DOI: 10.1002/ejoc.201001412

Total Synthesis of Plagiochin D by an Intramolecular S_NAr Reaction

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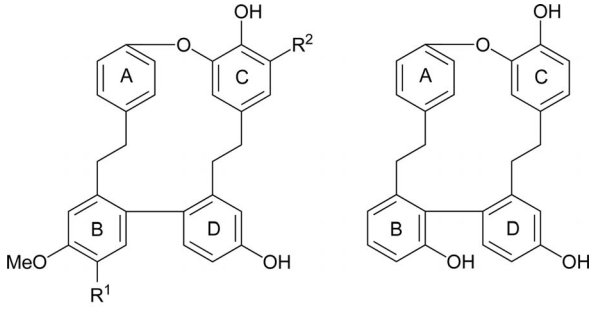
Keywords: Natural products / Cyclization / Nucleophilic substitution / Total synthesis

The total synthesis of plagiochin D, a macrocyclic bis(bibenzyl) compound isolated from the liverwort *plagiochila acanthophylla*, has been accomplished. Closure of the key 16-membered ring, which contained biphenyl ether and biaryl units, was achieved in good yield by an intramolecular S_NAr reaction. The Suzuki and Wittig protocols proved to be powerful tools for the construction of a linear precursor that was crucial for ring cyclization.

Introduction

Bis(bibenzyl) systems (riccardins, plagiochins, and marchantins) are structurally simple phenolic natural products that are found exclusively in bryophytes (liverworts) and exhibit remarkable biological activity.[1–3] Cyclic bis(bibenzyl) compounds are categorized into three structural types (1, 2, or 3) that comprise macrocyclic rings linked through two biphenyl ether C–O bonds, biphenyl ether C–O and biaryl C–C bonds, or two biaryl C–C bonds, respectively. Plagiochins A–D (**1**–**4**), isolated in 1984 from *Plagiochila acanthophylla*[4] (Figure 1), are of structural type 2 and feature a highly strained 16-membered ring system[5] made up of biphenyl ether C–O and biaryl C–C bonds. Of these plagiochins, plagiochin A (**1**), in particular, exhibits significant neurotrophic properties.[6]



1 Plagiochin A R^1 = OH R^2 = OH
2 Plagiochin B R^1 = OH R^2 = H
3 Plagiochin C R^1 = H R^2 = OH
4 Plagiochin D R^1 = H R^2 = H

5 Plagiochin E

Figure 1. Plagiochins A–E.

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Recently, a novel bis(bibenzyl) compound, plagiochin E (**5**), was isolated from the liverwort plant *Marchantia polymorpha L.*[7] and shown to have significant antifungal activity towards *Candida albicans*[8] with a minimum inhibitory concentration of MIC = 16.0 $\mu g\,mL^{-1}$, which is considerably lower than that of fluconazole (MIC = 128.0 $\mu g\,mL^{-1}$). Moreover, an additive effect was observed when *C. albicans* was simultaneously treated with plagiochin E and fluconazole.[9] Remarkable antitumor activity has been observed, and the compound may be a potential candidate for reversing drug resistance in cancer chemotherapy.[10] In 1992, Nógrádi and co-workers reported the synthesis of plagiochin D (**4**), the simplest member of the plagiochins,[11] using a Wurtz-type radical coupling at position a to form the macrocycle (Figure 2). In 1999, Fukuyama et al.[12] reported the synthesis of the same plagiochin

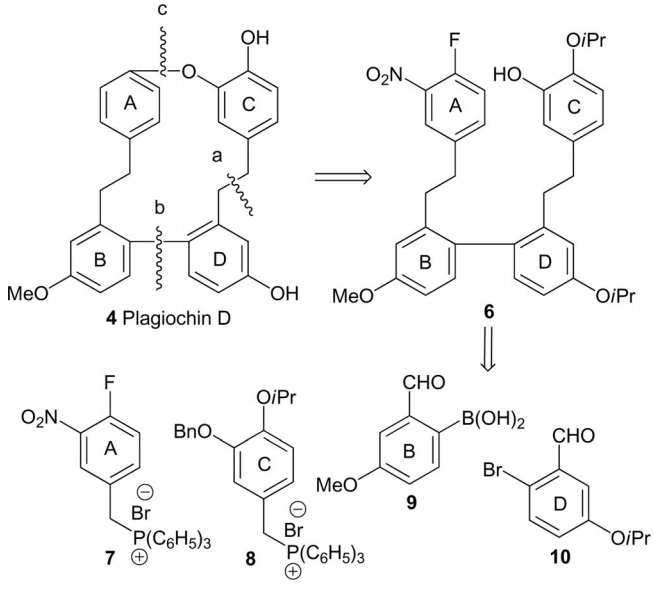


Figure 2. Retrosynthetic analysis of plagiochin D, fragments A–D.

by an intramolecular Still–Kelly reaction at position b to achieve the key 16-membered ring closure. Both methods gave poor yields of 17 and 20%, respectively.

In 2001, Fukuyama et al.[13] extended the intramolecular Still–Kelly reaction approach to the crucial 16-membered ring cyclization to synthesize plagiochin A (**1**) in 31% yield.

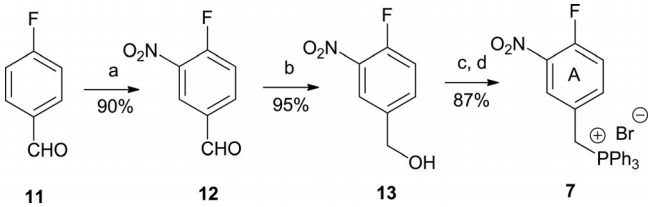
In 2009, the total synthesis of the proposed structure of plagiochin E (**5**) was achieved by Speicher and coworkers[14] using the McMurry protocols for the key 16-membered macrocyclization at position a, with a similar yield (23%; Figure 2).

As part of our ongoing program to develop efficient and robust methods, and considering the biological activities of the bis(bibenzyl) compounds, we turned our attention to biaryl ether formation at position c (Figure 2). Herein, we describe a novel, efficient, and general methodology for the total synthesis of this class of bis(bibenzyl) system using an extension of the S_NAr reaction[15] to achieve the key 16-membered ring closure.

Results and Discussion

The synthesis began with the construction of the linear precursor **6**, which includes a nucleophilic phenol function *ortho* to the isopropoxy group (ring C) and an electrophilic ring A for carrying out the ring closure. This precursor was formed by coupling four fragments, two phosphonium salts **7** and **8**, a boronic acid **9**, and a bromo derivative **10**. The fragments containing the corresponding protected phenol moieties, the nucleophilic and the electrophilic functionalities, are indicated in Figure 2.

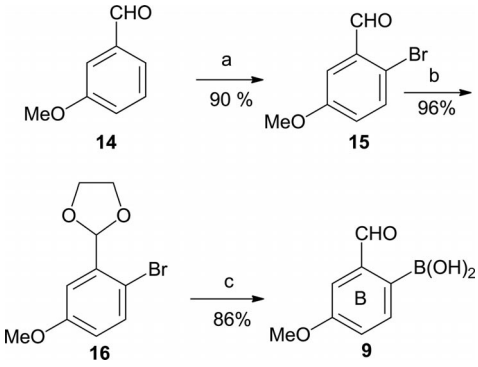
The phosphonium salt **7** (fragment A), was prepared in 74% overall yield from 4-fluorobenzaldehyde (**11**) by a four-step sequence involving nitration, hydride reduction, bromination, and PPh_3 addition[16] (Scheme 1).



Scheme 1. Synthesis of fragment A. Reagents and conditions: (a) HNO_3, H_2SO_4; (b) $NaBH_4$, MeOH; (c) PBr_3, toluene; (d) P-$(Ph)_3$, toluene.

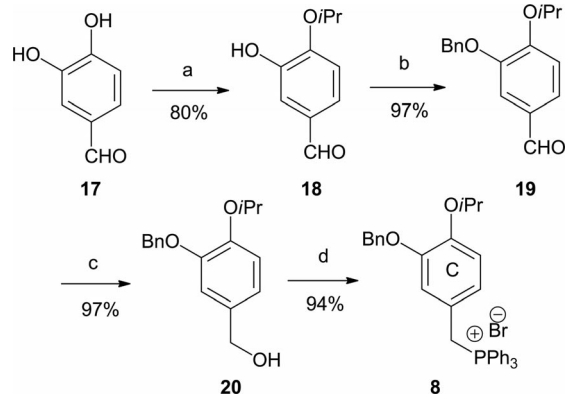
Boronic acid **9** (fragment B) was prepared in 74% overall yield starting from 3-methoxybenzaldehyde (**14**) by a three-step sequence involving bromination, protection of the aldehyde moiety with ethane-1,2-diol, then treatment with *n*BuLi and B(O*i*Pr)$_3$, and then hydrolysis under hydrochloric acid[17] (Scheme 2).

The phosphonium salt **8** (fragment C) was prepared in 70% overall yield from the commercially available 3,4-dihydroxybenzaldehyde (**17**) by selective protection of the phenol moieties with isopropyl and benzyl bromide, respectively, followed by reduction with lithium hydride to the



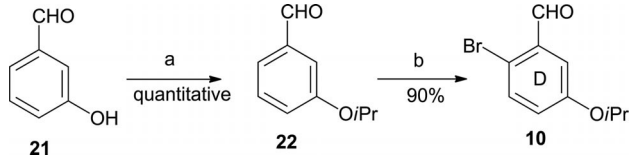
Scheme 2. Synthesis of fragment B. Reagents and conditions: (a) Br_2, CH_2Cl_2; (b) $HOCH_2CH_2OH$, APTS, benzene; (c) (i) *n*BuLi, THF; (ii) B(*i*PrO)$_3$; (iii) HCl, H_2O.

corresponding alcohol and then bromination with PBr_3 to give the bromo derivative, which, upon treatment with PPh_3, led to the phosphonium salt (Scheme 3).



Scheme 3. Synthesis of fragment C. Reagents and conditions: (a) *i*PrBr, K_2CO_3, DMF, 40 °C; (b) BrBn, K_2CO_3, DMF, 40 °C; (c) $LiAlH_4$, diethyl ether; (d) (i) PBr_3, toluene; (ii) $P(Ph)_3$, toluene.

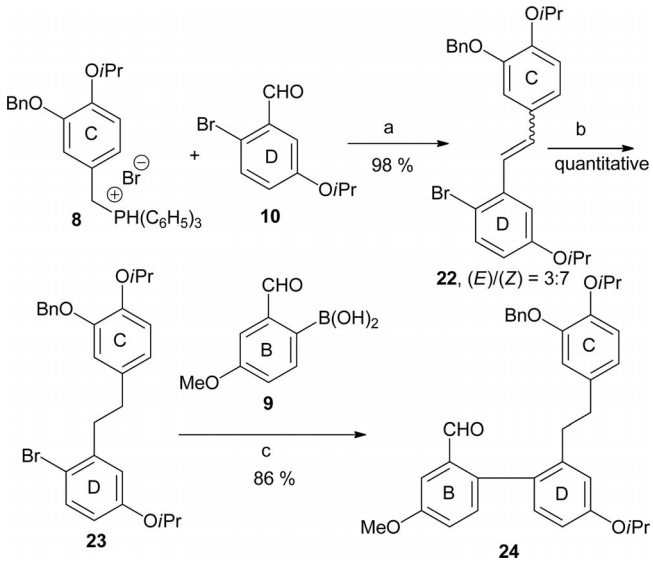
Fragment D, 2-bromo-5-isopropoxybenzaldehyde (**10**), was prepared in 90% overall yield by protecting the phenol moiety of 3-hydroxybenzaldehyde (**21**) with isopropyl bromide and subsequent bromination with bromine by the Lian-Yun protocol[18] (Scheme 4).



Scheme 4. Synthesis of fragment D. Reagents and conditions: (a) *i*PrBr, K_2CO_3, DMF; (b) Br_2, CH_2Cl_2.

Coupling of the units **8** and **10** by using the Wittig reaction under optimized conditions [Na_2CO_3(aq.), CH_2Cl_2] furnished the D–C segment **22** as an (*E*)/(*Z*) mixture in a ratio of 3:7 in 98% yield, and the pure forms (**22*E*** and **22*Z***) were obtained by silica gel column chromatography (Scheme 5). The double bond of each isomer was then reduced quantitatively by using Wilkinson's catalyst[19] to give a single compound **23**. The benzyl ether and even the aryl

bromide were tolerated under these mild hydrogenation conditions. Compound **23** was prepared on a larger scale for use in the next steps by reduction of the (*E*)/(*Z*) mixture of the crude product of the Wittig reaction. The biaryl compound **24**, segment B–D–C, was obtained in 86% yield by Suzuki reaction between segment **23** and the boronic acid **9**.

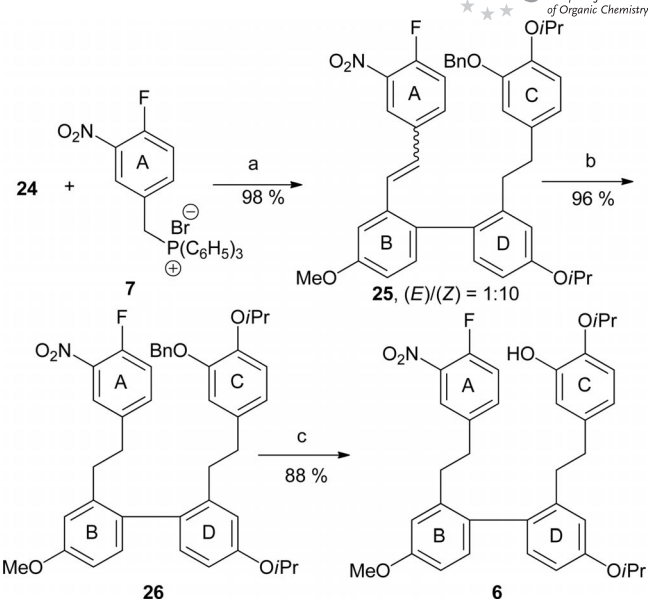


Scheme 5. Preparation of the precursor **24**. Reagents and conditions: (a) Na_2CO_3(aq.), CH_2Cl_2; (b) Wilkinson's cat., THF/*t*BuOH; (c) [$Pd(PPh_3)_4$], K_2CO_3, DME.

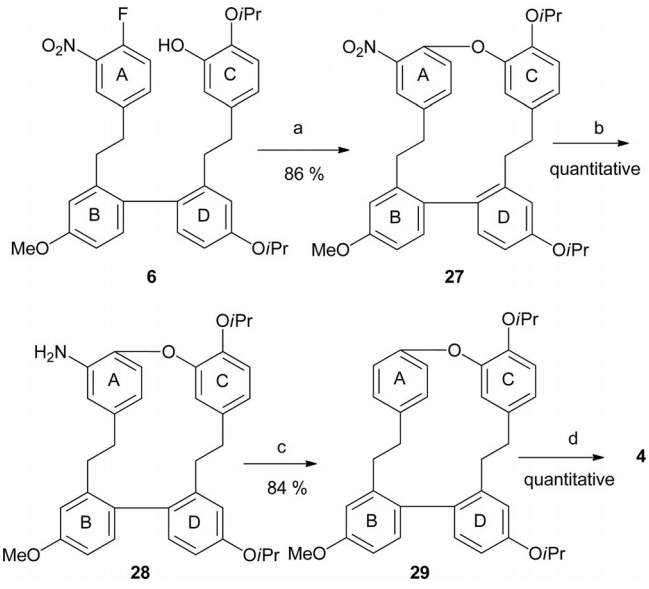
Wittig reaction between unit **24** and the phosphonium salt **7** gave the stilbene **25** as a 1:10 (*E*)/(*Z*) mixture in 98% yield. The (*E*)/(*Z*) mixture was reduced to compound **26** by catalytic hydrogenation[19] in 96% yield. Selective removal of the benzyloxy group was realized under carefully controlled conditions using a solution of concentrated HCl in AcOH to afford the precursor **6**, with a free hydroxy group for the crucial C–O ring-closure step, in 88% yield (Scheme 6).

Macrocyclization was achieved in 86% yield through an intramolecular S_NAr reaction using K_2CO_3 in DMF. A diastereomeric mixture was expected as a consequence of two distinct processes: (i) Creation of an axial chiral center at the biaryl axis (segment B–D–C) and (ii) creation of a chiral planar center on biaryl ether bond formation (segment A–O–C). However, the desired compound **27** was obtained as a mixture of two inseparable atropisomers (S_p)/(R_p) (Scheme 7) in a ratio of 1:1.[20]

Intramolecular S_NAr-based cyclization reactions were expected to produce atropisomeric mixtures of 14-, 15-, 16-, and 17-membered cyclic macropolypeptides as a consequence of the creation of a chiral planar center[21] that could be destroyed by removal of the activating nitro group in the next stages of the synthesis. Reduction (H_2, Pd/C in THF) gave the amine **28** as a mixture of separable atropisomers in quantitative yield, and the diastereomerically pure forms (**28a** and **28b**) were obtained by silica gel column chromatography. These compounds were submitted to reductive deamination[22] to afford a common product (**29**) devoid of the chiral planar center. Finally, removal of the isopropyl groups by using BCl_3 afforded the natural compound plagiochin D (**4**; Scheme 7). The spectroscopic data for compound **4** are identical to those of plagiochin D reported in the literature.[4,11,23]



Scheme 6. Preparation of the precursor **6**. Reagents and conditions: (a) Na_2CO_3(aq.), CH_2Cl_2; (b) Wilkinson's cat., THF/*t*BuOH; (c) AcOH, HCl (concd.).



Scheme 7. Key 16-membered ring closure and synthesis of plagiochin D (**4**). Reagents and conditions: (a) K_2CO_3, DMF; (b) Pd/C (10%), H_2, THF; (c) AcOH, $NaNO_2$, EtOH, $NaHSO_3$, H_2O; (d) BCl_3, CH_2Cl_2.

Thus, the bis(bibenzyl) system has been prepared by biaryl ether formation (S_NAr) in a critical key 16-membered ring-closing step in 50% overall yield starting from four simple and readily available aromatic subunits (fragments A–D). This compares with the previously described Wurtz-

type cyclization of an ethylene bridge (Nógrádi and co-workers, 7.4%),[11] the Still–Kelly reaction to form the biaryl (Fukuyama and co-workers, 8.6 and 9.0%),[12,13] and the McMurry protocol to form a stilbene bridge (Speicher and co-workers, 11.9%),[14] all of which start from elaborated precursors.

Conclusions

We have developed an efficient synthesis of plagiochin D (**4**). An intramolecular S_NAr reaction was useful for the key 16-membered ring-closing procedure and gave excellent and reproducible yields compared with other methodologies, which demonstrates the usefulness of intramolecular S_NAr-based methodologies for the construction of bis(bibenzyl) systems containing biaryl ether bonds. The synthesis of the other plagiochins by this methodology is currently underway, and the method may be extended to the synthesis of a small library by transformation of the nitro group into amino, amido, hydroxy, or halogenated derivatives.

Experimental Section

General: Commercially available reagents were used without further purification. Column chromatography (CC) was carried out on silica gel 60 from Merck with particle size 0.040–0.063 mm for normal-pressure and flash chromatography. IR spectra were determined with a Perkin-Elmer Spectrum GX instrument, and mass spectra were recorded with a JEOL JMS-700 instrument. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded with a Bruker AVANCE-III 500 instrument; the spectra were measured at 298 K in $CDCl_3$ solution with TMS as internal reference.

(*E*/*Z*)-2-(Benzyloxy)-4-(2-bromo-5-isopropoxystyryl)-1-isopropoxybenzene (22): Aq. Na_2CO_3 (25 mL of a 1 M solution) was added to a solution of aldehyde **10** (2.3 g, 9.46 mmol) and phosphorus salt **8** (7.36 g, 12.29 mmol) in CH_2Cl_2 (50 mL). After stirring the reaction mixture at 40 °C for 24 h, the mixture was cooled, and water was added and then extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford **22*E*** and **22*Z*** as a mixture of separable isomers [(*E*)/(*Z*) = 3:7; 4.48 g, 98% yield], which were separated by flash column chromatography (hexane/ethyl acetate, 200:1). **22*E***: FTIR: $\tilde{\nu}$ = 2975, 2901, 2338, 2116, 1586, 1506, 1462, 1371, 1262, 1224, 1178, 1164, 1108, 1026, 997, 955, 856, 801, 735 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.49–7.47 (m, 2 H), 7.42 (d, *J* = 8.8 Hz, 1 H), 7.39–7.36 (m, 2 H), 7.32–7.30 (m, 1 H), 7.20 (d, *J* = 16.1 Hz, 1 H, C*H*=CH), 7.14–7.12 (m, 2 H), 7.07 (ddd, *J* = 8.3, 2.1, 0.3 Hz, 1 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 16.1 Hz, 1 H, CH=C*H*), 6.66 (dd, *J* = 8.8, 3.0 Hz, 1 H), 5.17 (s, 2 H, CH_2Ph), 4.57–4.53 [m, 2 H, OC*H*$(CH_3)_2$], 1.37 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.34 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 157.24, 149.88, 148.53, 138.02, 137.37, 133.47, 131.01, 130.69, 128.48, 127.77, 127.32, 125.77, 120.91, 117.14, 116.34, 114.53, 113.95, 113.68, 72.03 [O*C*H$(CH_3)_2$], 71.48 (CH_2Ph), 70.27 [O*C*H$(CH_3)_2$], 22.21 [OCH(*C*H$_3)_2$], 21.99 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 480, 482 [M]$^+$. **22*Z***: FTIR: $\tilde{\nu}$ = 2974, 2908, 2338, 2112, 1604, 1507, 1472, 1371, 1254, 1222, 1196, 1164, 1115, 1048, 985, 940, 855, 810, 740 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.45 (d, *J* = 8.8 Hz, 1 H), 7.34–7.27 (m, 5 H), 6.78–6.74 (m, 4 H), 6.65 (ddd, *J* = 8.8, 3.0, 0.5 Hz, 1 H), 6.54 (d, *J* = 12.0 Hz, 1 H, CH=C*H*), 6.46 (d, *J* = 12.0 Hz, 1 H, C*H*=CH), 4.82 (s, 2 H, CH_2Ph), 4.46 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.24 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 1.31 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.14 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 156.85, 149.36, 147.45, 138.98, 137.25, 133.27, 130.95, 129.82, 128.36, 128.15, 127.64, 127.17, 122.77, 117.42, 117.38, 117.01, 115.65, 114.05, 72.01 [O*C*H$(CH_3)_2$], 70.94 (CH_2Ph), 70.07 [O*C*H$(CH_3)_2$], 22.16 [OCH(*C*H$_3)_2$], 21.77 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 480, 482 [M]$^+$.

2-(Benzyloxy)-4-(2-bromo-5-isopropoxyphenethyl)-1-isopropoxybenzene (23): Wilkinson's catalyst (4%, 20 mg) was added to a solution of compound **22** (457 mg, 0.94 mmol) in degassed solvent (THF/*t*BuOH, 1:1, 0.14 M) saturated by hydrogen. The solution was stirred under hydrogen at room temperature. When the hydrogenation was deemed complete by TLC, the reaction mixture was filtered through a short Celite pad and washed thoroughly with THF. The solvent was removed to afford **13** in quantitative yield. FTIR: $\tilde{\nu}$ = 2975, 2908, 2338, 2117, 1604, 1507, 1477, 1383, 1254, 1222, 1162, 1115, 1048, 985, 940, 854, 810, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.45 (m, 2 H), 7.41–7.36 (m, 3 H), 7.32–7.31 (m, 1 H), 6.86 (d, *J* = 8.1 Hz, 1 H), 6.78 (d, *J* = 2.1 Hz, 1 H), 6.74 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.65 (d, *J* = 3.0 Hz, 1 H), 6.62 (dd, *J* = 8.7, 3.0 Hz, 1 H), 5.09 (s, 2 H, CH_2Ph), 4.47 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.43 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 2.93–2.89 (m, 2 H, CH_2CH$_2$), 2.81–2.77 (m, 2 H, CH$_2$CH_2), 1.34 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.28 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 157.11, 149.88, 146.43, 141.85, 137.59, 136.15, 135.09, 133.20, 128.39, 127.67, 127.31, 121.39, 118.23, 118.08, 116.11, 115.19, 114.58, 72.33 [O*C*H$(CH_3)_2$], 71.38 (CH_2Ph), 70.10 [O*C*H$(CH_3)_2$], 38.63 (*C*H$_2$CH$_2$), 35.61 (CH$_2$*C*H$_2$), 22.30 [OCH(*C*H$_3)_2$], 21.93 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 482, 484 [M]$^+$.

2′-[3-(Benzyloxy)-4-isopropoxyphenethyl]-4′-isopropoxy-4-methoxybiphenyl-2-carbaldehyde (24): The boronic acid **9** (244 mg, 1.35 mmol) in ethanol (5 mL) was added to a mixture of compound **23** (437 mg, 0.90 mmol), 1,2-dimethoxyethane (25 mL), [Pd(PPh_3)$_4$] (104 mg, 0.09 mmol), and 2 M aq. Na_2CO_3 (4.6 mL). After heating at reflux for 24 h, the mixture was cooled, water was added, and then the mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($NaSO_4$) and concentrated. The product was isolated by flash chromatography on silica gel (hexane/ethyl acetate, 20:1) in 86% yield. FTIR: $\tilde{\nu}$ = 2973, 2915, 2338, 2117, 1685, 1604, 1507, 1479, 1383, 1253, 1222, 1162, 1115, 1045, 986, 939, 854, 813, 732 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.68 (s, 1 H, CHO), 7.48 (d, *J* = 2.7 Hz, 1 H), 7.42–7.40 (m, 2 H), 7.37–7.34 (m, 2 H), 7.31–7.29 (m, 1 H), 7.15 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.09 (dd, *J* = 8.4, 0.4 Hz, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.81 (d, *J* = 2.6 Hz, 1 H), 6.77 (dd, *J* = 8.3, 2.6 Hz, 1 H), 6.74 (d, *J* = 7.9 Hz, 1 H), 6.44–6.41 (m, 2 H), 4.93 (s, 2 H, CH_2Ph), 4.56 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.41 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 3.85 (s, 3 H, OCH_3), 2.70–2.56 (m, 4 H, CH_2CH_2), 1.36 [dd, *J* = 6.1, 0.9 Hz, 6 H, OCH(C*H*$_3)_2$], 1.30 [dd, *J* = 6.1, 0.9 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 192.32 (CHO), 158.92, 157.75, 149.79, 146.30, 141.71, 138.14, 137.46, 135.13, 134.85, 132.71, 132.06, 128.91, 128.31, 127.64, 127.26, 121.21, 121.09, 117.96, 116.71, 115.55, 112.78, 109.18, 72.32 [O*C*H$(CH_3)_2$], 71.12 (CH_2Ph), 69.81 [O*C*H$(CH_3)_2$], 55.50 (OCH_3), 36.65 (CH_2CH_2), 35.67 (CH_2CH_2), 22.26 [OCH(*C*H$_3)_2$], 22.09 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 538 [M]$^+$.

(*E*/*Z*)-2-[3-(Benzyloxy)-4-isopropoxyphenethyl]-2′-(4-fluoro-3-nitrostyryl)-4-isopropoxy-4′-methoxybiphenyl (25): Aq. Na_2CO_3 (1.0 mL of a 1 M solution) was added to a solution of aldehyde **24** (210 mg, 0.390 mmol) and phosphorus salt **7** (292 mg, 0.585 mmol) in CH_2Cl_2 (10 mL). After stirring the reaction mixture at 40 °C for 24 h, the mixture was cooled, water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford **25** as an (*E*)/(*Z*) mixture (1:10; 258 mg, 98%), which was purified by flash column chromatography (hexane/ethyl acetate, 10:1) to eliminate the triphenylphosphane oxide. Complex NMR spectroscopic data. MS (FAB): *m*/*z* = 675 $[M]^+$.

2-[3-(Benzyloxy)-4-isopropoxyphenethyl]-2′-(4-fluoro-3-nitrophenethyl)-4-isopropoxy-4′-methoxybiphenyl (26): Wilkinson's catalyst (4%, 10 mg) was added to a solution of compound **25** (245 mg, 0.362 mmol) in degassed solvent (THF/*t*BuOH, 1:1, 0.14 M) saturated by hydrogen. The solution was stirred under hydrogen at room temperature. When the hydrogenation was deemed complete by TLC, the reaction mixture was filtered through a short pad of Celite and washed thoroughly with THF. The solvent was removed to afford **26** (236 mg, 96% yield). FTIR: $\tilde{\nu}$ = 2973, 2915, 2338, 2117, 1685, 1604, 1507, 1479, 1383, 1253, 1222, 1162, 1115, 1045, 986, 939, 854, 813, 732 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.56–7.54 (m, 1 H), 7.43–7.41 (m, 2 H), 7.38–7.34 (m, 2 H), 7.31–7.28 (m, 1 H), 7.05–7.04 (m, 2 H), 6.98–6.96 (m, 1 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 6.81–6.78 (m, 3 H), 6.75 (dd, *J* = 8.2, 2.9 Hz, 2 H), 6.46 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.41 (d, *J* = 2.0 Hz, 1 H), 4.93 (d, *J* = 1.7 Hz, 2 H, CH_2Ph), 4.57 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.40 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 3.79 (s, 3 H, OCH_3), 2.72–2.48 (m, 8 H, CH_2CH_2), 1.37 [dd, *J* = 6.1, 3.4 Hz, 6 H, OCH(C*H*$_3)_2$], 1.30 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 158.75, 157.17, 153.83 (d, *J* = 262.83 Hz, *C*F), 149.83, 146.19, 141.33, 139.97, 138.66 (d, *J* = 4.33 Hz, CH_2CCH), 137.49, 136.97 (d, *J* = 7.53 Hz, *C*NO_2), 135.42 (d, *J* = 7.59 Hz, C*C*HCHCF), 135.33, 133.15, 132.34, 131.65, 131.07, 128.33, 127.62, 127.25, 125.45, 121.07, 117.94 (d, *J* = 18.67 Hz, CH*C*HCF), 116.66, 115.50, 114.46, 112.67, 111.17, 72.35 [O*C*H$(CH_3)_2$], 71.08 (CH_2Ph), 69.79 [O*C*H$(CH_3)_2$], 55.20 (OCH_3), 36.92 (CH_2CH_2), 36.03 (CH_2CH_2), 35.41 (CH_2CH_2), 22.25 [OCH(*C*H$_3)_2$], 22.13 [OCH(*C*H$_3)_2$], 22.09 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 677 $[M]^+$.

5-{2-[2′-(4-Fluoro-3-nitrophenethyl)-4-isopropoxy-4′-methoxybiphenyl-2-yl]ethyl}-2-isopropoxyphenol (6): Concd. HCl was added drop by drop (4 mL) to a solution of compound **26** (65 mg, 0.09 mmol) in acetic acid (4 mL). After heating at 70 °C for 4 h, the reaction mixture was cooled and then extracted with ethyl acetate. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated under vacuum. The pure product was isolated by flash column chromatography on silica gel (hexane/ethyl acetate, 10:1) in 88% yield. FTIR: $\tilde{\nu}$ = 3520, 2976, 2921, 2098, 1604, 1535, 1504, 1480, 1349, 1272, 1231, 1162, 1113, 1047, 970, 943, 862, 816, 745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.55 (d, *J* = 7.0 Hz, 1 H), 7.04 (dd, *J* = 16.8, 8.0 Hz, 3 H), 6.88 (d, *J* = 8.3 Hz, 1 H), 6.83 (d, *J* = 2.3 Hz, 1 H), 6.81–6.79 (m, 2 H), 6.74 (dd, *J* = 8.3, 2.4 Hz, 1 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 6.51 (d, *J* = 1.7 Hz, 1 H), 6.38 (dd, *J* = 8.1, 1.7 Hz, 1 H), 5.61 (s, 1 H, OH), 4.57 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.47 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 3.84 (s, 3 H, OCH_3), 2.72–2.50 (m, 8 H, CH_2CH_2), 1.37 [dd, *J* = 5.9, 3.3 Hz, 6 H, OCH(C*H*$_3)_2$], 1.31 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 158.77, 157.15, 153.82 (d, *J* = 262.83 Hz, *C*F), 146.36, 142.70, 141.35, 139.88, 138.71 (d, *J* = 3.61 Hz, CH_2CCH), 136.96 (d, *J* = 7.40 Hz, *C*NO_2), 135.38 (d, *J* = 8.03 Hz, C*C*HCHCF), 135.09, 133.12, 132.34, 131.53, 131.06, 125.45, 119.54, 117.95 (d, *J* = 20.89 Hz, CH*C*HCF), 116.56, 114.53, 113.31, 112.70, 111.27, 71.77 [O*C*H$(CH_3)_2$], 69.82 [O*C*H$(CH_3)_2$], 55.24 (OCH_3), 36.61 (CH_2CH_2), 36.00 (CH_2CH_2), 35.75 (CH_2CH_2), 35.41 (CH_2CH_2), 22.17 [OCH(*C*H$_3)_2$], 22.12 [OCH(*C*H$_3)_2$], 22.08 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 587 $[M]^+$.

Macrocycle 27: A solution of **6** (160 mg, 0.27 mmol) and anhydrous K_2CO_3 (113 mg, 0.82 mmol) in dry DMF (27 mL) was stirred at room temperature for 24 h. Then the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with H_2O (5 × 100 mL), dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography to afford **27** as a mixture of inseparable atropisomers in a ratio of 1:1 (132 mg, 86%). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.64 (d, *J* = 2.1 Hz, 1 H), 7.56 (d, *J* = 2.1 Hz, 1 H), 7.17–7.10 (m, 5 H), 7.05 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.87–6.77 (m, 5 H), 6.75–6.67 (m, 5 H), 6.61 (d, *J* = 2.2 Hz, 1 H), 6.55 (d, *J* = 2.2 Hz, 1 H), 5.26 (d, *J* = 1.7 Hz, 1 H), 5.21 (d, *J* = 1.7 Hz, 1 H), 4.58 [sept, *J* = 6.1 Hz, 2 H, OC*H*$(CH_3)_2$], 4.46–4.36 [m, 2 H, OC*H*$(CH_3)_2$], 3.89 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.19–2.83 (m, 14 H, CH_2CH_2), 2.24–2.18 (m, 1 H, CH_2CH_2), 2.11–2.03 (m, 1 H, CH_2CH_2), 1.40 [dd, *J* = 6.1, 3.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.37 [d, *J* = 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.30 [dd, *J* = 7.6, 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.23 [d, *J* = 6.1 Hz, 3 H, OCH(C*H*$_3)_2$], 1.16 [d, *J* = 6.1 Hz, 3 H, OCH-(C*H*$_3)_2$] ppm. MS (FAB): *m*/*z* = 567 $[M]^+$.

Macrocycle 28: Pd/C catalyst (10%, 13 mg) was added to a stirred solution of compound **27** (130 mg, 0.23 mmol) in THF (10 mL). The mixture was then hydrogenated under H_2 (balloon) at room temperature for 5 h. Then the mixture was filtered through a short pad of Celite. The solvent was removed to afford **28a** and **28b** as a mixture of atropisomers (122 mg, quantitative yield), which were separated by flash column chromatography. **28a**: FTIR: $\tilde{\nu}$ = 3474, 3376, 2977, 2926, 1723, 1605, 1507, 1479, 1439, 1371, 1341, 1283, 1255, 1222, 1164, 1116, 1048, 986, 939, 854, 811, 719 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.17 (d, *J* = 2.3 Hz, 1 H), 7.01 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 6.81 (d, *J* = 8.2 Hz, 1 H), 6.72 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.69 (t, *J* = 2.7 Hz, 1 H), 6.67 (t, *J* = 2.6 Hz, 1 H), 6.64 (d, *J* = 2.5 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 6.35 (d, *J* = 2.0 Hz, 1 H), 6.31 (dd, *J* = 8.0, 2.1 Hz, 1 H), 5.57 (d, *J* = 2.1 Hz, 1 H), 4.55 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 4.45 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 3.87 (s, 3 H, OCH_3), 3.41 (br. s, 2 H, NH_2), 2.88 (s, 7 H, CH_2CH_2), 2.17 (m, 1 H, CH_2CH_2), 1.38 [dd, *J* = 9.1, 6.1 Hz, 6 H, OCH(C*H*$_3)_2$], 1.32 [d, *J* = 6.1 Hz, 3 H, OCH(C*H*$_3)_2$], 1.21 [d, *J* = 6.1 Hz, 3 H, OCH(C*H*$_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 158.06, 156.50, 150.61, 144.59, 142.07, 140.53, 140.19, 140.13, 139.89, 134.59, 132.94, 132.09, 132.04, 131.80, 122.84, 121.20, 120.08, 116.90, 116.40, 115.39, 114.92, 114.76, 111.18, 110.11, 72.35 [O*C*H$(CH_3)_2$], 69.55 [O*C*H$(CH_3)_2$], 55.25 (OCH_3), 34.78 (CH_2CH_2), 34.69 (CH_2CH_2), 32.05 (CH_2CH_2), 30.66 (CH_2CH_2), 22.29 [OCH(*C*H$_3)_2$], 22.26 [OCH(*C*H$_3)_2$], 21.92 [OCH(*C*H$_3)_2$] ppm. MS (FAB): *m*/*z* = 537 $[M]^+$. **28b**: FTIR: $\tilde{\nu}$ = 3469, 3374, 2973, 2915, 1723, 1605, 1507, 1478, 1439, 1371, 1341, 1286, 1255, 1222, 1195, 1116, 1048, 986, 940, 854, 811, 719 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.15 (d, *J* = 2.7 Hz, 1 H), 7.06 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 6.73 (dd, *J* = 8.1, 2.2 Hz, 1 H), 6.69 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.67 (dd, *J* = 8.0, 2.7 Hz, 1 H), 6.60 (d, *J* = 2.5 Hz, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 6.35 (d, *J* = 2.0 Hz, 1 H), 6.29 (dd, *J* = 8.2, 2.0 Hz, 1 H), 5.57 (d, *J* = 2.1 Hz, 1 H), 4.55 [sept, *J* = 6.1 Hz, 1 H, OC*H*-$(CH_3)_2$], 4.41 [sept, *J* = 6.1 Hz, 1 H, OC*H*$(CH_3)_2$], 3.87 (s, 3 H, OCH_3), 3.43 (br. s, 2 H, NH_2), 3.02–2.93 (m, 7 H, CH_2CH_2), 2.25–

2.18 (m, 1 H, CH_2CH_2), 1.38 [dd, J = 13.7, 6.1 Hz, 6 H, OCH(CH_3)$_2$], 1.30 [d, J = 6.1 Hz, 3 H, OCH(CH_3)$_2$], 1.18 [d, J = 6.0 Hz, 3 H, OCH(CH_3)$_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 158.06, 156.49, 150.64, 144.52, 141.49, 140.27, 140.19, 139.99, 138.73, 134.28, 132.88, 132.25, 132.01, 131.55, 124.09, 121.32, 119.03, 117.35, 117.03, 114.97, 114.88, 111.61, 110.01, 72.31 [O*C*H(CH_3)$_2$], 69.72 [O*C*H(CH_3)$_2$], 55.25 (OCH_3), 35.21 (CH_2CH_2), 34.68 (CH_2CH_2), 31.26 (CH_2CH_2), 30.13 (CH_2CH_2), 22.30 [OCH(*C*H_3)$_2$], 22.26 [OCH(*C*H_3)$_2$], 22.24 [OCH(*C*H_3)$_2$], 21.73 [OCH(*C*H_3)$_2$] ppm. MS (FAB): m/z = 537 $[M]^+$.

Macrocycle 29: Macrocycle **28** (70 mg, 0.13 mmol) was dissolved in ethanol (5 mL) and acetic acid (3 mL) at room temperature. Solutions of sodium nitrite (1.30 mmol in 3 mL water) and sodium bisulfite (1.30 mmol in 4 mL of water) were added sequentially to the stirred solution. The reaction was monitored by TLC. Upon completion (12 h), the reaction mixture was extracted with ethyl acetate, and the organic phase was washed with water. The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The pure product was isolated by flash chromatography on silica gel (hexane/ethyl acetate, 12:1) in 84% yield. FTIR: $\tilde{\nu}$ = 2928, 2522, 2159, 1733, 1605, 1505, 1476, 1371, 1259, 1220, 1163, 1115, 1049, 985, 938, 906, 808, 729, 598 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.19 (d, J = 2.7 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 6.94–6.90 (m, 3 H), 6.80 (d, J = 8.2 Hz, 1 H), 6.74–6.67 (m, 5 H), 6.61 (d, J = 2.5 Hz, 1 H), 5.29 (d, J = 2.1 Hz, 1 H), 4.55 [sept, J = 6.1 Hz, 1 H, OC*H*(CH_3)$_2$], 4.43 [sept, J = 6.1 Hz, 1 H, OC*H*(CH_3)$_2$], 3.88 (s, 3 H, OCH_3), 3.10–2.83 (m, 7 H, CH_2CH_2), 2.19–2.12 (m, 1 H, CH_2CH_2), 1.38 [d, J = 6.1 Hz, 3 H, OCH(CH_3)$_2$], 1.37 [d, J = 6.1 Hz, 3 H, OCH(CH_3)$_2$], 1.31 [d, J = 6.1 Hz, 3 H, OCH(CH_3)$_2$], 1.20 [d, J = 6.1 Hz, 3 H, OCH(CH_3)$_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 158.08, 156.51, 155.10, 152.98, 144.27, 140.13, 139.72, 139.00, 134.01, 132.27, 132.04, 131.39, 130.10, 129.68, 123.89, 122.57, 120.74, 117.13, 115.99, 115.01, 114.87, 111.47, 110.05, 72.43 [O*C*H(CH_3)$_2$], 69.67 [O*C*H(CH_3)$_2$], 55.23 (OCH_3), 34.83 (CH_2CH_2), 34.80 (CH_2CH_2), 31.41 (CH_2CH_2), 30.21 (CH_2CH_2), 22.25 [OCH(*C*H_3)$_2$], 22.21 [OCH(*C*H_3)$_2$], 21.76 [OCH(*C*H_3)$_2$] ppm. MS (FAB): m/z = 522 $[M]^+$.

Plagiochin D (4): A solution of **29** (45 mg, 0.08 mmol) in dichloromethane (5 mL) was treated at 0 °C with BCl_3 (0.51 mL, 1 M in CH_2Cl_2). After 30 min, dry methanol (10 mL) was added. The mixture was stirred at 0 °C for 5 min, and then the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to afford plagiochin D (**4**) in quantitative yield. FTIR: $\tilde{\nu}$ = 3902, 3177, 2927, 2533, 2159, 2023, 1741, 1668, 1604, 1504, 1445, 1347, 1285, 1218, 1162, 1112, 1021, 996, 817, 760 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.59 (s, 1 H, OH), 7.97 (s, 1 H, OH), 7.17 (d, J = 2.6 Hz, 1 H), 7.06 (d, J = 8.5 Hz, 1 H), 6.96 (dd, J = 8.2, 2.1 Hz, 1 H), 6.90 (dd, J = 8.2, 2.1 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 6.72 (dd, J = 8.3, 2.4 Hz, 1 H), 6.70 (dd, J = 8.3, 2.4 Hz, 2 H), 6.65 (dd, J = 8.1, 2.5 Hz, 1 H), 6.62 (dd, J = 8.1, 2.5 Hz, 1 H), 6.58 (d, J = 2.4 Hz, 1 H), 5.26 (d, J = 2.0 Hz, 1 H), 3.88 (s, 3 H, OCH_3), 3.09–2.81 (m, 7 H, CH_2CH_2), 2.19 (m, 1 H, CH_2CH_2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ = 157.44, 155.42, 154.15, 149.31, 142.70, 139.32, 139.17, 138.96, 132.51, 131.97, 131.59, 129.50, 129.43, 129.35, 123.22, 121.96, 120.83, 115.22, 114.49, 114.37, 113.42, 111.02, 109.54, 54.76 (OCH_3), 34.17 (CH_2CH_2), 30.57 (CH_2CH_2), 29.14 (CH_2CH_2) ppm. HRMS: calcd. for $[MH]^+$ 438.18; found 438.18.

Acknowledgments

The authors thank the Consejo Nacional de Ciencia y Tecnología (CONACYT) for financial support (project 51346-Q) and for the scholarship awarded to J. C. C. M. We thank A. Gutiérrez-Carrillo for NMR spectra. We also thank V. Labastida for her valuable technical help in obtaining mass spectra.

[1] H. D. Zinsmeister, H. Becker, T. Eicher, *Angew. Chem.* **1991**, *103*, 134–151; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 130–147.
[2] H. D. Zinsmeister, H. Becker, T. Eicher, R. Mues, *Naturwiss. Rundschau* **1994**, *47*, 131–136.
[3] a) Y. Asakawa, *Progress in the Chemistry of Organic Natural Products* (Eds.: E. Herz, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm), Springer, Vienna, New York, **1995**, p. 5; b) Y. Asakawa, M. Toyota, M. Tori, T. Hashimoto, *Spectroscopy* **2000**, *14*, 149–175; c) Y. Asakawa, A. Ludwiczuk, F. Nagashima, M. Toyota, T. Hashimoto, M. Tori, Y. Fukuyama, L. Harinantenaina, *Heterocycles* **2009**, *77*, 99–150.
[4] T. Hashimoto, M. Tori, Y. Asakawa, Y. Fukazawa, *Tetrahedron Lett.* **1987**, *28*, 6295–6298.
[5] G. M. Keserü, M. Nógrádi, *Phytochemistry* **1992**, *31*, 1573–1576.
[6] Y. Fukuyama, K. Nakamura, M. Kodama, *111th Annual Meeting of the Pharmaceutical Society of Japan*, Tokyo, Japan, **1991**, Abstracts 2, p. 4.
[7] C. Niu, J.-B. Qu, H.-X. Lou, *Chem. Biodivers.* **2006**, *3*, 34–40.
[8] a) X.-Z. Wu, W.-Q. Chang, A.-X. Chen, L.-M. Sun, H.-X. Lou, *Biochim. Biophys. Acta* **2010**, 439–447; b) X.-Z. Wu, A.-X. Chen, L.-M. Sun, S.-J. Sun, H.-X. Lou, *Biochim. Biophys. Acta* **2009**, 770–777.
[9] X.-L. Guo, P. Leng, Y. Yang, L.-G. Yu, H.-X. Lou, *J. Appl. Microbiol.* **2008**, *104*, 831–838.
[10] Y.-Q. Shi, X.-J. Qu, Y.-X. Liao, C.-F. Xie, Y.-N. Cheng, S. Li, H.-X. Lou, *Eur. J. Pharmacol.* **2008**, 66–71.
[11] G. M. Keserü, G. Mezey-Vandor, M. Nógrádi, B. Vermes, M. Kajtar-Peredy, *Tetrahedron* **1992**, *48*, 913–922.
[12] Y. Fukuyama, H. Yaso, K. Nakamura, M. Kodama, M. Kajtar-Peredy, *Tetrahedron Lett.* **1999**, *40*, 105–108.
[13] Y. Fukuyama, H. Yaso, T. Mori, H. Takahashi, H. Minami, M. Kodama, *Heterocycles* **2001**, *54*, 259–274.
[14] a) A. Speicher, M. Groh, J. Zapp, A. Schaumlöffel, M. Knauer, G. Bringmann, *Synlett* **2009**, *11*, 1852–1858; b) A. Speicher, M. Groh, M. Hennrich, A.-M. Huynh, *Eur. J. Org. Chem.* **2010**, 6770–6778.
[15] J. Zhu, *Synlett* **1997**, 133–144.
[16] R. Beugelmans, P. S. Girij, M. Bois-Choussy, J. Chastanet, J. Zhu, *J. Org. Chem.* **1994**, *59*, 5535–5542.
[17] M. Lautens, T. Marquardt, *J. Org. Chem.* **2004**, *69*, 4607–4614.
[18] Z. Lian-Yun, L. Quiao, R. Suo-Bao, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 955–959.
[19] A. Jourdan, E. González-Zamora, J. Zhu, *J. Org. Chem.* **2002**, *67*, 3163–3164.
[20] Identified by NMR spectroscopy. See the NMR spectroscopic data for macrocycle **27** in the Exp. Sect.
[21] R. Beugelmans, G. Roussi, E. González-Zamora, A.-C. Carbonnelle, *Tetrahedron* **1999**, *55*, 5089–5112.
[22] O. J. Geoffroy, T. A. Morinellib, G. P. Meier, *Tetrahedron Lett.* **2001**, *42*, 5367–5369.
[23] Y. Fukuyama, H. Yaso, T. Mori, H. Takahashi, H. Minami, M. Kodama, *Heterocycles* **2001**, *54*, 259–274.

Received: October 15, 2010
Published Online: April 21, 2011

