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Total Synthesis of Plagiochins C, and D, Macrocyclic Bis(bibenzyl) Constituents of Plagiochila acantophylla

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Abstract: Plagiochins C (**3**) and D (**4**) were synthesized by convergent schemes. Rings C and B were joined by Ullman ether synthesis, the aryl-aryl bond between rings A and D was formed by Pd(0)-catalysed coupling of an arylboronic acid (ring D) and a bromobenzoic ester (ring A). Rings C and D were linked by the Wittig reaction, while final ring closure was effected by tetraphenylethene assisted Wurtz reaction.

Macrocyclic bis(bibenzyls) are characteristic phenolic constituents of liverwort species and interestingly their occurrence is strictly limited to these plants[1]. All representatives of this class of compounds isolated so far can be derived from a single hypothetical precursor (such as e.g. perrottetin E) by oxidative C-C or C-O coupling at positions indicated by arrows and biochemical oxygenations giving rise to 16-, 18-, and 20-membered rings[2].

Plagiochins A, B, C, and D, all having the same skeleton, but slightly different oxygenation patterns were isolated from *Plagiochila acantophilla* subsp. *japonica*[3]. Following our interest in the synthesis of natural bis(bibenzyls)[1,4] we undertook the synthesis of plagiochins and now we report that of plagiochins C and D.

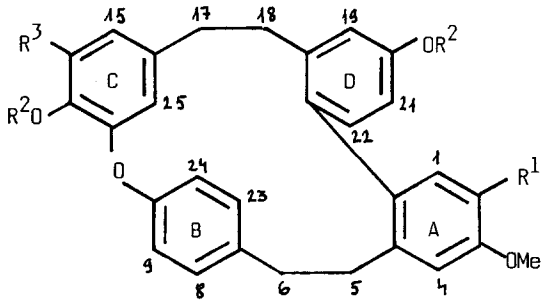
A remarkable feature of the plagiochins is the biphenyl linkage between positions ortho to the benzyl groups, which is also the main challenge when devising a route to them. Earlier, in the synthesis of riccardin A[1] we established the biphenyl linkage by Ni(0) catalysed intramolecular coupling of a diiodo compound. Low yields of this reaction, mainly due to reductive de-iodination prompted us to envisage another approach involving, as the penultimate step C-C coupling but now of a dibromide hoping that the aryl-Br bond would be less prone to reductive dehalogenation than the iodo analogues. This concept however failed because it was not possible to saturate the double bonds in intermediates obtained by Wittig condensation without reductive loss of bromine. The linear scheme was therefore abandoned and we turned to a convergent strategy.

The latter required first joining rings B and C, as well as rings A and D, followed by linking the two-ring segments and finally cyclization. The B-C element (**19**) was available from earlier work[1], thus we concentrated on establishing the aryl-aryl bond between rings A and D. Palladium(0) catalysed coupling of a heteroaromatic boronic acid with a heteroaromatic bromo compound has been reported first by Miyaura et al.[5] and later much improved by Gronowitz and Lawitz[6]. In order to test wether the scope of this reaction could be extended also to

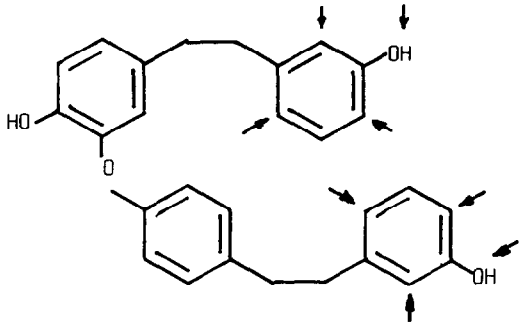
methoxy substituted benzeneboronic acids, **8** was prepared from acetal **7** and coupled with 2-bromo-5-methoxybenzaldehyde[7]. Since the desired biphenyl (**9**) could in fact be obtained, next coupling of an ester, not yet used in this reaction, was tested. For this purpose boronic acid **11** was prepared from 2-bromo-5-methoxybenzaldehyde[7] and coupled with methyl 2-bromo-5-methoxybenzoate[8]. Again the expected biphenyl (**15**) was obtained. Finally the biphenyl actually needed (**16**) was prepared in 44% yield from boronic acid **14** and the same ester.

Now the ring B-C component, the phosphonium salt **19** was reacted with biphenyl **15** to yield a mixture of *E* and *Z* olefins (**20**). Hydrogenation to the saturated diphenol **21**, rebenzylation to **22** and conversion of the ester groups by reduction to a diol (**23**) followed by treatment with phosphorus tribromide provided a dibromo compound **24** which was finally cyclized with the aid of the radical anion generated from tetraphenylethene with sodium[9]. Since cyclization was accompanied with partial debenzylation, the crude cyclization product was directly debenzylated to the macrocyclic diphenol **4**, identified by high field NMR with plagiochin D.

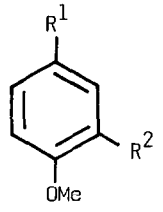
The synthesis of plagiochin C (**3**) required the same phosphonium salt (**19**) but another biphenyl (**17**) which was obtained in a similar way from the methyl ester **31** prepared in seven steps from vanilline[10]. The rest of the synthesis was analogous to that of plagiochin D and proceeded through compounds **25**, **26**, **27**, **28** and **29**. In order to avoid debenzylation cyclization of **29** was interrupted after a few hours permitting the isolation of the primary product, the tribenzylether **5**. Debenzylation led to the triphenol **3**, i.e. plagiochin C, which was characterized as its triacetate **6**.



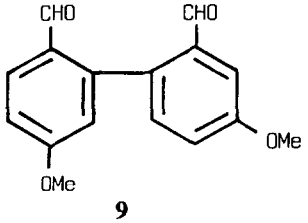
	R^1	R^2	R^3	
1	OH	H	OH	plagiochin A
2	H	H	OH	plagiochin B
3	OH	H	H	plagiochin C
4	H	H	H	plagiochin D
5	OCH_2Ph	OCH_2Ph	H	
6	OAc	OAc	H	



Perrottetin E



	R^1	R^2
7	$CH(OEt)_2$	Br
8	CHO	$B(OH)_2$



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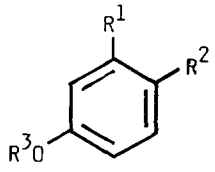
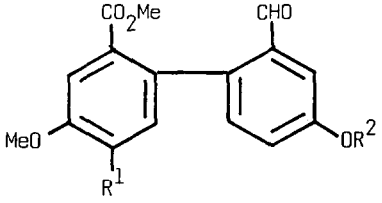
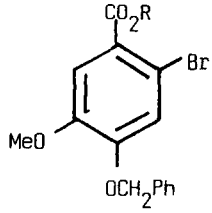


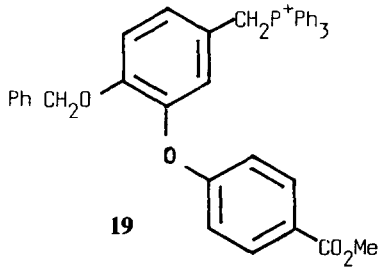
	R^1	R^2	R^3
10	$CH(OEt)_2$	Br	Me
11	CHO	$B(OH)_2$	Me
12	HO	Br	CH_2Ph
13	$CH(OEt)_2$	Br	CH_2Ph
14	CHO	$B(OH)_2$	CH_2Ph



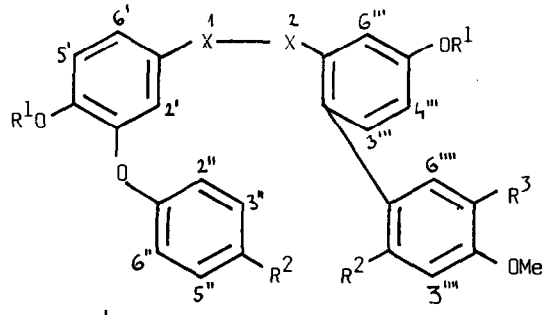
	R^1	R^2
15	H	Me
16	H	CH_2Ph
17	OCH_2Ph	CH_2Ph
18	OH	H



	R
30	$PhCH_2$
31	Me



19



	R¹	R²	R³	-X-X-
20	$PhCH_2$	CO_2Me	H	-CH=CH-
21	H	CO_2Me	H	$-CH_2CH_2-$
22	$PhCH_2$	CO_2Me	H	$-CH_2CH_2-$
23	$PhCH_2$	CH_2OH	H	$-CH_2CH_2-$
24	$PhCH_2$	CH_2Br	H	$-CH_2CH_2-$
25	$PhCH_2$	CO_2Me	OCH_2Ph	-CH=CH-
26	H	CO_2Me	OH	$-CH_2CH_2-$
27	$PhCH_2$	CO_2Me	OCH_2Ph	$-CH_2CH_2-$
28	$PhCH_2$	CH_2OH	OCH_2Ph	$-CH_2CH_2-$
29	$PhCH_2$	CH_2Br	OCH_2Ph	$-CH_2CH_2-$

EXPERIMENTAL

Evaporations were carried under reduced pressure. For chromatography silica gel (Merck 60) was used. M.p.s are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on Varian XL 400 and Perkin-Elmer R12 instruments (at 400 and 60 MHz, resp.). Mass spectra were taken on a JEOL 0156-2 double focus instrument.

3-Bromo-4-methoxybenzaldehyde Diethyl Acetal (7). 3-Bromo-4-methoxybenzaldehyde[11] (15.8 g, 0.735 mmol), NH_4NO_3 (0.3 g), ethanol and triethyl orthoformate (16.5 ml, 0.10 mol) were stirred for 24 h. After the addition of triethylamine (0.4 mL) and evaporation (finally in high vacuum) **7** was obtained as an oil (20.6 g, 97%). - Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93; Br, 27.64. Found: C, 49.77; H, 5.99; Br, 27.17. 60 MHz ^1H NMR δ 1.10 (t, *J*=6 Hz, 6 H, CH_3), 3.45 (q, *J*=6 Hz, 4 H; OCH_2), 3.70 (s, 3 H, OCH_3), 5.32 (s, 1 H, CH), 6.70 (d, *J*=8 Hz, 1 H, 5-H), 7.25 (dd, *J*=8, 2 Hz, 1 H, 6-H), 7.50 (d, *J*=2 Hz, 1 H, 2-H).

3-Borono-4-methoxybenzaldehyde (8). To a solution of acetal **7** (2.89 g, 10 mmol) in dry ether (10 mL) butyl lithium in hexane (11.1 mmol) was added under nitrogen at -70 °C. After 30 min. tributyl borate (2.8 g, 12.2 mmol) in ether (12 mL) was added, stirring at -70 °C continued for 4 h. After letting the mixture to warm up to 0 °C slowly 2M hydrochloric acid (14 mL) was added and thereafter the mixture refluxed for 1 h with stirring. Part of the product (0.75 g) precipitated directly, the rest was recovered by extraction of the etheral phase with 2M NaOH and acidification of the extract. Combined yield 1.35 g (75%), m.p. 158-160 °C. - Anal. Calcd for $C_8H_9BO_2$: C, 64.93; H, 6.13. Found: C, 65.01; H, 6.16. 60 MHz ^1H NMR δ 3.95 (s, 3 H, OCH_3), 3.80 (s, 2 H, $B(OH)_2$), 7.00 (d, *J*=8 Hz, 1 H, 5-H), 7.90 (dd, *J*=8, 2 Hz, 1 H, 6-H), 8.20 (br. s, 1 H, 2-H), 9.83 (s, 1 H, CHO).

2,4'-Dimethoxybiphenyl-2',4-dialdehyde (9). 2-Bromo-5-methoxybenzaldehyde[7] (0.20 g, 1.1 mmol) and $(Ph_3P)_4Pd(0)$ (35 mg), were stirred in dimethoxyethane (5 mL) for 20 min. followed by the addition of boronic acid **7** (0.21 g, 1.0 mmol) and satd. aq. $NaHCO_3$ solution (2.5 mL). The mixture was reflux for 1 h, evaporated and the residue chromatographed (eluant hexane-EtOAc 8:1) to give the biphenyl **9** (170 mg, 63%) as a resin. - Anal. Calcd for $C_{16}H_{14}O_4$: C, 45.94; H, 3.37. Found: C, 45.73; H, 3.40. 60 MHz ^{1}H NMR δ 3.80 and 3.85 (2xs, 6 H, OCH3) 6.9-8.0 (m, 6 H, aryl H), 9.65 and 9.90 (2xs, 2 H, 2xCHO).

5-Benzyloxy-2-bromobenzaldehyde (12)[12]. 2-Bromo-5-hydroxybenzaldehyde[11] (20.1 g, 0.1 mol), benzyl chloride (13 ml, 0.12 mol) and dry K_2CO_3 (20 g, 0.15 mol) in DMF (120 ml) were stirred at 90 °C for 3.5 h. Removal of the solvent and excess benzyl chloride by steam distillation afforded almost pure **12** (26 g, 90%). Recrystallization from hexane gave m.p. 52-54 °C. - Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.75; H, 3.81; Br, 27.45. Found: C, 57.63; H, 3.60; Br, 27.12. 60 MHz ^{1}H NMR δ 5.02 (s, 3 H, OCH_2), 7.05 (dd, *J*=8, 2.5 Hz, 1 H, 4-H), 7.2-7.6 (m, 7 H, 3,6-H, C_6H_5).

2-Bromo-5-methoxybenzaldehyde Diethyl Acetal (10). 2-Bromo-5-methoxybenzaldehyde[7] was converted to the diethylacetal **10** as described for **7** in 91% yield. - Anal. Calcd for $C_{12}H_{17}BrO_3$: C, 49.84; H, 5.93. Br, 27.64. Found: C, 49.98; H, 5.71; Br, 27.33. 60 MHz ^{1}H NMR δ 1.10 (t, *J*=6 Hz, 6 H, CH_3), 3.48 (q, *J*=6 Hz, OCH_2), 5.42 (s, 1 H, CH), 6.55 (dd, *J*=8, 2.5 Hz, 1 H, 4-H), 7.05 (d, *J*=2.5 Hz, 1 H, 6-H), 7.25 (d, *J*=8 Hz, 1 H, 3-H).

3-Methoxy-5-boronobenzaldehyde (11). Acetal **10** (2.9 g, 10 mmol) was converted to the boronic acid **11** as described for **8**. The product (0.54 g, 30%, m.p. 158-163 °C, dec.) was isolated by extraction with 2M NaOH followed by acidification. - Anal. Calcd for $C_8H_9BO_2$: C, 64.93; H, 6.13. Found: C, 64.73; H, 6.02. 60 MHz ^{1}H NMR (in $CDCl_3$+CD_3OD) δ 3.7 (br. s, 2 H, $B(OH)_2$), 3.90 (s, 3 H, OCH_3), 6.9-7.1 (m, 2 H, 2,4-H), 7.4 (br. s, 1 H, 2-H), 7.6 (d, *J*=8 Hz, 3'-H), 9.76 (s, 1 H, CHO).

Methyl 5-methoxy-2-(2-formyl-4-methoxyphenyl)-benzoate (15). Boronic acid **11** (0.36 g, 2.0 mmol) was coupled with methyl 2-bromo-5-methoxybenzoate[8] (0.49 g, 2.0 mmol) as described for biphenyl **9** to give biphenyl **15** (0.22 g, 37%) as an oil. - Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.71; H, 5.45. 400 MHz ^{1}H NMR δ 3.63, 3.898 and 3.902 (3xs, 9 H, OCH_3), 7.11 (dd, *J*=8.5, 2.8 Hz, 1 H, 5-H), 7.12-7-17 (m, 2 H, 5',6'-H), 7.19 (d, *J*=8.5 Hz, 1 H, 6'-H), 7.21 (d, *J*=8.5 Hz, 1 H, 6-H), 7.48 (m, 1 H, 3'-H), 7.53 (d, *J*=2.5 Hz, 1 H, 3-H), 9.76 (s, 1 H, CHO).

5-Benzyloxy-2-bromobenzaldehyde diethyl acetal (13). Aldehyde **12** (3.3 g, 11.3 mmol) was converted to the oily diethylacetal **13** as described for **7** in 93% yield. - Anal. Calcd for $C_{18}H_{21}BrO_3$: C, 59.19; H, 5.79; Br, 21.88. Found: C, 59.22; H, 5.60; Br, 21.34. 60 MHz ^{1}H NMR δ 1.20 (t, *J*=6 Hz, 6 H, CH_3), 3.55 (q, *J*=6 Hz, 4 H, OCH_2), 5.00, (s, 2 H, OCH_2Ph), 5.52 (s, 1 H, CH), 6.75 (dd, *J*=8 and 2.5 Hz, 1 H, 4-H), 3.1-3.5, m, 7 H, C_6H_5, 3,5-H).

3-Benzyloxy-6-boronobenzaldehyde (14). Acetal **13** (7.0 g, 19.0 mmol) was converted to the boronic acid **14** (3.7 g, 74%, m.p. 159-161 °C as described for **8**. - Anal. Calcd for $C_{14}H_{13}BO_4$: C, 65.72; H, 5.12. Found: C,

65.91; H, 5.23. 60 MHz ^{1}H NMR in $CDCl_3$+d6-DMSO δ 5.12 (s, 2 H, CH_2), 7.0-7.6 (m, 7 H, aromatic-H), 7.87 (d, *J*=8 Hz, 1 H, 5-H).

Methyl 2-(4-benzyloxy-2-formylphenyl)-5-methoxybenzoate (16). Boronic acid **14** (0.77 g, 3 mmol) was coupled with methyl 2-bromo-5-methoxybenzoate[8] (0.74 g, 3 mmol) as described for biphenyl **9** to give after chromatography (eluant hexane-EtOAc 4:1) biphenyl **16** (0.40 g, 35%). - Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H, 5.36. Found: C, 73.42; H, 5.16. 400 MHz ^{1}H NMR δ 3.62 and 3.90 (2xs, 6 H, OCH_3), 5.15 (s, 2 H, OCH_2), 7.10 (dd, *J*=8.0, 2.8 Hz, 1 H, 4-H), 7.15 (dd, *J*=8.5, 0.8 Hz, 1 H, 6'-H), 7.19 (d, *J*=8.0 Hz, 1 H, 3-H), 7.22 (dd, *J*=8.0, 2.5 Hz, 1 H, 5'-H), 7.32-7.49 (m, 5 H, C_6H_5), 7.53 (d, *J*=2.8 Hz, 1 H, 6-H), 7.58 (dd, *J*=2.5, 0.8 Hz, 1 H, 3'-H), 9.76 (s, 1 H, CHO).

(*E*)- and (*Z*)-1-[4-Benzyloxy-3-(4-methoxycarbonylphenoxy)phenyl]-2-[5-benzyloxy-2-(2-methoxycarbonyl-4-methoxyphenyl)phenyl]-ethene (20). Phosphonium salt **19** (1.7 g, 2.8 mmol) and aldehyde **16** (1.04 g, 2.8 mmol) were dissolved in methanol (50 mL) and under nitrogen 1 M sodium methoxide in methanol (3.0 mL) was added. After 3 and 6 h more of **19** (2x0.34 g, 1.12 mmol) was added. After 8 h the reaction mixture was worked up giving after chromatography (eluant benzene) 1.6 g (85%) of a 55:45 mixture of *E* and *Z* olefins. - Anal. Calcd for $C_{45}H_{38}O_5$: C, 73.39; H, 5.42. Found: C, 73.11; H, 5.48. 400 MHz ^{1}H NMR δ 3.53, 3.56, 3.85, 3.86, 3.87, 3.90 (6xs, 6 H, OCH_3), 4.89, 5.02, 5.03, 5.13 (4xs, 4 H, OCH_2), 6.13 and 6.28 (2xd, *J*=12.0 Hz, (*Z*)-CH=CH), 6.67 (d, *J*=16.0 Hz, (*E*)-CH=), 6.85-7.50 (m), 7.93 (d, *J*=9.0 Hz) and 7.97 (d, *J*=8.5 Hz, 2 H, 3",5"-H).

1-[4-Hydroxy-3-(4-methoxycarbonylphenoxy)phenyl]-2-[5-hydroxy-2-(2-methoxycarbonyl-4-methoxyphe-nyl)phenyl]-ethane (21). Olefin **20** (1.55 g (2.25 mmol) was hydrogenated over Pd/C in EtOH-EtOAc (1:1, 30 mL) and gave after the ususal work up the diester **21** as a colourless resin (1.10 g, 98%). - Anal. Calcd for $C_{31}H_{28}O_8$: C, 70.44; H, 5.34. Found: C, 70.13; H, 5.31. 400 MHz ^{1}H NMR δ 2.50-2.70 (m, 4 H, CH_2CH_2), 3.57, 3.83, and 3.90 (3xs, 9 H, OCH_3), 5.65 and 6.05 (2xbr. s, 2 H, OH), 6.49 (d, *J*=2.5 Hz, 1 H, 6'-H), 6.63 (d, *J*=2.5 Hz, 1 H, 2"'-H), 6.66 (dd, *J*=8.0, 2.5 Hz, 1 H, 4"'-H), 6.675 (dd, *J*=8.2, 2.0 Hz, 2'-H), 6.875 (d, *J*=8.0 Hz, 2-H, 3",5"-H), 6.89 (d, *J*=9.0 Hz, 2 H, 2",6"-H), 7.41 (dd, *J*=2.3, 1.0 Hz, 1 H, 3""-H), 7.97 (d, *J*=9.0 Hz, 2 H, 3",5"-H).

1-[2-Benzyloxy-4-(4-methoxycarbonylphenoxy)phenyl]-2-[5-benzyloxy-2-(2-methoxycarbonyl-4-methoxy-phenyl)phenyl]-ethane (22). Diester **21** (1.10 g, 2.23 mmol), K_2CO_3 (2.0 g), KI (0.10 g) and benzyl chloride (1.15 ml, 10 mmol) were refluxed in acetone (25 ml) for 3 h. After steam distillation the residue was extracted with CH_2Cl_2, the extract dried and evaporated to give the dibenzylether **22** (1.25 g, 83%). - Anal. Calcd for $C_{45}H_{40}O_8$: C, 76.25; H, 5.69. Found: C, 76.44; H, 5.63. 400 MHz ^{1}H NMR δ 2.5-2.8 (m, 4 H, CH_2CH_2), 3.59, 3.84, and 3.89 (3xs, 9 H, OCH_3), 4.97 and 5.05 (2xs, 4 H, OCH_2), 6.67 (d, *J*=2.0 Hz, 1-H, 2'-H), 6.71 (dd, *J*=8.5, 2.0 Hz, 6'-H), 6.83 (dd, *J*=8.5 and 2.8 Hz, 1 H, 4"'-H), 6.85 (dd, *J*=2.5, 0.8 Hz, 1 H, 6"'-H), 6.85 (d, *J*=9.0 Hz, 2 H, 2",6"-H), 6.87 (d, *J*=8.5 Hz, 1 H, 5'-H), 6.97 (dd, *J*=8.5, 0.8 Hz, 1 H, 3"'-H), 6.99 (dd, *J*=8.3, 2.8 Hz, 1 H, 5""-H), 7.02 (dd, *J*=8.5, 1.0 Hz, 1 H, 6""-H), 7.06-7.1 (m, 2H), 7.21-7.24 (m, 3 H, aryl H), 7.30-7.46, (m, 4 H, aromatic-H), 7.95 (d, *J*=8.5 Hz, 2 H, 3",5"-H).

1-[2-Benzyloxy-4-(4-hydroxymethylphenoxy)phenyl]-2-[5-benzyloxy-2-(2-hydroxymethyl-4-methoxyphenyl)phenyl]-ethane (23). Dibenzylether **22** (1.25 g, 1.82 mmol) in ether (50 mL) was treated with $LiAlH_4$ (0.38 g, 10 mmol) at O °C for 2.5 h. 20% H_2SO_4 was carefully added until a sticky precipitate formed. The solution was decanted and evaporated to give after chromatography (eluant benzene-EtOAc 2:1) diol **23** (0.80 g, 70%) as a resin. - Anal. Calcd for $C_{43}H_{40}O_6$: C, 79.12; H, 6.18. Found: C, 79.23; H,6.04. 400 MHz ^{1}H NMR δ 1.7 (br. s, 2 H, OH), 2.45-2.68 (m, 4 H, CH_2CH_2), 3.83 (s, 3 H, OCH_3), 4.23 and 4.30 (2xd, *J*=12.5 Hz, 2 H, 2""-CH_2), 4.62 (s, 2 H, 4'-CH_2), 5.03 (s, 4 H, OCH_2Ph), 6.49 (d, *J*=2.0 Hz, 1 H, 2'-H), 6.62 (dd, *J*=8.0, 2.0 Hz, 1 H, 4'-H), 6.77 (dd, *J*=8.5. 2.5 Hz, 1 H, 5""-H), 6.83 (d, *J*=8.0 Hz, 1 H, 5'-H), 6.82-6.85 (m, 2 H, 3"',5"'-H), 6.92 (d, *J*=8.0 Hz, 1 H, 6""-H), 7.00 (d, *J*=9.0 Hz, 1 H, 6"'-H), 6.85 (d, *J*=8.5 Hz, 2 H, 2",6"-H), 7.06 (d, *J*=2.5 Hz, 1 H, 3""-H), 7.17-7.45 (m, 10H, aromatic-H).

1-[2-Benzyloxy-4-(4-bromomethylphenoxy)phenyl]-2-[5-benzyloxy-2-(2-bromomethyl-4-methoxyphenyl) phenyl]-ethane (24). Diol **23** (0.80 g, 1.28 mmol) was dissolved in benzene (10 mL) and treated overnight with PBr_3 (0.76 g, 2.8 mmol). After washing several times with water the solution was dried and evaporated to give the dibromide **23** (0.90 g, 90%), as a colorless resin. - Anal. Calcd for $C_{43}H_{38}Br_2O_4$: C, 67.72; H, 5.02; Br, 20.96. Found: C, 67.71; H, 4.88; Br, 20.53. 400 MHz ^{1}H NMR δ 2.50-2.75 (m, 4 H, CH_2CH_2), 3.86 (s, 3 H, OCH_3), 4.11 and 4.24 (2xd, *J*=9.8 Hz, 2 H, 2""-CH_2), 4.49 (s, 2 H, 4"-CH_2), 4.99 and 5.06 (2xs, 4 H, OCH_2Ph), 6.63-6.68 (m, 2 H, 2',6'-H), 6.81 (d, *J*=8.5 Hz, 2 H, 3",5"-H), 6.83-6.93 (m, 4H, aryl H), 7.02 (d, *J*=2.5 Hz, 1 H, 6""-H), 7.08-7.12 (m, 2 H), 7.22-7.47 (m, 10 H), 7.28 (d, *J*=8.5 Hz, 2 H, 2",6"-H).

5,6,17,18-Tetrahydro-3-methoxy-7,10-etheno-12,16-metheno-16H-dibenz [h,j] oxacyclooctadecin-13,20-di-ol, plagiochin D. (4) To a solution of tetraphenylethene (350 mg) in dry THF (30 mL) freshly distilled from benzophenone-sodium a small piece of sodium was added. As soon as the solution turned deep purple a solution of dibromide **24** (0.45 g, 0.58 mmol) in THF (12 mL) was added over 4 h. After standing overnight a few drops of acetic acid was added, the solution decanted from the remainder of sodium, evaporated, the residue treated with water and extracted with CH_2Cl_2. After evaporation the residue was hydrogenated over Pd/C in EtOH-EtOAc (1:1) overnight. After the usual work-up the product was purified by plate chromatography (eluant benzene-EtOAc 8:1) to give **4** (43 mg, 17%) as an amorphous solid. - 400 MHz ^{1}H NMR δ 2.80-3.15 (m, 8 H, 2xCH_2CH_2), 3.89 (s, 3 H, OCH_3), 5.23 (d, *J*=2.0 Hz, 1 H, 25-H), 6.53 (d, *J*=3.0 Hz, 1 H, 19-H), 6.695 (dd, *J*=8.0, 2.0 Hz, 1 H, 15-H), 6.71 (dd, *J*=8.5, 2.8 Hz, 1 H, 2-H), 6.81 (d, *J*=8.0 Hz, 1 H, 14-H), 6.85 (m, 2 H, 9,24-H), 6.89 (d, *J*=8.5 Hz, 1 H, 21-H), 6.91-6.97 (m, 2 H, 8,23-H), 7.08 (d, *J*=8.5 Hz, 1 H, 1-H), 7.18 (d, *J*=2.8 Hz, 1 H, 4-H). MS m/z (rel. int%): 438=M^+ (100), 394 (3), 352 (4), 332 (8), 300 (4), 255 (4), 225 (0), 213 (75), 197 (20), 165 (15), 149 (30), 121 (18), 107 (40), 91 (30), 77 (21), 55 (15), 43 (30).

Benzyl 4-benzyloxy-2-bromo-5-methoxybenzoate (30). 2-Bromo-4-hydroxy-5-methoxybenzoic acid[13] (2.4 g, 8.3 mmol), benzyl chloride (2.84 mL, 25 mmol) and dry K_2CO_3 (4.15 g, 30 mmol) were stirred at 120 °C for 1 h. Dilution with water precipitated the benzyl ester **30** (3.5 g, 90%). A small sample was recrystallized from ethanol, m.p. 113.5-114 °C, - Anal. Calcd. for $C_{22}H_{19}BrO_4$: C, 61.84; H, 4.48; Br, 18.70. Found: C, 61.99; H, 4.53; Br, 1855. 60 MHz ^{1}H NMR δ 3.80 (s, 3 H, OCH_3), 5.08 and 5.30 (2xs, 4 H, OCH_2), 7.09 and 7.19 (2xs, 2 H, 3,6-H), 7.35 (br. s, 10 H, 2xC_6H_5).

Methyl 4-benzyloxy-2-bromo-5-methoxybenzoate (31). Benzylester **30** (16.0 g, 34 mmol) was boiled in methanol (100 mL) with hydrochloric acid (1.0 mL) for 16 h. After the addition of water (50 ml) and neutralization with solid Na_2CO_3, the methyl ester **31** (12.0 g, 90%) crystallized. A sample was recrystallized from hexane-Me_2CO the (12.0 g, 90%), m.p. 108-109 °C. - Anal. Calcd for $C_{16}H_{15}BrO_4$: C, 54.71; H, 4.30; Br, 22.75. Found: C, 54.83; H, 4.42; Br, 22.30. 60 MHz ^{1}H NMR δ 3.85 (s, 6 H, OCH_3), 5.10 (s, 2 H, OCH_2), 7.11 (s, 1 H, 3-H), 7.35 (s, 5 H, C_6H_5), 7.40 (s, 1 H, 6-H).

Methyl 4-benzyloxy-2-(4-benzyloxy-2-formylphenyl)-5-methoxybenzoate (17). Ester **31** (0.70 g, 2.0 mmol) was coupled with boronic acid **14** as described for **9**. Chromatography of the crude product (eluant hexane-EtOAc 4:1) gave biphenyl **17** (0.58 g, 60%). - Anal. Calcd for $C_{30}H_{26}O_6$: C, 74.67; H, 9.41. Found: C, 74.60; H, 9.47. 400 MHz ^{1}H NMR δ 3.60 and 4.98 (2xs, 6 H, OCH_3), 5.15 (s, 4 H, 2xOCH_2), 6.76 (s, 3-H), 7.11 (d, *J*=8.5 Hz, 1 H, 6'-H), 7.20 (dd, *J*=8.5, 3.0 Hz, 1 H, 5'-H), 7.3-7.5 (m, 10 H, C_6H_5), 7.57 (d, *J*=3.0 Hz, 1 H, 3'-H), 7.59 (s, 1 H, 6-H), 9.64 (s, 1 H, CHO). For NMR studies a small sample of **17** was hydrogenated to **methyl 4-hydroxy-2-(4-hydroxy-2-formylphenyl)-5-methoxybenzoate (18).** - 400 MHz ^{1}H NMR δ 3.67 and 3.96 (2xs, 6 H, OCH_3), 6.77 (s, 1 H, 3-H), 7.04 (dd, *J*=8.0, 2.5 Hz, 1 H, 4'-H), 7.09 (dd, *J*=8.0, 0.8 Hz, 1 H, 5'-H), 7.37 (dd, *J*=2.5, 0.8 H, 1 H, 2'-H), 7.61, (s, 1 H, 6-H), 9.68 (s, 1 H, CHO).

(*E*)- and (*Z*)-1-[5-benzyloxy-2-(5-benzyloxy-2-methoxycarbonyl-4-methoxyphenyl)-phenyl]-2-[4-benzyloxy-4-(4-methoxycarbonylphenoxy)phenyl]-ethene (25). Phosphonium salt **19** (0.69 g, 1.0 mmol) was reacted with aldehyde **17** (0.50g, 0.9 mmol) and worked up as described for **20**. Chromatography (eluant benzene) gave **25** (0.67 g, 83%) as a colourless resin. - Anal. Calcd for $C_{52}H_{44}O_9$: C, 76.83; H, 5.46. Found: C, 76.62; H,5.55. 400 MHz ^{1}H NMR δ 3.54, 3.87 and 3.96 (3xs, (*Z*)-OCH_3), 3.53, 3.89 and 3.96 (3xs, (*E*)-OCH_3), 4.89 and 4.98 (2xs, (*Z*)-OCH_2, 5.02 and 5.04 (2xd, *J*=10 Hz, (*Z*)-5''''-OCH_2), 5.02 and 5.13 (2xs, (*E*)-OCH), 5.10 and 5.12 (2xd, *J*=11 Hz, (*E*)-5''''-OCH_2), 6.06 and 6.20 (2xd, *J*=12 Hz, (*Z*)-CH=CH), 6.62 (d, *J*=16 Hz, (*E*)-CH=), 6.63 (s, (*Z*)-6''''-H), 6.77 (s, (*E*)-6''''-H), 6.82-7.48 (m, aromatic-H, (*E*)-CH=), 7.45 (s, (*Z*)-3''''-H), 7.50 (s, (*E*)-3''''-H), 7.91 (d, *J*=9.0 Hz, (*Z*)-3'',5''-H), 7.97 (d, (*E*)-3'',5''-H).

1-[5-Hydroxy-2-(5-hydroxy-2-methoxycarbonyl-4-methoxyphenyl)phenyl]-2-[4-hydroxy-4-(4-methoxycarbonylphenoxy)phenyl]-ethane (26). Hydrogenation of **25** (1.35 g, 1.66 mmol) as described for **20** gave the ethane **26** (0.85 g, 94%), as a colourless resin. - Anal. Calcd for $C_{31}H_{28}O_9$: C, 68.37; H, 5.18. Found: C, 68.44; H, 5.03. 400 MHz ^{1}H NMR δ 2.57-2.68 (m, 4 H, CH_2CH_2), 3.55, 3.92, and 3.93 (3xs, OCH_3), 4.90, 5.76 and 5.97 (3xs, 3 H, OH), 6.49 (d, *J*=2.0 Hz, 1 H, 2'-H), 6.61 (s, 1 H, 6''''-H), 6.64-6.68 (m, 2 H, 2''',4'''-H), 6.71 (dd, *J*=8.0, 2.0 Hz, 1 H, 6'-H), 6.88 (d, *J*=8.5 Hz, 1 H, 5'/3'''-H), 6.90 (d, *J*=8.5 Hz, 1 H, 5'/3'''-H), 6.93 (d, *J*=8.5 Hz, 2 H, 2'',6''-H), 7.47 (s, 1 H, 3''''-H), 8.00 (d, *J*=8.5 Hz, 2 H, 3'',5''-H).

1-[5-Benzyloxy-2-(5-benzyloxy-2-methoxycarbonyl-4-methoxyphenyl)phenyl]-2-[4-benzyloxy-4-(4-methoxycarbonylphenoxy)phenyl]-ethane (27). Benzylation of **26** (0.80 g, 1.47 mmol) with benzyl bromide as described for **21** followed by chromatography (eluant benzene) gave the tribenzylether **27** (0.84 g, 84%) as a colourless resin. - Anal. Calcd for $C_{52}H_{46}O_9$: C, 76.64;H, 5.69. Found: C, 76.71; H, 5.52. 400 MHz ^{1}H NMR δ 2.45-2.60 (m, 4 H, CH_2CH_2), 3.57, 3.88 and 3.94 (3xs, 9 H, OCH_3), 4.96 and 5.03 (2xs, 4 H, OCH_2), 5.08 and

5.16 (2xd, *J*=12 Hz, 2 H, 5""-OCH_2), 6.63-6.68 (m, 2 H, 2',6'-H), 6.64 (s, 1 H, 6""-H), 6.86 (d, *J*=9.0 Hz, 2 H, 2",6"-H), 6.78-7.46 (m, 19 H, aromatic-H), 7.52 (s, 1 H, 3""-H), 7.96 (d, *J*=9.0 Hz, 2 H, 3",5"-H).

1-[5-Benzyloxy-2-(5-benzyloxy-2-hydroxymethyl-4-methoxyphenyl)phenyl]-2-[4-benzyloxy-4-(4-hydroxymethylphenoxy)phenyl]-ethane (28). Tribenzylether **27** (1.12 g, 1.38 mmol) was reduced as described for **23** to give the diol **28** (0.76 g, 72%) as a colourless resin. Anal. Calcd for $C_{50}H_{46}O_9$: C, 75.93; H, 5.86. Found: C, 75.77; H,6.01. 400 MHz ^{1}H NMR δ 2.35-2.56 (m, 4 H, CH_2CH_2), 3.93 (s, 3 H, OCH_3), 4.19 and 4.23 (2xd, *J*=12.5 Hz, 2 H, 2""-CH_2), 4.58 (br. s, 2 H, 4"-CH_2), 5.01 and 5.03 (2xs, 4 H, 4',5"'-CH_2), 5.03 and 5.11 (2xd, *J*=12.5 Hz, 2 H, 5""-CH_2), 6.44 (d, *J*=2.0 Hz, 1 H, 2'-H), 6.57 (dd, *J*=2.0, 8.0 Hz, 1 H, 6'-H), 6.59 (s, 1 H, 6""-H), 6.77 (d, *J*=2.5 Hz, 1 H, 6"'-H), 6.81 (dd, *J*=2.5, 8.0 Hz, 1 H, 4"'-H), 6.83 (d, *J*=8.0 Hz, 1 H, 5'-H), 6.85 (d, *J*=8.5 Hz, 2 H, 2",6"-H), 6.99 (d, *J*=8.0 Hz, 1 H, 3"'-H), 7.04 (s, 1 H, 3""-H), 7.24 (d, *J*=8.5 Hz, 2 H, 3",5"-H), 7.16-7.44 (m, 15 H, aromatic-H).

1-[5-Benzyloxy-2-(5-benzyloxy-2-bromomethyl-4-methoxyphenyl)phenyl[-2-[4-benzyloxy-4-(4-bromomethylphenoxy)phenyl]-ethane (29). Diol **28** (0.58 g, 0.76 mmol) was treated with PBr_3 for 3 h in benzene as described for **23** to give the dibromide **29** as a colourless oil, which was used in the next step without purification since it decomposed on chromatography. 400 MHz ^{1}H NMR δ 2.43-2.56 (m, 4 H, CH_2CH_2), 3.93 (s, 3 H, OCH_3), 4.11 and 4.26 (2xd, *J*=9.5 Hz, 2 H, 2""-CH_2), 4.48 (s, 2 H, 4"-CH_2), 4.97 and 4.99 (2xs, 4 H, 4',5"'-OCH_2), 4.99 and 5.13 (2xd, *J*=12.0 Hz, 2 H, 5""-OCH_2), 6.56 (s, 1 H, 6""-H), 6.59-6.62 (m, 2 H, 2',6'-H), 6.81 (d, *J*=8.5 Hz, 2 H, 2",6"-H), 6.85 (d, *J*=8.5 Hz, 1 H, 5'-H), 6.99 (s, 1 H, 3""-H), 7.11 (d, *J*=8.0 Hz, 1 H, 3"'-H), 7.27 (d, *J*=8.5 Hz, 2 H, 3",5"-H), 6.97-7.47 (m, 15 H, aryl H).

2,13,20-Tribenzyloxy-15,6,17,18-tetrahydro-3-methoxy-7,10-etheno-12,16-metheno-16H-dibenz [h,j] oxacyclooctadecin (5). Dibromide **29** (0.51 g, 0.57 mmol) was cyclized as described for **4** but the reaction was quenched after 5 h in order to avoid debenzylation. Chromatography (eluant hexane-EtOAc 4:1) gave the tribenzylether **5** (0.14 g, 34%) as a colourless resin. - Anal. Calcd for $C_{50}H_{44}O_7$: C, 79.34; H, 5.86. Found: C, 79.29; H, 5.50. 400 MHz ^{1}H NMR δ 1.93 and 2.50 (2xm, 2 H, 17-CH_2), 2.64 and 2.78 (2xm, 2 H, 18-CH_2), 2.85-3.15 (m, 4 H, 5,6-CH_2), 4.03 (s, 3 H, OCH_3), 4.95 and 5.22 (2xs, 4 H, 13,20-OCH_2), 4.98 and 5.17 (2xd, *J*=12.5 Hz, 2 H, 2-OCH_2), 5.21 (d, *J*=2.0 Hz, 1 H, 25-H), 6.56 (s, 1 H, 1-H), 6.62 (d, *J*=2.5 Hz, 1 H, 19-H), 6.64 (dd, *J*=8.0, 2.0 Hz, 1 H, 15-H), 6.69 (symm. m, 2 H, 9,24-H), 6.74 (dd, *J*=8.5, 2.5 Hz, 1 H, 21-H), 6.80 (d, *J*=8.5 Hz, 1 H, 14-H), 6.88 (symm. m, 2 H, 8,23-H), 6.93 (d, *J*=8.5 Hz, 1 H, 22-H), 7.13 (s, 1 H, 4-H), 7.14-7.54 (m, 15H, aromatic-H).

2,13,20-Triacetoxy-5,6,17,18-tetrahydro-3-methoxy-7,10-etheno-12,16-methe-no-16H-dibenz [h,j] oxacyclooctadecin, plagiochin C-triacetate (6). Tribenzylether **5** (32 mg, 0.044 mmol) was hydrogenated as described for **4** and the triol **3** was directly acetylated in pyridine with acetic anhydride. The usual work-up and layer chromatography gave the triacetate **6** (18 mg, 78%). - Anal. Calcd for $C_{35}H_{32}O_7$: C, 74.45; H, 5.71. Found: C, 74.35; H, 5.60. 400 MHz ^{1}H NMR δ 2.27, 2.29 and 2.35 (3xs, 9 H, CH_3CO), 2.88-3.18 (m, 7.5 H, CH_2CH_2), 3.25-3.35 (m, 0.5 H, CH_2CH_2), 5.32 (d, *J*=2.0 Hz, 1 H, 25-H), 6.70 (dd, *J*=2.0, 0.8 Hz, 1 H, 19-H), 6.73 (symm. m, 2 H, 9,24-H), 6.78 (dd, *J*=8.0, 2.0 Hz, 1 H, 15-H), 6.86 (s, 1 H, 1-H), 6.91 (dd, *J*=8.0, 2.0 Hz, 1 H, 21-H), 6.90 (m, 2 H, 9,24-H), 6.93 (d, *J*=8.0 Hz, 1 H, 14-H), 7.06 (d, *J*=8.0 Hz, 1 H, 22-H), 7.20 (s, 1 H, 4-

H). MS z/e, (rel. int.) 580 (2.7) (M^+), 539 (20), 497 (18), 454 (12), 283 (5.8), 241 (13), 213 (13) 105 (38), 44 (100).

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