Efficient Synthesis of New Steroids Possessing an Aromatic A-Ring with a 2-Hydroxy or a 2-Fluoro Substituent

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5-Fluoro-1-iodobenzocyclobutene (**7**) and 5-*tert*-butoxy-1-iodobenzocyclobutene (**8**) have been used for the synthesis of the title compounds. This strategy involves the use of an intramolecular Diels–Alder cycloaddition of *o*-xylylenes as the key step. We have shown that the introduction of a *tert*-butyl ether as a protecting group at the beginning of the synthesis, in place of the methyl ether used previously, is a judicious choice by which to obtain steroids possessing an aromatic A-ring with a 2-OH substituent. Finally, the vinyl groups of the synthesized fluoro and hydroxy steroids have been oxidized by the Wacker process in good yields. An X-ray crystal structure of the fluoro steroid **14b**, the *trans*-*anti*-*trans* ring configuration of which matches those in natural products, is reported.

Introduction

Sex hormones, estrogens, progestogens, and androgens play a major role in cell biology. Efforts to use these molecules judiciously for the treatment of cancer have resulted in a number of drugs.[1] In a previous paper in this series,[2] we reported the first successful synthesis of steroids possessing an aromatic A-ring with a 3-OH substituent, by means of a strategy in which the two central rings were constructed by means of an intramolecular Diels−Alder reaction of an intermediate *o*-xylylene.[3]

If carefully selected substituents are added to the basic skeleton of steroids, there can be considerable changes in the properties of the new compound. The 3- and 11-positions are well known to be particularly amenable to such changes.[4] The 2-position, on the other hand, has not been studied adequately from a biological point of view. Most reports relate to estrogens, particularly to the synthesis of 2-methoxyestradiol or analogues and of A-ring fluorinated estrones, due to their use as chemotherapy reagents and more recently to their role as radiolabeled compounds.[5] Thus, introduction of fluorine at position 2 in estradiol does not affect hormonal activity or binding affinities for the estrogen receptor, but does influence A-ring catabolic rates.[6] Otherwise, the major endogenous metabolite of estradiol, 2-methoxyestradiol, has significant antiangiogenic properties and in vivo antitumor activity, and also has the ability to inhibit the binding of colchicine to tubuline.[7] These findings motivated us to prepare 2-substituted steroid derivatives that might present interesting biological potential.

In this paper, we wish to report the extension of our strategy for the preparation of new steroids through the introduction of a hydroxy group or a fluorine atom at the 2-position in the aromatic A-ring. Introduction of these substituents might alter the possible in vitro and in vivo behavior of the steroid.

It was therefore hoped that intramolecular cycloaddition of *o*-xylylene would occur with good stereoselectivity to provide the carbocyclic framework of the naturally occurring A-ring aromatic steroids. In a recent paper,[2] we demonstrated that a *tert*-butyl ether[8] as protecting group was easier than a methyl ether to remove at the final step of the synthesis. It was thus interesting to use this strategy to extend this result to the preparation of steroids with a hydroxy group at C-2, which had not previously been achieved.

Results and Discussion

We therefore used the same synthetic approach to prepare steroids **14** and **16**. Firstly, using a procedure analogous to that described by Stevens and Bisacchi,[9] we efficiently prepared 5-fluoro-1-iodobenzocyclobutene (**7**) and 5-*tert*-butoxy-1-iodobenzocyclobutene (**8**). The synthetic pathway is depicted in Scheme 1.

Firstly, the synthesis of substituted benzocyclobutenones **3** or **4** involved the [2 + 2] cycloaddition of substituted benzynes to 2-methylene-1,3-dioxepane.[10] The benzynes were generated from the corresponding bromobenzenes **1** or **2** by sodium amide induced dehydrobromination in refluxing THF. Cycloaddition proceeded regioselectively with these bromobenzenes.[10] Benzocyclobutenones **3** and **4** were then quantitatively reduced with $LiAlH_4$ in diethyl ether to

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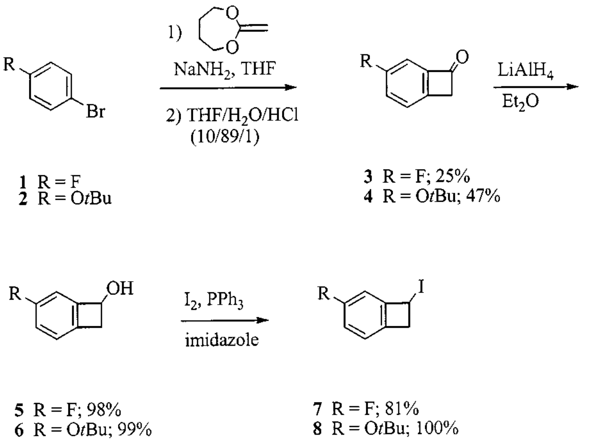
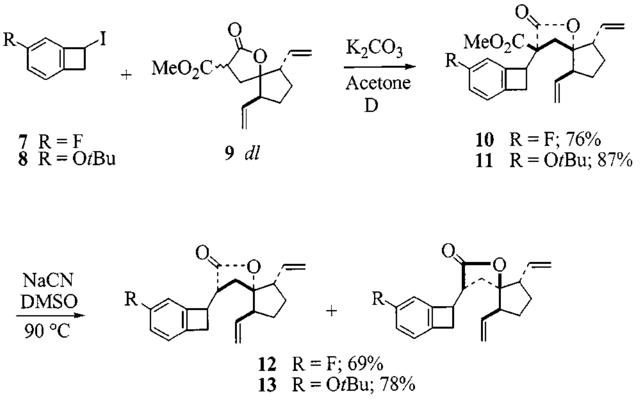


Scheme 1. Synthesis of iodobenzocyclobutenes **7** and **8**

the corresponding benzocyclobutenols **5** and **6**. Iodination of **5** and **6** with PPh_3/I_2 and imidazole gave the corresponding iodobenzocyclobutenes **7** and **8** in good yields.

The next step in our work was to obtain the steroid precursors **12** and **13** (Scheme 2). The alkylation of the activated spiro lactone **9**[11] was carried out in refluxing acetone in the presence of anhydrous potassium carbonate and benzocyclobutenes **7** or **8**. A demethoxycarbonylation according to the Krapcho procedure (NaCN/DMSO[12]), applied to compounds **10** and **11**, provided the corresponding mixture of benzocyclobutene diastereoisomers, in 69% yield for **12** and 78% yield for **13**.

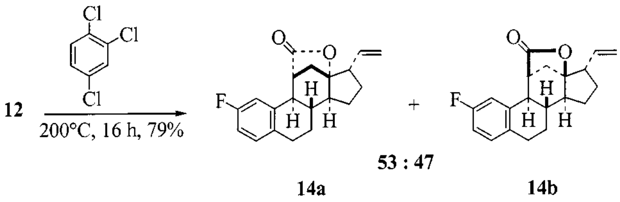


Scheme 2. Synthesis of the steroid precursors **12** and **13**

In the case of **12**, upon thermolysis at 200 °C in 1,2,4-trichlorobenzene, the cycloadducts **14a** and **14b** were produced in a 53:47 ratio and a 79% overall yield (Scheme 3). These fluoro steroids were easily separated by flash chromatography on silica gel. They had *trans-anti-cis* and *trans-anti-trans* ring fusions, respectively.

Their structures were characterized on the basis of their spectroscopic properties, including a series of NMR experiments (COSY and phase NOESY, 400 MHz), while that of **14b** was also confirmed unambiguously by single-crystal X-ray analysis[13] (Figure 1).

A similar procedure was used to introduce a hydroxy group into the 2-position of the steroid tetracyclic skeleton.



Scheme 3. Synthesis of fluoro steroids **14**

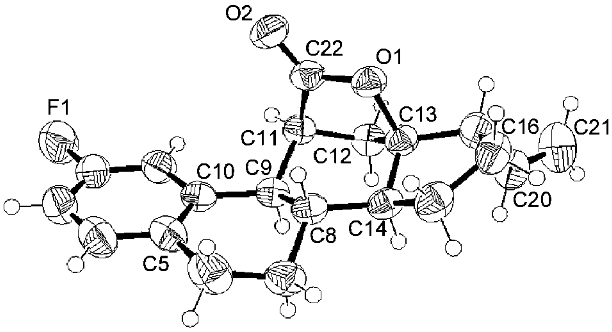
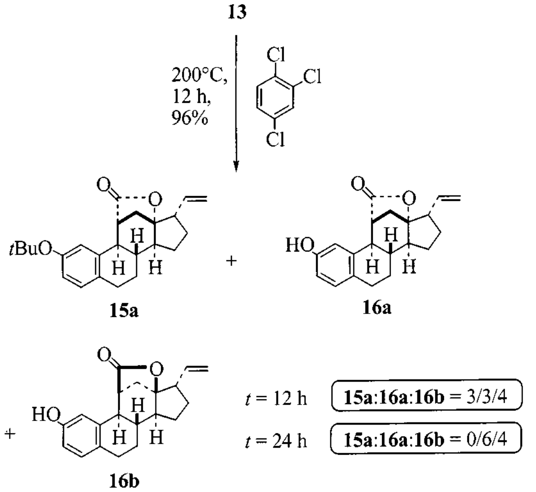


Figure 1. ORTEP drawing of the crystal structure of 2-fluoro steroid **14b**

Thus, heating of **13** at 200 °C for 12 h yielded cycloadducts **15a**, **16a**, and **16b** in 30%, 28%, 38% yields, respectively (96% in total, Scheme 4). Steroids **15a** and **16a** exhibited *trans-anti-cis* structures, while the isomer **16b** matched the *trans-anti-trans* ring-fusion configuration found in the natural products. The relative stereochemistries of these steroids were determined as for **14a−b** (COSY, NOESY experiments). Much to our surprise, the key-step thermolysis had occurred with partial removal of the *tert*-butyl ether group in the *trans-anti-cis* isomer and complete removal in the other isomer.

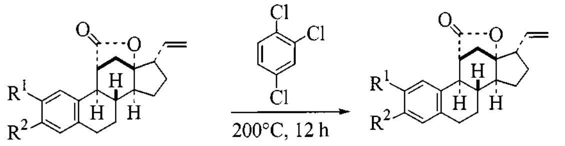


Scheme 4. Synthesis of 2-hydroxy steroids **16**

After several attempts, we concluded that this deprotection was dependent on the reaction time. The proportion of deprotected adduct increased with the time until completion after 24 h of heating, providing **16a** and **16b** in a 6:4

ratio. It was interesting to see that in only one step we thus had two reactions, the intramolecular Diels−Alder cycloaddition and the removal of the *tert*-butyl ether protecting group. Moreover, the relative configurations of six stereogenic centers were controlled during the cycloaddition process.

Otherwise, it is worth pointing out a contrast with the work we described recently;[2] the thermolysis step did not provide the corresponding deprotected cycloadduct when the *tert*-butyl ether group was positioned at C-3. Removal of the protecting group in this case required mild conditions (TFA/CH_2Cl_2, 1:1). To confirm this difference in behavior between the two steroids, several experiments were conducted directly on compounds **15a** and **17**, by heating them at 200 °C for a further period in the same solvent. While the deprotection was total and quantitative for **15a**, it failed for **17**, resulting only in the partial degradation of the molecule after 12 h (Scheme 5).



15a R^1 = O*t*Bu, R^2 = H
17 R^1 = H, R^2 = O*t*Bu
16a R^1 = OH, R^2 = H; 100%
17 (no deprotection)

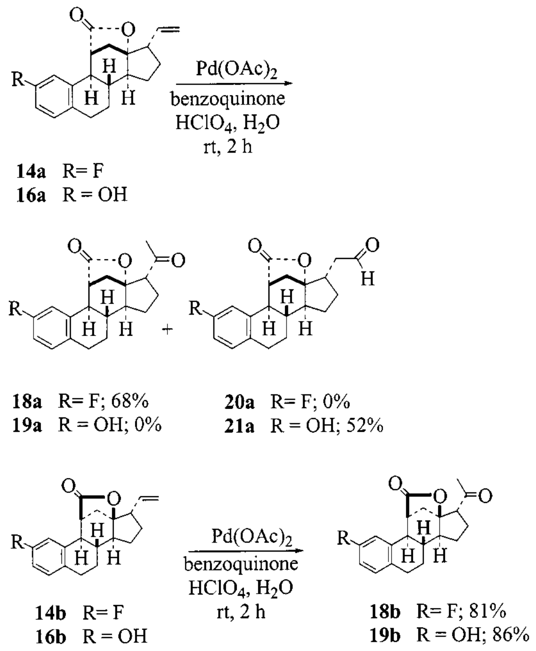
Scheme 5

Having achieved the stereoselective formation of the steroid carbocyclic framework, we turned our attention to the introduction of an acetyl group at the C-17 position. Wacker-type oxidation is well established as a synthetic organic reaction.[14] The process, palladium acetate/benzoquinone oxidation in the presence of perchloric acid,[15] was first applied to compounds **14a** and **16a**, and then to compounds **14b** and **16b**, matching the *trans*-*anti*-*trans* ring fusion of natural products (Scheme 6).

Derivatives bearing the lactone bridge on the β-face, as is the case for **14b** and **16b**, afforded the expected acetyl derivatives **18b** and **19b** in good yields.[16] On the other hand, and surprisingly, compound **14a** gave only ketone **18a** in 68% yield, while for **16a**, aldehyde **21a** was obtained as the sole product. Indeed, normally when the lactone bridge is present on the α-face, aldehydes resulting from an *anti*-Markovnikov hydroxypalladation are isolated in minor amounts.[17] This result is interpreted in terms of intramolecular coordination of the palladium atom with the oxygen atom present at the α-face. This is the first time that no traces of the corresponding ketone have been observed for this reaction, applied here for **16a**.

Conclusion

In conclusion, we have succeeded in introducing a hydroxy group and a fluoro atom onto the steroid skeleton by use of a simple synthetic sequence based on an intramolecular cycloaddition of *o*-xylylene. Studies to extend our strategy to other heterocyclic structures are currently underway and will be reported in due course.



14a R= F
16a R = OH
18a R= F; 68%
19a R = OH; 0%
20a R= F; 0%
21a R = OH; 52%
14b R= F
16b R = OH
18b R= F; 81%
19b R = OH; 86%

Scheme 6. Wacker-type oxidation of **14** and **16**

Experimental Section

General: All reactions were run under argon in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded at 200 or 300 and 50 and 75 MHz respectively, in $CDCl_3$ solutions. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded with a Perkin−Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merck 60 F_{254}) and TLC on silica gel. Dichloromethane was distilled from P_2O_5 and tetrahydrofuran (THF) from sodium/benzophenone.

(*dl*)-6,9-Divinyl-1-oxaspiro[4.4]nonan-2-one 9 was prepared according to the previously described procedure.[15]

General Procedure for the Preparation of Benzocyclobutenones 3 and 4: A mixture of bromobenzene **1** or **2** (1 equiv.), $NaNH_2$ (2 equiv.), and 2-methylene-1,3-dioxepane (2 equiv.) in THF (approximately 3 mL/mmol of bromobenzene) was stirred at reflux. The reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature and poured carefully onto crushed ice to destroy excess $NaNH_2$. The product was extracted with ether and the combined ether extracts were then washed with water and brine and dried with anhydrous $MgSO_4$. Removal of the solvent left a brown oil. Hydrolysis of the ketal was effected by stirring the brown oil in a THF/water/HCl mixture (89:10:1) until completion of the reaction (TLC). Most of the THF was removed in vacuo and the residue was extracted with ether. The combined ether extracts were then washed with water and brine and dried with anhydrous $MgSO_4$. Removal of the ether and purification by flash chromatography (petroleum ether/diethyl ether, 95:5) afforded the pure benzocyclobutenone.

5-Fluorobenzocyclobutenone (3): Yield 5.79 g (25%). IR (film): $\tilde{\nu}$ = 1737 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.89 (s, 2 H), 7.00

(dd, J = 7.8, J = 1.9, 1 H), 7.20 (ddd, J = 10.0, J = 8.1, J = 1.9 Hz, 1 H), 7.46 (dd, J = 8.1, J = 4.2, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 107.3 ($J_{C,F}$ = 22.4 Hz), 122.7 ($J_{C,F}$ = 24.6 Hz), 125.2 ($J_{C,F}$ = 9.2 Hz), 146.7 ($J_{C,F}$ = 2.3 Hz), 149.1 ($J_{C,F}$ = 6.3 Hz), 163.4 ($J_{C,F}$ = 250 Hz), 187.0. HRMS (EI+): calcd. for C_8H_5FO 136.0324, found 136.0326.

5-*tert*-Butoxybenzocyclobutenone (4): Yield 3.90 g (47%). IR (film): $\tilde{\nu}$ = 1760 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 3.83 (s, 2 H), 6.91 (d, J = 1.7 Hz, 1 H), 7.07 (dd, J = 8.0, J = 1.7, 1 H), 7.35 (d, J = 8.0 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.3, 51.5, 80.5, 117.0, 122.4, 124.8, 141.6, 152.9, 162.8, 187.0. HRMS (EI+): calcd. for $C_{12}H_{14}O_2$ 190.0994, found 190.0998.

General Procedure for the Reduction of 3 and 4: A flask equipped with a magnetic stirring bar and an argon outlet was charged with $LiAlH_4$ (1 g, 26 mmol) and anhydrous diethyl ether. The solution was cooled to −20 °C and the benzocyclobutenone (26 mmol) was then added. After completion of the reaction (TLC), it was quenched by addition of aqueous saturated NH_4Cl and extracted with ether. The extracts were dried with $MgSO_4$, filtered, and then concentrated under vacuum. The residue was chromatographed on silica gel (petroleum ether/diethyl ether, 5:5 for **5**, 7:3 for **6**).

5-Fluorobenzocyclobutenol (5): Yield 0.996 g (98%) − IR (film): $\tilde{\nu}$ = 3308 cm^{-1}, 1603, 1466. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.86 (d, J = 14.2 Hz, 1 H), 3.42 (ddd, J = 14.2, J = 4.5, J = 0.9 Hz, 1 H), 3.82 (br. s, 1 H), 5.08 (d, J = 4.5 Hz, 1 H), 6.85 (dd, J = 7.5, J = 1.9, 1 H), 6.97 (ddd, J = 8.0, J = 7.5, J = 1.9 Hz, 1 H), 7.03 (dd, J = 8.0, J = 4.6, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.9, 69.5 ($J_{C,F}$ = 2.8 Hz), 109.8 ($J_{C,F}$ = 22.4 Hz), 116.8 ($J_{C,F}$ = 24.1 Hz), 125.1 ($J_{C,F}$ = 8.8 Hz), 137.1 ($J_{C,F}$ = 2.8 Hz), 148.5 ($J_{C,F}$ = 6.9 Hz), 162.5 ($J_{C,F}$ = 244 Hz). HRMS (EI+): calcd. for C_8H_7FO 138.0481, found 138.0484.

5-*tert*-Butoxybenzocyclobutenol (6): Yield 1.005 g (99%). IR (film): $\tilde{\nu}$ = 3354 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.00 (s, 9 H), 2.60 (m, 1 H), 3.18 (m, 1 H), 4.91 (m, 1 H), 6.58 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.6, 41.2, 69.9, 78.5, 118.4, 123.9, 126.1, 136.9, 147.9, 154.1. HRMS (EI+): calcd. for $C_{12}H_{16}O_2$ 192.1150, found 192.1154.

Procedure for the Preparation of Iodobenzocyclobutenes 7 and 8: Iodine (10.14 g, 0.04 mol) was added at 0 °C to a CH_2Cl_2 solution (70 mL) containing the benzocyclobutenol (0.03 mol), imidazole (2.7 g, 0.04 mol), and PPh_3 (10.5 g, 0.04 mol). The solution was allowed to warm to room temp. during 1 h, and then washed with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The organic layer was dried with $MgSO_4$ and concentrated. The crude product was then diluted in pentane in order to precipitate the triphenylphosphane oxide. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (petroleum ether ether/diethyl ether, 7:3).

5-Fluoro-1-iodobenzocyclobutene (7): Yield 6.04 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.43 (dt, J = 14.5, J = 2.3, J = 2.3 Hz, 1 H), 3.83 (ddd, J = 14.5, J = 4.7, J = 1.9 Hz, 1 H), 5.44 (dd, J = 4.7, J = 2.3, 1 H), 6.80 (d, J = 6.9 Hz, 1 H), 6.97 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4 ($J_{C,F}$ = 3.4 Hz), 44.0, 110.2 ($J_{C,F}$ = 23.0 Hz), 117.2 ($J_{C,F}$ = 24.1 Hz), 124.9 ($J_{C,F}$ = 9.2 Hz), 136.8 ($J_{C,F}$ = 2.9 Hz), 148.3 ($J_{C,F}$ = 8.1 Hz), 163.0 ($J_{C,F}$ = 245.0 Hz). HRMS (EI+): calcd. for C_8H_6FI 247.9498, found 247.9500.

5-*tert*-Butoxy-1-iodobenzocyclobutene (8): Yield 9.02 g (100%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 3.34 (dd, J = 14.4, J = 2.2, 1 H), 3.73 (dd, J = 14.4, J = 4.5, 1 H), 5.35 (dd, J = 4.5, J = 2.2, 1 H), 6.65 (s, 1 H), 6.82 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4, 29.9, 44.6, 79.0, 119.1, 124.2, 127.1, 136.7, 147.8, 156.1. HRMS (EI+): calcd. for $C_{12}H_{15}IO$ 302.0168, found 302.0173.

General Procedure for the Alkylation of Spiro Lactone 9: K_2CO_3 (1.3 equiv., 17.4 mmol, 2.41 g) and a solution of iodobenzocyclobutene **7** or **8** (1.2 equiv., 16.1 mmol) in anhydrous acetone (161 mL, 10 mL/mmol) were added successively to a stirred solution of the spiro lactone **9** (3.35 g, 13.4 mmol) in anhydrous acetone (15 mL, 1.1 mL/mmol) under argon. The mixture was stirred for 72 h at reflux and then allowed to cool to room temperature, filtered through Celite, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether ether/diethyl ether, 9:1) to give **10** (76% from **7**) or **11** (87% from **8**) as a mixture of two diastereoisomers.

Methyl 3-(5-Fluorobenzocyclobuten-1-yl)-2-oxo-6,9-divinyl-1-oxaspiro[4,4]-nonane-3-carboxylate (10): Yield 3.79 g (76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (m, 6 H), 2.82 (m, 2 H), 3.20 (ddd, J = 14.7, J = 2.5, J = 1.3 Hz, 1 H), 3.70 (s, 3 H), 3.76 (dd, J = 14.7, J = 5.3, 1 H), 4.09 (dd, J = 5.3, J = 2.5, 1 H), 5.05 (m, 4 H), 5.68 (m, 2 H), 6.74 (dd, J = 7.6, J = 2.1, 1 H), 6.94 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 28.3, 30.6, 32.3, 45.6, 52.8, 53.0, 53.4, 57.2, 94.1, 110.4 (d, $J_{C,F}$ = 22.4 Hz), 116.1 (d, $J_{C,F}$ = 23.5 Hz), 117.3, 118.1, 124.6 (d, $J_{C,F}$ = 8.6 Hz), 135.3, 137.0, 139.0 (d, $J_{C,F}$ = 2.9 Hz), 143.8 (d, $J_{C,F}$ = 7.4 Hz), 162.6 (d, $J_{C,F}$ = 245 Hz), 170.2, 173.3. HRMS (EI+): calcd. for $C_{22}H_{23}FO_4$ 370.1580, found 370.1581.

Methyl 3-(5-*tert*-Butoxybenzocyclobuten-1-yl)-2-oxa-6,9-divinyl-1-oxaspiro[4,4]nonane-3-carboxylate (11): Yield 4.97 g (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 2.00 (m, 6 H), 2.70 (m, 2 H), 3.20 (dd, J = 14.7, J = 2.3, 1 H), 3.67 (s, 3 H), 3.73 (dd, J = 14.7, J = 5.1, 1 H), 4.04 (dd, J = 5.1, J = 2.3, 1 H), 5.03 (m, 4 H), 5.68 (m, 2 H), 6.66 (d, J = 1.8 Hz, 1 H), 6.85 (dd, J = 7.9, J = 1.8, 1 H), 6.92 (d, J = 7.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7, 28.3, 28.7, 30.3, 32.4, 45.8, 52.8, 53.4, 57.3, 78.3, 94.2, 117.6, 118.1, 118.9, 123.4, 125.6, 135.3, 137.0, 138.4, 142.7, 155.1, 170.5, 173.6. HRMS (EI+): calcd. for $C_{26}H_{32}O_5$ 424.2250, found 424.2252.

Krapcho Decarboxylation of 10 and 11 into 12 and 13: A mixture of **10** or **11** (1 mmol), DMSO (3 mL/mmol), and NaCN (148 mg, 3 mmol) was heated at 90 °C under argon for 24 h. After cooling to room temperature, the mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, filtered, and concentrated under vacuum. The residue was chromatographed on silica gel, eluted with petroleum ether ether/diethyl ether (9:1). Compounds **12** and **13** were isolated in 69% and 78% yields, respectively, as mixtures of isomers.

3-(5-Fluorobenzocyclobuten-1-yl)-6,9-divinyl-1-oxaspiro[4,4]nonan-2-one (12): Yield 0.21 g (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 7 H), 2.70 (m, 1 H), 2.92 (m, 2 H), 3.32 (m, 1 H), 3.75 (m, 1 H), 4.98 (m, 4 H), 5.60 (m, 2 H), 6.69 (m, 1 H), 6.89 (m, 1 H), 6.97 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.8, 30.2, 33.7, 42.5, 43.4, 52.5, 53.0, 94.9, 110.4 ($J_{C,F}$ = 22.3 Hz), 115.3 ($J_{C,F}$ = 23.5 Hz), 117.1, 118.2, 124.4 ($J_{C,F}$ = 9.2 Hz), 135.6 ($J_{C,F}$ = 2.3 Hz), 137.6, 138.5, 146.2 ($J_{C,F}$ = 6.8 Hz), 162.5 ($J_{C,F}$ = 244 Hz), 177.1. HRMS (EI+): calcd. for $C_{20}H_{21}FO_2$ 312.1526, found 312.1525.

3-(5-*tert*-Butoxybenzocyclobuten-1-yl)-6,9-divinyl-1-oxaspiro-[4,4]nonan-2-one (13): Yield 0.29 g (78%). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 1.28 (s, 9 H), 1.98 (m, 7 H), 2.73 (dd, J = 2.4, J = 14.1 Hz, 1 H), 2.95 (m, 2 H), 3.31 (dd, J = 5.3, J = 14.1 Hz, 1 H), 3.71 (m, 1 H), 5.05 (m, 4 H), 5.70 (m, 2 H), 6.64 (d, J = 1.7 Hz, 1 H), 6.82 (dd, J = 1.7, J = 7.7, 1 H), 6.91 (d, J = 7.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 28.6, 28.7, 29.9, 33.8, 42.2, 43.5, 53.3, 53.7, 78.1, 94.9, 117.0, 118.4, 119.7, 123.1, 124.9, 135.7, 137.6, 145.1, 146.1, 154.6, 177.8. HRMS (EI+): calcd. for $C_{24}H_{30}O_3$ 366.2195, found 366.2202.

Experimental Procedure for the Preparation of 14, 15, and 16: A solution of **12** or **13** (3 mmol) in 1,2,4-trichlorobenzene (40 mL) was stirred under argon at 200 °C. The progress of the reaction was monitored by TLC. After the mixture had cooled to room temperature, the solvent was removed under reduced pressure (0.2 Torr). The resulting oil was purified by flash chromatography on silica gel (petroleum ether ether/diethyl ether, 7:3).

(±)-(8β,9α,14α)-2-Fluoro-17α-vinylgona-1,3,5(10)-triene-11α,13α-carbolactone (14a): Yield 0.39 g (42%). M.p. 117 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (dq, J = 5.7, J = 11.9 Hz, 1 H), 1.51 (m, 4 H), 1.95 (m, 4 H), 2.11 (m, 1 H), 2.45 (m, 1 H), 2.71 (d, J = 10.9 Hz, 1 H), 2.84 (m, 2 H), 3.11 (d, J = 3.4 Hz, 1 H), 5.11 (m, 2 H), 5.90 (ddd, J = 2.3, J = 9.7, J = 17.6 Hz, 1 H), 6.83 (dt, J = 2.6, J = 8.3 Hz, 1 H), 7.01 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 28.1, 29.8, 31.6, 32.9, 39.9, 40.5, 41.3, 51.3, 52.0, 94.3, 111.2 ($J_{C,F}$ = 11.2 Hz), 113.1 ($J_{C,F}$ = 12.4 Hz), 116.5, 130.6 ($J_{C,F}$ = 8.0 Hz), 135.6, 137.5, 140.7 ($J_{C,F}$ = 6.8 Hz), 161.2 ($J_{C,F}$ = 240.0 Hz), 180.1. $C_{20}H_{21}FO_2$ (312.4): calcd. C 76.90, H 6.78; found C 76.72, H 6.66.

(±)-(8β,9α,14α)-2-Fluoro-17α-vinylgona-1,3,5(10)-triene-11β,13β-carbolactone (14b): Yield 0.35 g (37%). M.p. 126 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.60 (m, 5 H), 1.78 ($^1/_2$ AB, J = 11.7 Hz, 1 H), 2.12 (m, 3 H), 2.48 ($^1/_2$ AB, J = 5.5, J = 11.7 Hz, 1 H), 2.65 (d, J = 9.8 Hz, 1 H), 2.87 (m, 3 H), 3.36 (dd, J = 1.2, J = 5.3, J = 5.5 Hz, 1 H), 5.10 (m, 2 H), 5.65 (ddd, J = 8.1, J = 8.9, J = 17.0 Hz, 1 H), 6.82 (dt, J = 2.3, J = 8.6, 1 H), 7.01 (dd, J = 6.1, J = 8.6, 1 H), 7.11 (dd, J = 2.3, J = 10.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1, 27.6, 28.4, 29.6, 39.0, 40.8, 42.4, 44.5, 49.1, 49.5, 96.2, 112.2 ($J_{C,F}$ = 21.8 Hz), 113.5 ($J_{C,F}$ = 21.2 Hz), 116.6, 130.5 ($J_{C,F}$ = 8.0 Hz), 132.0 ($J_{C,F}$ = 3.4 Hz), 137.4, 137.7 ($J_{C,F}$ = 6.9 Hz), 161.1 ($J_{C,F}$ = 243.2 Hz), 175.8. $C_{20}H_{21}FO_2$ (312.4): calcd. C 76.90, H 6.78; found C 76.76, H 6.64.

(±)-(8β,9α,14α)-2-*tert*-Butoxy-17α-vinylgona-1,3,5(10)-triene-11α,13α-carbolactone (15a): Yield 0.33 g (30%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9 H), 1.53 (m, 3 H), 2.00 (m, 6 H), 2.11 (m, 1 H), 2.43 (dt, J = 7.4, J = 10.9 Hz, 1 H), 2.70 (d, J = 10.9 Hz, 1 H), 2.84 (m, 2 H), 3.14 (br. s, 1 H), 5.10 (m, 2 H), 5.90 (m, 1 H), 6.78 (dd, J = 2.2, J = 8.1, 1 H), 6.88 (d, J = 2.2 Hz, 1 H), 6.97 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2, 28.2, 28.8, 29.8, 31.6, 32.9, 40.1, 40.4, 41.3, 51.3, 52.1, 78.2, 94.3, 116.4, 120.1, 121.9, 127.9, 129.5, 135.7, 139.3, 153.3, 180.4. HRMS (EI+): calcd. for $C_{24}H_{30}O_3$ 366.2195, found 366.2184.

(±)-(8β,9α,14α)-2-Hydroxy-17α-vinylgona-1,3,5(10)-triene-11α,13α-carbolactone (16a): Yield 0.312 g (28%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (m, 3 H), 2.00 (m, 7 H), 2.44 (dt, J = 7.2, J = 11.5 Hz, 1 H), 2.65 (d, J = 10.4 Hz, 1 H), 2.77 (m, 2 H), 3.13 (br. s, 1 H), 5.09 (m, 2 H), 5.87 (m, 1 H), 6.16 (br. s, 1 H), 6.64 (dd, J = 2.0, J = 8.1, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 28.1, 29.8, 31.6, 33.0, 40.0, 40.7, 41.4, 51.4, 52.1, 95.0, 111.7, 113.6, 116.5, 128.3, 130.3, 135.6, 139.6, 154.1, 181.5. $C_{20}H_{22}O_3$ (310.4): calcd. C 77.39, H 7.14; found C 77.25, H 7.02.

(±)-(8β,9α,14α)-2-Hydroxy-17α-vinylgona-1,3,5(10)-triene-11β,13β-carbolactone (16b): Yield 0.42 g (38%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.61 (m, 5 H), 1.76 ($^1/_2$ AB, J = 11.5 Hz, 1 H), 2.00 (m, 2 H), 2.23 (m, 1 H), 2.46 ($^1/_2$ AB, J = 11.5, J = 4.7, 1 H), 2.62 (d, J = 9.6 Hz, 1 H), 2.83 (m, 3 H), 3.39 (d, J = 4.7 Hz, 1 H), 5.10 (m, 2 H), 5.63 (m, 1 H), 6.02 (br. s, 1 H), 6.64 (dd, J = 2.3, J = 8.1, 1 H), 6.83 (d, J = 2.3 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 28.1, 28.3, 29.6, 39.1, 41.1, 42.6, 44.6, 49.1, 49.5, 96.8, 112.3, 113.9, 116.5, 128.0, 130.1, 136.5, 137.5, 153.8, 177.1. HRMS (EI+): calcd. for $C_{20}H_{22}O_3$ 310.1569, found 310.1568.

Preparation of 18 and 19: A 25-mL, three-necked flask, equipped with an argon inlet, a magnetic stirring bar, and a septum cap, was charged with $Pd(OAc)_2$ (0.01 g, 0.045 mmol) and benzoquinone (0.044 g, 0.41 mmol). A solution of CH_3CN/H_2O (7:1) (6.4 mL) and $HClO_4$ (0.3 M, 92 µL) was added. The resulting solution was stirred at room temp. for 1 h and steroid **14** or **16** (0.45 mmol) was then added. The reaction mixture was stirred at this temperature for 2 h and hydrolyzed with an NaOH solution (30%). The aqueous phase was extracted with ether, and the organic layers were dried ($MgSO_4$) and filtered, and the solvents were evaporated. After purification by flash chromatography, products **18** (petroleum ether ether/diethyl ether, 7:3) or **19** (CH_2Cl_2/MeOH, 98:2 to 95:5) were obtained.

(±)-(8β,9α,14α)-17α-Acetyl-2-fluorogona-1,3,5(10)-triene-11α,13α-carbolactone (18a) from 14a: Yield 0.10 g (68%). IR (film): $\tilde{\nu}$ = 1778 cm^{-1}, 1712. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.85 (m, 8 H), 2.20 ($^1/_2$ AB, J = 11.7 Hz, 1 H), 2.25 (s, 3 H), 2.32 (m, 1 H), 2.74 ($^1/_2$ AB, J = 11.7 Hz, 1 H), 2.90 (m, 2 H), 3.19 (d, J = 3.8 Hz, 1 H), 3.49 (s, 1 H), 6.84 (m, 1 H), 6.97 (m, 1 H), 7.04 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1, 28.2, 28.9, 29.4, 30.6, 34.0, 40.0, 40.7, 41.1, 51.5, 58.5, 93.2, 111.3 ($J_{C,F}$ = 21.0 Hz), 113.3 ($J_{C,F}$ = 21.0 Hz), 130.6 ($J_{C,F}$ = 8.0 Hz), 132.1, 140.3, 162.9, 178.9, 204.7. $C_{20}H_{21}FO_3$ (328.3): calcd. C 73.15, H 6.45; found C 73.02, H 6.33.

(±)-(8β,9α,14α)-2-Hydroxy-17α-(2-oxoethyl)gona-1,3,5-(10)-triene-11α,13α-carbolactone (21a) from 16a: Yield 0.08 g (52%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.23 (m, 4 H), 1.90 (m, 4 H), 2.07 (d, J = 12.4 Hz, 1 H), 2.19 (dd, J = 4.2, J = 12.4 Hz, 1 H), 2.47 (dq, J = 11.1, J = 6.8, 1 H), 2.59 (dd, J = 0.6, J = 7.0, J = 18.1 Hz, 1 H), 2.67 (d, J = 10.6 Hz, 1 H), 2.78 (m, 2 H), 2.88 (dd, J = 6.8, J = 18.1 Hz, 1 H), 3.13 (d, J = 4.2 Hz, 1 H), 5.82 (br. s, 1 H), 6.64 (dd, J = 2.5, J = 8.3, 1 H), 6.77 (d, J = 2.5 Hz, 1 H), 6.92 (d, J = 8.3 Hz, 1 H), 9.81 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 28.2, 29.7, 31.6, 33.2, 39.8, 40.0, 41.2, 41.3, 44.3, 51.8, 94.3, 111.7, 113.6, 128.4, 130.4, 139.5, 154.1, 180.9, 201.4. $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.42, H 6.58.

(±)-(8β,9α,14α)-17α-Acetyl-2-fluorogona-1,3,5(10)-triene-11β,13β-carbolactone (18b) from 14b: Yield 0.12 g (81%). IR (film): $\tilde{\nu}$ = 1713 cm^{-1}, 1709. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (m, 3 H), 1.90 (m, 5 H), 2.20 ($^1/_2$ AB, J = 11.7 Hz, 1 H), 2.22 (s, 3 H), 2.46 ($^1/_2$ AB d, J = 5.4, J = 11.7 Hz, 1 H), 2.69 (d, J = 10.8 Hz, 1 H), 2.81 (m, 2 H), 3.36 (dd, J = 5.1, J = 9.5, 1 H), 3.39 (d, J = 5.4 Hz, 1 H), 6.81 (dd, J = 2.6, J = 8.3, 1 H), 6.99 (dd, J = 6.0, J = 8.3, 1 H), 7.09 (dd, J = 2.3, J = 10.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 27.7, 28.0, 28.3, 31.4, 39.0, 40.6, 42.1, 44.1, 50.1, 56.6, 94.7, 112.1 ($J_{C,F}$ = 21.4 Hz), 113.5 ($J_{C,F}$ = 21.3 Hz), 130.6 ($J_{C,F}$ = 8.0 Hz), 132.0 ($J_{C,F}$ = 2.9 Hz), 137.5 ($J_{C,F}$ = 6.9 Hz), 161.0 ($J_{C,F}$ = 43.9 Hz), 175.5, 208.7. $C_{20}H_{21}FO_3$ (328.4): calcd. C 73.15, H 6.45; found C 72.95, H 6.28.

(±)-(8β,9α,14α)-17α-Acetyl-2-hydroxygona-1,3,5(10)-triene-11β,13β-carbolactone (19b) from 16b: Yield 0.12 g (86%). IR (film):

$\tilde{\nu}$ = 1775 cm^{-1}, 1709. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (m, 3 H), 1.93 (m, 5 H), 2.14 (d, J = 11.7 Hz, 1 H), 2.22 (s, 3 H), 2.48 (dd, J = 5.3, J = 11.7 Hz, 1 H), 2.65 (d, J = 10.8 Hz, 1 H), 2.75 (m, 2 H), 3.36 (d, J = 5.3 Hz, 1 H), 3.38 (dd, J = 4.7, J = 9.4, 1 H), 6.56 (dd, J = 2.1, J = 8.2, 1 H), 6.86 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7, 27.8, 28.1, 29.2, 31.4, 39.1, 40.8, 42.3, 44.2, 50.1, 56.7, 95.2, 112.2, 114.0, 128.0, 130.2, 136.5, 153.8, 176.6, 209.0. $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.48, H 6.52.

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