Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron

Tetrahedron 64 (2008) 328–338

www.elsevier.com/locate/tet

Palladium-catalyzed cross-coupling of *N*-benzenesulfonyl-3,4-dibromopyrrole and its application to the total syntheses of lamellarins O, P, Q, and R

Tsutomu Fukuda [a], Ei-ichi Sudo [a], Kozue Shimokawa [b], Masatomo Iwao [b,]*

[a] *Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*
[b] *Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*

Received 30 September 2007; received in revised form 29 October 2007; accepted 29 October 2007
Available online 1 November 2007

Abstract

Palladium-catalyzed Suzuki–Miyaura coupling of *N*-benzenesulfonyl-3,4-dibromopyrrole with a variety of arylboronic acids gave the corresponding 3,4-diarylpyrroles in high yields. The 3,4-differentially arylated pyrroles could also be prepared by stepwise cross-coupling approach. The total syntheses of lamellarins O, P, Q, and R have been achieved by using the cross-coupling and the directed lithiation as key reactions.

1. Introduction

Recently, much attention has been focused on a family of heterocyclic marine natural products having 3,4-diarylpyrrole as the common structural unit.[1] It is comprised of lamellarins, ningalins, polycitones, purpurone, halitulin, dictyodendrins, and so on (Fig. 1). The biological activities of this class of compounds are pronounced. For example, polycitone A (**1**) strongly inhibits both retroviral reverse transcriptases and cellular DNA polymerases.[2] Halitulin (**2**) exhibits strong cytotoxicity against several human tumor cell lines with IC_{50} value in the 0.012–0.025 μg/mL range.[3] Lamellarins D (**3**) and N (**4**) exhibit potent cytotoxicity against P-glycoprotein-mediated multi-drug-resistant (MDR) cancer cell lines as well as their parental cell.[4] The lamellarin derivatives have been extensively studied as the potential leads of new anticancer agent.[5] Lamellarin α 20-sulfate (**5**), on the other hand, is an inhibitor of HIV-1 integrase and is active against live HIV-1 virus in vitro at non-toxic concentrations.[6] Dictyodendrin A (**6**) inhibits telomerase completely at a concentration of 50 μg/mL.[7]

Although a variety of synthetic routes to this class of compounds have been developed, the strategy via palladium-catalyzed arylation of the central pyrrole core may be most versatile and straightforward.[8] Banwell reported the first cross-coupling approach to the simple lamellarins O and Q using 3,4-dibromopyrrole-2-carboxylate **7a** as a substrate.[9] The selective introduction of different aryl groups at C3 and C4 was effected by regioselective Br–Li exchange of **7b** followed by transmetalation and Negishi cross-coupling reaction. Wong reported regioselective *ipso*-iodination of 3,4-disilylpyrrole **8** and consequently achieved the selective functionalization of the pyrrole core via a range of cross-coupling reactions.[10] Fürstner synthesized 3,4-dibromopyrrole-2,5-dicarboxylate **9** from *N*-(*tert*-butoxycarbonyl)pyrrole in three-steps and utilized this compound as a substrate for the Suzuki–Miyaura coupling.[11] He also tested the utility of 3,4-dibromo-*N*-(triisopropylsilyl)-pyrrole (**10**) for the synthesis of halitulin core.[11] Banwell and Steglich, on the other hand, utilized the umpoled pyrrole **11** in their total synthesis of halitulin (**2**).[12] We prepared 3,4-dihydroxypyrrole bistriflates **12** from 2-arylethylamines in three-

---

* Corresponding author.
E-mail address: iwao@nagasaki-u.ac.jp (M. Iwao).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.10.105

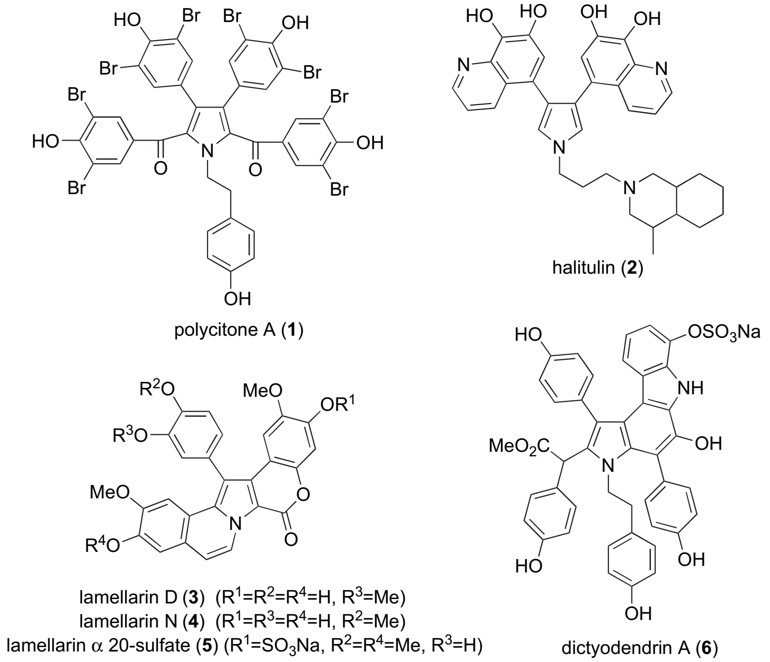


Figure 1. 3,4-Diarylpyrrole marine alkaloids.

steps via Hinsberg reaction and demonstrated that compounds **12** are the excellent substrates for Suzuki–Miyaura coupling.[13] Total syntheses of lamellarins D (**3**), L, N (**4**), and α 20-sulfate (**5**) have been achieved starting from **12**.[14] Handy developed the iterative halogenation/cross-coupling strategy for the synthesis of lamellarin G trimethyl ether starting from simple 4-bromo-pyrrole-2-carboxyalte **13**.[15] Finally, Smith devised a protocol for regioselective arylation of pyrrole-2-carboxylate core utilizing chlorine as a protecting group. The 3,4-diarylpyrrole-2-carboxylates can be produce from **14** after selective cross-coupling at 3,4-positions followed by hydrogenolysis of the chlorine at 5-position.[16] In this paper, we present a new cross-coupling approach to the 3,4-diarylpyrrole marine alkaloids using *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**) (Fig. 2) .

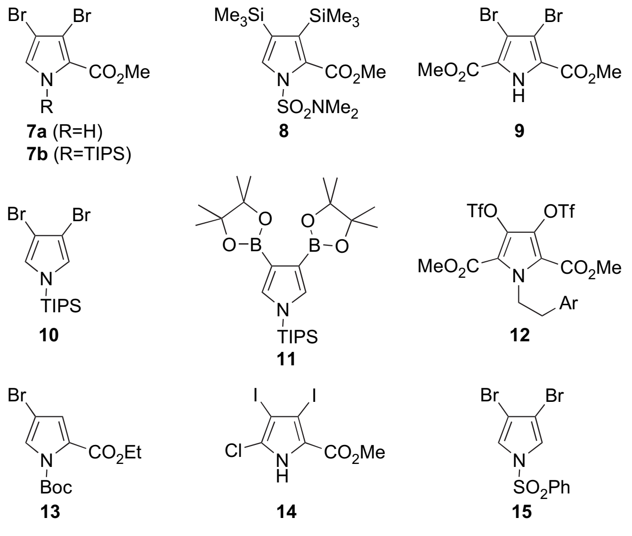
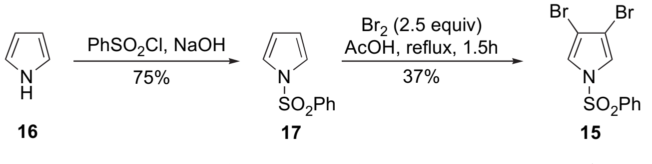


Figure 2. Pyrrole substrates used for cross-coupling reactions.

2. Results and discussion

2.1. Synthesis and palladium-catalyzed cross-coupling of *N*-benzenesulfonyl-3,4-dibromopyrrole (*15*)

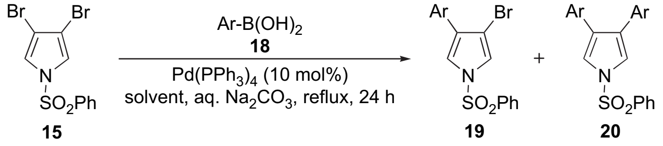
It is well-known that the electrophilic substitutions of *N*-protected pyrroles proceed at the α-position selectively. Recently, however, Zonta reported the synthesis of 3,4-dibromo-*N*-(*p*-toluenesulfonyl)pyrrole via the direct bromination of *N*-(*p*-toluenesulfonyl)pyrrole under thermodynamically controlled conditions (2 equiv Br_2, acetic acid, reflux).[17] Based upon the procedure of Zonta, we prepared *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**) in two-steps from pyrrole (**16**) (Scheme 1). Although the yield of the direct bromination of *N*-benzenesulfonylpyrrole (**17**) is modest (37%), easy availability of **17** from inexpensive starting materials may compensate this drawback. An attempted synthesis of **15** via acid-catalyzed isomerization (TFA/CH_2Cl_2/rt, CF_3SO_3H/toluene/rt, AcOH/reflux) of easily available *N*-benzenesulfonyl-2,5-dibromopyrrole failed.



Scheme 1. Synthesis of *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**).

Next, we examined palladium-catalyzed Suzuki–Miyaura coupling of **15** with arylboronic acids **18**. A mixture of **15** (1.0 mmol), arylboronic acid **18** (2.0 or 3.0 mmol), $Pd(PPh_3)_4$ (0.1 mmol), aqueous Na_2CO_3 (6.6 mmol in 2 mL of H_2O) in THF or DME (10 mL) was heated under reflux for 24 h (Table 1). At the THF-refluxing temperature (65 °C), the cross-

Table 1
Palladium-catalyzed cross-coupling of *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**)



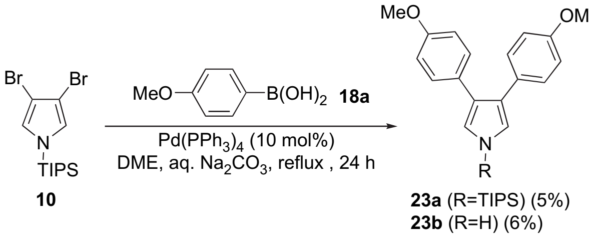
Entry	**18** (equiv)	Ar	Solvent	**15**[a] (%)	**19**[a] (%)	**20**[a] (%)
1	**18a** (2.0)	4-Methoxyphenyl	THF	23	56	12
2	**18a** (3.0)	4-Methoxyphenyl	THF	5	56	32
3	**18a** (3.0)	4-Methoxyphenyl	DME	0	0	93
4	**18b** (3.0)	4-Isopropoxyphenyl	DME	0	0	94
5	**18c** (3.0)	4-Fluorophenyl	DME	0	0	96
6	**18d** (3.0)	4-Chlorophenyl	DME	0	0	95
7	**18e** (3.0)	2-Methoxyphenyl	DME	0	0	93
8	**18f** (3.0)	2,6-Dimethoxyphenyl	DME	0	0	93
9	**18g** (3.0)	3,4-Dimethoxyphenyl	DME	0	0	91
10	**18h** (3.0)	3,4,5-Trimethoxyphenyl	DME	0	0	91

[a] Isolated yields.

coupling reactions of **18a** were insufficiently fast, and as a result, a mixture of starting material **15**, monoarylpyrrole **19a**, and diarylpyrrole **20a** were obtained (entries 1 and 2). As shown in entry 3, however, the coupling reaction of **18a** (3 equiv) became fast at the DME-refluxing temperature (85 °C) to give diarylpyrrole **20a** as the sole product in excellent yield. Under the similar conditions, a variety of arylboronic acids **18b**–**h**, having electron-donating or electron-withdrawing or sterically demanding substituent at the aryl ring, were reacted smoothly to produce the corresponding diarylpyrroles **20b**–**h** in excellent yields (>90%) (entries 4–10). Of our delight, cleavage of the alkaline-sensitive *N*-benzenesulfonyl protecting group of the pyrrole was negligible under the reaction conditions.

Selective monoarylation of **15** is also useful for the synthesis of 3,4-unsymmetrically arylated pyrroles. It was assumed from the results indicated in entries 1 and 2 of Table 1 that the preferential monoarylation could be achieved by using reduced amount of arylboronic acid at lower temperatures. In fact, the cross-coupling of **15** with 1.5 equiv **18a** in refluxing THF for 24 h afforded 41% of monoarylpyrrole **19a**, 5% of diarylpyrrole **20a**, and 41% of starting material **15**. Somewhat improved selectivity was realized by using less reactive pinacol borate **21** (Scheme 2). For example, when **15** was reacted with 1.5 equiv **21** in the presence of 10 mol % of tetrakis-(triphenylphosphine)palladium (0) in THF at 70 °C for 48 h, monoarylpyrrole **19a** was isolated in 44% yield accompanied by a trace amount (<3%) of diarylated pyrrole **20a** and 47% of unreacted **15**. The yield of **19a** based upon the consumed starting material was 83%. Cross-coupling of **19a** with 1.5 equiv 3,4-dimethoxyphenylboronic acid (**18g**) afforded 3,4-unsymmetrically substituted pyrrole **22** in quantitative yield.

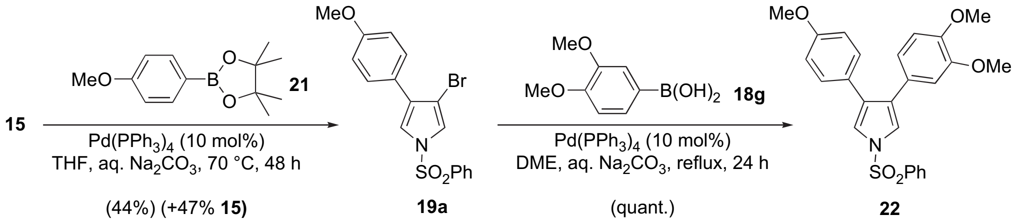
The *N*-triisopropylsilyl protected 3,4-dibromopyrrole **10** has been widely used as a versatile intermediate for the synthesis of a variety of 3,4-disubstituted pyrroles.[11,18] Fürstner has reported successful Negishi coupling of **10** in his synthesis of halitulin core.[11] Thus, we tested Suzuki–Miyaura coupling of **10** with 3.0 equiv boronic acid **18a** under the conditions utilized for dicoupling of **15** (Scheme 3). Under these conditions, however, expected dicoupling product **23a** and deprotected **23b** were isolated in only 5 and 6% yields, respectively, from a complex mixture of the products. This result indicated that *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**) is far superior to 3,4-dibromo-*N*-triisopropylsilylpyrrole (**10**) as a substrate at least in Suzuki–Miyaura coupling. It is reasonable to assume that the electron-withdrawing *N*-benzenesulfonyl group facilitates the initial oxidative addition of C–Br bonds to Pd(0) and, as a consequence, promotes overall cross-coupling reaction cleanly.



Scheme 3. Palladium-catalyzed cross-coupling of *N*-triisopropylsilylpyrrole **10**.

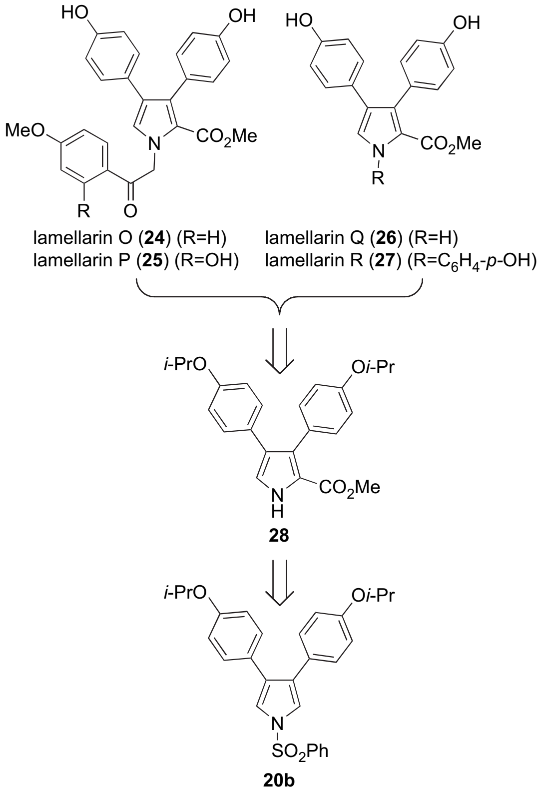
2.2. Total syntheses of lamellarins O, P, Q, and R

Simple and non-fused 3,4-diarylpyrrole marine alkaloids, lamellarins O, P, Q, and R, were isolated from the southern Australian sponge *Dendrilla cactos* by Capon and co-workers.[19] Boger reported that lamellarin O (**24**) exhibits micromolar cytotoxic activity against wild-type and multidrug-resistant tumor cell lines, suggesting that it may serve as a new lead for the development of antitumor agents insensitive to MDR.[20] The syntheses of lamellarins O and Q were achieved by several groups using independent synthetic strategies.[9,20,21] The syntheses of lamellarins P and R have not been reported so far. Due to our continuous interests on lamellarin alkaloids,[13,14,22]

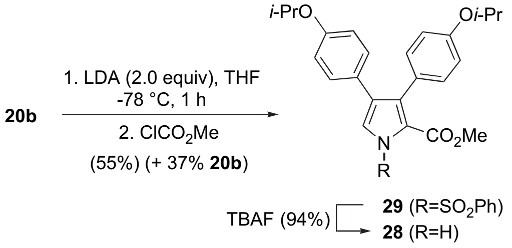


Scheme 2. Synthesis of 3,4-unsymmetrically arylated pyrrole **22**.

we planned to perform the total syntheses of all of these four natural products. The retrosynthetic analysis shown in Scheme 4 indicates that the alkaloids could be obtained by simple transformations of the common intermediate **28**, which in turn could be synthesized by directed α-lithiation of the cross-coupling product **20b**.



Scheme 4. Retrosynthetic analysis of lamellarins O, P, Q, and R.



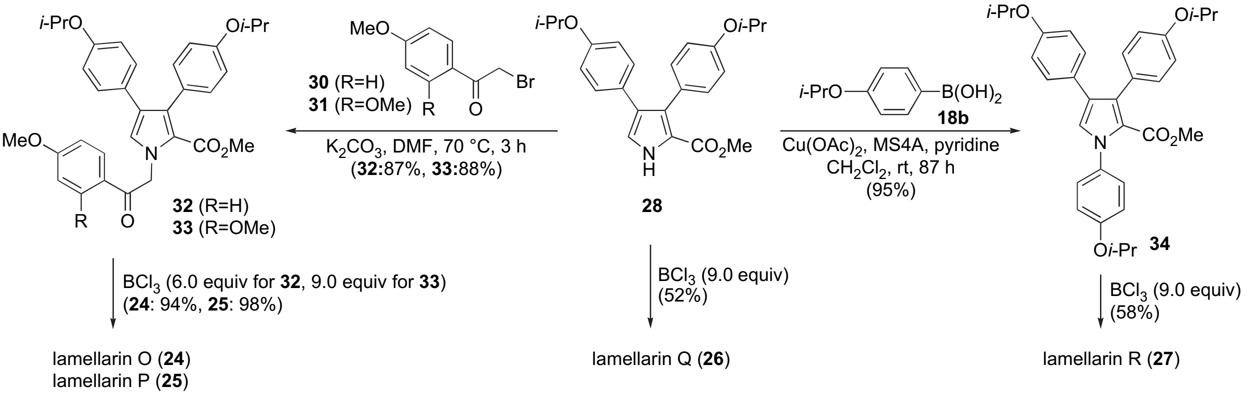
Scheme 5. Synthesis of the common intermediate **28**.

Synthesis of the common intermediate **28** is shown in Scheme 5. Directed lithiation of **20b** with 2 equiv LDA in THF at −78 °C for 1 h followed by a reaction with methyl chloroformate provided methyl ester **29** in 55% yield accompanied by unreacted **20b** (37%). Although we tested a variety of lithiation conditions (longer reaction time, larger amount of LDA, other bases such as LTMP and BuLi), the yield of **29** was not improved. Treatment of **29** with 1.5 equiv tetrabutylammonium fluoride (TBAF) in refluxing THF for 2 h produced **28** in 94% yield.[23]

Total syntheses of lamellarins O, P, Q, and R from **28** are shown in Scheme 6. Alkylation of **28** with phenacyl bromide **30** in the presence of K_2CO_3 in DMF produced **32** in 87% yield. Selective deprotection of isopropyl group of **32** with 6 equiv BCl_3 provided lamellarin O (**24**) in 94% yield. In a similar manner, lamellarin P (**25**) was synthesized using a different phenacyl bromide **31** at the initial step in comparable overall yield. It is noteworthy that one of the methoxy groups in the phenacyl moiety of **33** was selectively deprotected under the BCl_3 conditions. This is apparently due to assistance of the *ortho*-carbonyl function. Lamellarin Q (**26**) was synthesized in a single step by deprotection of **28**. The copper(II)-mediated N-arylation of **28** with boronic acid **18b** produced **34** in excellent yield.[24] Deprotection of **34** provided lamellarin R (**27**). Modest yields of the deprotection steps of **28** and **34** were due to partial demethylation of the ester moiety by BCl_3.

3. Conclusion

We have disclosed that *N*-benzenesulfonyl-3,4-dibromopyrrole (**15**) is an excellent substrate for palladium-catalyzed Suzuki–Miyaura coupling to produce 3,4-symmetrically or unsymmetrically diarylated pyrroles. *N*-Benzenesulfonyl group in the coupling products can serve as a directing group for α-lithiation of the pyrrole ring. Combination of these reactions allowed us to synthesize marine alkaloids, lamellarins O, P, Q, and R.



Scheme 6. Synthesis of lamellarins O, P, Q, and R.

4. Experimental

4.1. General

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer System 2000 instrument. NMR spectra were recorded on a Varian Gemini-300 instrument (300 MHz for ^{1}H) or a JEOL JNM-AL400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. High resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. HPLC analyses were performed on a Shimadzu LC-6A apparatus. Flash chromatography was conducted on Silica Gel 60N, 40–50 μm (Kanto Chemical Co., Inc.). Column chromatography was conducted on Silica Gel 60N, 63–210 μm (Kanto Chemical Co., Inc.) or Chromatorex NH-DM1020 silica gel (Fuji Silysia Chemical Ltd.). *n*-Butyllithium was purchased from Aldrich Chemical Co., Inc. *tert*-Butyllithium was purchased from Kanto Chemical Co., Inc. The alkyllithiums were used after titration with 2,5-dimethoxybenzyl alcohol. Dry diethyl ether and THF were distilled from Na-benzophenone ketyl under argon immediately before use.

4.2. Synthesis of N-benzenesulfonyl-3,4-dibromopyrrole ***15***

4.2.1. N-Benzenesulfonylpyrrole (***17***)

A solution of benzenesulfonyl chloride (47.2 mL, 370 mmol) was added as a neat liquid to a suspension of pyrrole (20.0 g, 298 mmol) and powdered NaOH (47.8 g, 1.20 mol) in dichloroethane (200 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with water and the products were extracted with dichloromethane. The extract was washed several times with water, dried over Na_2SO_4, and evaporated under reduced pressure to give **17** as colorless solid (46.4 g, 75%). This crude product was found to be essentially pure and used for the next reaction without further purification. Recrystallization from methanol gave colorless cube. Mp 87–88 °C; IR (KBr): 1454, 1367, 1186, 1170, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (t, J=2.3 Hz, 2H), 7.17 (t, J=2.3 Hz, 2H), 7.47–7.52 (m, 2H), 7.56–7.62 (m, 1H), 7.83–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 113.70, 120.80, 126.75, 129.37, 133.82, 139.07. Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76. Found: C, 57.92; H, 4.28; N, 6.60.

4.2.2. N-Benzenesulfonyl-3,4-dibromopyrrole (***15***)

A solution of bromine (25.4 g, 159 mmol) in acetic acid (100 mL) was added dropwise to a solution of **17** (13.2 g, 63.7 mmol) in acetic acid (100 mL) at room temperature. After being stirred for 1 h, the reaction mixture was refluxed for 1.5 h. The mixture was cooled to room temperature, and evaporated under reduced pressure. To the residue was added saturated aqueous $NaHCO_3$ and the mixture was extracted with dichloromethane. The extract was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane–toluene=2:1) to give 3,4-dibromopyrrole **15** as colorless solid (8.50 g, 37%). Recrystallization from methanol gave colorless needles. Mp 116.5–117 °C; IR (KBr): 1380, 1242, 1184, 1173, 1091, 1057, 957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 2H), 7.56 (t, J=7.6 Hz, 2H), 7.70 (t, J=7.6 Hz, 1H), 7.89 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 105.52, 120.05, 127.17, 129.76, 134.65, 137.92. Anal. Calcd for $C_{10}H_7Br_2NO_2S$: C, 32.90; H, 1.93; N, 3.84. Found: C, 32.99; H, 1.75; N, 3.76.

4.3. Synthesis of arylboronic acids ***18a–h*** and pinacol ester ***21***

Except for **18f**, arylboronic acids were prepared from the corresponding aryl bromide or iodide (for **18h**) via halogen–lithium exchange reaction. Boronic acid **18f** was prepared by directed lithiation of 1,3-dimethoxybenzene. All boronic acids and a pinacol ester used in this research are known compounds.

4.3.1. 4-Methoxyphenylboronic acid (***18a***)

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (1.28 M, 51.5 mL, 66.0 mmol) was added dropwise to a solution of 4-bromoanisole (5.61 g, 30.0 mmol) in THF (150 mL) at −78 °C. After being stirred for 1 h, trimethyl borate (5.02 mL, 45.0 mmol) was added as a neat liquid and the mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH_4Cl and evaporated under reduced pressure. To the residue was added 3 M aqueous HCl to adjust the pH to 3 and then the mixture was extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residual solid was washed with hexane, filtered, and dried under reduced pressure to give **18a** as colorless powder (2.70 g, 59%). This compound was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.01 (d, J=8.6 Hz, 2H), 8.17 (d, J=8.6 Hz, 2H).

4.3.2. 4-Isopropoxyphenylboronic acid (***18b***)

This compound was prepared from 4-isopropoxybromobenzene in 71% yield in a similar manner as described for **18a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, J=6.0 Hz, 6H), 4.60–4.75 (m, 1H), 6.99 (d, J=8.6 Hz, 2H), 8.15 (d, J=8.6 Hz, 2H).

4.3.3. 4-Fluorophenylboronic acid (***18c***)

This compound was prepared from 4-bromofluorobenzene in 59% yield in a similar manner as described for **18a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (t, J=8.5 Hz, 2H), 8.22 (dd, J=6.3 and 8.5 Hz, 2H).

4.3.4. 4-Chlorophenylboronic acid (***18d***)

This compound was prepared from 4-bromochlorobenzene in 74% yield in a similar manner as described for **18a**. ^{1}H

NMR (300 MHz, $CDCl_3$): δ 7.49 (d, J=8.1 Hz, 2H), 8.13 (dd, J=8.1 Hz, 2H).

4.3.5. 2-Methoxyphenylboronic acid (*18e*)

This compound was prepared from 2-bromoanisole in 87% yield in a similar manner as described for **18a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.13 (s, 2H), 6.92 (d, J=8.3 Hz, 1H), 7.04 (t, J=7.3 Hz, 1H), 7.45 (dd, J=7.3 and 8.3 Hz, 1H), 7.85 (d, J=7.3 Hz, 1H).

4.3.6. 2,6-Dimethoxyphenylboronic acid (*18f*)

Under an argon atmosphere, a hexane solution of *n*-butyllithium (1.54 M, 3.24 mL, 5.00 mmol) was added dropwise to a solution of 1,3-dimethoxybenzene (655 μL, 5.00 mmol) and TMEDA (750 μL, 5.00 mmol) in diethyl ether (25 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 25 h. After being cooled to 0 °C, trimethyl borate (836 μL, 7.50 mmol) was added as a neat liquid and the mixture was stirred for 30 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The mixture was quenched with saturated aqueous NH_4Cl and evaporated under reduced pressure. To the residue was added 3 M aqueous HCl to adjust the pH to 3 and then the mixture was extracted with dichloromethane. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residual solid was washed with hexane, filtered, and dried under reduced pressure to give **18f** as pale brown powder (553 mg, 61%). This compound was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 6H), 6.64 (d, J=8.4 Hz, 2H), 7.23 (s, 2H), 7.40 (t, J=8.4 Hz, 1H).

4.3.7. 3,4-Dimethoxyphenylboronic acid (*18g*)

This compound was prepared from 1-bromo-3,4-dimethoxybenzene in 39% yield in a similar manner as described for **18a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.02 (s, 3H), 7.02 (d, J=7.9 Hz, 1H), 7.68 (d, J=1.2 Hz, 1H), 7.86 (dd, J=1.2 and 7.9 Hz, 1H).

4.3.8. 3,4,5-Trimethoxyphenylboronic acid (*18h*)

This compound was prepared from 1-iodo-3,4,5-trimethoxybenzene[25] in 69% yield in a similar manner as described for **18a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 3.99 (s, 6H), 7.44 (s, 2H).

4.3.9. 4-Methoxyphenylboronic acid pinacol ester (*21*)

Boronic acid **18a** (200 mg, 1.32 mmol) was added to a suspension of pinacol (157 mg, 1.33 mmol) and $MgSO_4$ (317 mg, 2.63 mmol) in dichloromethane (6.6 mL) and the mixture was stirred for 20 h at room temperature. After removal of $MgSO_4$ by filtration, the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate=3:1) to give **21** as colorless solid (283 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 12H), 3.82 (s, 3H), 6.89 (d, J=8.7 Hz, 2H), 7.75 (d, J=8.7 Hz, 2H).

4.4. Synthesis of 3,4-symmetrically arylated N-benzenesulfonylpyrroles *20a–h*

4.4.1. N-Benzenesulfonyl-3,4-bis(4-methoxyphenyl)pyrrole (*20a*)

Under an argon atmosphere, a degassed solution of Na_2CO_3 (1.92 g, 18.1 mmol) in water (6.0 mL) was added to a solution of **15** (1.00 g, 2.74 mmol), **18a** (1.25 g, 8.22 mmol), and $Pd(PPh_3)_4$ (317 mg, 0.274 mmol) in 1,2-dimethoxyethane (25 mL) at room temperature and the mixture was refluxed for 24 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–toluene=1:3 ∼ toluene) to give **20a** as pale yellow solid (1.07 g, 93%). Recrystallization from dichloromethane–hexane gave pale yellow needles. Mp 140–142 °C; IR (KBr): 1541, 1505, 1375, 1243, 1172, 1094, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 6H), 6.79 (d, J=8.8 Hz, 4H), 7.10 (d, J=8.8 Hz, 4H), 7.19 (s, 2H), 7.52 (t, J=7.6 Hz, 2H), 7.61 (t, J=7.6 Hz, 1H), 7.94 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.21, 113.76, 118.30, 125.93, 126.97, 128.50, 129.46, 129.66, 133.90, 139.00, 158.74. Anal. Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34. Found: C, 68.77; H, 5.02; N, 3.29.

4.4.2. N-Benzenesulfonyl-3,4-bis(4-isopropoxyphenyl)-pyrrole (*20b*)

This compound was prepared from **15** (730 mg, 2.00 mmol) and **18b** (1.08 g, 6.00 mmol) in a similar manner as described for **20a**. After chromatographic purification over Silica Gel 60N (hexane–toluene=1:1 ∼ 1:2), **20b** was obtained as pale yellow solid (891 mg, 94%). Recrystallization from dichloromethane–hexane gave colorless needles. Mp 123–124 °C; IR (KBr): 1612, 1537, 1502, 1376, 1244, 1183, 1093, 1050, 948 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, J=6.0 Hz, 12H), 4.45–4.56 (m, 2H), 6.77 (d, J=8.7 Hz, 4H), 7.09 (d, J=8.7 Hz, 4H), 7.18 (s, 2H), 7.52 (t, J=7.6 Hz, 2H), 7.61 (t, J=7.6 Hz, 1H), 7.93 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.06, 69.80, 115.58, 118.27, 125.70, 126.95, 128.58, 129.44, 129.65, 133.86, 139.03, 157.05. Anal. Calcd for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.15; N, 2.95. Found: C, 70.65; H, 6.33; N, 2.96.

4.4.3. N-Benzenesulfonyl-3,4-bis(4-fluorophenyl)pyrrole (*20c*)

This compound was prepared from **15** (183 mg, 0.500 mmol) and **18c** (210 mg, 1.50 mmol) in a similar manner as described for **20a**. After chromatographic purification over Silica Gel 60N (hexane–dichloromethane=2:1), **20c** was obtained as colorless solid (189 mg, 96%). Recrystallization from diethyl ether–hexane gave colorless needles. Mp 112–113 °C; IR (KBr): 1536, 1504, 1448, 1380, 1223, 1186, 1172, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94 (t, J=8.8 Hz, 4H), 7.11 (dd, J=5.4 and 8.8 Hz, 4H), 7.23 (s, 2H), 7.55 (t, J=7.6 Hz, 2H), 7.64 (t, J=7.6 Hz, 1H), 7.96 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 115.37 (d, J=21 Hz), 118.79, 127.07, 127.70, 129.24 (d, J=3.4 Hz), 129.58, 130.15 (d, J=8.0 Hz), 134.14, 138.80, 162.12 (d, J=247 Hz). Anal. Calcd for $C_{22}H_{15}F_2NO_2S$: C, 66.82; H, 3.82; N, 3.54. Found: C, 67.08; H, 3.80; N, 3.47.

4.4.4. N-Benzenesulfonyl-3,4-bis(4-chlorophenyl)pyrrole (***20d***)

This compound was prepared from **15** (334 mg, 0.916 mmol) and **18d** (432 mg, 2.76 mmol) in a similar manner as described for **20a**. After chromatographic purification over Silica Gel 60N (hexane–toluene=1:2∼toluene), **20d** was obtained as colorless solid (375 mg, 95%). Recrystallization from dichloromethane–pentane gave colorless needles. Mp 160–163 °C; IR (KBr): 1525, 1488, 1378, 1185, 1172, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05–7.10 (m, 4H), 7.21–7.25 (m, 4H), 7.25 (s, 2H), 7.53–7.59 (m, 2H), 7.62–7.68 (m, 1H), 7.94–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 119.04, 127.10, 127.38, 128.65, 129.62, 129.76, 131.59, 133.15, 134.23, 138.63. HREIMS *m/z* calcd for $C_{22}H_{15}Cl_2NO_2S$ (M^+): 427.0201. Found: 427.0193.

4.4.5. N-Benzenesulfonyl-3,4-bis(2-methoxyphenyl)-pyrrole (***20e***)

This compound was prepared from **15** (183 mg, 0.500 mmol) and **18e** (228 mg, 1.50 mmol) in a similar manner as described for **20a**. After purification by flash chromatography over Silica Gel 60N (hexane–toluene=1:2∼toluene), **20e** was obtained as colorless solid (196 mg, 93%). Mp 47–51 °C; IR (KBr): 1585, 1529, 1478, 1370, 1245, 1175, 1079, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 6H), 6.78–6.83 (m, 4H), 7.04 (dd, J=1.7 and 7.4 Hz, 2H), 7.17 (dt, J=1.7 and 7.8 Hz, 2H), 7.36 (s, 2H), 7.51 (t, J=7.6 Hz, 2H), 7.60 (t, J=7.6 Hz, 1H), 7.95 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.05, 111.00, 119.60, 120.29, 123.78, 125.75, 127.05, 128.13, 129.37, 130.33, 133.76, 139.21, 156.44. HREIMS *m/z* calcd for $C_{24}H_{21}NO_4S$ (M^+): 419.1191. Found: 441.1194.

4.4.6. N-Benzenesulfonyl-3,4-bis(2,6-dimethoxyphenyl)-pyrrole (***20f***)

This compound was prepared from **15** (183 mg, 0.500 mmol) and **18f** (273 mg, 1.50 mmol) in a similar manner as described for **20a**. After successive purification by flash chromatography over Silica Gel 60N (hexane–ethyl acetate=2:1) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate=1:1), **20f** was obtained as colorless solid (223 mg, 93%). Recrystallization from dichloromethane–diethyl ether gave colorless plates. Mp 232–233 °C; IR (KBr): 1589, 1471, 1366, 1251, 1179, 1112, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (s, 12H), 6.44 (d, J=8.3 Hz, 4H), 7.07 (t, J=8.3 Hz, 2H), 7.31 (s, 2H), 7.46–7.52 (m, 2H), 7.54–7.60 (m, 1H), 7.90–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.39, 104.00, 113.32, 120.87, 121.72, 126.87, 127.80, 129.11, 133.37, 139.80, 157.62. Anal. Calcd for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.22; H, 5.13; N, 2.94.

4.4.7. N-Benzenesulfonyl-3,4-bis(3,4-dimethoxyphenyl)-pyrrole (***20g***)

This compound was prepared from **15** (365 mg, 1.00 mmol) and **18g** (545 mg, 3.00 mmol) in a similar manner as described for **20a**. After chromatographic purification over Silica Gel 60N (hexane–toluene=1:2∼toluene∼toluene–ethyl acetate=10:1), **20g** was obtained as colorless solid (436 mg, 91%). Recrystallization from dichloromethane–hexane gave colorless needles. Mp 187–188 °C; IR (KBr): 1509, 1372, 1253, 1177, 1140, 1096, 1059, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 6H), 3.86 (s, 6H), 6.70 (s, 2H), 6.78 (s, 2H), 6.78 (s, 2H), 7.23 (s, 2H), 7.52–7.58 (m, 2H), 7.62–7.67 (m, 1H), 7.95–7.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.72, 55.88, 111.01, 111.99, 118.25, 120.89, 126.12, 127.06, 128.52, 129.52, 133.99, 138.92, 148.17, 148.53. Anal. Calcd for $C_{26}H_{25}NO_6S$: C, 65.12; H, 5.25; N, 2.92. Found: C, 65.03; H, 5.16; N, 2.88.

4.4.8. N-Benzenesulfonyl-3,4-bis(3,4,5-trimethoxyphenyl)-pyrrole (***20h***)

This compound was prepared from **15** (183 mg, 0.500 mmol) and **18h** (318 mg, 1.50 mmol) in a similar manner as described for **20a**. After successive purification by flash chromatography over Silica Gel 60N (hexane–ethyl acetate=2:1) and column chromatography over Chromatorex NH-DM1020 silica gel (hexane–ethyl acetate=1:1), **20h** was obtained as colorless solid (246 mg, 91%). Recrystallization from dichloromethane–hexane gave colorless plates. Mp 159.5–162 °C; IR (KBr): 1586, 1500, 1450, 1412, 1359, 1240, 1175, 1127, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 12H), 3.82 (s, 6H), 6.42 (s, 4H), 7.28 (s, 2H), 7.57 (t, J=7.6 Hz, 2H), 7.66 (t, J=7.6 Hz, 1H), 7.99 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 56.06, 60.92, 106.01, 118.44, 127.13, 128.61, 128.80, 129.60, 134.13, 137.36, 138.84, 153.02. HREIMS *m/z* calcd for $C_{28}H_{29}NO_8S$ (M^+): 539.1614. Found: 539.1616.

4.5. Synthesis of 3,4-unsymmetrically arylated N-benzenesulfonylpyrrole **22**

4.5.1. N-Benzenesulfonyl-3-bromo-4-(4-methoxyphenyl)-pyrrole (***19a***)

Under an argon atmosphere, a mixture of **15** (73.0 mg, 0.200 mmol), **21** (70.2 mg, 0.300 mmol), $Pd(PPh_3)_4$ (23.1 mg, 20.0 μmol), Na_2CO_3 (140 mg, 1.32 mmol), water (0.40 mL), and THF (2.0 mL) was heated in a sealed tube at 70 °C for 48 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–toluene=1:1∼1:2∼toluene) to give **19a** as pale yellow semisolid (34.5 mg, 44%) and unreacted **15** (34.1 mg, 47%). IR (KBr): 1511, 1376, 1315, 1250, 1178, 1134, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.89–6.94 (m, 2H), 7.17 (d, J=2.7 Hz, 1H), 7.27 (d, J=2.7 Hz, 1H), 7.39–7.44 (m, 2H), 7.51–7.57 (m, 2H), 7.62–7.67 (m, 1H), 7.89–7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.30, 102.83, 113.90, 117.44, 120.68, 124.37, 127.06, 128.91, 129.43, 129.62, 134.30, 138.41, 159.29. HREIMS *m/z* calcd for $C_{17}H_{14}BrNO_3S$ (M$^+$): 390.9878. Found: 390.9868.

*4.5.2. N-Benzenesulfonyl-3-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole (**22**)*

Under an argon atmosphere, a degassed solution of Na_2CO_3 (469 mg, 4.42 mmol) in water (2.0 mL) was added to a solution of **19a** (264 mg, 0.672 mmol), **18g** (182 mg, 1.00 mmol), and $Pd(PPh_3)_4$ (77.4 mg, 67.0 μmol) in 1,2-dimethoxyethane (10 mL) at room temperature and the mixture was refluxed for 24 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified successively by column chromatography over Silica Gel 60N (hexane–toluene=1:1∼toluene) and over Chromatorex NH-DM1020 silica gel (toluene) to give **22** as colorless solid (302 mg, quant.). Recrystallization from dichloromethane–pentane gave colorless needles. Mp 73–75 °C; IR (KBr): 1509, 1374, 1249, 1177, 1096, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 6.65 (s, 1H), 6.77 (s, 1H), 6.78 (s, 1H), 6.78–6.82 (m, 2H), 7.09–7.14 (m, 2H), 7.20 (d, *J*=2.5 Hz, 1H), 7.23 (d, *J*=2.5 Hz, 1H), 7.51–7.57 (m, 2H), 7.60–7.65 (m, 1H), 7.93–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 56.25, 55.63, 55.82, 111.04, 111.93, 113.71, 118.19, 118.30, 120.65, 125.87, 126.15, 127.01, 128.47, 128.54, 129.49, 129.82, 133.95, 138.93, 148.11, 148.50, 158.76. Anal. Calcd for $C_{25}H_{23}NO_5S$: C, 66.80; H, 5.16; N, 3.12. Found: C, 66.52; H, 5.10; N, 2.99.

*4.6. Cross-coupling of 3,4-dibromo-N-triisopropylsilylpyrrole **10** with **18a***

Under an argon atmosphere, a degassed solution of Na_2CO_3 (700 mg, 6.60 mmol) in water (2.0 mL) was added to a solution of **10** (381 mg, 1.00 mmol), **18a** (456 mg, 3.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.100 mmol) in 1,2-dimethoxyethane (10 mL) at room temperature and the mixture was refluxed for 24 h. The mixture was cooled to room temperature and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane–dichloromethane=10:1∼5:1∼3:1∼2:1∼ethyl acetate) to give **23a** (22.1 mg, 5%) and **23b** (15.4 mg, 6%).

*4.6.1. 3,4-Bis(4-methoxyphenyl)-N-triisopropylsilylpyrrole (**23a**)*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, *J*=7.4 Hz, 18H), 1.42–1.55 (m, 3H), 3.80 (s, 6H), 6.78 (s, 2H), 6.79–6.84 (m, 4H), 7.18–7.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.66, 17.91, 55.22, 113.55, 123.01, 124.92, 128.92, 129.43, 157.66. HREIMS *m/z* calcd for $C_{27}H_{37}NO_2Si$ (M$^+$): 435.2594. Found: 435.2593.

*4.6.2. 3,4-Bis(4-methoxyphenyl)pyrrole (**23b**)*

Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 6H), 6.79–6.84 (m, 4H), 6.85 (s, 2H), 7.17–7.22 (m, 4H), 8.24 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 55.20, 113.63, 116.74, 123.10, 128.37, 129.60, 157.81. HREIMS *m/z* calcd for $C_{18}H_{17}NO_2$ (M$^+$): 279.1259. Found: 279.1249.

4.7. Total synthesis of lamellarins O, P, Q, and R

*4.7.1. Methyl N-benzenesulfonyl-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (**29**)*

Under an argon atmosphere, a hexane solution of *n*-butyllithium (1.42 M, 297 μL, 0.422 mmol) was added dropwise to a solution of diisopropylamine (73.7 μL, 0.526 mmol) in THF (5.0 mL) at −78 °C. The mixture was allowed to warm to 0 °C and immediately re-cooled to −78 °C. A solution of **20b** (100 mg, 0.210 mmol) in THF (3.0 mL) was added dropwise to the mixture at −78 °C. After being stirred for 1 h, methyl chloroformate (48.7 μL, 0.630 mmol) was added as a neat liquid and the mixture was stirred for 30 min at −78 °C. The reaction mixture was allowed to warm to room temperature, quenched with saturated aqueous NH_4Cl, and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene–ethyl acetate=100:1) to give **29** as yellow solid (61.9 mg, 55%). Recrystallization from diethyl ether–hexane gave yellow needles. Mp 166–167 °C; IR (KBr): 1711, 1611, 1532, 1505, 1364, 1245, 1173, 1132, 1049, 954 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J*=6.3 Hz, 6H), 1.32 (d, *J*=6.3 Hz, 6H), 3.61 (s, 3H), 4.44–4.58 (m, 2H), 6.73 (d, *J*=8.7 Hz, 2H), 6.77 (d, *J*=8.7 Hz, 2H), 6.98 (d, *J*=8.7 Hz, 2H), 7.04 (d, *J*=8.7 Hz, 2H), 7.55 (s, 1H), 7.57 (t, *J*=7.6 Hz, 2H), 7.65 (t, *J*=7.6 Hz, 1H), 8.04 (d, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.04, 22.06, 52.00, 69.78, 69.79, 115.15, 115.56, 122.47, 122.83, 124.45, 124.71, 127.46, 127.76, 129.02, 129.60, 131.23, 132.98, 133.87, 139.21, 157.12, 157.39, 161.47. HREIMS *m/z* calcd for $C_{30}H_{31}NO_6S$ (M$^+$): 533.1872. Found: 533.1870.

*4.7.2. Methyl 3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (**28**)*

Under an argon atmosphere, a THF solution of tetrabutylammonium fluoride (1.0 M, 157 μL, 0.157 mmol) was added dropwise to a solution of **29** (56.0 mg, 0.105 mmol) in THF (5.0 mL) at room temperature and the mixture was refluxed for 2 h. The mixture was cooled to room temperature, quenched with water, and evaporated under reduced pressure. The products were extracted with dichloromethane and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (toluene−ethyl acetate=20:1) to give **28** as yellow solid (38.7 mg, 94%). Recrystallization from ethyl acetate−hexane gave yellow needles. Mp 141−141.5 °C; IR (KBr): 3420, 1697, 1486, 1372, 1241, 1118 $\mathrm{cm^{-1}}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J*=6.0 Hz, 6H), 1.34 (d, *J*=6.0 Hz, 6H), 3.72 (s, 3H), 4.44−4.58 (m, 2H), 6.71 (d, *J*=8.8 Hz, 2H), 6.81 (d, *J*=8.8 Hz, 2H), 6.97−7.01 (m, 3H), 7.16 (d, *J*=8.8 Hz, 2H), 9.23 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.06, 22.12, 51.16, 69.66, 69.69, 114.85, 115.37, 119.11, 119.93, 126.05, 126.35, 126.72, 128.96, 129.26, 131.71, 156.10, 156.63, 161.42. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.14; H, 7.00; N, 3.47.

*4.7.3. Methyl 3,4-bis(4-isopropoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylate (**32**)*

Under an argon atmosphere, a mixture of **28** (100 mg, 0.254 mmol), 2-bromo-4′-methoxyacetophenone (**30**) (146 mg, 0.635 mmol), K_2CO_3 (105 mg, 0.762 mmol), and DMF (6.0 mL) was stirred for 3 h at 70 °C. The reaction mixture was cooled to room temperature and quenched with water. The product was diluted with ethyl acetate, washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography over Silica Gel 60N (hexane−ethyl acetate=3:1) to give **32** as colorless solid (119 mg, 87%). Recrystallization from diethyl ether−hexane gave pale yellow plates. Mp 135−136 °C; IR (KBr): 1698, 1602, 1533, 1443, 1367, 1235, 1170, 1103, 957 $\mathrm{cm^{-1}}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J*=6.0 Hz, 6H), 1.34 (d, *J*=6.0 Hz, 6H), 3.46 (s, 3H), 3.88 (s, 3H), 4.41−4.60 (m, 2H), 5.71 (s, 2H), 6.69 (d, *J*=8.8 Hz, 2H), 6.80 (d, *J*=8.8 Hz, 2H), 6.91 (s, 1H), 6.98 (d, *J*=8.8 Hz, 4H), 7.13 (d, *J*=8.8 Hz, 2H), 8.01 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.10, 22.13, 50.72, 55.49, 55.53, 69.71, 69.84, 114.10, 114.98, 115.41, 119.75, 124.71, 126.82, 127.17, 127.84, 127.99, 129.39, 130.32, 131.20, 131.87, 156.16, 156.57, 162.38, 163.99, 191.84. HREIMS *m/z* calcd for $C_{33}H_{35}NO_6$ (M^+): 541.2464. Found: 541.2465.

*4.7.4. Methyl 1-[2-(2,4-dimethoxyphenyl)-2-oxoethyl]-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (**33**)*

This compound was prepared from **28** (50.0 mg, 0.127 mmol) and 2-bromo-2′,4′-dimethoxyacetophenone (**31**)[26] (82.3 mg, 0.318 mmol) in a similar manner as described for **32**. After chromatographic purification over Silica Gel 60N (hexane−ethyl acetate=2:1), **33** was obtained as colorless solid (64.0 mg, 88%). Recrystallization from diethyl ether−hexane gave pale yellow needles. Mp 138−139 °C; IR (KBr): 1685, 1599, 1529, 1443, 1368, 1243, 1129, 1100 $\mathrm{cm^{-1}}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J*=6.0 Hz, 6H), 1.34 (d, *J*=6.0 Hz, 6H), 3.46 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 4.41−4.60 (m, 2H), 5.64 (s, 2H), 6.50 (d, *J*=2.3 Hz, 1H), 6.59 (dd, *J*=2.3 and 8.8 Hz, 1H), 6.68 (d, *J*=8.8 Hz, 2H), 6.80 (d, *J*=8.8 Hz, 2H), 6.90 (s, 1H), 6.98 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=8.8 Hz, 2H), 8.00 (d, *J*=8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.11, 22.14, 50.62, 55.60, 55.62, 60.24, 69.70, 69.83, 98.22, 105.85, 114.95, 115.37, 118.52, 119.92, 124.32, 127.03, 127.09, 128.10, 129.36, 130.85, 131.91, 133.36, 156.05, 156.48, 161.35, 162.29, 165.23, 192.64. HREIMS *m/z* calcd for $C_{34}H_{37}NO_7$ (M^+): 571.2570. Found: 571.2567.

*4.7.5. Lamellarin O (**24**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 583 μL, 0.583 mmol) was added dropwise to a solution of **32** (52.7 mg, 0.0973 mmol) in dichloromethane (5.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 3 h. The mixture was quenched with water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (ethyl acetate) to give **24** as pale brown solid (41.8 mg, 94%). Recrystallization from ethyl acetate−hexane gave pale brown powder. Mp 225−235 °C (dec) (sealed capillary); IR (KBr): 3357, 1686, 1598, 1536, 1443, 1369, 1244, 1170, 1102, 835 $\mathrm{cm^{-1}}$; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.39 (s, 3H), 3.90 (s, 3H), 5.88 (s, 2H), 6.66 (d, *J*=8.7 Hz, 2H), 6.77 (d, *J*=8.7 Hz, 2H), 6.94 (d, *J*=8.7 Hz, 2H), 7.03 (d, *J*=8.7 Hz, 2H), 7.08 (d, *J*=9.0 Hz, 2H), 7.17 (s, 1H), 8.06 (d, *J*=9.0 Hz, 2H), 8.17 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): 50.63, 55.98, 56.35, 114.75, 115.06, 115.68, 120.59, 124.99, 127.06, 127.95, 128.13, 129.07, 129.99, 130.88, 131.33, 132.54, 156.32, 156.76, 162.62, 164.67, 192.41. HREIMS *m/z* calcd for $C_{27}H_{23}NO_6$ (M^+): 457.1525. Found: 457.1527.

*4.7.6. Lamellarin P (**25**)*

This compound was prepared from **33** (64.0 mg, 0.112 mmol) and BCl_3 (1.0 M, 1.01 mL, 1.01 mmol) in a similar manner as described for **24**. After chromatographic purification over Silica Gel 60N (ethyl acetate), **25** was obtained as pale brown solid (51.7 mg, 98%). Recrystallization from ethyl acetate−hexane gave pale brown needles. Mp 230−245 °C (dec) (sealed capillary); IR (KBr): 3351, 1687, 1639, 1442, 1365, 1238, 1173, 1130, 1084, 837 $\mathrm{cm^{-1}}$; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.41 (s, 3H), 3.89 (s, 3H), 5.92 (s, 2H), 6.50 (d, *J*=2.5 Hz, 1H), 6.59 (dd, *J*=2.5 and 9.0 Hz, 1H), 6.66 (d, *J*=8.7 Hz, 2H), 6.78 (d, *J*=8.7 Hz, 2H), 6.95 (d, *J*=8.7 Hz, 2H), 7.03 (d, *J*=8.7 Hz, 2H), 7.20 (s, 1H), 7.98 (d, *J*=9.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): 50.71, 55.69, 56.15, 101.70, 108.40, 112.66, 115.01, 115.62, 120.60, 125.17, 126.93, 127.78, 128.28, 130.01, 131.48, 131.98, 132.52, 156.29, 156.73, 162.65, 165.49, 167.21, 198.56. HREIMS *m/z* calcd for $C_{27}H_{23}NO_7$ (M^+): 473.1475. Found: 473.1464.

*4.7.7. Lamellarin Q (**26**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 723 μL, 0.723 mmol) was added dropwise to a solution of **28** (31.6 mg, 0.0803 mmol) in dichloromethane (5.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to room temperature and stirred for an additional 4 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate=1:1∼ethyl acetate) to give **26** as yellow powder (12.9 mg, 52%). Mp 145–210 °C (dec) (sealed capillary); IR (KBr): 3310, 1687, 1509, 1486, 1441, 1370, 1251, 1177, 1085, 835 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.64 (s, 3H), 6.67 (d, J=8.8 Hz, 2H), 6.76 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 7.14 (d, J=3.2 Hz, 1H), 8.23 (br s, 2H), 10.90 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): 50.99, 115.18, 115.77, 120.02, 121.37, 126.90, 126.97, 127.45, 129.73, 130.22, 132.80, 156.50, 157.01, 161.89. HREIMS *m/z* calcd for $C_{18}H_{15}NO_4$ (M^+): 309.1001. Found: 309.0983.

*4.7.8. Methyl 1,3,4-tris(4-isopropoxyphenyl)pyrrole-2-carboxylate (**34**)*

Under an argon atmosphere, a suspension of 4-isopropoxyphenylboronic acid (137 mg, 0.762 mmol) and powdered molecular sieves 4 Å (350 mg) in dichloromethane (5.0 mL) was stirred for 3 h. After successive addition of **28** (100 mg, 0.254 mmol), pyridine (82.2 μL, 1.02 mmol), and $Cu(OAc)_2$ (92.3 mg, 0.508 mmol) to the suspension, the mixture was stirred for 87 h. The mixture was passed through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (dichloromethane) to give **34** as pale yellow semisolid (127 mg, 95%). IR (KBr): 1708, 1509, 1373, 1243, 1120, 951, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, J=6.0 Hz, 6H), 1.35 (d, J=6.0 Hz, 6H), 1.37 (d, J=6.0 Hz, 6H), 3.46 (s, 3H), 4.42–4.63 (m, 3H), 6.71 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 6.99 (s, 1H), 7.01 (d, J=8.8 Hz, 2H), 7.18 (d, J=8.8 Hz, 2H), 7.27 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.08, 22.10, 22.15, 50.83, 69.74, 69.83, 70.22, 115.06, 115.52, 115.57, 121.25, 124.96, 126.49, 126.65, 126.98, 127.16, 129.33, 131.03, 131.83, 133.78, 156.31, 156.75, 157.29, 161.73. HREIMS *m/z* calcd for $C_{33}H_{37}NO_5$ (M^+): 527.2672. Found: 527.2678.

*4.7.9. Lamellarin R (**27**)*

Under an argon atmosphere, a heptane solution of BCl_3 (1.0 M, 358 μL, 0.358 mmol) was added dropwise to a solution of **34** (21.0 mg, 0.0398 mmol) in dichloromethane (5.0 mL) at −78 °C. After being stirred for 30 min at this temperature, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 2 h. The mixture was quenched with water and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate=1:1∼ethyl acetate) to give **27** as brown powder (9.2 mg, 58%). Mp 140–240 °C (dec) (sealed capillary); IR (KBr): 3347, 1670, 1611, 1519, 1441, 1373, 1238, 1130, 834 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ 3.40 (s, 3H), 6.68 (d, J=8.7 Hz, 2H), 6.78 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.7 Hz, 2H), 7.00 (d, J=8.7 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H), 7.12 (s, 1H), 7.24 (d, J=8.7 Hz, 2H), 8.20 (br s, 1H), 8.28 (br s, 1H), 8.61 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6): 50.90, 115.28, 115.83, 116.09, 122.42, 125.82, 126.64, 126.85, 127.17, 127.55, 130.24, 131.24, 132.71, 134.07, 156.70, 157.13, 157.61, 162.15. HREIMS *m/z* calcd for $C_{24}H_{19}NO_5$ (M^+): 401.1263. Found: 401.1254.

Acknowledgements

We thank the Ministry of Education, Culture, Sports, Science and Technology of Japan for financial support; Grant-in-Aid for Scientific Research (C) (No. 18510188).

References and notes

1. For reviews, see: (a) Cironi, P.; Albericio, F.; Álvarez, M. *Prog. Heterocycl. Chem.* **2004**, *16*, 1–26; (b) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363–378; (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256.
2. Loya, S.; Rudi, A.; Kashman, Y.; Hizi, A. *Biochem. J.* **1999**, *344*, 85–92.
3. Kashman, Y.; Koren-Goldshlager, G.; Gravalos, M. D. G.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
4. Quesada, A. R.; Gravalos, M. D. G.; Puentes, J. L. F. *Br. J. Cancer* **1996**, *74*, 677–682.
5. (a) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392–7399; (b) Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. *J. Med. Chem.* **2005**, *48*, 3796–3807; (c) Kluza, J.; Gallego, M.-A.; Loyens, A.; Beauvillain, J.-C.; Sousa-Faro, J.-M. F.; Cuevas, C.; Marchetti, P.; Bailly, C. *Cancer Res.* **2006**, *66*, 3177–3187.
6. Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907.
7. Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765–2770.
8. Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043–3060.
9. Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207–208.
10. Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587–3595.
11. Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380.
12. (a) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1340–1343; (b) Heinrich, M. R.; Steglich, W.; Banwell, M. G.; Kashman, Y. *Tetrahedron* **2003**, *59*, 9239–9247.
13. Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett.* **2003**, *44*, 4443–4446.
14. (a) Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594–604; (b) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755–3757.
15. Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362–2366.
16. Smith, J. A.; Ng, S.; White, J. *Org. Biomol. Chem.* **2006**, *4*, 2477–2482.
17. Zonta, C.; Fabris, F.; De Lucchi, O. *Org. Lett.* **2005**, *7*, 1003–1006.
18. (a) Muchowski, J. M.; Naef, R. *Helv. Chim. Acta.* **1984**, *67*, 1168–1172; (b) Alvarez, A.; Guzmán, A.; Ruiz, A.; Velarde, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653–1656; (c) Shum, P. W.; Kozikowski, A. P. *Tetrahedron Lett.* **1990**, *31*, 6785–6788; (d) Sugiura, K.; Ushiroda, K.; Johnson, M. T.; Miller, J. S.; Sakata, Y. *J. Mater. Chem.* **2000**, *10*, 2507–2514; (e) Synder, L. B.; Meng, Z.; Mate, R.; D'Andrea, S. V.; Marinier, A.; Quesnelle, C. A.; Gill, P.; DenBleyker, K. L.; Fung-Tomc, J. C.; Frosco, M.; Martel, A.; Barrett, J. F.; Bronson, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4735–4739.
19. (a) Urban, S.; Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1919–1924; (b) Urban, S.; Hobbs, L.; Hooper, J. N. A.; Capon, R. J. *Aust. J. Chem.* **1995**, *48*, 1491–1494.
20. Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.
21. Marfil, M.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8659–8668.

22. (a) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951−5962; (b) Ishibashi, F.; Tanabe, S.; Oda, T.; Iwao, M. *J. Nat. Prod.* **2002**, *65*, 500−504.
23. Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595−596.
24. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.
25. Hoye, T. R.; Kaese, P. A. *Synth. Commun.* **1982**, *12*, 49−52.
26. Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170−1176.