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Short and flexible route to 3,4-diarylpyrrole marine alkaloids: syntheses of permethyl storniamide A, ningalin B, and lamellarin G trimethyl ether

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Abstract—A highly efficient route to 3,4-diarylpyrrole marine alkaloids has been developed using Hinsberg-type pyrrole synthesis and palladium-catalyzed Suzuki cross-coupling of the 3,4-dihydroxypyrrole bis-triflate derivatives as key reactions. Based on this approach, formal syntheses of permethyl storniamide A and ningalin B, and a total synthesis of lamellarin G trimethyl ether have been achieved.

The natural products possessing a common 3,4-diarylpyrrole unit have been isolated from a marine prosoblanch mollusk, ascidians, and sponges. These include lamellarins A–β,[1] lukianols A–B,[2] storniamides A–D,[3] ningalins A–D,[4] polycitones A–B,[5] and polycitrins A–B.[5] Many of these natural products and their derivatives exhibit unique and highly useful biological activities. For examples, lamellarin K (**1**) displayed potent cytotoxic activity against multidrug-resistant (MDR) tumor cell lines, while at non-toxic doses lamellarin I (**2**) effectively increased the cytotoxicity of approved anticancer agents on MDR cell lines by inhibition of P-glycoprotein-mediated drug efflux.[6] Permethyl storniamide A (**4**), permethyl ningalin B (**6**), and much simpler 3,4-diarylpyrrole derivatives also exhibited similar MDR reversal activity at non-toxic concentrations.[7] Lamellarin α 20-sulfate (**7**) showed inhibition of HIV-1 integrase.[1h] The sulfate **7** is active against live HIV-1 virus at non-toxic concentrations.[1h] These results suggested that this type of marine natural products are highly promising leads for new cancer and HIV chemotherapeutic agents (Fig. 1).

Due to such promising biological activities and their unique structures, a variety of synthetic approaches have been developed.[7,8] Herein, we report a new and highly efficient synthesis of this class of natural products using two key reactions: (1) Hinsberg-type condensation[9] of the iminodiacetates **9** with methyl oxalate to produce 3,4-dihydroxypyrrole-2,5-dicarboxylates **10**, and (2) palladium-catalyzed Suzuki cross-coupling[10] of the bis-triflate derivatives **11** with arylboronic acids.

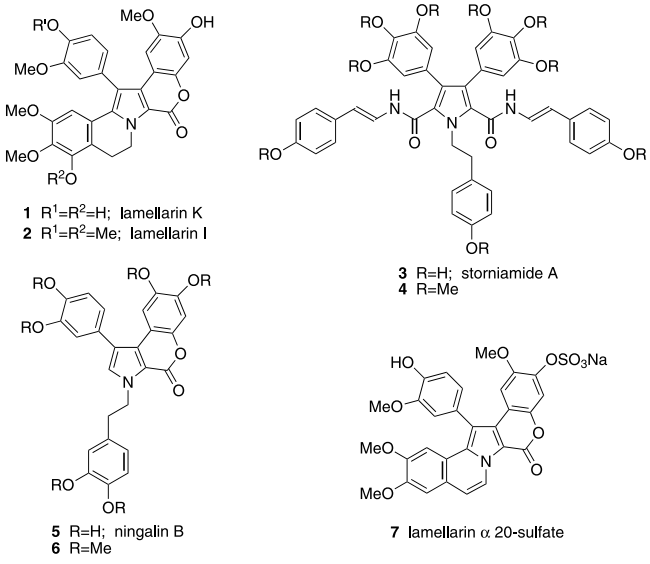

Figure 1. 3,4-Diarylpyrrole marine alkaloids.

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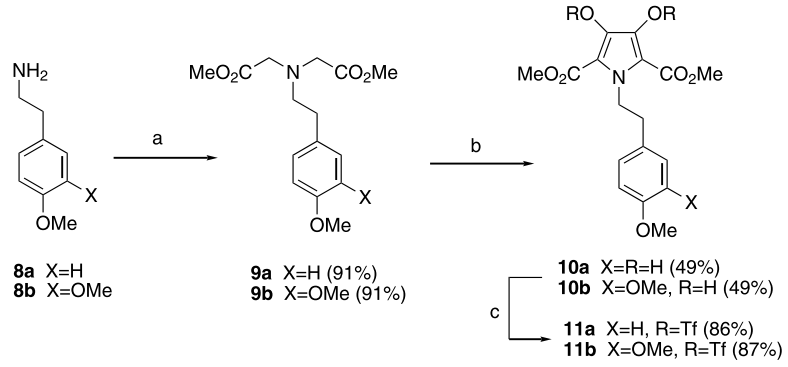
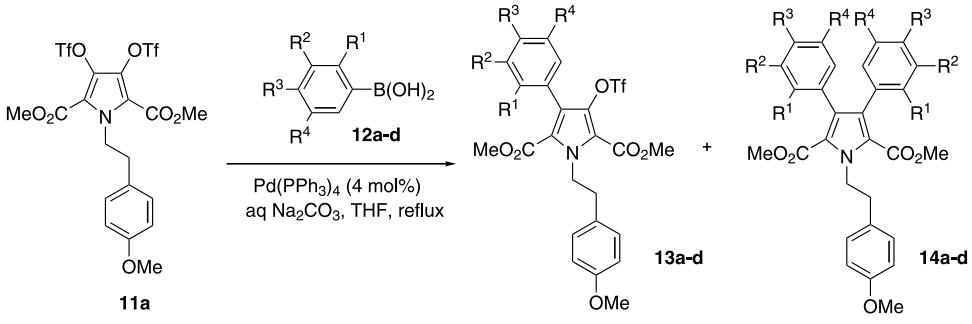
The synthesis of bis-triflates **11a**,**b** is shown in Scheme 1. 2-Arylethylamines **8a**,**b** were alkylated with 2.2 equiv. of methyl bromoacetate in acetonitrile in the presence of $NaHCO_3$ to give the iminodiacetates **9a**,**b** in over 90% yields. Condensation of **9a**,**b** with dimethyl oxalate using NaOMe as a base afforded 3,4-dihydroxypyrrole-2,5-dicarboxylates **10a**,**b** in modest yields. These pyrroles were converted to the bis-triflates **11a**,**b** in good yields by the standard procedure.

Next, we carried out palladium-catalyzed cross-coupling of the bis-triflate **11a** with a range of methoxy-substituted phenylboronic acids **12a–d**[11] (Table 1). A mixture of **11a** (1 mmol), an appropriate amount of a boronic acid **12**, $Pd(PPh_3)_4$ (0.04 mmol), aqueous Na_2CO_3 (6.6 mmol in 2 mL of H_2O) and THF (20 mL) was heated under reflux.[12] The reaction with 2.2 equiv. of 4-methoxyphenylboronic acid (**12a**) was essentially completed within 5 h to give the 3,4-diarylpyrrole **14a** in 99% yield after chromatographic purification (entry 1). On the other hand, reactions with 2-methoxy, 3,4-dimethoxy, and 3,4,5-trimethoxyphenylboronic acids (**12b–d**) were somewhat slow under similar conditions to give the mixtures of mono-arylated **13b–d** and di-arylated **14a–d** (entries 2–4). However, when the reaction time was elongated to 20 h using 3.0 equiv. of the boronic acids, the di-arylated products were obtained in excellent yields (entries 5–7). The 3,4-diarylpyrrole **14d** ($R^1=H$, $R^2=R^3=R^4=OMe$) thus prepared has previously been converted to permethyl storniamide A (**4**) in three steps by Boger et al.[7a] Synthesis of mono-arylated pyrroles as the major products may be possible using 1:1 stoichiometries of the triflates and the boronic acids. In fact, the reaction of **11a** with 1.0 equiv. of **12a** in the presence of 4 or 2 mol% of $Pd(PPh_3)_4$ gave the mono-substituted **13a** in good yields (entries 8 and 9).



Scheme 1. *Reagents and conditions*: (a) $BrCH_2CO_2Me$ (2.2 equiv.), $NaHCO_3$, CH_3CN, reflux, 2.5 h; (b) $(CO_2Me)_2$ (1.0 equiv.), MeONa, MeOH, reflux, 18 h; (c) $(CF_3SO_2)_2O$ (2.2 equiv.), pyridine, 0°C, 2 h.

Table 1. Palladium-catalyzed cross-coupling of bis-triflate **11a** with arylboronic acids **12a–d**



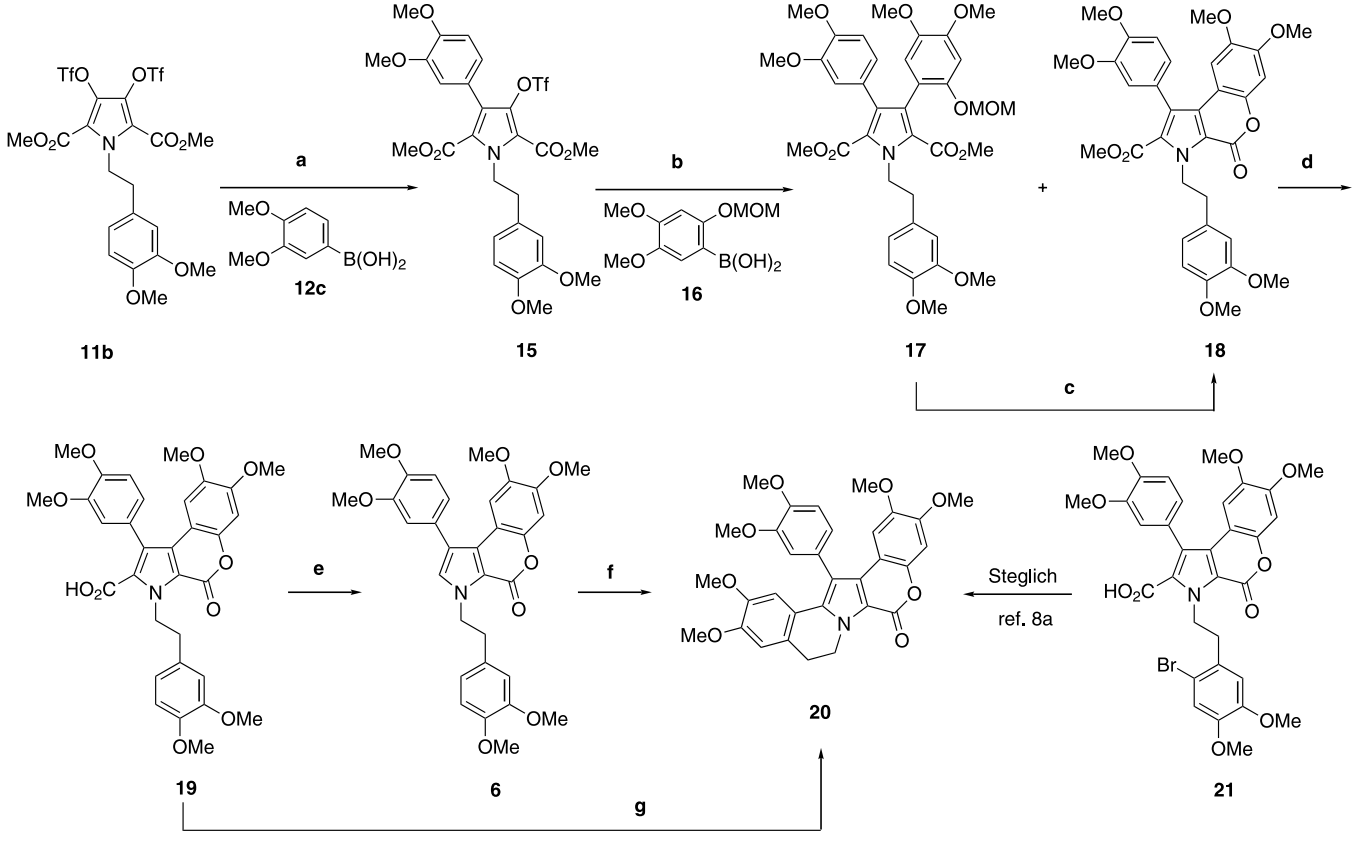
Entry	**12**	R^1	R^2	R^3	R^4	Equiv.	Time (h)	**13** (%)[a]	**14** (%)[a]
1	**12a**	H	H	OMe	H	2.2	5	1	99
2	**12b**	OMe	H	H	H	2.2	5	66	34
3	**12c**	H	OMe	OMe	H	2.2	5	45	54
4	**12d**	H	OMe	OMe	OMe	2.2	5	44	55
5	**12b**	OMe	H	H	H	3.0	20	1	99
6	**12c**	H	OMe	OMe	H	3.0	20	0	100
7	**12d**	H	OMe	OMe	OMe	3.0	20	0	100
8	**12a**	H	H	OMe	H	1.0	3	77	9
9	**12a**	H	H	OMe	H	1.0[b]	4	78	8

[a] Isolated yields after column chromatography.
[b] 2 mol% of $Pd(PPh_4)$ was used.

An efficient synthesis of 3,4-diarylpyrroles being established, we planned to develop a new and general route to pentacyclic lamellarins,[8a–j,13] structurally most complex and biologically most significant natural products in the 3,4-diarylpyrole alkaloids family. We selected lamellarin G trimethyl ether (**20**) as a model compound and executed its total synthesis (Scheme 2). The bistriflate **11b** was coupled with 1.0 equiv. of 3,4-dimethoxyphenyboronic acid (**12c**)[11] under standard conditions described above to give the mono-arylated **15** in 78% yield, accompanied by 11% yield of the di-arylated product. The second cross-coupling of **15** with 4,5-dimethoxy-2-methoxymethoyphenylboronic acid (**16**)[11] was found to be somewhat inefficient due to rapid decomposition of the boronic acid **16** under the coupling conditions. However, when the reaction was carried out using excess (2.0 equiv.) of **16** and 8 mol% of $Pd(PPh_3)_4$, the coupling product **17** and its lactone **18** were obtained in 58 and 12% yields, respectively. The compound **17** was converted to **18** by treatment with hydrochloric acid in methanol in 90% yield. Alkaline hydrolysis of **18** followed by heating with *p*-TsOH in refluxing toluene produced the acid **19** in 76% yield.[8e] Cu_2O-mediated decarboxylation of **19** in hot quinoline afforded permethyl ningalin B (**6**) in 93% yield.[7b] This compound has previously been converted to ningalin B (**5**) by exhaustive demethylation.[7b] The ring closure of **6** to lamellarin G trimethyl ether (**20**) was cleanly effected by application of Kita's oxidative biaryl coupling conditions[14] [phenyliodine bis(trifluoroacetate) (PIFA)/$BF_3{\cdot}Et_2O$] in 86% yield. The spectroscopic data of **20** were identical with those reported previously.[8a]

Finally, we examined a more straightforward ring closure of **19** to **20**. Steglich has reported an interesting Pd(0)-mediated decarboxylative cyclization of the bromo-acid **21** to **20**.[8a,e] We envisioned that a similar ring closure could be feasible if Pd(II) salt was applied to the acid **19**. In fact, when **19** was heated with 1.1 equiv. of $Pd(OAc)_2$ in acetonitrile under reflux for 12 h, **20** was obtained in 65% yield, accompanied by 12% of the decarboxylated product **6**. The ring closure was found to be regioselective at C-6 of the pendant aromatic ring. This novel cyclization may proceed via initial decarboxylative palladation[15] of the pyrrole ring, followed by electrophilic palladation of the electron-rich aromatic ring and reductive elimination of Pd(0).

In conclusion, we have developed a highly efficient route to 3,4-diarylpyrrole marine alkaloids, including pentacyclic lamellarins. We believe this route is flexible enough to be applied to the syntheses of diverse natural products and their analogues. Studies along this line are in progress in our laboratories.



Scheme 2. *Reagents and conditions*: (a) **12c** (1.0 equiv.), $Pd(PPh_3)_4$ (2 mol%), aq. Na_2CO_3, THF, reflux, 4 h (78%); (b) **16** (2.0 equiv.), $Pd(PPh_3)_4$ (8 mol%), aq. Na_2CO_3, THF, reflux, 20 h (**17**: 58%, **18**: 12%); (c) conc. HCl, MeOH, reflux, 1 h (90%); (d) (i) 40% aq. KOH, reflux, 3 h, (ii) cat. *p*-TsOH, toluene, reflux, 30 min (76%); (e) Cu_2O, quinoline, 220°C, 7 min (93%); (f) $PhI(OCOCF_3)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40°C, 1.5 h (86%); (g) $Pd(OAc)_2$ (1.1 equiv.), CH_3CN, reflux, 12 h (**20**: 65%, **6**: 12%).

Acknowledgements

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