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An Efficient Synthesis of Coumestrol and Coumestans by Iodocyclization and Pd-Catalyzed Intramolecular Lactonization

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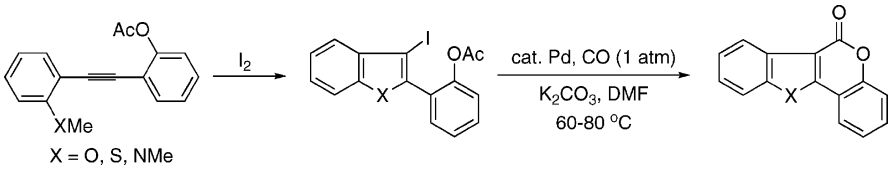

The iodocyclization of acetoxy-containing 2-(1-alkynyl)anisoles and subsequent direct palladium-catalyzed carbonylation/lactonization provide an efficient route to naturally occurring coumestan and coumestrol, and their related analogues.

Introduction

Coumestrol was first isolated from alfalfa, strawberry, Lucerne, and ladino clover by Bickoff et al. in the 1950s.[1] Because the structure of coumestrol resembles the well-known (*E*)-4,4′-dihydroxystilbene derivatives, which have potent pharmacological activity, it is not surprising that coumestrol shows estrogenic activity.[2] Coumestrol has higher binding affinities for ERβ than do other phytoestrogen compounds.[3] In vitro, coumestrol has been reported to inhibit bone resorption and stimulate bone mineralization.[4]

The total synthesis of coumestrol has been reported by several groups using quite different approaches.[5] However, most of the reported syntheses have required multiple steps, and produced only modest overall yields. Recently, a number of naturally occurring coumestan isoflavones have been discovered,[6] and their biological effects are currently under investigation.[7] In view of the many important physiological effects that estrogens have on the human body and the potential of phytoestrogens for human health, it is highly desirable to develop more efficient and general methods for the synthesis of coumestans and their derivatives.

Recently, we reported an efficient synthesis of substituted 3-iodobenzofurans by iodocyclization of the corresponding *o*-alkynylanisoles.[8] This iodocyclization of functionally substituted aryl acetylenes, when followed by subsequent Pd-catalyzed lactonization, appeared to provide a particularly promising route to this important class of biologically interesting polycyclic lactones.

Palladium-catalyzed lactonization via CO insertion is a very useful synthetic method that has become an important tool in organic synthesis.[9] The most widely used process for the conversion of acylpalladium derivatives into lactones is the direct reaction of the derivatives with a neighboring alcohol group. To the best of our knowledge, no reaction of acylpalladium species with a protected alcohol group has been previously reported. We now disclose an efficient synthetic route to coumestans

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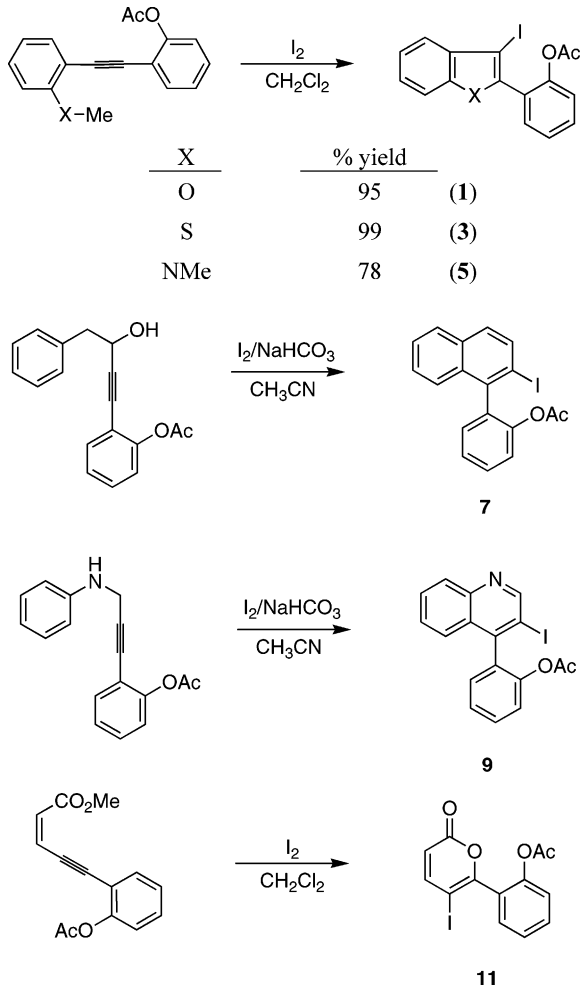
involving iodocyclization followed by palladium-catalyzed carbonylative lactonization. The nucleophile employed in our lactonization process is an acetoxy group, which serves as a latent hydroxyl group.[10] Deprotection of the hydroxy group is not necessary in this one-pot carbonylation process.

Results and Discussion

We and others have previously reported efficient approaches to the synthesis of benzofurans,[8,11] benzothiophenes,[12] indoles,[13] quinolines,[14] isoquinolines,[15] isocoumarins and α-pyrones,[16] and naphthalenes and polycyclic aromatic hydrocarbons[17] by the iodocyclization of the appropriate functionally substituted aryl acetylenes. These processes generally provide the desired aromatic heterocycles in good to excellent yields under very mild reaction conditions. Although these processes are very attractive for preparation of the starting materials required in our coumestrol synthesis, protection of the neighboring hydroxyl group during iodocyclization and subsequent facile liberation of this functionality during Pd-catalyzed lactonization are critical to the efficacious synthesis of the coumestrol ring system. When an acetyl group was employed as the protecting group, the desired starting materials could be efficiently prepared by iodocyclization of the appropriate alkynes (Scheme 1). All of these reactions afforded cyclized products with excellent chemoselectivity. The acetoxy group remains intact in all cases, and does not undergo cyclization. These starting materials are readily available, which makes our overall process particularly attractive.

The corresponding benzofuran, compound **1** (see Table 1, entry 1), was then treated with a palladium catalyst and 1 atm of CO in the hope that carbonylation and lactonization might occur in a single step. After brief optimization of the reaction conditions, we were pleased to find that coumestan (**2**) could be obtained in an almost quantitative yield by using 5 mol % $PdCl_2(PPh_3)_2$ and 2.0 equiv of K_2CO_3 in DMF under a balloon of CO at 60 °C for 6 h (Table 1, entry 1). The corresponding sulfur analogue, 6*H*-benzothieno[3,2-*c*]benzopyran-6-one (11-thiacoumestan, **4**), can also be prepared in good yield under these conditions, but at a higher temperature,

SCHEME 1



which may be because of intermolecular coordination of the palladium by the sulfur of the benzothiophene (entry 2). When using 3-iodoindole **5**, only a 21% yield of the desired lactone **6** was obtained in 6 h at 60 °C, along with recovery of 56% of the indole starting material **5** (entry 3). This low yield may be the result of the increased steric hindrance provided by the methyl group on the nitrogen of the indole, which hinders free rotation about the carbon−carbon bond between the two aryl groups. Fortunately, when the temperature was increased to 90 °C and the reaction was run for 6 h, the desired lactone **6** was isolated in a 75% yield with complete disappearance of the starting material (entry 4). This method is not limited to five-membered heterocyclic starting materials. Naphthalene **7** and quinoline **9** have also provided the corresponding lactones in 95 and 73% yields, respectively (entries 5 and 6), when allowed to react at 90 °C for 6 h. α-Pyrone **11** provided cyclized product in only a low yield, presumably because of its instability under the reaction conditions (entry 7). In none of the above examples is there observed any direct intramolecular coupling of the aryl halide and the oxygen without incorporation of CO, a possible side reaction when using an unprotected hydroxyl group.[18]

A proposed mechanism for this carbonylation process is shown in Scheme 2. Oxidative addition of Pd(0) to aryl

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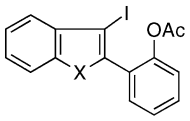
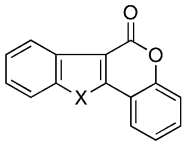
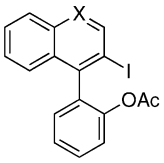
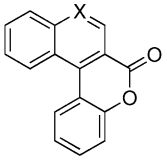
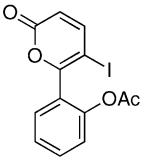
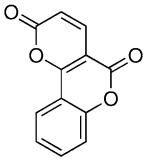
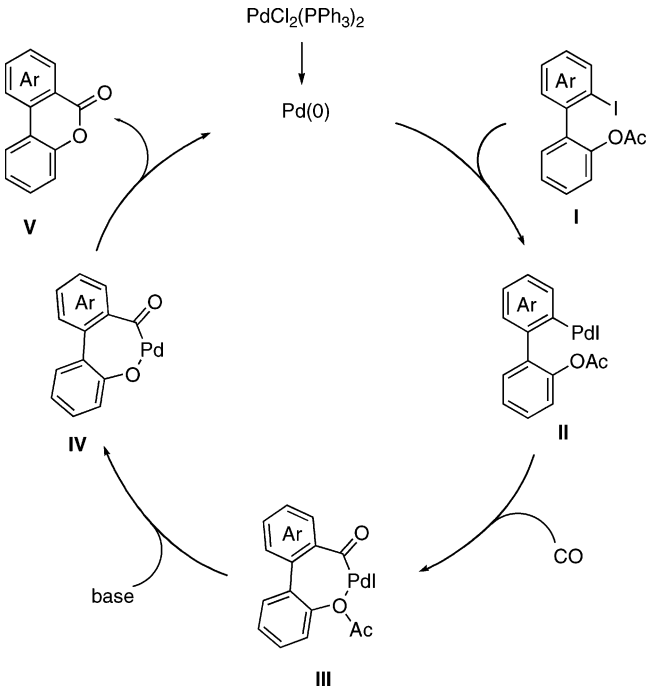
TABLE 1. Palladium-Catalyzed Intramolecular Lactonization[a]

entry	ArI		temp. (°C)	product		% yield
						
1	X = O	**1**	60		**2**	98
2	X = S	**3**	80		**4**	76
3	X = NMe	**5**	60		**6**	21[b]
4	X = NMe	**5**	90		**6**	75
						
5	X = CH	**7**	90		**8**	95
6	X = N	**9**	90		**10**	73
7		**11**	90		**12**	31

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the starting material, 5 mol % $PdCl_2(PPh_3)_2$, 2.0 equiv of K_2CO_3 in 1 mL of DMF under CO (1 atm) for 6 h. [b] Fifty-six percent of the starting material was recovered.

SCHEME 2

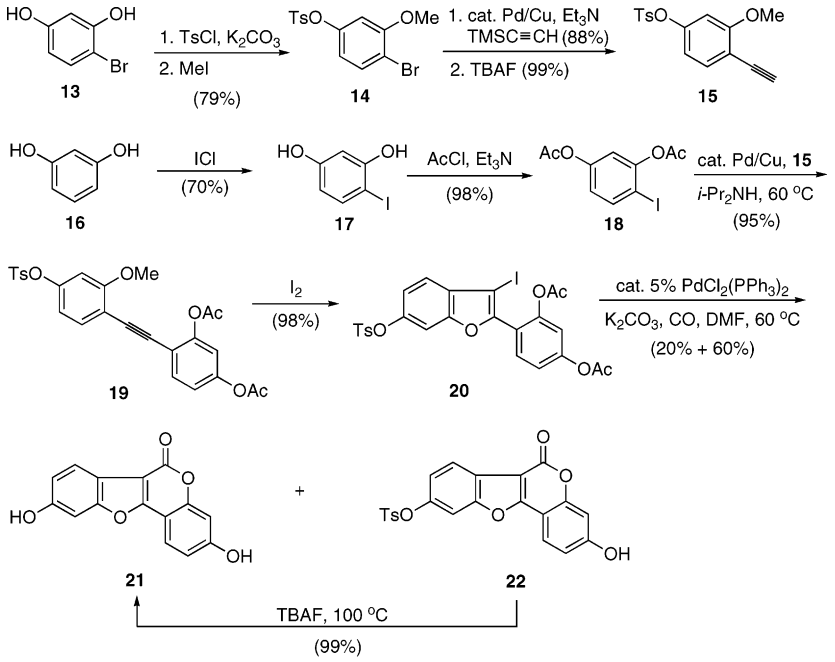


iodide **I** is presumably followed by insertion of CO to generate the acylpalladium intermediate **III**. Coordination of the acetoxy oxygen to the acylpalladium moiety presumably accelerates deacylation of intermediate **III** by the base present in the reaction mixture, as suggested by previous work on Pd-catalyzed processes.[10] Finally, complex **IV** undergoes reductive elimination to give the final product **V**, and regenerates the palladium catalyst.

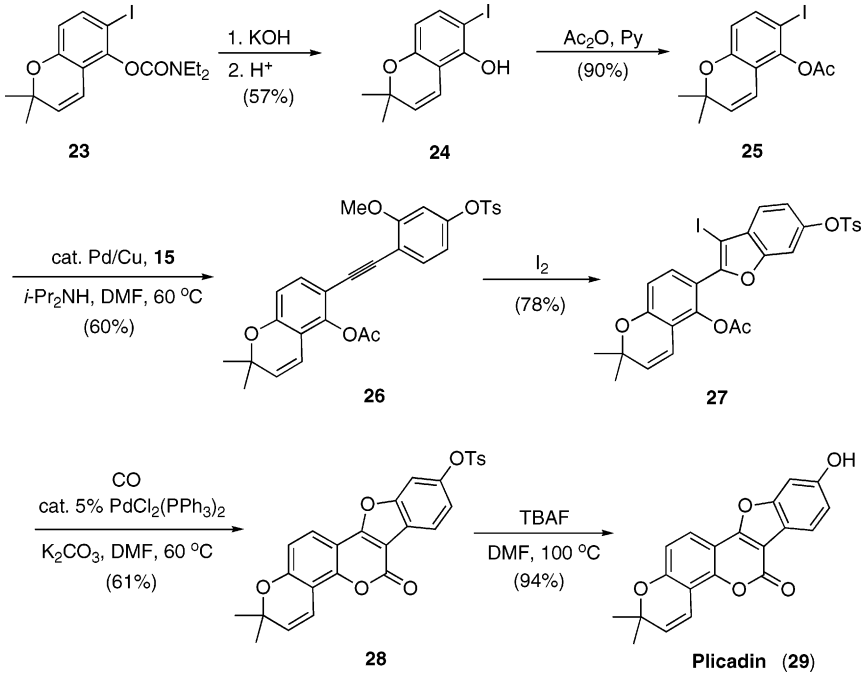
To further demonstrate the versatility of this palladium-catalyzed carbonylative lactonization, we have applied this methodology to the synthesis of coumestrol, a natural product with interesting phytoestrogenic effects.[5] Our synthesis of coumestrol is quite straightforward, and should be readily adapted to the synthesis of analogues (Scheme 3). Thus, commercially available 4-bromoresorcinol (**13**) was selectively tosylated, and the resulting phenol was converted into the methyl ether **14** in two steps in a 79% overall yield.[5e] The Sonogashira coupling of **14** with trimethylsilyl acetylene, followed by desilylation with TBAF, provides alkyne **15** in an 88% overall yield.

2,4-Diacetoxyiodobenzene (**18**) was prepared in almost a quantitative yield by acetylation of 4-iodoresorcinol (**17**), which was in turn prepared by the iodination of resorcinol using ICl. Our usual Sonogashira reaction conditions (2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI, and 1.5 equiv of Et_3N in DMF at 25 °C) were ineffective for the coupling of **18** and **15**. A large amount of the homocoupling product of acetylene **15** was obtained. A brief optimization showed that using *i*-Pr_2NH as the base and DMF as the solvent at 60 °C provided the best yield of acetylene **19** (95%).[5e] Compound **19** was successfully cyclized to benzofuran **20** in a 98% yield when employing 2.5 equiv of I_2 as the electrophile. With compound **20** in hand, we examined the Pd-catalyzed carbonylative lactonization. Under our usual carbonylation conditions, compound **20** was converted to coumestrol (**21**) in a 20% yield, along with a 60% yield of the coumestrol tosylate **22**. The tosyl derivative was easily converted to coumestrol in a quantitative yield by using 1.1 equiv of TBAF in DMF under reflux for 2 h. A separate experiment showed that without any purification, the mixture of coumestrol (**21**) and tosyl derivative **22** could be converted to

SCHEME 3



SCHEME 4



coumestrol in a 75% yield using 1.2 equiv of TBAF in DMF under reflux for 4 h.

We have also applied our methodology to the synthesis of another derivative of coumestan, a proposed natural product "plicadin", whose structure was originally misassigned.[2,19] Plicadin was isolated from the herb *Psoralea plicata* and apparently has a compact, oxygen-rich, heterocyclic structure. A total synthesis by Snieckus et al. proved the original proposed structure wrong,[20] and since then, a correct structure has not been established. Hydrolysis of the known chromene carbamate **23**,[20] followed by protection of the resulting OH group as an acetoxy group, afforded chromene **25** in a 51% overall yield (Scheme 4). Sonogashira coupling of **25** with **15** under our previous optimized conditions led to alkyne **26** in a moderate yield. Iodocyclization of **26** afforded 3-iodobenzofuran **27** in a good yield. Under our optimal conditions for the Pd-catalyzed lactonization, we converted benzofuran **27** to the proposed plicadin tosylate **28** in a 61% yield, which was nearly quantitatively converted to the structure proposed for plicadin by

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deprotection with TBAF. The ^{1}H NMR spectrum of our synthesized plicadin is identical to that of Snieckus' plicadin.[20] Although it does not establish the correct structure of plicadin, our iodocyclization/carbonylation methodology should provide direct access to a large number of biologically interesting coumestan derivatives.

In summary, we have developed an efficient approach to biologically interesting coumestans that involves simple, high-yielding Sonogashira cross-coupling, iodocyclization, and Pd-catalyzed lactonization using an acetoxy group as the nucleophile. A variety of biaryls can be utilized in this process to generate aromatic lactones in good yields. More importantly, the methodology we have developed can be applied to the synthesis of coumestan, coumestrol, plicadin, other coumestan family members, and a wide variety of coumestan analogues.

Experimental Section

General Procedure for the Sonogashira Cross-Coupling: 2-(2-Methoxyphenylethynyl)phenyl Acetate. A mixture of 2-ethynylanisole (6.0 mmol), 2-iodophenyl acetate (5.0 mmol), CuI (0.06 mmol), and $PdCl_2(PPh_3)_2$ (0.12 mmol) in a mixture of Et_3N (2.0 equiv) and DMF (50 mL) was heated at 60 °C for 2 h. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure. The residue was extracted with Et_2O, and the combined extracts were washed successively with water and satd aq NaCl. The organic solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to give the above product (96%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.87 (s, 3H), 6.88 (d, J = 8.7 Hz, 1H), 6.92 (td, J = 7.5, 0.9 Hz, 1H), 7.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.26−7.35 (m, 2H), 7.46 (dd, J = 7.5, 1.8 Hz, 1H), 7.59 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 55.8, 88.3, 90.9, 110.9, 112.3, 118.0, 120.6, 122.4, 126.0, 129.4, 130.2, 133.1, 133.7, 151.6, 160.1, 169.1; IR (neat) 1771 cm^{-1}; HRMS calcd for $C_{17}H_{14}O_3$ 266.0946, found 266.0943.

General Procedure for Iodocyclization: 2-(2-Acetoxyphenyl)-3-iodobenzo[*b*]furan (1). This compound was prepared according to a literature procedure.[8] A solution of 2-(2-methoxyphenylethynyl)phenyl acetate (2.50 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 1 min. I_2 (2.5 equiv) was added, and the resulting mixture was allowed to stir at 25 °C for 12 h. Satd aq $Na_2S_2O_3$ (5 mL) was added to the mixture, which was further stirred for 2 min. The resulting mixture was then extracted with Et_2O. The combined organic solution was washed successively with water and satd aq NaCl, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (4:1 hexane/EtOAc) to afford **1** as a yellow oil (95%): ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H), 7.25 (dd, J = 8.1, 1.2 Hz, 1H), 7.32−7.40 (m, 3H), 7.44−7.53 (m, 3H), 7.82 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 65.4, 111.4, 122.1, 123.3, 123.7, 123.8, 126.0, 126.1, 131.2, 131.7, 131.9, 148.8, 152.3, 154.6, 169.4; IR (neat) 1771 cm^{-1}; HRMS calcd for $C_{16}H_{11}IO_3$ 377.9758, found 377.9753.

General Procedure for Palladium-Catalyzed Intramolecular Lactonization. DMF (1.0 mL), $PdCl_2(PPh_3)_2$ (0.0125 mmol), K_2CO_3 (0.5 mmol), and the aryl iodide (0.25 mmol) were stirred under an Ar atmosphere at room temperature for 5 min. The mixture was flushed with CO, and the flask was fitted with a balloon of CO. The reaction mixture was heated at the specified temperature with vigorous stirring for 6 h. The reaction mixture was then cooled to room temperature, diluted with diethyl ether (35 mL), and washed with brine (30 mL). The aqueous layer was extracted with diethyl ether (15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on a silica gel column.

Coumestan (2). This compound was obtained as a white solid (99%): mp 180−181 °C (lit.[21] mp 181−182 °C); ^{1}H NMR ($CDCl_3$) δ 7.39−7.53 (m, 4H), 7.59−7.69 (m, 2H), 8.04 (dd, J = 7.8, 1.5 Hz, 1H), 8.13−8.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 106.1, 112.0, 112.9, 117.7, 122.1, 123.7, 124.9, 125.4, 127.0, 132.1, 153.9, 155.8, 158.3, 160.2; IR (neat) 1737 cm^{-1}; HRMS calcd for $C_{15}H_8O_3$ 236.0476, found 236.0473. The spectral properties were identical to those previously reported.[21]

Plicadin (29). Compound **28** was converted to the structure originally proposed for plicadin (**29**) by following the same procedure used to prepare lactone **21**. This afforded the proposed plicadin (94%) as a yellow solid: mp 290−291 °C (sublim). The spectral properties were identical to those previously reported.[20]

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Supporting Information Available: Characterization data for the compounds listed in Table 1 and experimental procedures and characterization data for the reactions summarized in Schemes 3 and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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