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Aryl Amidation Routes to Dihydropyrrolo[3,2-*e*]indoles and Pyrrolo[3,2-*f*]tetrahydroquinolines: Total Synthesis of the (±)-CC-1065 CPI Subunit

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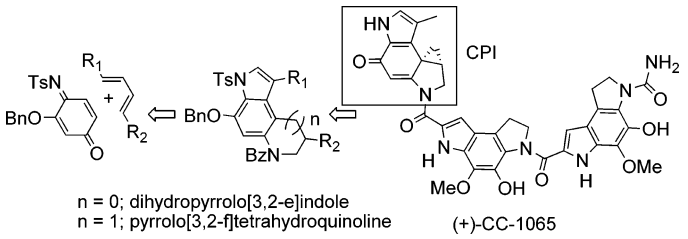
Received October 5, 2006



CC-1065 and the related duocarmycins are members of a structurally unique family of naturally occurring molecules and remain some of the most rigorously studied antitumor compounds to date. Herein we describe a total synthesis of the (±)-CC-1065 CPI subunit in an overall yield of 9.3% from commercially available 5-fluoro-2-nitrophenol. The key steps of this synthesis are a Diels−Alder reaction of an *o*-benzoxy-monoimine quinoid and an intramolecular aryl triflate amidation, which formed the pyrrolo-[3,2-*f*]tetrahydroquinoline intermediate en route to CPI.

Introduction

Over the past two decades CC-1065 and related compounds have received intense scrutiny as antitumor agents. Their derivatives remain as some of the strongest candidates for new exceptionally potent and highly selective therapeutic agents against tumorgenic cells.

CC-1065 was isolated from cultures of *Streptomyces zelensis* (*S. zelensis*) at Upjohn in 1978, and the structure was disclosed in 1980.[1] Subsequently, it was found that CC-1065 exhibited a 20 pM cytotoxicity against tumorgenic cells. Comparatively, this activity was approximately 10^3 times greater than classical DNA intercalating agents, such as Adriamycin.[1] Structurally, CC-1065 (**1**, Figure 1) consists of two identical central and eastern pyrrolo[3,2-*e*]indole subunits linked together to the western subunit by amide bonds through the pyrrolidine nitrogen. The western portion is referred to as the 1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-*e*]indol-4-one, or CPI subunit for simplicity, and boasts an unprecedented and potentially reactive pyrrolo-fused cyclopropane which is bonded directly at C4 of the pyrrole and fused to a hexadienone moiety. The natural enantiomer of CC-1065 has the 8b*R*,9a*S* stereochemical orientation of the cyclopropane ring in the CPI subunit (Figure 1).[2]

Several syntheses of the CC-1065 CPI subunit have been accomplished,[1] although Tietze's elegant synthesis of protected CPI by two metal-mediated cyclizations constitutes the most expedient route to this molecule.[3] Pertinent to this study is Kraus' imaginative synthesis of protected CPI through a Plieninger indolization.[4] Preparation of the N,N′-unprotected CPI subunit, which is useful for the total synthesis of CC-1065, has been demonstrated only a few times.[5] Related compounds (Figure 1), such as duocarmycin A (**2**) and duocarmycin SA (**3**), have been synthesized numerous times[6] and studied extensively by Boger and co-workers.[6c,d] More recently, the absolute configuration, structural revision, and first total synthesis of a similar antitumor compound called yatakemycin (**4**)

(1) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787−828.
(2) Martin, D. G.; Kelly, R. C.; Watt, W.; Wicnienski, N.; Mizsak, S. A.; Nielsen, J. W. Prairie, M. D. *J. Org. Chem.* **1988**, *53*, 4610−4613.
(3) (a) Tietze, L. F.; Buhr, W.; Looft, J.; Grote, T. *Chem. Eur. J.* **1998**, *4*, 1554−1560. (b) Tietze, L. F.; Buhr, W. *Angew. Chem., Int. Ed.* **1995**, *34*, 1366−1368. (c) Tietze, L. F.; Grote, T. *Chem. Ber.* **1993**, *126*, 2733−2737. (d) Tietze, L. F.; Grote, T. *J. Org. Chem.* **1994**, *59*, 192−196.
(4) (a) Kraus, G. A.; Yue, S.; Sy, J. *J. Org. Chem.* **1985**, *50*, 283−284. (b) Kraus, G. A.; Yue, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1198−1199.
(5) (a) Magnus, P.; Gallagher, T.; Schultz, J.; Or, Y.-S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706−2711. (b) Moody, C. J.; Pass, M.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1986**, *14*, 1062−1063.

10.1021/jo062064j CCC: $37.00 © 2007 American Chemical Society
Published on Web 12/15/2006

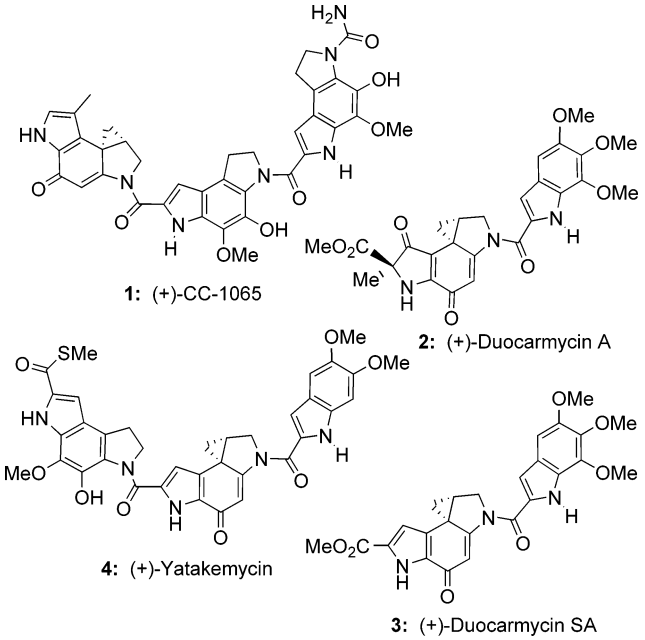


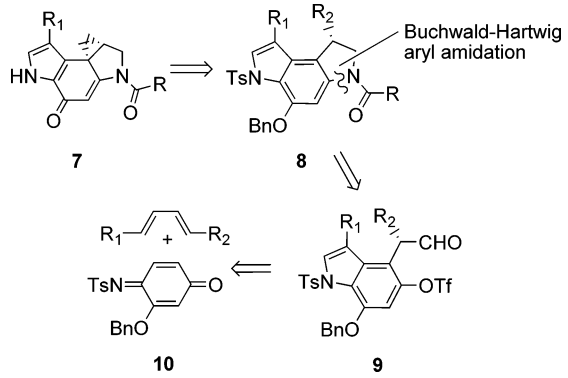
FIGURE 1. CC-1065 and related spirocyclopropyl dienone containing compounds.

was accomplished by Boger and co-workers.[7] This synthesis was followed soon thereafter by Fukuyama and co-workers, who utilized highly efficient copper-mediated aryl amination protocols to construct the indole and indoline moieties of yatakemycin.[8]

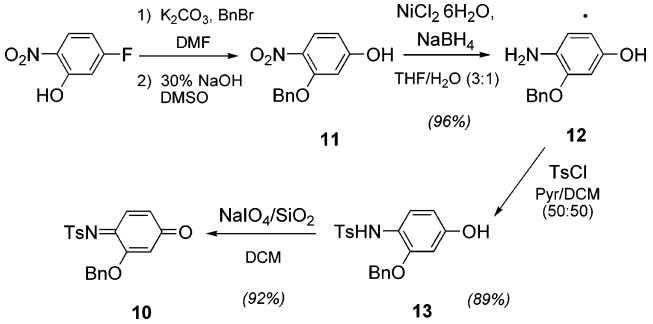
Results and Discussion

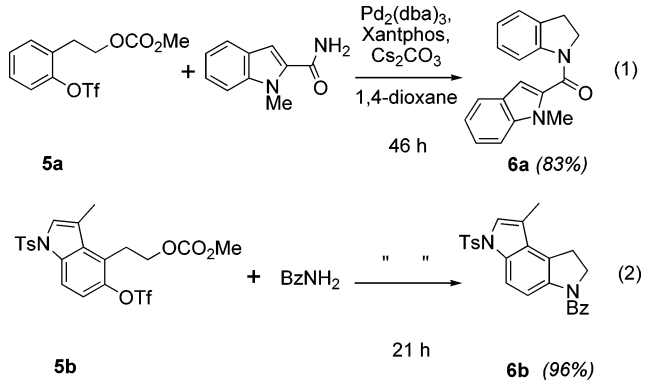
We recently disclosed a methodology that allows for the sequential palladium-catalyzed aryl amidation of trifluoromethanesulfonates (triflates) followed by displacement of a phenethyl carbonate to yield indolines in one pot.[9] The scope of this reaction was fairly general, tolerating a wide array of substitution patterns on the aryl subunit and a plethora of amide cross-coupling partners. This is illustrated briefly in eqs 1 and 2 with selected examples. Most notably and relevant to the synthesis of CC-1065 and CPI, *N*-methyl indole-2-carboxamide was found to be a competent cross-coupling partner with *o*-trifloxyphenethylcarbonate **5a** in this domino reaction, forming indoline **6a** in good yield (eq 1). Likewise, reaction of 5-trifloxy-4-ethylindolylcarbonate **5b** with benzamide formed the pyrrolo[3,2-*e*]indole **6b** in excellent yield (eq 2). Therefore, we reasoned that it may be possible to access the CPI subunit with an amide linkage to the other subunits via such sequential intermolecular domino amidation protocols.

SCHEME 1. Initial Retrosynthesis of CC-1065 CPI



SCHEME 2. Synthesis of Quinone Mono-imine 10





Using this intermolecular amidation protocol as a guide, we proposed a retrosynthesis as outlined in Scheme 1. The spirocyclopropyldienone moiety of CPI (**7**) may be accessed from a Winstein Ar-3′ alkylation[10] of pyrrolo[3,2-*e*]indole **8** arising from a suitable domino amidation precursor derived from the 5-trifloxy-7-benzoxy indole **9**. This indole could, in turn, be accessed from a suitably functionalized dihydronaphthalene obtained from a Diels−Alder cycloaddition of a 1,4-substituted butadiene and the quinone mono-imine **10**.[11]

Our synthesis of the quinone mono-imine **10** (Scheme 2) commenced with commercially available 5-fluoro-2-nitrophenol, which was alkylated with benzyl bromide and subjected to S_N-

(6) (a) Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* **2004**, *6*, 2953−2956. For an excellent enantioselective synthetic route to duocarmycins A and SA, see: (b) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630−6631. (c) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311−325. (d) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1996**, *118*, 2301−2302. See also ref 1 for earlier examples of the total synthesis of these molecules.

(7) For the total synthesis, see: (a) Tichenor, M. S.; Kastrinsky, D. B.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 8396−8398. For biological activity studies, see: (b) Parrish, J. P.; Kastrinsky, D. B.; Wolkenberg, S. E.; Igarashi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 10971−10976.

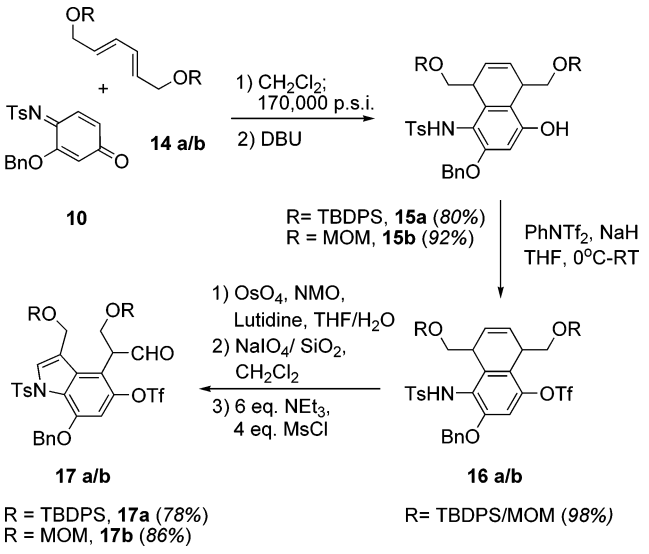
(8) Okano, K.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7136−7137.

(9) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777−4779.

(10) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567−578.

(11) For Diels−Alder reactions of quinone−monoimines and indole formation from the resulting dihydronaphthalenes, see: (a) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519−6522. For previous examples of this methodology in natural product synthesis, see: (b) England, D. B.; Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 2209−2212. (c) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215−1218.

SCHEME 3. Synthesis of 5-Trifloxyindole (17a/b)

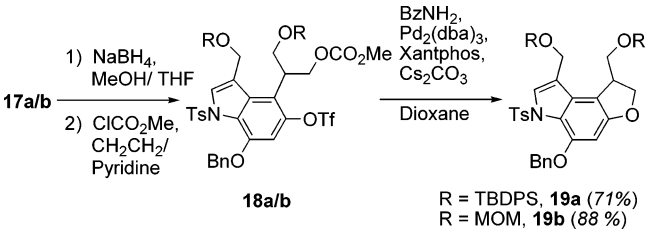


Ar conditions, thereby affording **11**.[12] The resulting *p*-nitrophenol **11** was reduced using nickel boride[13] and immediately tosylated to stabilize the resulting electron-rich and therefore unstable aniline. The *N*-tosylated *p*-aminophenol **13** was then easily oxidized using silica-supported sodium periodate[11a,14] to **10** in 5 steps and an overall yield of 74% from 5-fluoro-2-nitrophenol.

While this dienophile readily underwent a Diels−Alder reaction with common dienes such as piperylene, we wished to investigate a more convergent route to CPI which incorporated a symmetrical diene, allowing for substitution at the 3 position of indole, and a protected 3-hydroxy-2-indolo-propanal moiety at the 4 position of the indole. To this end, we chose a protected hexa-2,4-diene-1,6-diol, previously reported by Roush et al.[15] For our purposes, the TBDPS ether or the MOM ether (**14a** or **14b**, respectively) was found to be the most robust (Scheme 3). Upon attempted cycloaddition of either diene with the dienophile **10**, we found that classical conditions (room temperature, reflux, microwave heating, and Lewis acids in a variety of solvents) were inadequate to yield the required Diels−Alder adducts. Fortunately, treatment of dienes **14a** and **14b** with **10** at high pressure[16] was found to be effective in producing adducts **15a** and **15b** in 80% and 92% yields, respectively, after re-aromatization with DBU.

Having secured a route to these highly functionalized dihydronaphthalenes, we embarked upon the synthesis of the required indole using modifications of the methodology dis-

SCHEME 4. Attempted Dihydropyrrolo[3,2-*e*]indole Synthesis



closed previously from our group.[11a,17] Triflation using NaH/$PhNTf_2$ of either the TBDPS and the MOM-protected dihydronaphthalenes (Scheme 3) occurred without consequence to afford triflated compounds **16a** and **16b**, respectively. This was followed by dihydroxylation,[18] and silica-supported $NaIO_4$[14] mediated oxidative cleavage of the resulting diol to yield a hemiaminal, which was dehydrated using an excess of MsCl/NEt_3 to afford **17a** and **17b** in 78% and 86% yields, respectively, as overall yields for three steps from the triflated dihydronaphthalenes **16a/b**.

Following borohydride reduction of these aldehyde-containing indoles, (Scheme 4) and protection with methyl chloroformate to yield **18a** and **18b**, we were ready to investigate formation of a dihydropyrrolo[3,2-*e*]indole through our domino amidation sequence.[9] Unfortunately, in both cases the dihydrofurano[3,2-*e*]indole products **19a** and **19b** were formed exclusively, likely as a result of triflate cleavage followed by intramolecular S_N2 attack of the unmasked phenolate on the carbonate leaving group. The bulky TBDPS protecting groups may have caused steric crowding around the triflate cross-coupling partner, leading to inefficient oxidative addition and thereby allowing for the competitive side reaction of the phenolate to occur instead. With this in mind, we attempted the reaction with the MOM-protected substrate; however, the same result was obtained. After extensive variation of reaction conditions, no improvement was observed and we were forced to conclude that any branching β to the carbonate on such substrates prohibits the desired cross-coupling event. The reasons for this are unclear to us at this time.

We then turned our attention to an intramolecular variant of the Buchwald−Hartwig aryl amination protocol.[19a,b] Having obtained a larger quantity of the MOM-protected indole-aldehyde **17b**, we proceeded to perform a reductive amination using the HCl salt of benzylamine to afford secondary amine **20** (Scheme 5). This process was then followed by intramolecular aryl amination, which proceeded in moderate to good yields of the required dihydropyrrolo[3,2-*e*]indole **21**. We were now faced with a protecting group predicament. Any attempt to selectively manipulate the dual MOM ethers met with little success. Moreover, de-tosylation by various methods at any

(12) Otten, P. A.; London, R. E.; Levy, L. A. *Bioconjugate Chem.* **2001**, *12*, 76−83.

(13) For selective aryl nitro group Ni_2B reductions in the presence of halogens, see: (a) Seltzman, H. H.; Berrang, B. D. *Tetrahedron Lett.* **1993**, *34*, 3083−3086. (b) Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1989**, *37*, 816−818.

(14) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

(15) Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708−8721 and references therein.

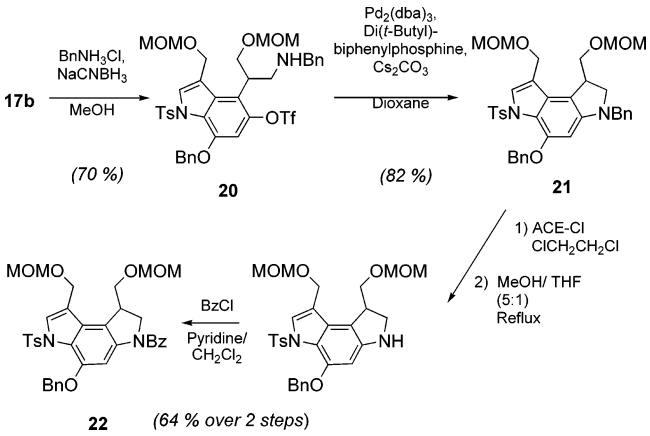
(16) For some literature on the subject of high-pressure reactions, see: (a) Klärner, F.-G.; Diedrich, M. K.; Wigger, A. E.; Jurczak, J.; Gryko, D. T. In *Chemistry Under Extreme or Non-Classical Conditions;* van Eldik, R., Hubbard, C. D., Eds.; Wiley: New York, 1997; Chapters 3 and 4, pp 103−188. (b) Isaacs, N. S. In *High-Pressure Techniques in Chemistry and Physics*; Holzapfel, W. B., Isaacs, N. S., Eds.; Oxford University Press: New York, 1997; Chapter 7, pp 307−309.

(17) (a) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, *7*, 971−974. (b) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325−7.

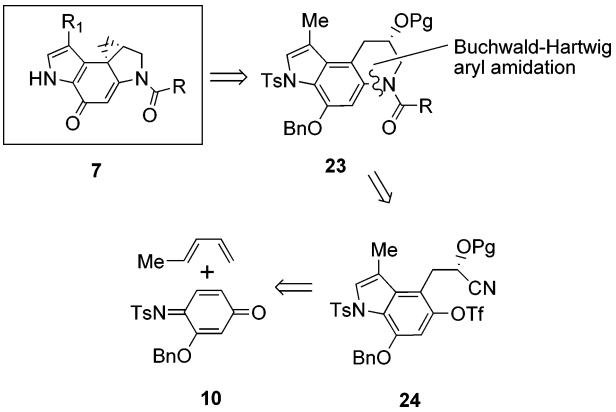
(18) A significant rate enhancement was observed with certain tertiary amines, as per the recent findings of Yu, et al., see: Yu, W.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219.

(19) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron.* **1996**, *52*, 7525−7546. (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, 1158−1174. (c) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104. (d) The intramolecular aryl amidation is also known, see: Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (e) Aoki, K.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 3068.

SCHEME 5. Synthesis of a Dihydropyrrolo[3,2-*e*]indole



SCHEME 6. Revised Retrosynthesis of the CC-1065 CPI Subunit

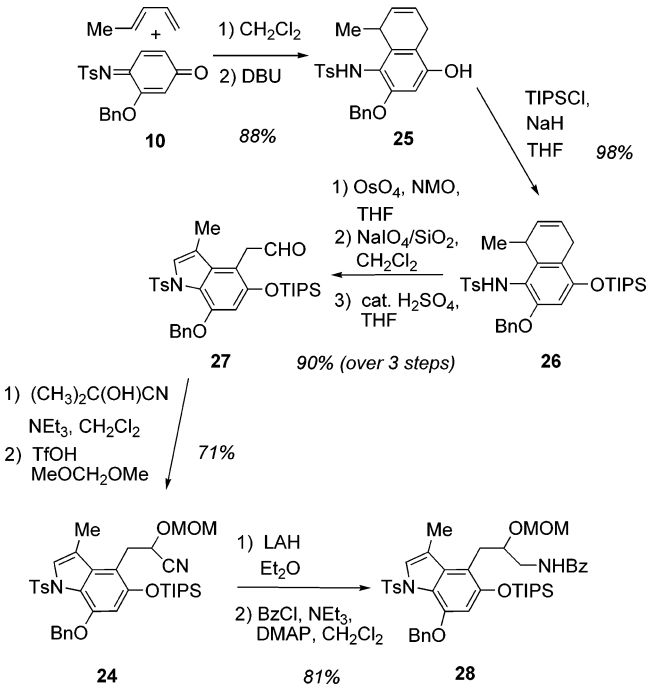


stage led to dimer formation, presumably through a gramine-like fragmentation. Attempts to selectively hydrogenate the phenolic benzyl group and benzylic MOM ether led to multiple products which would not converge to a single product (even if forced using high pressures of H_2 and various Pd, Pt, and other transition-metal catalysts for hydrogenation). We decided to simplify this process by selectively debenzylating the dihydropyrrole nitrogen using α-chloroethylchloroformate (ACE-Cl)[20] followed by benzoylation. However, attempts to elaborate the resulting amide-linked dihydropyrroloindole **22** to CPI met with negligible success.

The simplest (and most obvious) solution to our protecting group woes was to use a much simpler diene. We settled upon piperylene due to the ease with which the corresponding Diels–Alder occurred and the ability to perform this reaction on tens of grams per reaction (high pressure was limited to the synthesis of 1 g of product every 48 h). However, our approach involving piperylene required a modified retrosynthesis (Scheme 6). Instead of targeting a dihydropyrroloindole precursor to CPI, we reasoned that a pyrrolo[3,2-*f*]tetrahydroquinoline CPI precursor **23** should be easier to access through the cyanohydrin **24**, which could arise from an indole synthesized from piperylene and our previously described dienophile **10**.

The Diels–Alder reaction of dienophile **10** and piperylene occurred readily at room temperature overnight at scales of up to 25 g to yield dihydronaphthalene **25** in excellent yield after a simple trituration (Scheme 7). Since we wished to reduce a cyanohydrin in subsequent steps, clearly a trifloxy group would be untenable. Therefore, we decided to protect the naphtholic

SCHEME 7. Synthesis of Indole Benzamide 28



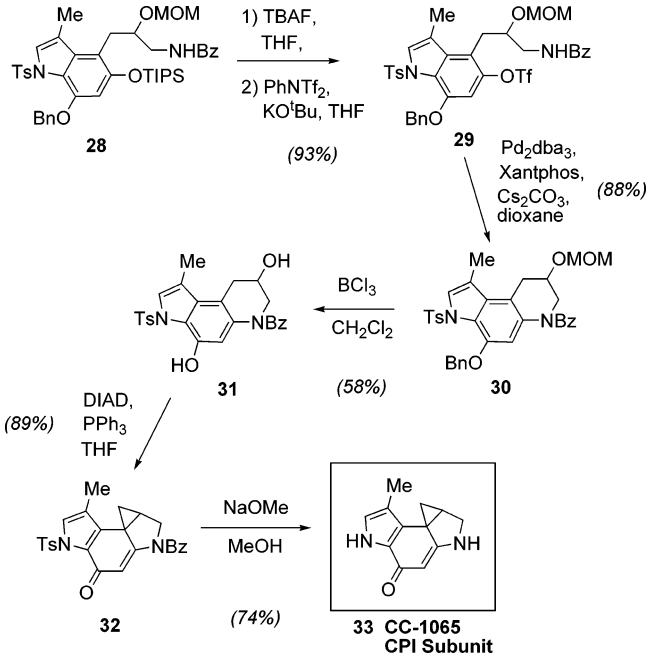
hydroxyl group as a TIPS ether **26** (this would later be converted to a triflate for cross-coupling). Dihydroxylation of the resulting TIPS-protected naphthol followed by oxidative cleavage and treatment with a catalytic amount of H_2SO_4 cleanly led to the corresponding indole **27** in high yield over four steps. Notably, we found that this indole only required a simple wash through a plug of silica in a sintered glass funnel. This purification could be carried out on scales upward of 20 g with ease. Formation of **24** with acetone cyanohydrin and triethylamine was then followed by protection of the resulting secondary alcohol as a MOM ether using stoichiometric trifluoromethanesulfonic acid and dimethoxymethane as the solvent.[21] This was the first instance of flash chromatography in the entire synthesis. As predicted, reduction of the cyanohydrin with an excess of LAH occurred cleanly with the TIPS-protected phenol. This was followed by amidation with benzoyl chloride to form the required amide **28** in good yield.

An exchange of the TIPS protecting group for a triflate occurred smoothly to afford the indole triflate **29** (Scheme 8). This intramolecular aryl amidation substrate was then subjected to standard Buchwald–Hartwig amidation conditions[19c–e] to cleanly afford the pyrrolo[3,2-*f*] tetrahydroquinoline CPI precursor **30** in excellent yield. Although many deprotection strategies were attempted at this point, we found that only fresh BCl_3 in CH_2Cl_2 would afford the deprotected CPI precursor **31** in adequate yield. Although Mitsunobu activation of an alcohol has been used to affect Winstein Ar-3′ alkylation with a primary alcohol of the dihydropyrroloindole in many instances, to our knowledge, the corresponding alkylation of a pyrrolo[3,2-*f*]-tetrahydroquinoline to form a CPI precursor has not been attempted.[1] We were pleased to find that this alkylation occurred

(20) (a) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196. (b) Gubert, S.; Braojos, C.; Sacristán, A.; Ortiz, J. A. *Synthesis* **1991**, 1991, 318–319. (c) Olofson, R. A.; Martz, J. T. *J. Org. Chem.* **1984**, *49*, 2081–2082.

(21) David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796.

SCHEME 8. Completion of the Synthesis of CC-1065 CPI Subunit

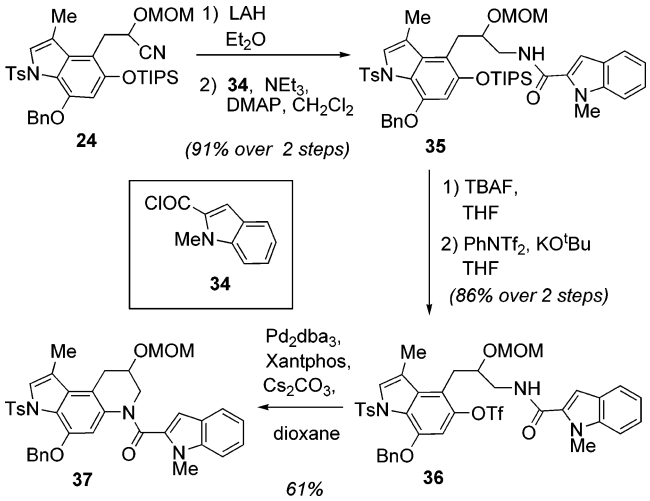


readily under standard Mitsunobu conditions to afford **32** in high yield. We were then faced with our final deprotection of the tosyl group. Although we were unable to selectively remove the tosyl in the presence the benzoyl amide, we found that treatment of **32** under the conditions of Magnus et al. (1 N NaOMe in methanol overnight) cleanly afforded unprotected CC-1065 CPI **33** in good yield.[5a]

While we were cognisant of the fact that we would be unable to remove the tosyl pyrrole protecting group without rupturing the amide bond, we thought it would be interesting if we investigated more complex amides in this intramolecular cross-coupling reaction. We were particularly interested in use of the intramolecular reaction with indole-2-carboxamide substrates. The amide formations with (N-unprotected)indole-2-carbonyl chloride (compound not shown) and *N*-methylindole-2-carbonyl chloride **34**[9] were facile, and elaboration to the corresponding triflates occurred, in both cases, without incident (Scheme 9). However, we found that the aryl amidation with the indole-N-unprotected substrate did not occur, even after prolonged reaction times. However, the N-protected substrate **36**, which was obtained via an exchange of the TIPS protecting group of compound **35** for a triflate, readily afforded pyrrolo[3,2-*f*]-tetrahydroquinoline **37** in an acceptable yield. Although attempts to elaborate this to a tosyl-protected indole-2-carboxamide-containing CPI-like molecule were attempted, we found that any attempt to deprotect the MOM ether led to a complex mixture, possibly due to competing reaction pathways at the 3 position of the indole-2-carboxamide.

In summary, we developed an efficient synthesis of CC-1065 CPI through an intramolecular aryl amidation that formed the key pyrrolo[3,2-*f*]tetrahydroquinoline precursor. This route allowed access to N,N′-unprotected CPI in a 9.3% overall yield from commercially available 5-fluoro-2-nitrophenol. Notably, this yield is competitive with existing syntheses of N,N′-unprotected CPI.[5] Moreover, silica-mediated purification was not required for the first 10 steps of the synthetic sequence. Elaboration of unprotected CPI toward a total synthesis of CC-1065 is underway.

SCHEME 9. Intramolecular Aryl Amidation with a More Complex Cross-Coupling Partner



Experimental Section

Quinone Mono-imine (10). Refer to the Supporting Information for experimental details pertaining to the synthesis of *p*-aminophenol **13** from **12**. To a solution of **13** (12.0 g, 32.0 mmol) in 400 mL of dichloromethane was added 75 g of 0.68 mmol/g of silica-supported $NaIO_4$, and the mixture was mechanically stirred for 4 h. The resulting ochre solution was filtered to remove silica and concentrated in vacuo to leave 11.47 g (96%) of pale orange solid **10**: mp = 154−156 °C (darkens upon heating). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 9.6, 1H), 7.93 (d, J = 8.0, 2H), 7.34 (m, 6H), 7.26 (s, 1H), 6.56 (dd, J = 9.6, 1.6, 1H), 5.95 (d, J = 1.6, 1H), 5.05 (s, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 160.8, 159.5, 144.8, 136.9, 134.7, 134.4, 129.8, 129.0, 128.7, 127.8, 127.2, 109.2, 71.1, 32.2. IR (thin film) ν 3088, 2921, 2853, 1647, 1632, 1595, 1317, 1238, 1154 cm^{-1}. HRMS calcd for $C_{20}H_{17}NO_4S$: 367.0878. Found: 367.0880.

Rearomatized Dihydronaphthol High-Pressure Diels−Alder Adduct (15a). Refer to the Supporting Information for experimental details pertaining to the synthesis of diene **14a**. Dienophile **10** (50 mg, 0.135 mmol) and diene **14a** (84 mg, 0.142 mmol) were added to high−pressure tubing and dissolved in 2.0 mL of DCM. The high-pressure tube was sealed with a brass fitting and placed in a high-pressure reactor (180 000 psi) for 20 h. After this time the contents of the tube were transferred to a round-bottomed flask and a catalytic amount of DBU was added. The resulting mixture was stirred for 30 min, after which time the aromatized adduct was washed with 5% HCl and re-extracted twice with dichloromethane. After concentration to a residue, the compound was purified by flash chromatography (2−20% ethyl acetate in hexanes) to afford, after rotary evaporation, 0.104 g (80%) yield of dihydronaphthol **15a** as an off-white foam: mp = 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.65−7.62 (m, 2H), 7.56 (d, J = 8.4, 2H), 7.50−7.48 (m, 3H), 7.42−7.37 (m, 2H), 7.35−7.18 (m, 15H), 7.14−7.09 (m, 5H), 6.98 (d, J = 8.4, 2H), 6.51 (s, 1H), 5.92 (dd, J = 9.2, 5.4,1H), 5.63 (dd, J = 10.0, 5.4 1H), 4.79 (d, J = 12.2, 1H), 4.51 (d, J = 12.2, 1H), 4.47−4.40 (m, 1H), 3.90−3.82 (m, 1H), 3.65 (dd, J = 10.0, 2.8, 1H), 3.41 (dd, J = 9.2, 6.0, 1H), 3.26 (t, J = 8.8, 1H), 3.06 (t, J = 10.0, 1H), 2.29 (s, 3H), 1.03 (s, 9H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.8, 14207, 128.5, 137.5, 136.8, 135.8, 135.7, 135.6, 132.9, 130.5, 130.2, 130.0, 129.9, 129.4, 129.0, 128.5, 128.2, 128.0 (2C), 127.9, 127.8, 127.6, 127.2, 125.9, 117.8, 116.7, 101.3, 71.6, 70.1, 39.6, 39.0, 27.0, 26.8, 21.7, 19.3, 19.2. IR (thin film) ν 3289, 2931, 2859, 1654, 1559, 1457, 1113 cm^{-1}. HRMS calcd for $C_{58}H_{63}NO_6SSi_2$: 957.3915. Found: 957.3922.

Rearomatized Dihydronaphthol High-Pressure Diels−Alder Adduct (15b). Refer to the Supporting Information for experimental

details pertaining to the synthesis of diene **14b**. Dienophile (**10**) (300.0 mg, 0.814 mmol) and **14b** (199.0 mg, 0.985) of diene were added to high−pressure tubing and dissolved in 7.5 mL of DCM. This was duplicated, and the two high-pressure tubes were sealed with brass fittings and placed side-by-side in a high-pressure reactor (180 000 psi) for 24 h. After this time the contents of the tubes were transferred to a round-bottomed flask, and a catalytic amount of DBU was added. The resulting mixture was stirred for 30 min, after which time the aromatized adduct was washed with saturated ammonium chloride and re-extracted twice with dichloromethane. After concentration to a residue, the compound was allowed to solidify overnight and then triturated in diethyl ether to afford 0.860 g (92%) yield of dihydronaphthol **15b** as an off-white foam: mp = 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.49 (d, J = 8.4, 2H), 7.34−7.29 (m, 3H), 7.13−7.11 (m, 2H), 6.95 (d, J = 8.4, 2H), 6.67 (s, 1H), 6.37 (s, 1H), 6.05 (dd, J = 10.0, 5.6, 1H), 5.94 (dd, J = 10.0, 5.6, 1H), 4.72 (d, J = 12.0, 1H), 4.68−4.61 (m, 2H), 4.55−4.52 (m, 2H), 4.50−4.46 (m, 1H), 4.35 (d, J = 12.0, 1H), 3.88−3.82 (m, 2H), 3.65 (dd, J = 9.2, 5.6, 1H), 3.49 (dd, J = 9.2, 5.6, 1H), 3.44 (t, J = 9.2, 1H), 3.29 (s, 3H), 3.20 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.2, 142.8, 137.8, 137.5, 136.3, 129.4, 128.9, 128.3, 127.8, 127.3, 127.0, 125.7, 118.1, 115.6, 100.8, 96.3, 95.9, 74.2, 72.2, 69.8, 55.7, 55.1, 36.8, 36.7, 21.5. IR (thin film) ν 3269, 2927, 1612, 1596, 1327, 1153 cm^{-1}. HRMS calcd for $C_{30}H_{35}NO_8S$: 569.2083. Found: 569.2077.

Dihydrofurano[3,2-*e*]indole (19a). Refer to the Supporting Information for experimental details pertaining to the synthesis of indole-4-ethylcarbonate **18a** from 5-trifloxyindole **17a**. To the aryl trifloxy cross-coupling partner **18a** (0.116 g, 0.099 mmol) was added 1.5 mL of dry dioxane. The resulting solution was stirred with argon purging for 30 min at room temperature to remove any dissolved gases in the solvent/aryl trifloxy substrate. Meanwhile, to a Schlenk tube, which had been previously purged and back-filled with argon three times, was added the benzamide cross-coupling partner (0.015 g, 0.020 mmol) of 0.045 g (0.139 mmol) of Cs_2CO_3 (0.009 g, 0.010 mmol) and $Pd_2(dba)_3$ (0.012 g, 0.020 mmol) of Xantphos. After addition of these solid reagents, the Schlenk tube was again purged and back-filled with argon three times before exchanging a screw cap for a septum and adding the aryl trifloxy substrate in dioxane by cannula to the Schlenk tube. The septum was then quickly exchanged for a screw cap, the Schlenk tube was then placed in a sand bath, and the reaction was allowed to occur over 36 h. After this time 10 mL of 5% HCl was added, and the aqueous phase was then washed three times with diethyl ether. The organic extracts were then washed with brine and dried over $MgSO_4$ before being concentrated with SiO_2 in vacuo to yield solid supported adduct which was then subjected to column chromatography (2−24% gradient of ethyl acetate in hexanes) to yield 58 mg (71% yield) of dihydrofuran **19a** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0, 2H), 7.56 (d, J = 8.0, 2H), 7.49 (t, J = 4.8, 3H), 7.42−7.20 (m, 20H), 7.02 (d, J = 8.0, 2H), 6.24 (s, 1H), 4.93 (s, 2H), 4.72−4.68 (m, 2H), 4.60 (d, J = 8.8, 1H), 4.46 (t, J = 8.0, 1H), 3.84−3.76 (m, 1H), 3.67 (dd, J = 10.0, 4.0, 1H), 3.49 (dd, J = 10.0, 8.0, 1H), 2.32 (s, 3H), 1.04 (s, 9H), 0.92 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 157.9, 146.7, 143.5, 137.4, 136.4, 135.6, 135.4, 133.4 (2C), 133.2, 133.0, 129.8, 129.7, 129.6 (2C), 129.5, 129.2, 128.8, 128.4, 128.1, 127.9, 127.7, 127.6 (3C), 126.9, 123.7, 120.3, 118.8, 109.3, 92.7, 75.2, 70.7, 66.2, 59.1, 44.5, 26.8, 26.7, 21.5, 19.2, 19.1. IR (thin film) ν = 2925, 2852, 1696, 1540, 1109 cm^{-1}. HRMS calcd for $C_{58}H_{61}NO_6SSi_2$: 955.3758. Found: 955.3751.

Dihydrofurano[3,2-*e*]indole (19b). Refer to the Supporting Information for experimental details pertaining to the synthesis of indole-4-ethylcarbonate **18b** from 5-trifloxyindole **17b**. To 0.0483 g (0.062 mmol) of the aryl trifloxy cross-coupling partner **18b** was added 1.5 mL of dry dioxane. The resulting solution was stirred with argon purging for 30 min at room temperature to remove any dissolved gases in the solvent/aryl trifloxy substrate. Meanwhile, to a Schlenk tube, which had been previously purged and back-filled with argon three times, was added 0.009 g (0.0741 mmol) of benzamide cross-coupling partner, 0.028 g (0.0805 mmol) of Cs_2CO_3, 0.003 g (0.0031 mmol) of $Pd_2(dba)_3$, and 0.004 g (0.476 mmol) of Xantphos. After addition of these solid reagents, the Schlenk tube was again purged and back-filled with argon three times before exchanging a screw cap for a septum and adding the aryl trifloxy substrate in dioxane by cannula to the Schlenk tube. The septum was then quickly exchanged for a screw cap, the Schlenk tube was then placed in a sand bath, and the reaction was allowed to occur over 40 h. After this time 10 mL of 5% HCl was added, and the aqueous phase was then washed three times with diethyl ether. The organic extracts were then washed with brine and dried over $MgSO_4$ before being concentrated with SiO_2 in vacuo to yield solid supported adduct which was then subjected to column chromatography (5−35% gradient of ethyl acetate in hexanes) to yield 30.4 mg (87%) of dihydrofuran **19b** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.41 (d, J = 7.6, 2H), 7.31 (s, 3H), 7.16−7.12 (m, 2H), 7.01 (d, J = 7.6, 2H), 6.21 (s, 1H), 4.92−4.84 (AB, J_{AB} = 13.6, 1H), 4.69 (s, 4H), 4.60−4.52 (m, 3H), 4.43 (at, J = 8.4, 1H), 3.82−3.67 (m, 2H), 3.39 (s, 3H), 3.26 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 146.8, 143.8, 137.2, 136.1, 129.7, 129.3, 128.8, 127.9, 127.6, 127.0, 115.2, 108.7, 96.4, 95.1, 92.9, 75.6, 70.6, 69.9, 61.4, 55.5, 55.2, 42.3, 21.5. IR (thin film) ν 2931, 2888, 1609, 1497, 1362, 1040 cm^{-1}. HRMS calcd for $C_{30}H_{33}NO_8S$: 567.1927. Found: 567.1924.

***N*-Alkyl, *N*′-Benzylamino-indole (20).** Refer to the Supporting Information for experimental details pertaining to the synthesis of 5-trifloxyindole **17b**. Benzylamine hydrochloride was prepared by adding a 5.7 M solution of dry HCl in diethyl ether to neat benzylamine. The salt precipitated as a white solid immediately and after filtration was washed three times with diethyl ether and dried in vacuo. Benzylamine hydrochloride salt (0.392 g, 2.3 mmol) was added to a suspension of aldehyde **17b** (0.550 g, 0.763 mmol) in 10 mL of methanol. Sodium cyanoborohydride (0.048 g, 0.763 mmol) was added, and the reaction was stirred at room temperature for 3 h. The resulting reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$, followed by water. Combined aqueous washes were re-extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried, and suspended on 4 g of SiO_2 by concentrating in vacuo. This crude, silica-supported indole was then purified by FCC (elution with a gradient of 30−50% ethyl acetate in hexanes) to yield 0.433 g (70% yield) of pure **20** as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.53 (d, J = 8.4, 2H), 7.40−7.38 (m, 3H), 7.30−7.22 (m, 7H), 7.15 (d, J = 8.4, 2H), 6.67 (s, 1H), 5.00 (s, 2H), 4.98−4.93 (AB, δ_A = 4.96, δ_B = 4.94, J_{AB} = 12.0, 2H), 4.78 (d, J = 6.6, 1H), 4.74 (d, J = 6.6, 1H), 4.59−5.56 (AB, δ_A = 4.58, δ_B = 4.56, J_{AB} = 6.6, 2H), 4.02−3.95 (m, 2H), 3.86 (dd, J = 9.6, 7.8, 1H), 3.79−3.74 (AB, δ_A = 3.77, δ_B = 3.75, J_{AB} = 9.2, 2H), 3.45 (s, 3H), 3.24 (s, 3H), 3.16−3.13 (dd, J = 12.0, 7.2, 1H), 3.09−3.05 (dd, J = 12.0, 7.2), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 144.6, 144.3, 140.4, 136.8, 135.1, 132.5, 130.9, 129.4, 128.5, 128.4, 128.2, 128.0, 127.8, 127.1, 126.7, 124.4, 119.1, 118.2 [(trifluoromethanesulfonate CF_3) q, J = 318.6], 116.6, 101.8, 96.2, 95.1, 70.9, 69.2, 62.0, 55.5, 55.0, 53.9, 50.6, 40.1, 21.5. IR (thin film) ν 2925, 1614, 1416, 1215, 1148, 1035 cm^{-1}. HRMS calcd for $C_{38}H_{41}F_3N_2O_{10}S_2$: 806.2155. Found: 806.2155.

Dihydropyrrolo[3,2-*e*]indole (21). To the aryl trifloxy cross-coupling partner **20** (1.30 g, 1.59 mmol) was added 10.0 mL of dry dioxane. The resulting solution was stirred with argon purging for 30 min at room temperature to remove any dissolved gases in the solvent/aryl trifloxy substrate. Meanwhile, to a Schlenk tube, which had been previously purged and back-filled with argon three times, was added Cs_2CO_3 (0.720 g, 7.22 mmol), $Pd_2(dba)_3$, (0.145 g, 0.159 mmol), and di-*tert*-butylbiphenylphosphine (0.142 g, 0.476 mmol). After addition of these solid reagents, the Schlenk tube was again purged and back-filled with argon three times before exchanging a screw cap for a septum and adding the aryl trifloxy

substrate in dioxane by cannula to the Schlenk tube. The septum was then quickly exchanged for a screw cap, the Schlenk tube was then placed in a sand bath, and the reaction was allowed to occur over 40 h. After this time 10 mL of 5% HCl was added, and the aqueous phase was then washed three times with diethyl ether. The organic extracts were then washed with brine and dried over $MgSO_4$ before being concentrated with SiO_2 in vacuo to yield solid supported adduct which was then subjected to column chromatography (5−60% gradient of ethyl acetate in hexanes) to yield 0.887 g (82% yield) of dihydropyrrolo[3,2-*e*]indole **21** as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.51 (d, J = 8.4, 2H), 7.32−7.22 (m, 8H), 7.15 (m, 2H), 7.08 (d, J = 8.4, 2H), 6.01 (s, 1H), 4.92−4.85 (AB, δ_A = 4.91, δ_B = 4.86, J_{AB} = 12.0, 1H), 4.77−4.75 (m, 4H), 4.64−4.59 (AB, δ_A = 4.63, δ_B = 4.60, J_{AB} = 6.0, 2H), 4.24 (d, J = 15.0, 1H), 3.95 (d, J = 15.0, 1H), 3.71 (m, 2H), 3.53 (t, J = 9.6, 2H), 3.45 (s, 3H), 3.31 (s, 3H), 3.23 (t, J = 7.8, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 146.5, 143.5, 138.2, 137.5, 136.6, 129.5, 129.2, 128.4, 128.3, 127.8, 127.6, 127.0, 119.3, 115.4, 111.5, 96.3, 95.2, 92.4, 70.5, 69.2, 61.5, 57.9, 55.4, 55.1, 53.9, 40.3, 21.5. IR (thin film) ν 2926, 1599, 1094, 1036 cm^{-1}. HRMS calcd for $C_{37}H_{40}N_2O_7S$: 656.2556. Found: 656.2572.

Dihydronaphthol (25). The dienophile **10** (3.25 g, 8.8 mmol) was dissolved into 60 mL of dichloromethane. Piperylene (3.07 mL, 31 mmol) was then added, and the reaction mixture was stirred at room temperature for 15 h. At this point the reaction mixture was concentrated in vacuo to approximately 30 mL of solution, then 12 drops of DBU were added, and the re-aromatized Diels−Alder cycloadduct precipitated out of solution after stirring the mixture at 0 °C over a period of 20 min. Tosic acid was added until the reaction mixture turned yellow. The resulting neutral precipitate was filtered and washed with 50 mL of 1:1 methanol to water. This product was then triturated with chloroform at 0 °C for 30 min, filtered, and left on the pump to afford 3.08 g (80% yield) of pure cycloadduct **25** as a white powder: mp = 195 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.83 (s, 1H), 7.36 (d, J = 8.0, 2H), 7.23 (m, 3H), 7.08 (d, J = 6.4, 2H), 6.96 (d, J = 8.0, 2H), 6.15 (s, 1H), 5.78 (m, 2H), 4.58 (d, J = 12.8, 1H), 4.20 (d, J = 12.8, 1H), 3.90 (m, 1H), 3.10 (d, J = 22, 1H), 2.85 (d, J = 22, 1H), 2.16 (s, 3H), 1.03 (d, J = 6.8, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 155.1, 154.7, 143.2, 142.2, 140.0, 137.6, 129.3, 128.8, 128.1, 127.5, 127.3, 123.4, 114.1, 113.6, 97.8, 69.2, 30.7, 23.5, 21.6 (2 C). IR (thin film) ν 3415, 3258, 3030, 2960, 2924, 2866, 1593, 1321, 1156 cm^{-1}. HRMS cald for $C_{25}H_{25}NO_4S$: 435.1504. Found: 435.1505.

Indole (27). Refer to the Supporting Information for experimental details pertaining to the synthesis of the dihydronaphthalene **26**. The dihydronaphthalene **26** (2.93 g, 4.95 mmol) was suspended in a mixture of THF (140 mL) and H_2O (60 mL). A crystal of osmium tetraoxide (∼2 mg) was added, and the mixture was stirred for 30 min, giving a black solution, after which NMO (0.695 g, 5.94 mmol) was added. The solution was stirred until the starting material was consumed by TLC (∼15 h), at which point $Na_2S_2O_3$ (3.74 g, 29.7 mmol) was added and the mixture stirred for a further 30 min. The mixture was extracted with ethyl acetate, and the aqueous phase was then re-extracted. Combined extracts were dried and concentrated in vacuo to leave the crude diol. The crude diol was used without further purification and suspended in 100 mL of CH_2Cl_2, and $NaIO_4/SiO_2$ (10.91 g, 7.43 mmol) was then added. The mixture was stirred for 2 h, filtered, and concentrated to yield the crude dialdehyde, which was taken up in 80 mL of dry THF. A 0.743 mmol amount of H_2SO_4 was then added, and the mixture was stirred for 5 h. The reaction mixture was then washed with 5% HCl and extracted with ethyl acetate. Aqueous washes were re-extracted three times with 10 mL of ethyl acetate, combined with the original extract, dried, and concentrated to a thick oil. This crude indole was then purified through a short plug of silica in a sintered glass funnel (elution with isocratic 30% ethyl acetate in hexanes) to yield 3.00 g (90% over 3 steps) of indole **27** as a white powder: mp = 86−87 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.64 (t, J = 2.4, 1H), 7.63 (d, J = 9.0, 2H), 7.57 (s, 1H), 7.28−7.22 (m, 3H), 7.16 (d, J = 9.0, 2H), 7.11 (d, J = 8.4, 2H), 6.11 (s, 1H), 4.95 (s, 2H), 3.95 (d, J = 2.4, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 1.00−0.90 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 150.6, 145.1, 143.7, 137.8, 136.5, 133.2, 129.3, 128.4, 127.7, 127.6, 127.1, 126.3, 120.4, 115.7, 106.3, 100.6, 69.9, 40.7, 21.5, 17.9, 13.3, 12.8. IR (thin film) ν = 2943, 2867, 1726, 1598, 1494, 1353, 1153 cm^{-1}. HRMS calcd for $C_{34}H_{43}NO_5SSi$: 605.2631. Found: 605.2628.

Indole Cyanohydrin (24). To indole **27** (2.366 g, 3.9 mmol) of in 50 mL of dry DCM was added acetone cyanohydrin (0.428 mL, 4.68 mmol) followed by triethylamine (0.652 mL, 4.68 mmol), and the resulting reaction mixture was stirred for 2 h. After this time the reaction mixture was partitioned between 5% HCl and diluted with DCM. The resulting biphasic mixture was extracted, and the organic phase was washed with saturated sodium bicarbonate, followed by brine, dried over $MgSO_4$, and concentrated to yield a light yellow oil, which was used without purification in the next step. A 2.36 g amount of this residue was taken up in 40 mL of dimethoxymethane, and 0.559 mL (4.10 mmol) of trifluoromethanesulfonic acid was added dropwise under argon. After 1 h saturated sodium bicarbonate was added, and the mixture was extracted three times with diethyl ether. The organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash chromatography (2−20% ethyl acetate, 2% intervals, 250 mL each) to yield 1.79 g (71% yield over two steps) of the cyano-indole **24** as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0, 2H), 7.58 (s, 1H), 7.28−7.24 (m, 3H), 7.15 (d, J = 9.0, 2H), 7.08−7.06 (m, 2H), 6.06 (s, 1H), 4.97−4.92 (AB, δ_A = 4.95, δ_B = 4.94, J_{AB} = 13.8, 2H), 4.70 (d, J = 6.6, 1H), 4.59 (dd, J = 9.0, 6.0, 1H), 4.45 (d, J = 6.6, 1H), 3.50 (dd, J = 13.8, 9.6, 1H), 3.41 (dd, J = 13.8, 6.0, 1H), 2.95 (s, 3H), 2.48 (s, 3H), 2.34 (s, 3H), 1.03−0.93 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 145.0, 143.6, 137.8, 133.5, 129.2, 128.4, 127.8, 127.7, 127.0, 126.3, 120.4, 118.5, 116.3, 109.1, 100.6, 95.3, 70.0, 64.4, 55.6, 29.8, 21.5, 17.9, 13.7, 12.9. IR (thin film) ν 2931, 1597, 1153, 1028 cm^{-1}. HRMS calcd for $C_{37}H_{48}N_2O_6SSi$: 676.3002. Found: 676.3005.

Indole Benzamide (28). To the cyano-indole **24** (1.39 g, 2.05 mmol) in 20 mL of dry diethyl ether was added powdered lithium aluminum hydride (LAH) (0.311 g, 8.20 mmol) portion-wise at 0 °C. After completion of the addition of LAH, the reaction mixture was warmed to room temperature and 1 N NaOH was added dropwise, after 20 min, until a white precipitate formed. The reaction mixture was then filtered over celite and concentrated to yield a residue which was immediately taken up in 20 mL of dry THF. To this solution was added triethylamine (0.541 mL, 3.89 mmol), followed by benzoyl chloride (0.226 mL, 1.94 mmol). This reaction mixture was stirred for 22 h, at which point 50 mL of 1 N NaOH was added, and the biphasic mixture was then stirred vigorously for 1 h. After this time the mixture was extracted twice with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated to yield a residue. The residue was purified by flash chromatography (2−30% ethyl acetate:hexanes gradient) to yield, after concentration of the pure fractions, 1.17 g (81% yield over two steps) of the white, crystalline solid **28**: mp = 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.2, 2H), 7.62 (d, J = 8.0, 2H), 7.55 (s, 1H), 7.46−7.42 (m, 1H), 7.37 (t, J = 8.0, 2H), 7.30−7.26 (m, 2H), 7.14 (d, J = 7.2, 2H), 7.13−7.07 (m, 3H), 6.08 (s, 1H), 5.00−4.91 (AB, δ_A = 4.97, δ_B = 4.93, J_{AB} = 13.6, 2H), 4.42 (d, J = 6.4, 1H), 4.18 (d, J = 6.4, 1H), 4.02−3.93 (m, 1H), 3.78−3.70 (m, 1H), 3.51−3.44 (m, 1H), 3.29 (dd, J = 13.6, 9.2, 1H), 3.13 (s, 3H), 3.08 (dd, J = 13.6, 4.4, 1H), 2.46 (s, 3H), 2.33 (s, 3H), 1.00−0.90 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 150.1, 144.1, 143.5, 137.7, 136.5, 134.4, 133.2, 131.1, 129.1, 128.3, 127.5, 127.3, 126.9, 126.7, 126.3, 120.3, 116.6, 122.1, 100.7, 96.9, 79.1, 69.8, 55.0, 43.8, 29.6, 21.4, 17.8, 13.7, 12.8. IR (thin film) ν 2868, 1654, 1597, 1265, 1153, 1029 cm^{-1}. HRMS calcd for $C_{44}H_{56}N_2O_7SSi$: 783.3499. Found: 783.3506.

5-Trifloxyindole Benzamide (29). To the indole amide **28** (0.625 g, 0.795 mmol) in 20 mL of dry THF was added 0.835 mL (8.35 mmol) of TBAF (1.0 M in THF), and the reaction was stirred for 30 min. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate and diethyl ether and extracted, and then the aqueous wash was re-extracted twice. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to yield a residue. A 0.501 g amount of this residue was dissolved in 5 mL of dry THF and was added via cannula to KO^{t}Bu (0.117 g, 0.957 mmol) in 5 mL of dry THF at 0 °C and stirred for 15 min before $PhNTf_2$ (0.313 g, 0.876 mmol) in 5 mL of dry THF was added via cannula. The reaction was allowed to warm to room temperature, and after 30 min at this temperature, the reaction mixture was quenched with 5% HCl and extracted thrice with diethyl ether. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue which was purified by column chromatography (5−70% ethyl acetate: hexanes gradient) to yield 0.562 g (93% yield over two steps) of **29** as a white foam: mp = 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4, 2H), 7.72 (s, 1H), 7.53−7.42 (m, 5H), 7.39−7.35 (m, 3H), 7.28−7.24 (m, 2H), 7.11 (d, J = 8.4, 2H), 6.56 (s, 1H), 4.98 (s, 2H), 4.52 (d, J = 6.8, 1H), 4.25 (d, J = 6.8, 1H), 3.97−3.91 (m, 1H), 3.81 (ddd, J = 14.0, 6.0, 3.6, 1H), 3.55−3.49 (m, 1H), 3.38 (dd, J = 14.4, 9.6, 1H), 3.18 (dd, J = 14.4, J = 4.4, 1H), 3.09 (s, 3H), 2.50 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 145.2, 144.2 (2C), 137.0, 135.2, 134.3, 132.6, 131.4, 129.4, 128.9, 128.5 (2C), 128.4, 128.0, 127.0, 126.9, 116.6, 116.3, 101.5, 96.5, 78.7, 71.1, 55.4, 43.3, 29.4, 21.5, 13.4. IR (thin film) ν 3341, 2942, 1650.3, 1536, 1217, 1140, 1074 cm^{-1}. HRMS calcd for $C_{36}H_{35}F_3N_2O_9S_2$: 760.1736. Found: 760.1750.

Pyrrolo[3,2-*f*]tetrahydroquinoline (30). To the aryl trifloxy cross-coupling partner **29** (0.430 g, 0.566 mmol) was added 12.0 mL of dry dioxane. The resulting solution was stirred with argon purging for 30 min at room temperature to remove any dissolved gases in the solvent/aryl trifloxy substrate. Meanwhile, to a Schlenk tube, which had been previously purged and back-filled with argon three times, was added Cs_2CO_3 (0.258 g, 0.792 mmol), $Pd_2(dba)_3$ (0.052 g, 0.057 mmol), and Xantphos (0.098 g, 0.170 mmol). After addition of these solid reagents the Schlenk tube was again purged and back-filled with argon three times before exchanging a screw cap for a septum and adding the aryl trifloxy substrate in dioxane by cannula to the Schlenk tube. The septum was then quickly exchanged for a screw cap, the Schlenk tube was then placed in a sand bath, and the reaction was allowed to occur over 18 h, at which time the Schlenk tube was charged with a further $Pd_2(dba)_3$ (0.026 g, 0.027 mmol) and the reaction continued for a further 20 h. After this time 10 mL of 5% HCl was added, and the aqueous phase was then washed three times with diethyl ether. The organic extracts were then washed with brine and dried over $MgSO_4$ before being concentrated with SiO_2 in vacuo to yield solid supported adduct, which was then subjected to column chromatography (5−45% gradient of ethyl acetate in hexanes) to yield 0.378 g (88%) of pyrrolo[3,2-*f*] tetrahydroquinoline **30** as a white semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.38 (d, J = 9.0, 2H), 7.35−7.22 (m, 8H), 7.01 (d, J = 9.0, 4H), 5.97 (br s, 1H), 4.74 (d, J = 4.8, 1H), 4.68 (d, J = 4.8, 1H), 4.42−4.16 (m, 4H), 3.77 (dd, J = 12.6, 3.0, 1H), 3.49 (dd, J = 16.8, 5.7, 1H), 3.36 (s, 3H), 3.33 (dd, J = 17.4, 4.8, 1H), 2.48 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.6, 137.2, 136.4, 136.2, 131.6, 129.9, 129.1, 128.5, 128.3, 128.1, 127.8, 127.3, 127.2, 126.9, 123.0, 116.4, 113.2, 94.9, 70.9, 69.7, 55.6, 31.2, 21.4, 13.5. IR (thin film) ν 2927, 1653, 1362, 1168, 1095, 1040 cm^{-1}. HRMS calcd for $C_{35}H_{34}N_2O_6S$: 610.2138. Found: 610.2138.

Protected CC-1065 CPI Subunit (32). To the pyrrolo[3,2-*f*]-tetrahydroquinoline **30** (0.500 g, 0.883 mmol) in 25 mL of dry DCM at −78 °C was added BCl_3 (2.65 mL, 2.65 mmol), and after 15 min the reaction mixture was quenched with saturated sodium bicarbonate. After warming to room temperature the phases were separated and the aqueous phase was re-extracted thrice with DCM, washed with brine, and dried over $MgSO_4$ before being concentrated to yield 0.228 g of debenzylated secondary alcohol. In 5.0 mL of dry THF containing 0.100 g (0.298 mmol) of this compound was added diisopropylazodicarboxylate (0.041 mL, 0.298 mmol), followed by triphenylphosphine (0.055 g, 0.298 mmol) at room temperature. After 15 min the reaction mixture was concentrated with SiO_2 to leave a silica-supported crude product. The crude mixture was purified by flash chromatography (1−3% acetone in DCM) to yield 0.0851 g (89% yield) of white semisolid **32**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4, 2H), 7.54 (s, 1H), 7.47−7.44 (m, 3H), 7.35 (t, J = 7.8, 2H), 7.25 (d, J = 7.8, 2H), 5.42 (s, 1H), 4.12−4.07 (m, 2H), 2.93 (ddd., J = 12.0, 6.0, 4.8, 1H), 2.36 (s, 3H), 2.08 (dd, J = 7.2, 4.8, 1H), 2.03 (s, 3H), 1.50 (t, J = 4.8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 169.6, 158.2, 144.6, 135.7, 134.8, 134.2, 131.9, 129.1, 128.7, 128.5, 127.8, 127.3, 115.5, 112.7, 53.4, 32.2, 21.9, 21.6, 21.5, 9.9. IR (thin film) ν 2959, 1722, 1631, 1390, 1246, 1106 cm^{-1}. HRMS calcd for $C_{26}H_{22}N_2O_4S$: 458.1300. Found: 458.1286.

1,2,8,8′-Tetrahydrocyclopropa[*c*]indol-4-one (CPI−33). The tosylated pyrrole **32** (0.045 g, 0.10 mmol) was dissolved in 1.0 mL of 1 N NaOMe at 0 °C and stirred overnight, after which time the reaction mixture was worked up with 2.5 mL of 10% aqueous Na_2HPO_4 and extracted seven times with DCM. The organic phase was washed with brine and triethylamine, and silica was added to it before concentration to leave solid-supported crude **33**. A column was equilibrated with 5% triethylamine/1:1 THF:ethyl acetate, and the supported product was flashed with this eluent to give 0.014 g (74% yield) of the white semisolid CC-1065 CPI (**33**). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.23 (br s, 1H), 6.70 (d, J = 1.8, 1H), 5.51 (s, 1H), 4.66 (br s, 1H), 3.78 (ddd, J = 9.6, 5.4, 1.8, 1H), 3.62 (d, J = 9.6, 1H), 2.95 (m, 1H), 1.99 (s, 3H), 1.85 (dd, J = 7.8, 4.2, 1H), 1.20, (t, J = 4.2, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 120.8, 113.6, 96.0, 51.0, 23.1, 22.7, 14.1, 10.0. IR (thin film) ν 3462, 1611 cm^{-1}. HRMS calcd for $C_{12}H_{12}N_2O$: 200.0950. Found: 200.0959.

Note: All data given above are in agreement with the literature values.[5a]

***N*-Methylindole-2-carboxamide-Linked Indole (35).** To the cyanoindole **24** (0.500, 0.738 mmol) in 10 mL of dry diethyl ether was added powdered lithium aluminum hydride (LAH) (0.112 g, 2.95 mmol) portion-wise at 0 °C. After completion of the addition of LAH, the reaction mixture was warmed to room temperature, and after 20 min, 1 N NaOH was added dropwise until a white precipitate formed. The reaction mixture was then filtered over celite and concentrated to yield a residue which was immediately taken up in 5 mL of dry dioxane. To this solution was added triethylamine (0.207 mL, 1.48 mmol), followed by catalytic DMAP, and finally *N*-methylindole-2-carbonyl chloride **34** (0.131 g, 0.724 mmol).[9] This reaction mixture was stirred for 22 h, at which point the mixture was extracted twice with diethyl ether; the organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to yield a residue. The residue was purified by flash chromatography (2−20% ethyl acetate:hexanes gradient) to yield 0.555 g (91% yield over two steps) of the white semisolid (**35**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4, 2H), 7.58 (d, J = 12.8, H), 7.36 (d, J = 8.4, 1H), 7.35−7.26 (m, 5H), 7.16−7.09 (m, 5H), 7.03 (t, J = 4.8, 1H), 6.77 (s, 1H), 4.95−4.82 (AB, δ_A = 4.93, δ_B = 4.84, J_{AB} = 13.6, 2H), 4.45 (d, J = 6.4, 1H), 4.23 (d, J = 6.4, 1H), 4.01 (s, 3H), 4.01−3.94 (m, 1H), 3.69 (ddd, J = 14.0, 6.0, 4.2, 1H), 3.46 (ddd, J = 13.6, 7.6, 4.2, 1H), 3.30 (dd, J = 14.4, 8.8, 1H), 3.20 (s, 3H), 3.07 (dd, J = 13.2, 5.2, 1H), 2.48 (s, 3H), 1.09−0.88 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 150.1, 144.2, 143.5, 138.7, 137.7, 136.6, 133.2, 132.1, 129.1, 128.3, 127.5, 127.3, 126.9, 126.3, 125.9, 123.7, 121.6, 120.3, 120.2, 116.6, 112.2, 109.9, 103.3, 100.8, 96.8, 78.8, 69.8, 55.2, 43.4, 31.3, 29.7, 21.4, 17.8, 13.8, 12.8. IR (thin film) ν 3375, 2945, 1662, 1533, 1490, 1394, 1153, 1029 cm^{-1}. HRMS calcd for $C_{47}H_{59}N_3O_7SSi$: 837.3843. Found: 837.3834.

***N*-Methylindole-2-carboxamide-Linked 5-Trifloxyindole (36).** To the indole amide **35** (0.497 g, 0.590 mmol) of in 20 mL of dry

THF was added 0.651 mL (0.651 mmol) of TBAF (1.0 M in THF), and the reaction was stirred for 30 min. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate and diethyl ether and extracted, and then the aqueous wash was re-extracted twice. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to yield a residue. This residue was dissolved in 5 mL of dry THF and added via cannula to a solution of KO^{t}Bu (0.104 g, 0.853 mmol) in 5 mL of dry THF at 0 °C. This mixture was stirred for 15 min before $PhNTf_2$ (0.307 g, 0.860 mmol) in 5 mL of dry THF was added via cannula. The reaction was allowed to warm to room temperature, and after 30 min at this temperature, the reaction mixture was quenched with 5% HCl and extracted thrice with diethyl ether. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue which was purified by column chromatography (2−30% ethyl acetate:hexanes gradient) to yield 0.414 g (93% yield over two steps) of white foam **36**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J = 1.2$, 1H), 7.65 (d, $J = 8.0$, 1H), 7.47 (d, $J = 8.4$, 1H), 7.40−7.30 (m, 5H), 7.26−7.23 (m, 2H), 7.15 (td, $J = 8.0$,1.2, 1H), 7.10 (d, $J = 8.4$, 3H), 6.93 (s, 1H), 6.56 (s, 1H), 4.97 (s, 2H), 4.53 (d, $J = 6.8$, 1H), 4.28 (d, $J = 6.8$, 1H), 4.07 (s, 3H), 3.98−3.92 (m, 1H), 3.77 (ddd, $J = 14.0$, 6.4, 3.6, 1H), 3.51 (ddd, $J = 14.0$, 6.4, 4.8, 1H), 3.39 (dd, $J = 14.4$, 9.6, 1H), 3.18 (dd, $J = 14.4$, 4.4, 1H), 3.12 (s, 3H), 2.51 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 145.1, 144.1, 139.0, 137.0, 135.2, 132.6, 131.8, 129.4, 128.9, 128.5, 128.4, 127.9, 127.0, 126.0, 124.4, 123.9, 121.8, 120.3, 116.5, 116.2, 110.1, 103.9, 101.5, 96.5, 78.6, 71.1, 55.4, 42.8, 31.5, 29.5, 21.5, 13.5. IR (thin film) ν 3406, 2936, 1654, 1540, 1420, 1220, 1140 cm^{-1}. HRMS calcd for $C_{40}H_{42}F_3N_3O_9S_2$: 813.2002. Found: 813.2013.

***N*-Methylindole-2-carboxamide-*N*′-pyrrolo[3,2-*f*]tetrahydroquinoline (37).** To the aryl trifloxy cross-coupling partner **36** (0.353 g, 0.566 mmol) was added 6.0 mL of dry dioxane. The resulting solution was stirred with argon purging for 30 min at room temperature to remove any dissolved gases in the solvent/aryl trifloxy substrate. Meanwhile, to a Schlenk tube, which had been previously purged and back-filled with argon three times, was added Cs_2CO_3 (0.277 g, 0.849 mmol), $Pd_2(dba)_3$ (0.040 g, 0.043 mmol), and Xantphos (0.075 g, 0.130 mmol). After addition of these solid reagents, the Schlenk tube was again purged and back-filled with argon three times before exchanging a screw cap for a septum and adding the aryl trifloxy substrate in dioxane by cannula to the Schlenk tube. The septum was then quickly exchanged for a screw cap, the Schlenk tube was then placed in a sand bath, and the reaction was allowed to occur over 22 h, at which time 10 mL of 5% HCl was added and the aqueous phase was then washed three times with diethyl ether. The organic extracts were then washed with brine and dried over $MgSO_4$ before being concentrated with SiO_2 in vacuo to yield solid-supported adduct which was then subjected to column chromatography (5−55% gradient of ethyl acetate in hexanes) to yield 0.176 g (61% yield) of pyrrolo[3,2-f]-tetrahydroquinoline **37** as a white semisolid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, $J = 0.8$, 2H), 7.53 (d, $J = 8.0$, 1H), 7.35 (dt, $J = 8.4$, 2.0, 2H), 7.31−7.26 (m, 1H), 7.24−7.16 (m, 4H), 7.12 (dt, $J = 8.0$, 0.8, 1H), 7.01 (d, $J = 8.4$, 2H), 6.85 (d, $J = 6.4$, 2H), 6.52 (s, 1H), 6.12 (br s, 1H), 4.73−4.64 (AB, $\delta_A = 4.72$, $\delta_B = 4.68$, $J_{AB} = 6.8$, 2H), 4.43 (dd, $J = 12.8$, 4.8, 1H), 4.31−4.36 (m, 1H), 4.21 (br s, 2H), 3.73 (dd, $J = 13.2$, 2.8 1H), 3.57 (s, 3H), 3.47 (d, $J = 5.6$, 1H), 3.38 (d, $J = 2.8$, 1H), 3.34 (s, 3H), 2.49 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 144.2, 143.6, 137.8, 137.1, 136.2, 133.8, 132.9, 131.5, 129.2, 128.1, 127.7, 127.2, 127.0, 126.9, 126.4, 123.5, 123.2, 121.8, 120.2, 116.4, 113.3, 109.8, 106.0, 105.6, 94.8, 70.7, 69.3, 55.6, 31.0, 30.9, 21.5, 13.6. IR (thin film) ν 2928, 1654, 1636, 1457 cm^{-1}. HRMS calcd for $C_{38}H_{37}N_3O_6S$: 663.2403. Found: 663.2397.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), Medmira Laboratories, Inc., the Ontario Ministry of Science and Technology, and GlaxoSmithKline for funding. We thank the donors of the American Chemical Society Petroleum Research Fund for partial support of this research. M.D.G. is a recipient of NSERC PGSA, PGSD, and OGSST scholarships. We thank Mr. Doug Hairsine of the UWO Mass Spectrometry Facility for performing MS analysis.

Supporting Information Available: Experimental details for the preparation of compounds **12**, **13**, **14a**, **14b**, **16a**, **16b**, **17a**, **17b**, **18a**, **18b**, and **26**; spectroscopic data in the form of ^{1}H and ^{13}C NMR for all compounds, except **22** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062064J