Synthesis of Isoplagiochin A†

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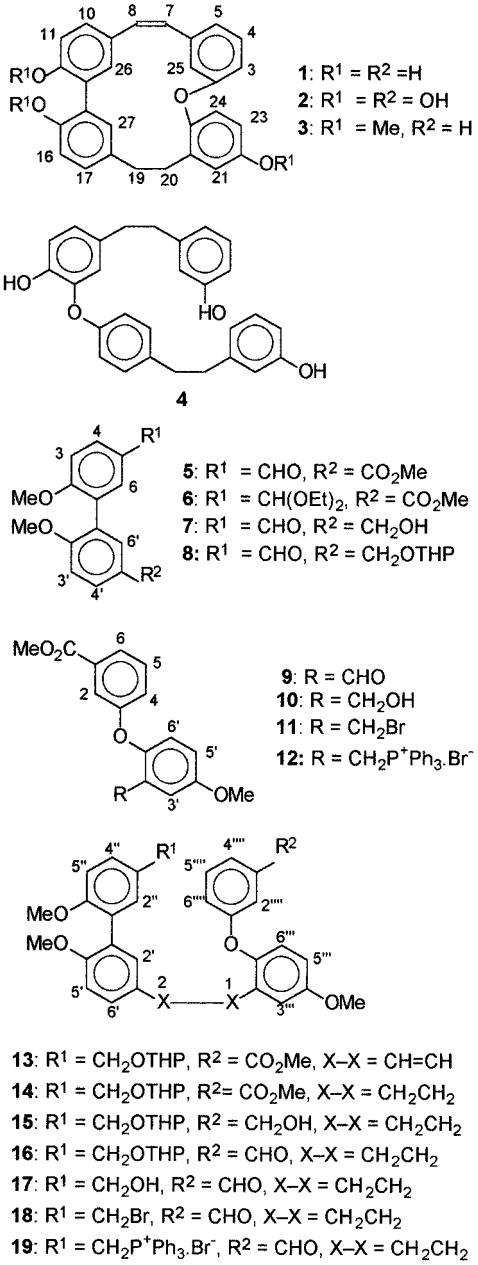
An unambigous synthesis of the title compound (**1**) was carried out in 23 steps following a convergent scheme involving, as the key step, macrocyclization by an intramolecular Wittig reaction.

Bis(bibenzyls) are plant metabolites occurring exclusively in liverwort species. Their isolation and structural elucidation can be mainly attributed to Asakawa and his co-workers,[1] while their synthesis has been almost exclusively realized in our laboratory.[2] In a study of *Plagiochila* species, Asakawa and his co-workers isolated in 1987 the plagiochins A−D[3] from *P. acantophylla*, the structures of which has been confirmed by total synthesis.[2f,g] Recently from another *Plagiochila* species (*P. fruticosa*) four new compounds called isoplagiochins A−D were isolated.[4] Structural elucidation of isoplagiochins A and B[5] yielded structures (**1** and **2**, respectively; Chart 1) rather exceptional in the family of macrocyclic bis(bibenzyls). Notably in **1** and **2** the linkages between the two bibenzyl units deviate from the pattern present in all the other known bis(bibenzyls) (at least 35 different compounds by 1994).[1] The latter can be invariably derived by oxidative C−C or C−O coupling of an open chain species such as, for example, **4** (or oxygenated and/or methylated variants thereof).[6,7] The isoplagiochins, in turn, cannot be derived from a precursor of type **4** since in them rings B and C are linked by a C−C bond. Also in the isoplagiochins, one of the two C_2 bridges is present as a *Z* double bond. This feature is less unexpected since for example in marchantins D, F, J, and L,[1] a hydroxy group is attached to one of the C_2 bridges, which can readily lead to a stilbene structure by dehydration. The intriguing structures reported for the isoplagiochins prompted us to tackle their synthesis, and in the present paper that of soplagiochin A (**1**) is presented.

Chart 1



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Both linear[8] and convergent schemes can be envisaged for the synthesis of macrocyclic bis(bibenzyls). We preferred the latter one[2] because some low-yield steps could be overcome in early stages of the synthesis. It seemed to be evident that the olefinic bond in **1** was to be established as the penultimate step of the sequence, preferably by an intramolecular Wittig reaction, because at this stage ring strain in the product would preclude the formation of an *E* olefin.[9]

The "Western" half of the tetracyclic structure including rings B and C was constructed by an improved version[12] of the Suzuki reaction,[13] *i.e.* by Pd(0)-catalyzed coupling of methyl 3-bromo-4-methoxybenzoate[14] with 3-borono-4-methoxybenzaldehyde,[2f] to give the biphenyl **5**. After protection of the aldehyde function (**6**) the ester group was transformed to a protected primary alcohol group in two steps (**6** → **7** → **8**)[15] to provide the aldehyde partner (**8**) for the Wittig reaction.

For the preparation of the "Eastern" half (rings A and B) the notoriously unsatisfactory but still unavoidable Ullmann ether synthesis was used. In order to exploit activation by the neighboring aldehyde group, 2-bromo-5-methoxybenzaldehyde[16] was selected as the halogeno component, which gave on reaction with methyl 3-methoxybenzoate under standard conditions the diphenyl ether **9** in 20% yield. After transforming the aldehyde group in three steps (**9** → **10** → **11** → **12**) into a triphenylphosphonio group, we arrived at our second building block.

Joining "East" (**12**) and "West" (**8**) in a Wittig reaction provided an olefin (**13**) as an *E*/*Z* mixture. Hydrogenation of the double bond, transformation of the ester group to an aldehyde group by reduction and reoxidation, deprotection of the primary alcohol function, and its conversion to a (triphenylphosphonio)methyl group (**13** → **14** → **15** → **16** → **17** → **18** → **19**) led to our open chain key intermediate **19**.

Intramolecular Wittig reaction of **19** in DMF in the presence of KOtBu at high (0.0024 M) dilution gave as the only monomeric product the trimethyl ether **3** in 32% yield, satisfactory in macrocyclization reactions. Demethylation with BBr_3 in dichloromethane yielded, along with unidentifiable byproducts, the trihydroxy compound **1**. At this point a comparison with the few available NMR data[4,17] reported for **1** became possible. The spectrum of our product showed the following significant deviations with the available NMR data for isoplagiochin A: (i) The coupling constants for the olefinic protons for **3** and **1** were $J = 12.1 \pm 0.3$ and 12.3 ± 0.3 Hz, respectively, and (ii) while in the trimethyl ether **3** the protons of the CH_2CH_2 bridge gave a complex multiplet extending over about 0.2 ppm, in the trihydroxy derivative **1** the same group produced a sharp singlet splitting up to a multiplet at −63 °C (in $CDCl_3 + CD_3OD$). As for the ^{13}C data, our values for CH_2CH_2 in **1** were 34.8 and 36.02 ppm. The discrepancy prompted us to carry out a detailed NMR and computational study on both **1** and **3**.

Since the value $^3J_{H-7,8}$ was just in the range where literature values for *cis*- and *trans*-oriented proton pairs overlap, first we wished to ascertain that our product was a *cis* olefin. Molecular mechanics calculations (details are below) clearly indicated that the *trans* diastereomer of **1** was not viable, its total energy exceeding by 79 kJ mol^{-1} that of *cis*-**1**. In view of the remarkable contrast in the ^1H NMR splitting pattern of the ethano bridge in **3** and **1** (multiplet *vs* singlet), we carried out a flexibility analysis on these compounds. We found that the fragmental flexibility value (*f*) for the ethano bridge in the methylated compound (**3**) was 15% lower than that for that in the hydroxy compound (**1**).

NMR Studies

^1H signal assignments for **3** and **1** were based on COSY[18] and TOCSY (total correlation spectroscopy)[19] spectra. Aromatic ^{13}C signal assignment was carried out with the aid of HMQC (heteronuclear multiple-quantum coherence)[20] and HMBC (heteronuclear multiple-bond coherence)[21] spectra. In the latter experiment the delay for evolution of long range couplings was set to 70 ms ($J = 7$ Hz) permitting not only safe signal assignments but an independent structural determination, proving the aromatic ring sequence too. Some of the crucial correlations were H-26−C-14, H-17−C-19, H-21−C-20, H-5−C-7, and H-10−C-8.

In the phase sensitive NOESY spectrum[22] (mixing time 400 ms), the volume integrals of cross peaks for H-7 and H-8 exceeded by 25 and 15%, respectively, those elicited by the *ortho* proton pairs H-3−H-4 and H-10−H-11, indicating again the *Z* disposition of the bridge protons. Further, as shown by a Dreyding model, in *trans*-**3** H-26 and H-7 would be within the range of van der Waals radii and should therefore induce a very strong NOE. However, only a week cross peak was observed between the signals for H-7 and H-8 and the coinciding signals of H-25 and H-26. This is not in contradiction with the *cis* configuration, since in certain conformations H-25 is close to H-7.

Molecular Modeling

The conformational space of **1** was explored by molecular mechanics based on the "ringmaker" approach employed in the SUMM algorithm.[23] Conformers obtained by the pseudorandom variation of torsional angles of the temporarily opened macrocycle followed by reclosure of the ring were minimized to give the global minimum of the conformational space. The energy hypersurface of *trans*-**1** and *cis*-**1** were effectively sampled

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(17) ^1H NMR (no solvent and field strength given)[6] $\delta = 2.66$ (m, 4 H, 19,20-CH_2), 6.59 and 6.63 (2×d, $J = 9.1$ Hz, −CH=CH−); ^{13}C NMR $\delta = 35.2$ (C-19) and 37.6 (C-20) ppm.

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Table 1. Selected Energy Terms (kJ mol^{-1}) for the Global Minima of *trans*- and *cis*-1 Obtained by SUMM Calculations

energy term	*trans*-**1**	*cis*-**1**
stretching	7.9	6.0
bending	58.6	41.2
torsion	107.9	56.5
van der Waals	75.4	66.8
total	250.5	171.7

by this method in 3000 steps, resulting in 642 and 923 unique conformations, respectively. The lower number of conformations for *trans*-**1** suggests it is more strained than *cis*-**1**, which was further supported by the analysis of energetic terms. From Table 1 it is apparent that the major contribution to the above difference comes from the torsional term. This trend was reproduced by calculations in the presence of chloroform and indicated that solvent effects have no influence on the relative stability.

In exploring the relative flexibility of *trans*-**1** and *cis*-**1**, we used our recently developed fast and effective approach based on the statistical analysis of molecular dynamics datasets.[24] Sampling pre-equilibrated molecular dynamics simulations of **1** and **3** resulted in 5000 independent conformations for each, which were further analyzed by statistical methods. Torsional angles associated with the ethano bridge were monitored and fragmental flexibilities (*f*), defined as the standard deviation of the relative frequency of the given angle, were calculated. A smaller *f* value for the methylated analogue **3** (7.78 in contrast to 8.98 for **1**) indicated that the ethano bridge in **3** was less flexible than the one in the hydroxy compound. This is in accordance with the multiplet vs singlet character of the CH_2CH_2 proton signals in **3** and **1**, respectively.

On our request (10/17/96, repeated 2/27/97) Prof. Asakawa kindly sent us the original spectra (taken in $CDCl_3$ + CD_3OD) and a sample of isoplagiochin A. Recording a ^{1}H and ^{13}C NMR spectrum (at 500 and 125 MHz, respectively) in the same solvent revealed that (i) the spectra of **1** and the natural product were superimposable (ii) $J_{7,8}$ was in fact 12.0 Hz and not 9.1 Hz, and (iii) the CH_2CH_2 signal was a singlet and not a multiplet, as stated in ref 6. Thus the identity of **1** with isoplagiochin A could be established without doubt.

Experimental Section

General. 1,2-Dimethoxyethane = DME. Silica gel was used for column chromatography. Evaporations were carried out in vacuum. NMR spectra were recorded on Varian XL 400 and Bruker DRX-500 spectrometers in $CDCl_3$ using standard pulse programs provided by the manufacturers.

All calculations were performed by the MacroModel 4.5 program package[25] on a SGI Indy workstation. Molecular mechanics calculations on the conformational space of **1** were carried out using the efficient systematic unbounded multiple minimum (SUMM) search algorithm, the MM2* force field, and distance dependent electrostatics (ϵ = 1). Structures generated during the conformational search were minimized by the truncated Newton conjugate gradient technique[26] (maximum number of iterations, 250; convergence criteria in gradient, 0.01) to yield unique conformers within an energy window (50 kJ mol^{-1}) above the global minimum. Unique conformations were further analyzed using the filtering option of MacroModel.

The global minimum of **1** and its methylated analogue were then subjected to molecular dynamics simulations. The starting structure was heated to 300 K over 20 ps using a Maxwell−Boltzmann distribution of initial velocities. After an equilibration period (40 ps, 300 K) analysis was carried out over 500 ps at 300 K. The coupling factor was 0.1 and previous velocities were used. The thermal bath constant was set to 0.2 ps. A total of 5000 conformers were sampled during the data collection period in which torsional angles of interest were monitored and their values in each conformation were collected to datasheets which were directly used in the Statistica program[27] to obtain flexibility data.

Methyl 3-(2-methoxy-5-formylphenyl)-4-methoxybenzoate (5). To a stirred solution of methyl 3-bromo-4-methoxybenzoate[14] in DME (40 mL) was added $Pd(PPh_3)_4$ (275 mg), after 20 min 3-borono-4-methoxybenzaldehyde[2e] (1.4 g, 7.85 mmol) and 1 N $NaHCO_3$ (18 ml) were added, and the mixture was refluxed for 1.5 h. After evaporation of DME the product was extracted with CH_2Cl_2 and purified by chromatography (eluant hexane/acetone (5:1)) to give **5** (0.7 g, 37%): mp 144 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.81 (s, 4-OMe), 3.84 (s, 2′-OMe), 3.87 (s, CO_2Me), (9 H), 7.00 (d, J = 8.6 Hz, 1 H, 5-H), 7.08 (d, J = 8.5 Hz, 1 H, 3′-H), 7.78 (d, J = 2.2 Hz, 1 H, 6′-H), 7.89 (dd, J = 8.5 and 2.3 Hz, 1 H, 4′-H), 7.94 (d, J = 2.3 Hz, 1 H, 2-H), 8.07 (dd, J = 8.6 and 2.3 Hz, 1H, 6-H), 9.90 (s, 1 H, CHO);[28] ^{13}C-NMR (125 MHz) δ = 51.72 (CO_2*Me*) 55.66 (4-OMe), 55.81 (2′-OMe), 110.25 (C-5), 110.74 (C-3′), 122.12 (C-1), 126.14 (C-3), 127.41 (C-1′), 129.35 (C-5′), 131.25 (C-6), 131.65 (C-4′), 132.84 (C-6′), 160.56 (C-4), 161.91 (C-2′), 166.54 (*CO*OMe), 190.68 (CHO).[29] Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.83; H, 5.42.

Methyl 3-(5-(diethoxymethyl)-2-methoxyphenyl)-4-methoxybenzoate (6). Compound **4** (100 mg, 0.33 mmol), NH_4NO_3 (9.5 mg), EtOH (1 mL), and $HC(OEt)_3$ (5 mL) were stirred for 48 h. Evaporation gave a quantitative yield of **6**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 1.36 (t, J = 7.4 Hz, 6 H, 2× CH_2CH_3), 3.18 (q, J = 7 Hz, 4 H, OCH_2), 3.73, 3.83 and 3.85 (3×s, 9 H, 3×OMe), 5.42 (s, 1 H, CH), 6.78 and 6.90 (2×d, J = 8.5 Hz, 2 H, 3′- and 5-H), 7.1 (mc, 2 H, 4′,6′-H), 7.93 (d, J = 2.0 Hz, 1 H, 2-H), 8.08 (dd, J = 9.0 and 2.0 Hz, 1 H, 6-H). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.35; H, 7.00. Found: C, 67.47; H, 6.95.

3-(5-(Hydroxymethyl)-2-methoxyphenyl)-4-methoxybenzaldehyde (7). To a solution of **6** (2.06 g, 5.6 mmol) in THF (30 mL) was added $LiAlH_4$ (0.52 g). After 2 h Et_2O (100 mL) was added, the ice cooled mixture was acidified with 20% H_2SO_4, and the clear solution was decanted from the precipitate, washed with brine, dried over $MgSO_4$, and evaporated to afford **7** (1.17 g, 77%) as a gum: ^{1}H-NMR (80 MHz, $CDCl_3$) δ = 3.79 and 3.88 (2×s, 6 H, 2×OMe), 4.69 (s, 2 H, CH_2), 7.00 (d, J = 8.5 Hz, 1 H, 5-H), 7.10 (d, J = 8.5 Hz, 1 H, 3′-H), 7.27 (d, J = 2.0 Hz, 1 H, 2-H), 7.40 7.80 (d, J = 2.0 Hz, 1 H, 6′-H), 7.91 (dd, J = 8.5 and 2.0 Hz, 1 H, 4′-H), 9.29 (s, 1 H, CHO). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.44; H, 6.01.

4-Methoxy-3-(2-methoxy-4-(((tetrahydropyran-2-yl)-oxy)methyl)phenyl)benzaldehyde (8). Compound **7** (1.16 g, 4.3 mmol) and dihydropyran (1.3 mL) were stirred in CH_2Cl_2 (30 mL) in the presence of a few milligrams of *p*-toluenesulfonic acid for 24 h. After washing with aqueous $NaHCO_3$ and drying, the solvent was evaporated to give a quantitative yield of **8** as an oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.5−1.9 (m, 6-H, $-(CH_2)_3-$), 3.50−3.55 (m, 1 H, OCH_AH_B), 3.85 and 3.87 (2×s, 6 H, 2×OMe), 4.72 (mc, 2 H, 1-CH_2), 3.93 (mc, 1 H, OCH_ACH_B), 4.74 (mc, 1 H, OCHO), 6.96 (d, J =

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(29) Protonated carbons were assigned by HETCOR, quaternary carbons by long range correlations (FLOCK).

8.5 Hz, 1 H, 5-H), 7.08 (d, J = 8.5 Hz, 1 H, 4′-H), 7.24 (d, J = 2.1 Hz, 1 H, 2-H), 7.37 (dd, J = 8.5 and 2.1 Hz, 1 H, 6-H), 7.78 (d, J = 2.1 Hz, 1 H, 6′-H), 7.88 (dd, J = 8.5 and 2.1 Hz, 1 H, 3′-H), 9.91 (s, 1 H, CHO). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.52; H, 6.61.

Methyl 3-(2-Formyl-4-methoxyphenoxy)benzoate (9). A mixture of 2-bromo-4-methoxybenzaldehyde (7.3 g, 34 mmol),[15] methyl 3-hydroxybenzoate (6.7 g, 44 mmol), CuO (0.9 g), and dry K_2CO_3 (8.0 g) in pyridine (80 mL) was refluxed with stirring for 48 h. Dilution with 10% HCl (200 mL) and extraction with CH_2Cl_2, drying the extract over $MgSO_4$, evaporation, and chromatography (eluant hexane/acetone (5:1)) gave **9** (2.5 g, 25%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.87 (s, CO_2Me), 3.90 (s, 4′-OMe), (6 H), 6.94 (d, J = 9.1 Hz, 1 H, 6′-H), 7.15 (dd, J = 3.3 and 9.1 Hz, 1 H, 5′-H), 7.21 (ddd, J = 8.2, 2.7 and 1.2 Hz, 1 H, 4-H), 7.42 (d, J = 3.3 Hz, 1 H, 3′-H), 7.43 (dd, J = 8.2 and 7.8 Hz, 1 H, 5-H), 7.62 (dd, J = 2.5 and 1.5 Hz, 1 H, 2-H), 7.80 (ddd, J = 7.8, 1.5 and 1.2 Hz, 1 H, 6-H);[30] ^{13}C NMR (100 MHz, $CDCl_3$) δ = 52.35 (CO_2Me), 55.86 (4′-OMe), 110.09 (C-3′), 122.47 (C-4), 123.81 (C-5′), 124.59 (C-6), 128.08 (C-2′), 130.04 (C-5), 132.11 (C-1), 152.68 (C-1′), 156.24 (C-4′), 158.03 (C-3), 166.26 (*C*OMe).[31] Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.97; H, 5.01.

Methyl (2-(Hydroxymethyl)-4-methoxyphenoxy)benzoate (10). To a solution of **9** (2.5 g, 8.7 mmol) in EtOH (60 mL) was added $NaBH_4$ (0.45 g). After the disappearance of **10** the mixture was acidified with AcOH and the solution evaporated. The residue was treated with water and extracted with CH_2Cl_2. Evaporation gave **10** as an oil (2.33 g, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 3.84 and 3.89 (2×s, 6 H, OMe), 4.67 (s, 2 H, CH_2), 6.83 (dd, J = 8.8 and 3 Hz, 1 H, 5′-H), 6.89 (d, J = 8.8 Hz, 1 H, 6′-H), 7.07 (d, J = 2.0 Hz, 1 H, 3′-H), 7.12 (ddd, J = 8.1, 2.5 and 1 Hz, 1 H, 4-H), 7.37 (t, J = 8.0 Hz, 1 H, 5-H), 7.54 (dd, J = 2.5 and 1.5 Hz, 1 H, 2-H), 7.74 (ddd, J = 7.5, 1.5 and 1 Hz, 1 H, 6-H). Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.73; H, 5.52.

Methyl 3-(2-(Bromomethyl)-4-methoxyphenoxy)benzoate (11). To a solution of **9** (0.16 g, 0.55 mmol) in DME (2 mL) was added PBr_3 (0.15 g, 0.55 mmol) in DME (2.75 mL). After a few hours the mixture was diluted with Et_2O, the solution extracted several times with water, dried over $MgSO_4$, and evaporated, and the crude product purified by chromatography (benzene/EtOAc (8:1) to give **11** (0.124 g, 64%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 3.82 and 3.89 (2×s, 6 H, OMe), 4.48 (s, 2 H, CH_2), 6.85 (m, 2 H, 5′,6′-H), 6.99 (d, J = 2.5 Hz, 1 H, 3′-H), 7.14 (ddd, J = 8.0, 2.5 and 1 Hz, 1 H, 4-H), 7.38 (t, J = 8 Hz, 1 H, 5-H), 7.60 (dd, J = 2.5 and 1.5 Hz, 1 H, 2-H), 7.74 (ddd = 7.5 1.5 and 1 Hz, 1 H, 6-H). Anal. Calcd for $C_{16}H_{15}BrO_4$: C, 54.72; H, 4.31. Found: C, 54.64; H, 4.40.

Methyl 3-(2-(Phosphoniomethyl)-4-methoxyphenoxy)benzoate (12). A solution of **11** (1.44 g, 4.1 mmol) and Ph_3P (1.18 g, 4.5 mmol) in MeCN (50 mL) was refluxed for 2 h. Evaporation and treatment of the residue with hot hexane gave **12** (2.1 g, 83%): mp 152−154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.60 and 3.91 (2×s, 6 H, OMe), 5.35 (d, J = 14.5 Hz, 2 H, CH_2), 6.53 (dd, J = 9 and 1 Hz, 1 H, 6′-H), 6.75 (dd, J = 9 and 2.8 Hz, 1 H, 5′-H), 6.75 (ddd, J = 8.0, 2.5 and 1.0 Hz, 1 H, 4-H), 7.08 (dd, J = 2.5 and 1.5 Hz, 1 H, 2-H), 7.23 (dd, J = 3 and 2.5 Hz, 1 H, 3′-H), 7.31 (t, J = 7.5 Hz, 4 H, 5-H), 7.61−7.68 (m, 2 H, Ar-H), 7.72 (ddd, J = 7.5, 1.5 and 1 Hz, 1 H, 6-H), 7.73−7.82 (m, 10 H, Ar-H). Anal. Calcd for $C_{34}H_{30}BrO_4P$: C, 66.57; H, 4.93. Found: C, 66.40; H, 4.88.

1-[5-Methoxy-2-(3-(methoxycarbonyl)phenoxy)phenyl]-2-[4-methoxy-3-(2-methoxy-5-(((tetrahydropyran-2-yl)-oxy)methyl)phenyl)phenyl]ethene (13). To a solution of **12** (495 mg, 0.87 mmol) in dry MeOH (5 mL) was added 1 N NaOMe (1.5 mL) under argon. After 1 h **7** (240 mg, 0.67 mmol) dissolved in MeOH (5 mL) was added and stirring continued for 1 h. The usual workup and chromatography (eluant benzene/EtOAc (8:1)) gave **13** (152 mg, 37%) as an *E*/*Z* mixture: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.5−1.9 (m, 6H, −$(CH_2)_3$−), 3.55 (mc, 1 H, O$CH_A$$CH_B$), 3.9 (mc, 1 H, O$CH_A$$CH_B$), 3.62, 3.72, 3.73, 3.74, 3.75, 3.76, 3.83, 3.85 and 3.86 (8×s, 12 H, 4×(*Z*)-OMe, 4×(*E*)-OMe), 4.4−4.5 (m) and 4.7−4.8 (m) (3 H, Ar$CH_A$$CH_B$O, OCHO), 6.40 and 6.53 (2×d, J = 12 Hz, (*Z*)-CH = CH−), 6.75−7.7 (m, Ar-H). Anal. Calcd for $C_{37}H_{38}O_8$: C, 72.77; H, 6.27. Found: C, 72.65; H, 6.33.

1-[5-Methoxy-2-(3-(methoxycarbonyl)phenoxy)phenyl]-2-[4-methoxy-3-(2-methoxy-5-(((tetrahydropyran-2-yl)-oxy)methyl)phenyl)phenyl]ethane (14). Hydrogenation of **12** (280 mg) in EtOH over Pd/C followed by the usual workup gave **14** (250 mg, 89%) as a resin: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.5−1.9 (m, 6 H, −$(CH_2)_3$−), 2.84 (s, 4 H, Ar$(CH_2)_2$Ar), 3.55 (mc, 1 H, O$CH_A$$CH_B$), 3.73, 3.74, 3.78 and 3.87 (4×s, 12 H, 4×OMe), 4.45 (d, J = 11.5 Hz, 1 H, Ar$CH_A$$CH_B$O), 4.72 (mc, 1H, OCHO), 4.74 (d, J = 11.5 Hz, 1 H, Ar$CH_A$$CH_B$O), 6.75 (dd, J = 8.6 and 3 Hz, 1 H, 4‴-H), 6.78 (d, J = 8.5 Hz, 1 H, 6‴-H), 6.83 (d, J = 8.3 Hz, 1 H, 3″-H), 6.88 (d, J = 8 Hz, 1 H, 3‴-H), 6.93 (d, J = 8 Hz, 1 H, 5′-H), 7.00 (d, J = 2.5 Hz, 1 H, 6″-H), 7.03 (dd, J = 8.3 and 2.4 Hz, 1 H, 4″-H), 7.06 (ddd, J = 8, 2.5 and 1.0 Hz, 1 H, 6⁗-H), 7.17 (d, J = 2 Hz, 1 H, 2′-H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1 H, 6′-H), 7.32 (t, J = 8 Hz, 1 H, 5⁗-H), 7.51 (dd, J = 2.5, and 1.5 Hz, 1 H, 2⁗-H), 7.67 (ddd, J = 7.5, 1.5, and 1 Hz, 1 H, 4⁗-H). Anal. Calcd for $C_{37}H_{40}O_8$: C, 72.53; H, 6.58. Found: C, 72.41; H, 6.48.

1-[5-Methoxy-2-(3-(hydroxymethyl)phenoxy)phenyl]-2-[4-methoxy-3-(2-methoxy-5-(((tetrahydropyran-2-yl)-oxy)methyl)phenyl)phenyl]ethane (15). Compound **14** (250 mg, 0.41 mmol) was reduced in dry Et_2O (30 mL) with $LiAlH_4$ (50 mg). Excess reagent was destroyed with a saturated aqueous solution of Seignettes's salt. Evaporation, extraction of the product with CH_2Cl_2, and evaporation gave **15** (220 mg, 92%) as a resin: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.5−1.9 (m, 6 H, −$(CH_2)_3$−), 2.83 (s, 4 H, Ar$(CH_2)_2$Ar), 3.55 (mc, 1 H, O$CH_A$$CH_B$), 3.72, 3.73 and 3.78 (3×s, 9 H, 3×OMe), 3.93 (mc, 1 H, O$CH_A$$CH_B$), 4.45 (d, J = 11.5 Hz, 1 H, 5″-$CH_A$$CH_B$O), 4.55 (s, 2 H, 3‴-$CH_2$), 4.73 (mc, 1 H, OCHO), 4.74 (d, J = 11.5 Hz, 1 H, 5″-$CH_A$$CH_B$O), 6.73 (dd, J = 9 and 3 Hz, 1 H, 4⁗-H), 6.735 (ddd, J = 9, 3 and <1 Hz, 1 H, 6⁗-H), 6.78 (d, J = 3.0 Hz, 1 H, 6‴-H), 6.83 (d, J = 8.5 Hz, 1 H, 3″-H), 6.85 (t, J = 2.5 Hz, 1 H, 2⁗-H), 6.90 (d, J = 9 Hz, 1 H, 3‴-H), 6.92 (d, J = 8.5 Hz, 1 H, 5′-H), 6.94 (d, J = 2.5 Hz, 1 H, 6″-H). 6.96 (ddd, J = 8.5 ∼2 and <1 Hz, 1 H, 4⁗-H), 7.04 (dd, J = 8.5 and 2.5 Hz, 1 H, 4″-H), 7.12 (d, J = 2.0 Hz, 1 H, 2′-H), 7.21 (t, J = 8 Hz, 1 H, 5⁗-H), 7.32 (dd, J = 8.5 and 2.5 Hz, 1 H, 6′-H). Anal. Calcd for $C_{36}H_{40}O_7$: C, 73.95; H, 6.90. Found: C, 74.02; H, 6.95.

1-[2-(3-Carbonylphenoxy)-5-methoxyphenyl]-2-[4-methoxy-3-(2-methoxy-5-(((tetrahydropyran-2-yl)oxy)methyl)-phenyl)phenyl]ethane (16). To a suspension of pyridinium chlorochromate (360 mg, 1.7 mmol) and NaOAc in dry CH_2Cl_2 (20 mL) was added **15** (640 mg, 1.1 mmol) in CH_2Cl_2. After stirring for 1 h the solution was evaporated and the residue chromatographed (eluant: benzene/EtOAc (8:1)) to give **16** (330 mg, 51%) as a resin: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.5−1.9 (m, 6 H, −$(CH_2)_3$−), 2.84 (s, 4 H, Ar$(CH_2)_2$Ar), 3.50−3.65 (m, 1 H, O$CH_A$$CH_B$), 3.74, 3.76 and 3.83 (3×s, 9 H, 3×OMe), 3.93 (mc, 1 H, O$CH_A$$CH_B$), 4.46 (d, J = 11.5 Hz, 1 H, 5″-$CH_A$$CH_B$O), 4.74 (mc, 1 H, OCHO), 4.77 (d, J = 11.5 Hz, 1 H, 5″-$CH_A$$CH_B$O), 6.77 (dd, J = 8.7 and 3.0 Hz, 1 H, H_x[b]), 6.82 (d, J = 2.9 Hz, 1 H, H_x[c]), 6.83 (d, J = 8.3 Hz, 1 H, H_y[a]), 6.95 (d, J = 8.7 Hz, 1 H, H_x[a]), 6.93 (d, J = 8.3 Hz, 1 H, H_z[a]), 6.99 (d, J = 2.1 Hz, 1 H, H_z[c]), 7.03 (dd, J = 8.3 and 2.1 Hz, 1 H, H_z[b]), 7.15 (d, J = 1.7 Hz, 1 H, H_y[c]), 7.16 (dd, J = 9.1 and 2.1 Hz, 1 H, H_y[b]), 7.27 (br. s, 1 H, 2⁗-H), 7.31 (dd, J = 8.4 and 2.0 Hz, 1 H, 6⁗-H), 7.43 (t, J = 7.8 Hz, 1 H, 5⁗-H), 7.51 (d, J = 7.6 Hz, 1 H, 4⁗-H), 9.91 (s, 1 H, CHO). Anal. Calcd for $C_{36}H_{38}O_7$: C, 74.21; H, 6.57. Found: C, 74.15; H, 6.39.

1-[2-(3-Carbonylphenoxy)-5-methoxyphenyl]-2-[4-methoxy-3-(2-methoxy-5-(hydroxymethyl)phenyl)phenyl]-ethane (17). A solution of **16** (230 mg, 0.40 mmol) in EtOH (5 ml) was refluxed for 1 h in the presence of Amberlite IR 120 strongly acidic ion exchange resin. Filtration, evaporation, and chromatography (eluant: benzene/EtOAc (8:1)) afforded **17** (70 mg, 36%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.83 (s, 4 H, Ar-$(CH_2)_2$-Ar) 3.74, 3.76 and 3.81 (3×s, 9 H, 3×OMe), 4.65 (s, 2 H, CH_2O), 6.78 (dd, J = 8.5 and 3.0 Hz, 1 H, H_x[b]), 6.81 (d, J

(30) Assignments were confirmed by NOEs on H-6′ and CHO, H-2′ and H-5′, on irradiation of H-2 and 4′-OMe, respectively.

(31) Protonated carbons were assigned by 1D HETCOR, quaternary carbons by 1D long range correlations (INEPTL).

= 3 Hz, 1 H, H_x^c), 6.84 (d, J = 8.5 Hz, 1 H, H_y^a), 6.93 (d, J = 8.5 Hz, 1 H, H_x^a), 6.93 (d, J = 2.5 Hz, 1 H, H_y^c), 6.96 (d, J = 8.5 Hz, 1 H, H_z^a), 7.04 (dd, J = 8.5 and 2.5 Hz, 1 H, H_y^b), 7.14 (d, J = 2.5 Hz, 1 H, H_z^c), 7.15 (dd, J = 8.1 and 2.5 Hz, 1 H, 6‴‴-H), 7.32 (br. s, 1 H, 2‴‴-H), 7.34 (dd, J = 8.5 and 2.5 Hz, 1 H, H_z^b), 7.43 (t, J = 8.0 Hz, 1 H, 5‴‴-H), 7.51 (d, J = 8.0 Hz, 1 H, 4‴‴-H), 9.88 (s, 1 H, CHO). Anal. Calcd for $C_{31}H_{30}O_6$: C, 74.68; H, 6.06. Found: C, 74.45; H, 5.97.

1-[2-(3-Carbonylphenoxy)-5-methoxyphenyl]-2-[3-(5-(bromomethyl)-2-methoxyphenyl)-4-methoxyphenyl]-ethane (18). To a solution of **17** (70 mg, 0.14 mmol) in benzene (10 mL) was added dibromotriphenylphosphorane (100 mg, 0.24 mmol). After 24 h precipitated Ph_3PO was filtered off, the solution was evaporated, and the residue was used without purification for the preparation of **18**. (The bromide undergoes partial hydrolysis on chromatography.) ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.75 (s, Ar$(CH_2)_2$Ar), 3.64 3.66 and 3.71 (3×s, OMe), 4.45 (s, CH_2Br), 6.6−7.5 (Ar-H), 9.82 (s, CHO). Anal. Calcd for $C_{31}H_{29}BrO_5$: C, 66.41; H, 5.22. Found: C, 66.50; H, 5.39.

1-[2-(3-Carbonylphenoxy)-5-methoxyphenyl]-2-[3-(2-methoxy-5-((triphenylphosphonio)methyl)phenyl)-4-methoxyphenyl]ethane Bromide (19). A solution of the crude **18** arising from the previous step in MeCN (5 mL) and Ph_3P was refluxed for 2 h. After removing Ph_3PO by filtration and evaporation, the residue was chromatographed (eluant benzene/EtOH (9:2)) to give **19** (109 mg, 94% from **17**) as a resin: ^{1}H NMR (DMSO-d_6, 500 MHz) δ = 2.74 (s, 4 H, Ar$(CH_2)_2$Ar), 3.53, 3.62 and 3.76 (3×s, 9 H, OMe), 5.55 (d, J = 14.9 Hz, 2 H, P^+CH_2), 6.8−7.9 (m, 28 H, Ar-H), 9.91 (s, 1 H, CHO). Anal. Calcd for $C_{49}H_{44}BrO_5P$: C, 71.45; H, 5.38. Found: C, 71.65; H, 5.11.

(*Z*)-19,20-Dihydro-12,15,22-trimethoxy-2,6:9,13:14,18-trimetheno-6*H*-1-benzoxacyclodocosin (3). To a solution of **19** (95 mg, 0.12 mmol) in dry DMF (50 mL) was added KOtBu (10 mg) and the solution stirred under argon for 1 h. The solvent was evaporated at 0.1 mm Hg and the residue chromatographed (eluant benzene/EtOAc (20:1)) to give **3** (17 mg, 32%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.62−2.71 (m, 2 H, CH_2), 2.75−2.88 (m, 2 H, CH_2), 3.78 (s, 3 H, 15-OMe), 3.85 (s, 3 H, 22-OMe), 3.83 (s, 3 H, 12-OMe), 6.28 (dd, J = 8.3 and 2.6 Hz, 1 H, 3-H), 6.52 (d, J = 12.3 Hz, 1 H, 7-H), 6.57 (d, J = 12.3 Hz, 1 H, 8-H), 6.73 (br. d, J = 7.6 Hz, 1 H, 5-H), 6.80 (d, J = 8.1 Hz, 1 H, 16-H), 6.84 (dd, J = 8.7 and 3.1 Hz, 1 H, 23-H), 6.92 (d, J = 3.1 Hz, 1 H, 21-H), 6.93 (d, J = 8.2 Hz, 1 H, 11-H), 6.96 (br s, 1 H, 27-H), 7.07 (d, J = 8.7 Hz, 1 H, 24-H), 7.09 (dd, J = 8.1 Hz, 1 H, 4-H), 7.11 (dd, J = 8.1 and 2.5 Hz, 1 H, 17-H), 7.24 (dd, J = 8.2 and 2.3 Hz, 1 H, 10-H), 7.54 (br. s, 2 H, 25,26-H); ^{13}C NMR ($CDCl_3$) δ = 34.56 (C-20), 36.74 (C-19), 55.6, 55.7, and 55.9 (OMe), 110.44 (C-16), 110.65 (C-11), 111.17 (C-3), 112.65 (C-23), 115.63 (C-21), 115.91 (C-25), 123.18 (C-5), 123.75 (C-24), 127.38 (C-17), 127.96 (C-7), 128.04 (C-13), 128.90 (C-14), 128.96 (C-9), 129.54 (C-4), 130.01 (C-8), 130.42 (C-10), 132.09 (C-26), 134.04 (C-27), 135.28 (C-18), 137.56 (C-20a), 140.19 (C-6), 145.53 (C-24a), 155.49 (C-15), 156.57 (C-12), 157.02 (C-22), 159.30 (C-2); MS *m*/*z* (%) 466 (7) (M^+ + 2), 465 (40) (M^+ + 1), 464 (100) (M^+), 450 (11), 433 (11), 417 (6), 236 (3), 211 (3). Anal. Calcd for $C_{31}H_{28}O_4$: C, 80.15; H, 6.08. Found: C, 80.03; H, 6.14.

(*Z*)-19,20-Dihydro-2,6:9,13:14,18-trimetheno-6H-1-benzoxacyclodocosin-12,15,22-triol (1) (Isoplagiochin A). To a solution of **1** (42 mg, 0.090 mmol) in CH_2Cl_2 (5 mL) was added 5 drops of BBr_3 at −78 °C. After 1 h the solution was left to warm to room temperature and treated with ice. Evaporation of the organic phase and chromatography of the residue (eluant benzene/EtOH (9:2)) gave **1** (4 mg, 10%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.71 (s, 4 H, CH_2CH_2), 6.37 (dd, J = 8.3 and 2.0 Hz, 1 H, 3-H), 6.58 (d, J = 12.1 Hz, 1 H, 8-CH=), 6.64 (d, J = 12.1 Hz, 1 H, 7-CH=), 6.68 (br s, 1 H, 27-H), 6.74 (m, 1 H, 5-H), 6.75 (dd, J = 8.5 and 2.9 Hz, 1 H, 23-H), 6.80 (d, J = 8.0 Hz, 1 H, 16-H), 6.85 (d, J = 2.9 Hz, 1 H, 21-H), 6.94 (d, J = 8.3 Hz, 1 H, 11-H), 7.02 (d, J = 8.5 Hz, 1 H, 24-H), 7.05 (dd, J = 8.0 and 1.9 Hz, 1 H, 17-H), 7.11 (dd, J = 8.3 Hz, 1 H, 4-H), 7.18 (dd, J = 8.3 and 1.6 Hz, 1 H, 10-H), 7.43 (br. s, 1 H, 25-H), 7.46 (d, J = 1.6 Hz, 1 H, 26-H); ^{13}C NMR ($CDCl_3$) δ = 34.08 (C-20), 36.42 (C-19), 111.09 (C-3), 114.40 (C-23), 116.13 (C-16 and -25) (this signal splits on the addition of CD_3OD), 116.97 (C-11), 117.02 (C-21), 122.78 (C-5), 124.00 (C-24), 125.30 (C-13), 126.17 (C-14), 128.45 (C-17), 128.80 (C-7), 129.75 (C-4), 129.76 (C-9), 130.06 (C-8), 130.97 (C-10), 132.95 (C-26), 133.95 (C-27), 136.24 (C-18), 137.19 (C-20a), 140.77 (C-6), 145.49 (C-24a), 150.09 (C-15), 151.84 (C-12), 153.01 (C-22), 159.74 (C-2); MS *m*/*z* (%) 422 (4) (M^+), 330 (2), 298 (5), 238 (2), 210 (4), 167 (28), 157 (100), 135 (20). Anal. Calcd $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.43; H, 5.09.

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