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Graphical Abstract

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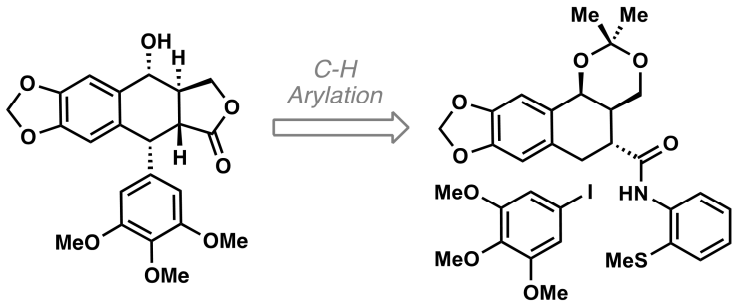

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Total Synthesis of Podophyllotoxin and Select Analog Designs via C–H Activation

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ABSTRACT

An account of our previously disclosed total synthesis of the aryltetralin lignan natural product podophyllotoxin, a building block used in the synthesis of the FDA-approved anticancer drug etoposide, is disclosed. A C–H activation disconnection was viewed as being amenable to the preparation of E-ring modified analogs but proved challenging to execute. Various insights into palladium-catalyzed C-H arylation reactions on complex scaffolds are reported ultimately leading to the implementation of this strategy and the synthesis of compounds inaccessible by semisynthetic means.

1. Introduction

Natural products and their derivatives are instrumental and proven weapons in the fight against human disease and their study continues to turn up unexpected biological findings even today.[1] Perhaps nowhere have such molecules proven more influential than in the area of cancer chemotherapy wherein their structures have influenced an estimated 60% of oncology drugs.[2] The conversion of the aryltetralin lignan natural product podophyllotoxin (**1**) into the anticancer drugs etoposide (**2**) and teniposide (**3**) represents one such success story.[3] These chemotherapeutics remain in use today for the treatment of a variety of cancers including small cell lung and testicular cancer, lymphoma, Kaposi's sarcoma, and various forms of leukemia.[4] Over a period of 20 years spanning more than 600 prepared derivatives, von Wartburg, Stähelin, and co-workers found that podophyllotoxin derivatives possessing a free phenol at C-4' and a glycosylated, epimerized C-4 secondary hydroxyl group (see **2** and **3**) represented a superior class of cytotoxins relative to **1**. Importantly, this work did not simply improve on the potency of **1**, but rather fundamentally changed its mechanism of action entirely. Whereas **1** is known to bind tubulin, **2** and **3** accessed a novel mode of action wherein they function as "poisons" of human topoisomerase II (TOPII).[3,4,5] These compounds act not by inhibiting the free TOPII enzyme, but rather by stabilizing the cleavage complex formed between DNA and TOPII as part of the enzyme's mechanism for regulating DNA supercoiling.[5] In this scenario, the double strand DNA break induced by TOPII cannot be re-ligated thus ultimately triggering apoptotic cell death pathways.

In addition to the foundational medicinal chemistry work that initially led to **2** and **3**, significant structure activity relationship (SAR) studies have been constructed around the etoposide nucleus, but most has been limited to semisynthetic modification of **1** and its derivatives.[6] In 2011, Chan and co-workers disclosed the first X-ray crystal structure of **2** bound to its biological target at 2.16 Å resolution (Figure 2).[7] This molecular snapshot revealed two molecules of **2**, separated by four base pair units, stabilizing the DNA/TOPIIβ cleavage complex. This crystallographic study also confirmed, and expanded on, previously suspected molecular interactions, such as the binding of the flat, aromatic B-ring of **2** with the DNA bases and the importance of the free phenol on the E ring (C-4').[6,8] The E-ring phenol was found to engage in hydrogen bonding with an aspartic acid residue (D479) of topoisomerase II (Figure 3A).

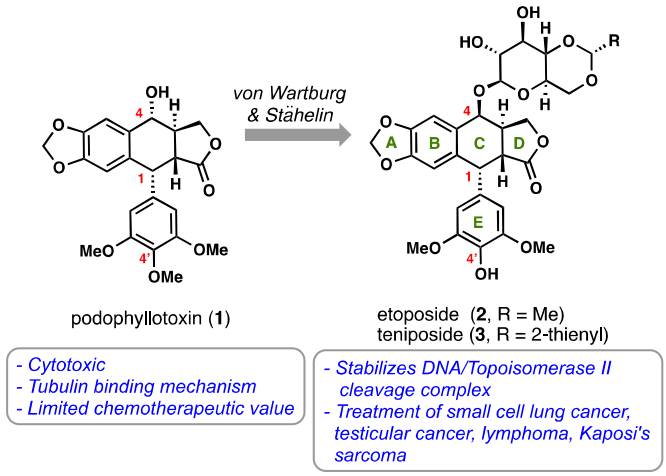


Figure 1. Cytotoxic aryltetralin lignan natural products and their derivatives.

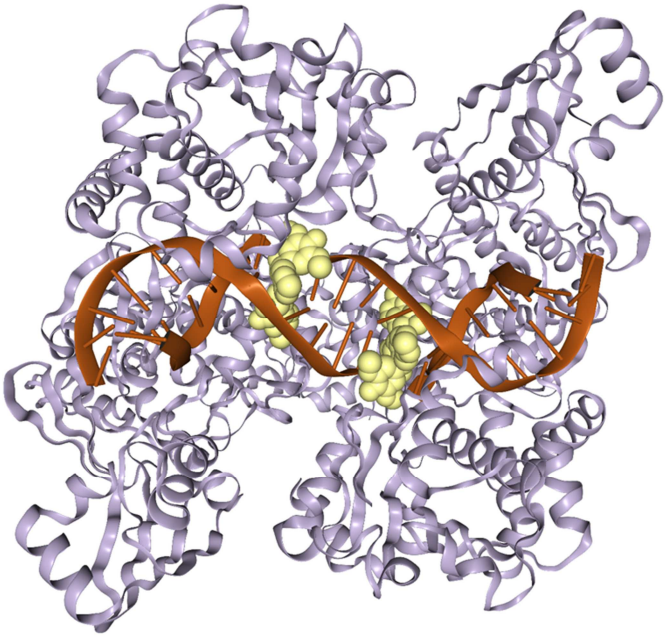


Figure 2. X-ray crystal structure of an etoposide/DNA/human TOPIIβ cleavage complex as determined by Chan *et al*.[7] Etoposide molecules are shown in yellow, DNA in brown, and enzyme in purple (RSCB PDB: 3QX3)

This finding is important as it clarifies the molecular interactions responsible for stabilizing the DNA/protein interface. The E-ring of etoposide, however, is also a metabolic liability as it readily forms both catechol and quinone intermediates upon cytochrome P450-mediated metabolic oxidation.[9] Etoposide quinone in particular is thought to have additional targets and mechanisms of action and may contribute to deleterious chromosomal translocations (11q23 chromosome translocations) seen in a small percentage of the patient population.[10] Such translocations are associated with the formation of secondary cancers (leukemias).[11] Thus the formation of more metabolically robust E-rings which can still engage D479 and stabilize the DNA/protein interface could be of therapeutic value.[12]

We envisioned that aromatic compounds of similar size, but without the propensity for oxidation (i.e. non-phenolic derivatives) could represent interesting lead scaffolds; moreover, such structures are not easily accessible from semisynthetic alteration of podophyllotoxin (Figure 3B). Carboxylic acid **4** is envisaged to present an altered motif capable of hydrogen-bonding to TOPII, but from a not easily oxidized thiophene core. Pyridine *N*-oxide **5** possesses similar shape to the natural phenolic substrate, but can only act as a hydrogen-bond acceptor and features an aromatic ring already in a highly oxidized form. Finally, difluoromethyl-containing **6** could probe the effectiveness of an acidic C-H bond as a hydrogen bond donor. An ideal strategy to prepare these, and other, aromatic groups would be to append them late-stage to a common building block containing the A, B, and C-rings (Figure 3C). Direct C–H bond arylation, which has become a powerful tool in synthesis,[13] was imagined as being an ideal platform for this endeavor (see **8** to **7**). Herein we detail the evolution of this synthetic platform toward novel podophyllotoxins.[14cc]

To evaluate a C–H arylation strategy toward derivatives of **2** and **3**, a suitable stereodefined tricyclic precursor was needed (see **8**, Figure 3C). While many elegant strategies have been developed to synthesize **1**,[14,15] we were particularly inspired by the work of Durst *et al.* which utilized an intramolecular cycloaddition of an *in-situ* generated *o*-quinodimethane to assemble the aryltetralin lignan framework (Figure 4).[14f,14j,16] Upon heating urethane

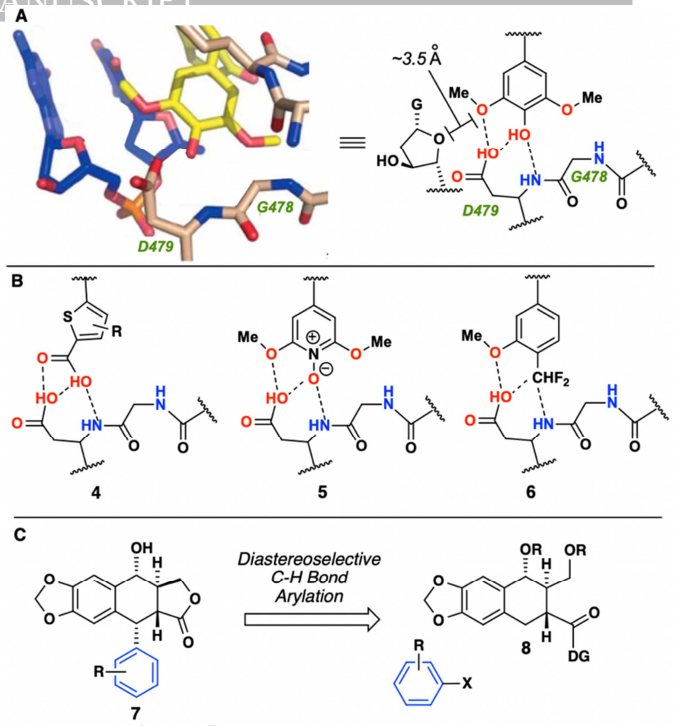


Figure 3. **A**) Etoposide E-ring binding as determined by Chan's X-ray crystallographic studies.[7] **B**) Nonnatural E-ring designs. **C**) synthetic strategy to access podophyllotoxin derivatives employing C-H activation. (G = guanine, DG = directing group)

derivative **9**, these researchers obtained adducts **10** and **11** as a 3:1 mixture of diastereomers in over 80% combined yield. By merging these findings with a late stage C–H arylation reaction of a common intermediate, we envisioned reducing the number of steps needed to make multiple analogs. Moroever, cyclobutanols lacking the aryl group present in **9** are easily prepared.

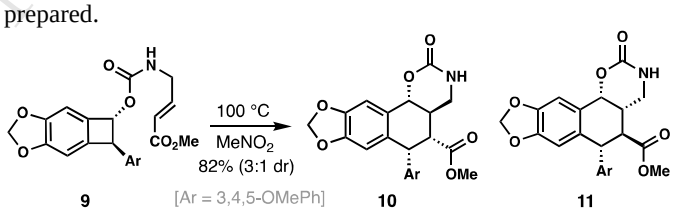


Figure 4. Durst's benzocyclobutane ring opening/intramolecular cycloaddition strategy to access the aryltetralin lignan scaffold.[14f,14j]

2. Results and Discussion

2.1 Construction and Reactivity of C-H Arylation Precursors

Initial forays into the construction of a suitable C–H activation precursor substrate focused on the examination of intermolecular *o*-quinodimethane cycloadditions between a range of benzocyclobutanols (see **12**-**14**) and dienophiles containing commonly employed amide directing groups (see **15**-**18**) (Figure 5).[17] Reacting TIPS (see **13**) and TBS-protected (see **14**) benzocyclobutanols with these dienophiles under thermal conditions (PhH, 80°C) led to tricyclic Diels-Alder adducts **19**-**24** in moderate yields (23-59%). Notably these yields refer to isomerically pure material obtained after recrystallization. The relative stereochemistry of adduct **19** was also secured via X-ray crystallographic analysis. We were unable to promote the cycloaddition using free alcohol **12** as a more rapid proton transfer/aromatization event ensued leading to aldehyde **25**.

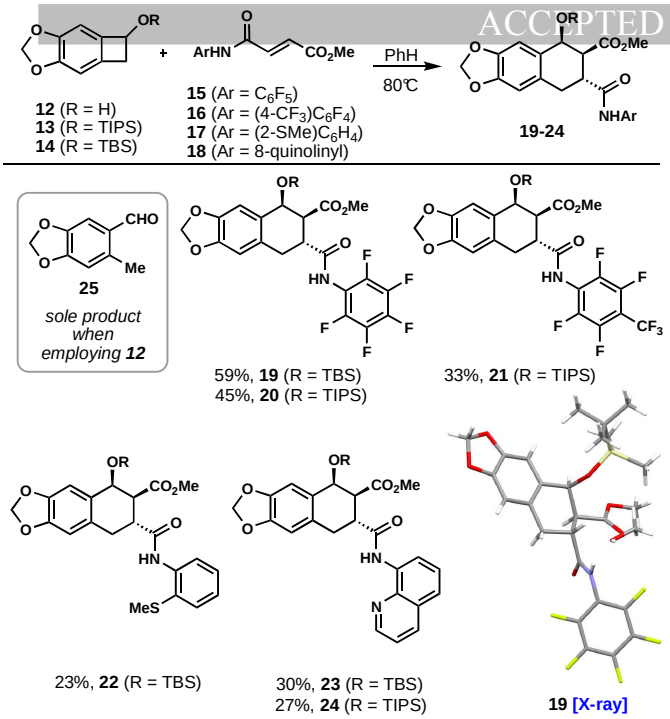
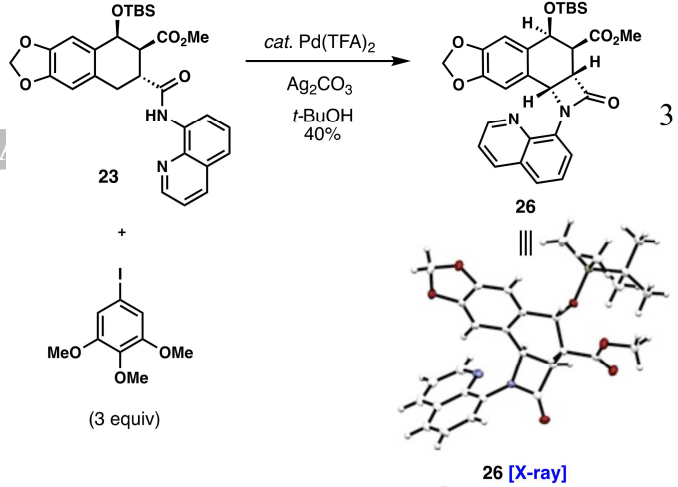


Figure 5. Synthesis of substrates for downstream C–H activation studies via a thermal *o*-quinodimethane cycloaddition. Yields shown are for single isomers obtained after re-crystallization.

With access to sufficient quantities of a range of cycloadducts, we proceeded to examine the key C-H arylation reaction (Figure 6). Subjecting tricycle **23**, which contains the strongly coordinating aminoquinoline directing group, to Pd-catalyzed arylation conditions with trimethoxyiodobenzene did not form the desired product, but rather β-lactam **26** whose structure was confirmed by X-ray analysis.[18] This unexpected result was both encouraging and troubling; it suggested that C–H activation was indeed possible in this rigid polycyclic system, but that reductive elimination, or a formal equivalent, of a C–N bond outcompeted that of a C–C one. These studies also led us to question if the ester functional group was ideal for this work as the yields of **26** were modest and products which appeared to stem from E1cB elimination of the OTBS group and subsequent aromatization (i.e naphthalenes) were detected in various crude reaction mixtures.[19]

In an effort to better understand the origins of **26**, and the reductive elimination process in general, we prepared cyclometallated, acetonitrile-bound palladium complex **27** in one step from **24** (Figure 7). An X-ray crystal structure of **27** was obtained and was in accordance with previously characterized palladacycles with respect to bond lengths and geometry.[20] Unlike previous complexes, however, this material gave high yields of β-lactam product (see **28**) when heated with an excess of trimethoxyiodobenzene in *t*-BuOH solvent. Notably, if this stoichiometric reaction was conducted in MeOH, ether **29** was formed as the major product as a mixture of diastereomers. Complex **27** was also reacted with a variety of aryl nucleophiles based on boron, tin, zinc, and copper, but C–C coupled product **30** was not produced in any case.[21]

Based on these results, we prepared acetonide **31** in 3 steps from **24** via a reduction/deprotection/ketalization sequence (Figure 8A). In analogy to **27**, reacting **31** with palladium acetate yielded palladacycle **32** which was also crystallographically characterized. To our delight, when **32** was heated in the presence of trimethoxyiodobenzene, the major product formed



was arylated product **33** (Figure 8B). Solid state structural inspection of the two

Figure 6. Initial attempts to elicit Pd-catalyzed C–H bond arylation instead led to β-lactam **26**.

obtained palladacycles (**27** and **32**) revealed significant differences with respect to the conformation of the cyclohexene ring to which the palladium is attached (podophyllotoxin C-ring). In **27**, the ring adopts a distorted twist boat-like structure while in **32** a more chair-like ring is observed (Figure 8C). It appears plausible that these differences affect the reductive elimination process, which presumably occurs from a high-valent Pd^{IV} intermediate.[22] The desired C–C reductive elimination of an aryl group requires the palladium complex to rotate underneath the C-ring in the transition state as the metal center becomes amide-ligated Pd^{II}. For **32** this is presumably possible, but for **27**, significant steric encumbrance would be encountered and thus the reductive elimination of a

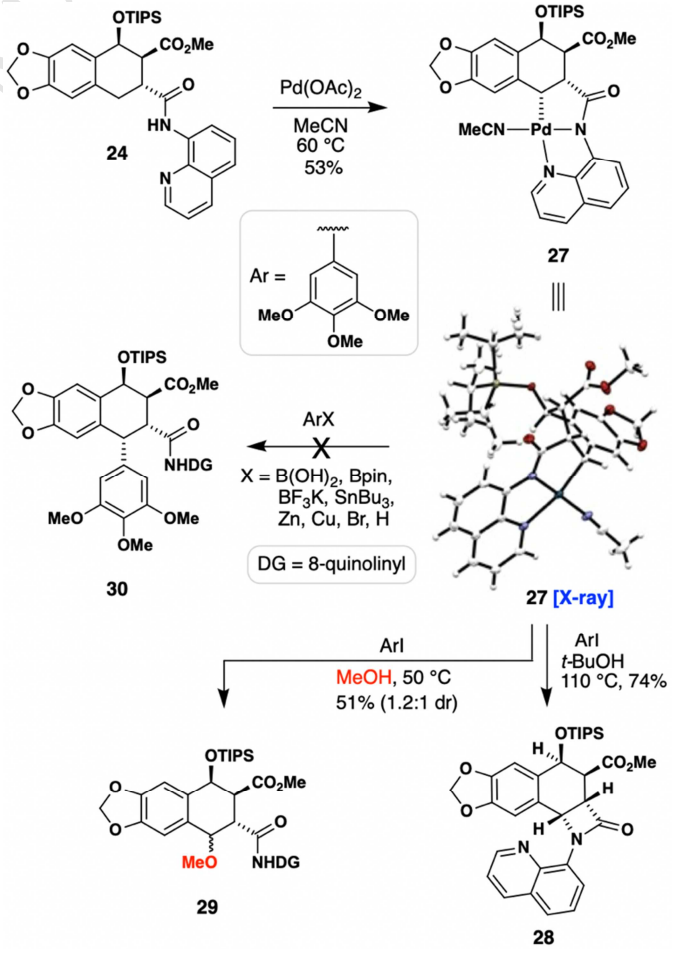


Figure 7. Synthesis and reactivity of palladacycle **27**.

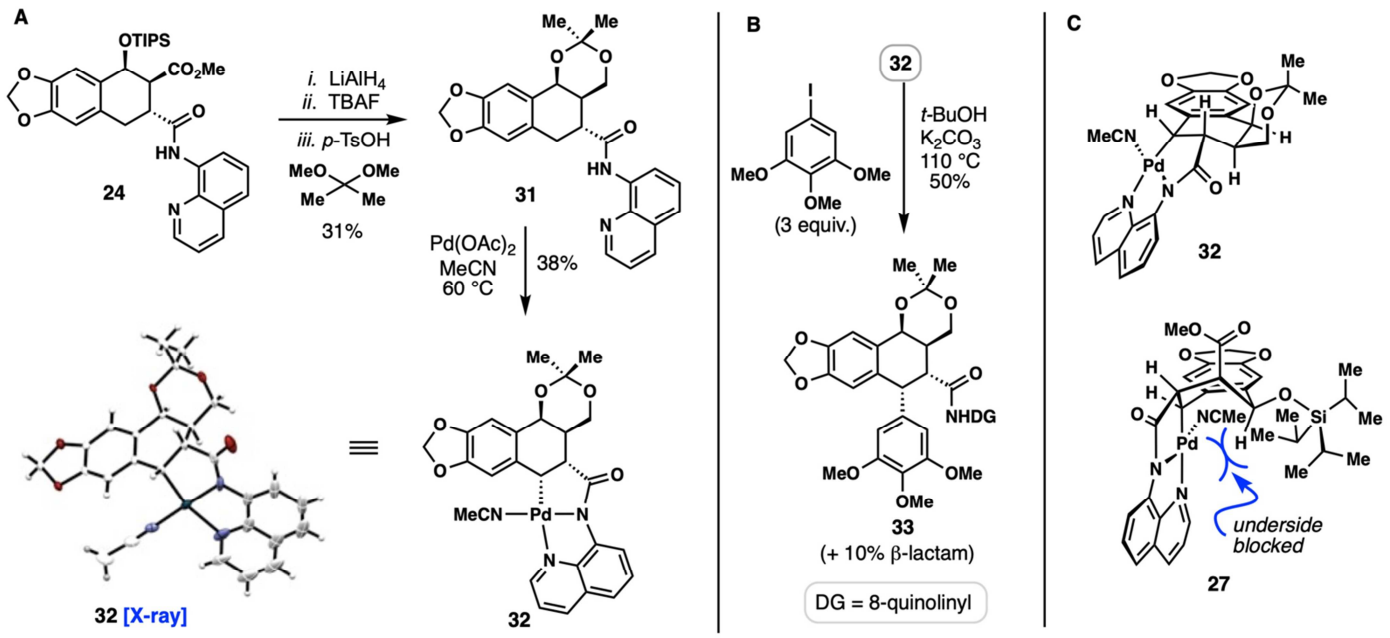
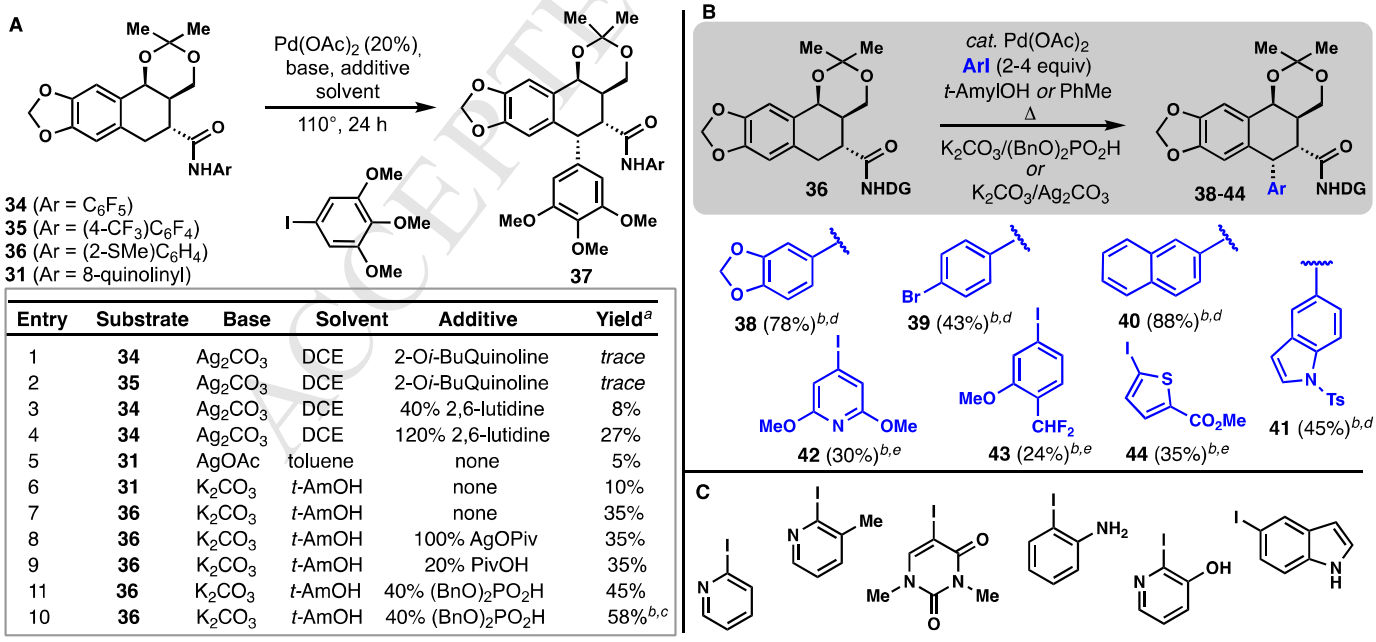


Figure 8. **A**) Synthesis of cyclic acetonide-containing palladacycle **32**. **B**) Successful C–C reductive elimination. **C**) Conformational difference between palladacycles **27** and **32**.

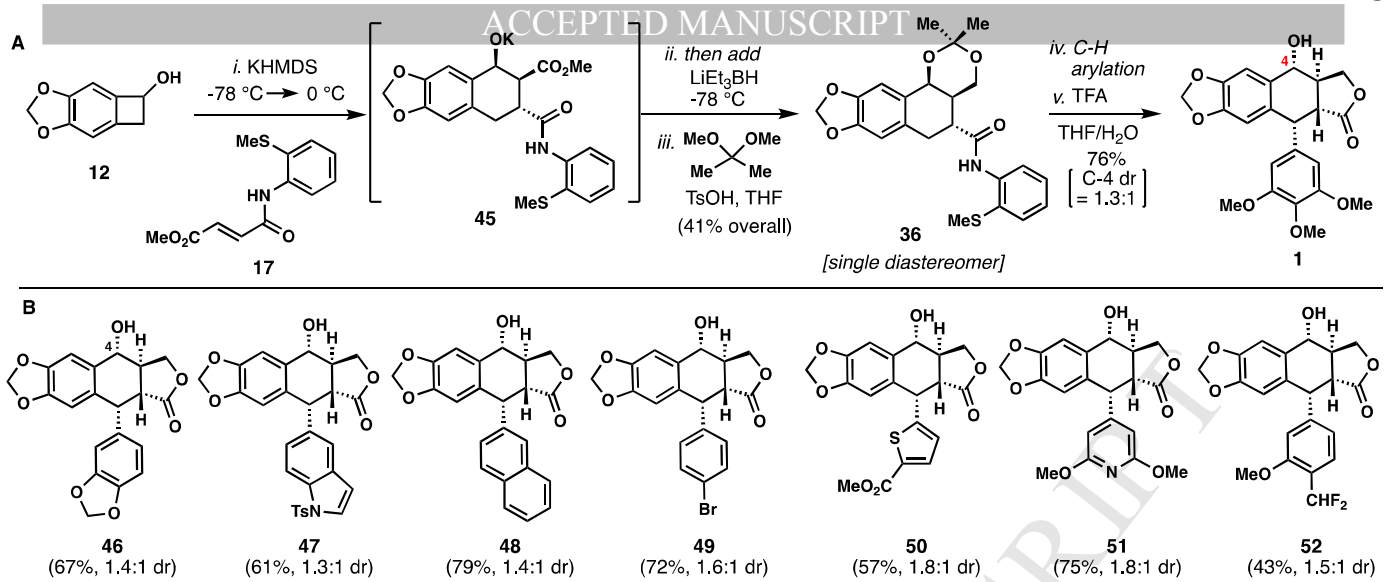
typically less-favored ligand may be preferred.[23]

The successful formation of **33** led us to investigate a catalytic arylation process, a task which proved challenging (Figure 9). A variety of acetonide substrates with different directing groups (see **34**-**36**) were prepared in analogy to **31** and their reactivity probed (Figure 9A). We observed very little product when employing weakly-coordinating fluoroamide directing groups and a designer quinoline ligand (See entries 1 and 2).[24] Substantial quantities of product were observed, however, when using superstoichiometric 2,6-lutidine as additive (entry 4). Similarly, substrate **31**, which possesses the strongly coordinating aminoquinoline directing group, did not perform well under catalytic conditions (entries 5 and 6). The thiomethyl aniline-based directing group (see **36**) proved superior and was selected for further optimization (entry 7).[25,26] An extensive evaluation of additives revealed that dibenylphosphate could improve the yield further (entry 11).[27] We suspect this agent helps promote catalyst turnover by facilitating transfer of the palladium from the metal-ligated product back to **36**. Extending the reaction time to fifty hours led to a synthetically useful 58% yield of arylated product **37** (entry 12). We then extended these conditions to the C–H arylation of other aryl iodides (Figure 9B). Simple arenes containing a dioxolane group and bromine atom underwent coupling (see **38** and **39**) as did a naphthalene and *N*-protected indole substrate (see **40** and **41**). Compounds required for our ongoing etoposide medicinal chemistry efforts also could be synthesized, albeit in lower yields. A dimethoxy pyridine ring (see **42**) could be coupled as well as a thiophene ester unit (**44**). For these substrates, simple potassium carbonate/silver carbonate additives proved optimal.



Entry	Substrate	Base	Solvent	Additive	Yield[a]
1	**34**	Ag_2CO_3	DCE	2-O*i*-BuQuinoline	*trace*
2	**35**	Ag_2CO_3	DCE	2-O*i*-BuQuinoline	*trace*
3	**34**	Ag_2CO_3	DCE	40% 2,6-lutidine	8%
4	**34**	Ag_2CO_3	DCE	120% 2,6-lutidine	27%
5	**31**	AgOAc	toluene	none	5%
6	**31**	K_2CO_3	*t*-AmOH	none	10%
7	**36**	K_2CO_3	*t*-AmOH	none	35%
8	**36**	K_2CO_3	*t*-AmOH	100% AgOPiv	35%
9	**36**	K_2CO_3	*t*-AmOH	20% PivOH	35%
11	**36**	K_2CO_3	*t*-AmOH	40% $(BnO)_2PO_2H$	45%
10	**36**	K_2CO_3	*t*-AmOH	40% $(BnO)_2PO_2H$	58%[b,c]

Figure 9. Catalytic C–H arylation studies **A)** Selected optimization results. **B)** Successful couplings. **C**) Aryliodide substrates which did not undergo C–H bond arylation. [a]yields determined by ^{1}H NMR. [b] isolated yield.[c] reaction run for 50 h. [d]$K_2CO_3/(BnO)_2PO_2H$ used. [e]Ag_2CO_3/K_2CO_3 used.



Scheme 1. A) Short total synthesis of **1**. **B**) Novel podophyllotoxins prepared.

Additionally, a difluoromethyl-containing arene (see **43**) could also be incorporated, albeit it in low yield (24%). Despite these successes though, many substrates gave trace or no product at all under these optimized sets of reaction conditions (Figure 9C). Aryl iodides containing a coordinating group *ortho* to the iodide, including a pyridine nitrogen, aniline amino group, or oxygen atom all proved problematic as did unprotected heteroatoms such as a free indole N-H and free phenol O-H.

2.2 Total Synthesis of Podophyllotoxin and Derivatives

With a successful C–H arylation reaction established, we then developed a synthesis of **1** and derivatives (Scheme 1). Owing to the low diastereoselectivity observed in the thermal cycloaddition reactions of benzocyclobutanols (typically ~2:1-4:1 dr) (Figure 5), we sought to improve on this process with optimal dienophile **17** (Scheme 1A). Inspired by the work of Choy,[28] we found that low temperature anionic ring opening of **12** followed by cycloaddition with **17** proceeded smoothly and diastereoselectively. Further experimentation also revealed that the intermediate potassium alkoxide formed (see **45**) could be directly reduced with lithium triethylborohydride, and upon ketalization of the crude reaction mixture, C–H activation precursor **36** was easily accessed. Notably **36** can be made using only one chromatographic event from commercial materials. Following C–H arylation, we discovered that **1** and 4-*epi* **1** were accessible in a single operation, which was fortuitous since directing group removal can be problematic and often requires forcing conditions. By simply stirring the arylated products in a mixture of TFA/THF/H_2O, a cascade of events ensued wherein the ketal was hydrolyzed and the lactone D-ring assembled with concomitant expulsion of the directing group. The strong acidity of the reaction mixture, combined with the electron-rich nature of the B-ring also served to also promote epimerization of the C-4 hydroxyl group-presumably by a S_N1 process. Thus **1** was formed with a substantial amount of *epi*-**1**, a compound which can also be used in the synthesis of etoposides.[29] Using these conditions, previously described arylation adducts **38**-**44** could be transformed into fully synthetic podophyllotoxin analogs (**46**-**52**) as a mixture of hydroxyl diastereomers (~1.5:1 dr at C-4). Efforts to convert these compounds into derivatives of **2** and **3** are underway.

3. Conclusion

In conclusion, a short total synthesis of the therapeutically vital plant natural product podophyllotoxin (**1**) has been developed using a C–H bond arylation strategy. During these investigations we uncovered some previously underappreciated aspects of the reductive elimination process from high valent palladium centers. These organometallic studies proved to be crucial in developing a workable synthesis of **1** as well as derivatives not accessible via semi-synthetic modification of the natural product. From a strategic perspective, the incorporation of a C–H activation disconnection late-stage enabled the synthesis of multiple derivatives from a common building block. While late-stage compound diversification involving C–C bond formation is commonplace in medicinal chemistry settings, its power has not been fully realized in the natural product arena, particularly in dense, stereochemically-rich compound space. Approaching total synthesis from the vantage point of medicinal chemistry brings significant challenges, but can also offer great opportunity for innovation and the exploration of cutting-edge methodologies in complex settings.

4. Experimental section

4.1 General

Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware sealed with rubber septa under a nitrogen atmosphere. Dry tetrahydrofuran (THF), and toluene were obtained by passing these previously degassed solvents through activated alumina columns. Anhydrous methanol and benzene were used directly from SureSeal® bottles from Aldrich. Volatile amines, and ethanol were distilled over calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) on SilicycleSiliaplate^{TM} glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation and potassium permanganate stain. Volatile solvents were removed under reduced pressure with a rotary evaporator. Flash column chromatography was performed using Silicycle F60 Å, 230x400 mesh silica gel (40-63 μm). ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker spectrometers operating at 400, 500, or 600 MHz for ^{1}H, 150 MHz for ^{13}C or 365 MHz for ^{19}F. Chemical shifts are reported relative to the residual solvent signal (^{1}H NMR: δ = 7.26; ^{13}C NMR: δ = 77.16). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. IR spectra were taken on a Nicolet 380 spectrometer as thin films on NaCl plates and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained by the mass spectral facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo electron corporation). X-ray crystal structures were obtained by the X-ray crystallography facility at the University of California, Berkeley.

4.2 Experimental procedures and data for synthetic compounds

*4.2.1. Cycloadduct **19**:* A flame-dried 500 mL round-bottom flask was charged with **14** (3.07 g, 10.8 mmol, 3.0 equiv), **15** (1.06 g, 3.59 mmol, 1.0 equiv) and benzene (100 mL). The reaction mixture was heated to 80 °C and held at this temperature for 12 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 10% EtOAc in hexanes) to afford the product as a mixture of diastereomers (~2.5:1). The mixture was recrystallized from ether and hexanes to afford **19** (1.2 g, 59%) as a white solid: mp 174-175 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (bs, 1 H), 6.66 (s, 1 H), 6.63 (s, 1 H), 5.94 (d, *J* = 15.6 Hz, 2 H), 5.13 (s, 1 H), 3.77 (s, 3 H), 3.58 (td, *J* = 15.0, 13.8, 13.8 Hz, 1 H), 3.19 (dd, *J* = 16.2, 7.2 Hz, 1 H), 3.01 (m, 2 H), 0.79 (s, 9 H), 0.09 (s, 3 H), -0.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 173.0, 148.1, 146.0, 129.8, 128.3, 108.8, 101.2, 70.9, 52.4, 50.0, 38.1, 31.6, 25.9, 18.2, -3.84, -4.65; ^{19}F NMR (376 MHz, $CDCl_3$) δ -144.0 (d, *J* = 18.8 Hz), -156.0 (t, *J* = 22.6 Hz), -161.7 (t, *J* = 22.6 Hz); IR (thin film) 3263, 2954, 2931, 2896, 2858, 1743, 1682, 1654 cm^{-1}; HRMS (ESI) calcd for $[C_{26}H_{28}O_6N_1F_5NaSi]^+$ $(M+Na)^+$: *m/z* 596.1498, found 596.1498; Carbons that are heavily split by fluorine were not observed in ^{13}C NMR. Crystals suitable for X-ray diffraction were obtained by slow vapor diffusion of heptane into a diisopropyl ether solution of **19**.

*4.2.2. Cycloadduct **20**:* A flame-dried 100 mL round-bottom flask was charged with **13** (3.33 g, 10.3 mmol, 2.0 equiv), **15** (1.5 g, 5.1 mmol, 1.0 equiv) and benzene (30 mL). The reaction mixture was heated to 80 °C and held at this temperature for 24 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 5% → 20% EtOAc in hexanes) to afford the product as a 4.0:1 mixture of diastereomers. The mixture was recrystallized using 30% ether in hexanes to afford **20** (1.4 g, 45% yield) as a white solid: mp 183-184 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (bs, 1 H), 6.74 (s, 1 H), 6.66 (s, 1 H), 5.93 (d, *J* = 13.8 Hz, 2H), 5.31 (s, 1H), 3.77 (s, 3 H), 3.69 (td, *J* = 10.8, 7.8, 7.8 Hz, 1 H), 3.26 (dd, *J* = 16.2, 7.8 Hz, 1 H), 3.03 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.98 (d, *J* = 10.8, 1H), 1.01-0.98 (m, 12 H), 0.86 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 173.2, 148.2, 146.9, 130.6, 128.7, 109.1, 108.5, 101.2, 71.5, 52.3, 50.5, 37.9, 30.9, 18.3, 18.0, 13.1; ^{19}F NMR (376.5 MHz , $CDCl_3$) δ -144.1 (d, *J* = 26.4 Hz), -156.0 (t, *J* = 22.6 Hz), -161.7 (t, *J* = 22.6 Hz); IR (thin film) 3261, 2946, 2867, 1742, 1681 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_6N_1F_5NaSi]^+$ $(M+H)^+$: *m/z* 638.1968, found 638.1976. Carbons that are heavily split by fluorine were not observed in the ^{13}C NMR.

*4.2.3. Cycloadduct **21**:* A flame-dried 500 mL round-bottom flask was charged with **13** (7.5 g, 23 mmol, 4.0 equiv), **16** (2.0 g, 5.8 mmol, 1.0 equiv) and anhydrous benzene (150 mL). The reaction mixture was heated to 80 °C and held at this temperature for 24 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 20% → 30% EtOAc in hexanes) to afford the product as 2.0:1 mixture of diastereomers. The mixture was recrystallized using 20% ether in hexanes to afford **21** (1.2 g, 33% yield) as a white solid: mp 167-168 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (bs, 1 H), 6.74 (s, 1 H), 6.65 (s, 1 H), 5.94 (d, *J* = 7.2 Hz, 2 H), 5.31 (d, *J* = 2.0 Hz, 1 H), 3.77 (s, 3 H), 3.72 (td, *J* = 10.8, 8.0, 8.0 Hz, 1 H), 3.26 (dd, *J* = 16.4, 8.0 Hz, 1 H), 3.03 (dd, *J* = 16.4, 8.0 Hz, 1 H), 2.96 (d, *J* = 2.0 Hz, 1 H), 1.01 - 0.97 (m, 12 H), 0.85 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 173.3, 148.1, 145.9, 130.4, 128.5, 108.9, 108.6, 101.2, 71.3, 52.4, 50.5, 38.0, 30.8, 18.3, 18.0, 13.1; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -55.2 (t, *J* = 22.6 Hz, CF_3), -140.1, -142.4 (d, *J* = 15.1 Hz); IR (thin film) 3256, 2947, 2868, 1743, 1687, 1655, 1508 cm^{-1}; HRMS (ESI) calcd for $[C_{30}H_{34}O_6N_1F_7NaSi]^+$ $(M+H)^+$: *m/z* 688.1936, found 688.1947. Carbons that are heavily split by fluorine were not observed in the ^{13}C NMR.

*4.2.4. Cycloadduct **22**:* A flame-dried 250 mL round-bottom flask was charged with **14** (2.52 g, 9.08 mmol, 3.0 equiv), **17** (760 mg, 3.03 mmol, 1.0 equiv), and benzene (50 mL). The reaction mixture was heated to 80 °C and held at this temperature for 12 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford the product as a 2.0:1 mixture of diastereomers. The mixture was recrystallized from EtOAc to afford **22** (370 mg, 23% yield): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (bs, 1 H), 8.29 (d, *J* = 7.8 Hz, 1 H), 7.50 (d, *J* = 7.8, 1 H), 7.28 (m, 1 H), 7.05 (m, 1 H), 6.68 (s, 1 H), 6.62 (s, 1 H), 5.94 (d, *J* = 17.4 Hz, 2 H), 5.14 (d, *J* = 2.4 Hz, 1 H), 3.71 (s, 3 H), 3.48 (td, *J* = 10.8, 9.6, 7.2 Hz, 1 H), 3.18 (dd, *J* = 16.8, 7.2 Hz, 1 H), 3.10 (dd, *J* = 10.8, 2.4 Hz, 1 H), 2.99 (dd, *J* = 16.8, 9.6 Hz, 1 H), 2.48 (s, 3H), 0.81 (s, 9 H), 0.10 (s, 3 H), -0.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 172.6, 147.9, 145.9, 138.9, 133.5, 130.0, 129.2, 128.6, 125.5, 124.4, 120.9, 109.0, 108.7, 101.2, 70.8, 52.2, 49.7, 39.3, 32.4, 25.9, 19.1, 18.3, -3.69, -4.71.

*4.2.5. β-lactam **26**:* A flame-dried reaction tube was charged with **23** (50 mg, 0.094 mmol, 1.0 equiv), 5-iodo-1,2,3-trimethoxybenzene (110 mg, 0.375 mmol, 4.0 equiv), $Pd(OAc)_2$ (4.0 mg, 0.019 mmol, 0.2 equiv), and Ag_2CO_3 (78 mg, 0.282 mmol, 3.0 equiv). Under a nitrogen atmosphere, *t*-BuOH (2 mL) was added into the reaction vessel. The reaction mixture was

stirred for 24 hours at 110 °C. After cooling to room temperature, the reaction was quenched with 1 M HCl and the mixture extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography using (gradient 10% → 25% EtOAc in hexanes) to afford **26** (20 mg, 40% yield) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.00 (d, *J* = 3.0 Hz, 1 H), 8.13 (d, *J* = 7.8 Hz, 1 H), 7.89 (d, *J* = 7.2 Hz, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.47 - 7.42 (m, 2 H), 6.96 (bs, 1 H), 6.88 (bs, 1 H), 6.36 (d, *J* = 4.8 Hz, 1 H), 5.80 (d, *J* = 39.6 Hz, 2 H), 5.22 (bs, 1 H), 4.14 (bs, 1 H), 3.77 (bs, 1 H), 3.60 (bs, 3 H), 0.90 (bs, 9 H), 0.260 (bs, 3 H), 0.158 (bs, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 149.3, 141.8, 136.1, 132.6, 129.1, 126.4, 125.4, 121.6, 100.8, 60.9, 56.2, 51.7, 46.7, 29.6, 25.7, 18.2, -4.82, -5.02. Crystals suitable for X-ray diffraction were obtained by slow diffusion of pentane into an ether solution of **26**

*4.2.6. Methyl ether **29**:* A flame-dried reaction tube was charged with **27** (30 mg, 0.042 mmol, 1.0 equiv) and 5-iodo-1,2,3-trimethoxybenzene (48 mg, 0.16 mmol, 3.9 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times before the addition of anhydrous methanol (1 mL). The reaction mixture was heated to 70 °C and held at this temperature for 24 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude mixture was purified by column chromatography using 20% EtOAc in hexanes as the eluting solvent to afford **29** and *epi*-**29** (13 mg, 51% yield) as a 1.2:1 mixture of diastereomers: Major diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (bs, 1 H), 8.86 (d, *J* = 1.6 Hz, 1 H), 8.78 (d, *J* = 1.6 Hz, 1 H), 8.16 (d, *J* = 1.6 Hz, 1 H), 7.53 – 7.45 (m, 3 H), 6.96 (s, 1 H), 6.82 (s, 1 H), 5.99 (d, *J* = 3.6 Hz, 2 H), 5.22 (d, *J* = 2.8 Hz, 1 H), 4.83 (d, *J* = 9.6 Hz, 1 H), 3.94 – 3.85 (m, 1 H), 3.67 (s, 3 H), 3.49 (s, 3 H), 3.33 (dd, *J* = 10.9, 2.0 Hz, 1 H), 1.08 - 0.96 (m, 12 H), 0.97 – 0.93 (m, 9 H); Minor diastereomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (bs, 1 H), 8.86 (d, *J* = 1.6 Hz, 1 H), 8.77 (d, *J* = 1.6 Hz, 1 H), 8.15 (d, *J* = 1.6 Hz, 1 H), 7.53 – 7.45 (m, 3 H), 6.96 (s, 1 H), 6.92 (s, 1 H), 5.96 (d, *J* = 4.0 Hz, 2 H), 5.52 (d, *J* = 4.8 Hz, 1 H), 5.05 (d, *J* = 5.6 Hz, 1 H), 3.81 – 3.78 (m, 2 H), 3.72 (s, 3 H), 3.54 (s, 3 H), 1.08 - 0.96 (m, 12 H), 0.97 – 0.93 (m, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 172.6, 172.0, 170.5, 148.5, 148.3, 148.3, 147.3, 147.1, 147.0, 138.8, 138.8, 136.3, 136.3, 134.9, 134.9, 132.0, 131.9, 130.0, 129.3, 128.1, 128.1, 127.5, 127.4, 121.7, 121.6, 121.6, 121.5, 116.9, 116.7, 108.2, 107.5, 107.4, 107.1, 101.3, 101.2, 79.0, 77.8, 70.6, 70.2, 58.1, 55.2, 52.0, 51.9, 49.2, 48.5, 47.3, 44.6, 29.8, 18.4, 18.2, 18.2, 18.1, 13.2, 12.8.

*4.2.7. Acetonides **31**, **34**, **35**: i.* A flame-dried round-bottom flask was charged with ester **24** (1.30 g, 2.25 mmol, 1.0 equiv) and anhydrous THF (60 mL). The reaction vessel was evacuated and backfilled with nitrogen, cooled to -78 °C, and $LiAlH_4$ solution (1.0 M in THF, 4.5 mL, 4.5 mmol, 2.0 equiv) added dropwise. After 15 minutes at -78 °C, the reaction mixture was warmed to 0 °C, stirred for 10 minutes at this temperature, and slowly quenched by the addition of EtOAc (1 mL) followed by saturated aqueous ammonium chloride (1 ml). The reaction mixture was diluted with 10% Rochelle's salt solution (100 ml) and thoroughly extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by column chromatography (gradient 10% → 20% EtOAc in hexanes) to afford the intermediate primary alcohol (470 mg, 38%) as a white solid. *ii.* A flask was charged with the aforementioned primary alcohol (547 mg, 1.00 mmol, 1.0 equiv) and anhydrous THF (10 mL). The reaction vessel was evacuated and backfilled with nitrogen, cooled to -78 °C, and TBAF (1 M in THF, 2.0 mL, 2.0 mmol, 2.0 eq) added dropwise. After 15 minutes of stirring at -78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 4 hours. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 mL) and thoroughly extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford a diol intermediate (528 mg) as a white solid that was used without further purification. *iii.* To a round-bottom flask containing the aforementioned crude diol was added *p*-toluenesulfonic acid monohydrate (16.0 mg, 0.08 mmol, 0.1 equiv), 2,2-dimethoxypropane (12.0 mL), and anhydrous THF (20 mL). The reaction mixture was stirred for 12 hours before it was quenched with saturated *aq.* $NaHCO_3$ (50 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (gradient 20% → 50% EtOAc in hexanes) to afford **31** (432 mg, 31% overall yield from **24**). Using this general procedure, acetonide **34** was obtained in 57% overall yield from **20** and acetonide **35** was obtained in 39% overall yield from **21**. Data for **34**: IR (thin film) 3270, 3004, 2903, 1696, 1523 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.60 (d, *J* = 16.7 Hz, 2H), 6.02 – 5.86 (m, 2H), 4.89 (d, *J* = 2.7 Hz, 1H), 4.24 (dd, *J* = 13.4, 2.9 Hz, 1H), 3.95 (d, *J* = 12.9 Hz, 1H), 3.41 (td, *J* = 12.0, 4.7 Hz, 1H), 3.05 (dd, *J* = 16.5, 12.3 Hz, 1H), 2.86 (dd, *J* = 16.7, 4.8 Hz, 1H), 1.94 (d, *J* = 11.4 Hz, 1H), 1.64 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3, 148.4, 146.7, 129.2, 127.3, 109.5, 108.3, 101.3, 100.0, 68.6, 61.7, 39.2, 36.7, 32.9, 29.9, 19.4; ^{19}F NMR (565 MHz, $CDCl_3$) δ -145.3 (d, *J* = 17.7 Hz), -157.0 (t, *J* = 21.5 Hz), -163.3 (dd, *J* = 22.2, 6.2 Hz). Data for **35**: IR (thin film) 3267, 3226, 3005, 2252, 1708 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 6.61 (s, 1H), 6.47 (s, 1H), 5.92 (d, *J* = 5.2 Hz, 2H), 4.89 (s, 1H), 4.22 (d, *J* = 12.9 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.36 (td, *J* = 12.0, 4.5 Hz, 1H), 2.95 (dd, *J* = 16.3, 12.4 Hz, 1H), 2.73 (dd, *J* = 16.6, 4.5 Hz, 1H), 1.94 (d, *J* = 11.7 Hz, 1H), 1.64 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 148.3, 146.5, 128.9, 126.9, 109.1, 107.9, 101.3, 100.1, 68.4, 61.4, 39.3, 36.1, 33.3, 29.4, 19.2; ^{19}F NMR (565 MHz, $CDCl_3$) δ -57.0 (t, *J* = 21.7 Hz), -140.7 – -142.3 (m), -143.5 (d, *J* = 18.0 Hz). Data for **31**: IR (thin film) 3324, 2985, 1674, 1525, 1483, 1275 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (bs, 1H), 8.81 (d, *J* = 3.2 Hz, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 5.92 (d, *J* = 11.3 Hz, 2H), 4.92 (d, *J* = 3.0 Hz, 1H), 4.22 (dd, *J* = 12.5, 3.3 Hz, 1H), 3.96 (d, *J* = 11.9 Hz, 1H), 3.57 (dt, *J* = 11.4, 5.7 Hz, 1H), 3.35 – 3.01 (m, 2H), 2.11 (d, *J* = 13.1 Hz, 1H), 1.62 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 148.6, 148.1, 146.5, 138.6, 136.4, 134.5, 129.7, 128.1, 127.8, 127.5, 121.9, 121.8, 116.6, 109.8, 108.5, 101.2, 99.5, 68.5, 62.0, 41.0, 36.9, 33.5, 29.8, 19.6; HRMS (ESI) calcd for $[C_{25}H_{25}O_5N_2]^+$ $(M+H)^+$: *m/z* 433.1758, found 433.1751.

*4.2.9. C-H Arylation Products **37-41**:* [General Procedure using $(BnO)_2PO_2H$ and K_2CO_3 as additives]: An oven-dried reaction tube was charged with acetonide **32** (0.1 mmol, 1 equiv), aryliodide (0.2 mmol, 2 equiv), $Pd(OAc)_2$ (0.015 mmol, 0.15 equiv), K_2CO_3 (0.15 mmol, 1.5 equiv), and dibenyl phosphate (0.04 mmol, 0.4 equiv). The vessel was evacuated and backfilled with argon and this cycle repeated twice. *t*-AmylOH (1 mL) was added and the sealed reaction vessel was heated to 110 °C for 50 hours. After cooling to room temperature, the mixture was diluted with EtOAc (5 mL) and quenched with saturated *aq*. NaI solution (5 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel

column chromatography of the crude material afforded the arylated product.

Product **37:** Obtained in 58% using 26 mg of **36**: IR (thin film) 3002, 2933, 2836, 1702, 1587, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (bs, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 6.46 (s, 1H), 6.03 (s, 2H), 5.95 (d, *J* = 1.4 Hz, 1H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 1H), 4.22 (dd, *J* = 12.4, 4.7 Hz, 1H), 3.92 (dd, *J* = 12.4, 3.6 Hz, 1H), 3.73 (s, 3H), 3.70 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.50 (s, 6H), 2.45 – 2.38 (m, 1H), 2.36 (s, 3H), 1.63 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 152.9, 148.5, 147.3, 138.4, 137.3, 136.7, 133.2, 132.0, 129.2, 128.2, 124.8, 124.5, 120.2, 109.6, 109.2, 107.0, 101.4, 99.9, 67.7, 62.0, 60.9, 56.0, 48.8, 46.3, 31.4, 29.9, 28.2, 20.7, 19.3; HRMS (ESI) calcd for $[C_{32}H_{35}O_8NNaS]^+$ $(M+Na)^+$: *m/z* 616.1976, found 616.1972.

Product **38**: Obtained in 78% yield using 50 mg of **36**: IR (thin film) 2959, 2925, 2854, 2360, 1699, 1505, 1486, 1436, 1275, 1260, 1231, 1039, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.78 (s, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.43 (s, 1H), 6.40 (d, *J* = 7.6 Hz, 1H), 6.28 (s, 1H), 5.91 (d, *J* = 10.7 Hz, 2H), 5.86 (d, *J* = 4.2 Hz, 2H), 5.01 (d, *J* = 3.5 Hz, 1H), 4.46 (d, *J* = 5.7 Hz, 1H), 4.18 (dd, *J* = 12.5, 4.4 Hz, 1H), 3.88 (dd, *J* = 12.7, 3.1 Hz, 1H), 3.69 (dd, *J* = 12.1, 5.7 Hz, 1H), 2.45 – 2.34 (m, 4H), 1.62 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 148.5, 147.6, 147.3, 146.7, 138.4, 135.0, 133.3, 132.3, 129.3, 128.3, 125.0, 124.4, 122.9, 120.6, 109.9, 109.5, 109.3, 108.0, 101.3, 101.1, 99.7, 67.9, 61.8, 48.4, 46.0, 31.0, 28.6, 20.5, 19.2; HRMS (ESI) calcd for $[C_{30}H_{29}O_7NNaS]^+$ $(M+Na)^+$: *m/z* 570.1557, found 570.1576.

Product **39**: Obtained in 43% (^1H NMR yield) from 50 mg of **36**: IR (thin film) 3304, 2925, 1506, 1275, 1260, 1232, 1077, 764, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.14 (d, *J* = 8.1, 1H), 7.51 (d, *J* = 7.8, 1H), 7.31 – 7.26 (m, 3H), 7.08 (t, *J* = 7.8, 1H), 6.79 (s, 1H), 6.73 (d, *J* = 8.5, 2H), 6.38 (s, 1H), 5.92 (d, *J* = 11.9, 2H), 5.02 (d, *J* = 3.4, 1H), 4.49 (d, *J* = 5.7, 1H), 4.17 (dd, *J* = 12.6, 4.3, 1H), 3.86 (dd, *J* = 12.6, 3.0, 1H), 3.74 (dd, *J* = 12.1, 5.8, 1H), 2.39 (s, 3H), 2.33 – 2.28 (m, 1H), 1.62 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 148.6, 147.4, 140.3, 138.3, 133.4, 131.7, 131.4, 131.3, 129.3, 128.5, 125.1, 124.6, 121.4, 120.5, 109.4, 109.4, 101.4, 99.7, 67.9, 61.8, 48.2, 45.7, 31.0, 28.7, 20.4, 19.2; HRMS (ESI) calcd for $[C_{29}H_{28}O_5NBrNaS]^+$ $(M+Na)^+$: *m/z* 604.0764, found 604.0786.

Product **40**: Obtained in 88% yield from 50 mg of **36**: IR (thin film) 3334, 2988, 1539, 1577, 1435, 1230, 1163, 1038, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.07 (d, *J* = 8.2, 1H), 7.75 – 7.70 (m, 1H), 7.64 (d, *J* = 8.5, 1H), 7.59 – 7.54 (m, 1H), 7.49 (dd, *J* = 7.9, 1.6, 1H), 7.41 – 7.34 (m, 2H), 7.28 (d, *J* = 1.7, 1H), 7.22 (t, *J* = 8.4, 7.9, 1H), 7.05 (t, *J* = 7.7, 1H), 7.02 (d, *J* = 8.5, 1H), 6.85 (s, 1H), 6.44 (s, 1H), 5.92 (s, 1H), 5.90 (s, 1H), 5.10 (d, *J* = 3.5, 1H), 4.72 (d, *J* = 5.8, 1H), 4.18 (dd, *J* = 12.6, 4.5, 1H), 3.87 (dd, *J* = 12.7, 3.2, 1H), 3.81 (dd, *J* = 12.1, 5.8, 1H), 2.50 – 2.44 (m, 1H), 2.30 (s, 3H), 1.64 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 148.6, 147.3, 138.8, 138.5, 133.3, 133.3, 132.7, 132.2, 129.2, 128.6, 128.5, 127.9, 127.8, 127.8, 127.7, 126.1, 125.9, 125.0, 124.4, 120.5, 109.7, 109.3, 101.3, 99.7, 68.0, 61.8, 48.8, 46.1, 31.2, 28.6, 20.5, 19.1; HRMS (ESI) calcd for $[C_{33}H_{31}O_5NNaS]^+$ $(M+Na)^+$: *m/z* 576.1815, found 576.1833.

Product **41**: Obtained in 45% yield from 50 mg of **36**: IR (thin film) 3337, 3054, 2988, 2885, 1733, 1649, 1578, 1371, 1091, 754 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.06 (d, *J* = 8.2, 1H), 7.76 (d, *J* = 8.7, 1H), 7.72 (d, *J* = 8.4, 2H), 7.48 (d, *J* = 7.8, 1H), 7.45 (d, *J* = 3.7, 1H), 7.24 (t, *J* = 7.6, 1H), 7.21 (d, *J* = 8.0, 2H), 7.07 (t, *J* = 7.6, 1H), 6.95 (s, 1H), 6.87 (d, *J* = 8.6, 1H), 6.81 (s, 1H), 6.43 (d, *J* = 3.7, 1H), 6.37 (s, 1H), 5.89 (d, *J* = 12.9, 2H), 5.04 (d, *J* = 3.6, 1H), 4.62 (d, *J* = 5.6, 1H), 4.15 (dd, *J* = 12.7, 4.6, 1H), 3.84 (dd, *J* = 12.6, 3.3, 1H), 3.73 (dd, *J* = 12.1, 5.7, 1H), 2.45 – 2.36 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 148.4, 147.2, 145.0, 138.4, 136.3, 135.7, 134.0, 133.4, 132.5, 130.8, 130.1, 130.0, 129.2, 128.4, 127.0, 127.0, 126.6, 126.4, 125.0, 124.4, 122.3, 120.4, 113.0, 109.6, 109.2, 109.0, 101.3, 100.2, 99.8, 67.8, 61.8, 48.5, 46.1, 31.1, 28.4, 21.8, 20.6, 19.0; HRMS (ESI) calcd. for $[C_{38}H_{36}O_7N_2NaS_2]^+$ $(M+Na)^+$: *m/z* 719.1856, found 719.1884.

*4.2.10. C-H Arylation Products **42-44**:* [General Procedure using Ag_2CO_3 and K_2CO_3 as additives]: An oven-dried reaction tube was charged with acetonide **36** (0.1 mmol, 1 equiv.), $Pd(OAc)_2$ (0.02 mmol, 0.20 equiv), K_2CO_3 (0.3 mmol, 3 equiv), Ag_2CO_3 (0.4 mmol, 0.4 equiv), and aryliodide (0.4 mmol, 4 equiv). The tube was evacuated and back-filled with nitrogen and then toluene (1 mL) added. The reaction tube was placed into a pre-heated 115 °C oil bath and heated for 38-44 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), and quenched with saturated *aq.* $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc three times and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Silica gel column chromatography afforded the arylated product.

Product **42:** Obtained in 30% yield using 260 mg of **36** (in 10 mL of toluene): ^1H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.29 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.39 (s, 1H), 5.92 (d, *J* = 4.7 Hz, 2H), 5.83 (s, 2H), 5.00 (d, *J* = 3.5 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 1H), 4.18 (dd, *J* = 12.8, 4.5 Hz, 1H), 3.88 (dd, *J* = 12.5, 2.6 Hz, 1H), 3.77 (s, 6H), 3.72 (m, 1H), 2.39 (s, 3H), 2.38 (d, *J* = 3.0 Hz, 1H), 1.62 (s, 3H), 1.42 (s, 3H). HRMS (ESI) calcd for $[C_{30}H_{32}O_7N_2S]$+ [M+H]+: *m/z* 565.2003, found 565.2006.

Product **43:** Obtained in 24% yield using 51 mg of **36**: ^1H NMR (600 MHz, $CDCl_3$): δ = 8.50 (br s, 1H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.07 (td, *J* = 7.6, 1.4 Hz, 1H), 6.80 (s, 1H), 6.80 (t, *J* = 56.5 Hz, 1H), 6.51 (s, 1H), 6.41 (s, 1H), 6.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.92 (dd, *J* = 13.4, 1.4 Hz, 2H), 5.03 (d, *J* = 3.5 Hz, 1H), 4.55 (d, *J* = 5.8 Hz, 1H), 4.19 (dd, *J* = 12.6, 4.4 Hz, 1H), 3.90 (dd, *J* = 12.8, 3.1 Hz, 1H), 3.77 (dd, *J* = 12.1, 5.9 Hz, 1H), 3.45 (s, 3H), 2.38 (s, 3H), 2.35 (dd, *J* = 12.0, 3.7 Hz, 1H), 1.63 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9, 157.0, 148.6, 147.4, 145.6, 138.1, 133.1, 131.4, 129.2, 128.4, 126.0, 126.0, 125.9, 125.0, 124.6, 121.8, 121.3, 120.4, 119.0, 113.2, 112.5, 111.7, 110.1, 109.4, 109.3, 108.8, 101.4, 99.7, 67.8, 61.8, 55.7, 55.3, 48.8, 45.9, 31.1, 30.1, 29.9, 28.5, 20.4, 19.1. HRMS (ESI^-) calcd for $[C_{31}H_{30}O_6SNF_2]^-$ $[M-H]^-$: *m/z* 582.1762, found 582.1761.

Product **44:** Obtained in 35% yield using 50 mg of **36**: ^1H NMR (600 MHz, $CDCl_3$): δ = 8.15 (br s, 1H), 7.54 (d, *J* = 3.8 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 6.69 (d, *J* = 3.8 Hz, 1H), 6.50 (s, 1H), 5.91 (d, *J* = 6.4 Hz, 2H), 5.00 (d, *J* = 3.4 Hz, 1H), 4.79 (d, *J* = 5.6 Hz, 1H), 4.23 (dd, *J* = 12.7, 4.2 Hz, 1H), 3.94 (dd, *J* = 12.7, 2.8 Hz, 1H), 3.77 (s, 3H), 2.53 (dd, *J* = 12.2, 3.5 Hz, 1H), 2.39 (s, 3H), 1.62 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3, 162.4, 152.8, 148.4, 147.6, 137.9, 133.1, 132.9, 132.8, 131.2, 128.9, 127.7, 127.2, 125.3, 124.6, 120.8, 109.4, 109.2, 101.3, 99.5, 67.5, 61.6, 52.0, 45.2, 44.3, 31.3, 28.6, 20.0, 18.9.

HRMS (ESI) calcd for $[C_{29}H_{29}O_7NS_2Na]^+$ $(M+Na)^+$: *m/z* 590.1283, found 590.1272.

*4.2.10. Podophyllotoxin (**1**) and Analogs **46**-**52**: [General procedure]:* A 10 mL round bottom flask was charged with the arylated product (0.1 mmol, 1 equiv), THF (1 mL), and H_2O (1 mL). The mixture was cooled to 0°C and TFA (1 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature over the course of 24 hours at which point it was diluted with EtOAc (5 mL), quenched with $NaHCO_3$ (15 mL), and extracted with EtOAc (3 x 10 mL). The organic phase was washed with brine, dried over $MgSO_4$ concentrated *in vacuo*, and purified by column chromatography to give the podophyllotoxin derivative as a mixture of C-4 diastereomers (typically ~ 1.5:1 dr)

Podophyllotoxin (**1**): obtained in 76% on 43 mg scale (1.3:1 mixture): IR (thin film) 3465, 2893, 2837, 1773, 1587, 1482 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.51 (s, 1H), 6.37 (s, 2H), 5.98 (d, *J* = 12.2 Hz, 2H), 4.77 (d, *J* = 9.5 Hz, 1H), 4.70 – 4.54 (m, 2H), 4.09 (t, *J* = 9.5 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 6H), 2.84 (dd, *J* = 14.4, 4.7 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.03 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.5, 152.8, 148.0, 147.9, 137.5, 135.6, 133.3, 131.4, 110.0, 108.6, 106.5, 101.7, 73.1, 71.5, 61.0, 56.5, 45.5, 44.3, 41.0; HRMS (ESI) calcd for $[C_{22}H_{22}O_8Na]^+$ $(M+Na)^+$: *m/z* 437.1207, found 437.1206

Analog **46**: obtained in 67% on 18 mg scale (1.4:1 mixture): IR (thin film) 3411, 3005, 2359, 2340, 1767, 1502, 1482, 1257, 1260, 1037, 764 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.12 (s, 1H), 6.69 (d, *J* = 8.0, 1H), 6.64 – 6.59 (m, 2H), 6.46 (s, 1H), 5.96 (s, 2H), 5.90 (dd, *J* = 7.5, 1.4, 2H), 4.75 (d, *J* = 9.4, 1H), 4.60 (dd, *J* = 8.8, 7.0, 1H), 4.56 (d, *J* = 4.7, 1H), 4.09 (d, *J* = 9.0, 1H), 2.82 (dd, *J* = 14.2, 4.8, 1H), 2.80 – 2.72 (m, 1H), 1.96 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 148.1, 147.9, 147.6, 146.9, 133.8, 133.2, 131.8, 124.4, 111.3, 109.9, 107.9, 106.3, 101.6, 101.2, 73.1, 71.5, 45.3, 43.8, 40.9; HRMS (ESI) calcd for $[C_{20}H_{16}O_7Na]$+ (M+Na)+: m/z 391.0788, found 391.0799.

Analog **47**: obtained in 61% on 20 mg scale (1.3:1 mixture): (major isomer): ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7, 1H), 7.76 (d, *J* = 8.4, 2H), 7.52 (d, *J* = 3.6, 1H), 7.26 (s, 1H), 7.24 (d, *J* = 8.3, 2H), 7.16 – 7.10 (m, 2H), 6.56 (d, *J* = 3.6, 1H), 6.41 (s, 1H), 5.95 (d, *J* = 1.7, 1H), 4.78 (d, *J* = 9.4, 1H), 4.71 (d, *J* = 4.9, 1H), 4.54 (dd, *J* = 8.8, 7.2, 1H), 4.08 (dd, *J* = 10.3, 8.8, 1H), 2.87 (dd, *J* = 14.2, 5.1, 1H), 2.82 – 2.72 (m, 1H), 2.36 (s, 3H), 2.02 (bs, 1H). (minor isomer): ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6, 1H), 7.76 (d, *J* = 8.0, 2H), 7.51 (d, *J* = 3.8, 1H), 7.24 (d, *J* = 8.1, 2H), 7.17 (s, 1H), 7.03 (d, *J* = 8.7, 1H), 6.89 (s, 1H), 6.54 (d, *J* = 3.7, 1H), 6.46 (s, 1H), 5.96 (d, *J* = 7.2, 2H), 4.89 (d, *J* = 3.5, 1H), 4.72 (d, *J* = 5.3, 1H), 4.36 (dd, *J* = 10.8, 8.2, 1H), 4.29 (t, *J* = 8.1, 1H), 3.32 (dd, *J* = 14.2, 5.2, 1H), 2.91 – 2.80 (m, 1H), 2.36 (s, 3H), 1.82 (d, *J* = 4.2 1H). ^{13}C NMR (150 MHz, $CDCl_3$) (combined minor and major isomers) δ = 175.0, 174.3, 148.9, 148.1, 147.9, 147.7, 145.2, 145.1, 135.6, 135.6, 135.1, 134.7, 134.0, 134.0, 133.3, 132.8, 132.0, 131.9, 130.7, 130.6, 130.2, 130.2, 127.5, 127.4, 127.1, 126.7, 126.7, 123.8, 123.6, 112.9, 112.9, 110.7, 110.0, 109.1, 109.0, 108.9, 106.4, 101.7, 101.6, 73.1, 71.5, 67.8, 67.0, 45.4, 44.0, 43.8, 40.7, 40.6, 38.2, 21.8; IR (thin film) 3458, 3056, 2913, 17773, 1596, 1483 cm-1; HRMS (ESI) calcd for $[C_{28}H_{23}O_7NNaS]$+ (M+Na)+: m/z 540.1087, found 540.1095.

Analog **48**: obtained in 79% on 18 mg scale (1.4:1 mixture): IR (thin film) 3411, 3005, 2359, 2340, 1767, 1502, 1482, 1257, 1260, 1037, 764 cm-1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 1H), 7.76 – 7.71 (m, 2H), 7.48 – 7.40 (m, 4H), 7.19 (s, 1H), 6.48 (s, 1H), 6.03 – 5.90 (m, 2H), 4.85 – 4.79 (m, 2H), 4.56 (dd, *J* = 8.9, 7.2, 1H), 4.10 (dd, *J* = 10.3, 8.9, 1H), 2.94 (dd, *J* = 14.3, 5.0, 1H), 2.85 (dtd, *J* = 14.2, 10.0, 7.2, 1H), 2.05 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 148.2, 148.0, 137.7, 133.4, 133.1, 132.7, 131.7, 130.0, 129.0, 128.2, 127.7, 127.7, 126.2, 110.1, 106.4, 101.7, 73.2, 71.5, 45.4, 44.3, 41.0; HRMS (ESI) calcd for $[C_{23}H_{18}O_5Na]$+ (M+Na)+: m/z 397.1046, found 397.1058.

Analog **49**: obtained in 72% on 22 mg scale (1.6:1 mixture): IR (thin film) 3456, 3004, 2970, 1738, 1365, 1229, 1217, 757 cm^{-1}; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 7.41 (d, *J* = 8.5, 2H), 7.20 (s, 1H), 7.10 (d, *J* = 8.4, 2H), 6.47 (s, 1H), 5.98 (d, *J* = 4.4, 2H), 4.96 (bs, 1H), 4.82 (d, *J* = 9.7, 1H), 4.62 (d, *J* = 5.2, 1H), 4.51 (dd, *J* = 8.7, 7.1, 1H), 4.16 (dd, *J* = 10.5, 8.6, 1H), 3.13 (dd, *J* = 14.4, 5.3, 1H), 2.77 – 2.65 (m, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ 175.1, 148.6, 148.6, 141.5, 136.2, 134.1, 132.0, 131.7, 121.6, 110.2, 107.7, 102.5, 72.7, 72.2, 45.4, 44.5, 41.7.

Analog **50**: obtained in 57% on 42.4 mg scale (1.8:1 mixture): ^1H NMR (600 MHz, $CDCl_3$): major isomer: δ = 7.64 (d, *J* = 3.9 Hz, 1H), 7.14 (s, 1H), 7.06 (dd, *J* = 3.9, 0.8 Hz, 1H), 6.58 (s, 1H), 5.99 (s, 2H), 4.82 (d, *J* = 4.2 Hz, 1H), 4.75 (d, *J* = 8.7 Hz, 1H), 4.66 (dd, *J* = 8.9, 6.4 Hz, 1H), 4.15 (t, *J* = 9.6 Hz, 1H), 3.83 (m, *J* = 5.6 Hz, 1H), 3.82 (s, 3H), 2.86 (m, 1H). minor isomer: δ = 7.62 (d, *J* = 3.9 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 6.85 (s, 1H), 6.62 (s, 1H), 6.00 (m, 2H), 4.87 (d, *J* = 3.3 Hz, 1H), 4.84 (d, *J* = 5.2 Hz, 1H), 4.42 (d, *J* = 2.1 Hz, 1H), 4.13 (m, 1H), 3.81 (s, 3H), 3.33 (dd, *J* = 14.2, 5.1 Hz, 1H), 2.83 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) (combined minor and major isomers): δ = 175.0, 174.2, 162.7, 162.7, 151.8, 151.3, 148.6, 148.4, 148.1, 147.9, 133.6, 133.2, 133.0, 132.8, 131.6, 131.1, 130.3, 129.0, 129.0, 110.5, 109.8, 109.5, 106.8, 101.9, 101.7, 72.5, 71.7, 68.1, 66.6, 52.3, 52.3, 45.2, 41.5, 40.4, 39.8, 39.6, 38.9, 29.8.

Analog **51**: obtained in 75% on 41.4 mg scale (1.8:1 mixture): ^1H NMR (600 MHz, $CDCl_3$): major isomer: δ = 7.12 (s, 1H), 6.41 (s, 1H), 6.11 (s, 2H), 5.96 (d, *J* = 1.4 Hz, 2H), 4.72 (d, *J* = 9.7 Hz, 1H), 4.58 (dd, *J* = 8.9, 7.2 Hz, 1H), 4.49 (d, *J* = 5.1 Hz, 1H), 4.08 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.85 (s, 6H), 2.85 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.72 (m, 1H). minor isomer: δ = 6.84 (s, 1H), 6.46 (s, 1H), 6.02 (s, 2H), 5.95 (d, *J* = 1.4 Hz, 2H), 4.84 (d, *J* = 3.3 Hz, 1H), 4.51 (d, *J* = 5.5 Hz, 1H), 4.35 (m, 2H), 3.85 (s, 6H), 3.31 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.81 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) (combined minor and major isomers): δ = 174.7, 174.0, 163.1, 163.1, 154.3, 154.0, 148.8, 148.1, 148.1, 147.9, 133.5, 132.0, 131.0, 130.1, 110.3, 109.6, 109.3, 106.5, 103.5, 103.4, 101.8, 101.6, 72.9, 71.5, 67.8, 66.8, 53.6, 44.8, 43.5, 43.4, 41.3, 40.0, 38.6, 29.8.

4.4 X-ray crystallographic data

Crystallographic data for structures **19** and **26** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/ (CDCC # 1899263 for **19**, #1899264 for **26**, #1502051 for **27**, and # 1502052 for **32**).

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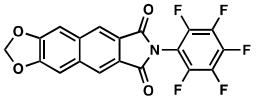
References and notes

1. Kearney, S. E. et. al. *ACS Cent. Sci.* **2018**, *4*, 1727.
2. (a) Newman, D. G.; Cragg, G. M. *Nat. Prod. Rep*. **2016**, *79*, 629. (b) Cragg, G. M.; Pezzuto, J. M., *Med. Princ. Pract.* **2016**, *25*, 41.
3. Stähelin, H. F.; von Wartburg, A. Cancer. Res. **1991**, *51*, 5.
4. (a) Fortune, J. M.; Osheroff, N. *Prog. Nucleic Acid Res.* **2000**, *64*, 221. (b) Nitiss, J. L. *Nat. Rev. Cancer* **2009**, 9, 338. (c) Burden, D. A.; Osheroff, N. *BBA-Gene Struct. Expr*. **1998**, *1400*, 139.
5. Wang, J. C. *Nat. Rev. Mol. Cell. Bio*. **2002**, *3*, 430.
6. (a) Saulnier, M. G.; Vyas, D. M.; Langley, D. R.; Doyle, T. W.; Rose, W. C.; Crosswell, A. R.; Long, B. H. *J. Med. Chem*. **1989,** *32*, 1418. (b) Long, B. H.; Casazza, A.-M. *Cancer Chemoth. Pharm.* **1994**, *34*, 26. (c) Hu, H.; Wang, Z.-Q.; Liu, S.-Y.; Cheng, Y.-C.; Lee, K.-H. *J. Med. Chem*. **1992**, *35*, 866. (d) Bertounesque, E.; Meresse, P.; Monneret, C.; Florent, J.-C. *Tetrahedron Lett*. **2007**, *48*, 5781. (e) Cho, S. J.; Kashiwada, Y.; Bastow, K. F.; Cheng, Y.-C.; Lee, K.-H. *J. Med. Chem*. **1996**, *39*, 1396. (f) G. M. Cragg, D. G. I. Kingston, D. Newman, *Anticancer Agents from Natural Products*; CRC Press: Boca Raton, 2012; Chapter 5.
7. Wu, C.-C.; Li, T.-K.; Farh, L.; Lin, L.-Y.; Lin, T.-S.; Yu, Y.-J.; Yen, T.-J.; Chiang, C.-W.; Chan, N.-L. *Science*, **2011**, *333*, 459.
8. Wilstermann, A. M.; Bender, R. P.; Godfrey, M.; Choi, S.; Anklin, C.; Berkowitz, D. B.; Osheroff, N.; Graves, D. E. *Biochemistry* **2007**, *46*, 8217.
9. Relling, M. V.; Nemec, J.; Schuetz, E. G.; Schuetz, J. D.; Gonzalez, F. J.; Korzekwa, K. R. *Mol. Pharmacol.* **1994**, *45*, 352.
10. (a) Jacob, D. A.; Mercer, S. L.; Osheroff, N.; Deweese, J. E. *Biochemistry* **2011**, *50*, 5660. (b) Smith, N. A.; Byl, J. W.; Mercer, S. L.; Deweese, J. E.; Osheroff, N. *Biochemistry* **2014**, *53*, 3229.
11. a) Ezoe, S. *Int. J. Environ. Res. Public Health* **2012**, *9*, 2444. (b) Azarova, A. M.; Lyu, Y. L.; Lin, C.-P.; Tsai, Y.-C.; Lau, J. Y.-N.; Wang, J. C.; Liu, L. F. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 11014. b) Kollmannsberger, C.; Beyer, J.; Droz, J. P.; Harstrick, A.; Hartmann, J. T.; Biron, P.; Flechon, A.; Schoffski, P.; Kuczyk, M.; Schmoll, H. J.; Kanz, L.; Bokemeyer, C. *J. Clin. Oncol*. **1998**, *16*, 3386. c) Winick, N. J.; McKenna, R. W.; Shuster, J. J.; Schneider, N. R.; Borowitz, M. J.; Bowman, W. P.; Jacaruso, D.; Kamen, B. A.; Buchanan, G. R. *J. Clin. Oncol*. **1993**, *11*, 209.
12. Felix, C. A.; Walker, A. H.; Lange, B. J.; Williams, T. M.; Winick, N. J.; Cheung, N.-K. V.; Lovett, B. D.; Nowell, P. C.; Blair, I. A.; Rebbeck, T. R. *Proc. Natl. Acad. Sci*. USA **1998**, *95*, 13176.
13. For examples of C(sp3)-H bond arylation (and vinylation) in total synthesis, see: a) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed*. **2010**, *49*, 958; b) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc*. **2011**, *133*, 19076; c) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed*. **2012**, *51*, 7507. (d) He, G.; Zhang, S.-Y.; Nack, W. A.; Pearson, R.; Rabb-Lynch, J.; Chen, G. *Org. Lett.* **2014**, *16*, 6488. (e) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem*. **2014**, *79*, 2430. (f) Dailler, D.; Danoun, G.; Baudoin, O. *Angew. Chem. Int. Ed*. **2015**, *54*, 4919. (g) Dailler, D.; Danoun, G.; Ourri, B.; Baudoin, O. *Chem. Eur. J*. **2015**, *21*, 9370. (h) Zhou, M. *et al*. *Org. Lett.* **2015**, *17*, 6062. (i) Panish, R. A.; Chintala, S. R.; Fox, J. M. *Angew. Chem. Int. Ed*. **2016**, *55*, 4983. (j) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc*. 2016, *138*, 9803. (k) Chapman, L. M.; Beck, J. C.; Lackner, C. R.; Wu, L.; Reisman, S. E. *J. Org. Chem*. **2018**, *83*, 6066.
14. For total and formal syntheses of **1** and 4-*epi* **1**, see: a) Gensler, W. J.; Gatsonis, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 1748. b) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004. c) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082. d) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc. Chem. Commun.* **1980**, 262. e) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. f) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1986**, *51*, 4749. g) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099. h) Kaneko, T.; Wong, H. *Tetrahedron Lett*. **1987**, *28*, 517. i) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc*. **1988**, *110*, 7854. j) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663. k) Jones, D. W.; Thompson, A. M. *J. Chem. Soc. Chem. Commun.* **1989**, 1370. l) Van Speybroeck, R.; Guo, H.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron* **1991**, *47*, 4675. m) Charlton, J. L.; Koh, K. *J. Org. Chem*. **1992**, *57*, 1514. n) Kraus, G. A.; Wu, Y. *J. Org. Chem.* **1992**, *57*, 2922. o) Bush, E. J.; Jones, D. W. *J. Chem. Soc. Chem. Commun*. **1993**, 1200. p) Bush, E. J.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 151. q) Medarde, M.; Ramos, A. C.; Caballero, E.; López, J. L.; Peláez-Lamamié de Clairac, R.; San Feliciano, A. S. *Tetrahedron Lett.* **1996**, *37*, 2663. r) Hadimani, S. B.; Tanpure, R. P.; Bhat, S. V. *Tetrahedron Lett*. **1996**, *37*, 4791. s) Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem*. **2000**, *65*, 847. t) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem. Int. Ed*. **2003**, *42*, 2487. u) Reynolds, A. J.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 12108. v) Casey, M.; Keaveney, C. M. *Chem. Commun.* **2004**, 184. w) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325. x) Wu, Y.; Zhang, H.; Zhao, Y.; Zhao, J.; Chen, J.; Li, L. *Org. Lett.* **2007**, *9*, 1199. y) Stadler, D.; Bach, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 7557. z) Mingoia, F.; Vitale, M.; Madec,D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760. aa) Wu, Y.; Zhao, J.; Chen, J.; Pan, C.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 597. bb) Takahashi, M.; Suzuki, N.; Ishikawa, T. *J. Org. Chem.* **2013**, *78*, 3250. (cc) Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3115. (dd) Lisiecki, K.; Krawczyk, K. K.; Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. *Org. Biomol. Chem*. **2016**, *14*, 460. (ee) Hajra, S.; Garai, S.; Hazra, S. *Org. Lett.* **2017**, *19*, 6530. (ff) Xiao, J.; Cong, X.-W.; Yang, G.-Z.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2018**, *20*, 1651.
15. For a recent review on the chemistry and biology of podophyllotoxins, see: Yu, X.; Che, Z.; Xu, H. *Chem. Eur. J.* **2017**, *23*, 4467.
16. For a recent review on thermal *o*-quinodimethane cycloadditions, see: Yang, B.; Gao, S. *Chem. Soc. Rev.* **2018**, *47*, 7926.
17. a) Corbet, M.; De Campo, F.; *Angew. Chem. Int. Ed*. **2013**, *52*, 9896. b) Sambiago, C. *et al*. *Chem. Soc. Rev.* **2018**, *47*, 6603.
18. For the synthesis of β–lactams via related processes, see: a) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. b) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed*. **2013**, *52*, 13588.
19. As an example, when employing **19** or **20** the napthalene shown below could be detected in crude reaction mixtures:



20. Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

21. Heating **27** with $B_2(pin)_2$ afforded a product believed to be the result of C-1 borylation. Unfortunately, however, this compound failed to take part in a Suzuki cross coupling.
22. a) Canty, A. J. *Acc. Chem Res*. **1992**, *25*, 83. b) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. c) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev*. **2010**, *110*, 824. d) Topczewski, J. J.; Sanford, M. S. *Chem. Sci*. **2015**, *6*, 70.
23. Electronic factors also influence the reductive elimination pathway in these reactions. For a pertinent example, see: Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett*. **2014**, *16*, 480.
24. a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. c) Figg, T. M.; Wasa, M.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc.* **2013**, *135*, 14206. d) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. e) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598. f) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. g) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc*. **2007**, *129*, 3510. h) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 7190. i) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res*. **2012**, *45*, 788.
25. a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. b) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed*. **2012**, *51*, 5188. c) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. d) Nadres, E. T.; Franco Santos, G. I.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689.
26. For related early examples, see: a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. b) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. c) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc*. **2012**, *134*, 7313. d) He, G.; Chen, G. *Angew. Chem. Int. Ed*. **2011**, *50*, 5192. e) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc*. **2012**, *134*, 3. f) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 11124. g) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712. h) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. i) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. j) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2013**, *52*, 13588. k) Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 1.
27. a) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. b) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc*. **2013**, *135*, 2124. c) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906.
28. Choi, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796
29. Allevi, P.; Anastasia, M.; Ciuffreda, P.; Bigatti, E.; Macdonald, P. *J. Org. Chem*. **1993**, *58*, 4175.