Total Synthesis Hot Paper

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C–H Bond Arylation in the Synthesis of Aryltetralin Lignans: A Short Total Synthesis of Podophyllotoxin**

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Abstract: *A short total synthesis of podophyllotoxin, the prototypical aryltetralin lignan natural product, is reported. Key to the success of this synthetic pathway is a Pd-catalyzed C(sp^3)–H arylation reaction enabled by a conformational biasing element to promote C–C reductive elimination over an alternative C–N bond-forming pathway. This strategy allows for access to the natural product in five steps from commercially available bromopiperonal, and sheds light on subtle conformational effects governing reductive elimination pathways from high-valent palladium centers.*

Plant-derived aryltetralin lignans have found myriad use in the treatment of disease owing to their potent antiviral, antibacterial, and antineoplastic properties.[1] In the area of cancer chemotherapy, they have proven particularly valuable as the prototypical member, podophyllotoxin (**1**), serves as starting material for the widely used type II topoisomerase targeting drugs etoposide (VP-16) (**2**) and teniposide (VM-26) (**3**) used for the treatment of lung and testicular cancer, lymphoma, leukemia, and Kaposi's sarcoma (Figure 1 a).[2] Owing to perceived future scarcity of **1**, as well as the desire to produce superior anticancer agents, there has been intense interest in the synthesis of these compounds for 50 years.[3] While numerous total syntheses of **1** and 4-*epi* **1** have been reported to date, many of which utilize uniquely creative synthetic strategies, the development of clinical candidates superior to **2** has been exceedingly slow. Without question, a lack of three-dimensional structural insight into the binding of **2** to the cleavage complex formed between DNA and type II topoisomerase (Top2) has been a significant impediment. Given the recently disclosed X-ray crystal structure of a Top2/DNA/**2** cleavage complex,[4] the sophistication of this drug class is poised to undergo further advancement. A synthesis of this family of compounds which can easily modify the aromatic residues in a manner that is independent of their electronic nature would be highly enabling from the vantage point of diverse analogue preparation.[5] Herein we report a C–H arylation approach to the aryltetralin lignans that is distinct from all other synthetic strategies. These studies have shed light on subtle conformational effects influencing reductive elimination pathways from high-valent palladium centers.

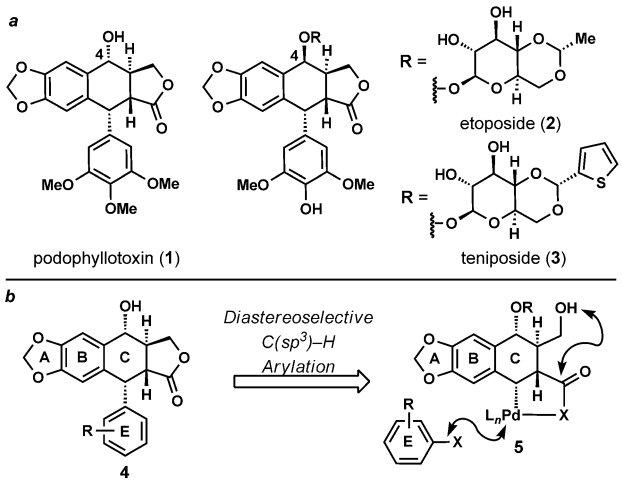

Figure 1. a) Podophyllotoxin and related anticancer agents. b) A C–H activation approach to the aryltetralin lignan class.

Our retrosynthetic analysis of the aryl tetralin lignan class is shown (Figure 1 b). We envisioned that a cyclopalladated intermediate (**5**) could serve as a late-stage entry into the aromatic-ring-modified substrates (**4**). The pioneering work of Daugulis,[6] Yu,[7] Chen,[8] and others,[9] in the area of amide-directed, Pd-catalyzed C(sp^3)–H arylation and alkylation, as well as several formidable applications in total synthesis,[10] served as our inspiration for this work. Nevertheless, construction of the highly hindered C–C bond in **4** in the presence of multiple electron-rich aryl rings and an epimerizeable chiral center, and the opportunity for thermodynamically favorable naphthalene formation, was of particular concern to us in the context of the task at hand.

We began our studies by preparing C–H arylation precursor **8** bearing the extensively utilized 8-aminoquinoline-derived directing group (Scheme 1).[6,11] Epoxidation of 6-bromopiperonal, benzocyclobutenol formation, and silylation afforded **6** in a scalable, three-step procedure.[12] Thermal cycloaddition of **6**, via an *o*-quinodimethane intermediate, with fumarate-derived amide **7** afforded C–H activation precursor **8**. While the yield and diastereoselectivity of this reaction was poor, this process allowed for the preparation of gram quantities of **8** and no optimization attempts were made at this point. Attempted coupling of **8** with 3,4,5-trimethoxyiodobenzene under a variety of common catalytic C–H arylation conditions ($Pd(OAc)_2$, base, solvent) surprisingly afforded β-lactam **9** as the major product along with

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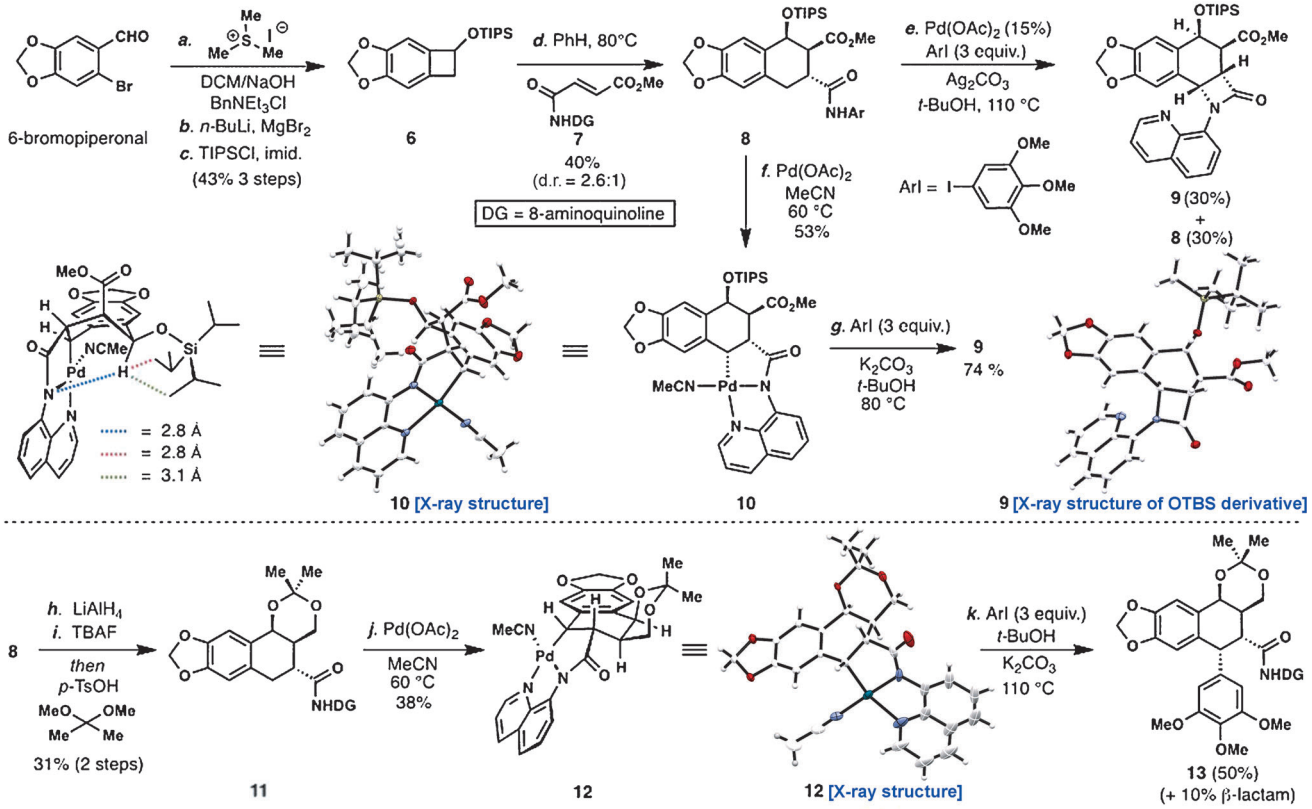


Scheme 1. Initial C–H arylation attempts. Reagents and conditions: a) 6-bromopiperonal (1 equiv), Me_3SI (2.7 equiv), $BnNEt_3Cl$ (4 mol%), 1:1 DCM/19 M NaOH (v/v), 0°C→RT, 24 h; b) *n*BuLi (1.2 equiv), $MgBr_2$ (2 equiv), 10:3 Et_2O/THF (v/v), −78°C→0°C, 1 h, 50% over two steps; c) TIPSCl (2.2 equiv), imidazole (3.0 equiv), DMF, RT, 12 h, 90%; d) **6** (3 equiv), **7** (1 equiv), PhH, 80°C, 24 h, 40% (d.r. 2.6:1); e) $Pd(OAc)_2$ (15 mol%), 3,4,5-trimethoxyiodobenzene (3 equiv), Ag_2CO_3 (3.0 equiv), *t*BuOH, 110°C, 24 h, 30% of **9** + 30% **8**; f) $Pd(OAc)_2$ (1 equiv), MeCN, 60°C, 1.5 h, 53%; g) **10** (1 equiv), 3,4,5-trimethoxyiodobenzene (3 equiv), K_2CO_3 (1 equiv), *t*BuOH, 80°C, 3 h, 74%; h) $LiAlH_4$ (2 equiv), THF, −78°C→0°C, 1 h, 38%; i) 1. TBAF (2 equiv), THF, −78°C→25°C, 4 h; 2. *p*-TsOH (10 mol%), 5:3 2,2-dimethoxypropane/THF (v/v), RT, 12 h, 81%; j) $Pd(OAc)_2$ (1 equiv), MeCN, 60°C, 1.5 h, 38%; k) **12** (1 equiv), 3,4,5-trimethoxyiodobenzene (3 equiv), K_2CO_3 (1 equiv), *t*BuOH, 110°C, 50%. DCM = dichloromethane, DG = directing group, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.

substantial amounts of recovered starting material. An X-ray crystal structure of the OTBS derivative of **9** confirmed the structure of this unusual product. These results were similar with and without silver additives, and in all cases the typically observed arylated product was not formed. While direct C–N bond reductive elimination of the amide directing group nitrogen has been documented,[6d,13] as has the formation of four-membered azetidine[8d,9c] and β-lactam rings,[9f,13,14] these results were particularly surprising given that the majority of prior reports utilized conditions incapable of forming C–C bonds.[14] In an effort to better understand the origins of **9** in our system, we prepared acetonitrile-bound, Pd^{II} complex **10** postulated to be an intermediate in these arylation reactions (Scheme 1). Unlike previous reports involving similar palladacycles,[6b] heating this complex in the presence of excess aryl iodide (*t*BuOH, K_2CO_3, 80°C) cleanly formed β-lactam **9** in 75% yield, again without formation of the typical C–C coupled product. Small amounts of biaryl side product were also detected in these experiments.[15]

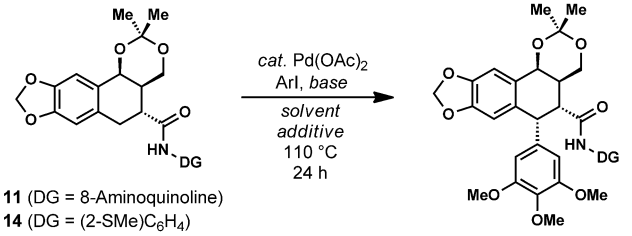
Compared to similar cyclometalated species which have been crystallographically characterized,[6b] the structure of **10** shows no abnormalities with respect to the bonding arrangement around the palladium center. The conformation of the cyclohexene-type ring (podophyllotoxin C-ring), however, is unusual in **10**; this ring adopts a twist-boat conformation, presumably to accommodate the palladacycle and position the bulky OTIPS group in an equatorial position. The measured distances shown in Scheme 1 attest to the highly crowded environment surrounding the underside of this ring. It has been proposed that Pd^{IV} species are involved in these amide-directed C–H arylation reactions,[6b] and if such conformational constraints are present in an octahedral or square-pyramidal Pd^{IV} intermediate, C–C reductive elimination from a high-valent form of **10** would incur significant strain as the axial $C–C_{aryl}$ bond begins to form, and the resulting amide-ligated Pd^{II} center is forced to rotate underneath this crowded ring.[16,17]

Taking this hypothesis in account, we then prepared conformationally distinct substrate **11** by a selective ester reduction/desilylation/ketalization sequence from **8** (Scheme 1). In analogy to **8**, treatment of this substrate with stoichiometric $Pd(OAc)_2$ in MeCN formed square-planar Pd^{II} complex **12**. An X-ray crystal structure of **12** revealed that the bonding arrangement at the Pd^{II} center is nearly identical to that in **10**, yet the rigid cyclic acetonide locks the six-membered C-ring into a half-chair-like conformation. This

conformational controlling element forces the palladacycle away from the underside of the six-membered ring relative to the orientation in **10**. When **12** was heated in the presence of excess 3,4,5-trimethoxyiodobenzene and K_2CO_3 (*t*BuOH, 110 °C), arylated product **13** was formed as the major product (50 %) along with small amounts of β-lactam (10 % yield). These results suggest that subtle conformational effects dictate the mode of reductive elimination (C–C vs. C–N) in the context of this rigid polycyclic system.

With confirmation that C–C coupling is possible, we began to examine catalytic conditions for the C–H arylation reaction (Table 1). In addition to 8-aminoquinoline-derived substrate **11**, amide **14**, which contains the related 2-thiomethylaniline-based directing group, was also evaluated.[6] The

Table 1: Pd-catalyzed C-H arylation: selected optimization.[a–d]



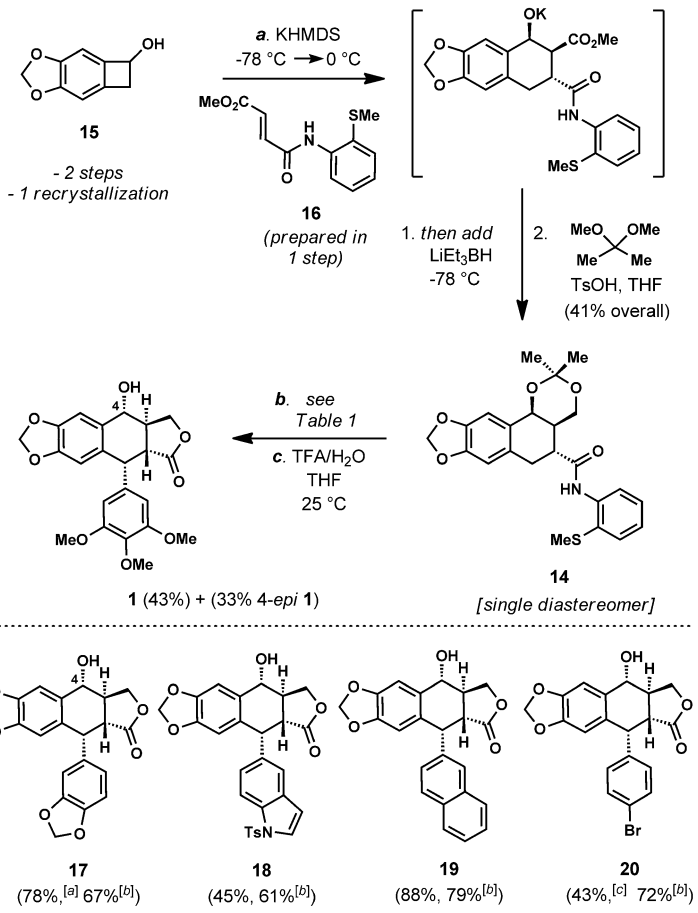
11 (DG = 8-Aminoquinoline)
14 (DG = (2-SMe)C_6H_4)

Entry	Substrate	Base	Solvent	Additive	Yield[b]
1	**11**	CsOAc	toluene	AgOAc	5 %
2	**11**	Ag_2CO_3	*t*-AmOH	none	10 %
3	**14**	K_2CO_3	*t*-AmOH	none	35 %
4	**14**	K_2CO_3	*t*-AmOH	40 % PivOH	35 %
5	**14**	K_2CO_3	*t*-AmOH	40 %$(BnO)_2PO_2H$	45 %
6	**16**	K_2CO_3	*t*-AmOH	40 %$(BnO)_2PO_2H$	58 %[c,d]

[a] Conditions: **11** or **14** (0.02 mmol), $Pd(OAc)_2$ (20 mol %), base (3.0 equiv), ArI (4 equiv), solvent (1 mL), 110 °C, 24 h. [b] Yield determined by ^{1}H NMR spectroscopy using 2-chloroquinoline as an internal standard. [c] Yield of isolated product. [d] $Pd(OAc)_2$ loading = 15 mol %, ArI (2 equiv), K_2CO_3 (1.5 equiv), [**14**] = 0.1 M, *t* = 50 h, 15 % recovered **14** also isolated. ArI = 3,4,5-trimethoxyiodobenzene.

optimization of the C–H arylation reaction proved to be a daunting challenge and was plagued by low yields, decomposition pathways, and poor catalyst turnover. After we had examined a variety of bases and solvents (selected examples shown), results remained modest. While incorporation of pivalic acid as an additive[10b] had little effect on the outcome of this C–H arylation, the addition of substoichiometric quantities of dibenzyl phosphate, recently utilized by the Chen[8a,b] and Shi groups,[9d] improved the yield of coupling to 45 % (Table 1, entry 5). After adjusting the concentration and reaction time, we were able to achieve a synthetically useful 58 % yield of arylated product using 2 equivalents of ArI and 15 mol % $Pd(OAc)_2$ loading (Table 1, entry 6).

With suitable conditions for C–H arylation in hand, we returned to the total synthesis of **1** (Scheme 2, top). Deprotonation of free cyclobutanol **15** with potassium hexamethyldisilazide allowed for low-temperature *o*-quinodimethane formation[18] and a subsequent highly diastereoselective cycloaddition with 2-methylthioaniline-containing amide **16** (prepared in one step from monomethyl fumarate). Addition



Scheme 2. Top: Short total syntheses of **1** and 4-*epi*-**1**. Bottom: Analogues synthesized in two steps from **14**. Reagents and conditions: a) **16** (1 equiv), **15** (2 equiv), KHMDS (2.2 equiv), THF, −78 °C → 0 °C → −78 °C, 1 h, 1. then $LiEt_3BH$ (4 equiv), 30 min; 2. *p*-TsOH (10 mol %), 2:1 2,2-dimethoxypropane/THF (v/v), RT, 12 h, 41 % overall; b) see Table 1, entry 6, 58 %; c) 1:1:1 TFA/THF/H_2O (v/v/v), RT, 24 h, 43 % yield of **1**, 33 % yield of 4-*epi*-**1**. [a] Yield of isolated C–H arylated product. [b] Yield of isolated cyclization products as C-4 diastereomers (crude d.r. ≈ 1.5:1 in all cases). [c] Yield determined by ^{1}H NMR analysis. HMDS = hexamethyldisilazide, TFA = trifluoroacetic acid.

of superhydride directly to this mixture led to efficient in situ ester reduction, and following workup and ketalization of the crude material (dimethoxypropane, *p*TsOH), arylation precursor **14** was obtained in 41 % overall yield as a single diastereomer from **15** with only one chromatographic purification. Following C–H arylation, we investigated conditions for removal of the directing group—a task that has historically proven quite challenging. After significant experimentation, it was found that simply stirring the arylated product in a mixture of TFA/THF/H_2O at room temperature directly affords podophyllotoxin (**1**) (43 % yield of isolated product) as well as C-4 *epi*-**1** (33 % yield of isolated product) which has the same configuration as etoposide. Overall this constitutes a five-step total synthesis of these compounds requiring only three chromatographic purifications.

To date, the vast majority of aryltetralin lignan derivatives have come from semisynthetic modification of podophyllo-

toxin (**1**) and the facility in which **1** isomerizes to its more stable *cis*-lactone counterpart (picropodophyllotoxin) largely limits the chemistry that can be employed during such endeavors.[5] A C–H arylation approach allows for the preparation of novel arene-modified podophyllotoxins (see **17**–**20**), including heteroaryl derivatives, in only two steps from amide **14** (Scheme 2, bottom). Notably, these compounds cannot be easily accessed from natural sources, and would otherwise require more lengthy individual syntheses. Given the outstanding track record of this natural product class in drug discovery, we envision that this synthetic pathway will greatly accelerate the pace at which new aryltetralin lignans with improved and/or novel biological activity are discovered.

In summary, we have developed a short total synthesis of the therapeutically important plant natural product podophyllotoxin (**1**) and 4-*epi* **1** enabled by a C–H arylation strategy for aryltetralin lignan construction. Synthetic methodologies involving high-valent metal centers have historically been complicated with mixtures of products resulting from competing reductive elimination pathways,[19] and recent work has shown that these pathways can be tuned by both directing-group control as well as electronic modulation of the aryl iodide.[9c,14] The studies reported herein imply that even with the same directing group, these pathways can be substantially altered by remote conformational effects and even the normally facile C–C bond reductive elimination pathway can become unfavorable. While conformational analysis has remained the bedrock of diasteroselective synthesis for many decades, exploiting these principles to manipulate the pathways available to organopalladium intermediates is a vastly underutilized tactic in synthesis. A better understanding of these effects will certainly elevate the applicability and generality of these unquestionably powerful C-H activation methodologies to more complex and unpredictable molecular settings.

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