5-(Trimethylstannyl)-2*H*-pyran-2-one and 3-(Trimethylstannyl)-2*H*-pyran-2-one: New 2*H*-Pyran-2-one Synthons

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5-(Trimethylstannyl)-2H-pyran-2-one (**11**) and 3-(trimethylstannyl)-2H-pyran-2-one (**30**), readily prepared from the corresponding bromo-2H-pyran-2-ones, undergo Pd(0)-catalyzed coupling reactions with a variety of enol triflates to give 5- and 3- substituted 2H-pyran-2-ones, respectively. This reaction is applicable to the enol triflates of 14β-hydroxy-17-ketosteroids, and therefore may prove useful in convergent syntheses of lucibufagins and bufadienolides.

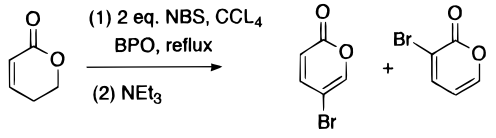
Introduction

Lucibufagins and bufadienolides,[1] powerful cardiotonic agents from invertebrates and vertebrates, respectively, pose a challenging synthetic problem, in part because both groups of compounds are characterized by the presence of a 2*H*-pyran-2-one ring at the C-17 position of a steroidal nucleus. Since the first successful bufadienolide synthesis,[2] many ingenious methods for the elaboration of steroidal 2*H*-pyran-2-ones have been described.[3] These methods have all been based on a linear strategy in which a suitable five-carbon chain is first built up at C-17 and then cyclized and dehydrogenated (if necessary) to give the desired 2*H*-pyran-2-one.[3] We now report a convergent strategy whereby an intact 2*H*-pyran-2-one ring can be joined directly to a variety of substrates, including steroids.

Discussion

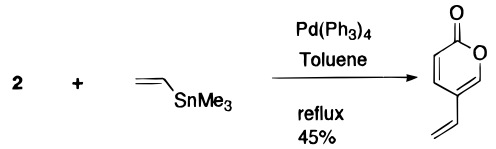
While the addition of phenyllithium or phenyl Grignard reagents to carbonyl compounds or to other appropriate substrates provides a versatile method for the joining of a benzene ring to a desired structure, these nucleophilic additions are not suitable for introducing a 2*H*-pyran-2-one moiety. The difficulty is that the 2*H*-pyran-2-one ring itself is susceptible to attack by many nucleophiles. Thus, when 5-bromo-2*H*-pyran-2-one is treated with lithium reagents (*n*-butyllithium, *sec*-butyllithium, *tert*-butyllithium, or phenyllithium) at −78 °C, the heterocyclic ring opens instead of undergoing the hoped for lithium−bromine exchange reaction. Posner *et al.* have reported similar results in their attempts to prepare 3-lithio-2*H*-pyran-2-one.[4] Nevertheless, this group did succeed in preparing an organocopper reagent from 3-bromo-2*H*-pyran-2-one. This novel reagent reacts with a selected set of organic halides, although in modest yields, giving the expected coupling products; it offers the first successful approach to the convergent synthesis of targets containing a 2*H*-pyran-2-one moiety.

Scheme 1



1 2 3

Scheme 2



4 5

We here describe two broadly applicable, closely related approaches to the synthesis of 3- and 5-substituted 2*H*-pyran-2-ones: the cross-coupling of organotin reagents with 5-bromo-2*H*-pyran-2-one or 3-bromo-2*H*-pyran-2-one and the coupling of stannylated 2*H*-pyran-2-ones with vinyl halides or enol triflates. The Pd^0-catalyzed cross-coupling of a wide variety of organotin reagents with vinyl halides and enol triflates has been intensively studied by Stille.[5] This type of reaction, catalyzed by a number of palladium-containing compounds, provides a versatile method for joining two sp^2 carbon atoms. The reaction is especially attractive because it is tolerant of a wide variety of functional groups in either of the coupling partners and because it is both stereospecific and regioselective.[5]

To explore the applicability of this methodology to the problem in hand, we prepared 5-bromo-2*H*-pyran-2-one from 5,6-dihydro-2*H*-pyran-2-one (**1**) as previously described[6] (Scheme 1).

The first organotin reagent we chose to couple with **2** was vinyltrimethyltin (**4**), prepared as previously described.[7] The coupling reaction was carried out in refluxing toluene for 24 h, catalyzed by tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$). A 45% yield of 5-vinyl-2*H*-pyran-2-one (**5**) was obtained (Scheme 2).

As a cross-conjugated triene, 5-vinyl-2*H*-pyran-2-one presents an interesting ambiguity with respect to its

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(2) Sondheimer, F.; McCrae, W.; Salmond, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 1228.

(3) Riffel, N., Master's Thesis submitted to Cornell University, 1992.

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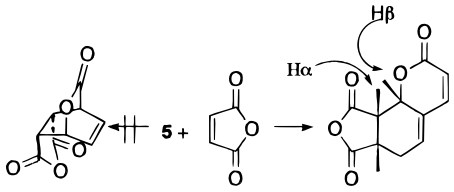
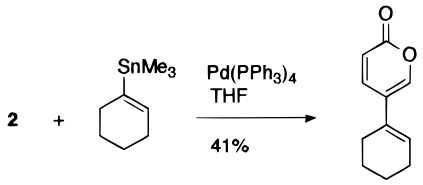
Scheme 3



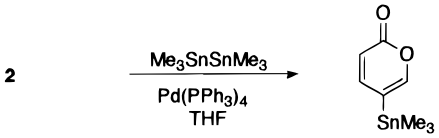
8 **6** **7**

Scheme 4

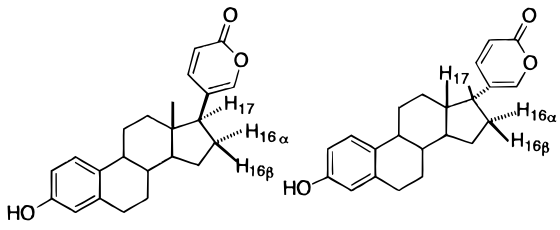


9 **10**

Scheme 5



11



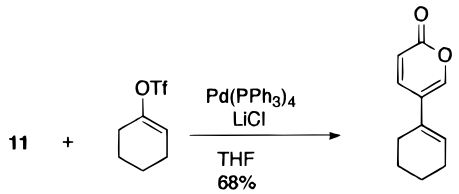
17 β isomer **17 α isomer**

$J_{H17\text{-}16\alpha}$=9.9 Hz $J_{H17\text{-}16\alpha}$=9.4 Hz

$J_{H17\text{-}16\beta}$=7.8 Hz $J_{H17\text{-}16\beta}$=1.5 Hz

Figure 1. MM2 calculated coupling constants.

Scheme 6



12 **10**

reactivity as a diene component in Diels−Alder reactions.[8] For example, **5** might react with maleic anhydride (**6**) to give either **7** or **8**. When 5-vinyl-2*H*-pyran-2-one was refluxed with maleic anhydride in benzene for 2 h, 48% of an adduct was obtained (Scheme 3). ^{1}H NMR and ultraviolet spectroscopy established that this product has structure **7** rather than **8**, with the stereochemistry determined to be that shown in Scheme 3 by a NOE experiment (31% enhancement of Hβ when Hα was irradiated).

To explore the scope of the 5-bromo-2*H*-pyran-2-one plus stannane coupling technique a bit further, we set out to prepare 5-(1-cyclohexenyl)-2*H*-pyran-2-one (**10**). For this purpose, 1-(trimethylstannyl)cyclohexene (**9**) was prepared according to a literature procedure.[9] The first trial of the coupling reaction, carried out in toluene, gave a low conversion to the desired product. Of the number of solvents surveyed, tetrahydrofuran gave the best results (Scheme 4). Nevertheless, a yield of only 41% could be obtained. This partial success encouraged us to explore the alternative strategy of preparing and coupling stannyl-2*H*-pyran-2-ones with enol triflates.

The preparation of tin-substituted benzenes was widely studied by several investigators in the 1980s. Using methods analogous to those used to prepare phenylstannanes,[10,11] we prepared 5-(trimethylstannyl)-2*H*-pyran-2-one (**11**) (Scheme 5); 5-bromo-2*H*-pyran-2-one reacted with hexamethylditin in THF, catalyzed by Pd(PPh$_3$)$_4$, to give the desired 5-(trimethylstannyl)-2*H*-pyran-2-one (**11**) in 68% yield. In order to determine whether a tin-substituted 2*H*-pyran-2-one might be a useful coupling partner, the reaction of **11** with cyclohexenyl triflate (**12**) was explored. The coupling reaction, carried out in THF and catalyzed by Pd(PPh$_3$)$_4$, gave a 68% yield of the previously characterized **10** (Scheme 6).

Comparing this result with that summarized in Scheme 3, the use of 5-(trimethylstannyl)-2*H*-pyran-2-one is clearly an improvement. In fact, 5-(trimethylstannyl)-2*H*-pyran-2-one provides a useful synthon for coupling a 2*H*-pyran-2-one ring to a variety of substrates.

Since most naturally occurring 2*H*-pyran-2-ones are also steroids, it was important to determine whether this coupling method can be applied to steroidal triflates. This is not a trivial question, since coupling at C-17 might be hampered by steric hindrance. Toward this end, Pd^0-catalyzed stannane coupling with the estrone-derived enol triflate **14** was examined. Lithium diisopropylamide was used to deprotonate the α carbon on the D-ring of *tert*-butyldimethylsilated estrone **13**, followed by quenching of the enolate with *N*-phenyltrifluoromethanesulfonimide. A 67% yield of desired enol triflate (**14**) was thus obtained. This product was then coupled with 5-(trimethylstannyl)-2*H*-pyran-2-one (**11**), using tetrakis(triphenylphosphine)palladium(0) as catalyst. The desired steroidal 2*H*-pyran-2-one **15** was formed in 68% yield; subsequent deprotection of the 3-hydroxyl group by reaction of **15** with tetrabutylammonium fluoride gave **16** in 79% yield. Selective reduction of this steroidal pyrone at atmospheric pressure with Pd/CaCO$_4$ at 0 °C for 20 min gave the desired product **17** in 80% yield (Scheme 7).

The stereochemistry at C17 in this product was confirmed by a consideration of the ^{1}H NMR coupling constants between H-17/H-16α and H-17/H-16β (Figure 1). On the basis of an MM2 calculation from PC Model, the anticipated coupling constants for the 17-α isomer are 9.4 and 1.5 Hz, while the corresponding expected coupling constants for the 17-β isomer are 9.9 and 7.8 Hz. Since the observed values of 8.8 and 9.0 Hz for the

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(9) Dueber, T. E.; Stang, R. J.; Pfeiffer, W. D.; Summerville, R. H.; Imhoff, M. A.; Schleyer, P. v. R.; Hummel, K.; Bocher, S.; Harding, C. E.; Hanack, M. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 521.
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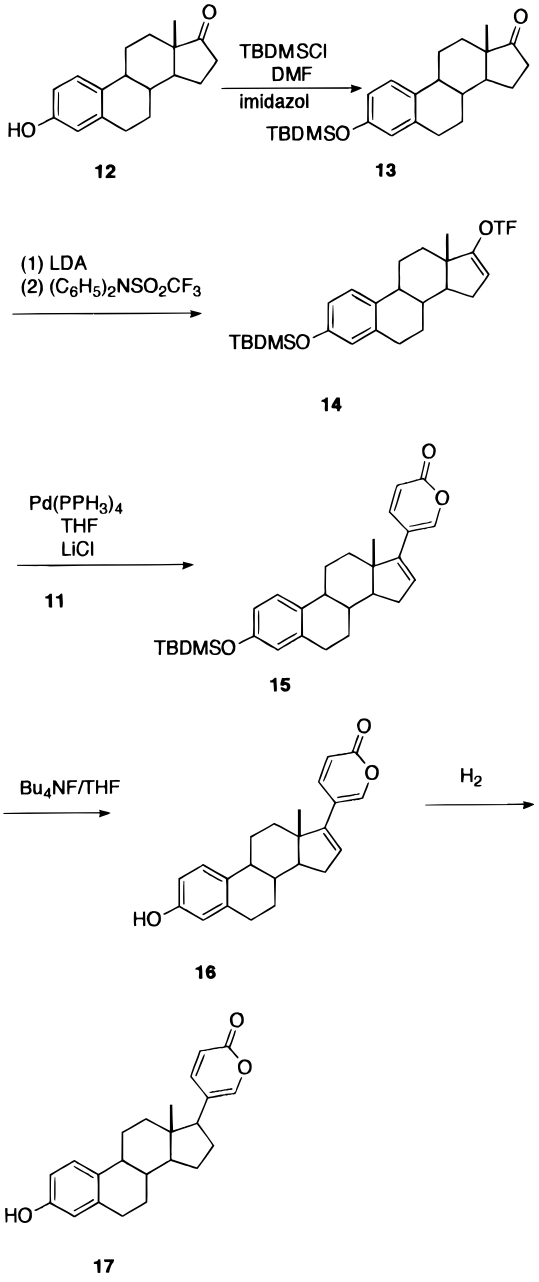
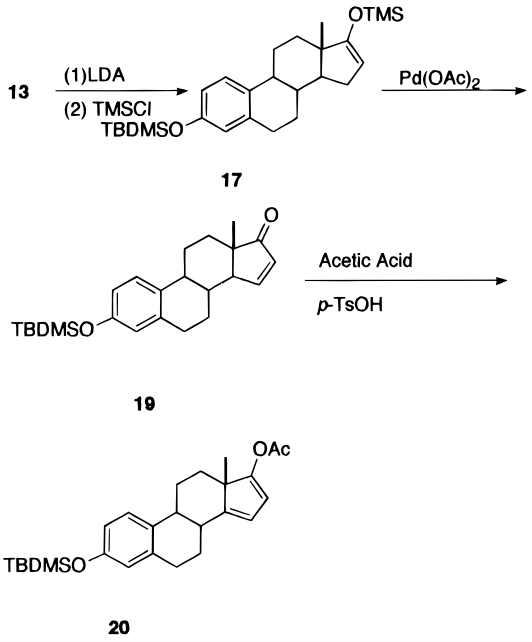
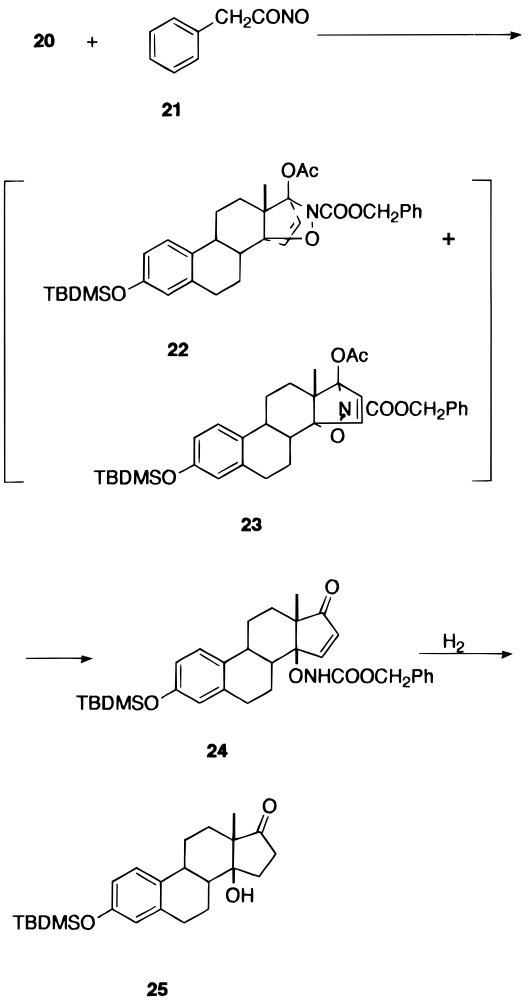
Scheme 7



Scheme 8



Scheme 9



coupling constants of H-17/H-16α and H-17/H-16β agree well with the expectations for the 17-β 2*H*-pyran-2-one configuration, the stereochemistry of **17** can be considered to be established.

Since both the bufadienolides and the lucibufagins are also characterized by a *cis* C/D ring fusion and a 14β-hydroxyl group, we examined the possibility of coupling 5-(trimethylstannyl)-2*H*-pyran-2-one (**11**) with 14β-hydroxyestrone. The enol triflate of 14β-hydroxylestrone was prepared as summarized in Schemes 8 and 9, based on close literature analogies.[12] TBDMS-protected estrone **13** was deprotonated by LDA, and the reaction mixture was quenched with chlorotrimethylsilane. The crude enol silyl ether was dissolved in benzonitrile and oxidized with 1 equiv of palladium acetate.[13] The resulting enone (**19**) was treated with acetic anhydride and a catalytic amount of *p*-toluenesulfonic acid to give the 14,16-dienyl acetate **20**. The (4 + 2)-cycloaddition between **20** and benzyl nitrosoformate (**21**), carried out in methylene chloride at 0 °C, gave the anticipated two stereoisomeric Diels−Alder products.[12] This mixture was hydrolzed in methanol for 12 h. After chromatography, a 62% yield of compound **24** was obtained. Subsequent hydrogena-

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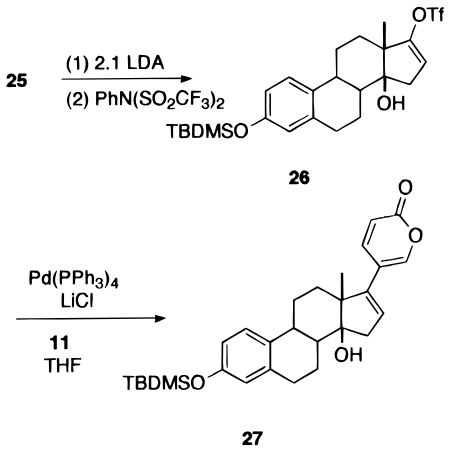
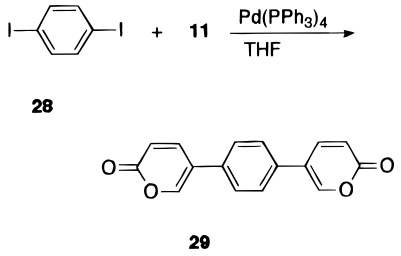
Scheme 10



Scheme 11



tion of this compound, using palladium on charcoal (5%), led to the protected 14β-hydroxylestrone **25**.

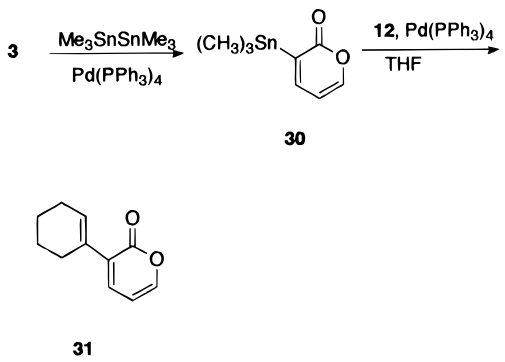
Treatment of **25** with 2.1 equiv of lithium diisopropylamide with subsequent quenching of the reaction mixture with 1.8 equiv of *N*-phenyltrifluoromethanesulfonimide gave the desired enol triflate (**26**) in 65% yield. The coupling reaction between 5-(trimethylstannyl)-2*H*-pyran-2-one and enol triflate **26** was carried out in THF with 7.0 equiv of LiCl, catalyzed by tetrakis(triphenylphosphine)palladium(0). This gave the expected product (**27**) in 61% yield (Scheme 10). With this result in hand, it appears that the stannane coupling methodology will be useful for the synthesis of natural lucibufagins and bufadienolides.

Having demonstrated that the coupling of 5-(trimethylstannyl)-2*H*-pyran-2-one with enol triflates is applicable in steroid chemistry, we turned to another interesting application of this synthon. In 1972, VanKerckhoven, Gilliams, and Stille reported a new method of making polyphenylenes *via* a chain Diels−Alder reaction between 5,5′-*p*-phenylenebis(2*H*-pyran-2-one) and 1,4-diethynylbenzene.[14] In contrast with the product obtained from earlier studies, polyphenylenes from their synthesis had number-average molecular weights of 40 000−100 000, were amorphous, and were soluble in common organic solvents in concentrations of up to 10 wt %.

Our interest was in an improved synthesis of monomer **29**, 5,5′-*p*-phenylenebis(2*H*-pyran-2-one). Toward this end, the coupling of 5-(trimethylstannyl)-2*H*-pyran-2-one with 1,4-diiodobenzene was investigated and was found to give a 68% yield of **29** (Scheme 11).

Although 3-substituted 2*H*-pyran-2-ones are not common in nature, we were curious to know whether the analogous stannane chemistry would provide a convenient route to this class of compounds as well. We therefore examined the conversion of 3-bromo-2*H*-pyran-2-one (**3**) into the corresponding trimethylstannane (**30**), using the procedure described for the preparation of **11**. This conversion proceeded smoothly, and the resulting stannane coupled readily with enol triflate **12** to give the expected 3-(1-cyclohexenyl)-2*H*-pyran-2-one (**31**) in 72% yield (Scheme 12). In summary, both 5- and- 3-substituted 2*H*-pyran-2-ones should now be readily accessible via the stannane chemistry that was pioneered by Stille and his co-workers.

Scheme 12



Experimental Section

General. Tetrahydrofuran (THF) was distilled from Na/benzophenone. Methylene chloride, benzene, and toluene were distilled from CaH_2. *N*,*N*-Dimethylformamide (DMF), methoxyethoxymethyl chloride, and diisopropylethylamine were distilled over anhydrous magnesium sulfate at 8 mmHg. Tetrakis(triphenylphosphine)palladium(0), hexamethylditin, *N*-phenyltrifluoromethanesulfonimide, estrone, *tert*-butyldimethylsilyl chloride, imidazole, benzyl *N*-hydroxycarbamate, tetraethyl periodate (Et_4IO_4), *N*-bromosuccinimide (NBS), benzoyl peroxide, methyltriphenoxyphosphonium iodide, and tetrabutylammonium fluoride were purchased from Aldrich Chemical Co. Lithium chloride was dried at 120 °C overnight and stored in a desiccator. 5-Bromo-2*H*-pyran-2-one and 3-bromo-2*H*-pyran-2-one were prepared according to the literature prcedures.[6] All reactions were carried out under the protection of Ar unless noted otherwise. TLC was performed with precoated silica gel (Baker-flex, silica gel IB2-F, 0.25 mm). Flash chromatography was carried out on silica 60 from EM Science.

5-Vinyl-2*H*-pyran-2-one (5). 5-Bromo-2*H*-pyran-2-one (0.14 g, 0.80 mmol), vinyltrimethyltin (0.19 g, 1.00 mmol), and Pd(PPh_3)$_4$ (0.03 g, 0.03 mmol) were placed in a dry 10 mL round-bottom flask together with 15 mL of toluene. The mixture was refluxed for 24 h. Upon completion of the reaction, the toluene was removed, the final crude material was partitioned between acetonitrile and hexane, and the acetonitrile layer was dried over $MgSO_4$. After the solvent was evaporated under reduced pressure, the product was purified by flash chromatography, eluting with 7:3 hexane−ether. The product **5** was obtained as a clear oil (44 mg, 45%): ^{1}H NMR (200 MHz) δ 7.58 (dd, J = 9.7, 2.8 Hz, 1 H), 7.45 (d, J = 2.5 Hz, 1 H), 6.35 (m, 2 H), 5.50 (d, J = 17.4 Hz, 1 H), 5.25 (d, J = 12.1 Hz, 1 H); ^{13}C NMR (400 MHz) δ 161.7, 149.4, 140.3, 128.4, 118.0, 116.7, 114.4; HRMS (EI) calcd for $C_7H_6O_2$ 122.0368, found 122.0369.

Diels−Alder Reaction between 5-Vinyl-2*H*-pyran-2-one and Maleic Anhydride. 5-Vinyl-2*H*-pyran-2-one (40 mg, 0.33 mmol) and maleic anhydride (33 mg, 0.33 mmol) were placed in a dry 50 mL round-bottom flask with 8 mL of benzene and refluxed. The progress of the reaction was monitored by TLC. After 2 h, the reaction was stopped and the crude product was collected by filtration. The brown solid was recrystalized from benzene, and 35 mg (48%) of pale brown solid (**7**, mp 186−187 °C) was collected: ^{1}H NMR (500 MHz, acetone) δ 7.21 (d, J = 9.5 Hz, 1 H), 6.41 (m, 1 H), 5.88 (dd, J

(14) VanKerckhoven, H.; Gilliams, Y.; Stille, J. *Macromolecules* **1972**, *5*, 541.

= 10, 1.0 Hz, 1 H), 5.50 (m, 1 H), 4.15 (dd, J = 9.5, 6.5 Hz, 1 H), 3.81 (m, 1 H), 2.89 (ddd, J = 16.5, 8.0, 1.5 Hz, 1 H), 2.58−2.52 (m, 1 H); results from proton decoupling NMR experiments and NOE experiments were consistent with the assigned structure (see the text for details); ^{13}C NMR (400 MHz, DMSO) δ 174.3, 170.3, 161.1, 140.8, 131.1, 129.8, 116.7, 73.2, 45.7, 38.1, 24.9; HRMS (EI) calcd for $C_{11}H_8O_5$ 220.0372, found 220.0372; UV λ_{max} (hexane) = 267 nm (ϵ = 8300).

5-(Trimethylstannyl)-2*H*-pyran-2-one (11). In a dry 10 mL round-bottom flask, hexamethylditin (1.19 g, 3.63 mmol), 5-bromo-2*H*-pyran-2-one (0.53 g, 3.02 mmol), and $Pd(PPh_3)_4$ (0.105 g, 0.09 mmol) were added to 4 mL of THF. The mixture was refluxed under Ar for 30 h. The reaction mixture was cooled to room temperature, the THF was evaporated under reduced pressure, and the crude material was purified by flash chromatography, eluting with 4:1 hexane−ether to obtain 0.53 g (68%) of a pale yellow oil (**11**): ^{1}H NMR (200 MHz, acetone) δ 7.48 (dd, J = 9.0, 2.0 Hz, 1 H), 7.43 (dd, J = 1.8, 1.5 Hz, 1 H), 6.24 (dd, J = 9.0, 1.4 Hz, 1 H), 0.31 (t, tin satellite, J = 55.9, 55.1 Hz, 9 H); ^{13}C NMR (300 MHz) δ 163.0, 154.5, 148.0, 117.3, 114.1, −7.5; MS (EI) *m*/*e* (relative intensity) 249 (18), 247 (15), 245 (100), 244 (33), 243 (76), 242 (28), 241 (44), 215 (26), 213 (20), 211 (11), 151 (20), 149 (15), 147 (10), 135 (19), 133 (15), 120 (10), 95 (15), 39 (18); HRMS (EI) calcd for $C_8H_{12}O_2{}^{118}$Sn 258.9853, found 258.9854.

5-(1-Cyclohexenyl)-2*H*-pyran-2-one (10). Method A. In a dry round-bottom flask, 5-bromo-2*H*-pyran-2-one (0.17g, 0.95 mmol), 1-(trimethylstannyl)cyclohexene (0.28 g, 1.14 mmol), and $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) were added to 5 mL of THF and refluxed under Ar for 36 h. The reaction mixture was cooled to room temperature and the THF was evaporated. The crude material was purified by flash chromatography, eluting with 6.5:3.5 hexane−ether to give a viscous pale yellow oil (0.069g, 41%).

Method B. 5-(Trimethylstannyl)-2*H*-pyran-2-one (0.35 g, 2.00 mmol), 1-cyclohexenyl triflate (**11**) (0.38 g, 1.67 mmol), lithium chloride (0.14 g, 11.69 mmol), and $Pd(PPh_3)_4$ (39 mg, 0.04 mmol) were placed in a 5 mL round-bottom flask together with 3 mL of THF. The mixture was refluxed under Ar for 36 h and cooled to room temperature. THF was evaporated and the crude material was purified by flash chromatography, eluting with 65:35 hexane−ether. A viscous oil (0.20 g, 68%) was obtained: ^{1}H NMR (200 MHz) δ 7.54 (dd, J = 9.9, 2.3 Hz, 1 H), 7.41 (dd, J = 1.9, 1.2 Hz, 1 H), 6.32 (dd, J = 9.9, 1.4 Hz, 1 H), 6.00 (dd, J = 3.8, 2.2 Hz, 1 H), 2.15 (m, 4 H), 1.60 (m, 4 H); ^{13}C NMR (400 MHz) δ 161.0, 146,4, 142.2, 129.4, 125.4, 121.1, 116.1, 26.1, 25.8, 22.6, 22.0; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0837; UV λ_{max} (hexane) = 316 nm (ϵ = 5500).

3-*tert*-Butyldimethylsilyl-estrone (13). In a dry round-bottom flask, estrone (0.36 g, 1.34 mmol), imidazole (0.23 g, 3.36 mmol), and *tert*-butyldimethylsilyl chloride (0.24 g, 1.62 mmol) were added to 5 mL of DMF. This DMF solution was stirred under Ar at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography, eluting with CH_2Cl_2. A white solid (0.44g, 95%) was collected: mp 172 °C; ^{1}H NMR (200 MHz) δ 7.12 (d, J = 7.9 Hz, 1 H), 6.61 (m, 2 H), 2.84 (m, 3 H), 2.06−1.45 (m, 12 H), 0.97 (s, 9 H), 0.91 (s, 3 H), 0.18 (s, 6 H); HRMS (EI) calcd for $C_{24}H_{36}O_2Si$ 384.2485, found 384.2486.

3-(*tert*-Butyldimethylsiloxy)estra-1,3,5(10),16-tetraen-17-yl Triflate (14). A flame-dried three-neck round-bottom flask was supplied with a magnetic stir bar, an additional funnel, an Ar line, diisopropylamine (0.31 mL, 2.20 mmol), and 3 mL of THF. *n*-Butyllithium (1.51 mL, 1.6 M in hexane) was added dropwise after the mixture was cooled to 0 °C. This solution was stirred for 15 min and cooled to −78 °C. A solution of **13** (0.84 g, 2.17 mmol) in 25 mL of THF was added dropwise over the course of 10 min, after which the mixture was stirred for an additional 2 h at −78 °C. *N*-Phenyltrifluoromethanesulfonimide (0.86 g, 2.42 mmol) in 10 mL of THF was added at −78 °C and the mixture was allowed to warm to room temperature overnight. The solvent was evaporated, the residue was dissolved in 50 mL of CH_2Cl_2, and the solution was washed twice with water (30 mL each time). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to give a pale yellow viscous oil. This crude material was purified by flash chromatography, eluting with hexane−ether (98.5:1.5) to yield a white solid (0.73 g, 67%): mp 69−71 °C; ^{1}H NMR (200 MHz) δ 7.08 (d, J = 8.3 Hz, 1 H), 6.59 (m, 2 H), 5.61 (m, 1 H), 2.82 (m, 3 H), 2.30−1.20 (m, 10 H), 1.00 (s, 3 H), 0.97 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (400 MHz) δ 159.3, 153.5, 137.5, 132.6, 125.8, 120.0, 117.3, 114.5, 94.7, 53.6, 45.1, 44.3, 36.6, 32.7, 29.3, 28.4, 26.8, 25.8, 25.7, 18.2, 15.4, −4.4; HRMS (EI) calcd for $C_{25}H_{35}O_4F_3SiS$ 516.1977, found 516.1976.

5-(3′-(*tert*-Butyldimethylsiloxy)estra-1′,3′,5′(10′),16′-tetraen-17′-yl)-2*H*-pyran-2-one (15). To a solution of **14** (1.25 g, 2.42 mmol) in 5 mL of THF was added $Pd(PPh_3)_4$ (56 mg, 0.05 mmol), lithium chloride (0.74 g, 17.45 mmol), and 5-(trimethylstannyl)-2*H*-pyran-2-one (**10**) (0.63 g, 2.42 mmol). This THF solution was stirred at 65 °C for 24 h. After the solution was cooled to room temperature, the solvent was evaporated and the crude material was dissolved in 40 mL of CH_2Cl_2. This solution was washed with brine twice (20 mL each time) and was dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography, eluting with hexane−ether (7:3) to give a white solid (0.71 g, 68%): mp 129−131 °C; ^{1}H NMR (300 MHz) δ 7.56 (d, J = 1.3 Hz, 1 H), 7.49 (dd, J = 7.3, 2.0 Hz, 1 H), 7.11 (d, J = 6.4 Hz, 1 H), 6.63 (dd, J = 8.2, 1.8 Hz, 1 H), 6.57 (d, J = 1.9 Hz, 1 H), 6.35 (d, J = 7.3 Hz, 1 H), 5.91 (m, 1 H), 2.95 (m, 3 H), 2.45−1.30 (m, 10 H), 0.99 (s, 9 H), 0.97 (s, 3 H), 0.20 (s, 6 H); ^{13}C NMR (400 MHz) δ 161.3, 153.4, 147.1, 146.7, 144.0, 137.7, 132.8, 128.3, 125.8, 120.0, 117.2, 116.3, 116.1, 56.5, 47.4, 44.0, 37.1, 35.4, 31.2, 29.4, 27.6, 26.4, 25.7, 18.2, 16.4, −4.4; HRMS (EI) calcd for $C_{29}H_{38}O_3Si$ 462.2590, found 462.2583.

5-(3′-Hydroxyestra-1′,3′,5′(10′),16′-tetraen-17′-yl)-2*H*-pyran-2-one (16). Compound **15** (0.11 g, 0.27 mmol) and tetrabutylammonium fluoride (0.35 mL, 1.0 M in THF) were added to 15 mL of THF in a round-bottom flask. The above solution was stirred at room temperature for 2 h. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography, eluting with hexane−ether−methanol (5.5:4.0:0.5) to yield 0.73 g (79%) of white solid: mp 237 °C (dec); ^{1}H NMR (200 MHz) δ 7.54 (dd, J = 2.4, 1.2 Hz, 1 H), 7.26 (dd, J = 10.0, 2.5 Hz, 1 H), 7.12 (d, J = 8.3 Hz, 1 H), 6.60 (m, 2 H), 6.33 (dd, J = 10.0, 1.2 Hz, 1 H), 5.89 (m, 1 H), 4.56 (s, 1 H), 2.86 (m, 3 H), 2.39−1.24 (m, 10 H), 0.95 (s, 3 H); ^{13}C NMR (400 MHz) δ 161.4, 153.4, 147.0, 146.6, 144.0, 138.1, 132.4, 128.4, 126.2, 116.3, 116.2, 115.3, 112.7, 56.5, 47.4, 43.9, 37.1, 35.4, 31.2, 29.4, 27.5, 26.5, 16.4; HRMS (EI) calcd for $C_{23}H_{24}O_3$ 348.1725, found 348.1727.

5-(3′-Hydroxyestra-1′,3′,5′(10′)-trien-17′-yl)-2*H*-pyran-2-one (17). Compound **16** (150 mg, 0.43 mmol) was dissolved in 10 mL of THF and 10 mL of methanol which contained 15 mg of Pd catalyst (5% Pd on $CaCO_3$). This solution was hydrogenated under atmospheric pressure at 0 °C until 10.5 mL of hydrogen was consumed. The crude material was filtered, concentrated, and purified by flash chromatography eluting with 10% ethyl acetate in benzene. A crop of white solid (120 mg, 80%) was collected: mp 249 °C (dec); ^{1}H NMR (400 MHz) δ 7.32 (dd, J = 9.2 Hz, 2.0 Hz, 1 H), 7.30 (d, J = 1.0 Hz, 1 H), 7.14 (d, J = 6.4 Hz, 1 H), 6.62 (dd, J = 6.4 Hz, 1.6 Hz, 1 H), 6.57 (d, J = 1.6 Hz, 1 H), 6.30 (d, J = 7.2 Hz, 1 H), 4.48 (s, 1 H), 2.83 (m, 3 H), 2.39 (dd, J = 8.0 Hz, 7.2 Hz, 1 H), 2.34−1.20 (m, 12 H), 0.60 (s, 3 H); ^{13}C NMR (400 MHz) δ 162.6, 153.8, 149.1, 145.9, 138.6, 132.8, 126.9, 118.9, 115.8, 115.7, 113.1, 55.1, 51.5, 44.7, 44.2, 39.4, 38.0, 30.0, 28.0, 26.6, 25.7, 24.3, 13.3; MS (EI) *m*/*e* (relative intensity) 41 (16), 55 (11), 66 (11), 77 (14), 79 (16), 91 (17), 105 (11), 107 (16), 115 (10), 122 (10), 131 (14), 133 (37), 144 (12), 145 (23), 146 (22), 157 (23), 158 (16), 159 (39), 160 (60), 171 (10), 172 (15), 211 (17), 213 (100), 214 (18), 228 (26), 350 (70); HRMS (EI) calcd for $C_{23}H_{26}O_3$ 350.1882, found 350.1883.

3-(*tert*-Butyldimethylsiloxy)estra-1,3,5(10),15(16)-tetraen-17-one (19). To a solution of diisopropylamine (0.60 mL, 4.3 mmol) in THF (5 mL) at 0 °C and under a nitrogen atmosphere was added dropwise a solution of *n*-butyllithium in hexane (2.9 mL, 4.7 mmol, 1.6 M). After the addition was complete, the above solution was stirred for an additional 15

min at 0 °C and then cooled to −78 °C. A solution of **13** (1.50 g, 3.5 mmol) in THF (10 mL) was added dropwise over 10 min, after which the mixture was stirred for an additional 40 min. Chlorotrimethylsilane (0.37 mL, 4.4 mmol) was injected via a syringe and then the mixture was allowed to warm to room temperature. The solvents were evaporated and the residue was dissolved in diethyl ether−methylene chloride (3:2, 80 mL). The solution was washed successively with water (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, decanted, and evaporated to give a yellowish-white solid which was immediately added to a solution of palladium(II) acetate (785 mg, 3.5 mmol) in 20 mL of benzonitrile. This solution was stirred at room temperature for 24 h, then the solvent was distilled under vacuum. The black solid was purified by flash chromatography, eluting with 20% diethyl ether in hexane to give 963 mg (77%) of white solid: ^{1}H NMR (200 Hz) δ 7.63 (dd, J = 7.0 Hz, 2.4 Hz, 1 H), 7.12 (d, J = 6.4 Hz, 1 H), 6.64 (dd, J = 6.4 Hz, 1.6 Hz, 1 H), 6.59 (d, J = 1.6 Hz, 1H), 6.09 (dd, J = 6.8 Hz, 3.0 Hz, 1 H), 2.90 (m, 3 H), 2.55−1.40 (m, 8 H), 1.10 (s, 3 H), 0.98 (s, 9 H), 0.18 (s, 6 H); HRMS (EI) calcd for $C_{24}H_{34}O_2Si$ 382.2328, found 382.2329.

3-(*tert*-Butyldimethylsiloxy)estra-1,3,5(10),14,16-pentaen-17-yl acetate (20). Into a round-bottom flask was placed **19** (383 mg, 1.0 mmol), 20 mL of acetic anhydride, and *p*-toluenesulfonic acid (80 mg). This mixture was stirred at room temperature for 20 h. The solution was concentrated under the reduced pressure and then neutralized with pyridine. This crude mixture was dissolved in diethyl ether (50 mL) which was washed successively with water (50 mL), saturated sodium bicarbonate solution (two times 50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, decanted, and evaporated to give a pale yellow oil. Purification by flash chromatography (diethyl ether−hexane 5:95) gave 305 mg (72%) of the title compound as a yellow oil: ^{1}H NMR (200 MHz) δ 7.14 (d, J = 8.3 Hz, 1 H), 6.60 (m, 2 H), 6.16 (d, J = 2.2 Hz), 5.85 (m, 1 H), 2.80 (m, 3 H), 2.38−1.12 (m, 10 H), 1.10 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (400 MHz) δ 168.1,162.4, 153.5, 151.1, 137.8, 132.2, 126.7, 120.1, 117.3, 116.2, 111.1, 50.4, 47.4, 38.5, 35.1, 29.5, 26.4, 25.7, 25.2, 21.3, 18.2, 17.9, −4.4; MS (EI) *m*/*e* (relative intensity) 43 (42), 73 (46), 75 (15), 108 (12), 163 (11), 217 (14), 273 (23), 274 (18), 286 (23), 287 (29), 325 (11), 382 (100), 424 (8); HRMS (EI) calcd for $C_{26}H_{36}O_3Si$ 424.2434, found 424.2435.

Diels−Alder Reaction between 3-(*tert*-Butyldimethylsiloxy)estra-1,3,5(10),14,16-pentaen-17-yl Acetate and Benzyl Nitrosoformate To Yield 24. To a 50 mL round-bottom flask provided with a magnetic stir bar and an additional funnel were added acetate **20** (126.7 mg, 0.30 mmol) and benzyl *N*-hydroxycarbamate (54.7 mg, 0.33 mmol) dissolved in methylene chloride (15 mL). After this solution was cooled to 0 °C, Et_4IO_4 (105 mg, 0.33 mmol) in 5 mL of methylene chloride was added dropwise to the reaction flask from the additional funnel. Two hours later, this crude material was concentrated and redissolved in 15 mL of anhydrous methanol. The above solution was refluxed under Ar for 12 h. After the solvent was evaporated, the product was purified by flash chromatography, eluting with 40% of ether in hexane, and gave a thick pale yellow oil (101.7 mg, 62%): ^{1}H NMR (200 MHz) δ 7.37−7.33 (m, 6 H), 7.00 (d, J = 8.8 Hz, 1 H), 6.80 (s, 1 H), 6.58 (dd, J = 8.3, 2.0 Hz, 1 H), 6.54 (m, 1 H), 6.28 (d, J = 6.0 Hz, 1 H), 5.13 (d, J = 21.8 Hz, 1 H), 5.02 (d, J = 21.8 Hz, 1 H), 2.79 (m, 3 H), 2.70−1.15 (m, 10 H), 1.12 (s, 3 H), 0.95 (s, 9 H), 0.15 (s, 6 H); HRMS (EI) calcd for $C_{32}H_{41}NO_5Si$ 547.2754, found 547.2750.

3-(*tert*-Butyldimethylsiloxy)-14β-hydroxyestrone (25). To a 50 mL round-bottom flask were placed the product from the above Diels−Alder reaction (191 mg, 0.35 mmol) and Pd on activated carbon (76 mg, 5%) with 15 mL of methanol. This solution was stirred at room temperature in an atmospheric pressure hydrogenator for 24 h and then filtered, and the solvent was evaporated. The crude material was purified by flash chromatography and gave 124 mg of white solid (88%): mp 167 °C−169 °C; ^{1}H NMR (400 MHz) δ 7.14 (d, J = 8.3 Hz, 1 H), 6.62 (dd, J = 8.3 Hz, 2.2 Hz, 1 H), 6.56 (d, J = 2,2 Hz, 1 H), 2.82 (m, 3 H), 2.42 (s, 1 H), 2.36−1.12 (m, 11 H), 1.14 (s, 3 H), 0.98 (s, 9 H), 0.18 (s, 6H); ^{13}C NMR (400 MHz) δ 221.2, 153.6, 137.4, 131.7, 126.5, 120.0, 117.6, 81.9, 53.4, 44.9, 40.0, 33.2, 32.1, 30.1, 26.7, 25.7, 25.6, 22.0, 18.2, 13.0, −4.4; MS (EI) *m*/*e* (relative intensity) 41 (13), 73 (22), 75 (17), 163 (15), 343-(100), 344 (31), 400 (32); HRMS (EI) calcd for $C_{24}H_{36}O_3Si$ 400.2434, found 400.2433.

3-(*tert*-Butyldimethylsiloxy)-14β-hydroxyestra-1,3,5-(10),16-tetraen-17-yl Triflate (26). A flame-dried three-neck round-bottom flask was equipped with a magnetic stir bar, an additional funnel, an Ar line, diisopropylamine (0.11 mL, 0.80 mmol), and 2 mL of THF. *n*-Butyllithium (0.50 mL, 0.80 mmol, 1.6 M in hexane) was introduced into the flask dropwise when the mixture was cooled to 0 °C. This solution was stirred for 15 min and cooled to −78 °C. A solution of **25** (153 mg, 0.38 mmol) in THF (2 mL) was added dropwise over 5 min, after which the mixture was stirred for an additional 2 h. A solution of *N*-phenyltrifluoromethanesulfonimide (287 mg, 0.80 mmol) in THF (4 mL) was injected, and the mixture was allowed to warm to room temperature in 2 h. The crude material was poured into water (20 mL) and THF was evaporated. Three portions of ether (10 mL each) were employed to extract the crude product from the aqueous solution. The ether layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% ether in hexane) was applied to purify the crude product and gave 131 mg of a thick oil (65%): ^{1}H NMR (200 MHz) δ 7.14 (d, J = 8.3 Hz, 1 H), 6.63 (dd, J = 8.3 Hz, 2.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 5.78 (dd, J = 3.1 Hz, 1.8 Hz, 1 H), 2.80−2.62 (m, 5 H), 2.53−1.20 (m, 8 H), 1.14 (s, 3 H), 0.96 (s, 9 H), 0.18 (s, 6 H); MS (EI) *m*/*e* (relative intensity) 55 (19), 57 (11), 59 (12), 69 (14), 73 (24), 75 (11), 229 (16), 231 (10), 286 (16), 287 (100), 288 (25), 379 (18), 383 (25), 399 (53), 400 (17), 475 (51), 476 (17), 532 (81); HRMS (EI) calcd for $C_{25}H_{35}O_5SSiF_3$ 532.1578, found 532.1581.

5-(3′-(*tert*-Butyldimethylsiloxy)-14′β-hydroxyestra-1′,3′,5′(10′),16′-tetraen-17′-yl)-2*H*-pyran-2-one (27). To a 50 mL round-bottom flask provided with a magnetic stir bar were added enol triflate **26** (74 mg, 0.14 mmol), 5-(trimethylstannyl)-2*H*-pyran-2-one (43 mg, 0.17 mmol), LiCl (41 mg, 0.97 mmol), and $Pd(PPh_3)_4$ (5 mg) with 4 mL of THF. This solution was purged with Ar and refluxed for 36 h. After the THF was evaporated, the crude mixture was purified by flash chromatography, eluting with 10% of acetone in benzene, and gave 40 mg of a brown solid (61%): ^{1}H NMR (200 MHz) δ 7.48 (m, 1 H), 7.41 (dd, J = 9.6 Hz, 2.6 Hz, 1 H), 7.15 (d, J = 8.3 Hz, 1 H), 6.63 (dd, J = 8.3 Hz, 2.4 Hz, 1 H), 6.58 (d, J = 2.4 Hz, 1 H), 6.36 (dd, J = 9.6 Hz, 0.9 Hz, 1 H), 5.82 (m, 1 H), 2.83 (m, 5 H), 2.69 (s, 1 H), 2.34−1.24 (m, 7 H), 1.18 (s, 3 H), 0.97 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (400 MHz) δ 161.1, 153.5, 147.6, 144.9, 144.2, 137.8, 131.6, 126.9, 125.3, 120.0, 117.5, 116.2, 116.1, 84.9, 52.5, 44.1, 40.1, 39.2, 38.8, 30.3, 25.8, 25.7, 23.5, 18.2, 16.3, −4.4; MS (EI) *m*/*e* (relative intensity) 43 (52), 44 (16), 55 (65), 56 (21), 57 (98), 59 (16), 67 (16), 69 (34), 71 (38), 73 (64), 75 (50), 77 (12), 79 (12), 81 (16), 83 (25), 85 (26), 91 (20), 95 (13), 97 (25), 105 (11), 107 (11), 111 (13), 115 (17), 128 (13), 129 (14), 145 (12), 163 (26), 173 (13), 189 (12), 191 (20), 201 (12), 203 (16), 215 (11), 217 (17), 229 (33), 230 (13), 231 (29), 260 (13), 286 (92), 287 (100), 288 (29), 421 (25), 478 (43); HRMS (EI) calcd for $C_{29}H_{38}O_4Si$ 478.2539, found 478.2539.

5,5′-*p*-Phenylenebis(2*H*-pyran-2-one) (29). 1,4-Diiodobenzene (0.11g, 0.33 mmol), 5-(trimethylstannyl)-2*H*-pyran-2-one (**11**) (0.20 g, 0.77 mmol), and $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) were placed in a 5 mL round-bottom flask together with 3 mL of THF. The mixture was refluxed for 50 h. The crude mixture was filtered to give 86 mg of a dark brown solid which was recrystalized from 1,2,4-trichlorobenzene to give 60 mg (68%) of a light brown solid: mp 307−309 °C (lit.[7] mp 308−310 °C); ^{1}H NMR (200 MHz, DMSO) δ 8.28 (dd, J = 2.7, 1.6 Hz, 2 H), 8.04 (dd, J = 9.8, 2.9 Hz, 2 H), 7.65 (s, 4 H), 6.47 (d, J = 9.8 Hz, 2 H); HRMS (EI) calcd for $C_{16}H_{10}O_4$ 266.0579, found 266.0579.

3-(Trimethylstannyl)-2*H*-pyran-2-one (30). In a dry 10 mL round-bottom flask, hexamethylditin (1.19 g, 3.63 mmol), 3-bromo-2*H*-pyran-2-one (0.53 g, 3.02 mmol), and $Pd(PPh_3)_4$ (0.105 g, 0.09 mmol) were added to 4 mL of THF. The mixture was refluxed for 32 h. After the reaction mixture was cooled

to room temperature, the THF was evaporated under reduced pressure, and the crude material was purified by flash chromatography, eluting with 7:3 hexane−ether to yield 0.57 g (73%) of yellow oil (**30**): ^{1}H NMR (200 MHz) δ 7.44 (dd, J = 5.2, 2.3 Hz, 1 H), 7.38 (dd, J = 6.0, 2.3 Hz, 1 H), 6.15 (dd, J = 6.0, 5.2 Hz, 1 H), 0.28 (t, tin satellite, J = 59.6, 59.9 Hz, 9 H); ^{13}C NMR (400 MHz) δ 164.7, 151.8, 150.6, 132.6, 106.7, −9.6; MS (EI) *m*/*e* (relative intensity) 249 (16), 247 (13), 245 (100), 244 (29), 243 (70), 242 (27), 241 (46), 215 (28), 213 (22), 211 (12), 165 (15), 163 (13), 161 (13), 159 (13), 157 (11), 151 (16), 149 (14), 135 (23), 133 (18), 131 (12), 120 (15), 118 (11), 95 (18), 39 (26); HRMS (FAB) calcd for $C_8H_{12}O_2{}^{119}Sn$ 258.9870, found 258.9929.

3-(1-Cyclohexenyl)-2*H*-pyran-2-one (31). Into a dry 5 mL round-bottom flask were placed 3-(trimethylstannyl)-2*H*-pyran-2-one (0.27 g, 1.04 mmol), 1-cyclohexenyl triflate (0.20 g, 0.87 mmol), lithium chloride (0.26 g, 6.09 mmol), and Pd(PPh$_3$)$_4$ (20 mg, 0.02 mmol) with 3 mL of THF. The mixture was refluxed for 34 h. After the solution was concentrated, the crude material was purified by flash chromatography, eluting with 65:35 hexane−ether to obtain 0.11 g (72%) of yellow oil (**30**): ^{1}H NMR (200 MHz, acetone) δ 7.56 (dd, J = 5.1, 2.0 Hz, 1 H), 7.32 (dd, J = 6.9, 2.0 Hz, 1 H), 6.58 (m, 1 H), 6.35 (dd, J = 6.8, 5.0 Hz, 1 H), 2.21 (m, 4 H), 1.65 (m, 4 H); ^{13}C NMR (300 MHz) δ 162.0, 149.0, 136.4, 132.1, 130.5, 129.4, 106.5, 26.5, 25.4, 22.6, 21.3; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0837; UV λ_{max} (hexane) = 314 nm (ϵ = 6900).

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Supporting Information Available: ^{1}H NMR spectra of **5**, **7**, **11**, **13**−**17**, **19**, **20**, **24**−**27**, and **29**−**31** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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