

Article

Concise Syntheses of Marine (Bis)indole Alkaloids Meridianin C, D, F, and G and Scalaridine A via One-Pot Masuda Borylation-Suzuki Coupling Sequence

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Abstract: *N*-Protected 3-iodoindoles were reacted with (di)azine halides in a sequentially Pd-catalyzed one-pot fashion, i.e., by Masuda borylation–Suzuki coupling (MBSC) sequence. This methodology was successfully applied to the concise syntheses of marine indole alkaloids meridianin C, D, F, and G, as well as to the bisindole alkaloid scalaridine A, which were obtained in moderate to excellent yield.

Keywords: natural products; one-pot reactions; alkaloids; Masuda borylation–Suzuki coupling



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1. Introduction

Marine flora and fauna display an extraordinary chemical diversity and harbor an enormous richness of natural products [1]. Every year, a large number of new natural products are discovered and studied, with nearly 1500 new compounds published in 2019 alone [2]. Since natural products often exhibit biological activity, the isolation and characterization of novel marine metabolites play major roles in the development of active ingredients and agrochemicals [3]. Indole alkaloids have been isolated from various marine sources, such as sponges, tunicates, red alga, acorn worms, and symbiotic bacteria [4], and are part of numerous in-depth studies due to their frequent bioactivities, such as cytotoxicity [5], antiviral [6], antimicrobial [7], antifungal [8], anti-inflammatory [9], and antiserotonin [10] properties. Interesting representatives amongst indole alkaloids include meridianins A–G, isolated from the tunicate *Aplidium meridianum* [11,12], described as potent inhibitors of various protein kinases [13], or the bisindole scalaridine A, discovered in the sponge *Scalarispongia* sp., exhibiting cytotoxicity against human leukemia cells (Figure 1) [14].

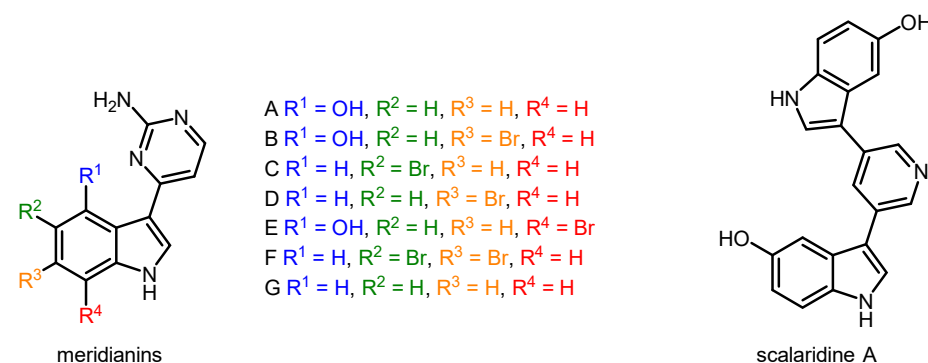


Figure 1. Indole alkaloids meridianins A–G from tunicate *Aplidium meridianum* and scalaridine A from marine sponge *Scalarispongia* sp.

The concatenation of a Masuda borylation [15,16] and a Suzuki coupling has been described in literature [17–21]; however, we conceptualized a general protocol for coupling of a broad spectrum of heterocycles [22–24], in particular a broad selection of 7-azaindoles, such as meriolins [25–32], which are potent kinase inhibitors [33–36], and apoptosis inducers were readily accessed [37]. Most characteristically, the Masuda borylation–Suzuki coupling (MBSC) sequence takes advantage of the concept of a single catalyst system without the addition of another catalyst loading in the sense of a sequentially Pd-catalyzed one-pot process [38,39]. In the first Pd-catalyzed step the (hetero)aryl halide is borylated with pinacolborane in the presence of triethylamine to scavenge the hydrohalide, furnishing the (hetero)aryl pinacolboronate. This borylated derivative is further reacted with a second (hetero)aryl halide in the sense of a Suzuki reaction in the same reaction vessel to provide an unsymmetrically substituted bis(hetero)aryl product.

As illustrations of this powerful MBSC protocol, several indole-containing natural products, such as meridianins A and G (Figure 1) [22], the bisindoles hyrtinadine A [23], alocasin A, and their analogues as efficient MRSA (methicillin-resistant *Staphylococcus aureus*) antibacterials [40], as well as the thiazole containing alkaloid camalexin [24] were synthesized in a concise fashion (Figure 2).

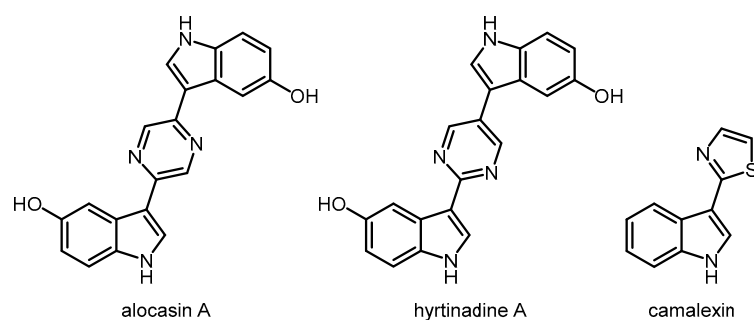


Figure 2. Natural products alocasin A, hyrtinadine A and camalexin synthesized via MBSC sequence.

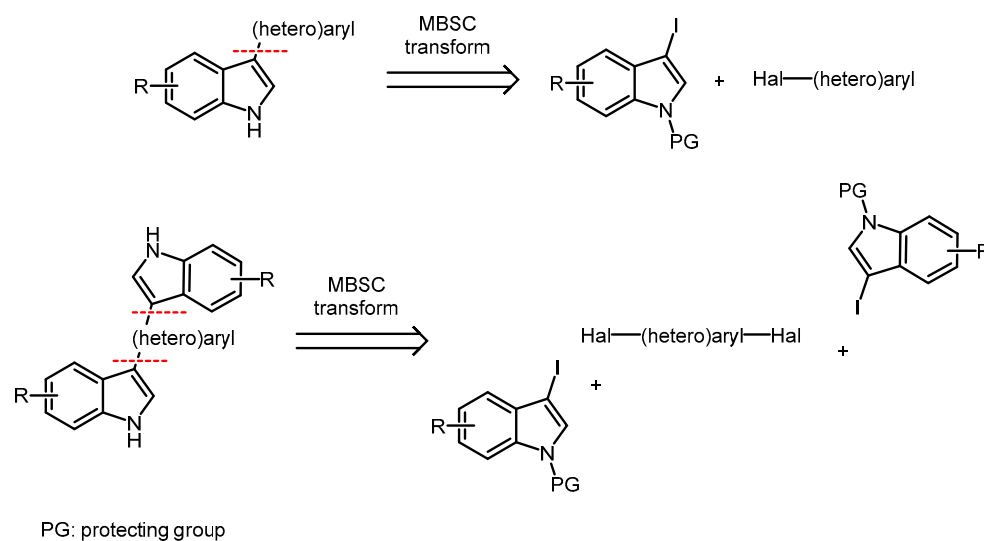
The first synthesis of meridianins set out from transforming 3-acetylindoles into the corresponding enamionones and subsequent cyclization with guanidine [25,26,28]. Later, cycloaddition of nitrosoarenes with alkynylpyrimidines [29], and Pd-catalyzed Cacchi ring-building indole synthesis [31] were introduced as shorter synthetic routes. Employing a three-component carbonylative alkylation as a key step, followed by cycloaddition, we disclosed a concise two-step protocol [41]. Already in 2000, Suzuki coupling was recognized as a key step towards syntheses of selected meridianins [32], and in 2011 we showed that the MBSC is well suited for the synthesis of meridianins A and G [22].

Total syntheses of scalaridine A have been achieved using Ir-catalyzed C–H borylation and Pd-catalyzed Suzuki coupling as key steps [42], as well as several Pd-catalyzed steps including hydrostannylation and Kosugi–Migita–Stille cross-coupling in a multistep synthesis [43], and a Cu-catalyzed Suzuki–Miyaura approach starting from indole boronates in a two-step fashion [44].

Herein, we report the syntheses of the bromo substituted meridianins C, D, and F, as well as meridianin G, and the synthesis of scalaridine A via one-pot Masuda borylation–Suzuki coupling sequence in mostly good yields.

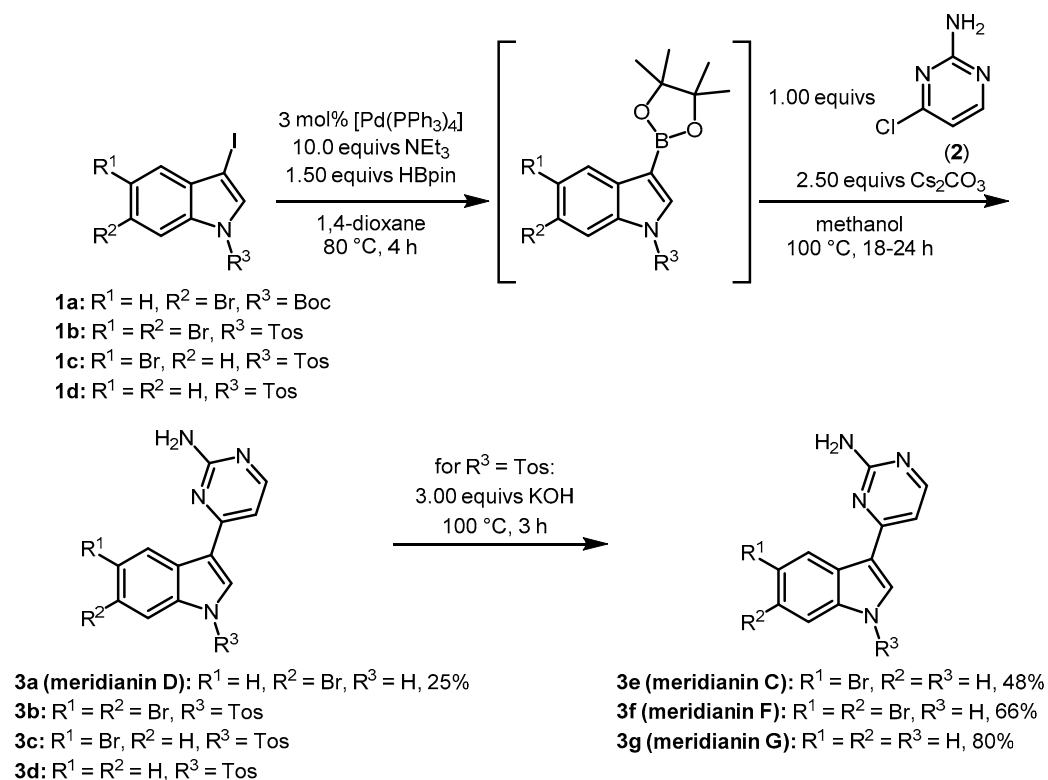
2. Results and Discussion

The MBSC sequence represents an elegant transform for the retrosynthetic analysis of complex heteroaromatic biaryl systems from (hetero)aryl halides as starting materials in a sequentially Pd-catalyzed one-pot procedure (Scheme 1).



Scheme 1. General MBSC transform of (hetero)aryl indoles and its extension to bridged bisindoles.

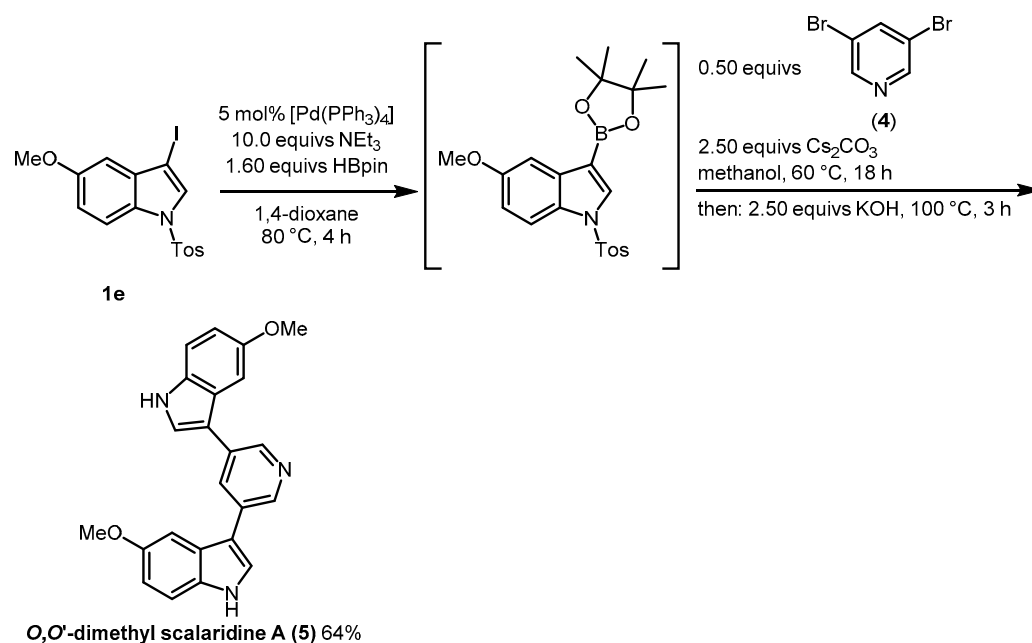
Therefore, in analogy to the synthesis of meridianins A and G [22], our approach to meridianins C, D, F, and G starts from *N*-Boc- and *N*-tosyl-protected 3-iodoindoles **1a–d**. The starting material is prepared in a one-pot process of selective iodination in position three and subsequent *N*-protection according to Witsulski's [45] and our protocols [23,24]. The indoles **1** are converted to the boronate intermediates by Masuda borylation in the presence of tetrakis(triphenylphosphane)palladium(0), pinacolyl borane (HBpin), and triethylamine in dry 1,4-dioxane (Scheme 2).



Scheme 2. Synthesis of meridianins C, D, F, and G by MBSC sequence.

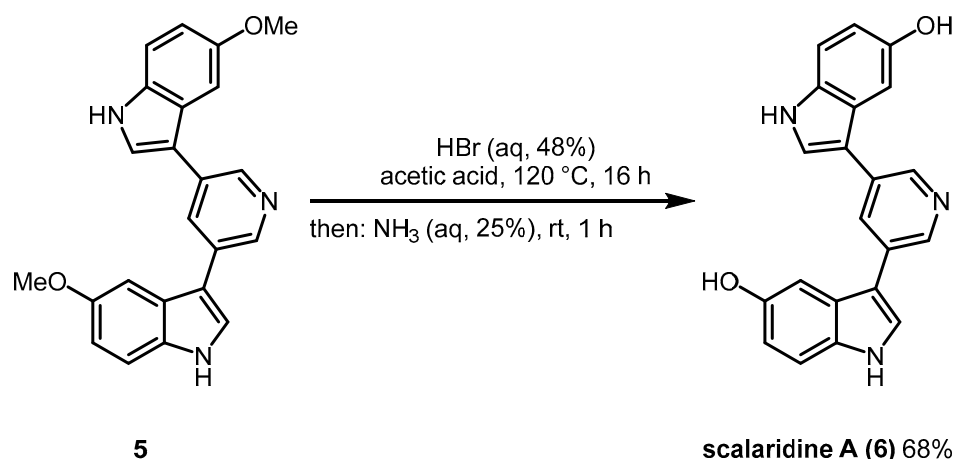
After full conversion of the indole **1**, methanol is added to scavenge the remaining excess of HBpin. Subsequent addition of cesium carbonate and 4-chloropyrimidine-2-amine (**2**) initiates the Suzuki coupling reaction in the same reaction vessel. The Boc protecting group is cleaved under the Suzuki conditions furnishing the natural product meridianin D (**3a**) in a yield of 25%. Although the concomitant cleavage of the protecting group during the Suzuki step is elegant, it turned out that this does not work equally well in all substrate combinations [24,37,40]. Indeed, the tosyl group is more robust and can be equally well cleaved upon reaction of the tosylated intermediates **3b–d** in the presence of potassium hydroxide in an additional step in the one-pot process to give access to meridianin C (**3e**) (48%), meridianin F (**3f**) (66%), and meridianin G (**3g**) (80%). The analytic data are in excellent agreement with the published data of the isolated natural compounds [11,12] (for the comparison of the NMR data, see Supplementary Materials, Chapter S3). Moreover, *N*-tosyl protected indoles **1** appear to be more stable and more practical than *N*-Boc protected substrates, because no dehalogenation is observed by storage at room temperature.

For the synthesis of scalaridine A (**7**), 3-iodo-5-methoxy-1-tosyl-1*H*-indole (**1e**) is employed as a starting material and similarly converted to the respective pinacoly boronate intermediate in the sense of a Masuda borylation (Scheme 3). After full conversion, methanol is added to scavenge the excess of HBpin. In comparison to the meridianin protocol, increasing the amount of catalyst and HBpin is favorable considering two Masuda borylations per *N*-heterocyclic-bridged bisindole. Then, cesium carbonate and half an equivalent of 3,5-dibromopyridine (**4**) are added for the concluding pseudo three-component Suzuki coupling. Addition of potassium hydroxide cleaves the tosyl group and the alkaloid precursor *O,O'*-dimethyl scalaridine A (**5**) is obtained in a yield of 64%.



Scheme 3. Synthesis of the natural product precursor *O,O'*-dimethyl scalaridine A (**5**).

The total synthesis is completed by twofold demethylation [46] of **5** in refluxing acetic acid with hydrobromic acid furnishing the bisindole alkaloid scalaridine A (**6**) in a good yield (Scheme 4). The disappearance of the signal for the methyl groups (δ 3.82) and appearance of the OH signal (δ 8.81) in the ^1H NMR spectrum indicates the formation of the natural compound **6** (see experimental section). The overall yield over 2 steps is 44% (starting from **1e**).



Scheme 4. Synthesis of scalaridine A (**6**) by demethylation of *O,O'*-dimethyl scalaridine A.

3. Materials and Methods

3.1. General Considerations

All cross-coupling reactions were carried out in oven-dried Schlenk tubes under nitrogen atmosphere. By using MBraun system MB-SPS-800, dry 1,4-dioxane was obtained. Dry triethylamine was stored in a Schlenk flask with potassium hydroxide pallets under nitrogen atmosphere. The used *N*-protected 3-iodo-1*H*-indoles **1** were prepared using a literature-known one-pot process [23,24,45]. 4-chloropyrimidine-2-amine (**2**) was synthesized by suspending 2,4-dichloropyrimidine in ammonia (aq, 5%) for 2 d [47]. All other used chemicals were purchased at Sigma-Aldrich Chemie GmbH (St. Louis, MO, USA), Acros Organics (Waltham, MA, USA), ABCR GmbH & CO. KG (Karlsruhe, Germany), Alfa Aesar GmbH (Tewksbury, MA, USA) and Merck Serono KGaA (Darmstadt, Germany) and used as supplied.

For purification of the reaction mixtures, a flash chromatography was performed on silica gel 60 (0.015–0.040 mm) from Macherey-Nagel GmbH & Co. KG under a pressure of 2 bar. Therefore, the crude reaction mixtures were adsorbed on Celite[®] 545 (0.02–0.10 mm) from Macherey-Nagel GmbH & Co. KG. For TLC Silica gel 60 F254 6 × 6 cm² aluminum sheets by Macherey-Nagel GmbH & Co. KG were used. The spots were detected with UV light at 254 and 365 nm. ¹H, ¹³C, and 135-DEPT NMR spectra were recorded on Bruker Avance III 300 and Bruker Avance III 600 spectrometers. DMSO-*d*₆ was used as deuterated solvents. For ¹H spectra, the residual proton signal of the deuterated solvent was locked as the internal standard (DMSO-*d*₆, δ H 2.50, δ C 39.5). The multiplicities of signals were abbreviated as follows: s: singlet, d: doublet, t: triplet, and dd: doublet of doublets. The types of carbon atoms were abbreviated as follows: CH₃: primary carbon atom, CH₂: secondary carbon atom, CH: tertiary carbon atom, and C_{quat}: quaternary carbon atom. For determination a 135-DEPT NMR spectra was used. Mass spectra were measured on Varian MAT 311 A. All peaks with an intensity of >10% corresponding to the base peak were stated. The melting points (uncorrected) were measured on Reichert-Jung S3 Thermovar [48]. Elementary analysis was carried out in the micro analytical laboratory of Institut für Pharmazeutische und Medizinische Chemie der Heinrich-Heine-Universität, Düsseldorf.

3.2. Synthesis of Meridianin D (**3a**)

[Pd(PPh₃)₄] (19 mg, 19 μmol, 3 mol %) and the *tert*-butyl 6-bromo-3-iodo-1*H*-indole-1-carboxylate (**1a**) (278 mg, 0.66 mmol) were placed in a dry screw-cap Schlenk vessel with a septum and a magnetic stir bar under nitrogen atmosphere and suspended in dry 1,4-dioxane (5.00 mL). After the addition of dry triethylamine (0.92 mL, 6.59 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.14 mL, 0.99 mmol) the mixture was stirred at 80 °C (preheated oil bath) for 4 h (monitored by TLC). After cooling to room temperature, methanol (5.00 mL), cesium carbonate (0.54 g, 1.65 mmol), and 4-chloropyrimidine-2-amine

(2) [47] (85 mg, 0.66 mmol) were added. Then, the mixture was stirred at 100 °C (preheated oil bath) for 18 h. After cooling to room temperature, the solution was diluted with dichloromethane and adsorbed onto Celite®. The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (eluent: dichloromethane/methanol/ammonia (aqueous 25%) 100:5:1). The obtained solid was dried under vacuo at 60 °C for 3 to 4 days. Compound **3a** (43 mg, 25%) was obtained as a yellow solid, Mp 211–213 °C (217–221 °C [26]). R_f (dichloromethane/methanol/ammonia (aqueous 25%) 100:5:1): 0.32.

^1H NMR (300 MHz, DMSO- d_6): δ 6.46 (s, 2H), 7.00 (d, $J = 5.3$ Hz, 1H), 7.23 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.62 (d, $J = 1.8$ Hz, 1H), 8.11 (d, $J = 5.3$ Hz, 1H), 8.23 (d, $J = 2.9$ Hz, 1H), 8.56 (d, $J = 8.5$ Hz, 1H), 11.78 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 105.2 (CH), 113.2 (C_{quat}), 113.3 (C_{quat}), 113.7 (CH), 124.5 (CH), 124.6 (CH), 127.0 (C_{quat}), 129.6 (CH), 135.7 (C_{quat}), 157.1 (CH), 162.2 (C_{quat}), 163.5 (C_{quat}). HR-MS (ESI) (m/z) calcd for ($\text{C}_{12}\text{H}_9^{79}\text{BrN}_4 + \text{H}$) $^+$: 289.0088; Found: 289.0081.

3.3. Synthesis of Meridianin C (3e), Meridianin F (3f), and Meridianin G (3g)

3.3.1. General Procedure for the Synthesis of Meridianins 3e–g via MBSC Sequence

[Pd(PPh $_3$) $_4$] (19 mg, 19 μmol , 3 mol %) and the 3-iodo-1-tosyl-1H-indole **1** (0.66 mmol) were placed in a dry screw-cap Schlenk vessel with a septum and a magnetic stir bar under nitrogen atmosphere and were suspended in dry 1,4-dioxane (5.00 mL). After the addition of dry triethylamine (0.92 mL, 6.59 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.14 mL, 0.99 mmol) the mixture was stirred at 80 °C (preheated oil bath) for 4 h (monitored by TLC). After cooling to room temperature methanol (5.00 mL), cesium carbonate (0.54 g, 1.65 mmol) and 4-chloropyrimidine-2-amin (**2**) [47] (85 mg, 0.66 mmol) were added. Then, the mixture was stirred at 100 °C (preheated oil bath) for 15 h. The solution was again cooled to room temperature before potassium hydroxide (0.11 g, 1.98 mmol) was added. After the mixture was allowed to cool down to room temperature it was diluted with dichloromethane and adsorbed onto Celite®. The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (eluent: dichloromethane/methanol/ammonia (aqueous 25%) (100:5:1)). The obtained solid was dried in vacuo at 60 °C for 4 d.

3.3.2. Synthesis of 4-(5-Bromo-1H-indol-3-yl)pyrimidin-2-amine, Meridianin C (3e)

According to the general procedure starting from 5-bromo-3-iodo-1-tosyl-1H-indole (**1c**) compound **3e** (91 mg, 48%) was isolated as a yellow solid, Mp 208–210 °C (238–240 °C [41]). R_f (dichloromethane/methanol/ammonia (aqueous 25%) 100:5:1): 0.25.

^1H NMR (300 MHz, DMSO- d_6): δ 6.50 (s, 2H), 7.01 (d, $J = 5.4$ Hz, 1H), 7.29 (dd, $J = 8.6$, 2.0 Hz, 1H), 7.41 (d, $J = 8.6$ Hz, 1H), 8.11 (d, $J = 5.3$ Hz, 1H), 8.26 (d, $J = 2.9$ Hz, 1H), 8.76 (d, $J = 2.0$ Hz, 1H), 11.86 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 105.2 (CH), 113.2 (C_{quat}), 113.3 (C_{quat}), 113.7 (CH), 124.5 (CH), 124.6 (CH), 127.0 (C_{quat}), 129.6 (CH), 135.7 (C_{quat}), 157.0 (CH), 162.2 (C_{quat}), 163.5 (C_{quat}). HR-MS (ESI) (m/z) calcd for ($\text{C}_{12}\text{H}_9^{79}\text{BrN}_4 + \text{H}$) $^+$: 289.0088; Found: 289.0083. Anal calcd for $\text{C}_{12}\text{H}_9\text{BrN}_4$ (289.1): C 49.85, H 3.14, N 19.38; Found: C 50.04, H 3.14, N 19.09.

3.3.3. Synthesis of 4-(5,6-Dibromo-1H-indol-3-yl)pyrimidin-2-amine, Meridianin F (3f)

According to the general procedure starting from 5,6-dibromo-3-iodo-1-tosyl-1H-indole (**1b**) compound **3f** (0.160 g, 66%) was obtained as a colorless solid Mp 290–292 °C (167–169 °C [28]). R_f (dichloromethane/methanol/ammonia (aq, 25%) 100:5:1): 0.22.

^1H NMR (300 MHz, DMSO- d_6): δ 6.56 (s, 2H), 7.02 (d, $J = 5.3$ Hz, 1H), 7.85 (s, 1H), 8.14 (d, $J = 5.3$ Hz, 1H), 8.31 (d, $J = 1.7$ Hz, 1H), 8.97 (s, 1H), 11.94 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 105.1 (CH), 113.2 (C_{quat}), 114.9 (C_{quat}), 116.1 (C_{quat}), 116.5 (CH), 126.1 (C_{quat}), 126.5 (CH), 130.4 (CH), 136.7 (C_{quat}), 157.3 (CH), 161.8 (C_{quat}), 163.5 (C_{quat}). HR-MS (ESI) (m/z) calcd for ($\text{C}_{12}\text{H}_8^{79}\text{Br}_2\text{N}_4 + \text{H}$) $^+$: 366.9188; Found: 366.9171. Anal calcd for $\text{C}_{12}\text{H}_8\text{Br}_2\text{N}_4$ (368.03): C 39.16, H 2.19, N 15.22; Found: C 39.36, H 2.36, N 14.93.

3.3.4. Synthesis of 4-(1H-indol-3-yl)pyrimidin-2-amine, Meridianin G (**3g**)

According to the general procedure starting from 3-iodo-1-tosyl-1H-indole (**1d**) compound **3g** (111 mg, 80%) was isolated as a colorless solid, Mp 190–191 °C (195–197 °C [22]). R_f (dichloromethane/methanol/ammonia (aqueous 25%) 100:5:1): 0.26.

^1H NMR (600 MHz, DMSO- d_6): δ 6.41 (s, 2H), 7.01 (d, $J = 5.3$ Hz, 1H), 7.12 (td, $J = 7.4$, 6.9, 1.1 Hz, 1H), 7.17 (ddd, $J = 8.1$, 6.9, 1.3 Hz, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 8.10 (d, $J = 5.3$ Hz, 1H), 8.19 (d, $J = 2.9$ Hz, 1H), 8.58 (d, $J = 7.9$ Hz, 1H), 11.66 (s, 1H). ^{13}C NMR (150 MHz, DMSO- d_6): 105.3 (CH), 111.8 (CH), 113.7 (C_{quat}), 120.2 (CH), 121.9 (CH), 122.4 (CH), 125.3 (C_{quat}), 128.2 (CH), 137.0 (C_{quat}), 157.0 (CH), 162.7 (C_{quat}), 163.5 (C_{quat}). HR-MS (ESI) (m/z) calcd for ($\text{C}_{12}\text{H}_{10}\text{N}_4 + \text{H}$) $^+$: 211.0978; Found: 211.0977.

3.4. Synthesis of Scalaridine A (**6**)

3.4.1. Synthesis of 3,5-Bis(5-methoxy-1H-indol-3-yl)pyridine (**5**)

[Pd(PPh $_3$) $_4$] (57.0 mg, 0.0490 μmol , 5 mol %) and 3-iodo-5-methoxy-1-tosyl-1H-indole (**1e**) (0.427 g, 1.00 mmol) were placed in a dry screw-cap Schlenk vessel with a septum and a magnetic stir bar under nitrogen atmosphere and were suspended in dry 1,4-dioxane (5.00 mL). The solution was degassed with nitrogen for 10 min. Dry triethylamine (1.40 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.23 mL, 1.60 mmol) were added before the reaction mixture was stirred at 80 °C (preheated oil bath) for 4 h. After cooling to room temp methanol (7.00 mL), cesium carbonate (0.810 g, 2.50 mmol), and 3,5-dibromopyridine (0.120 g, 0.500 mmol) were added and the suspension was stirred at 60 °C (preheated oil bath) for 18 h. Thereafter, the reaction mixture was again cooled to room temp and potassium hydroxide (0.140 mg, 2.50 mmol) was added, the suspension was stirred at 100 °C (preheated oil bath) for 3 h. The reaction mixture was cooled to room temp and the crude product was adsorbed onto Celite $^{\text{®}}$ and purified by flash chromatography on silica gel (eluent: dichloromethane/methanol/ammonia (aqueous 25%) 100:1:1). The obtained solid was suspended in diethyl ether, filtered, and dried in vacuo at 60 °C for 1 day. Compound **5** (0.120 g, 64%) was isolated as a beige solid, Mp 218–219 °C (107–111 °C [42]). R_f (dichloromethane/methanol/ammonia (aqueous 25%) 100:1:1): 0.37.

^1H NMR (300 MHz, DMSO- d_6): δ 3.82 (s, 6H), 6.86 (dd, $J = 8.8$, 2.4 Hz, 2H), 7.38 (d, $J = 2.4$ Hz, 2H), 7.40 (d, $J = 8.9$ Hz, 2H), 7.85 (d, $J = 2.7$ Hz, 2H), 8.24 (t, $J = 2.1$ Hz, 1H), 8.77 (d, $J = 2.7$ Hz, 2H), 11.39 (s, 2H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 55.4 (CH_3), 100.7 (CH), 111.6 (CH), 112.1 (C_{quat}), 112.8 (CH), 125.0 (CH), 125.2 (C_{quat}), 130.2 (CH), 131.8 (C_{quat}), 132.0 (C_{quat}), 143.9 (CH), 154.2 (C_{quat}). MS (EI) (m/z): 370 (26), 369 ([M] $^+$, 100), 326 (13), 184 ([$\text{C}_{12}\text{H}_{10}\text{NO}$] $^+$, 15), 177 (12), 163 (13), 155 ([$\text{C}_{11}\text{H}_8\text{O}$] $^+$, 14), 141 (26). HR-MS (ESI) (m/z) calcd. for ($\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_2 + \text{H}$) $^+$: 370.1550; Found: 370.1551.

3.4.2. Synthesis of 3,3'-(Pyridine-3,5-diyl)bis(1H-indol-5-ol), Scalaridine A (**6**) by Demethylation of Compound **5**

3,5-Bis(5-methoxy-1H-indol-3-yl)pyridine (**5**) (85.0 mg, 0.230 mmol) was placed in a dry screw-cap Schlenk vessel with a septum and a magnetic stir bar under nitrogen atmosphere and was dissolved in acetic acid (2.00 mL). After hydrobromic acid (2.00 mL, aq, 48%) were added the suspension was stirred at 120 °C (preheated oil bath) for 16 h. After cooling to room temp, the solvent was evaporated under reduced pressure. The residue was diluted in ammonia (10.0 mL, aqueous 25%) and stirred at room temp for 1 h. The crude product was extracted with ethyl acetate (3 \times 100 mL), adsorbed onto Celite $^{\text{®}}$ and purified by flash chromatography on silica gel (eluent: ethyl acetate). Compound **6** (53 mg, 68%) was obtained as a yellow solid, Mp 319–320 °C (319–320 °C [42]). R_f (ethyl acetate): 0.34.

^1H NMR (300 MHz, DMSO- d_6): δ 6.71 (dd, $J = 8.6$, 2.2 Hz, 2H), 7.23 (d, $J = 2.2$ Hz, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 7.78 (d, $J = 2.7$ Hz, 2H), 8.18 (t, $J = 2.2$ Hz, 1H), 8.69 (d, $J = 2.1$ Hz, 2H), 8.81 (s, 2H), 11.26 (d, $J = 2.7$ Hz, 2H). ^{13}C NMR (75 MHz, DMSO- d_6): δ 102.6 (CH), 111.1 (CH), 112.0 (CH), 112.6 (C_{quat}), 124.5 (CH), 125.7 (C_{quat}), 130.0 (CH), 130.6 (C_{quat}),

133.0 (C_{quat}), 144.5 (CH), 151.1 (C_{quat}). MS (ESI) (*m/z*): 342 (22), 341 ([M]⁺, 100), 312 (14). HR-MS (ESI) (*m/z*) calcd. for (C₂₁H₁₅N₃O₂ + H)⁺: 342.1237; Found: 342.1240.

4. Conclusions

The Masuda borylation–Suzuki coupling sequence is a practical and catalyst-efficient tool for the synthesis of bi(hetero)aryls and (hetero)aryl-bridged bisindoles. Here, we showcased the concise two-step syntheses of the naturally occurring brominated marine alkaloids meridianins C, D, and F, as well as meridianin G and the marine bisindole scalaridine A. The operational simplicity and concision of the MBSC sequence is well suited for the rapid synthesis of libraries of related bi(hetero)aryls and corresponding bridged systems with biological activity, which are currently underway.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/molecules27072233/s1>, Supporting Information: Synthetic and analytic details, and ¹H and ¹³C NMR spectra of compounds 1–6, comparison of experimental NMR data with NMR data of the isolated natural products.

Author Contributions: The work consists of parts of the planned Ph.D. thesis of M.K., which was supervised by T.J.J.M., and the master thesis of G.A.S., which was also supervised by T.J.J.M. The conceptualization was outlined and accompanied by T.J.J.M. Synthetic studies were performed by M.K. (80%) and G.A.S. (20%). All analytical assignments were performed by M.K. (85%) and G.A.S. (15%). Writing of the original draft was done by M.K., and review and editing by all coauthors. Project administration and funding acquisition was carried out by T.J.J.M. All authors have read and agreed to the published version of the manuscript.

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