 136.5 (ArC), 131.9 (ArC), 130.8 (ArC), 130.1 (ArCH), 127.7 (1-ArCH), 123.1 (4-ArCH), 113.5 (ArCH), 55.3 (OCH_3) 50.5 (CH), 48.0 (13-C), 44.2 (CH), 41.9 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.1 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 13.8 (18-CH_3), 14.0 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2965, 2930, 2877, 2835, 1711, 1608, 1151, 1023; HRMS (ESI) calcd for $C_{30}H_{38}NO_4$ $[M + H]^+$ 476.2795, found 476.2787.

Compound ***2c:*** yellow gum, 38 mg (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 9.2 Hz, 2H, ArH), 7.47 (d, J = 9.2 Hz, 2H, ArH), 7.27 (s, 1H, 1-ArH), 6.96 (s, 1H, 4-ArH), 3.93 (s, 3H, C(O)OCH_3), 3.23 (s, 4H, Et-CH_2), 2.96 (dd, J = 8.9, 4.1 Hz, 2H, 6-CH_2), 2.51 (dd, J = 18.8,[12] 9.1 Hz, 1H), 2.46−2.38 (m, 1H), 2.37−2.28 (m, 1H, 9-CH), 2.13 (dd, J = 18.8,[12] 9.2 Hz, 1H), 2.10−1.92 (m, 3H), 1.69−1.41 (m, 6H), 1.06−0.98 (m, 6H, Et-CH_3), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (17-C═O), 167.1 (C(O)OMe), 154.1 (OC(O)NEt_2), 146.2 (ArC), 143.2 (ArC), 137.8 (ArC), 137.2 (ArC), 131.3 (ArC), 129.3 (ArC), 129.1 (ArCH), 128.6 (1-ArCH), 127.5 (ArCH), 123.3 (4-ArCH), 52.1 (C(O)OCH_3), 50.4 (CH), 47.9 (13-C), 44.1 (CH), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.0 (CH), 35.8 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 14.0 (18-CH_3), 13.8 (NCH_2CH_3); IR (neat), ν(cm^{-1}) 2965, 2942, 2870, 1726, 1713, 1608, 1265, 1152, 1099, 798; HRMS (ESI) calcd for $C_{31}H_{38}NO_5$ $[M + H]^+$ 504.2744, found 504.2740.

Compound ***2d:*** yellow solid, 32 mg (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H, ArH), 7.50 (d, J = 8.4 Hz, 2H, ArH), 7.27 (s, 1H, 1-ArH), 6.95 (s, 1H, 4-ArH), 3.24 (q, J = 7.1 Hz, 4H, Et-CH_2), 2.96 (dd, J = 8.8, 3.8 Hz, 2H, 6-CH_2), 2.61 (s, 3H, C(O)CH_3), 2.51 (dd, J = 18.7,[12] 8.7 Hz, 1H), 2.45−2.38 (m, 1H), 2.37−2.28 (m, 1H, 9-CH), 2.13 (dd, J = 18.7,[12] 8.7 Hz, 1H), 2.09−1.91 (m, 3H), 1.70−1.41 (m, 6H), 1.03 (t, J = 7.1 Hz, 6H, Et-CH_3), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (17-C═O), 197.9 (C(O)CH_3), 154.0 (OC(O)NEt_2), 146.2 (ArC), 143.4 (ArC), 137.9 (ArC), 137.3 (ArC), 135.6 (ArC), 131.2 (ArC), 129.2 (ArCH), 128.1 (ArCH), 127.5 (1-ArCH), 123.3 (4-ArCH), 50.4 (CH), 47.9 (13- C), 44.1 (CH), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.0 (CH), 35.8 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 26.6 (C(O)CH_3), 26.4 (CH_2), 25.8 (CH_2), 21.6 (CH_2), 14.0 (18-CH_3), 13.1 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2969, 2936, 2881, 2858, 1717, 1681, 1605, 1264, 1147, 731; mp 179.2−177.6 °C; HRMS (ESI) calcd for $C_{31}H_{38}NO_4$ $[M + H]^+$ 488.2795, found 488.2789.

Compound ***2e:*** orange gum, 48 mg (69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H, ArH), 7.51 (d, J = 8.0 Hz, 2H, ArH), 7.26 (s, 1H, 1-ArH), 6.96 (s, 1H, 4-ArH), 3.23 (q, J = 7.1 Hz, 4H, Et-CH_2), 2.96 (dd, J = 9.0, 4.1 Hz, 2H, 6-CH_2), 2.51 (dd, J = 18.8,[12] 9.5 Hz, 1H), 2.44−2.38 (m, 1H), 2.37−2.29 (m, 1H, 9-CH), 2.14 (dd, J = 18.8,[12] 9.3 Hz, 1H), 2.09−1.92 (m, 3H), 1.70−1.43 (m, 6H), 1.01 (t, J = 7.1 Hz, 6H, Et-CH_3), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.8 (17-C═O), 161.6 (ArC), 154.1 (OC(O)NEt_2), 146.4 (ArC), 142.2 (CF_3), 138.1 (ArC), 137.4 (ArC), 131.1 (ArC), 129.5 (ArCH), 127.6 (1-ArCH), 125.1 (q, J = 3.7 Hz, CCF_3), 123.3 (4-ArCH), 50.5 (CH), 48.0 (13-C), 44.2 (CH), 42.1 (NCH_2CH_3), 41.7 (NCH_2CH_3), 38.1 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 21.7 (CH_2), 13.9 (18-CH_3), 13.1 (NCH_2CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.4; IR (neat), ν(cm^{-1}) 2969, 2932, 2873, 1713, 1607, 1322, 1152, 1066, 729; HRMS (ESI) calcd for $C_{30}H_{35}F_3NO_3$ $[M + H]^+$ 514.2564, found 514.2563.

Compound ***2f:*** yellow solid, 47 mg (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 9.2 Hz, 2H, ArH), 7.29−7.24 (m, 2H, ArH), 7.23 (s, 1H, 1-ArH), 6.93 (s, 1H, 4-ArH), 3.28−3.21 (m, 4H, Et-CH_2), 2.95 (dd, J = 9.0, 4.2 Hz, 2H, 6-CH_2), 2.51 (dd, J = 18.8,[12] 8.6 Hz, 1H), 2.45−2.37 (m, 1H), 2.36−2.28 (m, 1H, 9-CH), 2.14 (dd, J = 18.8,[12] 9.3 Hz, 1H), 2.10−1.92 (m, 3H), 1.69−1.40 (m, 6H), 1.08−1.01 (m, 6H, Et-CH_3), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (17-C═O), 154.1 (OC(O)NEt_2), 146.2 (ArC), 140.4 (ArC), 137.5 (ArC), 137.3 (ArC), 137.2 (ArC), 131.1 (ArCH), 130.7 (ArCH), 127.4 (1-ArCH), 123.2 (4-ArCH), 121.2 (ArC), 50.4 (CH), 47.9 (13-C), 44.1 (CH), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.0 (CH), 35.9 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 25.8 (CH_2) 21.6 (CH_2), 14.1 (18-CH_3), 13.8 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2977, 2928, 2877, 1711, 1607, 1268, 1154, 728; mp 72.6−73.4 °C; HRMS (ESI) calcd for $C_{29}H_{35}BrNO_3$ $[M + H]^+$ 524.1795, found 524.1791. Crystals suitable for X-ray diffraction were grown from a solution of diethyl ether layered with hexane. Crystallographic data are

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given in the Supporting Information and have been deposited at the Cambridge Crystallographic Data Centre (CCDC No. 1463811).

Compound ***2g****:* yellow solid, 33 mg (53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.12 (m, 2H, ArH), 6.89 (s, 1H, 4-ArH), 6.84 (ddd, J = 7.6, 1.5, 1.0 Hz, 1H, ArH), 6.75 (dd, J = 2.5, 1.5 Hz, 1H, ArH), 6.72 (ddd, J = 7.6, 2.5, 1.0 Hz, 1H, ArH), 3.29−3.17 (m, 4H, Et-CH_2), 2.89 (dd, J = 9.0, 4.2 Hz, 2H, 6-CH_2), 2.51 (dd, J = 19.0,[12] 8.6 Hz, 1H), 2.36−2.30 (m, 1H), 2.13 (dd, J = 19.0,[12] 9.0 Hz, 1H), 2.07−1.88 (m, 4H), 1.68−1.29 (m, 6H), 1.05 (t, J = 6.7 Hz, 3H, Et-CH_3), 0.98 (t, J = 6.9 Hz, 3H, Et-CH_3), 0.90 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.3 (17-C═O), 153.9 (OC(O)NEt_2), 152.7 (ArC), 144.1 (ArC), 137.6 (ArC), 135.0 (ArC), 134.9 (ArC), 130.2 (ArC), 127.1 (ArCH), 125.5 (ArCH), 121.2 (ArCH), 119.0 (ArCH), 114.1 (ArCH), 112.1 (ArCH), 48.5 (CH), 46.1 (13-C), 42.1 (CH), 40.1 (NCH_2CH_3), 39.7 (NCH_2CH_3), 36.0 (CH), 34.0 (CH_2), 29.6 (CH_2), 27.1 (CH_2), 24.4 (CH_2), 23.9 (CH_2), 19.7 (CH_2), 11.9 (18-CH_3), 11.8 (NCH_2CH_3), 11.2 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 3325 (broad), 2977, 2930, 2881, 1714, 1687, 1597, 1585, 1273, 1158, 784; mp 78.6−79.7 °C; HRMS (ESI) calcd for $C_{29}H_{36}NO_4$ $[M + H]^+$ 462.2639, found 462.2629.

Compound ***2h****:* yellow oil, 17 mg (27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.09 (m, ArH), 6.98 (s, 4-ArH), 6.94−6.93 (m, ArH), 3.31−3.32 (m, Et-CH_2), 2.98 (dd, J = 8.7, 4.8 Hz, 6-CH_2), 2.51 (m), 2.47−2.33 (m), 2.36 (s, $ArCH_3$), 2.30 (m, 9-CH), 2.19−1.90 (m), 1.69−1.55 (m), 1.09−0.96 (m, Et-CH_3), 0.92 (s, 18-CH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ 221.0 (17-C═O), 149.5 (ArC), 138.0 (ArC), 136.9 (ArC), 130.2 (ArC), 129.6 (ArC), 129.0 (ArC), 127.8 (ArCH), 127.8 (ArCH), 127.4 (ArCH), 125.3 (ArCH), 123.3 (ArCH), 122.8 (ArCH), 50.6 (CH), 48.1 (13-C), 44.3 (CH), 42.3 (NCH_2CH_3), 42.3 (NCH_2CH_3), 38.2 (CH), 35.9 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 21.7 (CH_2), 21.6 (Ar-CH_3), 14.0 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2926, 2873, 2855, 1790, 1650, 1415, 1265, 1155; HRMS (MALDI) calcd for $C_{30}H_{37}NNaO_3$ $[M + Na]^+$ 482.2666, found 482.2661.

Larger Scale Synthesis of Compound 2a. To a flame-dried Young's tube, equipped with a magnetic stir bar, were added **1** (2.5 g, 6.77 mmol), palladium acetate (75 mg, 0.34 mmol), silver acetate (2.83 g, 16.94 mmol), and trifluoroacetic acid (50 mL) under an atmosphere of nitrogen. The tube was wrapped in aluminum foil, and 4-iodotoluene was added (3.69 g 0.3375 mmol). The mixture was stirred at 60 °C for 18 h, cooled to room temperature, diluted with diethyl ether (50 mL), washed with water (2 × 50 mL), and dried over sodium sulfate, and then the volatiles were removed in vacuo. The crude material was purified by flash chromatography eluting with 3:1 petroleum ether/ethyl acetate (80%).

Preparation of 2-(4-tolyl)estradiol, ***3****.* To a solution of **2a** (542 mg, 1.18 mmol) in THF (20 mL) at room temperature, under nitrogen, was added $LiAlH_4$ (11.8 mL, 11.8 mmol; 1.0 M in THF) dropwise over 10 min. The reaction was heated at reflux for 2 h before being cooled in an ice/water bath and quenched with water (20 mL). The resulting solution was diluted with dichloromethane (20 mL). washed with 2 M HCl (2 × 20 mL) then water (1 × 20 mL), and dried over sodium sulfate, and the solvent removed in vacuo to afford **3** as a white solid, 414 mg (97%). The spectroscopic data are in agreement with the literature:[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 7.15 (s, 1H, 1-ArH), 6.72 (s, 1H, 4-ArH), 5.06 (s, 1H, Ar-OH), 3.73 (t, J = 8.4 Hz, 1H, 17-H), 2.90−2.84 (m, 2H, 6-CH_2), 2.41 (s, 3H, Ar-CH_3), 2.31 (dt, J = 13.3, 3.6 Hz, 1H), 2.26−2.18 (m, 1H), 2.18−2.07 (m, 1H), 1.96−1.87 (m, 2H), 1.76−1.67 (m, 1H), 1.58−1.16 (m, 8H), 0.79 (s, 3H, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (3-ArC), 137.8 (10-ArC), 137.4 (ArC), 134.4 (ArC), 132.7 (5-ArC), 129.9 (ArCH), 128.9 (ArCH), 127.2 (1-ArCH), 125.6 (2-ArC), 115.5 (4-ArCH), 81.9 (17-CH), 50.0 (CH), 43.9 (CH), 43.2 (13-C), 38.9 (CH), 36.7 (CH_2), 30.6 (16-CH_2), 29.4 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 23.1 (CH_2), 21.2 (Ar-CH_3), 11.0 (18-CH_3); IR (neat), ν (cm^{-1}) 3351 (broad), 2960, 2922, 2863, 1501, 1396, 1039, 1010, 817, 801; mp 153.3−154.8 °C; HRMS (ESI) calcd for $C_{25}H_{31}O_2$ $[M + H]^+$ 363.2319 and $C_{25}H_{30}NaO_2$ $[M + Na]^+$ 385.2138, found 363.2321 and 385.2141.

Preparation of Compound ***5****.* A solution of **2a** (210 mg, 0,457 mmol) in benzene (0.6 mL) containing ethylene glycol (0.04 mL, 0.717 mmol) was heated at reflux in the presence of *p*-toluensulfonic acid (2.7 mg) using a Dean−Stark apparatus for 16 h. The cooled mixture was washed with 5% aqueous sodium bicarbonate solution (10 mL) and saturated brine (10 mL) and extracted with dichloromethane. The organic layer was dried with sodium sufate and evaporated in vacuo. The crude material was purified by flash chromatography eluting with 3:1 petroleum ether/ethyl acetate to give **5**: pale yellow solid, 183 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.26 (m, 3H, ArH), 7.18 (d, J = 8.3 Hz, 2H, ArH), 6.91 (s, 1H, 4-ArH), 3.99−3.86 (m, 4H, OCH_2), 3.28 (q, J = 5.6 Hz, 4H, $EtCH_2$), 2.92 (dd, J = 8.2, 3.7 Hz, 2H, 6-CH_2), 2.36 (s, 3H, Ar-CH_3), 2.35−2.28 (m, 2H), 2.07−2.0 (m, 1H), 1.94−1.73 (m, 4H), 1.68−1.30 (m, 6H), 1.07−0.99 (m, 6H, Et-CH_3), 0.89 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.4 (OC(O)NEt_2), 146.3 (3-ArC), 137.7 (10-ArC), 137.1 (ArC), 136.6 (ArC), 135.7 (ArC), 132.1 (ArC), 129.1 (ArCH), 128.8 (ArCH), 127.8 (1-ArCH), 123.1 (4-ArCH), 119.5 ($Me_2C(OMe)_2$), 65.4 (CO), 64.7 (CO), 49.5 (CH), 46.2 (13-C), 43.9 (CH_3), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 38.9 (CH), 34.9 (CH_2), 34.3 (CH_2), 30.8 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 22.5 (CH_2), 21.3 ($ArCH_3$), 14.4 (18-CH_3), 13.3 (NCH_2CH_3); IR (neat), ν (cm^{-1}) 2934, 2871, 1714, 1471, 1393, 1266, 1155, 1103, 1041, 961, 893, 817, 755; mp 80.4−82.6 °C; HRMS (ESI) calcd for $C_{32}H_{41}NNaO_4$ $[M + Na]^+$ 526.2928, found 526.2915.

Preparation of 2-(4-Tolyl)estrone, ***4****.* To a solution of **5** (183 mg, 0.364 mmol) in THF (10 mL) at room temperature, under nitrogen, was added $LiAlH_4$ (3.63 mL, 3.636 mmol, 1.0 M in THF) dropwise over 10 min. The reaction was heated at reflux for 2 h before being cooled in an ice/water bath and quenched with water (10 mL). The resulting solution was diluted with dichloromethane (20 mL) and washed with 3 M HCl (2 × 10 mL) and water (1 × 20 mL) and then was dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography eluting with 3:1 petroleum ether/ethyl acetate to afford **4**: white solid, 137 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.1 Hz, 2H, ArH), 7.29 (d, J = 8.0 Hz, 2H, ArH), 7.14 (s, 1H, 1-ArH), 6.73 (s, 1H, 4-ArH), 5.07 (s, 1H, ArOH), 2.94 (dd, J = 8.4, 3.7 Hz, 2H, 6-CH_2), 2.54 (dd, J = 18.8,[12] 8.8 Hz, 1H), 2.42−2.37 (m, 1H), 2.41 (s, 3H, Ar-CH_3), 2.32−2.25 (m, 1H, 9-CH), 2.13 (dd, J = 18.8,[12] 9.1 Hz, 1H), 2.09−1.91 (m, 3H), 1.69−1.41 (m, 6H), 0.92 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 221.1 (17-CO), 150.5 (3-ArC), 137.6 (10-ArC, ArC), 134.4 (ArC), 132.3 (ArC), 130.1 (ArCH), 129.1 (ArCH), 127.3 (1-ArCH), 125.9 (2-ArC), 115.7 (4-ArCH), 50.5 (CH), 48.1 (CH), 44.1 (13-C), 38.5 (CH), 36.0 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 21.7 (CH_2), 21.3 (Ar-CH_3), 14.0 (18-CH_3); IR (neat), ν (cm^{-1}) 3353 (broad) 2916, 1719, 1501, 1399, 1259, 1191, 1054, 828, 734; mp 185.8−186.5 °C; HRMS (EI) calcd for $C_{25}H_{28}O_2$ $[M]^+$ 360.2089, found 360.2091.

Preparation of Estriol Diacetate, ***6****.* To a flame-dried Schlenk tube containing a solution of $BF_3{\cdot}Et_2O$ (0.11 mL, 0.87 mmol) in Ac_2O (3.21 mL) was added estriol (1.0 g, 3.46 mmol) in dry THF (5 mL) at room temperature with stirring. After being stirred for 4 h at 0 °C, excess cold 5% Na_2CO_3 (aq) was added. The solution was extracted with CH_2Cl_2, washed with brine, dried, and concentrated in vacuo. The crude material was purified by flash chromatography eluting with 9.5:0.5 CH_2Cl_2/acetone to afford **6** as a white solid, 1.21 g (94%). The spectroscopic data are in agreement with the literature:[13] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.4 Hz, 1H, ArH), 6.64 (dd, J = 8.3, 2.7 Hz, 1H, ArH), 6.57 (d, J = 2.7 Hz, 1H, ArH), 5.20−5.16 (m, 1H, 16-CH), 5.00 (d, J = 5.7 Hz, 1H, 17-CH), 2.84−2.80 (m, 2H, 6-CH_2), 2.29−2.20 (m, 2H), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.84−1.79 (m, 2H), 1.72−1.62 (m, 2H), 1.57−1.32 (m, 5H), 0.84 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.1 (OC(O)CH_3), 171.0 (OC(O)CH_3), 153.6 (ArC), 138.0 (ArC), 132.1 (ArC), 126.5 (ArCH), 115.3 (ArCH), 112.8 (ArCH), 86.2 (COC(O)CH_3), 78.2 (COC(O)CH_3), 48.1 (CH), 43.8 (13-C), 43.6 (CH), 38.1 (CH), 36.7 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 25.8(CH_2), 21.2 (OC(O)CH_3), 21.1 (OC(O)CH_3), 13.0 (18-CH_3); IR (neat), ν (cm^{-1}) 3305 (broad), 2925, 2857, 1738, 1702, 1620, 1583, 1499, 1361,

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1233, 1307, 822; mp 173.7−175.1 °C; HRMS (MALDI) calcd for $C_{22}H_{28}NaO_5$ $[M + Na]^+$ 395.1829, found 395.1825.

Preparation of Estriol-Carbamate Substrate ***7***. To a flame-dried Schlenk tube, equipped with a magnetic stir bar, were added estriol diacetate (**6**) (1.21 g, 3.25 mmol), anhydrous triethylamine (0.9 mL, 6.5 mmol), diethylcarbamoyl chloride (0.59 mL, 6.5 mmol), and anhydrous pyridine (20 mL) under nitrogen. The resulting solution was stirred at 80 °C for 18 h. The mixture was cooled to room temperature, diluted with dichloromethane, and washed with water (2 × 20 mL), 1 M HCl (5 × 20 mL) and brine (2 × 20 mL) before being dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography eluting with 9.5:0.5 CH_2Cl_2/acetone to afford **7**: pale pink solid, 1.42 g (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.5 Hz, 1H, ArH), 6.87 (dd, J = 8.4, 2.5 Hz, 1H, ArH), 6.82 (d, J = 2.4 Hz, 1H, ArH), 5.19−5.15 (m, 1H, 16-CH), 4.98 (d, J = 5.7 Hz, 1H, 17-CH), 3.41−3.36 (m, 4H), 2.85−2.82 (m, 2H, 6-CH_2), 2.30−2.24 (m, 2H), 2.07 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 1.82−1.79 (m, 2H), 1.71−1.61 (m, 2H), 1.57−1.32 (m, 5H), 1.26−1.15 (m, 6H), 0.84 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.8 ($OC(O)CH_3$), 170.7 ($OC(O)CH_3$), 154.4 ($OC(O)NEt_2$), 149.3 (ArC), 137.6 (ArC), 136.5 (ArC), 126.0 (ArCH), 121.7 (ArCH), 118.9 (ArCH), 86.1 ($COC(O)CH_3$), 78.0 ($COC(O)CH_3$), 48.1 (CH), 43.8 (13-C), 43.7 (CH), 42.2 (NCH_2CH_3), 41.8 (NCH_2CH_3), 37.8 (CH), 36.7 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 25.7 (CH_2), 21.2 ($OC(O)CH_3$), 21.0 ($OC(O)CH_3$), 14.2 (NCH_2CH_3), 12.9 (18-CH_3); IR (neat), ν (cm^{-1}) 2933, 1733, 1708, 1413, 1363, 1232, 1155, 1044, 963, 886; mp 133.4−135.8 °C; HRMS (MALDI) calcd for $C_{27}H_{37}NNaO_6$ $[M + Na]^+$ 494.2513, found 494.2509.

Palladium-Catalyzed Direct Arylation of ***7***. The same method was employed as for the arylation of **1**, using **7** (50 mg, 0.106 mmol), palladium acetate (1 mg, 4.5 μmol), silver acetate (35 mg, 0.21 mmol), and the appropriate aryl iodide (0.26 mmol).

Compound ***8a:*** beige solid, 45 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.23 (s, 1H, 1-ArH), 7.18 (d, J = 8.3 Hz, 2H, ArH), 6.91 (s, 1H, 4-ArH), 5.21−5.17 (m, 1H, 16-CH), 5.00 (d, J = 5.7 Hz, 1H, 17-CH), 3.27−3.21 (m, 4H), 2.92−2.87 (m, 2H, 6-CH_2), 2.36 (s, 3H, Ar-CH_3), 2.34−2.28 (m, 2H), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.88−1.78 (m, 2H), 1.72−1.64 (m, 2H), 1.58−1.38 (m, 5H), 1.06−1.00 (m, 6H), 0.86 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.0 ($OC(O)CH_3$), 170.9 ($OC(O)CH_3$), 154.4 ($OC(O)NEt_2$), 146.4 (3-ArC), 137.0 (10-ArC), 136.8 (ArC), 136.7 (ArC), 135.5 (ArC), 132.3 (ArC), 129.0 (ArCH), 128.8 (ArCH), 127.7 (1-ArCH), 123.2 (4-ArCH), 86.2 ($COC(O)CH_3$), 78.2 ($COC(O)CH_3$), 48.3 (CH), 43.9 (13-C), 43.8 (CH), 42.0 (NCH_2CH_3), 41.7 (NCH_2CH_3), 37.9 (CH), 36.8 (CH_2), 32.1 (CH_2), 29.2 (CH_2), 27.1 (CH_2), 25.8 (CH_2), 21.3 ($OC(O)CH_3$), 21.2 (Ar-CH_3), 21.8 ($OC(O)CH_3$), 14.0 (NCH_2CH_3), 13.1 (18-CH_3); IR (neat), ν (cm^{-1}) 2928, 1736, 1714, 1422, 1363, 1236, 1154, 1035, 962, 894; mp 94.1−95.7 °C; HRMS (MALDI) calcd for $C_{34}H_{43}NNaO_6$ $[M + Na]^+$ 584.2983, found 584.2978.

Compound ***8b:*** beige solid, 47 mg (72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H, ArH), 7.51 (d, J = 7.9 Hz, 2H, ArH), 7.23 (s, 1H, 1-ArH), 6.94 (s, 1H, 4-ArH), 5.22−5.17 (m, 1H, 16-CH), 5.01 (d, J = 5.7 Hz, 1H, 17-CH), 3.25 (q, J = 7.1 Hz, 4H), 2.93−2.90 (m, 2H, 6-CH_2), 2.39−2.24 (m, 2H), 2.09 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.98−1.80 (m, 2H), 1.74−1.65 (m, 2H), 1.55−1.38 (m, 4H), 1.28−1.24 (m, 1H), 1.02 (t, J = 7.01 Hz, 6H), 0.86 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.9 ($OC(O)CH_3$), 170.8 ($OC(O)CH_3$), 154.0 ($OC(O)NEt_2$), 146.3 (ArC), 142.2 (ArC), 138.0 (ArC), 137.4 (ArC), 131.0 (ArC), 129.0 (ArC), 129.5 (ArCH), 127.4 (1-ArCH), 125.7 (ArCH), 125.0 (m, CCF_3), 123.3 (4-ArCH), 86.1 ($COC(O)CH_3$), 78.1 ($COC(O)CH_3$), 48.2 (CH), 43.8 (13-C), 43.7 (CH), 42.0 (NCH_2CH_3), 41.6 (NCH_2CH_3), 37.8 (CH), 36.7 (CH_2), 32.0 (CH_2), 29.2 (CH_2), 27.0 (CH_2), 25.8 (CH_2), 21.2 ($OC(O)CH_3$), 21.1 ($OC(O)CH_3$), 13.9 (NCH_2CH_3), 13.0 (18-CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ - 62.3; IR (neat), ν (cm^{-1}) 2931, 1737, 1716, 1617, 1455, 1425, 1414, 1364, 1323, 1238, 1155, 1036, 1066, 1016, 962, 845; mp 92.9−94.4 °C; HRMS (MALDI) calcd for $C_{34}H_{40}F_3NNaO_6$ $[M + Na]^+$ 638.2700, found 638.2705.

Deprotection of Compounds ***8***. To a solution of **8a** or **8b** (45 mg, 0.08 mmol) in THF (2 mL) at room temperature, under nitrogen, was added $LiAlH_4$ (0.8 mL, 0.8 mmol; 1.0 M in THF) dropwise over 10 min. The reaction was heated at reflux for 2 h before being cooled in an ice/water bath and quenched with water (2 mL). The resulting solution was diluted with dichloromethane (5 mL), washed with 2 M HCl (2 × 5 mL) and then water (1 × 5 mL), and dried over sodium sulfate and the solvent removed in vacuo. The crude material was purified by flash chromatography eluting with 1:1 CH_2Cl_2/acetone to afford the desired product.

Compound ***9a:*** white solid, 22 mg (72%); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.85 (s, 1H, 1-ArH), 7.48 (d, J = 8.1 Hz, 2H, ArH), 7.21 (d, J = 9.2 Hz, 2H, ArH), 6.67 (s, 1H, 4-ArH), 4.10−4.05 (m, 1H, 16-CH), 3.85 (d, J = 4.7 Hz, 1H), 3.75 (d, J = 4.8 Hz, 1H), 3.52 (t, J = 5.1 Hz, 1H, 17-CH), 2.80−2.78 (m, 2H), 2.35 (s, 3H, $ArCH_3$), 2.35−2.30 (m, 1H), 2.26−2.20 (m, 1H), 1.93−1.77 (m, 2H), 1.62−1.28 (m, 5H), 0.82 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $(CD_3)_2CO$) δ 152.7 (3-ArC), 137.6 (10-ArC), 137.4 (ArC), 136.6 (ArC), 132.8 (5-ArC), 130.1 (ArCH), 129.5 (ArCH), 128.6 (1-ArCH), 126.8 (2-ArC), 116.9 (4-ArCH), 90.7 (17-CH), 78.8 (16-CH), 48.9 (CH), 45.0 (CH), 44.8 (13-C), 39.7 (CH), 37.9 (CH_2), 35.1 (CH_2), 28.3 (CH_2), 27.0 (CH_2), 21.2 (Ar-CH_3), 12.9 (18-CH_3); IR (neat), ν (cm^{-1}) 3389 (broad) 2918, 1621, 1519, 1491, 1232, 1127, 1054, 891, 821; mp 213.4−214.7 °C; HRMS (MALDI) calcd for $C_{25}H_{30}NaO_3$ $[M + Na]^+$ 401.2087, found 401.2084.

Compound ***9b:*** white solid, 24 mg (71%); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.82 (d, J = 8.0 Hz, 2H, ArH), 7.71 (d, J = 8.3 Hz, 2H, ArH), 7.26 (s, 1H, 1-ArH), 6.72 (s, 1H, 4-ArH), 4.09−4.05 (m, 1H, 16-CH), 3.90 (d, J = 4.2 Hz, 1H), 3.82−3.81 (m, 1H), 3.52 (t, J = 4.7 Hz, 1H, 17-CH), 2.84−2.80 (m, 2H), 2.38−2.32 (m, 1H), 2.26−2.20 (m, 1H), 1.92−1.77 (m, 2H), 1.61−1.28 (m, 5H), 0.80 (s, 3H, 18-CH_3); ^{13}C NMR (400 MHz, $(CD_3)_2CO$) δ 152.8 (ArC), 144.4 (CF_3), 139.1 (ArC), 133.1 (ArC), 130.7 (ArCH), 130.4 (ArC), 128.6 (ArC), 128.3 (1-ArCH), 125.5 (m, CCF_3), 125.1 (ArCH), 117.1 (4-ArCH), 90.6 (17-CH), 78.7 (16-CH), 48.7 (CH_2), 44.8 (CH), 44.7 (13-C), 39.5 (CH_2), 37.8 (CH_2), 35.0 (CH_2), 30.0 (CH_2), 28.1 (CH_2), 26.8 (CH), 12.8 (18-CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ −62.6; IR (neat), ν (cm^{-1}) 3325 (broad), 2924, 1703, 1615, 1501, 1397, 1322, 1161, 1119, 1065, 1019, 842.3; mp 216.2−218.6 °C; HRMS (MALDI) calcd for $C_{25}H_{27}F_3NaO_3$ $[M + Na]^+$ 455.1805, found 455.1801.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00532.

Crystallographic data for **2f** (CIF)
Optimization details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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