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Sensitized Aliphatic Fluorination Directed by Terpenoidal Enones: A "Visible Light" Approach

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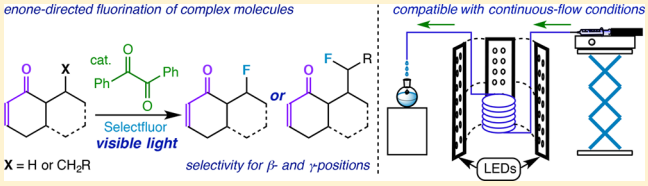
Supporting Information

ABSTRACT: In our continued effort to address the challenges of selective sp^3 C−H fluorination on complex molecules, we report a sensitized aliphatic fluorination directed by terpenoidal enones using catalytic benzil and visible light (white LEDs). This sensitized approach is mild, simple to set up, and an economical alternative to our previous protocol based on direct excitation using UV light in a specialized apparatus. Additionally, the amenability of this protocol to photochemical flow conditions and preliminary evidence for electron-transfer processes are highlighted.



Organic photosensitization can play a powerful role in making ultraviolet light-driven synthetic methods amenable to safe, inexpensive, and more accessible "visible light" protocols. What is more, developing an alternative visible light approach allows for milder reaction conditions that are often accompanied by increases in yields and/or selectivity. In our laboratory, we recently developed a site-selective fluorination of polycyclic terpenoids directed by enones under 300 nm irradiation (provided by a Rayonet reactor).[1] Although the selectivity of this sp^3 C−H fluorination reaction is remarkable given the complexity of the substrate scope, the product yields are moderate (38−72%), and the reaction is only accessible to laboratories that possess a dedicated ultraviolet light source. Ostensibly, this protocol could benefit from an alternative approach in order to make enone-directed fluorination more widely used. Accordingly, we now report an enone-directed β- and γ-fluorination of complex terpenoids using visible light (provided by white LEDs) and a catalytic amount of benzil. Not only does this protocol avoid the costs and hazards associated with ultraviolet light, but also it (1) affords significantly higher product yields (68−94%), (2) maintains (or, in some cases, improves) selectivity, (3) allows for easier scalability, and (4) can be adapted to multiple setups, including a visible light continuous flow apparatus. Thus, we believe this to be a more practical approach than our previous report (Figure 1).

Directed sp^3 C−H fluorination methods on complex structures are still scarce in the literature. While various methods using transition-metal catalysts,[2] radical initiators,[3] photosensitizers,[4] and organic molecules[5] have been reported to effect aliphatic fluorination,[6] *guiding selective fluorination on complex molecules through functional groups* remains a synthetic challenge. Thus, the few existing methods to date are notable. Outside of our recent reports on enone- and ketone-directed fluorination,[1,7] β-fluorination of amino acid derivatives has also been achieved using chelating auxiliaries and palladium catalysis.[8] Following our initial success with a sensitized

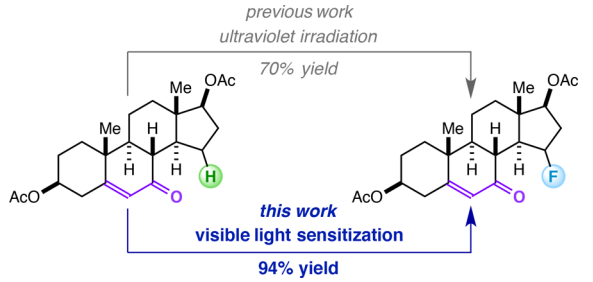


Figure 1. Direct excitation vs visible-light-sensitized enone-directed fluorination.

approach to ketone-directed fluorination, we asked if a similar protocol could be developed for enones.

Thus, we screened various photosensitizers that absorb light above 400 nm[9] using white LED lamps (with a sharp absorbance cutoff around 400 nm) on a steroidal enone test substrate **1**. This wavelength avoids direct excitation of enone substrates that have an absorbance around 365 nm. Although many photosensitizers effected the reaction, we found that 10 mol % benzil and 2.0 equiv of Selectfluor in MeCN under N_2 atmosphere afforded fluorinated compound **2** in 94% yield in 14 h (Table 1). The yield was not increased with greater sensitizer loadings, and no fluorinated products were observed upon irradiation without a photosensitizer. Furthermore, either higher or lower equivalents of Selectfluor resulted in diminished yields, and other N−F reagents (e.g., NFSI and *N*-fluoropyridinium tetrafluoroborate) did not furnish the desired fluorinated products. In addition, heating compound **1** and Selectfluor in MeCN did not afford **2**, only minor unidentified secondary fluorinated products.

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Table 1. Screening for an Optimal Visible-Light Sensitizer[a]

entry	sensitizer	^{19}F NMR yield (%)
1		0
2	4,4-difluorobenzil	67
3	9-fluorenone	47
4	2-chlorothioxanthone	73
5	dibenzosuberenone	55
6	9,10-phenanthrenequinone	64
7	**benzil**	**94**
8	methyl benzoylformate	89
9	2,7-dichloro-9-fluorenone	71
10	2-bromo-9-fluorenone	43

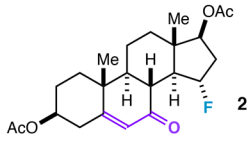
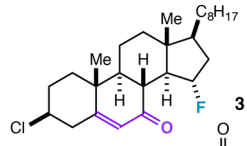
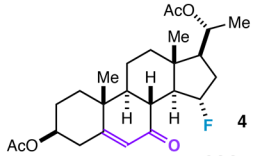
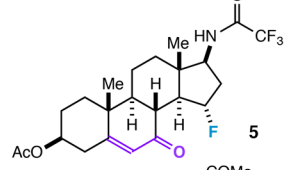
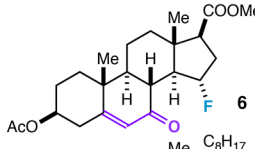
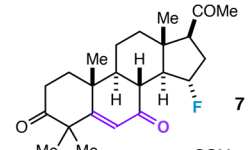
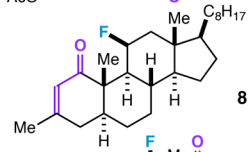
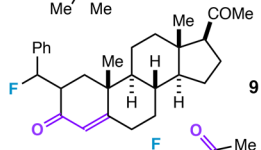
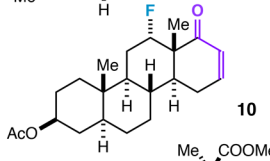
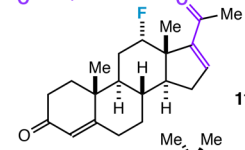
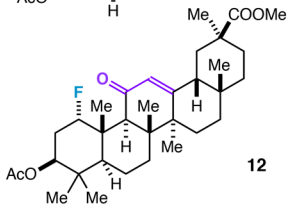
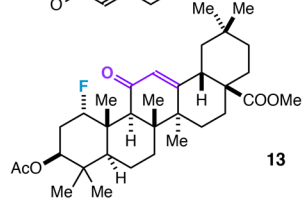
[a]Substrate (0.25 mmol, 1.0 equiv), Selectfluor (0.50 mmol, 2.0 equiv), and benzil (0.025 mmol, 10 mol %) were dissolved in MeCN (4.0 mL) and irradiated with cool white LEDs for 14 h.

With optimized conditions in hand, we investigated fluorination of the easily (synthetically) accessible and important class of steroidal substrates whereby an enone is poised to direct fluorination on the C15 position (compounds **2**–**7**) through a six-membered transition state (Table 2). These compounds are derivatives of common, biologically active steroids (e.g., testosterone, cholesterol, progesterone, androsterone, pregnenolone, etc.).[10,11] In all cases, selective fluorination was observed at the predicted site in high yields, wherein the α-isomer is slightly favored over the β-counterpart.

As a testament to the mild nature of this reaction, a secondary aliphatic chloride substituent is tolerated on the cholesterol derivative (compound **3**). In another example, the fluorination is compatible with an amide group, i.e., compound **5** derived from dehydroepiandrosterone (one of the most abundant steroids in humans[12]). Notably, electron-withdrawing groups cannot be placed in close proximity to the fluorination site (less than three carbon atoms away), as the reaction is completely shut down; we have attributed this previously to the polar effect.[13]

In order to access the C11 position on the steroidal core, we synthesized the starting material for compound **8** from 4-cholesten-3-one (a precursor of 7α-hydroxycholesterol, an

Table 2. Substrate Scope of Enone-Directed Fluorination in Complex Terpenoids*

Product	Yield (%)	d.r.	Product	Yield (%)	d.r.
 **2**	94 70 [300 nm]	1.4:1	 **3**	75	1.2:1
 **4**	87	1.5:1	 **5**	74[a]	1.5:1
 **6**	81	1.8:1	 **7**	68 51 [300 nm]	1.8:1
 **8**	74[a] 42 [300 nm]	>10:1	 **9**	75 68 [gram scale]	1:1
 **10**	70 60 [300 nm]	5.5:1	 **11**	82[a] 72 [300 nm]	1.6:1
 **12**	81[a] 72 [300 nm]	4.8:1	 **13**	71 57 [300 nm]	4.9:1

*Unless otherwise specified, the substrate (0.25 mmol, 1.0 equiv), Selectfluor (0.50 mmol, 2.0 equiv), and benzil (0.025 mmol 10 mol %) were stirred in MeCN (4.0 mL) and irradiated with cool white LEDs for 14 h. Yields include both diastereomers and were determined by integration of ^{19}F NMR signals relative to an internal standard and confirmed by isolation of products through column chromatography on silica gel. Major diastereomer (with respect to C–F bond) depicted where known. [a]Yield based on recovered starting material.

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intermediate in bile acid synthesis[14]) with the enone positioned at C1. Gratifyingly, we achieved C11 fluorination in good yield, regioselectivity, and diastereoselectivity (>10:1 ratio of α/β).

Beyond enones that target γ-positions, we also explored enones poised for β-fluorination. We synthesized two candidates that afforded selectively β-fluorinated products in yields up to 75% (**9** and **10**). Compound **10** represents a D-ring expanded enone (example of D-homo steroids that have been studied for various pharmacological activities[15]) that provides C12 fluorination in 70% yield with >5:1 ratio of α:β isomers. In another case, we synthesized C2-functionalized progesterone to direct benzylic fluorination (**9**). We observed a comparable yield (68%) on a gram scale, demonstrating the amenability of this procedure to larger scale syntheses. It is worth noting that ethylbenzene does not fluorinate under identical conditions, thus accentuating the necessary role of the enone.

As demonstrated on compounds **7** and **9**, substrates containing ketones are compatible. However, substrates whereby ketones can access either β- or γ-hydrogen atoms (for competitive fluorination) should be avoided. As a case in point, ~10% yields of fluorinated products at C12 and C16 were detected by ^{19}F NMR analyses of compounds containing C20 exocyclic ketones (Figure 2). Previously, we established

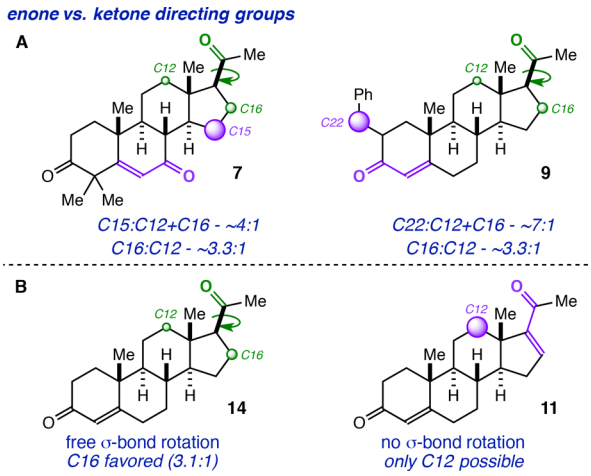


Figure 2. Comparison of reactivity (A) and applications (B) of enone and ketone directing groups.

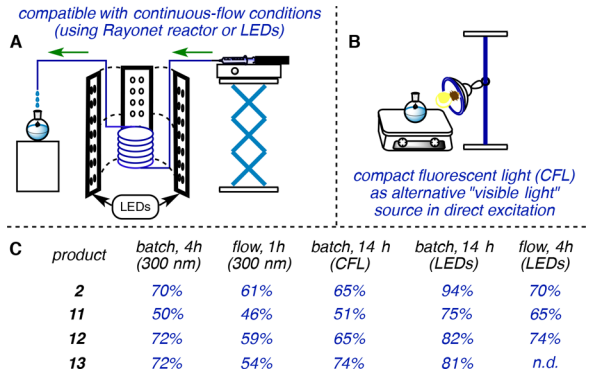
that compound **14** affords C12 and C16 fluorinated products in a 55% total yield using similar reaction conditions,[7] but in compounds **7** and **9**, it is clear the more rigid enone is the more effective director.

Another type of enone we had not previously explored is the exocyclic enone (e.g., **11**, which is also shown to have an antileukemic effect[16]). Although the diminished rigidity is not ideal, one can imagine circumstances where an exocyclic enone could have a regioselectivity advantage over an exocyclic ketone. Consider ketone **14** (directing both C12 and C16 fluorination). In comparison, exocyclic enone **11** blocks β-fluorination at C16, allowing selective fluorination instead at C12—the minor isomer when employing the ketone-directed approach (Figure 2).

At this juncture, we applied our protocol to triterpenoids. Using glycyrrhetinic and oleanolic acid derivatives **12** and **13**—accessible pentacyclic triterpenoids[17]—selective fluorination was accomplished at the C1 position in up to 81% yield (Table 2). Analogues of these compounds have been tested as potential anti-HIV,[18] anticancer,[19] anti-inflammatory,[20] and anti-HCV[21] agents. Efficient monofluorination of these compounds represents a significant leap forward in selective, radical-based aliphatic fluorination chemistry.

In comparison to our 300 nm light protocol, the mild nature of this reaction reduced the number of minor unidentified byproducts. Consequently, significant improvements in yield were observed (300 nm yields are highlighted in Table 2). In addition to being safer and cost-effective, improved chemical yields (e.g., nearly double the yield for **8**) make this protocol substantially more attractive than the ultraviolet light approach.

Additionally, we imagined ways to make the reaction amenable to photochemical continuous flow apparatuses that carry advantages of scalability, simplicity, and time efficiency. Microflow reactors have a clear advantage over standard glassware in photochemical reactions due to an immense increase in surface area (more light penetrates the reaction mixture). Using a simple setup, we found that fluorination is readily adaptable to flow conditions. Our reactor required ca. 7.5 m of FEP tubing (ID 1.6 mm, OD 3.2 mm) coiled around a Pyrex beaker, a chemical resistant Luer lock syringe adapter, and a syringe pump. When this configuration is surrounded by six 72-LED work light sources (Designers Edge L1923) and wrapped with aluminum foil, we found similar yields to the standard reaction conditions after only 4 h (Figure 3). Alternatively, this configuration can be placed inside a Rayonet reactor for 300 nm irradiation, and similar yields to our previous protocol are achieved after only 1 h.



C

product	batch, 4h (300 nm)	flow, 1h (300 nm)	batch, 14 h (CFL)	batch, 14 h (LEDs)	flow, 4h (LEDs)
2	70%	61%	65%	94%	70%
11	50%	46%	51%	75%	65%
12	72%	59%	65%	82%	74%
13	72%	54%	74%	81%	n.d.

Figure 3. (A) Cross-section depiction of photochemical flow reactor. (B) Depiction of reaction using a household fluorescent light bulb. (C) Comparison of ^{19}F NMR yields of products from Table 2 using standard glassware (batch) and the continuous-flow protocol (flow) with various light sources.

On another front, we discovered that a household compact fluorescent light (CFL) may serve as an economical alternative to ultraviolet light sources in direct excitation. Although CFLs are typically regarded as "visible light" sources, there exists a spectral line in the near-ultraviolet region (ca. 365 nm) that we have found to be sufficient in effecting the reaction. However, yields and selectivity are similar to or slightly lower than the ultraviolet light setup; therefore, we have found the sensitized approach using LEDs provides the most optimal results to date.

As a last point of interest, we conducted preliminary mechanistic experiments. Under our reaction conditions, benzil is the only chromophore above 400 nm. The photochemical properties of benzil are well established; for example, it is reported to undergo fast intersystem crossing upon irradiation,

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so we must consider the involvement of its triplet state.[22] Although the triplet sensitization of enones by benzil may be proposed, the reported triplet energy of benzil (53 kcal/mol[23]) is significantly lower than that of steroidal enones (approximately 70 kcal/mol[24]). Therefore, triplet−triplet energy transfer in this case is highly unfavorable,[25] and it is unlikely that the enone triplet state plays a role. What is more, no byproducts from classical excited enone processes[26] such as α-cleavage, β-elimination, or Norrish−Yang cyclization were detected.

Building upon these observations, we explored the possibility of pathways whereby "photochemistry" only plays a role in reaction initiation. For instance, we revisited the non-photochemical BEt_3[3b] protocol that has been shown to generate the *N*-centered radical cation from Selectfluor. In recent studies, we have found the BEt_3 protocol to be a reasonable test for the involvement of this intermediate in our light-driven fluorination chemistry.[7,27] (However, it is important to note that we have found a negative result of this test to be less informative, as this method may not have the same substrate compatibility or efficiency as the photochemical reaction.[28]) Using steroidal substrate **1**, we observed a similar product distribution as the sensitized conditions, albeit in a lower yield (Figure 4). Considering that the Selectfluor *N*-

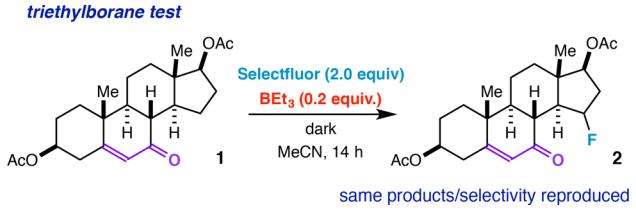

Figure 4. Non-photochemical result suggesting that an electron-transfer mechanism is plausible under visible-light conditions.

centered radical is established as a powerful oxidant,[29] an electron-transfer mechanism could be possible whereby the enone assists in a directed deprotonation.

In all, the visible-light-based photosensitized approach to enone-directed fluorination is a practical and universally accessible alternative to the ultraviolet light-based approach. We have observed notable increases in yields and selectivity, additional functional group compatibility, and better scalability using inexpensive, household LEDs. Furthermore, our assembly and comparative analysis of rudimentary continuous flow setups (using both the Rayonet reactor and a self-assembled LED reactor) demonstrate that this chemistry is a good candidate for microflow applications. For all of these reasons, we believe this is a very powerful protocol for "late-stage fluorination" of complex targets. Future studies will seek to elucidate the reaction mechanism and additional ways to apply directing groups to the fluorination of large, biologically relevant molecules.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous conditions and under N_2 atmosphere. All solvents were dried and distilled by standard methods. All ^1H spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$, ^{19}F spectra were acquired on a 300 MHz NMR spectrometer in CD_3CN or $CDCl_3$, and ^{13}C NMR spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$. The ^1H, ^{13}C, and ^{19}F NMR chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ = 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ = −64.2 ppm relative to $CFCl_3$).[30] NMR data are reported in the following format: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz)). IR data were obtained using an ATR-IR instrument. Spectral data were processed with Bruker software. Photochemical reactions were run in front of a 72-LED work light (Designers Edge L1923). HPLC purification (if necessary) was conducted on a Teledyne Isco CombiFlash EZ Prep system using a Dynamax-60A SiO_2 column and HPLC-grade EtOAc and hexanes. Spectral data match the literature for compounds **2**, **7**, **8**, **9**, **10**, **12**, and **13**.[1,3b] The syntheses and characterization of starting materials are reported in the Supporting Information.

General Fluorination Procedure. Selectfluor (177 mg, 0.50 mmol), benzil (5.0 mg, 0.025 mmol), and the substrate (0.25 mmol) were added to an oven-dried $\mu\omega$ vial equipped with a stir bar; the vial was then sealed with a cap w/septum using a crimper and evacuated/refilled with N_2 multiple times. Anhydrous MeCN (4 mL) was added, and the reaction mixture was irradiated with a cool white LED work light while stirring. After 14 h, a 0.3 mL aliquot was taken for ^{19}F NMR yield determination. Then the reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated. The crude reaction mixture was purified via gradient column chromatography on silica gel eluting with EtOAc/hexanes.

Continuous-Flow Fluorination Procedure. Selectfluor (0.21 g, 0.60 mmol) and the substrate (0.30 mmol) were added to a flame-dried round-bottom flask equipped with a stir bar under N_2. Anhydrous CH_3CN (14.4 mL) was added, and 12 mL of the reaction mixture was drawn into a syringe (0.25 mmol of substrate used in the reaction). The syringe containing the reaction mixture was attached to the microflow reactor with a chemical resistant Luer lock syringe adapter and placed on a syringe pump. (Note that the microflow reactor consisted of ca. 7.5 m of FEP tubing (ID 1.6 mm, OD 3.2 mm) coiled around a Pyrex beaker that was surrounded by six 72-LED work light sources and wrapped with aluminum foil. The tubing was purged with N_2 and anhydrous CH_3CN prior to use.) The flow rate was adjusted to pump the reaction mixture through the microflow reactor and into a collection flask over 4 h. The tubing was purged with additional CH_3CN, and the contents of the collection flask were concentrated. The crude residue was either dissolved in a known amount of solvent to be subjected to ^{19}F NMR analysis with an internal standard or purified via gradient column chromatography on silica gel eluting with EtOAc/hexanes followed by HPLC purification.

Characterization of Fluorinated Compounds. *Compound* ***2****.* Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical assignment was made on the basis of (1) chemical shift in the ^{19}F NMR spectrum that indicates a secondary fluoride, (2) $^2J_{HF}$-coupling in the ^1H and ^{19}F NMR spectra that indicates cyclopentane ring fluorination (52.2 Hz), and 3) identification of $^2J_{CF}$-coupling to distinguishable peaks in the ^{13}C NMR spectrum, i.e., C14, C16, and C17 vide infra. Stereochemical assignment was made on the basis of (1) chemical shift and splitting in the ^{19}F NMR spectrum, (2) accord with the calculated ^{19}F NMR shift, and (3) comparative analysis to compound **7**, for which the crystal structure was previously reported by our laboratory. White solid (53 mg, 55%). Mp = 215−216.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, J = 2.0 Hz, 1H), 5.24 (dm, J = 52.2 Hz, 1H), 4.89 (t, J = 9.1 Hz, 1H), 4.77−4.69 (m, 1H), 2.62 (ddd, J = 14.3, 5.0, 2.2 Hz, 1H), 2.51−2.33 (m, 3H), 2.22−2.08 (m, 1H), 2.07−2.04 (m, 6H), 2.03−1.94 (m, 2H), 177−1.58 (m, 5H), 1.55−1.44 (m, 1H), 1.37−1.23 (m, 2H), 1.17 (s, 3H), 0.83 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.0, 170.7, 170.2, 164.9, 127.1, 92.1 (d, J = 181.0 Hz, C15), 78.5 (d, J = 1.8 Hz, C17), 71.7, 53.4 (d, J = 19.5 Hz, C14), 50.3, 45.1 (d, J = 5.5 Hz), 43.1, 37.9, 37.7, 36.7 (d, J = 26.2 Hz, C16), 36.0, 35.7, 27.3, 21.2, 21.0, 20.8, 17.9, 13.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ −162.7 (m, 1F). IT ν_{max} (ATR-IR): 1733 (br), 1675 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{23}H_{31}FO_5Na$ 429.2048, found 429.2049.

Compound ***3****.* Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient

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column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **2**. White solid (43 mg, 41%). Mp = 142−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (d, J = 1.7 Hz, 1H), 5.26 (dm, J = 53.3 Hz, 1H), 3.90−3.82 (m, 1H), 2.79−2.66 (m, 2H), 2.33−1.82 (m, 6H), 1.73−1.42 (m, 6H), 1.40−1.21 (m, 5H), 1.16 (s, 3H), 1.15−0.98 (m, 4H), 0.92 (d, J = 6.5 Hz, 3H), 0.88−0.84 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.7 Hz, 3H), 0.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 198.6, 164.5, 126.9, 94.0 (d, J = 176.2 Hz, C15), 58.3 (d, J = 18.8 Hz, C14), 57.3, 52.6, 50.6, 45.1 (d, J = 5.9 Hz), 43.2, 42.5, 39.3, 39.1, 37.9 (d, J = 25.4 Hz, C16), 37.7, 37.4, 36.0, 34.8, 32.7, 28.0, 23.7, 22.8, 22.5, 21.2, 18.5, 17.8, 13.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ −160.8 (m, 1F). IR ν_{max} (ATR-IR): 1690 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{27}H_{42}ClFONa$ 459.2800, found 459.2799.

Compound ***4***. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **2**. White solid (54 mg, 52%). Mp = 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, J = 2.0 Hz, 1H), 5.28 (dm, J = 53.5 Hz, 1H), 4.89−4.82 (m, 1H), 4.77−4.69 (m, 1H), 2.63−2.58 (m, 1H), 2.51−2.44 (m, 1H), 2.31 (t, J = 11.4 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 1.99−1.85 (m, 4H), 1.84−1.72 (m, 2H), 1.69−1.60 (m, 3H), 1.55−1.44 (m, 1H), 1.41−1.22 (m, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.15 (s, 3H), 0.70 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 198.2, 170.28, 170.26, 164.8, 127.3, 93.5 (d, J = 178.0 Hz, C15), 71.8, 71.6, 57.7 (d, J = 19.2 Hz, C14), 51.6, 50.5, 44.6 (d, J = 5.9 Hz), 43.1, 38.5, 37.8, 37.7, 35.7, 35.4 (d, J = 26.9 Hz, C16), 27.3, 21.5, 21.24, 21.18, 19.9, 17.9, 13.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −161.0 (m, 1F). IR ν_{max} (ATR-IR): 1730 (br), 1671 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{25}H_{35}FO_5Na^+$ 457.2361, found 457.2358.

Compound ***5***. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **2**. Waxy white solid (49 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (d, J = 7.9 Hz, 1H), 5.82 (d, J = 1.8 Hz, 1H), 5.33 (dm, J = 51.9 Hz, 1H), 4.80−4.67 (m, 1H), 4.31−4.20 (m, 1H), 2.67−2.59 (m, 1H), 2.53−2.29 (m, 3H), 2.20−1.94 (m, 3H), 2.05 (s, 3H), 1.88−1.61 (m, 5H), 1.54−1.43 (m, 2H), 1.39−1.26 (m, 1H), 1.17 (s, 3H), 0.78 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 197.8, 170.3, 165.5, 157.3 (q, J = 37.2 Hz), 127.0, 115.8 (q, J = 288.2 Hz), 91.8 (d, J = 181.3 Hz, C15), 71.7, 56.2, 54.9 (d, J = 19.9 Hz, C14), 50.3, 46.1 (d, J = 5.5 Hz), 43.2, 37.9, 37.7, 37.1 (d, J = 27.3 Hz, C16), 36.1, 35.7, 27.2, 21.2, 20.8, 17.9, 13.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.1 (s, 3F), −162.4 (m, 1F). IR ν_{max} (ATR-IR): 3350, 1730 (br), 1680 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{23}H_{29}F_4NO_4Na$ 482.1925, found 482.1923.

Compound ***6***. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **2**. White solid (50 mg, 52%). Mp = 188−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, J = 2.0 Hz, 1H), 5.34 (dm, J = 52.2 Hz, 1H), 4.77−4.69 (m, 1H), 3.69 (s, 3H), 2.76−2.58 (m, 3H), 2.51−2.44 (m, 1H), 2.32 (t, J = 11.3 Hz, 1H), 2.21−2.07 (m, 1H), 2.05 (s, 3H), 2.04−1.94 (m, 3H), 1.79−1.61 (m, 4H), 1.56−1.38 (m, 2H), 1.33−1.24 (m, 1H), 1.17 (s, 3H), 0.71 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 197.9, 172.9, 170.2, 164.9, 127.1, 93.5 (d, J = 178.4 Hz, C15), 71.7, 57.6 (d, J = 19.5 Hz, C14), 51.9, 51.5, 50.4, 45.8 (d, J = 5.9 Hz), 43.4, 37.9, 37.7, 37.4, 35.7, 33.8 (d, J = 26.5 Hz, C16), 27.3, 21.2, 21.0, 17.8, 14.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −161.7 (m, 1F). IR ν_{max} (ATR-IR): 1721 (br), 1685 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{23}H_{31}FO_5Na$ 429.2048, found 429.2047.

Compound ***7***. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical assignment was made on the basis of (1) chemical shift in the ^{19}F NMR spectrum that indicates a secondary fluoride, (2) $^{2}J_{HF}$-coupling in the ^{1}H and ^{19}F NMR spectra that indicates cyclopentane ring fluorination (52.8 Hz), and (3) identification of $^{2}J_{CF}$-coupling to distinguishable peaks in the ^{13}C NMR spectrum, i.e., C14 and C16 vide infra. Stereochemical assignment was made on the basis of (1) chemical shift and splitting in the ^{19}F NMR spectrum and (2) accord with the calculated ^{19}F NMR shift. Assignments were previously confirmed by X-ray crystallography.[1] White solid (39 mg, 44%). Mp = 191−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H), 5.40 (dm, J = 52.9 Hz, 1H), 2.84−2.66 (m, 2H), 2.64−2.60 (m, 2H), 2.39 (t, J = 11.5 Hz, 1H), 2.16 (s, 3H), 2.15−1.96 (m, 3H), 1.93−1.73 (m, 5H), 1.58−1.55 (m, 1H), 1.34 (s, 6H), 1.07 (s, 3H), 0.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 212.2, 207.7, 198.1, 174.7, 125.0, 93.2 (d, J = 178.0 Hz, C15), 59.7, 58.8 (d, J = 19.9 Hz, C14), 50.3, 49.5, 45.9 (d, J = 6.3 Hz), 42.7, 38.2 (d, J = 22.5 Hz, C16), 33.5, 33.3, 33.2, 31.5, 30.9, 28.4, 26.3, 21.6, 17.7, 14.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −162.8 (dm, J = 52.8 Hz, 1F). IR ν_{max} (ATR-IR): 1706 (br), 1669 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{23}H_{31}FO_3Na$ 397.2149, found 397.2150.

Compound ***8***. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical assignment was made on the basis of (1) chemical shift in the ^{19}F NMR spectrum that indicates a secondary fluoride on a cyclohexane ring, (2) identification of $^{3}J_{HF}$-coupling (10.3 Hz) to the diagnostic C9 H_{ax} signal (ddd at 2.35) as confirmed by a ^{1}H{^{19}F} NMR spectrum, and (3) downfield shifts of the C18 ($\Delta\delta$ = 0.11 ppm) and C19 ($\Delta\delta$ = 0.21 ppm) Me signals in the ^{1}H NMR spectrum with respect to the starting material. Stereochemical assignment was made on the basis of (1) chemical shift and splitting in the ^{19}F NMR spectrum that indicates F_{eq} on a cyclohexane ring, (2) identification of antiperiplanar vicinal coupling in the ^{1}H NMR spectrum of H_{ax} at the C11 position to the axial hydrogen atoms at C9 and C12 (i.e., t, $^{3}J_{HH}$ = 11.3 Hz), (3) lack of long-range coupling of fluorine to the C18 and C19 Me hydrogen atoms in the ^{1}H NMR spectrum, and (4) accord with the calculated ^{19}F NMR shift.[1] White solid (67 mg, 67%). Mp = 120−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71−5.70 (m, 1H), 4.56 (dtd, J = 48.2, 11.3, 4.2 Hz, 1H), 2.35 (ddd, J = 11.7, 10.3, 4.1 Hz, 1H), 2.21−2.13 (m, 1H), 2.02 (dd, J = 18.9, 4.9 Hz, 1H), 1.96−1.85 (m, 2H), 1.82 (s, 3H), 1.81−1.74 (m, 1H), 1.71−1.58 (m, 3H), 1.56−1.44 (m, 3H), 1.40−1.19 (m, 8H), 1.17 (s, 3H), 1.16−0.94 (m, 5H), 0.92 (d, J = 6.6 Hz, 3H), 0.87−0.85 (m, 6H), 0.74 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 204.6, 152.9, 125.5, 91.3 (d, J = 181.2 Hz, C11), 56.3, 55.9, 49.4, 49.2, 46.6, 46.5, 46.4, 43.4, 43.34, 43.28, 39.4, 36.5, 35.9, 35.7, 34.7, 34.6, 29.7, 28.4, 28.01, 27.97, 23.9, 23.4, 22.8, 22.7, 22.5, 18.4, 13.7, 10.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ −178.3 (dm, J = 48.2 Hz, 1F). IR ν_{max} (ATR-IR): 1684 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{28}H_{45}FONa$ 439.3346, found 439.3347.

Compound ***9***. Fluorination was run according to the general procedure (a proportional scale up was used for the gram-scale synthesis), and one diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Characterization data are consistent with previous literature.[3b] White solid (0.35 g, 34%). Mp = 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.35 (m, 2H), 7.32−7.27 (m, 3H), δ 6.48 (dd, J = 46.1, 1.8 Hz, 1H), 5.82 (d, J = 1.4 Hz, 1H), 2.64 (dddd, J = 30.4, 13.5, 5.3, 2.2 Hz, 1H), 2.52 (t, J = 9.0 Hz, 1H), 2.41−2.27 (m, 2H), 2.21−2.13 (m, 1H), 2.10 (s, 3H), 2.01 (dt, J = 12.2, 3.1 Hz, 1H), 1.87−1.79 (m, 2H), 1.74−1.60 (m, 3H), 1.53−1.44 (m 2H), 1.42−1.29 (m, 2H), 1.27−1.20 (m, 1H), 1.18−1.11 (m, 1H), 1.08−0.96 (m, 2H), 1.04 (s, 3H), 0.60 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 209.1, 196.2, 170.7, 138.9 (d, J = 20.3 Hz, C23), 128.31, 128.29, 127.6 (d, J = 1.1 Hz), 124.6, 124.5, 123.7, 90.1 (d, J = 175.8 Hz, C22), 63.3, 55.8, 53.7, 47.9, (d, J = 22.9 Hz, C2), 43.7, 38.5, 38.4, 35.3, 33.6 (d, J = 5.2 Hz, C1), 32.3, 31.6, 31.4, 24.2, 22.7, 20.8, 17.5, 13.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −197.3 (dd, J = 45.9, 31.0 Hz, 1F). IR ν_{max} (ATR-IR): 1710, 1690 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{28}H_{35}FO_2Na$ 445.2513, found 445.2511.

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Compound **10**. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical assignment was made on the basis of 1) chemical shift in the ^{19}F NMR spectrum that indicates a secondary fluoride on a cyclohexane ring, 2) identification of $^{4}J_{HF}$-coupling to the distinguishable C18 Me hydrogen atoms in the ^{1}H NMR spectrum, and 3) identification of $^{2}J_{CF}$- and $^{3}J_{CF}$-coupling to distinguishable peaks in the ^{13}C NMR spectrum, i.e., C11, C13, C17a, and C18 vide infra. Stereochemical assignment was made on the basis of (1) chemical shift and splitting in the ^{19}F NMR spectrum that indicates F_{ax} on a cyclohexane ring and (2) accord with the calculated ^{19}F NMR shift.[1] White solid (51 mg, 59%). Mp = 135−137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92−6.87 (m, 1H), 5.98−5.95 (m, 1H), 5.17 (dm, J = 46.8 Hz, 1H), 4.72−4.64 (m, 1H), 2.56−2.49 (m, 1H), 2.16−2.09 (m, 1H), 2.05−1.96 (m, 2H), 2.02 (s, 3H), 1.89−1.80 (m, 2H), 1.73−1.63 (m, 2H), 1.58−1.18 (m, 8H), 1.10−0.97 (m, 2H), 0.96 (d, J = 1.1 Hz, 3H), 0.82 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.0 (d, J = 0.7 Hz, C17a), 170.6, 148.2, 128.2, 91.0 (d, J = 172.5 Hz, C12), 73.3, 48.3 (d, J = 19.2 Hz, C13), 45.9, 43.9, 39.8, 36.1, 35.2, 34.7, 33.8, 30.1, 28.2, 27.2, 26.3, 25.4 (d, J = 21.4 Hz, C11), 21.4, 14.9 (d, J = 7.0 Hz, C18), 11.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −185.6 (m, 1F). IR ν_{max} (ATR-IR): 1734, 1684 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{22}H_{31}FO_3Na$ 385.2149, found 385.2149.

Compound **11**. Fluorination was run according to the general procedure, and both major and minor diastereomers were isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **10**.

Major Diastereomer. White solid (39 mg, 50%). Mp = 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (dd, J = 3.4 Hz, 1.7 Hz, 1H), 5.74 (d, J = 1.5 Hz, 1H), 5.39 (dt, J = 48.7, 2.7 Hz, 1H), 2.44−2.33 (m, 4H), 2.28 (s, 3H), 2.15−2.10 (m, 1H), 2.08−1.86 (m, 5H), 1.83−1.64 (m, 3H), 1.41−1.33 (m, 1H), 1.23−1.15 (m, 1H), 1.19 (s, 3H), 0.94 (d, J = 1.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.2, 196.4, 169.9, 151.5 (d, J = 2.1 Hz, C17), 144.6, 124.3, 91.1 (d, J = 174.7 Hz, C12), 50.2 (d, J = 18.8 Hz, C13), 48.9 (d, J = 0.7 Hz), 46.9 (d, J = 1.5 Hz), 38.2, 35.3, 33.8, 33.5, 32.5, 31.4, 31.3, 26.8, 26.5 (d, J = 22.1 Hz, C11), 17.0, 16.0 (d, J = 7.4 Hz, C18). ^{19}F NMR (282 MHz, $CDCl_3$): δ −185.5 (td, J = 46.7, 12.4 Hz, 1F). IR ν_{max} (ATR-IR): 1698, 1667 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{21}H_{27}FO_2Na$ 353.1887, found 353.1888.

Minor Diastereomer. White solid (25 mg, 32%). Mp = 179−182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (dd, J = 3.4, 1.8 Hz, 1H), 5.77−5.75 (m, 1H), 4.57 (ddd, J = 49.5, 15.8, 5.6 Hz, 1H), 2.45−2.38 (m, 3H), 2.36−2.31 (m, 2H), 2.32 (s, 3H), 2.21−2.13 (m, 1H), 2.05−1.97 (m, 2H), 1.93−1.87 (m, 1H), 1.77−1.64 (m, 3H), 1.39−1.30 (m, 1H), 1.24 (s, 3H), 1.14−1.04 (m, 2H), 1.09 (d, J = 0.7 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.0, 196.7, 169.2, 154.6 (d, J = 2.2 Hz, C17), 143.2, 124.5, 94.1 (d, J = 185 Hz, C12), 52.5, 52.4 (d, J = 3.3 Hz), 51.1 (d, J = 17.3 Hz, C13), 38.4, 35.5, 33.8, 32.4, 31.3 (d, J = 1.8 Hz), 30.9 (d, J = 1.8 Hz), 28.28, 28.25, 27.9 (d, J = 22.5 Hz, C11), 17.0, 11.9 (d, J = 2.2 Hz, C18). ^{19}F NMR (282 MHz, $CDCl_3$): δ −170.3 (m, 1F). IR ν_{max} (ATR-IR): 1695, 1670 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{21}H_{27}FO_2Na$ 353.1887, found 353.1887.

Compound **12**. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes. Regiochemical assignment was made on the basis of (1) chemical shift in the ^{19}F NMR spectrum that indicates a secondary fluoride on a cyclohexane ring, (2) disappearance of the diagnostic C1 H_{eq} signal (dt at 2.76 ppm) in the ^{1}H NMR spectrum concomitant with appearance of a ^{1}H signal with the shift (5.58 ppm) and coupling constant ($^{2}J_{HF}$ = 47 Hz) that indicate a geminal fluoride, and (3) identification of $^{2}J_{CF}$- and $^{3}J_{CF}$-coupling to distinguishable peaks in the ^{13}C NMR spectrum, i.e., C2, C9, C10, and C25 vide infra. Stereochemical assignment was made on the basis of (1) chemical shift and splitting in the ^{19}F NMR spectrum that indicates F_{ax} on a cyclohexane ring and (2) accord with the calculated ^{19}F NMR shift.[1] White solid (88 mg, 67%). Mp = 265−265.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (s, 1H), 5.58 (ddd, J = 46.6, 3.4, 2.2 Hz, 1H), 4.92 (dd, J = 11.9, 5.1 Hz, 1H), 3.69 (s, 3H), 3.13 (s, 1H), 2.12−2.06 (m, 2H), 2.05 (s, 3H), 2.04−1.91 (m, 4H), 1.83 (td, J = 13.6, 4.3 Hz, 1H), 1.71−1.58 (m, 3H), 1.56−1.45 (m, 1H), 1.41−1.36 (m, 2H), 1.39 (s, 3H), 1.32−1.30 (m, 3H), 1.21−1.20 (m, 1H), 1.16 (d, J = 2.0 Hz, 3 H), 1.15 (s, 3H), 1.14 (s, 3H), 1.04−0.98 (m, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.2, 176.9, 170.5, 169.8, 128.3, 94.1 (d, J = 172.9 Hz, C1), 75.1, 52.6 (d, J = 8.1 Hz, C9), 51.8, 48.4, 47.6, 45.2, 44.0, 43.5, 41.1, 40.9, 40.7, 37.9, 37.7, 32.1, 31.8, 31.1, 28.4 (d, J = 25.8 Hz, C2), 28.2 (d, J = 21.7 Hz, C10), 27.8, 26.5, 26.4, 23.3, 21.2, 18.9, 17.0, 16.5 (d, J = 5.9 Hz, C25), 16.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −191.9 (m, 1F). IR ν_{max} (ATR-IR): 1734 (br), 1653 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{33}H_{49}FO_5Na$ 567.3456, found 567.3451.

Compound **13**. Fluorination was run according to the general procedure, and the major diastereomer was isolated via gradient column chromatography on silica gel eluting with EtOAc/hexanes followed by silica-based HPLC using EtOAc/hexanes. Regiochemical and stereochemical assignments were made by analogy to compound **12**. White solid (78 mg, 59%). Mp = 238−241 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (s, 1H), 5.62 (dm, J = 46.3 Hz, 1H), 4.92 (dd, J = 12.0, 4.9 Hz, 1H), 3.63 (s, 3H), 3.10 (s, 1H), 3.04−2.99 (m, 1H), 2.12−2.06 (m, 1H), 2.05 (s, 3H), 2.04−2.01 (m, 1H), 1.99−1.86 (m, 1H), 1.77−1.69 (m, 2H), 1.67−1.63 (m, 2H), 1.61−1.58 (m, 2H), 1.51−1.41 (m, 1H), 1.38 (s, 3H), 1.37−1.30 (m, 2H), 1.28−1.18 (m, 4H), 1.12 (d, J = 2.1 Hz, 3H), 0.99−0.92 (m, 10H), 0.90 (s, 3H), 0.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.3, 177.5, 170.5, 169.2, 127.6, 95.0 (d, J = 172.5 Hz, C1), 75.1, 52.6 (d, J = 8.1 Hz, C9), 51.9, 47.7, 46.2, 44.8, 44.2, 43.8, 41.6, 41.0, 40.9, 37.9, 33.7, 32.8, 32.2, 31.6, 30.7, 28.3, 28.1, 27.8, 23.5, 23.4, 22.9, 21.2, 19.1, 16.9, 16.4, 16.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ −192.2 (m, 1F). IR ν_{max} (ATR-IR): 1734 (br), 1652 cm^{-1}. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{33}H_{49}FO_5Na$ 567.3456, found 567.3452.

Syntheses and Characterization of Starting Materials. *Starting Material for Compound* **2** *(3β,17β-Diacetoxyandrost-5-en-7-one*[31−33]*)*. To a flame-dried round-bottom equipped with a stir bar under N_2 were added prasterone (4.0 g, 13.9 mmol) and MeOH (75 mL). The reaction mixture was treated with $NaBH_4$ (0.53 g, 13.9 mmol) in portions over 10 min and then stirred for an additional 2 h. The resulting white precipitate was collected by filtration and dried to provide 5-androstenediol (3.50 g, 87%).

The 5-androstenediol from the previous step (3.1 g, 10.7 mmol), *p*-TsOH·H_2O (60 mg, 0.30 mmol), and acetic anhydride (4.6 mL) were dissolved in pyridine (6.0 mL) under N_2. After stirring for 1 h at rt, the reaction mixture was heated to 95 °C and stirred for an additional 3.5 h. The reaction mixture was then cooled to rt and diluted with H_2O (150 mL). The white precipitate was collected by filtration, washed with H_2O, and dried to provide androstenediol-3,17-diacetate (3.52 g, 85%).

Androstenediol 3,17-diacetate (1.9 g, 5.2 mmol) was dissolved in a mixture of acetone (200 mL) and acetic acid (20 mL) in a round-bottom flask equipped with a stir bar and reflux condenser under N_2. The reaction mixture was treated with *N*-hydroxysuccinimide (5.9 g, 52 mmol) and $K_2Cr_2O_7$ (6.0 g, 21 mmol), and then the reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was cooled to rt, quenched with aq 10 % sodium metabisulfite solution, filtered through Celite, and extracted into Et_2O. The combined organic layers were washed with saturated aq $NaHCO_3$, brine, dried with $MgSO_4$, and concentrated. The crude residue was recrystallized in MeOH to provide 3β,17β-diacetoxyandrost-5-ene-7-one (1.64 g, 82%) as a white solid. Mp = 222−223 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (d, J = 1.8 Hz, 1H), 4.74−4.65 (m, 1H), 4.63−4.59 (m, 1H), 2.55 (ddd, J = 14.0, 5.1, 2.2 Hz, 1H), 2.49−2.39 (m, 2H), 2.29−2.14 (m, 2H), 2.03 (s, 3H), 2.02 (s, 3H), 2.00−1.93 (m, 2H), 1.77−1.68 (m, 2H), 1.67−1.57 (m, 2H), 1.54−1.47 (m, 3H), 1.43−1.35 (m, 1H), 1.30−1.25 (m, 1H), 1.20 (s, 3H), 1.18−1.11 (m, 1H), 0.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.1, 171.1, 170.2, 164.3, 126.5, 81.9, 72.0, 49.7, 45.0, 44.7, 43.0, 38.3, 37.8, 36.0, 35.8, 27.5, 27.3, 25.8, 21.2, 21.1, 20.7, 17.3, 12.0. IR ν_{max} (CaF_2, $CHCl_3$): 1729 (br), 1669 cm^{-1}. λ_{max}

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(CH_3CN): 329 nm. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{23}H_{32}O_5Na$ 411.2142, found 411.2144.

*Starting Material for Compound **3** (7-Ketocholesteryl Chloride[33]).* Cholesteryl chloride (5.0 g, 12 mmol) was dissolved in a mixture of acetone (300 mL) and acetic acid (30 mL) in a round-bottom flask equipped with a stir bar and reflux condenser under N_2. The reaction mixture was treated with *N*-hydroxysuccinimide (11.2 g, 99 mmol) and $K_2Cr_2O_7$ (14.5 g, 49 mmol), and then the reaction mixture was stirred at 40 °C for 18 h. The reaction mixture was cooled to rt, quenched with aq 10 % sodium metabisulfite solution, filtered through Celite, and extracted into Et_2O. The combined organic layers were washed with saturated aq $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide 7-ketocholesteryl chloride (4.0 g, 78%) as a white solid. Mp = 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (t, J = 1.1 Hz, 1H), 3.88−3.80 (m, 1H), 2.70 (dm, J = 8.2 Hz, 2H), 2.43−2.36 (m, 1H), 2.26−2.14 (m, 2H), 2.06−1.86 (m, 4H), 1.60−1.47 (m, 5H), 1.39−1.29 (m, 4H), 1.28−1.24 (m, 2H), 1.22 (s, 3H), 1.16−1.09 (m, 4H), 1.07−0.99 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.86−0.85 (m, 6H), 0.68 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 202.2, 164.1, 126.1, 57.7, 54.7, 49.83, 49.76, 45.4, 43.0, 42.6, 39.4, 38.6, 38.03, 38.00, 36.1, 35.6, 32.7, 28.4, 27.9, 26.2. IR ν_{max} (ATR-IR): 1700 cm^{-1}. λ_{max} (CH_3CN): 321, 287 nm. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{27}H_{43}ClONa$ 441.2895, found 441.2894.

*Starting Material for Compound **4** (3β,20β-Diacetoxy-5α-pregnen-7-one[31−33]).* To a flame-dried round-bottom flask equipped with a stir bar under N_2 were added pregnenolone (4.0 g, 13 mmol) and MeOH (80 mL). The reaction mixture was treated with $NaBH_4$ (0.96 g, 25 mmol) in portions over 10 min and then stirred for an additional 2 h. The resulting white precipitate was collected by filtration and dried to provide pregn-5-ene-3β,20α-diol (3.0 g, 75%).

The pregn-5-ene-3β,20α-diol from the previous step (2.5 g, 7.9 mmol), *p*-TsOH·H_2O (48 mg, 0.24 mmol), and acetic anhydride (4 mL) were dissolved in pyridine (5 mL) under N_2. After being stirred for 1 h, the reaction mixture was heated to 95 °C and stirred for an additional 4 h. The reaction mixture was then cooled to rt and diluted with H_2O (130 mL). The white precipitate was formed and collected by filtration, washed with H_2O, and dried to provide pregn-5-en-3β,20α-diyl diacetate (2.4 g, 76%).

Pregn-5-en-3β,20α-diyl diacetate (2.4 g, 5.0 mmol) was dissolved in a mixture of acetone (300 mL) and acetic acid (30 mL) in a round-bottom flask equipped with a stir bar and reflux condenser under N_2. The reaction mixture was treated with *N*-hydroxysuccinimide (6.9 g, 60 mmol) and $K_2Cr_2O_7$ (7.1 g, 24 mmol), and then the reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was cooled to rt, quenched with 10% aq sodium metabisulfite solution, filtered through Celite, and extracted into Et_2O. The combined organic layers were washed with saturated aq $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized in MeOH to provide 3β,20α-diacetoxypregn-5-en-7-one (1.6 g, 75%) as a white solid. Mp = 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (s, 1H), 4.89−4.82 (m, 1H), 4.75−4.67 (m, 1H), 2.58−2.44 (m, 3H), 2.26−2.21 (m, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.98−1.94 (m,1H), 1.87−1.67 (m, 3H), 1.62−1.50 (m, 6H), 1.43−1.34 (m, 1H), 1.33−1.24 (m, 3H), 1.20 (s, 3H), 1.16 (d, J = 6.2 Hz, 3H), 0.65 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 201.5, 170.3, 170.2, 164.1, 126.5, 72.8, 72.1, 53.6, 49.8, 49.3, 45.2, 42.8, 38.3, 38.0, 37.7, 36.0, 27.3, 26.2, 25.7, 21.5, 21.2, 21.0, 19.9, 17.2, 12.4. IR ν_{max} (ATR-IR): 1730, 1672 cm^{-1}. λ_{max} (CH_3CN): 332, 285 nm. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{25}H_{36}O_5Na$ 439.2455, found 439.2453.

*Starting Material for Compound **5** (17β-Trifluoroacetamido-3β-acetoxyandrost-5-en-7-one[34−38]).* To a flame-dried three-neck round-bottom flask equipped with a stir bar under N_2 were added prasterone (5.0 g, 17 mmol), acetic anhydride (10 mL), and pyridine (10 mL). The reaction mixture was stirred for 21 h and then diluted with CH_2Cl_2 (20 mL). The organic layer was washed with 1.0 M HCl, saturated aq $NaHCO_3$, and H_2O. The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide prasterone acetate (5.2 g, 90%) as a white solid.

Prasterone acetate (5.2 g, 16 mmol) from the previous step and NH_2OH·HCl (4.3 g, 62 mmol) were dissolved in pyridine (75 mL) under N_2. After being stirred for 16 h, the reaction mixture was quenched with H_2O, extracted into EtOAc, dried over $MgSO_4$, filtered through Celite, and concentrated. The crude product (5.1 g, 95%) was used without further purification.

To a flame-dried round-bottom flask equipped with a stir bar were added 3β-acetoxyandrost-5-en-17-one oxime (6.2 g, 18 mmol), MoO_3 (5.2 g, 54 mmol), MeOH (250 mL), and THF (100 mL). The reaction mixture was cooled to 0 °C, and $NaBH_4$ (6.8 g, 179 mmol) was added portionwise over 30 min. The reaction mixture slowly warmed to rt and stirred for 30 min. Then, KOH (7.5 g) in H_2O (40 mL) was added, and the flask was stored at 0 °C for 14 h. The crude mixture was filtered through Celite, and the filtrate was concentrated to 50 mL. The mixture was poured into H_2O, extracted into CH_2Cl_2, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized in EtOAc and hexanes to provide 17β-aminoandrost-5-en-3β-ol (2.6 g, 51%)

To a flame-dried round-bottom flask equipped with a stir bar were added 17β-aminoandrost-5-en-3β-ol (4.5 g, 16 mmol), Et_3N (2.2 mL, 16 mmol), and MeOH (45 mL). The reaction mixture stirred for 5 min, and ethyl trifluoroacetate was then added dropwise (2.4 mL, 20 mmol). After 20 h, the reaction mixture was concentrated, acidified with 1.0 M HCl, extracted into CH_2Cl_2, dried over $MgSO_4$, and concentrated. The crude residue was recrystallized in EtOAc and hexanes to provide 17β-trifluoroacetamidoandrost-5-en-3β-ol (3.9 g, 60%).

To a flame-dried round-bottom flask equipped with a stir bar were added 17β-trifluoroacetamidoandrost-5-en-3β-ol (2.3 g, 6.0 mmol), acetic anhydride (2 mL), and pyridine (2 mL). After the reaction mixture was stirred for 36 h at rt, CH_2Cl_2 (20 mL) was added and the mixture transferred to a separatory funnel. The mixture was then washed with 1.0 M HCl, saturated aq $NaHCO_3$, and H_2O. The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide 3β-acetoxy-17β-acetylamino-androst-5-ene (2.3 g, 90%).

To a flame-dried round-bottom flask equipped with a stir bar and reflux condenser were added 3β-acetoxy-17β-acetylamino-androst-5-ene (1.4 g, 3.1 mmol), CuI (0.41 g, 2.1 mmol), TBAB (0.12 g, 0.38 mmol), 70% *t*-BuOOH in H_2O (2.8 mL, 32 mmol), and CH_2Cl_2 (15 mL) under N_2. The reaction mixture was heated to reflux for 20 h (additional 70% *t*-BuOOH in H_2O (2.8 mL, 32 mmol) was added at 1.5 and 3 h marks). The reaction mixture was quenched with 1.0 M HCl, washed with 1.0 M $NaHSO_4$, dried over $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide 17β-trifluoroacetamido-3β-acetoxyandrost-5-en-7-one (0.8 g, 62%) as a white solid. Mp = 238−241 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.01 (d, J = 7.4 Hz, 1H), 5.73 (s, 1H), 4.76−4.68 (m, 1H), 3.93 (q, J = 9.2 Hz, 1H), 2.61−2.44 (m, 3H), 2.29−2.21 (m, 2H), 2.05 (s, 3H), 2.03−1.96 (m, 2H), 1.75−1.65 (m, 4H), 1.52−1.45 (m, 3H), 1.33−1.26 (m, 3H), 1.22 (s, 3H), 0.75 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.8, 170.2, 164.6, 157.2 (q, J = 36.7 Hz), 126.3, 115.6 (q, J = 288.3 Hz), 71.7, 58.6, 49.6, 46.4, 45.2, 44.1, 38.3, 37.7, 35.9, 35.7, 28.1, 27.2, 25.7, 21.2, 20.6, 17.2, 11.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −75.3 (s, 3F). IR ν_{max} (ATR-IR): 3350, 1728, 1682 cm^{-1}. λ_{max} (CH_3CN): 322, 280 nm. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{23}H_{30}F_3NO_4Na$ 464.2019, found 464.2017.

*Starting Material for Compound **6** (Methyl 3β-Acetoxy-7-oxo-5-etienate[39−41,33]).* In a three-neck round-bottom flask equipped with a stir bar, NaOH (8.3 g, 207 mmol) was dissolved in H_2O (70 mL) and cooled to −5 °C. To this solution was then slowly added Br_2 (2.7 mL, 52 mmol). The ice-cold solution was diluted with 1,4-dioxane (50 mL), and was kept at 0 °C. Meanwhile, to a three-neck round-bottom flask equipped with a stir bar and thermometer were added 5-pregnen-3β-ol-20-one (5.0 g, 16 mmol), 1,4-dioxane (220 mL), and H_2O (70

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mL). The reaction mixture was cooled to 0 °C, and the cold NaOBr solution was added while keeping the internal temperature below 10 °C. After the reaction mixture was stirred for 3 h, Na_2SO_4 (3.0 g) in H_2O (20 mL) was added, and the crude mixture was then heated to reflux for 30 min. The reaction mixture was acidified with concentrated HCl (10 mL) while still hot and was stored at 5 °C for 14 h. The crystallized etienic acid was collected via filtration.

The etienic acid (4.2 g, 13.2 mmol) from the previous step and acetic anhydride (60 mL) were added to a round-bottom flask under N_2. The reaction mixture was heated to reflux for 3 h, acetic acid (8 mL) and H_2O (15 mL) were then added to the hot mixture. Upon cooling, the precipitate of 3β-acetoxyetienic acid was collected via filtration, and washed successively with H_2O and minimal amount of Et_2O.

To a flame-dried round-bottom equipped with a stir bar under N_2 were added 3β-acetoxyetienic acid (1.5 g, 4.2 mmol), K_2CO_3 (1.0 g, 7.1 mmol), and DMF (20 mL). The reaction mixture was stirred for 30 min at rt. Iodomethane (0.49 mL, 8.4 mmol) was then added, and the reaction mixture was stirred for 18 h. At this point, TLC indicated the complete consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2, transferred to separatory funnel, and washed successively with H_2O, 1.0 M HCl, saturated aq NH_4Cl, and brine. The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated, and the crude product (1.5 g, 96%) was used without a further purification.

The crude product from the previous step was dissolved in a mixture of acetone (200 mL) and acetic acid (20 mL) in a round-bottom flask equipped with a stir bar and reflux condenser under N_2. The reaction mixture was treated with *N*-hydroxysuccinimide (3.7 g, 32 mmol) and $K_2Cr_2O_7$ (4.7 g, 16 mmol), and then the reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was cooled to rt, quenched with 10% aq sodium metabisulfite solution, filtered through Celite, and extracted into Et_2O. The combined organic layers were washed with saturated aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide methyl 3β-acetoxy-7-oxo-5-etienate (1.2 g, 75%) as white solid. Mp = 185−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (d, J = 1.8 Hz, 1H), 4.75−4.67 (m, 1H), 3.67 (s, 3H), 2.59−2.43 (m, 3H), 2.32 (t, J = 9.5 Hz, 1H), 2.28−2.22 (m, 1H), 2.18−2.08 (m, 1H), 2.05 (s, 3H), 2.05−1.95 (m, 3H), 1.92−1.82 (m, 1H), 1.74−1.63 (m, 2H), 1.60−1.51 (m, 2H), 1.49−1.38 (m, 2H), 1.32−1.24 (m, 2H), 1.21 (s, 3H), 0.68 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 200.7, 174.0, 169.8, 164.0, 126.1, 71.8, 53.7, 50.9, 49.4, 49.1, 45.1, 44.1, 38.1, 37.5, 36.8, 35.7, 27.0, 26.2, 23.7, 20.9, 20.7, 17.0, 13.1. IR ν_{max} (ATR-IR): 1720 (br), 1686 cm^{-1}. λ_{max} (CH_3CN): 326, 277 nm. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{23}H_{32}O_5Na$ 411.2142, found 411.2140.

Starting Material for Compound ***7*** *(4,4-Dimethyl-5-pregnen-3,7,20-trione*[42,43]*).* To a flame-dried three-neck round-bottom equipped with a stir bar and reflux condenser under N_2 were added progesterone (6.0 g, 19 mmol) and benzene (160 mL). The reaction mixture was stirred and heated to reflux. A solution of KOtBu (6.4 g, 57 mmol) in *t*-BuOH (74 mL) was added dropwise, immediately followed by a solution of iodomethane (24 mL, 382 mmol) in benzene (120 mL); the reaction mixture was stirred at reflux for 10 min and then cooled to rt. The reaction mixture was quenched with H_2O (5.3 mL), diluted with Et_2O, filtered through Celite, and concentrated. The crude residue was recrystallized from MeOH three times to provide 4,4-dimethyl-5-pregnen-3,20-dione (3.9 g, 62%).

To a flame-dried three-neck round-bottom equipped with a stir bar and reflux condenser under N_2 were added CrO_3 (0.035 g, 0.35 mmol) and CH_2Cl_2 (55 mL), followed by a 5−6 M solution of *t*-BuOOH in decane (9.8 mL, 49 mmol). The product from the previous step, 4,4-dimethyl-5-pregnen-3,20-dione (2.4 g, 7.0 mmol), was then added as a solution in CH_2Cl_2 (25 mL). The reaction mixture was stirred at rt for 14 h, then filtered through neutral alumina and concentrated. The crude residue was purified via gradient column chromatography eluting with EtOAc/hexanes to provide 4,4-dimethyl-5-pregnen-3,7,20-trione (1.4 g, 55%) as a beige solid. Mp = 194−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (s, 1H), 2.53−2.38 (m, 2H), 2.36−2.28 (m, 2H), 2.19−2.13 (m, 1H), 2.03−1.90 (m, 3H), 1.96 (s, 3H), 1.72−1.66 (m, 1H), 1.64−1.51 (m, 3H), 1.45−1.35 (m, 1H), 1.33−1.19 (m, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 0.92 (s, 3H), 0.49 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 212.1, 208.8, 200.5, 173.8, 123.9, 61.7, 49.8, 49.0, 48.6, 44.2, 44.0, 38.4, 37.3, 32.7, 31.1, 30.6, 28.6, 26.0, 25.7, 23.2, 21.1, 16.1, 12.9. IR ν_{max} (CaF_2, $CHCl_3$): 1704 (br), 1666 cm^{-1}. λ_{max} (CH_3CN): 334, 288 nm. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{23}H_{32}O_3Na$ 379.2244, found 379.2242.

Starting Material for Compound ***8*** *(3-Methyl-2-cholesten-1-one*[44,45]*).* To a flame-dried three-neck round-bottom equipped with a stir bar and reflux condenser under N_2 were added $Pd(TFA)_2$ (0.42 g, 1.3 mmol), a suspension of 5α-cholestan-3-one (9.7 g, 25.0 mmol) in AcOH (125 mL), and DMSO (0.18 mL, 2.5 mmol). The reaction mixture was stirred, and the N_2 atmosphere was replaced with an O_2 balloon. The reaction mixture was then heated to 80 °C for 16 h. Upon cooling, the reaction mixture was neutralized with saturated aq $NaHCO_3$ and extracted into $CHCl_3$. The combined organic layers were dried with $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via gradient column chromatography eluting with hexanes to 15:85 EtOAc/hexanes to provide 1-cholesten-3-one (8.7 g, 90%).

The product from the previous step, 1-cholesten-3-one (2.1 g, 5.5 mmol), was added to a flame-dried three-neck round-bottom equipped with a stir bar and reflux condenser under N_2, followed by Et_2O (25 mL). The reaction mixture was stirred and cooled to 0 °C. A 1.6 M solution of methyllithium in Et_2O (14 mL, 22 mmol) was added dropwise while stirring. After addition, the reaction mixture was stirred for 1 h and allowed to gradually warm to rt. The reaction mixture subsequently was cooled to 0 °C and quenched with saturated aq NH_4Cl slowly while stirring. The organic layer was separated and washed with H_2O and brine, then dried with $MgSO_4$, filtered through Celite, and concentrated in a round-bottom flask. To the crude reaction mixture were added a stir bar, pyridinium dichromate (5.0 g, 13 mmol), and CH_2Cl_2 (75 mL) under N_2. The reaction mixture was stirred at rt for 16 h, diluted with Et_2O, filtered through a pad of Celite and silica gel, and then concentrated. The crude residue was purified via gradient column chromatography eluting with hexanes to 25:75 EtOAc/hexanes to provide 3-methyl-2-cholesten-1-one (1.2 g, 55%) as a white solid. Mp = 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57 (s, 1H), 2.44−2.35 (m, 1H), 2.09 (dd, J = 18.8, 11.1 Hz, 1H), 1.98−1.87 (m, 2H), 1.79 (s, 3H), 1.76−1.69 (m, 2H), 1.58−1.35 (m, 5H), 1.32−1.14 (m, 9H), 1.11−0.99 (m, 6H), 0.97−0.92 (m, 1H), 0.96 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.62 (s, 3H). ^{13}C{ ^{1}H} NMR (100 MHz, $CDCl_3$): δ 205.9, 155.9, 125.5, 56.3, 47.4, 45.9, 42.9, 42.4, 40.1, 39.4, 36.6, 36.1, 36.0, 35.7, 30.6, 27.99, 27.97, 27.8, 24.1, 23.8, 23.4, 23.0, 22.7, 22.4, 18.5, 12.2, 10.5. IR ν_{max} (CaF_2, $CHCl_3$): 1663 cm-1. λ_{max} (CH_3CN): 331 nm. HRMS (ESI-FTICR-MS) m/z: [M + Na]$^+$ calcd for $C_{28}H_{46}ONa$ 421.3441, found 421.3438.

Starting Material for Compound ***9*** *(2-Benzylprogesterone*[46]*).* To a flame-dried three-neck round-bottom flask equipped with a stir bar and reflux condenser under N_2 were added LiBr (1.9 g, 22 mmol), diisopropylamine (3.2 mL, 23 mmol), and THF (50 mL). The reaction mixture was cooled to −20 °C and then slowly treated with *n*-BuLi (14.4 mL, 23 mmol, 1.6 M in hexanes) and stirred for 30 min. The reaction mixture was cooled to −78 °C, and then progesterone (6.3 g, 20 mmol) in THF (15 mL) was added dropwise and the mixture stirred for an additional 30 min. Subsequently, benzyl bromide (4.8 mL, 40 mmol) dissolved in THF (5.0 mL) was added dropwise, the reaction mixture was slowly warmed to rt, and stirred for 12 h. Then, the reaction was quenched with 1.0 M HCl, extracted into Et_2O (×3), the combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via column chromatography on silica gel eluting with EtOAc/hexanes to provide 2-benzylprogesterone (6.2 g, 78%) as a white solid. Mp = 142−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.27 (m, 2H), 7.22−7.16 (m, 3H), 5.75 (d, J = 1.6 Hz, 1H), 3.46 (dd, J = 14.1, 3.8 Hz, 1H), 2.65−2.57 (m, 1H), 2.53−2.42 (m, 2H), 2.39−2.25 (m, 2H),

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2.21−2.12 (m, 1H), 2.1 (s, 3H), 2.03−1.99 (m, 1H), 1.95−1.90 (m, 1H),1.87−1.81 (m, 1H), 1.74−1.62 (m, 2H), 1.55−1.45 (m, 2H),1.37−1.20 (m, 4H), 1.16−1.10 (m, 1H), 1.09 (2, 3H), 1.05−0.87 (m, 2H), 0.61 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 209.1, 200.0, 169.7, 140.2, 129.0, 128.3, 125.9, 123. 5, 63.4, 55.9, 53.9, 43.8, 43.6, 41.3, 39.0, 38.5, 35.3, 35.0, 32.3, 31.7, 31.4, 24.3, 22.7, 20.8, 17.3, 13.2. IR ν_{max} (ATR-IR): 1710, 1686 cm^{-1}. λ_{max} (CH_3CN): 293 nm. HRMS (ESI-FTICR-MS) *m*/*z*: $[M + Na]^+$ calcd for $C_{28}H_{36}O_2Na$ 427.2608, found 427.2606.

Starting Material for Compound **10** *(3β-Acetoxy-D-homo-5α-androst-16-en-17a-one*[47,48]*).* Prasterone acetate (5.0 g, 15 mmol) was dissolved in EtOH (150 mL) and treated with KCN (31.5 g, 484 mmol) while stirring. The reaction mixture was cooled to 0 °C, and AcOH (35 mL) was added dropwise; the reaction mixture was stirred for 1 h. The reaction mixture was stirred for an additional 2 h at rt and then quenched with H_2O. The white precipitate was collected by filtration, washed with H_2O, washed with 2% aq AcOH, and then dried. The crude residue (4.8 g, 12 mmol), PtO_2 (1.0 g), and AcOH (150 mL) were shaken under H_2 at 40 psi in a Parr apparatus for 48 h. The solution was filtered through Celite, concentrated, and diluted with water (80 mL). Neutral impurities were removed by extracting into Et_2O. The aqueous layer was then transferred to a round-bottom flask, along with AcOH (10 mL), and cooled to 0 °C. Then, $NaNO_2$ (2.4 g, 35 mmol) dissolved in water (8 mL) was added to the reaction mixture, which was then stirred for 2 h at 0 °C. The reaction mixture was warmed to rt and stirred for additional 16 h. The precipitated white solid was collected via filtration, washed with H_2O, and dried. The crude residue was purified via column chromatography eluting with EtOAc/hexanes to provide 3β-acetoxy-D-homo-5α-androstan-17a-one (2.4 g, 56%).

To a flame-dried three-neck round-bottom equipped with a stir bar and reflux condenser under N_2 were added 3β-acetoxy-D-homo-5α-androst-17a-one (1.0 g, 2.9 mmol) and benzeneseleninic acid anhydride (2.1 g, 5.8 mmol). Anhydrous chlorobenzene (12 mL) was added via syringe under N_2 atmosphere, and the reaction mixture was stirred and heated to reflux for 2.5 h. The reaction mixture was quenched with saturated aq $NaHCO_3$ and transferred to a separatory funnel. The crude mixture was extracted into EtOAc, and the combined organic layers were washed with H_2O and brine. The crude mixture was dried with $MgSO_4$, filtered through Celite, and concentrated. The crude residue was purified via column chromatography on silica gel eluting with 20:80 EtOAc/hexanes to provide 3β-acetoxy-D-homo-5α-androst-16-en-17a-one (0.9 g, 90%) as a white solid. Mp = 144−146 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 6.79−6.75 (m, 1H), 5.82−5.79 (m, 1H), 4.64−4.55 (m, 1H), 2.36 (dt, *J* = 19.4, 4.9 Hz, 1H), 1.96−1.83 (m, 2H), 1.93 (s, 3H), 1.80−1.67 (m, 3H), 1.60−1.52 (m, 2H), 1.50−1.36 (m, 3H), 1.32−1.03 (m, 6H), 0.97−0.89 (m, 1H), 0.92 (s, 3H), 0.85−0.76 (m, 1H), 0.74 (s, 3H), 0.65−0.59 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 205.3, 170.3, 147.6, 127.3, 73.2, 52.7, 46.5, 44.3, 43.7, 36.2, 35.30, 35.29, 33.6, 32.0, 30.3, 28.1, 27.10, 27.07, 21.2, 19.8, 15.5, 11.9. IR ν_{max} (CaF_2, $CHCl_3$): 1722, 1667 cm^{-1}. λ_{max} (CH_3CN): 335 nm. HRMS (FTMS) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{32}O_3Na$ 367.2244, found 367.2241.

Starting Material for Compound **11** *(16-Dehydroprogesterone*[49]*).* To a flame-dried three-neck round-bottom flask equipped with a stir bar and reflux condenser under N_2 were added 16α,17-epoxyprogesterone (2.0 g, 6.0 mmol), zinc−copper couple (5.0 g), and EtOH (30 mL). The reaction mixture was heated to reflux and stirred for 12 h. The crude mixture was then cooled to rt and filtered. The filtrate was transferred to a separatory funnel, washed with H_2O, 1.0 M HCl, and brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by gradient column chromatography on silica gel eluting with EtOAc/hexanes to provide 16-dehydroprogesterone (1.5 g, 80%) as a white solid. Mp = 178−180 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 6.70 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.74 (brs, 1H), 2.48−2.38 (m, 3H), 2.37−2.35 (m, 1H), 2.33−2.28 (m, 2H), 2.26 (s, 3H), 2.13−2.00 (m, 2H), 1.90−1.85 (m, 1H), 1.81−1.67 (m, 2H), 1.66−1.58 (m, 2H), 1.56−1.30 (m, 2H), 1.21 (s, 3H), 1.19−1.07 (m, 1H), 1.06−0.97 (m, 1H), 0.94 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.8, 196.1, 170.5, 154.6, 143.9, 123.5, 55.2, 53.7, 45.6, 38.3, 35.1, 34.1, 33.5, 33.4, 32.3, 31.7, 31.4, 26.7, 20.3, 16.8, 15.4. IR ν_{max} (ATR-IR): 1700, 1669 cm^{-1}. λ_{max} (CH_3CN): 319 nm. HRMS (ESI-FTICR-MS) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{28}O_2Na$ 335.1982, found 335.1984.

Starting Material for Compound **12** *(Methyl 3β-Acetoxyglycyrrhetinate*[41,40]*).* To a flame-dried round-bottom equipped with a stir bar under N_2 were added 18β-glycyrrhetinic acid (2.0 g, 4.3 mmol), K_2CO_3 (1.0 g, 7.2 mmol), and DMF (20 mL). The reaction mixture was stirred for 30 min at rt. Iodomethane (0.32 mL, 5.1 mmol) was then added, and the reaction mixture was stirred for 18 h. At this point, TLC indicated the complete consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2, transferred to separatory funnel, and washed successively with H_2O, 1.0 M HCl, saturated aq NH_4Cl, and brine. The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated, and the product (2.0 g, 92%) was used without further purification.

Methyl 3β-hydroxyl-glycyrrhetinate (1.8 g, 3.7 mmol) from the previous step was dissolved in acetic anhydride and heated to reflux for 3 h. Acetic acid (4 mL) and H_2O (8 mL) were added to the hot reaction mixture, and then the reaction mixture was cooled to rt. The crystalline precipitate was collected by filtration, washed with H_2O (4 × 10 mL) and Et_2O (3 mL), and dried to provide methyl 3β-acetoxyglycyrrhetinate (1.87 g, 96%) as a white solid. Mp = 295−296 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 1H), 4.47 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.64 (s, 3H), 2.76 (dt, *J* = 13.7, 3.6 Hz, 1H), 2.31 (s, 1H), 2.06−2.01 (m, 1H), 2.00 (s, 3H), 1.98−1.93 (m, 2H), 1.91−1.85 (m, 1H), 1.82−1.74 (m, 1H), 1.71−1.51 (m, 5H), 1.48−1.34 (m, 3H), 1.32 (s, 3H), 1.28−1.22 (m, 2H), 1.17−1.14 (m, 1H), 1.11 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05−0.95 (m, 2H), 0.83 (s, 6H), 0.78−0.74 (m, 1H), 0.76 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.9, 176.8, 170.8, 169.1, 128.4, 80.5, 61.6, 54.9, 51.6, 48.3, 45.3, 43.9, 43.1, 40.9, 38.7, 37.9, 37.6, 36.8, 32.6, 31.7, 31.0, 28.4, 28.2, 27.9, 26.4, 26.3, 23.4, 23.2, 21.2, 18.6, 17.3, 16.6, 16.3. IR ν_{max} (CaF_2, $CHCl_3$): 1724 (br), 1653 cm^{-1}. λ_{max} (CH_3CN): 336 nm. HRMS (ESI-FTICR-MS) *m*/*z*: $[M + Na]^+$ calcd for $C_{33}H_{50}O_5Na$ 549.3551, found 549.3545.

Starting Material for Compound **13** *(Methyl 3β-Acetyl-11-keto-oleanolate*[41,40,33]*).* To a flame-dried round-bottom equipped with a stir bar under N_2 were added oleanolic acid (3.0 g, 6.6 mmol), K_2CO_3 (1.5 g, 11 mmol), and DMF (30 mL). The reaction mixture was stirred for 30 min at rt. Iodomethane (0.49 mL, 8.4 mmol) was then added, and the reaction mixture was stirred for 18 h. At this point, TLC indicated the complete consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2, transferred to separatory funnel, and washed successively with H_2O, 1.0 M HCl, saturated aq NH_4Cl, and brine. The organic layer was dried over $MgSO_4$, filtered through Celite, and concentrated, and the product (2.85 g, 92%) was used without further purification.

Oleanolic acid methyl ester (2.8 g, 6.0 mmol) from the previous step was dissolved in acetic anhydride, and the reaction mixture was stirred and heated to reflux for 3 h. Acetic acid (7 mL) and H_2O (12 mL) were then added to the hot reaction mixture, and then the reaction mixture was cooled to rt. The crystalline precipitate was collected by filtration, washed with H_2O (4 × 15 mL) and Et_2O (4 mL), and then dried to provide methyl 3β-acetyloleanolate (2.93 g, 96%).

Methyl 3β-acetyloleanolate (2.0 g, 3.9 mmol) from the previous step was dissolved in a mixture of acetone (200 mL) and acetic acid (20 mL) in a round-bottom flask equipped with a stir bar and condenser. The reaction mixture was treated with *N*-hydroxysuccinimide (4.49 g, 39 mmol) and $K_2Cr_2O_7$ (4.6 g, 16 mmol), then stirred at 40 °C for 48 h. The reaction mixture was cooled to rt, quenched with aq 10% sodium metabisulfite solution, filtered through Celite, and extracted into Et_2O. The combined organic layers were washed with saturated aq $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated. The crude residue was recrystallized in MeOH to provide methyl 3β-acetyl-11-keto-oleanolate (1.52 g, 74%) as a white solid. Mp = 235.5−237 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.63 (s, 1H), 4.5 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.62 (s, 3H), 3.02−2.97 (m, 1H), 2.82 (dt, *J* = 13.7, 3.6 Hz, 1H), 2.33 (s, 1H), 2.08−2.00 (m, 1H), 2.04 (s, 3H), 1.76−1.52 (m, 9H), 1.45−1.30 (m, 3H), 1.35 (s, 3H), 1.28−1.17 (m, 3H), 1.12

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(s, 3H), 1.09−1.01 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.86 (s, 6H), 0.86−0.76 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.0, 177.3, 170.8, 168.5, 127.7, 80.5, 61.5, 54.9, 51.7, 46.1, 44.9, 44.1, 43.3, 41.5, 38.6, 37.9, 37.0, 33.6, 32.74, 32.69, 31.5, 30.5, 27.9, 27.6, 23.43, 23.39, 23.3, 22.8, 21.2, 18.8, 17.2, 16.6, 16.1. IR ν_{max} (CaF_2, $CHCl_3$): 1721 (br), 1651 cm^{-1}. λ_{max} (CH_3CN): 332 nm. HRMS (ESI-FTICR-MS) m/z: $[M + Na]^+$ calcd for $C_{33}H_{50}O_5Na$ 549.3551, found 549.3545.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02807.

NMR spectra, UV−vis spectra, and microflow-reactor setups (PDF)

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Notes

The authors declare no competing financial interest.

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