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TOTAL SYNTHESES OF PLAGIOCHINS A AND D, MACROCYCLIC BIS(BIBENZYLS), BY Pd(0) CATALYZED INTRAMOLECULAR STILLE-KELLY REACTION[1]

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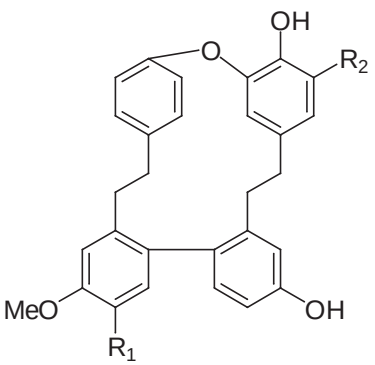
Abstract – Total syntheses of plagiochins A (**1**) and D (**4**), the former of which exhibits a significant neurotrophic activity, have been accomplished. The key 16-membered ring closure in **4** has been achieved directly from the dibromoperrottetin derivative (**7**) by Pd(0) catalyzed intramolecular Stille-Kelly reaction, whereas **1** has been synthesized from the dibromide (**28**) *via* the trimethylstannyl compounds (**29**) and (**30**) by Pd(0) catalyzed intramolecular Stille reaction.

Macrocyclic bis(bibenzyls) are natural products occurring exclusively in liverwort species, and over 60 analogues are known up to date.[2] Discovery of them can be mainly attributed to Prof. Asakawa and his research group.[3] Their novel structures and interesting biological activities (e.g. cytotoxicity[4] and 5-lipoxygenase inhibitor[5]) make them attractive targets for total synthesis.[6] The cyclic bis(bibenzyls) are further subdivided into three types 1, 2, and 3, which are made up of macrocyclic rings linked through two biphenyl ether C-O bonds, biphenyl ether C-O and biaryl C-C bonds, and two biaryl C-C bonds,



1 $R_1 = R_2 = OH$
2 $R_1 = H, R_2 = OH$
3 $R_1 = OH, R_2 = H$
4 $R_1 = R_2 = H$

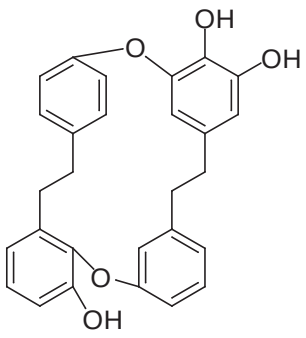


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Figure 1 Plagiochins A (**1**) ~ D (**4**) and marchantin A (**5**)

respectively. Two unsymmetrically substituted bis(bibenzyls) are presumably joined by oxidative phenol C-O or C-C couplings, thus forming these unique macrocyclic structures. Representatives of the type 1 are 18-membered ring marchantin A (**5**) and 20-membered ring riccardin B isolated from *Marchantia polymorpha*[7] and *Riccardia multifida*,[8] respectively, which have been already synthesized by us[9] and two other groups.[10,11] Plagiochins A (**1**) ~ D (**4**) belonging to the type 2, isolated from *Plagiochila acanthophylla*,[12] feature highly strained 16-membered ring system[13] made up through biphenyl C-O ether and biaryl C-C bonds. Among them, in particular, plagiochin A (**1**) has been found to exhibit significant neurotrophic properties, e.g. promotion of neurite dendrites and network formation of neurons, and protection of neuronal death in the cultures of rat cortical neurons.[14] Their unique structural features and intriguing biological activity have stimulated our interest in the type 2 cyclic bis(bibenzyls) so that we have recently completed the synthesis of plagiochin D (**4**), the simplest number of the plagiochins.[15] In this paper, we report the full details of synthesis of plagiochin D (**4**), and the first synthesis of plagiochin A (**1**) having the highest degree of oxidative stage among the plagiochins as well as neurotrophic property.

Synthesis of Plagiochin D (4)

The first synthesis of **4** reported by Nogradi *et al.*[16] involved the Wurtz-type radical coupling at the position **b** for the crucial macrocyclization as shown in Figure 2. However, all the procedures for the ring formation at the position **b** including Nogradi's protocol suffered considerably poor yield.[17] According to the biosynthesis of marchantin A (**5**) proposed by Zenk *et al.*,[18] perrottetin-type seco compounds[19] such as **6** as shown in Figure 2 can be transformed into **4** by oxidative phenol couplings, but we failed our all attempts to construct the biaryl C-C bond at the position **a** based on this approach utilizing the biomimetic oxidative couplings. Hence, we turned our attention to employ intramolecular C-C cross coupling at the

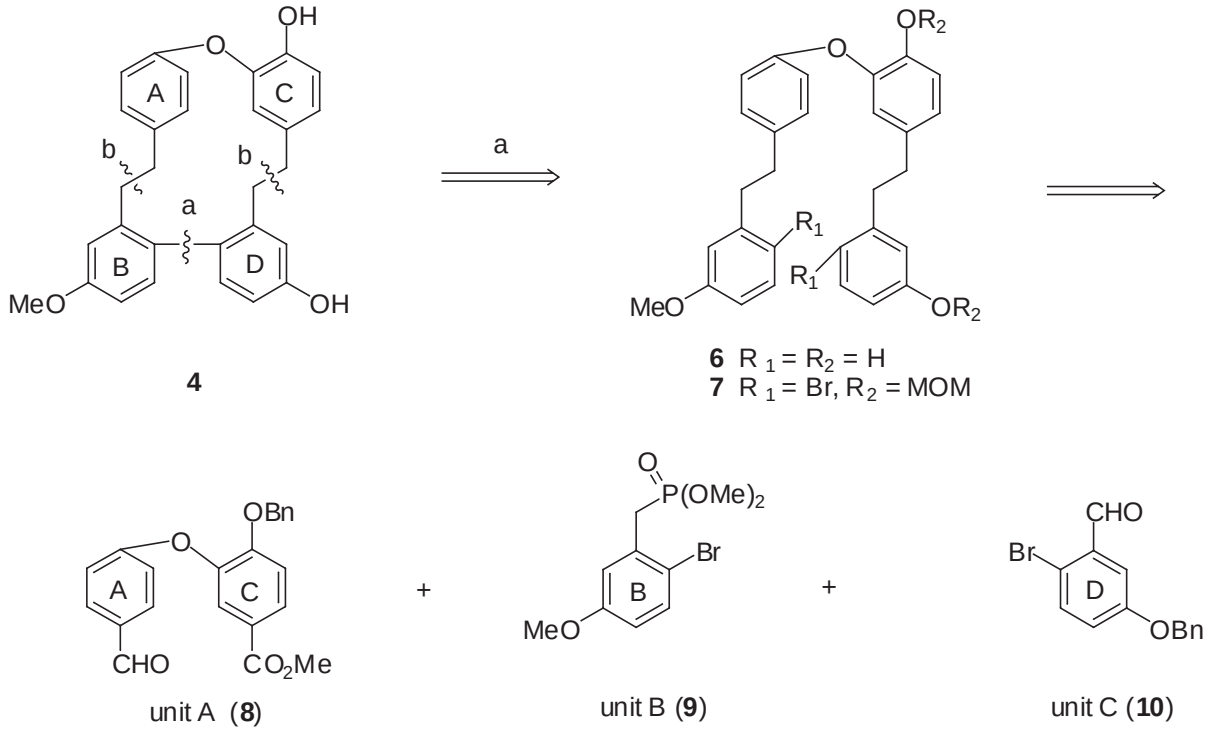
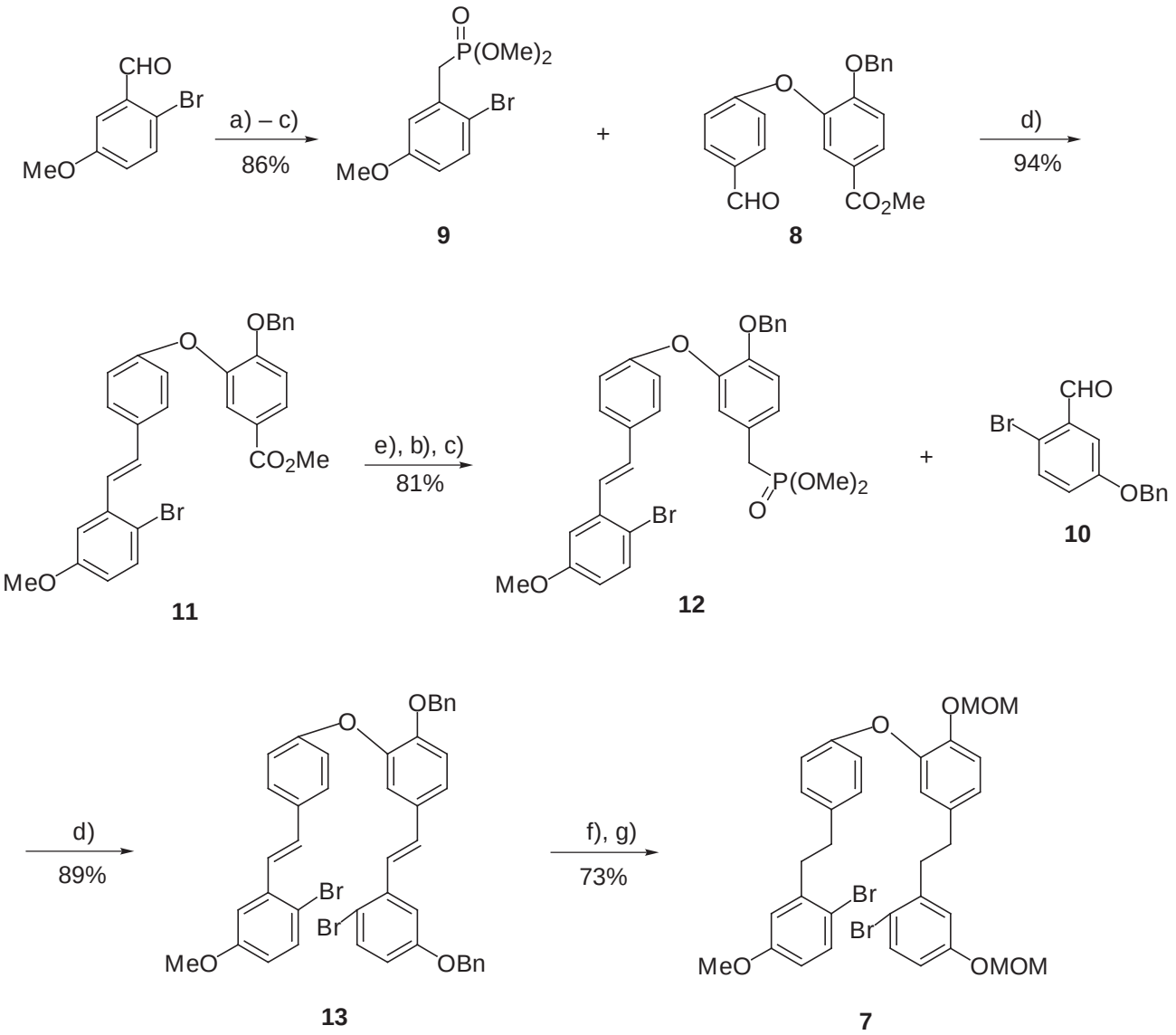


Figure 2 Synthetic plan of plagiochin D (**4**)

position **a** in halogenated bis(bibenzyl) (**7**) by using transition metals.

According to the procedure used for the synthesis of marchantin A (**5**),[9] dibromoperrottetin derivative (**7**), a key precursor for the crucial C-C bond formation and macrocyclization, was prepared as follows (Scheme 1). The unit A (**8**)[9] and the phosphonate **9** readily derivable from *o*-bromo-*m*-methoxy-benzaldehyde[20] were effectively combined by Wardworth-Emmons reaction using sodium hydride, giving rise to **11** in 94% yield. The ester group of **11** was reduced with lithium aluminum hydride to the hydroxy group, which was then brominated with tetrabromomethane/triphenylphsophine followed by heating with trimethyl phosphite to afford the phosphonate (**12**) in 81% yield. The Wardworth-Emmons reaction between **10** and **12** smoothly proceeded to yield the bis(dibromostilbene) (**13**) in 89%. Next catalytic hydrogenations of **13** were frustrated in the selective reduction of the double bonds by accompanying the debromination. After several attempts, **13** was cleanly hydrogenated over PtO_2 as catalyst and methylene

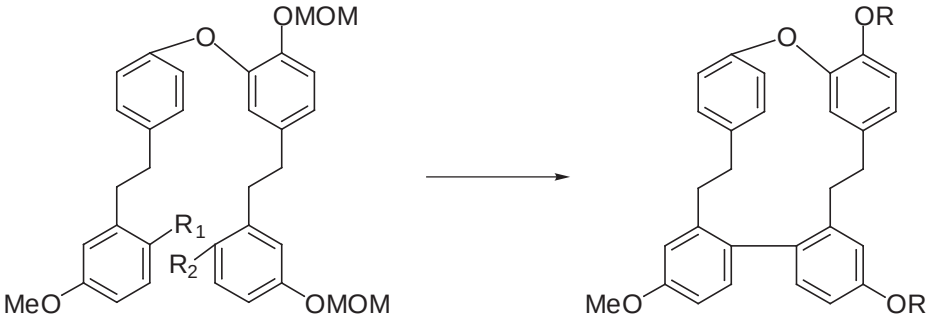


Reagents and conditions: a) $NaBH_4$, THF, 0˚C; b) CBr_4, Ph_3P, MeCN; c) $P(OMe)_3$, 90˚C
d) NaH, THF, 0˚C; e) $LiAlH_4$, THF, 0˚C; f) H_2, PtO_2, CH_2Cl_2; g) NaH, MOMCl, DMF

Scheme 1 Preparation of dibromobis(bibenzyls) (**7**)

chloride as solvent, giving rise to the seco compound (**7**) in 73% yield after protecting the liberated hydroxy groups as the MOM ethers. We are now in a position to employ key intramolecular aryl-aryl cross coupling reactions for the construction of the 16-membered ring.

For the first of all, Ni(0) mediated intramolecular coupling[21] which was recently utilized for the construction of the 12-membered biaryl ring system in vancomysin[22] as well as of the 17-membered biaryl ring system[23] was applied to the seco compounds (**7**) and (**14**) (Runs 1 and 2 in Table 1). Under Ni(0) mediated coupling conditions, no cross coupling proceeded to solely give the recovery and/or the reduced product (**17**).

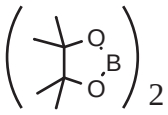


7 $R_1 = R_2 = Br$
14 $R_1 = R_2 = I$
15 $R_1 = Br$, $R_2 = SnMe_3$
16 $R_1 = SnMe_3$, $R_2 = Br$
17 $R_1 = R_2 = H$

18 R = MOM
4 R = H

Scheme 2 Synthesis of plagiochin D (**4**)

Table 1 Intramolecular Cross Coupling Reaction of (**7**) by Transition Metals

Run	Reagent (equiv.)	Solvent	Temp (˚C)	Yield (%)		
				7	**15** or **16**	**18**
1*	$Ni(PPh_3)_2Cl_2$ (1.2) Zn, PPh_3	DMF	160	100	-	0
2*	$Ni(PPh_3)_4$ (1.2)	DMF	160	100	-	0
3	 (1.1) $Pd(PPh_3)_4$ (0.05) dppf (0.1) KOAc (5.0)	toluene	120	100	-	0
4*	$(Me_3Sn)_2$ (1.1) $Pd(PPh_3)_4$ (0.05)	toluene	120	45	9	17
5	$(Me_3Sn)_2$ (1.1) $Pd(PPh_3)_4$ (0.05)	THF	60	41	10	0

* also using **14**.

On the other hand, the intramolecular Suzuki-Miyaura Pd(0) catalyzed reaction for **7** using bis(pinacolate)diborane[24] was also fruitless (Run 3). In contrast, the intramolecular version of Stille-Kelly reaction[25] led **7** to the crucial cross coupling (Run 4). A diluted solution of **7** was heated at 120˚C with 1.1 equivalent of hexamethylditin and 5 mol% tetrakis(triphenylphosphine)palladium in a sealed tube to afford the cyclized product (**18**) in 17% yield along with a mixture of trimethylstannyl compounds (**15**) and (**16**) (9%) and the recovered (**7**) (45%). The cyclization of the diiodide (**14**)[26] under the same conditions was comparable to that of **7**, but no cross coupling reaction could be affected in other solvents (THF, DMF and MeCN) except for toluene. The key intermediate for this ring closure can be regarded as the isolated trimethylstannyl compounds (**15**) and (**16**). In fact, a diluted solution of **15** and **16** in toluene was again heated at 120˚C with 5 mol% tetrakis(triphenylphosphine)palladium in a sealed tube, resulting in the formation of the biaryl system (**18**) in 20% yield. Finally, removal of the MOM groups in **18** with 47% HBr in MeOH afforded plagiochin D (**4**) in 87% yield. Its spectral data were superimposable with those of natural plagiochin D.

Synthesis of Plagiochin A (1)

As the intramolecular Stille-Kelly reaction was proved to be quite useful for the crucial 16-membered ring formation at the position **a** in the plagiochins, we applied this methodology to our synthesis of neurotrophic plagiochin A (**1**), the highest substitueted member of the plagiochins.

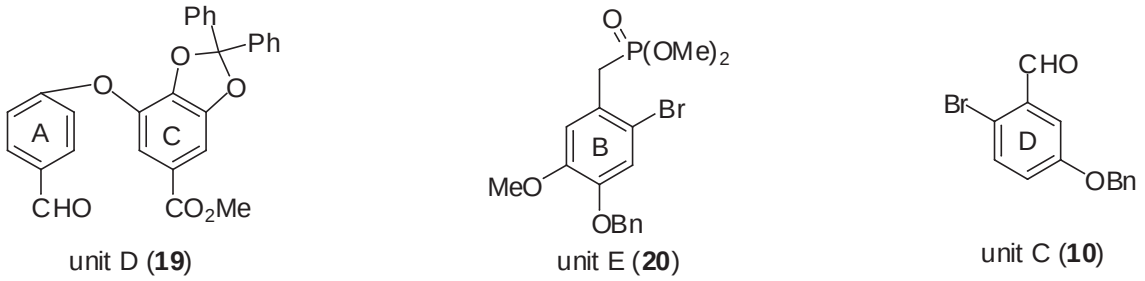
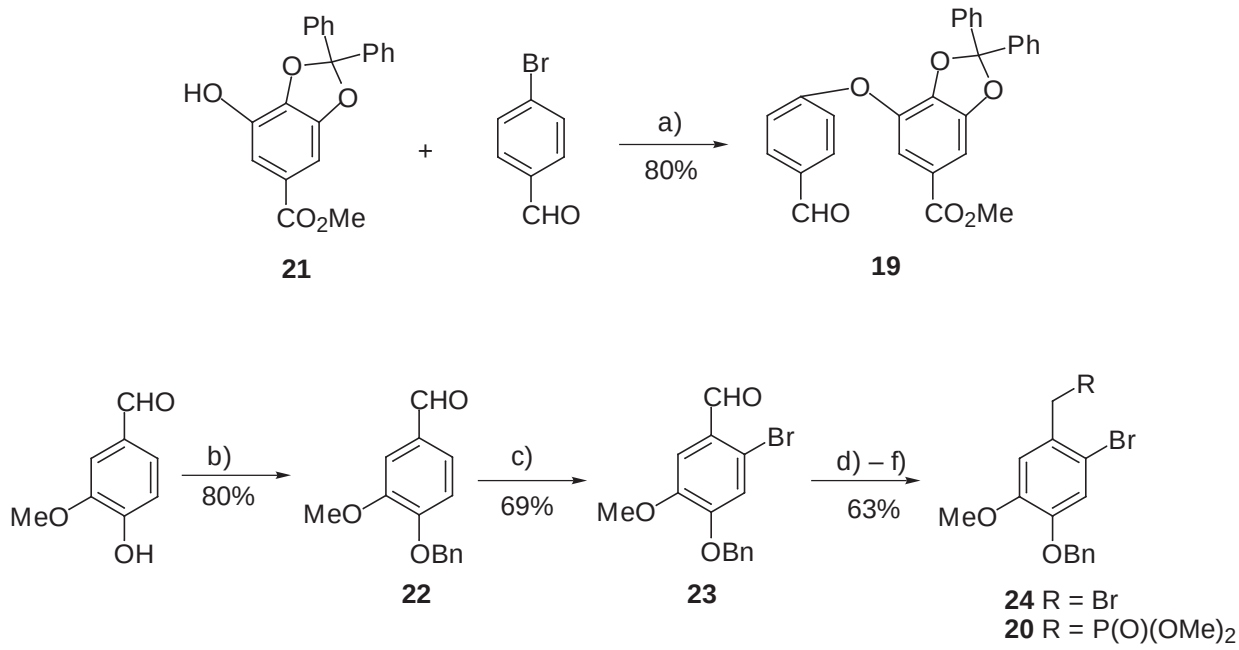


Figure 3 Units required for synthesis of plagiochin A (**1**)

We need to prepare units D and E as shown in Figure 3, which are to be assembled with unit C (**10**), according to similar sequence used for the synthesis of **4**, to attain **1**. Thus, the synthesis of **1** began with the preparation of unit D (**19**) and unit E (**20**) as shown in Scheme 3. The diphenyl acetal (**21**) of methyl gallate[27] was coupled with *p*-bromobenzaldehyde under Ullmann condition (K_2CO_3 and CuO in pyridine under reflux) to give rise to the unit D (**19**) in 80% yield. The unit E (**20**) was readily derived from vanillin in five steps by the process as shown in Scheme 3. Thus the obtained **19** and **20** were coupled by Wardwoth-Emmons reaction using sodium hydride in THF to afford **25** in 63% yield. The methyl ester (**25**) was converted to the phosphonate (**26**) in 52% yield by $LiAlH_4$ reduction and bromination with thionyl bromide, followed by heating with trimethyl phosphite. The phosphonate (**26**) was again subjected

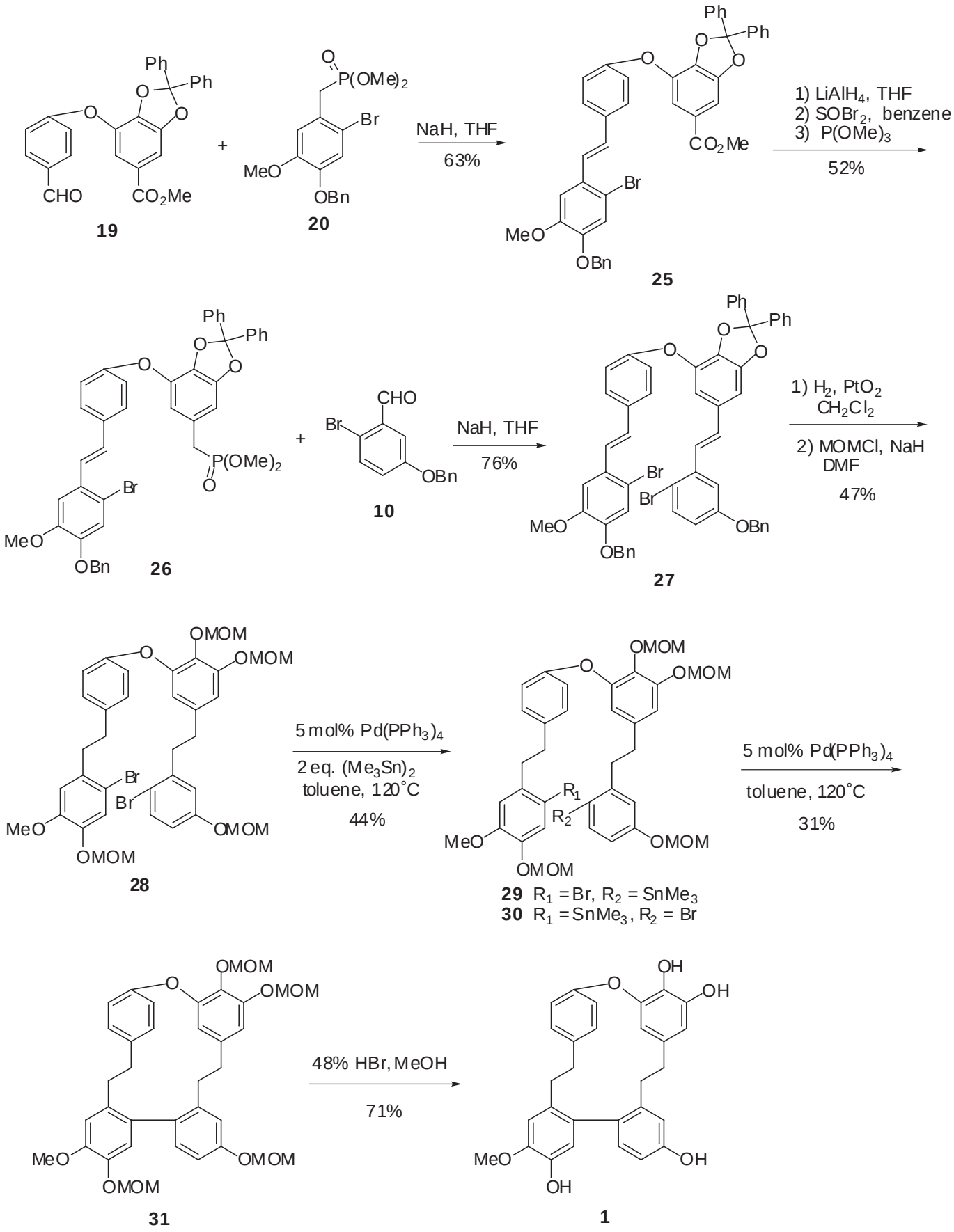


Reagents and conditions: a) CuO, K_2CO_3, pyridine, 145˚C; b) BnBr, *i*Pr_2NEt, DMF; c) Br_2, AcONa, AcOH; d) $NaBH_4$, THF: e) CBr_4, PPh_3, MeCN; f) $P(OMe)_3$.

Scheme 3 Preparation of units D (**19**) and E (**20**)

to Wardworth-Emmons reaction with unit C (**10**), thereby giving rise to the key compound (**27**) having all the benzene rings required for the synthesis of **1** in 76% yield. The double bonds in **27** were hydrogenated over PtO_2 in CH_2Cl_2 to yield the seco compound (**28**) in 47% yield after protecting the liberated hydroxy groups as the MOM groups. Cross coupling of the dibromide (**28**) was attempted under the same Stille-Kelly conditions successfully used for the direct ring closure of **7**. In the case of **28**, however, no direct cyclization proceeded, but only metal exchanges took place to yield a mixture of the trimethylstannyl compounds (**29**) and (**30**) in 44% yield. A diluted solution of a mixture of **29** and **30** in toluene was again heated at 120˚C with 5 mol% tetrakis(triphenylphosphine)palladium in a sealed tube, thereby yielding the cyclized product (**31**) in 31% yield. After all, the key macrocyclization of **28** was achieved by employing, in turn, Stille-Kelly and Stille reactions. Deprotection of the MOM groups in **31** with 48% HBr afforded **1**, which was identical in all respects with natural plagiochin A.

In conclusion, we have synthesized plagiochin D (**4**), the simplest member of the type 2 macrocyclic bis(bibenzyls), by using an intramolecular Stille-Kelly reaction for the construction of the rigid 16-membered biaryl ring system, and then have been succeeded in the first synthesis of the most biologically intriguing plagiochin A (**1**) by applying the established methodology. Neurotrophic properties for plagiochin A will be reported in due time.



Scheme 4 Synthesis of plagiochin A (**1**)

EXPERIMENTAL

Melting points were determined on a Yanagimoto MPJ-2 micro melting-point apparatus and were uncorrected. IR spectra were on a JASCO FT-IR 5300 spectrophtometer. ^{1}H NMR spectra were recorded on Varian Gemini-200 and Unity-200, and JEOL ECP-400 instruments in $CDCl_3$ solution with TMS as an internal standard. MS spectra were measured on a JEOL AX-500 spectrometer. Thin-layer chromatography was performed on Merck Kiselgel $60F_{254}$ precoated silica gel plates, and spots were visualized by irradiation with UV (254 nm) and/ or by spraying with $Ce_2(SO_4)_3$-H_2SO_4 followed by heating. Column chromatography was performed with silica gel (Wakogel C-300).

THF was distilled from sodium-benzophenone and other solvents were distilled from calcium hydride.

Dimethyl [(2-bromo-5-methoxyphenyl)methyl]phosphonate (9). To a solution of 2-bromo-5-methoxy-benzaldehyde (4.72 g, 21.8 mmol) in THF (20 mL) was slowly added $NaBH_4$ (990 mg, 26.2 mmol) at 0˚C. After being stirred for 4 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed successively with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeCN (50 mL). To this solution was added triphenylphosphine (11.4 g, 43.6 mmol) and CBr_4 (14.4 g, 43.6 mmol). The mixture was stirred at rt overnight, and then concentrated *in vacuo* to leave the residue, which was chromatographed on silica gel (200 g) with hexane-EtOAc (3:1) to afford 2-bromo-5-methoxybenzylbromide (5.42 g, 89%) as colorless needles (mp 88˚C). A mixture of this dibromide (5 g , 17.9 mmol) and trimethyl phosphite (7 mL) was heated at 90˚C with stirring for 2 h. After being cooled to rt, the reaction mixture was directly chromatographed on silica gel (240 g) with EtOAc to give unit B (**9**) (5.34 g, 97%) as a colorless oil: IR 1600, 1580, 1480 cm^{-1}; ^{1}H NMR (200 MHz) δ 3.38 (2H, d, *J* = 22.2 Hz), 3.69 (3H, s), 3.75 (3H, s), 3.79 (3H, s), 6.70 (1H, m), 7.00 (1H, s), 7.45 (1H, m); EIMS *m/z* (rel. int.) 310 (M^+, 4), 308 (M^+, 4), 229 (100); HRMS (EI) calcd for $C_{10}H_{14}O_4BrP$ 307.9813, found: 307.9788.

Methyl 3-(4-formylphenoxy)-4-benzyloxybenzoate (8). A mixture of methyl 3-hydroxy-4-benzoate (1.5 g, 5.64 mmol), *p*-bromobenzaldehyde (1.26 g, 6.78 mmol), anhydrous K_2CO_3 (1.56 g, 11.3 mmol) and anhydrous pyridine (30 mL) was heated with stirring at 90˚C for 10 min. To this solution was added cupric oxide (1.14 g, 14.1 mmol). The reaction mixture was vigorously stirred at 145˚C for 2 days. After being cooled to rt, the reaction solution was filtered, and concentrated *in vacuo* to leave the residue. CH_2Cl_2 was added to the residue. The obtained organic layer was washed successively with saturated $Cu(NO_3)_2$, saturated $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the residue (6.0 g), which was chromatographed on silica gel (240 g) with CH_2Cl_2-hexane (3:1) to afford **8** (1.42 g, 81%) as yellow color prisms: mp 94˚C (MeOH); IR 1715, 1610, 1600, 1580 cm^{-1}; FABMS *m/z* 385 (M^+ + Na), 363 (M^+ + 1); ^{1}H NMR (200 MHz) δ 3.89 (3H, s), 5.11 (2H, s), 7.00 (2H, d, *J* = 8.8 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.10 (1H, d, *J* = 8.8 Hz), 7.25 (3H, m), 7.83 (2H, d, *J* = 8.8 Hz), 7.84 (1H, d, *J* = 1.8 Hz), 7.92 (1H, dd, *J* = 8.8, 1.8 Hz), 9.92 (1H, s); HRMS (FAB) calcd for $C_{22}H_{19}O_5$ 363.1233, found: 363.1248; Anal. Cacld for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.85; H, 5.13.

(*E*)-1-[4-(2-Benzyloxy-5-methoxycarbonylphenoxy)phenyl]-2-[2-bromo-5-methoxyphenyl]ethene (11). A solution of **9** (1.5 g, 4.8 mmol) in THF (5 mL) was added to a suspension of 60% NaH (200 mg, 5.0 mmol) in THF (10 mL) at 0˚C. After 30 min at 0˚C, a solution of **8** (1.4 g, 4.5 mmol) in THF (5 mL) was added over 30 min. After being stirred at rt overnight, the reaction mixture was poured into an ice-water and extracted with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g) with hexane-EtOAc (3:2) to afford **11** (2.26 g, 94%) as a yellow color amorphous material: IR 1715, 1590, 1500 cm^{-1}; EIMS *m/z* (rel. int.) 546 (M^+, 65), 544 (M^+, 64), 374 (23), 256 (26); ^{1}H NMR (200 MHz) δ 3.85 (3H, s), 3.87 (3H, s), 5.16 (2H, s), 6.71 (1H, dd, *J* = 8.8, 2.9 Hz), 6.92 – 7.52 (10H, m), 7.23 (1H, d, *J* = 15.8 Hz), 7.48 (1H, d, *J* = 15.8 Hz), 7.77 (1H, d, *J* = 2.0 H z), 7.85 (1H, dd, *J* =8.8, 2.0 Hz); HRMS (EI) calcd for $C_{30}H_{25}O_5Br$ 544.0886, found: 544.0848.

(*E*)-1-[[4-(2-Benzyloxy-5-dimethylphosphonomethyl)phenoxy]phenyl]-2-[2-bromo-5-methoxyphenyl]ethene (12). A solution of **11** (720 mg, 1.32 mmol) in THF (1 mL) was added to a suspension of $LiAlH_4$ (76 mg, 1.59 mmol) at 0˚C. After being stirred at rt overnight, EtOAc, water, $MgSO_4$and celite were successively added to the reaction mixture and filtered. The filtrate was concentrated *in vacuo* to give the residue, which was dissolved in MeCN. To this solution were added triphenyl phosphine (520 mg, 1.98 mmol), and CBr_4 (657 mg, 1.98 mmol). The reaction mixture was stirred at rt overnight and then concentrated *in vacuo* to give the residue, which was purified by chromatography on silica gel (30 g) eluting with hexane-EtOAc (4:1) to afford the dibromide (620 mg). This was heated in trimethyl phosphite (0.5 mL) at 90˚C for 2 h. The crude product obtained by the same work-up as described in the preparation of **9** was chromatographed on silica gel (20 g) with EtOAc to yield **12** (651 mg, 81%) as a colorless oil. IR 1590, 1505 cm^{-1}; EIMS *m/z* (rel. int.) 610 (M^+, 100), 608 (M^+, 95), 438 (68), 320 (29); ^{1}H NMR (200 MHz) δ 3.09 (2H, d, *J* = 21.4 Hz), 3.65 (3H, s), 3.70 (3H, s), 3.84 (3H, s), 5.07 (2H, s), 6.71 (1H, dd, *J* = 8.8, 2.9 Hz), 6.92–7.51 (14H, m); HRMS (EI) calcd for $C_{31}H_{30}O_6BrP$ 608.0964, found: 608.0955.

2-Bromo-5-benzyloxybenzaledyde (10). To a solution of 3-benzyloxybenzaldehyde (200 mg, 0.92 mmol) in acetic acid (6 mL) containing sodium acetate (200 mg) was added a solution of bromine (0.6 mL, 1.1 mmol) in acetic acid (2 mL) at 40˚C. After being stirred at 40˚C for 11 h, ether was added. The solution was washed successively with 2M NaOH, water and brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was chromatographed on silica gel (24 g) with hexane-EtOAc (4:1) to afford **10** (184.8 mg, 68%) as a yellow color oil. IR 1695, 1590, 1485 cm^{-1}; EIMS *m/z* (rel. int.) 292 (M^+, 17), 290 (M^+, 17), 262 (33), 208 (23), 183 (27); ^{1}H NMR (200 MHz) δ 5.09 (2H, s), 7.10 (1H, dd, *J* = 8.8, 3.2 Hz), 7.34–7.43 (5H, m), 7.51 (1H, d, *J* = 3.2 Hz), 7.53 (1H, d, *J* = 8.8 Hz), 10.30 (1H, s); HRMS (EI) calcd for $C_{14}H_{11}O_2Br$ 289.9942, found: 289.9855.

Wardworth-Emmons reaction between 12 and 10.

A solution of **12** (490 mg, 0.82 mmol) in THF (2 mL) was added to a suspension of 60% NaH (60 mg, 1.50 mmol) in THF (4 mL) at 0˚C. After 30 min at 0˚C, a solution of **10** (226 mg, 0.74 mmol) in THF (2 mL) was added over 30 min. After being stirred at rt overnight, the reaction mixture was poured into an ice-water and extracted with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product obtained by the same work-up as described in the preparation of **11** was chromatographed on silica gel (60 g) with hexane-$CHCl_3$ (1:1) to yield **13** (560 mg, 89%) as a colorless amorphous powder. IR 1590, 1500 cm^{-1}; EIMS *m/z* (rel. int.) 776 (M^+, 23), 774 (M^+, 63), 772 (M^+, 19), 604 (17), 432 (10); ^{1}H NMR (200 MHz) δ 3.84 (3H, s), 5.08 (2H, s), 5.11 (2H, s), 6.68–7.53 (27H, m); HRMS (EI) calcd for $C_{43}H_{34}O_4Br_2$ 772.0824, found: 772.0804.

Hydrogenation of 13. A solution of **13** (195 mg, 0.25 mmol) in CH_2Cl_2 (6 mL) was hydrogenated over PtO_2 (80 mg) under atmospheric pressure at rt. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (20 g) with $CHCl_3$-EtOAc (9:1) to afford the reduced product, which was dissolved in DMF (2 mL). This solution was added to a solution of 60% NaH (48 mg, 1.2 mmol) at 0˚C under argon. After being stirred at 0˚C for 30 min, chloromethyl methyl ether (0.1 mL, 1.2 mmol) was added. The reaction mixture was stirred at rt for 14 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (6 g) with $CHCl_3$-hexane (9:1) to afford **7** (125 mg, 74%) as a colorless oil. IR 1574, 1508 cm^{-1}; EIMS *m/z* (rel. int.) 688 (M^+, 50), 686 (M^+, 90), 684 (M^+, 47), 485 (42), 425 (100), 211 (50); ^{1}H NMR (200 MHz) δ 2.82 - 2.98 (8H, m), 3.43 (3H, s), 3.44 (3H, s), 3.74 (3H, s), 5.09 (2H, s), 5.14 (2H, s), 6.64 (1H, dd, *J* = 8.4, 2.9 Hz), 6.71 (1H, d, *J* = 2.9 Hz), 6.76 (1H, dd, *J* = 8.4, 2.9 Hz), 6.78 - 6.89 (4H, m), 6.94 (1H, dd, *J* = 8.4, 2.0 Hz), 7.12 (1H, d, *J* = 1.8 Hz), 7.16 (1H, d, *J* = 1.1 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 7.42 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (50 MHz) δ 35.1, 35.2, 38.4, 38.6, 55.3, 55.9, 56.1, 94.4, 95.5, 113.2, 114.8, 115.8, 116.1, 117.8, 118.3, 121.2, 124.5, 129.5, 133.2, 133.3, 135.4, 136.2, 141.7, 141.8, 146.1, 146.9, 156.2, 156.5, 158.8; HRMS (EI) calcd for $C_{33}H_{34}O_6Br_2$ 684.0710, found: 684.0722.

Intramolecular Stille-Kelly reaction of 7. To a solution of **7** (50 mg, 0.073 mmol) in toluene (10 mL) was added hexamethylditin (26 mg, 0.08 mmol) and tetrakis(triphenylphosphine)palladium (4.2 mg, 0.0037 mmol). The reaction mixture in a sealed tube was heated at 120˚C for 24 h. After being filtered and concentrated *in vacuo*, the crude product was purified by prep. TLC (hexane-EtOAc, 2:1) to yield **18** (7 mg, 17%), a mixture of **15** and **16** (2.7 mg, 9%) and the recovery **7** (11.7 mg, 45%) as a colorless oil, respectively. **18**: IR 1606, 1504, 1224, 1153 cm^{-1}; EIMS *m/z* (rel. int.) 526 (M^+, 100), 449 (12), 225 (49); ^{1}H NMR (400 MHz) δ 2.10 (1H, m), 2.87–2.91 (3H, m), 3.05–3.12 (4H, m), 3.45 (3H, s), 3.57 (3H, s), 3.89 (3H, s), 5.12 (2H, s), 5.27 (2H, s), 5.30 (1H, d, *J* = 1.8 Hz), 6.68–6.78 (5H, m), 6.84 (1H, d, *J* = 8.3 Hz), 6.95 (3H, m), 7.02 (1H, d, *J* = 8.3 Hz), 7.03 (1H, d, *J* = 8.3 Hz), 7.21 (1H, d, *J* = 2.4 Hz); HRMS (EI) calcd for $C_{33}H_{34}O_6$ 526.2355, found: 526.2364.

15 and **16**: EIMS *m/z* (rel. int.) 754 (M^+, 20).

Intramolecular Stille reaction of 15 and 16. To a solution of **15** and **16** (13.0 mg, 0.016 mmol) in toluene (2 mL) was added tetrakis(triphenylphosphine)palladium (0.5 mg). The reaction mixture in a sealed tube was heated at 120˚C for 12 h. After being filtered and concentrated, the obtained product was subjected to prep. TLC (hexane-EtOAc, 2:1) to afford **18** (3 mg, 20%).

Plagiochin D (4). A solution of **18** (1.8 mg, 0.034 mmol) in methanol (1 mL) containing one drop of 48% HBr was stirred at 50˚C for 15 min. The reaction mixture was concentrated *in vacuo* to give the residue, which was purified by prep. TLC (hexane-EtOAc, 2:1) to afford plagiochin D (**4**) (1.3 mg, 87%) as a colorless oil. Its spectral data shown below were identical with those of natural plagiochin D.

IR 3404, 1604, 1228 cm^{-1}; EIMS *m/z* (rel. int.) 438 (M^+, 100), 332 (11), 225 (53), 213 (38); ^1H NMR (400 MHz) δ 2.16 (1H, m), 2.71–3.05 (7H, m), 3.82 (3H, s), 4.58 (1H, s), 5.17 (1H, d, *J* = 1.8 Hz), 5.39 (1H, s), 6.45 (1H, d, *J* = 2.6 Hz), 6.56 (1H, dd, *J* = 8.4, 2.6 Hz), 6.63 (1H, dd, *J* = 8.4, 2.7 Hz), 6.65 (1H, dd, *J* = 8.1, 1.8 Hz), 6.67 (1H, dd, *J* = 8.8, 2.6 Hz), 6.75 (1H, d, *J* = 8.1 Hz), 6.83 (1H, d, *J* = 8.4 Hz), 6.85 (1H, dd, *J* = 8.4, 2.6 Hz), 6.90 (1H, dd, *J* = 8.4, 2.6 Hz), 7.01 (1H, d, *J* = 8.8 Hz), 7.11 (1H, d, *J* = 2.6 Hz); HRMS (EI) calcd for $C_{29}H_{26}O_4$ 438.1797, found: 438.1763.

Methyl 4,5-diphenylmethylenedioxy-3-(4-formylphenoxy)benzoate (19). According to the same procedure used for the preparation of **8**, **19** (2.94 g, 80%) was prepared from **21** (1.5 g, 5.64 mmol), *p*-bromobenzaldehyde (1.26 g, 6.78 mmol), anhydrous K_2CO_3 (1.56 g, 11.3 mmol), cupric oxide (1.14 g, 14.1 mmol) and pyridine (30 mL). **19**: IR 1720, 1700, 1600, 1590, 1505 cm^{-1}; EIMS *m/z* (rel. int.) 452 (M^+, 73), 375 (100), 331 (16), 165 (20); ^1H NMR (200 MHz) δ 3.87 (3H, s), 7.04 (2H, d, *J* = 8.8 Hz), 7.32–7.59 (12H, m), 7.83 (2H, d, *J* = 8.8 Hz), 9.95 (1H, s); HRMS (EI) calcd for $C_{28}H_{20}O_6$ 452.1259, found: 452.1248.

3-Methoxy-4-phenylmethoxybenzaldehyde (22). To a cooled (0˚C) solution of vanillin (10.0 g, 65.7 mmol) in DMF (30 mL) was successively added *N*,*N*-diisopropylethylamine (11.5 mL, 65.7 mmol) and benzyl bromide (7.8 mL, 65.7 mmol). After being stirred at rt overnight, the reaction mixture was diluted with water and extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (420 g) with hexane-EtOAc (2:1) to afford **22** (13.0 g, 80%) as colorless plates: mp 63˚C (MeOH); IR 1680, 1590, 1510 cm^{-1}; EIMS *m/z* (rel. int.) 242 (M^+, 58), 91 (100); ^1H NMR (200 MHz) δ 3.93 (3H, s), 5.23 (2H, s), 6.97 (1H, d, *J* = 8.2 Hz), 7.30–7.46 (7H, m), 9.82 (1H, s); HRMS (EI) calcd for $C_{15}H_{14}O_3$ 242.0943, found: 242.0923.

2-Bromo-5-methoxy-4-benzyloxybenzaldehyde (23). To a solution of **22** (1.1 g, 4.55 mmol) in acetic acid (11 mL) containing sodium acetate (1.1 g) was added bromine (0.58 mL, 11.4 mmol). The reaction mixture was stirred at 40˚C for 11 h. After being cooled to rt, ether was added. The solution was washed with 2M NaOH, water and brine, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was

chromatographed on silica gel (24 g) with hexane-EtOAc (4:1) to afford **23** (999 mg, 69%) as colorless prisms: mp 98˚C (MeOH); IR 1670, 1580, 1495 cm^{-1}; EIMS *m/z* (rel. int.) 322 (M^+, 32), 320 (M^+, 33); ^1H NMR (200 MHz) δ 3.92 (3H, s), 5.20 (2H, s), 7.10 (1H, s), 7.36–7.45 (6H, m), 10.18 (1H, s); HRMS (EI) calcd for $C_{15}H_{13}BrO_3$ 320.0048, found: 320.0051.

5-Bromo-4-bromomethyl-1-benzyloxy-2-methyloxybenzene (24). To a solution of **23** (5.77 g, 18.0 mmol) in THF (35 mL) was added $NaBH_4$ (0.82 g, 21.6 mmol) at 0˚C. After being stirred for 4 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The obtained crude alchohol was dissolved in MeCH (40 mL), and then CBr_4 (8.96 g, 27.0 mmol) and triphenylphosphine (7.1 g, 27.0 mmol) were added. The reaction solution was stirred at rt overnight, and then concentrated *in vacuo* to leave the residue, which was chromatographed on silica gel (180 g) with hexane-$CHCl_3$ (1:1) to afford **24** (4.33 g, 63%) as white needles: mp 110˚C (from hexane-$CHCl_3$); IR 1505, 1208, 1013 cm^{-1}; EIMS *m/z* (rel. int.) 387 (M^+, 5), 385 (M^+, 9), 383 (M^+, 5), 307 (22), 91 (100); ^1H NMR (200 MHz) δ 3.88 (3H, s), 4.58 (2H, s), 5.12 (2H, s), 6.95 (1H, s), 7.07 (1H, s), 7.35–7.42 (5H, m); Anal. Cacld for $C_{15}H_{14}O_2Br_2$: C, 46.66; H, 3.65. Found C, 46.80; H, 3.72.

Dimethyl 2-bromo-4-benzyloxy-5-methoxybenzylphosphonate (20). A mixture of **24** (100 mg, 0.26 mmol) and trimethylphosphite (1 mL) was stirred at 90˚C for 3 h. The reaction mixture was chromatographed on silica gel (5 g) with EtOAc to give **20** (116.6 mg, 100%) as white needles: mp 69˚C (from hexane-CH_2Cl_2); EIMS *m/z* (rel. int.) 416 (M^+, 13), 414 (M^+, 13), 335 (36), 109 (20); ^1H NMR (200 MHz) δ 3.33 (2H, d, *J* = 21.6 Hz), 3.68 (3H, s), 3.73 (3H, s), 3.87 (3H, s), 5.10 (2H, s), 7.00 (1H, d, *J* = 2.6 Hz), 7.07 (1H, s), 7.34–7.42 (5H, m); Anal. Cacld for $C_{17}H_{20}O_5BrP$: C, 49.17; H, 4.86. Found: C, 49.26; H, 4.90.

(*E*)-1-[[4-(5-Methoxycarbonyl-2,3-diphenylmethylenedioxy)phenoxy]phenyl]-2-[2-bromo-4-benzyloxy-5-methoxyphenyl]ethene (25). A solution of **20** (3.37 g, 8.15 mmol) in THF (10 mL) was added to a suspension of 60% NaH (341.6 mg, 8.54 mmol) in THF (17 mL) at 0˚C. After 30 min at 0˚C, a solution of **19** (2.94 g, 7.76 mmol) in THF (10 mL) was added over 30 min. After being stirred at rt overnight, the reaction mixture was poured into an ice-water and extracted with EtOAc. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (200 g) with $CHCl_3$ to afford **25** (3.18 g, 63%) as white prisms: mp 186˚C (from hexane-CH_2Cl_2); IR 1718, 1504, 1207 cm^{-1}; FABMS *m/z* 742 (M^+), 740 (M^+); ^1H NMR (200 MHz) δ 3.85 (3H, s), 3.95 (3H, s), 5.14 (2H, s), 6.67 (2H, d, *J* = 8.8 Hz), 7.10 (1H, s), 7.35–7.52 (21H, m); HRMS (FAB) calcd. for $C_{43}H_{33}O_7Br$ 740.1410, found: 740.1425; Anal. Cacld for $C_{43}H_{33}BrO_7$: C, 69.64; H, 4.49. Found: C, 69.91; H, 4.50.

(*E*)-1-[[4-(5-Dimethylphosphonomethyl-2,3-diphenylmethylenedioxy)phenoxy]phenyl]-2-[2-bromo-

4-benzyloxy-5-methoxyphenyl]ethene (26). A solution of **25** (3.18 g, 4.30 mmol) of THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (280 mg, 5.81 mmol) in THF (40 mL) at 0˚C. The reaction mixture was stirred at rt for 12 h and then diluted with EtOAc. To this solution were added water, $MgSO_4$ and celite. After the solid was filtered off, the filtrate was concentrated *in vacuo* to yield the alcohol (3.07 g, 100%). This alcohol (1.86 g, 2.79 mmol) was dissolved in benzene (60 mL). To this solution was added thionyl bromide (0.19 mL, 2.79 mmol). The reaction mixture was stirred for 20 min, and then poured into an ice-water. The benzene layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the residue, to which trimethyl phsophite (0.99 mL, 8.37 mmol) was added. The reaction mixture was stirred at 90˚C for 3 h, and then directly purified by chromatography on silica gel (70 g) eluting with hexane-EtOAc (1:9) to afford **26** (1.05 g, 52%) as white powder: mp 159˚C (from hexane-CH_2Cl_2); IR 1601, 1504, 1263 cm^{-1}; EIMS *m/z* (rel. int.) 804 (M^+, 5), 713 (7), 313 (13), 252 (40), 182 (51); ^1H NMR (200 MHz) δ 3.03 (2H, d, *J* = 21.2 Hz), 3.66 (3H, s), 3.71 (3H, s), 3.95 (3H, s), 5.14 (2H, s), 6.54 (1H, s), 6.73 (1H, s), 6.87–6.89 (2H, m), 6.96 (2H, d, *J* = 8.1 Hz), 7.10 (1H, s), 7.17 (1H, s), 7.26–7.52 (17H, m); Anal. Cacld for $C_{44}H_{38}O_8Br$: C, 65.60; H, 4.75. Found: C, 66.02; H, 4.85.

Wardworth-Emmons reaction between 26 and 10. A solution of **26** (870 mg, 1.08 mmol) in THF (2 mL) was added to a suspension of 60% NaH (100 mg, 2.50 mmol) in THF (6 mL) at 0˚C. After 30 min at 0˚C, a solution of 2-bromo-5-benzyloxybenzaldehyde (530 mg, 1.82 mmol) in THF (2 mL) was added over 30 min. After being stirred at rt for 12 h, the crude product obtained by the same work-up as described in the preparation of **11** was chromatographed on silica gel (40 g) with hexane-$CHCl_3$ (3:2) to afford **27** (745 mg, 76%) as white powder: mp 189˚C (from hexane-CH_2Cl_2); IR 1599, 1504 cm^{-1}; ^1H NMR (200 MHz) δ 3.95 (3H, s), 5.06 (2H, s), 5.14 (2H, s), 6.72–6.78 (2H, m), 6.87 (2H, d, *J* = 4.8 Hz), 6.97 (1H, d, *J* = 4.4 Hz), 7.03–7.04 (2H, m), 7.11 (1H, s), 7.17–7.19 (2H, m), 7.33–7.55 (22H, m).

Hydrogenation of 27. A solution of **27** (585 mg, 0.60 mmol) in CH_2Cl_2 (12 mL) was hydrogenated over PtO_2 (150 mg) under atmospheric pressure at rt. After the catalyst was filtered off, the filtrate was concentrated *in vacuo* to give the product (190 mg), which was dissolved in DMF (2 mL). To this solution was added 60% NaH (154 mg, 4.0 mmol) at 0˚C. After being stirred for 30 min, chloromethyl methyl ether (0.3 mL, 4.0 mmol) was added. The reaction mixture was stirred at rt for 14 h, and then diluted with water, extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the residue, which was chromatographed on silica gel (20 g) with hexane-EtOAc (2:1) to afford **28** (216.7 mg, 47%) as a colorless oil. IR 1587, 1504, 1155 cm^{-1}; ^1H NMR (200 MHz) δ 2.76–2.97 (8H, m), 3.44 (3H, s), 3.51 (3H, s), 3.52 (3H, s), 3.53 (3H, s), 3.79 (3H, s), 5.09 (2H, s), 5.11 (2H, s), 5.18 (2H, s), 5.20 (2H, s), 6.47 (1H, d, *J* = 1.9 Hz), 6.63 (1H, s), 6.73–6.80 (3H, m), 6.87 (2H, d, *J* = 8.6 Hz), 7.13 (2H, d, *J* = 8.6 Hz), 7.33 (1H, s), 7.49 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (50 MHz) δ 35.6, 35.7, 38.2 (x2), 55.9, 56.0, 56.2, 57.0, 94.5, 95.4, 95.7, 98.5, 112.1, 113.6, 114.3, 115.9, 116.1, 117.4, 118.3, 120.6, 129.6, 133.3, 134.6, 135.7, 137.7, 141.5, 145.3, 149.0, 149.9, 151.3, 155.8, 156.5.

Intramolecular Stille-Kelly reaction of 28. A mixture of **28** (50 mg, 0.062 mmol), hexamethylditin (50 mg, 0.16 mmol) and tetrakis(triphenylphosphine)palladium (3.5 mg, 0.0031 mmol) in toluene (6 mL) was heated in a sealed tube at 120˚C for 48 h. After the catalyst was filtered off, the reaction mixture was concentrated *in vacuo* to give the residue, which was purified by prep. TLC (hexane-EtOAc, 1:1) to afford a mixture of **29** and **30** (13 mg, 44%). A mixture of **29** and **30** was dissolved in toluene (2 mL) and then tetrakis(triphenylphosphine)palladium (0.5 mg) was added under argon. This mixture was heated in a sealed tube at 120˚C for 20 h and then was concentrated *in vacuo* to give the residue, which was purified by prep. TLC (hexane-EtOAc, 2:1) to afford **31** (3 mg, 31%) as an oil. ^{1}H NMR (200 MHz) δ 2.05 (1H, m), 2.82–3.09 (7H, m), 3.44 (3H, s), 3.45 (3H, s), 3.53 (3H, s), 3.67 (3H, s), 4.01 (3H, s), 4.99 (1H, br s), 5.11 (2H, s), 5.15 (2H, d, *J* = 4.0 Hz), 5.21 (2H, d, *J* = 4.4 Hz), 5.23 (2H, s), 6.64 (1H, br s), 6.70-6.97 (6H, m), 6.95 (1H, s), 7.12 (1H, s); HRMS (FAB) calcd for $C_{37}H_{42}O_{10}$ 646.2778, found: 646.2801.

Plagiochin A (1). To a solution of **31** (2.4 mg) in MeOH (2 mL) was added one drop of 48% HBr. The reaction mixture was stirred at 50˚C for 15 min, and then concentrated *in vacuo* to give the residue, which was purified by prep. TLC (hexane-EtOAc, 1:1) to afford **1** (1.4 mg, 71%), which was identical in all respects with natural plagiochin A. ^{1}H NMR (400 MHz) δ 2.29–3.34 (1H, m), 2.81–3.15 (7H, m), 4.02 (3H, s), 4.56 (1H, s), 4.81 (1H, d, *J* = 1.5 Hz), 5.26 (2H, s), 5.45 (1H, s), 6.45 (1H, s), 6.47 (1H, d, *J* = 2.6 Hz), 6.62 (1H, dd, *J* = 8.4, 2.6 Hz), 6.70 (1H, dd, *J* = 8.4, 2.2 Hz), 6.73 (1H, dd, *J* = 8.4, 2.2 Hz), 6.76 (1H, s), 6.86 (1H, dd, *J* = 8.4, 2.2 Hz), 6.89 (1H, d, *J* = 8.4 Hz), 6.91 (1H, dd, *J* = 8.4, 2.2 Hz), 7.24 (1H, s).

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