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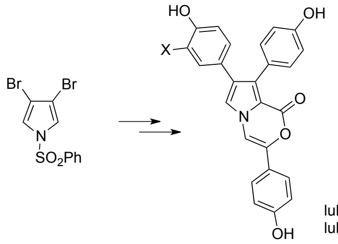

lukianol A (X=H)
lukianol B (X=I)

Tetrahedron
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Total synthesis of the marine natural products lukianols A and B

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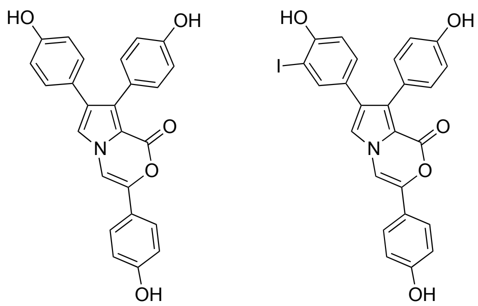
ABSTRACT

Total synthesis of the pyrrolic marine natural products lukianols A (**1**) and B (**2**) has been achieved using N-benzenesulfonyl-3,4-dibromopyrrole (**3**) as a common starting material. The key synthetic strategy developed is the combined bromine-directed lithiation and palladium-catalyzed cross-coupling of **3** to produce 3,4-diarylpyrrol-2-carboxylates. Regioselective iodination of the phenolic intermediate **24** was thoroughly investigated for the synthesis of lukianol B.

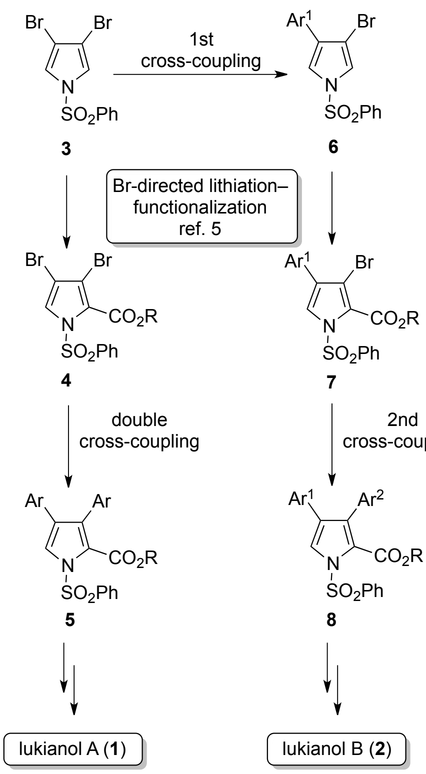
1. Introduction

Lukianols A (**1**) and B (**2**) were isolated from a tunicate collected in the lagoon of *Palmyra* atoll by Scheuer and coworkers (Figure 1).[1] Their unique 3,7,8-tris(4-hydroxyphenyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one structures were elucidated by spectral methods. Lukianol A exhibited moderate cytotoxicity against a cell line derived from a human epidermatoid carcinoma (*KB*), whereas lukianol B was inactive. Recently, Fuente and coworkers screened about two thousand marine natural products to find out structurally novel human aldose reductase (h-ALR2) inhibitors.[2] They reported lukianol B (**2**) was the most potent one among the compounds tested. Its h-ALR2 inhibitory activity (IC_{50}=0.6 μM) was 6-fold more potent than that of the known ALR inhibitor sorbinil. The therapeutic effects of h-ALR2



lukianol A (**1**) lukianol B (**2**)

Figure 1. Structures of lukianols A and B.



Scheme 1. Key synthetic strategy.

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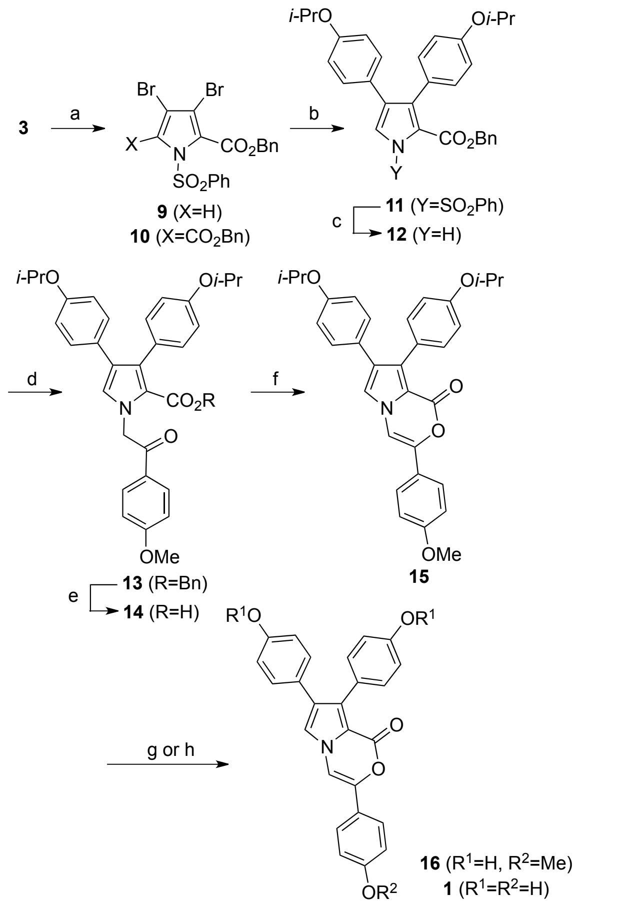
inhibitors for some degenerative complications of diabetes, such as neuropathy, nephropathy, and retinopathy, are well recognized.[3] Therefore, **2** can be regarded as a new lead to develop therapeutic agents for treatment of these disorders.

In spite of its impressive biological activity, total synthesis of lukianol B (**2**) has not been achieved so far, though simpler lukianol A (**1**) has been synthesized by several groups.[4] Herein, we report the total synthesis of both **1** and **2**.

2. Results and discussion

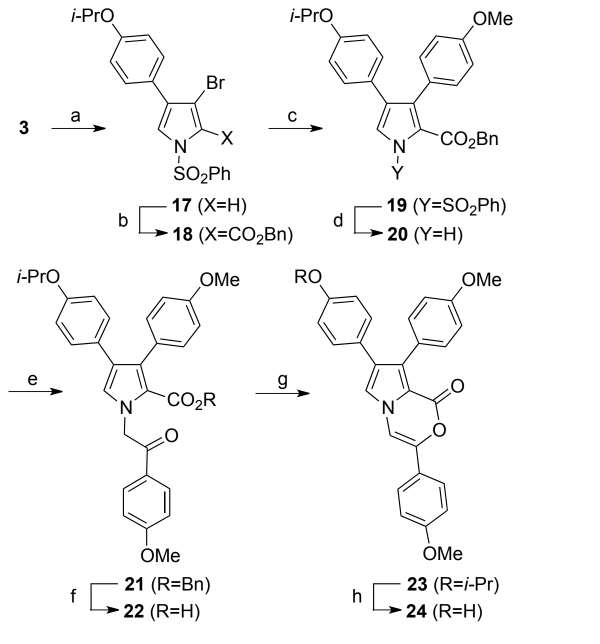
The key strategy employed in our total synthesis is the combined directed lithiation and palladium-catalyzed cross-coupling of N-benzenesulfonyl-3,4-dibromopyrrole (**3**) to produce 3,4-diarylpyrrole-2-carboxylates (Scheme 1). This method could provide not only 3,4-symmetrically substituted pyrrole-2-carboxylates **5**, but also 3,4-unsymmetrically substitute ones **8** by means of bromine-directed regioselective lithiation (**6**→**7**) developed in our laboratories.[5]

The synthesis of lukianol A (**1**) is shown in Scheme 2. A known N-benzenesulfonyl-3,4-dibromopyrrole (**3**)[6] was lithiated with 1.2 equiv of lithium diisopropylamide (LDA) in Et_2O at –78 °C for 1 h and the resulting lithio species was trapped with benzyl chloroformate to give 2-benzyloxycarbonylpyrrole **9** in 62% yield as a single product. When THF was used as a solvent, undesired 2,5-diester **10** was formed as a by-product. The palladium-catalyzed cross-coupling of **9** with 3.0 equiv of *p*-isopropoxyphenylboronic acid in the presence of bulky 1,1'-bis(di-*tert*-butylphosphino)ferrocene (d^{t}bpf) ligand produced 3,4-diarylated pyrrole **11** in 93% yield. The double cross-coupling in the presence of common $Pd(PPh_3)_4$ was sluggish. The benzenesulfonyl protecting group was then removed with tetrabutylammonium fluoride (TBAF). The resulting pyrrole **12** was alkylated with *p*-methoxyphenacyl bromide to give **13**. Hydrogenolysis of the benzyl ester provided the corresponding acid **14** in excellent yield.[7] Dehydrative cyclization of **14** by heating in acetic anhydride gave the pyrrolooxazinone **15**.[4] The isopropyl groups of **15** were selectively removed by treatment with BCl_3[8] in 99% yield to give 4'-O-methyllukianol A (**16**). Treatment of **15** with BBr_3 removed all of the isopropyl and the methyl groups to furnish lukianol A (**1**) in quantitative yield.



Scheme 2. Reagents and conditions: (a) (1) LDA (1.2 equiv), Et_2O, –78 °C, 1 h, (2) $ClCO_2Bn$ (1.8 equiv), –78 °C, 1 h (62%). (b) *p*-(*i*-PrO)-C_6H_4-$B(OH)_2$ (3.0 equiv), $Pd(dba)_2$ (5 mol%), d^{t}bpf (5 mol%), Na_2CO_3 (6.6 equiv), aq THF, reflux, 14 h (93%). (c) TBAF (1.5 equiv), THF, reflux, 2 h (92%). (d) *p*-(MeO)-C_6H_4-$COCH_2Br$ (2.5 equiv), K_2CO_3 (3.0 equiv), DMF, 70 °C, 3 h (81%). (e) H_2, Pd-C, EtOAc, rt, 4 h, (98%). (f) Ac_2O, NaOAc, 100 °C, 1 h (84%). (g) BCl_3 (6.0 equiv), CH_2Cl_2, –78 °C, 0.5 h → 0 °C, 2.5 h (**16**: 99%). (h) BBr_3 (9.0 equiv), CH_2Cl_2, –78 °C, 1 h → 0 °C, 3 h → rt, 0.5 h (**1**: quant).

Next, we turned our attention to the synthesis of lukianol B (**2**). We planned to introduce the pivotal iodo group at the late stage of the synthesis by a regioselective iodination of the key phenol intermediate **24**. The synthesis of **24** is shown in Scheme 3. Cross-coupling of **3** with 2.0 equiv of *p*-isopropoxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ gave the mono-coupling product **17** in 57% yield accompanied by a small amount the di-coupling product[6] (15%). Bromine-directed lithiation[5] of **17** with LDA in THF followed by a reaction with benzyl chloroformate afforded **18** in 75% yield as a single regioisomer. The regioselectivity of this reaction was confirmed at the later stage by the X-ray crystallographic analysis of the compound **25** (*vide infra*). Second cross-coupling of **18** with *p*-methoxyphenylboronic acid produced the key 3,4-unsymmetrically arylated pyrrol-2-carboxylate **19** in good yield. This compound was converted to the pyrrolooxazinone **23** in essentially same manner as described above without any complications. Selective deprotection of the isopropyl group of **23** with BCl_3 produced the phenol **24** in 99% yield.

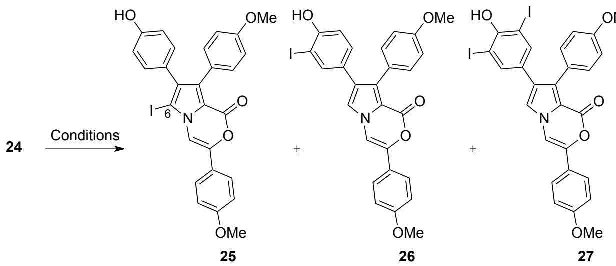


Scheme 3. Reagents and conditions: (a) *p*-(*i*-PrO)-C_6H_4-$B(OH)_2$ (2.0 equiv), $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (6.6 equiv), aq THF, reflux, 14.5 h (57%). (b) (1) LDA (1.2 equiv), THF, –78 °C, 1 h, (2) $ClCO_2Bn$ (1.8 equiv), –78 °C, 1 h (75%). (c) *p*-(MeO)-C_6H_4-$B(OH)_2$ (1.8 equiv), $Pd(PPh_3)_4$ (10 mol%), Na_2CO_3 (6.6 equiv), aq DME, reflux, 15 h (88%). (d) TBAF (1.5 equiv), THF, reflux 2 h (96%). (e) *p*-(MeO)-C_6H_4-$COCH_2Br$ (2.5 equiv), K_2CO_3 (3.0 equiv), DMF, 70 °C, 3 h (79%). (f) H_2, Pd-C, EtOAc, rt, 7 h, (85%). (g) Ac_2O, NaOAc, 100 °C, 1.5 h (93%). (h) BCl_3 (3.0 equiv), CH_2Cl_2, –78 °C, 0.5 h → 0 °C, 1.5 h (99%).

With the phenol **24** in hand, we examined the iodination of this compound. The results are summarized in Table. A reaction with N-iodosuccinimide (NIS) in DMF resulted in recovery of the starting material **24** (entry 1). Treatment with more electrophilic N-iodosaccharin (NISac)[9] or iodine monochloride (ICl) produced unexpected compound **25** in which the central pyrrolooxazinone core was iodinated at C6 (entries 2, 3). The position of the iodo group in **25** was confirmed by the X-ray crystallographic analysis (Figure 2). On the other hand, reaction with 1.0 equiv of iodine in the presence of ammonia[10] gave the desired iodide **26** in 20% yield accompanied by a small amount of diiodide **27** (entry 4). Use of 2.0 equiv of iodine under similar conditions afforded **27** selectively albeit in low yield (entry 5). Use of NISac instead of iodine improved the yields of the products **26** and **27** (entries 6–8). Although diiodide **27** was obtained selectively in good yield using 2.0 equiv of NISac (entry 8), the monoiodide **26** was hardly produced in acceptable yields even if lower amount of NISac was employed (entries 6, 7). Fortunately, however, **26** was produced from **27** by reductive elimination of an iodo group with Zn-Cu couple[11] (Scheme 4).

Finally the iodide **26** was converted to lukianol B (**2**) by demethylation with BBr_3 in excellent yield (Scheme 4). In a similar manner, diiodide **27** was also deprotected to provide diiodolukianol A (**28**) in good yield. The ^{1}H and ^{13}C NMR data

Table
Iodination of the phenol **24**.



Entry[a]	Conditions	Yield (%)[b]			
		24	25	26	27
1	NIS[c] (1.05 eq), DMF, 0 °C, 1 h	85	0	0	0
2	NISac[d] (1.0 eq), DMF, 0 °C, 2 h	40	13	0	0
3	ICl (2.3 eq), CH_2Cl_2, DMF, MeOH, 0 °C, 2.5 h	15	49	0	0
4	I_2 (1.0 eq), NH_3, EtOH, DMF, 0 °C, 2 h	26	0	20	6
5	I_2 (2.0 eq), NH_3, EtOH, DMF, 0 °C, 8.5 h	10	0	0	32
6	NISac (1.0 eq), NH_3, EtOH, DMF, 0 °C, 2 h	40	0	20	17
7	NISac (1.5 eq), NH_3, EtOH, DMF, 0 °C, 2 h	23	0	27	50
8	NISac (2.0 eq), NH_3, EtOH, DMF, 0 °C, 2 h	6	0	6	78

[a]All reactions were carried out using 30 mg of **24**. [b]Isolated yield. [c]NIS: N-Iodosuccinimide. [d]NISac: N-Iodosaccharin.

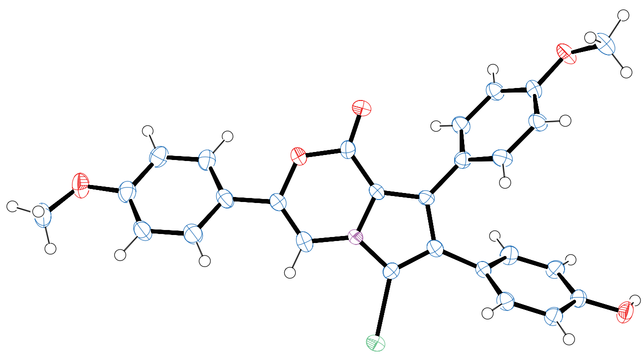
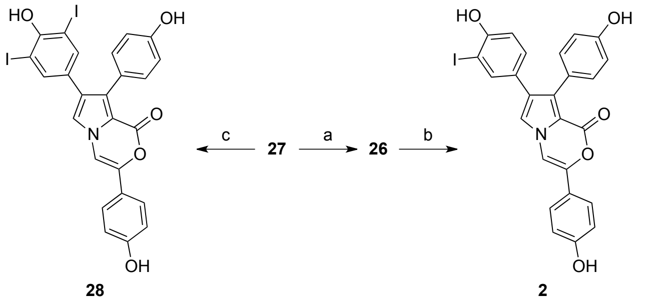


Figure 2. X-ray crystal structure of **25**.



Scheme 4. Reagents and conditions: (a) Zn-Cu, DMA, rt, 1.5 h (68%). (b) BBr_3 (7.0 equiv), CH_2Cl_2, –78 °C, 0.5 h → rt, 0.5 h → reflux, 3 h (95%). (c) BBr_3 (7.0 equiv), CH_2Cl_2, –78 °C, 0.5 h → 0 °C, 2.5 h → rt, 6.5 h → reflux, 3 h (74%).

of the synthetic lukianol B (**2**) were found to be identical with those of the natural product.[1] The first total synthesis of lukianol B (**2**) was thus completed.

3. Conclusion

In summary, we have achieved the total synthesis of lukianols A (**1**) and B (**2**) using a new method to produce 3,4-diarylpyrrole-2-carboxylates. The synthesis described herein can be applied to provide a wide range of lukianol analogues, which may be utilized for structure–activity relationship studies to develop effective h-ALR2 inhibitors. The studies along this line are in progress in our laboratories.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometers at 400 and 100 MHz, respectively, using TMS as an internal standard. IR spectra were recorded on a Nicolet Nexus 670 FT-IR spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-700N spectrometer. Elemental analyses were performed using a Perkin Elmer 2400II instrument. Gravity column chromatography was conducted using spherical silica gel 60N, 63–210 µm (Kanto Chemical Co. Inc.). Flash column chromatography was conducted using spherical silica gel 60N, 40–50 µm (Kanto Chemical Co. Inc.).

4.2. Synthesis of lukianol A (1)

4.2.1. Benzyl N-benzenesulfonyl-3,4-dibromopyrrole-2-carboxylate (9). A LDA solution was prepared by dropwise addition of 1.48 M hexane solution of BuLi (4.86 mL, 7.20 mmol) to a stirred solution of diisopropylamine (1.26 mL, 9.00 mmol) in dry Et_2O (31 mL) at –78 °C under Ar atmosphere followed by warming up to 0 °C over ca. 5 min. The solution was cooled again to –78 °C and a solution of **3** (2.19 g, 6.00 mmol) in dry Et_2O (45 mL) was added dropwise. After stirring for 1 h, benzyl chloroformate (1.54 mL, 10.8 mmol) dissolved in dry Et_2O (21 mL) was added dropwise. The reaction mixture was stirred for 1 h before being quenched with a saturated solution of NH_4Cl. The whole was extracted three times with Et_2O and the extracts were combined, washed successively with water and brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (188 mL) using toluene/hexane (1:1) as an eluent to give **9** (1.846 g, 62%) as white solid along with recovered **3** (0.551 g, 25%). Recrystallization of **9** from Et_2O–hexane gave colorless needles, mp 97–97.5 °C. IR (KBr): 1720, 1449, 1379, 1172, 1086 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 5.30 (s, 2H), 7.34–7.40 (m, 5H), 7.50 (dd, *J*

= 8.4, 7.6 Hz, 2H), 7.62–7.66 (m, 1H), 7.65 (s, 1H), 7.93 (dd, *J* = 8.4, 1.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 67.7, 104.7, 112.1, 123.7, 125.3, 128.1, 128.5, 128.5, 128.6, 129.1, 134.4, 134.7, 138.0, 158.3. *Anal.* Calcd for $C_{18}H_{13}Br_2NO_4S$: C, 43.31; H, 2.62; N, 2.81. Found: C, 43.22; H, 2.40; N, 2.80.

*4.2.2. Benzyl N-benzenesulfonyl-3,4-dibromopyrrole-2,5-dicarboxylate (**10**).* A LDA solution was prepared in a similar manner as described above using BuLi (1.47 M hexane solution, 814 μL, 1.2 mmol), diisopropylamine (210 μL, 1.5 mmol), and dry THF (5.2 mL). To this solution was added dropwise a solution of **3** (365 mg, 1.00 mmol) in dry THF (3.5 mL). After stirring for 1 h at –78 °C, a solution of benzyl chloroformate (257 μL, 1.8 mmol) in dry THF (3.5 mL) was added. The mixture was stirred for 1 h at the same temperature and quenched with saturated aqueous NH_4Cl. The products were extracted with Et_2O as described above and purified by a column chromatography (toluene/hexane 2:1) to give **10** (190 mg, 30%) as white solid along with **9** (63 mg, 13%) and the starting material **3** (159 mg, 44%). Recrystallization of **10** from Et_2O–hexane gave colorless needles, mp 95.5–96 °C. IR (KBr): 1739, 1717, 1202, 725, 602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 4H), 7.33–7.39 (m, 10H), 7.42 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.60 (tt, *J* = 7.6, 1.3 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.4, 110.1, 128.3, 128.6, 128.6, 128.6, 128.7, 128.8, 134.4, 134.5, 138.1, 159.0; HRFABMS *m/z* calcd. for $C_{26}H_{20}Br_2NO_6S$ $(M+H)^+$ 631.9378, found 631.9425.

*4.2.3. Benzyl N-benzenesulfonyl-3,4-bis(4-isopropoxyphenyl)pyrrole-2-carboxylate (**11**).* A mixture of **9** (100 mg, 0.200 mmol), 4-isopropoxyphenylboronic acid (108 mg, 0.602 mmol), $Pd(dba)_2$ (5.8 mg, 0.01 mmol), d^{t}bpf (4.8 mg, 0.01 mmol), Na_2CO_3 (140 mg, 1.32 mmol), dry THF (2.5 mL), and degassed water (0.5 mL) was stirred at refluxing temperature for 14 h under Ar atmosphere. After cooling, the solvent was removed under reduced pressure and the residue was extracted three times with Et_2O. The combined extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (47 mL) using toluene as an eluent to give **11** (113 mg, 93%) as white solid. Recrystallization from Et_2O–hexane gave colorless granules, mp 155.5–156 °C. IR (KBr): 1718, 1373, 1243, 1183, 1135 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (d, *J* = 6.1 Hz, 6H), 1.32 (d, *J* = 6.1 Hz, 6H), 4.48 (sep, *J* = 6.1 Hz, 1H), 4.48 (sep, *J* = 6.1 Hz, 1H), 5.08 (s, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.94–7.01 (m, 6H), 7.18–7.25 (m, 3H), 7.51 (dd, *J* = 8.0, 7.5 Hz, 2H), 7.56 (s, 1H), 7.62 (tt, *J* = 7.5, 1.4 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.0, 22.1, 67.1, 69.6, 69.7, 115.1, 115.5, 122.5, 122.8, 124.6, 124.7, 127.4, 127.9, 128.0, 128.1, 128.2, 129.0, 129.5, 131.2, 133.1, 133.8, 135.0, 139.0, 157.1, 157.4, 160.9. *Anal.* Calcd for $C_{36}H_{35}NO_6S$: C, 70.91; H, 5.79; N, 2.30. Found: C, 71.00; H, 5.72; N, 2.26.

*4.2.4. Benzyl 3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate (**12**).* To a solution of **11** (100 mg, 0.164 mmol) in dry THF (7.8 mL) was added dropwise a 1.0 M THF solution of TBAF (245 μL, 0.245 mmol) at room temperature. The whole was heated at reflux for 2 h and, after cooling to room temperature, the mixture was quenched with water. The solvent was removed under reduced pressure and the residue was extracted three times with CH_2Cl_2. The combined extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The oily residue was chromatographed on silica gel (31 mL) using toluene/EtOAc (30:1) as an eluent to give **12** (70.7 mg, 92%) as white solid. Recrystallization from Et_2O–hexane afforded colorless needles, mp 128–128.5 °C. IR (KBr): 3299, 1678, 1398, 1241, 1128 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (d, *J* = 6.0 Hz, 6H), 1.34 (d, *J* = 6.0 Hz, 6H), 4.47 (sep, *J* = 6.0 Hz, 1H), 4.52 (sep, *J* = 6.0 Hz, 1H), 5.19 (s, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.98–7.01 (m, 3H), 7.12–7.17 (m, 4H), 7.24–7.29 (m, 3H), 9.27 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 65.8, 69.7, 115.0, 115.5, 119.4, 120.2, 126.4, 126.6, 126.8, 127.9, 127.9, 128.3, ,129.3, 131.9, 135.9, 156.3, 156.9, 161.1. *Anal*. Calcd. for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 76.82; H, 6.75; N, 2.95.

*4.2.5. Benzyl 3,4-bis(4-isopropoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylate (**13**).* A mixture of **12** (1.19 g, 2.52 mmol), *p*-methoxyphenacyl bromide (1.45 g, 6.31 mmol), K_2CO_3 (1.05 g, 7.57 mmol) in DMF (59.6 mL) was stirred at 70 °C for 3 h under Ar atmosphere. After cooling the reaction mixture was diluted with AcOEt, washed successively with water (4 times) and brine (once), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by a flash chromatography on silica gel (141 mL) using toluene/AcOEt (30:1) as an eluent to give **13** (1.26 g, 81%) as white solid along with recovered **12** (169 mg, 14%). Recrystallization of **13** from Et_2O–hexane gave colorless granules, mp 131–133 °C. IR (KBr): 1686, 1598, 1241, 1172, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (d, *J* = 6.0 Hz, 6H), 1.33 (d, *J* = 6.0 Hz, 6H), 3.88 (s, 3H), 4.47 (sep, *J* = 6.0 Hz, 2H), 4.97 (s, 2H), 5.73 (s, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.82–6.83 (m, 2H), 6.92 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.14–7.17 (m, 3H), 7.99 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 55.5, 65.5, 69.62, 69.65, 114.1, 114.9, 115.3, 119.8, 124.8, 126.7, 127.2, 127.5, 127.6, 127.87, 127.93, 128.0, 129.3, 130.3, 131.4, 131.9, 135.6, 156.1, 156.7, 161.7, 164.0, 191.8. *Anal.* Calcd. for $C_{39}H_{39}NO_6$: C, 75.83; H, 6.36; N, 2.27. Found: C, 75.81; H, 6.15; N, 2.27.

*4.2.6. 3,4-Bis(4-isopropoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylic acid (**14**).* A mixture of **13** (46.5 mg, 0.0753 mmol) and 20% w/w Pd/C (9.3 mg) in AcOEt (5 mL) was vigorously stirred under hydrogen atmosphere (balloon) at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. Concentration of the filtrate gave practically pure **14** (41.0 mg, 98%). Recrystallization from CH_2Cl_2–hexane gave white powder, mp 192–193 °C. IR (KBr): 1686, 1652, 1598, 1456, 1242 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.20 (d, *J* = 6.0 Hz, 6H), 1.25 (d, *J* = 6.0 Hz, 6H), 3.85 (s, 3H), 4.49 (sep, *J* = 6.0 Hz, 1H), 4.56 (sep, *J* = 6.0 Hz, 1H), 5.82 (s, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.9 Hz, 2H), 7.21 (s, 1H), 8.02 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (DMSO-d_6): δ 22.7, 22.7, 56.4, 69.8, 69.8, 114.9, 115.3, 116.0, 120.9, 123.8, 127.3, 127.5, 128.5, 128.6, 129.6, 130.2, 131.0, 132.5, 156.3, 156.8, 163.2, 164.3, 193.3. *Anal*. Calcd. for $C_{32}H_{33}NO_6$: C, 72.85; H, 6.30; N, 2.65. Found: C, 73.06; H, 6.52; N, 2.64.

*4.2.7. 7,8-Bis(4-isopropoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (**15**).* A solution of **14** (971 mg, 1.75 mmol) and dehydrated AcONa (2.59 g, 31.6 mmol) in Ac_2O (130 mL) was heated at 100 °C for 1 h. After cooling to room temperature, the Ac_2O was removed azeotropically with toluene under reduced pressure. The oily residue was dissolved in Et_2O and the solution was washed three times with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a column chromatography on silica gel (163 mL) using hexane/AcOEt (3:1) as an eluent to give **15** (790 mg, 84%) as white solid. Recrystallization from Et_2O–hexane gave colorless granules, mp 131.5–132.5 °C. IR (KBr): 1733, 1248, 1178, 1118, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ

1.32 (d, J = 6.0 Hz, 6H), 1.35 (d, J = 6.0 Hz, 6H), 3.83 (s, 3H), 4.51 (sep, J = 6.0 Hz, 1H), 4.55 (sep, J = 6.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 7.17 (s, 1H), 7.27 (d, J = 8.8 Hz, 2H), 7.30 (s, 1H), 7.63 (d, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 55.4, 69.7, 69.8, 102.7, 112.8, 114.2, 115.0, 115.6, 119.0, 123.1, 124.4, 125.6, 125.8, 128.2, 129.78, 129.81, 132.1, 141.8, 154.3, 156.9, 157.3, 160.4. *Anal*. Calcd. for $C_{32}H_{31}NO_5$: C, 75.42; H, 6.13; N, 2.75. Found: C, 75.44; H, 5.96; N, 2.66.

*4.2.8. 7,8-Bis(4-hydroxyphenyl)-3-(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (**16**).* Boron trichloride (1 M heptane solution, 1.18 mL, 1.18 mmol) was added dropwise to a stirred solution of **15** (100 mg, 0.196 mmol) in dry CH_2Cl_2 (6 mL) at –78 °C under Ar atmosphere. The mixture was stirred for 0.5 h at –78 °C and for 2.5 h at 0 °C, and quenched with saturated aqueous $NaHCO_3$. To the mixture was added AcOEt and the whole was stirred at room temperature for 50 min and evaporated. The residue was washed with water and filtered to give practically pure **16** (82.9 mg, 99%) as white powder, mp >300 °C (sealed capillary). IR (KBr): 3446, 3234, 1690, 1610, 1515 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.81, (s. 3H), 6.67 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 6.97, (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 7.59, (s, 1H), 7.67 (d, J = 8.9 Hz, 2H), 8.14, (s, 1H), 9.45 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.3, 103.7, 112.0, 114.5, 114.6, 115.3, 120.1, 122.9, 123.2, 124.0, 125.4, 127.5, 129.0, 129.5, 131.8, 140.4, 153.6, 156.4, 156.7, 160.0. HRFABMS *m/z* calcd. for $C_{26}H_{19}NO_5$ (M^+) 425.1263, found 425.1127.

4.2.9. Lukianol A (1). Boron tribromide (1 M CH_2Cl_2 solution, 883 µL, 0.883 mmol) was added dropwise to a stirred solution of **15** (50.0 mg, 0.0981 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C. The mixture was stirred at –78 °C (1 h), 0 °C (3 h) and then room temperature (30 min), before being quenched with saturated aqueous $NaHCO_3$. To the mixture was added AcOEt and the whole was stirred at room temperature for 30 min and evaporated. The residue was washed with water and filtered. The crude product was dissolved in acetone and filtered through a short column on silica gel (4 mL) using AcOEt as an eluent to give **1** (41.8 mg, quant). Recrystallization from ethanol gave white powder, mp 220–300 °C (dec) (sealed capillary). IR (KBr): 3338, 1693, 1420, 1244, 1207 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.67 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.59 (s, 1H), 8.06 (s, 1H) 9.20–9.95 (br s, 3H). ^{13}C NMR (DMSO-d_6): δ 102.6, 111.5, 114.2, 114.8, 115.4, 119.5, 120.8, 122.8, 123.5, 125.1, 127.0, 128.4, 129.0, 131.3, 140.5, 153.2, 155.9, 156.2, 158.1. HRFABMS *m/z* calcd. for $C_{25}H_{17}NO_5$ (M^+) 411.1107, found 411.1107.

4.3. Synthesis of the phenol 24

4.3.1. N-Benzenesulfonyl-3-bromo-4-(4-isopropoxyphenyl) pyrrole (17). A mixture of **3** (365 mg, 1.00 mmol), 4-isopropoxyphenylboronic acid (304 mg, 2.00 mmol), $Pd(PPh_3)_4$ (116 mg, 0.100 mmol), Na_2CO_3 (700 mg, 6.60 mmol), THF (10 mL), and degassed water (2 mL) was stirred at refluxing temperature for 14.5 h under Ar atmosphere. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was extracted three times with Et_2O. The combined extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a column chromatography on silica gel (94 mL) using hexane/toluene (1:1 to 1:2) as an eluent to give **17** (241 mg, 57%) as pale yellow gum, along with 3,4-diarylated product (known compound. see, ref. 6) (75 mg, 15%) and recovered **3** (82 mg, 22%). The spectroscopic data of **17** are as follows. IR (KBr): 1375, 1247, 1186, 1135, 1057 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.34 (d, J = 6.0 Hz, 6H), 4.56 (sep, J = 6.0 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.17 (d, J = 2.6 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 7.39 (d, J = 8.9 Hz, 2H), 7.53 (dd, J = 8.3, 7.3 Hz, 2H), 7.63 (tt, J = 7.3, 1.4 Hz, 1H), 7.90 (dd, J = 8.3, 1.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 69.9, 102.8, 115.7, 117.4, 120.7, 124.1, 127.1, 129.0, 129.4, 129.6, 134.3, 138.5, 157.7. HRFABMS *m/z* calcd. for $C_{19}H_{18}BrNO_3S$ (M^+) 419.0191, found 419.0216.

*4.3.2. Benzyl N-benzenesulfonyl-3-bromo-4-(4-isopropoxyphenyl)pyrrole-2-carboxylate (**18**).* To a solution of LDA prepared from diisopropylamine (565 µL, 4.03 mmol) and BuLi (1.51 M in hexane, 2.14 mL, 3.23 mmol) in dry THF (14 mL), was added dropwise a solution of **17** (1.13 g, 2.69 mmol) in THF (5 mL) at –78 °C under Ar atmosphere. After 1 h, benzyl chloroformate (691 µL, 4.84 mmol) dissolved in THF (5 mL) was added dropwise. After 1 h, the reaction mixture was quenched by adding a saturated aqueous NH_4Cl and the solvent was evaporated *in vacuo*. The residue was extracted three times with Et_2O and the extracts were combined, washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (251 mL) using hexane/toluene (1:2) as an eluent to give **18** (1.12 g, 75%) as pale yellow solid. Recrystallization from Et_2O–hexane gave pale yellow powder, mp 136.5–137.5 °C. IR (KBr): 1725, 1375, 1234, 1187, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35 (d, J = 6.1 Hz, 6H), 4.57 (sep, J = 6.1 Hz, 1H), 5.32 (s. 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.33–7.42 (m, 7H), 7.47 (dd, J = 7.5, 8.5 Hz, 2H), 7.55 (s, 1H), 7.61 (tt, J = 7.5, 1.0 Hz, 1H), 7.94 (dd, J = 8.5, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 67.6, 69.9, 109.3, 115.7, 122.9, 123.5, 124.0, 127.9, 128.4, 128.5, 128.6, 129.1, 130.0, 134.1, 135.0, 138.5, 157.9, 159.4. *Anal*. Calcd. for $C_{27}H_{24}BrNO_5S$: C, 58.49; H, 4.36; N, 2.53. Found: C, 58.75; H, 4.15; N, 2.47.

4.3.3. Benzyl N-benzenesulfonyl-4-(4-isopropoxyphenyl)-3-(4-methoxyphenyl)pyrrole-2-carboxylate (19). A mixture of **18** (692 mg, 1.25 mmol), 4-methoxyphenylboronic acid (338 mg, 2.22 mmol), $Pd(PPh_3)_4$ (144 mg, 0.125 mmol), Na_2CO_3 (872 mg, 8.22 mmol), DME (18 mL), and degassed water (3.72 mL) was stirred at 85 °C for 15 h. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was extracted three times with Et_2O. The combined extracts were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a column chromatography on silica gel (188 mL) using toluene/AcOEt (30:1) as an eluent to give **19** (638 mg, 88%) as white solid. Recrystallization from Et_2O–hexane gave colorless granules, mp 120–122 °C. IR (KBr): 1713, 1367, 1247, 1174, 837 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.29 (d, J = 6.1 Hz, 6H), 3.76, (s. 3H), 4.48 (sep, J = 6.1 Hz, 1H), 5.07 (s, 2H), 6.69 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 8.9 Hz, 2H), 6.93–6.98 (m, 4H), 7.01 (d, J = 8.9 Hz, 2H), 7.18–7.25 (m, 3H), 7.51 (dd, J = 8.5, 7.4 Hz, 2H), 7.57 (s, 1H), 7.62 (tt, J = 7.4, 1.0 Hz, 1H), 8.04 (dd, J = 8.5, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.0, 55.1, 67.1, 69.8, 113.4, 115.6, 122.6, 122.9, 124.7, 125.0, 127.4, 127.9, 128.0, 128.2, 129.0, 129.5, 131.2, 133.1, 133.8, 135.0, 139.1, 157.1, 159.0, 160.8. *Anal*. Calcd. for $C_{34}H_{31}NO_6S$: C, 70.20; H, 5.37; N, 2.41. Found: C, 70.31; H, 5.14; N, 2.43.

*4.3.4. Benzyl 4-(4-isopropoxyphenyl)-3-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (**20**).* To a solution of **19** (1.13 g, 1.94 mmol) in dry THF (92 mL), was added dropwise a 1 M THF solution of TBAF (2.90 mL, 2.90 mmol) at room temperature. After refluxing for 2 h, the mixture was cooled to room temperature and quenched by addition of water. The solvent was evaporated *in vacuo* and the residue was extracted three times with CH_2Cl_2. The extracts were combined, washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a column chromatography on silica gel (251 mL) using toluene/AcOEt (30:1) as an eluent to give **20** (822 mg, 96%) as white solid. Recrystallization from Et_2O–hexane gave colorless needles, mp 128.5–129.5 °C. IR (KBr): 3308, 1678, 1288, 1240, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (d, J = 6.0 Hz, 6H), 3.80, (s, 3H), 4.46 (sep, J = 6.0 Hz, 1H), 5.18, (s, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 6.98–7.02 (m, 3H), 7.10–7.13 (m, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.24–7.28 (m, 3H), 9.25 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.1, 55.1, 65.9, 69.8, 113.2, 115.6, 119.5, 120.2, 126.6, 126.7, 126.8, 127.9, 128.3, 129.3, 131.9, 135.9, 156.4, 158.6, 161.0. *Anal.* Calcd. for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.17; H, 6.10; N, 3.13.

*4.3.5. Benzyl 4-(4-isopropoxyphenyl)-3-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylate (**21**).* A mixture of **20** (210 mg, 0.475 mmol), *p*-methoxyphenacyl bromide (272 mg, 1.19 mmol), and K_2CO_3 (197 mg, 1.43 mmol) in DMF (11 mL) was stirred at 70 °C for 3 h. The mixture was then cooled to room temperature, diluted with water, and extracted with AcOEt. The organic layer was washed successively with water (4 times) and brine (once), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a chromatography on silica gel (141mL) using hexane/AcOEt (3:1) as an eluent to give **21** (221 mg, 79%) as white solid along with recovered of **20** (38.8 mg, 18%). Recrystallization of **21** from AcOEt–hexane gave colorless needles, mp 142–144 °C. IR (KBr): 1701, 1686, 1229, 1177, 1096 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.28 (d, J = 6.0 Hz, 6H), 3.77 (s, 3H), 3.89 (s, 3H), 4.45 (sep, J = 6.0 Hz, 1H), 4.96 (s, 2H), 5.74 (s, 2H), 6.68 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.81 (dd, J = 8.0, 1.4 Hz, 2H), 6.93, (s, 1H), 6.972 (d, J = 8.8 Hz, 2H), 6.976 (d, J = 8.7 Hz, 2H), 7.11–7.20 (m, 5H), 7.99 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 55.0, 55.5, 65.6, 69.7, 113.0, 114.1, 115.4, 119.8, 124.8, 126.7, 127.2, 127.5, 127.7, 127.9, 128.0, 128.1, 129.2, 130.3, 131.4, 131.8, 135.5, 156.2, 158.3, 161.7, 164.0, 191.8. *Anal.* Calcd. for $C_{37}H_{35}NO_6$: C, 75.36; H, 5.98; N, 2.38. Found: C, 75.20; H, 5.95; N, 2.37.

4.3.6. 4-(4-Isopropoxyphenyl)-3-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrole-2-carboxylic acid (22). A suspension of **21** (350 mg, 0.593 mmol) and 20% w/w Pd-C (70 mg) in AcOEt (70 mL) was vigorously stirred at room temperature under hydrogen atmosphere (balloon) for 7 h. The mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. Concentration of the filtrate *in vacuo* gave practically pure **22** (300 mg, 85%) as white solid. Recrystallization from CH_2Cl_2–hexane gave colorless needles, mp 186–187 °C. IR (KBr): 1681, 1647, 1536, 1457, 1237 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.21 (d, J = 6.0 Hz, 6H), 3.75 (s, 3H), 3.87 (s, 3H), 4.52 (sep, J = 6.0 Hz, 1H), 5.86 (s, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.9 Hz, 2H), 7.25 (s, 1H), 8.04 (d, J = 8.9 Hz, 2H), 11.84 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 21.8, 54.8, 55.5, 55.6, 68.8, 112.8, 114.0, 115.1, 120.0, 122.8, 126.6, 127.1, 127.7, 128.0, 128.6, 129.1, 130.1, 131.5, 155.4, 157.7, 162.3, 163.3, 192.3. *Anal.* Calcd. for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80. Found: C, 71.88; H, 6.07; N, 2.78.

4.3.7. 7-(4-Isopropoxyphenyl)-3,8-bis(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (23). A mixture of **22** (91.0 mg, 0.182 mmol) and dehydrated AcONa (270 mg, 3.30 mmol) in Ac_2O (15 mL) was stirred at 100 °C for 1.5 h. The Ac_2O was azeotropically removed *in vacuo* using toluene. The residue was dissolved in Et_2O, washed three times with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by a column chromatography on silica gel (12 mL) using hexane/AcOEt (2:1) as an eluent to give **23** (81.6 mg, 93%) as white solid. Recrystallization from AcOEt–hexane gave colorless needles, mp 193.5–195 °C. IR (KBr): 1731, 1430, 1248, 1179, 1038 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.32 (d, J = 6.0 Hz, 6H), 3.82 (s, 3H), 3.84 (s, 3H), 4.51 (sep, J = 6.0 Hz, 1H), 6.77 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.19 (s, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.31 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.1, 55.1, 55.4, 69.8, 102.7, 112.9, 113.3, 114.3, 115.7, 119.0, 123.1, 124.7, 125.5, 125.8, 128.2, 129.7, 129.8, 132.1, 141.9, 154.3, 156.9, 158.9, 160.5. *Anal.* Calcd. for $C_{30}H_{27}NO_5$: C, 74.83; H, 5.65; N, 2.91. Found: C, 74.88; H, 5.63; N, 2.87.

4.3.8. 7-(4-Hydroxyphenyl)-3,8-bis(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (24). A 1 M solution of BCl_3 in heptane (10.9 mL, 10.9 mmol) was added dropwise to a cooled (–78 °C) and stirred solution of **23** (1.75 g, 3.63 mmol) in dry CH_2Cl_2 (187 mL). After 30 min at –78 °C, the reaction mixture was warmed up to 0 °C and stirred for an additional 1.5 h before being quenched with saturated aqueous $NaHCO_3$. AcOEt was added to the mixture and stirred at room temperature, during which time white crystals appeared. The whole was evaporated *in vacuo* and the residual solid was washed with water and collected by filtration to give **24** (1.59 g, 99%) as white solid. Recrystallization from acetone gave colorless granules, mp >300 °C (dec) (sealed capillary). IR (KBr): 3331, 1700, 1428, 1255, 1177 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.75 (s, 3H), 3.78 (s, 3H), 6.65 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 7.62 (s, 1H), 7.65 (d, J = 8.9 Hz, 2H), 8.11 (s, 1H), 9.53 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 55.2, 55.5, 103.8, 112.2, 113.3, 114.6, 115.5, 120.4, 123.0, 124.0, 125.0, 125.6, 127.8, 128.6, 129.7, 132.0, 140.7, 153.8, 156.5, 158.6, 160.1. *Anal.* Calcd. for $C_{27}H_{21}NO_5$: C, 73.79; H, 4.82; N, 3.19. Found: C, 73.51; H, 4.79; N, 3.11.

4.4. Selective iodination of the phenol 24

4.4.1. 7-(4-Hydroxyphenyl)-6-iodo-3,8-bis(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (25). Compound **24** (30.0 mg, 0.0683 mmol) was dissolved in DMF (2 mL) and MeOH (1 mL) was added slowly. The solution was cooled to 0 °C and ICl (1.0 M in CH_2Cl_2, 157 µL, 0.157 mmol) was added dropwise. After stirring 2.5 h at 0 °C, MeOH was evaporated and the residue was diluted with AcOEt. The solution was washed successively with water (3 times) and brine (once), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was applied on a column of silica gel (12 mL) and eluted successively with hexane/AcOEt (1:1), hexane/AcOEt (1:2), AcOEt, and acetone to give **25** (18.8 mg, 49%) as white solid along with the starting meterial **24** (4.4 mg, 15%). Recrystallization of **25** from CH_2Cl_2–Et_2O gave colorless powder, mp 221.5–227 °C (dec) (sealed capillary). IR (KBr): 3442, 1711, 1511, 1253, 1173 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.72, (s. 3H), 3.80, (s. 3H), 6.69 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.90, (d, J = 8.6 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 7.73, (s, 1H), 7.75 (d, J = 9.0 Hz, 2H), 9.50, (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.9, 55.3, 82.3, 104.2, 112.7, 114.3, 114.9, 115.2, 122.5, 124.0, 124.1, 125.9, 130.4, 131.5, 131.7, 133.6, 141.1, 152.9, 156.6, 158.3, 160.1. *Anal.* Calcd. for $C_{27}H_{20}INO_5$: C, 57.36; H, 3.57; N, 2.48. Found: C, 57.25; H, 3.28; N, 2.47.

*4.4.2. 7-(4-Hydroxy-3-iodophenyl)-3,8-bis(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (**26**) and 7-(4-Hydroxy-3,5-*

diiodophenyl)-3,8-bis(4-methoxyphenyl)-1H-pyrrolo[2,1-c][1,4]oxazin-1-one (27). To a cooled (0 °C) and stirred solution of **24** (30.1 mg, 0.0683 mmol) in a mixture of 2 M ethanolic ammonia (1 mL) and DMF (2 mL), was added dropwise a solution of *N*-iodosaccharin (31.7 mg, 0.102 mmol) in EtOH (1 mL). After 2 h, EtOH was removed *in vacuo* and the residue was diluted with AcOEt, washed successively with water (4 times) and brine (once), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was applied on a column of silica gel (16 mL) and eluted successively with toluene/AcOEt (5:1), AcOEt, and AcOEt/MeOH (3:1) to give monoiodode **26** (10.4 mg, 27%), diiodide **27** (23.4 mg, 50%) and the starting material **24** (6.9 mg, 23%).

Compound **26**: pale yellow powder, mp 286.5–287.5 °C (sealed capillary) (acetone). IR (KBr): 3398, 1696, 1518, 1248, 1180 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 3.83 (s, 3H), 3.87 (s, 3H), 6.83 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 7.00 (dd, J = 8.4, 2.1 Hz, 1H), 7.07 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 2.1 Hz, 1H), 7.64 (s, 1H), 7.74 (d, J = 9.0 Hz, 2H), 8.00 (s, 1H), 9.08–9.25 (br s, 1H). ^{13}C NMR (acetone-d_6): δ 55.5, 55.8, 84.3, 104.2, 114.0, 115.2, 115.6, 120.9, 124.2, 125.8, 126.5, 127.3, 128.1, 130.1, 130.8, 132.9, 140.0, 142.5, 154.3, 156.5, 160.1, 161.5. *Anal*. Calcd. for $C_{27}H_{20}INO_5$: C, 57.36; H, 3.57; N, 2.48. Found: C, 57.09; H, 3.27; N, 2.55.

Compound **27**: pale yellow powder, mp 159–161 °C (sealed capillary) (benzene–hexane). IR (KBr): 3473, 1718, 1515, 1409, 1248 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 2.66–3.10 (br s, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 6.95 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 7.59 (s, 2H), 7.72 (s, 1H), 7.74 (d, J = 9.0 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR (acetone-d_6): δ 55.6, 55.8, 84.2, 104.1, 113.8, 114.1, 115.2, 121.0, 124.1, 125.35, 125.38, 126.5, 130.1, 130.8, 132.9, 140.3, 142.6, 154.2, 154.9, 160.2, 161.5. HRFABMS *m/z* calcd. for $C_{27}H_{19}I_2NO_5$ (M^+) 690.9353, found 690.9340.

4.5. Conversion of diiodide 27 to monoiodide 26

A mixture of **27** (42.6 mg, 0.0616 mmol) and Zn-Cu couple (7.4 mg) in DMA (3 mL) was stirred at room temperature for 1.5 h. Silica gel (306 mg) was added and DMA was evaporated at 26 °C/190 Pa. The residue was charged on a silica gel column (16 mL) and eluted with toluene–AcOEt (5:1) to give **26** (23.5 mg, 68%) and the starting material **27** (4.5 mg, 11%).

4.6. Synthesis of lukianol B (2) and diiodolukianol A (28)

4.6.1. Lukianol B (2). A 1 M solution of BBr_3 in CH_2Cl_2 (362 µL, 0.362 mmol) was added dropwise to a cooled (–78 °C) and stirred solution of **26** (29.2 mg, 0.0516 mmol) in dry CH_2Cl_2 (10 mL) under Ar atmosphere. After 30 min, the mixture was gradually warmed up to room temperature and stirred for 0.5 h and heated at reflux for 3 h. After cooling to room temperature, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ and stirred until white crystals appeared. The whole was evaporated *in vacuo* and the residue was washed with water and filtered to give **2** (26.4 mg, 95%) as white solid. Recrystallization from acetone–hexane gave white powder, mp 278–300 °C (dec) (sealed capillary). IR (KBr): 1698, 1518, 1406, 1243, 1209 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 6.82 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.00 (dd, J = 8.4, 2.1 Hz, 1H), 7.18, (d, J = 8.7 Hz, 2H), 7.61 (s, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.93 (s, 1H), 8.30–9.15 (br s, 1H). ^{13}C NMR (acetone-d_6): δ 84.3, 103.7, 113.7, 115.5, 115.6, 116.6, 120.7, 123.2, 124.7, 126.7, 127.1, 128.3, 130.3, 130.8, 133.0, 139.9, 142.8, 154.4, 156.4, 157.7, 159.4. HRFABMS *m/z* calcd. for $C_{25}H_{16}INO_5$ (M^+) 537.0073, found 537.0061.

4.6.2. Diiodolukianol A (28). A 1 M solution of BBr_3 in CH_2Cl_2 (368 µL, 0.368 mmol) was added dropwise to a cooled (–78 °C) and stirred solution of **27** (36.3 mg, 0.0525 mmol) in CH_2Cl_2 (10 mL) under Ar atmosphere. The mixture was stirred at –78 °C (30min), 0 °C (2.5 h), room temperature (6.5 h), and then refluxing temperature (3 h). The mixture was cooed to room temperature, quenched by addition of saturated aqueous $NaHCO_3$ and stirred until white crystals appeared. The whole was evaporated *in vacuo* and the residue was washed with water and filtered to give **28** (25.6 mg, 74%). Recrystallization from acetone–hexane gave pale brown powder, mp 286–300 °C (dec) (sealed capillary) (acetone–hexane). IR (KBr): 1699, 1518, 1413, 1242, 1209 cm^{-1}. ^{1}H NMR (acetone-d_6): δ 3.64–3.96 (br, 1H), 6.85 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.60 (s, 2H), 7.65 (d, J = 8.9 Hz, 2H), 7.68 (s, 1H), 7.92 (s, 1H). ^{13}C NMR (acetone-d_6): δ 84.3, 103.7, 115.5, 115.6, 116.6, 121.0, 123.1, 124.3, 125.3, 126.7, 130.4, 130.9, 132.9, 140.3, 142.9, 154.3, 154.9, 157.9, 159.5. HRFABMS *m/z* calcd. for $C_{25}H_{15}I_2NO_5$ (M^+) 662.9040, found 662.9044.

4.7. X-ray crystallographic analysis of 25

Results are as follows: compound formula $C_{27}H_{20}INO_5$, Mw = 565.36, orthorhombic, $P2_12_12_1$, a = 6.8237(13) Å, b = 15.066(3) Å, c = 22.218(5) Å, V = 2284.2(8) Å^3, Z = 4, D_{calc} = 1.644 g/cm^3, monochromatized radiation λ(Mo Kα) = 0.71075 Å, μ = 1.443 mm^{-1}, F(000) = 1128.00, T = 123 K. Data were collected on a Rigaku Saturn724 CCD to a θ limit of 27.41° which yielded 22261 reflections. There are 5187 unique reflections with 4897 observed at the 2σ level. The structure was solved by direct methods (SIR92)[12] and refined using full-matrix least-squares on F2 (SHELXL97).[13] The final model was refined using 310 parameters and all 5187 data. All non-hydrogen atoms were refined with isotropic thermal displacements. The final agreement statistics are as follows: R = 0.0476 (based on 4897 reflections with $I > 2\sigma(I)$), wR = 0.0926, S = 1.097. The maximum peak height in a final difference Fourier map is 0.88 e Å^3, and this peak is without chemical significance. CCDC 918506 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all compounds synthesized in this work) associated with this article can be found, in the online version, at http://dx.doi.org/--.

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