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REGIOSELECTIVE BROMINATION: AN APPROACH TO THE D-RING OF THE GILVOCARCINS[1]

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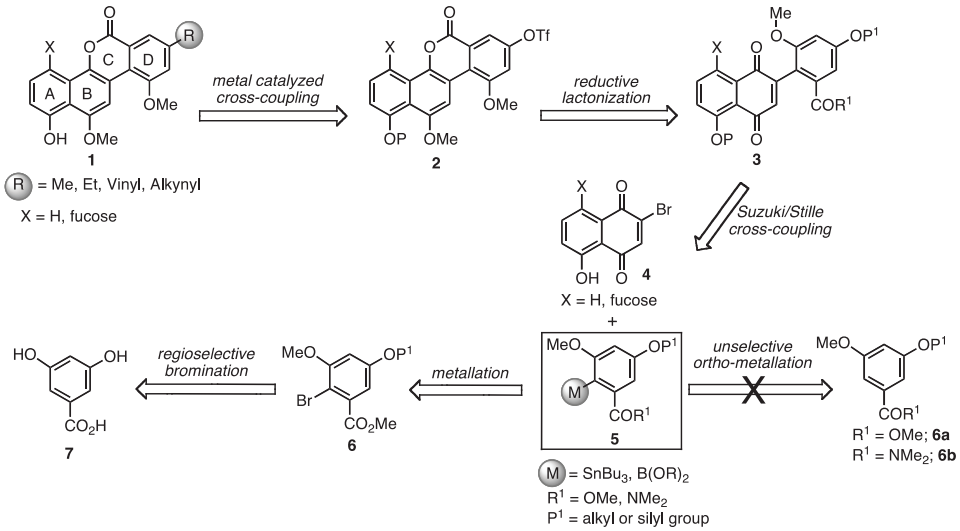
Abstract – A method for the regioselective *ortho*-bromination of unsymmetrically protected 3,5-dihydroxybenzoic acid esters has been developed. The route involves protecting group optimization studies to attain high regioselectivity for the *ortho*-bromination. Pd-catalyzed stannation and boration were performed to construct the D-ring coupling partners for the synthesis of gilvocarcin analogs.

INTRODUCTION

The angucycline family of natural products has long been known for their impressive biological activities and unique structures.[2] The gilvocarcins, a subset of angucycline family of natural products gained significance attention from synthetic and biological community because of its remarkably low *in vivo* cytotoxicity.[2b,3] As a result, there have been numerous synthetic approaches to the gilvocarcins and defucogilvocarcins.[4] The most potent member of this class of natural compounds is the gilvocarcin V, which also exhibits potent antiviral and antitumor activity. One of the mechanisms by which it exhibits antitumor activity is by inhibiting topoisomerase II.[5] It has been reported that the vinyl side chain of gilvocarcin V undergoes a [2+2]-cycloadduct formation with DNA thymidine. Gilvocarcin V can also cause cross-linking between DNA and histone H3.[6] In an effort to expand upon our synthetic endeavors toward the jadomycins,[7] we embarked upon the synthesis and biological evaluation of novel gilvocarcin analogs with the aim of finding analogs with improved DNA binding and/or topoisomerase inhibition. In particular, we were interested in modifying the alkyl side chain at C-8 position, by building upon Snieckus's late stage coupling strategy.[4d]

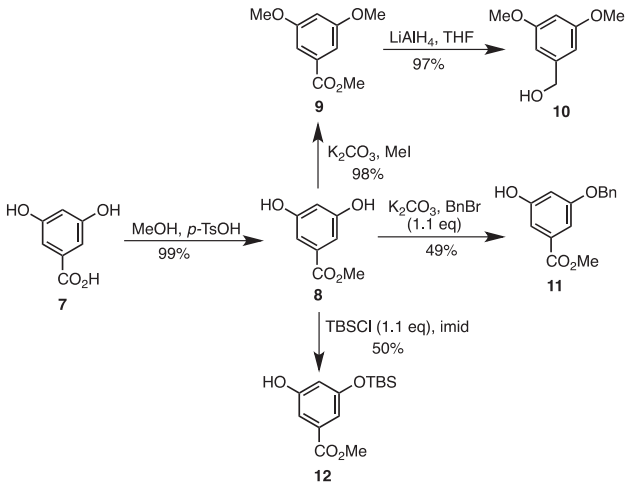


Scheme 1. Retrosynthetic analysis of gilvocarcin ring system

Retrosynthetically, we envisioned an alternative route to the gilvocarcins (Scheme 1) that combines aspects of the Snieckus's and Echavarren's syntheses.[4d,4i] The route will require the functionalization of triflate **2**, which could be prepared from biaryl quinone **3**. The quinone **3** could be obtained by coupling of bromojuglone **4** and metallated **5**. Importantly, this revised route replaces an ester (**3**, R^1 = OMe) for an amide (**3**, R^1 = NMe_2) used in the Echavarren's reductive lactonization for the construction of the tetracyclic ring system. This change required an alternative approach for the synthesis of the desired metalated coupling partner **5**, as the Snieckus's lithiation strategy fails for the ester substrate **6a** and the *ortho*-lithiation of amide (**6b** to **5**) would be unselective. Thus we sought to generate **5** from bromide **6**, which in turn could result from a regioselective bromination and orthogonal protection of 3,5-dihydroxy-benzoic acid **7**. Herein we report our successful synthesis of metallated **5**, which required the development of a regioselective bromination of 3,5-dihydroxybenzoic acid derivatives. This effort involved the search for suitable protecting groups and conditions for this synthesis.

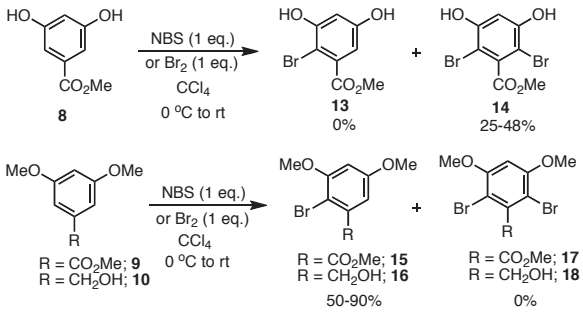
RESULTS AND DISCUSSION

The synthesis of **5** with either boron or tin metallation began with the preparation of the required bromination substrates **8**-**12** (with symmetrical or unsymmetrical substitutions) from readily available dihydroxybenzocic acid **7** (Scheme 2). The 3,5-dihydroxybenzoic acid **7** was converted to the corresponding methyl ester **8** upon treatment with catalytic *p*-TsOH in MeOH.[8] The methyl 3,5-dihydroxybenzoate **8** was then mono-benzylated (K_2CO_3/BnBr) to form **11** or silylated (TBSCl/Imid.) to give **12**.[9,10] Dimethylation of **8** using K_2CO_3 and MeI produced **9**,[11] which was then treated with $LiAlH_4$ to obtain the corresponding benzyl ether **10**.[12]



Scheme 2. Synthesis of 1,3,5-trisubstituted benzene derivatives for regioselective bromination

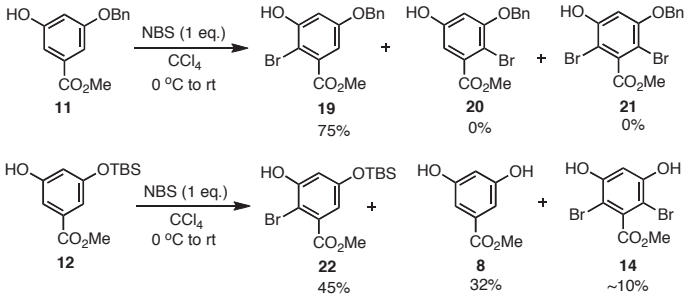
After synthesizing the symmetrical substrates (**8**-**10**) and the unsymmetrical substrates (**11** and **12**), we investigated their selective bromination. We first looked at the selective mono-bromination of the symmetrical substrates **8**-**10** (Scheme 3), which was undertaken with 1 eq. brominating reagent in CCl_4. In the case of methyl 3,5-dihydroxybenzoate **8**, we found that only bis-brominated product **14**[13] was observed along with recovered starting material. In contrast, if the phenols were protected as methyl ethers (**9** and **10**), only mono-bromination occurred to give **15** and **16**, respectively.[14,15] Although mono-bromination could be achieved selectively in case of symmetrical substrates (**9** and **10**), the regioselective deprotection of the methyl ethers (**15** and **16**) proved to be problematic. For instance, we were unable to find conditions for which only one methyl group was removed using reagents like BBr_3 and $AlCl_3$.



Scheme 3. Attempted mono-bromination of symmetrical 1,3,5-trisubstituted benzenes

Fortunately turning to the unsymmetrical substrates allowed for the identification of a practical alternative. The solution derived from the high reactivity and *ortho*-directing ability of the phenol. Thus, bromination of **11** yielded only the desired *ortho*-bromide **19** in 75% yield. This result was particularly appealing as under these conditions neither the bis-brominated product **21** nor the regioisomeric *ortho*-bromide **20** were observed. In an effort to maximize the utility of this approach, we investigated the bromination of silyl ether **12**. Unfortunately, the silyl protecting group proved not to be compatible with the bromination

conditions. While it appeared that regioselective bromination occurred (**12** to **22**), it was accompanied with loss of the silyl group (**12** to **8**) along with subsequent bis-bromination (**8** to **14**), (Scheme 4).



Scheme 4. Attempted mono-bromination of unsymmetrical 1,3,5-trisubstituted benzenes

Having found a suitable protecting group and substitution pattern for the regioselective bromination, we turned to the reaction optimization (**11** to **19**). First the reaction was performed using different brominating reagents in CCl_4 in order to find the optimum reagent. NBS was found to perform better than Br_2, while additives like HOAc did not improve the yield. Although acceptable yields of the desired brominated product were obtained, longer reaction times (~8 h) were required for reaction completion. Next we investigated the effect of solvents on the bromination reaction. Of all the solvents screened, $CHCl_3$ was the most effective. Thus under the optimum condition (1.05 eq. NBS in $CHCl_3$), the desired *ortho*-brominated product **19** was obtained in 97% yield and in ~7 min (Scheme 5).

Reagent screening in CCl_4

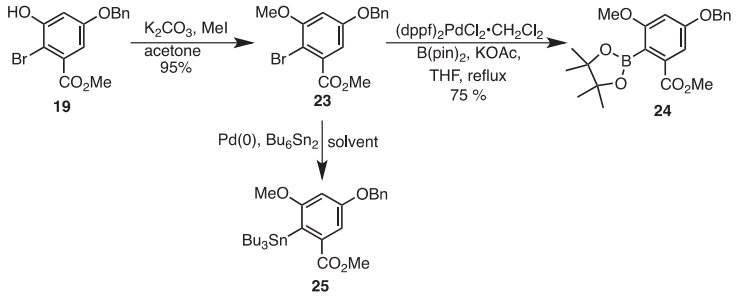
Reagent	eq.	Additive	Temp (°C)	Time	% yield of **19**
Br_2	0.5		0 - rt	12 h	< 10
Br_2	0.5	HOAc	0 - rt	12 h	< 10
Br_2	1.0		rt	8 h	42
NBS	0.5		0 - rt	6 h	40
NBS	1.0	HOAc	0 - rt	6 h	70
NBS	1.0		0	8 h	75
NBS	1.5		0	8 h	60

Solvent screening

NBS (eq.)	Solvent	Time	Temp (°C)	% yield of **19**
1.0	CCl_4	8 h	0	75
1.0	DMF	12 h	0 - rt	40
1.0	CH_2Cl_2	8 h	0	55
0.5	$CHCl_3$	6 h	0 - rt	45
1.0	$CHCl_3$	~10 min	0	93
1.05	$CHCl_3$	7 min	0	97

Scheme 5. Optimization of regioselective bromination reaction

After developing a successful procedure for regioselective bromination, the phenol **19** was substituted as methyl ether to form **23**. The aromatic bromide **23** was then converted to borate **24** or stannane **25** through Pd-catalyzed metallation (Scheme **6**).[16] The low yield of the stannation reaction led us to optimize the reaction conditions. The best yield (65%) of the stannation reaction was observed by using $Pd_2(dba)_3$•$CHCl_3$/PCy_3, in the presence of LiCl in dioxane. The moderate yield in stannation was attributed to the *in situ* proto-destannylation of product **25**.

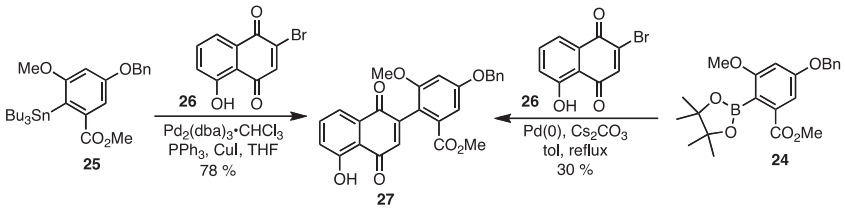


Optimization for stannation reaction (23 → 25)

Pd-cat.	Ligand	Additive	Solvent	Time	% yield of **25**
$Pd(PPh_3)_4$			THF	24 h	30
$Pd(PPh_3)_4$			benzene	20 h	40
$Pd(PPh_3)_4$			toluene	18 h	35
$Pd(PPh_3)_4$			dioxane	16 h	40
$PdCl_2$dppf			toluene	36 h	0
$PdCl_2(PhCN)_2$	PPh_3		toluene	24 h	20
$Pd_2(dba)_3$•$CHCl_3$	PPh_3		toluene	18 h	45
$Pd_2(dba)_3$•$CHCl_3$	PCy_3		toluene	16 h	50
$Pd_2(dba)_3$•$CHCl_3$	dppe		toluene	36 h	40
$Pd_2(dba)_3$•$CHCl_3$	$P(tBu)_3$		toluene	18 h	30
$Pd_2(dba)_3$•$CHCl_3$	PCy_3	LiCl	dioxane	10 h	65
$Pd_2(dba)_3$•$CHCl_3$	PCy_3	LiCl	toluene	12 h	51

Scheme 6. Synthesis of the key coupling partners

With the required coupling partners in hand, we next pursued their use in Pd-catalyzed cross-coupling reactions to produce substituted juglone **27** (Scheme 7). Both the Stille (**25** + **26** to **27**) and the Suzuki (**24** + **26** to **27**) type cross coupling reactions gave coupling product **27**, where the Stille reaction giving significantly higher yields (78% vs 30%). The moderate yield in Suzuki cross-coupling is probably due to less tendency of the arylboronic acid pinacol ester **24** to undergo hydrolysis to form the reactive boric acid. The more than satisfactory yields from the Stille reactions discouraged us from pursuing any further optimization of the Suzuki reaction conditions.



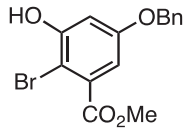
Scheme 7. Stille/Suzuki cross coupling

In conclusion a highly efficient and regioselective bromination of 3,5-dihydroxy benzoic acid derivatives has been developed. The strategy was successfully employed in the synthesis of the D-ring coupling partners **24** and **25**. A Suzuki and Stille cross coupling of the metallated compound **24** and **25** with 2-bromojuglone **26** is also demonstrated to obtain **27**, which is envisioned as being useful for the synthesis of gilvocarcin. The orthogonal protecting groups on the D-ring would allow ready installation of the desired functionality at C-8 position for rapid synthesis of analogs. Future works along these lines are ongoing and will be reported in due course.

EXPERIMENTAL

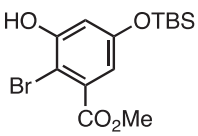
General Methods and Materials: ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz, and 500 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR. Infrared (IR) spectra were obtained on FT-IR spectrometer. Optical rotations were measured with a digital polarimeter in the solvent specified. Flash column chromatography was performed on 60-200 mesh silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (60 Å, F_{254}) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values are obtained by elution in the stated solvent ratios (v/v). Ether (Et_2O), THF, methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were dried by passing through activated alumina columns with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven-dried glassware and standard syringe/septa techniques.

Methyl 5-(benzyloxy)-2-bromo-3-hydroxybenzoate 19



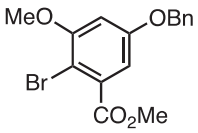
Phenol **11** (1.0 g, 3.87 mmol) was dissolved in 40 mL dry $CHCl_3$ and cooled to 0 ºC. To this cold solution was added *N*-bromosuccinimide (723.5 mg, 4.07 mmol) in one portion and the solution was stirred for 7 min. After exactly 7 min, saturated aqueous $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2. Combined organic layer was washed with saturated brine, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography, elution with 6-8% hexane/EtOAc afforded product **19** (1.26 g, 97%). Colorless solid; mp 72 ºC; R_f (10% hexanes/EtOAc) = 0.65; IR (thin film, cm^{-1}) ν 3368, 3310, 2842, 1724, 1680, 1412, 1264, 1033, 866; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.42 (m, 5H), δ 7.10 (d, J = 2.8 Hz, 1H), δ 6.82 (d, J = 2.8 Hz, 1H), δ 6.04 (brs, 1H), δ 5.05 (s, 2H), δ 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.3, 158.9, 154.1, 136.2, 132.4, 128.9,128.5, 127.7, 111.0, 105.8, 101.3, 70.6, 52.8; HRMS (ESI): calcd for $[C_{15}H_{13}BrO_4 + H]^+$ 337.0075, found 337.0075.

Methyl 2-bromo-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxybenzoate 22



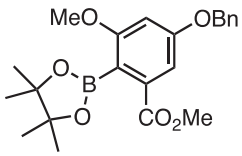
Phenol 1**2** (110.3 mg, 0.39 mmol) was dissolved in 3.9 mL dry CCl_4 and cooled to 0 ºC. To this cold solution was added *N*-bromosuccinimide (73 mg, 0.41 mmol) and stirred for 3 h, gradually rising to ambient temperature. Diluted with Et_2O (10 mL), and quenched by adding saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O twice and the combined organic layer was washed with saturated brine, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 5% hexane/EtOAc afforded product **22** (63.5 mg, 45%); viscous oil; R_f (15% hexanes/EtOAc) = 0.55; IR (thin film, cm^{-1}) ν 3410, 3300, 2842, 1724, 1680, 1412, 1264, 1033, 866; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.89 (d, J = 3.2 Hz, 1H), δ 6.68 (d, J = 3.2 Hz, 1H), δ 3.90 (s, 3H), δ 0.96 (s, 9H), δ 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4, 156.0, 154.0, 132.5, 115.8, 110.9, 101.7, 52.7, 25.7, 18.3, –4.3; HRMS (ESI): calcd for $[C_{14}H_{21}BrO_4Si + H]^+$ 361.0471, found 361.0474.

Methyl 5-(benzyloxy)-2-bromo-3-methoxybenzoate 23



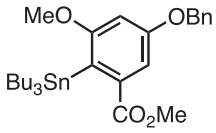
Bromophenol **19** (4.14 g, 12.28 mmol) was dissolved in 25 mL acetone. After forming a homogeneous solution, K_2CO_3 (3.4 g, 24.56 mmol) and MeI (3.8 mL, 61.4 mmol) was added. The reaction mixture was refluxed under argon for 1 h, then cooled to room temperature and acetone was removed under reduced pressure. The residue was redissolved in 100 mL Et_2O and H_2O. The aqueous layer was extracted with Et_2O thrice. Combined organic layer was washed with saturated brine, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded product **23** (4.1 g, 95%). Colorless solid: mp 60-61 ºC; R_f (10% hexanes/EtOAc) = 0.85; IR (thin film, cm^{-1}) ν 2842, 1736, 1680, 1434, 1254, 1029, 872; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.43 (m, 5H), δ 6.91 (d, J = 2.8 Hz, 1H), δ 6.65 (d, J = 2.8 Hz, 1H), δ 5.05 (s, 2H), δ 3.92 (s, 3H), δ 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 158.9, 157.3, 136.1, 134.8, 128.8, 128.4, 127.7, 107.2, 103.1, 102.4, 70.6, 56.6, 52.7; HRMS (ESI): calcd for $[C_{16}H_{15}BrO_4 + H]^+$ 351.0232, found 351.0225.

Methyl 5-(benzyloxy)-3-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 24



Aromatic bromide **23** (20 mg, 0.06 mmol) was dissolved in 1.0 mL THF and cooled to –78 ºC and vacuum degased and back filled with argon. To this degassed reaction mixture was added bis(pinacolato)diborane (28.95 mg, 0.11 mmol), KOAc (17.67 mg, 0.18 mmol) and $(dppf)_2PdCl_2$•CH_2Cl_2 (2.45 mg, 0.003 mmol). The reaction mixture was refluxed overnight under argon. The reaction mixture was cooled to 0 ºC and was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The organic layer was extracted with Et_2O (20 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash column chromatography using silica gel. Elution with 8-10% hexane-EtOAc gave borate **24** (17 mg, 75%) as a colorless solid: R_f (10% hexanes/EtOAc) = 0.30; mp 134 ºC; IR (thin film, cm^{-1}) ν 2910, 1741, 1680, 1429, 1320, 1154, 864; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.44 (m, 5H), δ 7.19 (d, J = 2.0 Hz, 1H), δ 6.64 (d, J = 1.2 Hz, 1H), δ 5.08 (s, 2H), δ 3.89 (s, 3H), δ 3.76 (s, 3H), δ 1.42 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.9, 163.9, 160.8, 136.6, 135.1, 128.8, 128.3, 127.9, 105.9, 103.4, 84.0, 70.4, 55.9, 52.6, 29.9, 25.1; HRMS (ESI): calcd for $[C_{22}H_{27}BO_6 + H]^+$ 399.1979, found 399.1982.

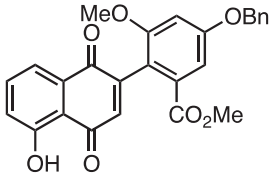
Methyl 5-(benzyloxy)-3-methoxy-2-(tributylstannyl)benzoate 25



Aromatic bromide **23** (1.5 g, 4.27 mmol) was dissolved in 85 mL dry dioxane followed by addition of LiCl (362.1 mg, 8.54 mmol). The reaction mixture was then cooled to –78 ºC, vacuum degassed and back filled with argon. To this degassed reaction mixture, added hexabutylditin (4.3 mL, 8.54 mmol), a premixed solution of $Pd_2(dba)_3$•$CHCl_3$ (155 mg, 0.11 mmol) and PCy_3 (180.8 mg, 0.43 mmol) in 5 mL dioxane. The reaction mixture was refluxed for 10 h under argon. The reaction was cooled to 0 ºC and diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The organic layer was extracted with Et_2O (100 mL X 2). The pooled organic layer was subsequently washed with saturated brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was subjected to flash column chromatography using silica gel neutralized with Et_3N. Elution with 10% hexane-Et_2O gave stannane **25** (1.56 g, 65%) as a colorless oil: R_f (10% hexanes/EtOAc) = 0.80; IR (thin film, cm^{-1}) ν 2950, 2920, 2854, 1740, 1684, 1456, 1378, 1280, 1237, 1169, 1146, 1138, 1048, 1023, 862; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.48 (m, 5H), δ 7.26 (d, J = 2.0 Hz, $J_{Sn\text{-}H}$ = 6.4 Hz, 1H), δ 6.65 (d, J = 2.4 Hz, $J_{Sn\text{-}H}$ = 6.0 Hz, 1H), δ 5.11 (s, 2H), δ 3.89 (s, 3H), d 3.75 (s, 3H), δ 1.46-1.54 (m, 6H), δ 1.29-1.38 (m, 6H), δ 1.02-1.06 (m, 6H), δ 0.91 (t, J = 6.4 Hz, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 166.0, 160.0, 139.3, 136.9, 128.8, 128.3, 127.9, 125.8, 107.2 ($^3J_{Sn\text{-}^{13}C}$ = 11.8 Hz), 102.1 ($^3J_{Sn\text{-}^{13}C}$ = 12.0 Hz), 70.4, 55.4, 52.5, 29.4 ($^3J_{Sn\text{-}^{13}C}$ = 10.8 Hz), 27.6 ($^2J_{Sn\text{-}^{13}C}$ = 32.4 Hz), 13.9, 12.9 ($^1J_{Sn\text{-}^{13}C}$ = 182.6 Hz); HRMS (ESI): calcd for

$[C_{28}H_{42}O_4Sn + H]^+$ 563.2183, found 563.2182.

Methyl 5-(benzyloxy)-2-(5-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-methoxybenzoate 27



A suspension of juglone **26** (398.73 mg, 1.58 mmol), stannane **25** (1.15 g, 2.05 mmol), and CuI (60.04 mg, 0.32 mmol) in 18 mL dry THF at rt was vacuum degased and backfilled with argon. To this mixture, added a solution of $Pd_2(dba)_3$•$CHCl_3$ (81.8 mg, 0.08 mmol) and PPh_3 (83.1 mg, 0.32 mmol) in THF (2 mL) under argon. The mixture was stirred at 80 ºC for 4 h. It was then cooled down to 0 ºC, diluted with EtOAc (50 mL), and quenched by adding saturated aqueous $NaHCO_3$ (20 mL). The mixture was stirred at 0 ºC for 30 min. After separation of the two phases, the aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded coupled product **27** (548 mg, 78%).

Alternative method: Bromojuglone **26** (16.8 mg, 0.07 mmol) and borate **24** (32 mg, 0.08 mmol) was dissolved in 0.8 mL THF/H_2O (9:1). To this added Cs_2CO_3 (65 mg, 0.2 mmol), $Pd(dppf)_2$•Cl_2•CH_2Cl_2 (3.0 mg, 0.003 mmol). The reaction mixture was vacuum degassed and refluxed under argon overnight. Diluted with EtOAc (5.0 mL), and quenched by adding saturated aqueous NH_4Cl (10 mL). The mixture was stirred at 0 ºC for 30 min. The aqueous layer was extracted with EtOAc twice and the combined organic layer was washed with saturated brine, and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to silica gel column chromatography, eluting with 8-10% hexane/EtOAc afforded product **27** (9.3 mg, 30%). Reddish-orange solid; mp 172 ºC; (R_f 15% hexanes/EtOAc)= 0.45; IR (thin film, cm^{-1}) ν 3325, 3060, 2975, 2919, 2903, 2866, 2842, 1654, 1578, 1446, 1379, 1342, 1290, 1258, 1241, 1148, 1050, 916; ^1H NMR ($CDCl_3$, 400 MHz): δ 12.15 (s, 1H), δ 7.60-7.67 (m, 3H), δ 7.37-7.48 (m, 5H), δ 7.29 (d, J = 2.4 Hz, 1H), δ 6.82 (s, 1H), δ 6.80 (d, J = 2.4 Hz, 1H), δ 5.14 (s, 2H), δ 3.74 (s, 3H), δ 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.7, 183.8, 166.7, 161.4, 160.5, 158.3, 148.8, 136.3, 135.9, 132.7, 132.1, 128.9, 128.6, 127.9, 124.1, 119.7, 117.1, 115.6, 107.2, 103.8, 70.7, 65.3, 52.6; HRMS (ESI): calcd for $[C_{26}H_{20}O_7 + H]^+$ 445.1287, found 445.1277.

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