JOURNAL OF NATURAL PRODUCTS

ARTICLE

pubs.acs.org/jnp

Total Synthesis of the Marine Metabolite (±)-Polysiphenol via Highly Regioselective Intramolecular Oxidative Coupling

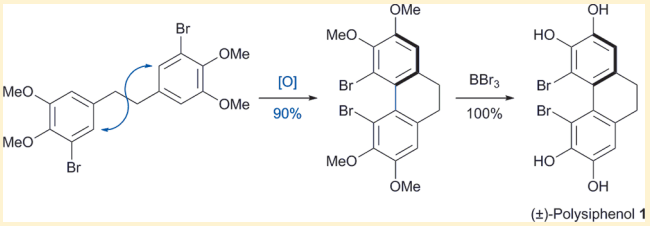
Tim N. Barrett,[†] D. Christopher Braddock,*[,†] Anna Monta,[†] Michael R. Webb,[‡] and Andrew J. P. White[†]

[†]Department of Chemistry, Imperial College London, London, South Kensington SW7 2AZ, U.K.

[‡]GlaxoSmithKline Research and Development Ltd, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.

Supporting Information

ABSTRACT: (±)-Polysiphenol (**1**), an atropisomerically stable 4,5-dibrominated 9,10-dihydrophenanthrene from *Polysiphonia ferulacea*, was prepared by a biomimetically inspired highly regioselective intramolecular oxidative coupling of a dibrominated dihydrostilbene. The installation of the two bromine atoms prior to oxidative coupling prevents further oxidation to a planar aromatized phenanthrene. By this strategy, the synthesis of (±)-polysiphenol was achieved in four steps in 70% overall yield. Synthesis of the naturally occurring 5,5′-(ethane-1,2-diyl)bis(3-bromobenzene-1,2-diol) (**2**) (the likely biogenetic precursor of polysiphenol) and 5,5′-(ethane-1,2-diyl)bis(3,4,6-tribromobenzene-1,2-diol) (**9**) are also reported. The origins of the regioselectivity in the oxidative coupling are explored.



(±)-Polysiphenol **1**

Polysiphenol (**1**)[1] is one of a number of naturally occurring bromophenols isolated from red marine algae Rhodomelaceae,[2−4] with members of this family showing assorted biological activities and other properties.[5] Polysiphenol, the first 9,10-dihydrophenanthrene[6] to be isolated from a marine source, was obtained from the red alga *Polysiphonia ferulacea* collected at Joal, Senegal, in 1990.[1] It was found to exist as a stable atropisomer at room temperature, and its *R* configuration was established from its CD spectrum.[1] Two more axially chiral bromophenol-9,10-dihydrophenanthrenes have recently been isolated from *Polysiphonia urceolata*.[3b] Biogenetically, it seems reasonable to propose that these bromophenolic 9,10-phenanthrenes could arise from dihydrostilbene derivatives by oxidative phenolic coupling.[7,8] Indeed, dihydrostilbene **2**, which could serve as the biogenetic precursor for **1** in this fashion, has been isolated from *P. urceolata*.[9] Such a coupling would present a direct and attractive synthetic route to these compounds (Figure 1). However, there are only a few reports on the synthesis[10] of naturally occurring bromophenols, and no syntheses of polysiphenol (**1**) or of the other phenanthrenes have been reported to date. Herein, we report on the first synthesis of (±)-polysiphenol (**1**) via a highly regioselective intramolecular oxidative coupling. We also report on the synthesis of dihydrostilbene **2** and a naturally occurring hexabromide (*vide infra*). Finally, the origins of the high regioselectivity of the oxidative coupling step are explored.

At the outset of our investigations we considered that successful oxidative coupling would require a substrate with the two bromine atoms already installed, leading necessarily (because of the bulky bromine substituents)[1] to a nonplanar atropisomeric dihydrophenanthrene framework, where further undesirable oxidation to a planar fully aromatized phenanthrene could not occur.[11] Moreover, we also recognized the need to control the regiochemistry of the proposed oxidative coupling, such that C−C biaryl bond formation occurs to form a 4,5-dibromodihydrophenanthrene (Figure 2, mode a) rather than a 2,7-dibromo- (mode b) or 2,5-dibromodihydrophenanthrene (mode c). We posited that such control could be gained by exploiting the well-known coplanar conformational preference of *ortho*-dimethoxybenzenes[12] to sterically shield the undesired sites of modes b and c coupling (Figure 2). This interaction was expected to be particularly severe in mode b, where two methoxy groups must approach each other. Further, we also recognized the need for an oxidative coupling that was compatible with aryl bromides.

RESULTS AND DISCUSSION

To test the validity of these propositions, we initially explored the chemistry of some model compounds. Thus stilbene **5**[11c] was prepared in a novel one-pot procedure from commercially available 3,4-dimethoxybenzyl alcohol (**3**) involving Appel bromination and *in situ* phosphonium salt formation with excess triphenyl phosphine, ylid formation by subsequent addition of base, and finally Wittig reaction with commercially available aldehyde **4** (Scheme 1). Subsequent hydrogenation of alkene **5**[11c] gave tetramethoxydihydrostilbene **6**. The X-ray crystal structure of dihydrostilbene **6** clearly shows the coplanar conformation in each of the *ortho*-dimethoxybenzene subunits (Figure 3).[13]

Dihydrostilbene **6** is known to undergo highly regioselective oxidative biaryl coupling with hypervalent iodine reagent

Received: July 15, 2011
Published: August 29, 2011

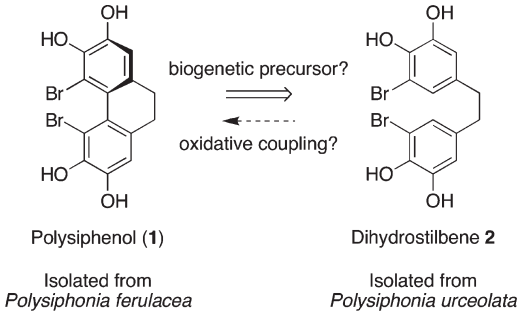


Figure 1. Proposed biogenesis of polysiphenol.

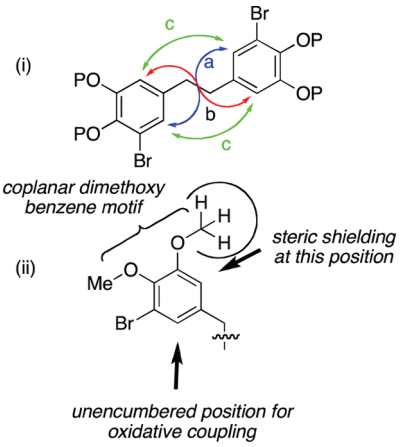
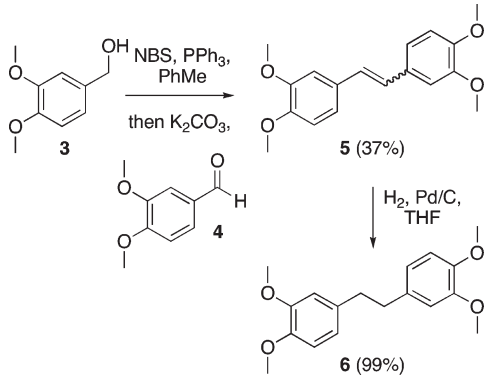


Figure 2. Considerations for regioselective biaryl bond formation: (i) possible modes of coupling; (ii) possible influence of coplanar dimethoxy benzene motif.

Scheme 1. Preparation of Model Compound 6



phenyliodine bis(trifluoroacetate) (PIFA) in conjunction with $BF_3 \cdot OEt_2$ with unavoidable aromatization to give phenanthrene **7** in excellent yield (Scheme 2).[11] Two aspects of this reaction deserve further comment. Although there has been no speculation in the literature, the observed regioselectivity may, in part, be controlled by the conformation of the methoxy groups in each dimethoxybenzene subunit, with their preferred coplanar *ortho*-dimethoxybenzene conformations disfavoring coupling by modes b or c (cf. Figure 2). Second, the dihydrophenanthrene (intemediate **A**, Scheme 2) that

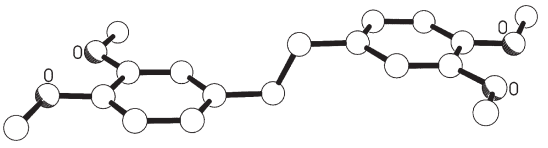
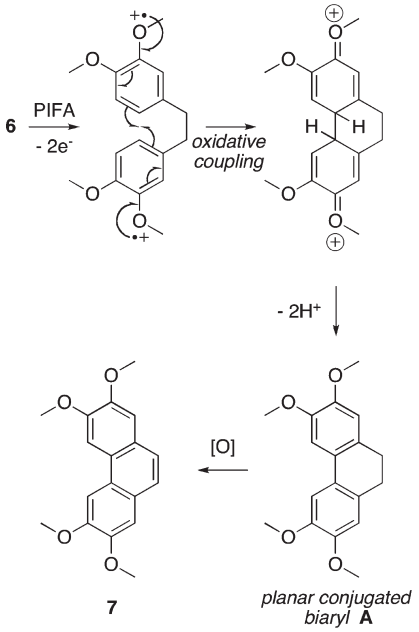
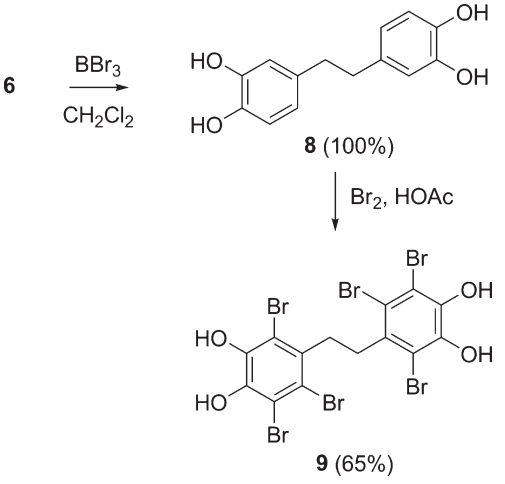


Figure 3. Molecular structure of **6**.

Scheme 2. Proposed PIFA-Mediated Oxidative Coupling–Aromatization Mechanism



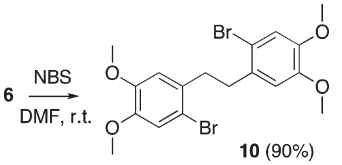
Scheme 3. Synthesis of Naturally Occurring Hexabromide 9



must be initially formed is subject to further oxidation. The coplanar nature of this initial biaryl adduct **A** evidently leads to extended conjugation of the π-system and a higher energy HOMO, thus facilitating competitive oxidation.[14] In our hands the oxidative cyclization–aromatization of **6** with PIFA proceeded as previously reported to give aromatic **7** in good isolated yield (81%).

dx.doi.org/10.1021/np200596q |J. Nat. Prod. 2011, 74, 1980–1984

Scheme 4. Regioselective Dibromination



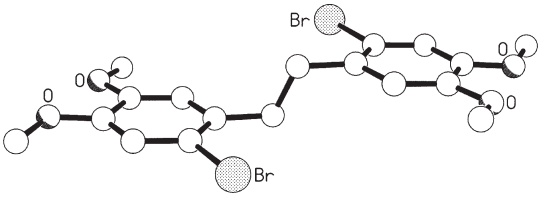
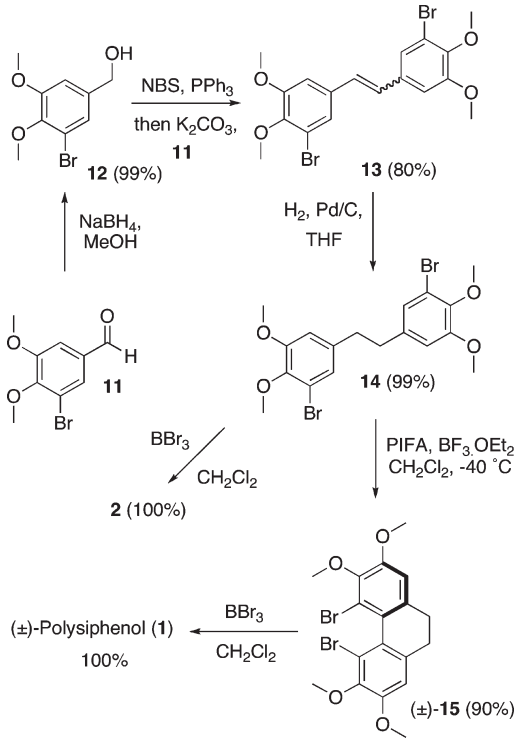


Figure 4. Molecular structure of **10**.

Scheme 5. Total Synthesis of (±)-Polysiphenol 1 and Dibromodihydrostilbene 2



Tetramethoxydihydrostilbene **6** could also be deprotected to tetrol **8** (Scheme 3).[15] Electrophilic bromination at all the available aromatic positions gave the naturally occurring hexabromide **9**.[16] This constitutes the first synthesis of this metabolite.

Tetramethoxydihydrostilbene **6** was dibrominated using NBS in DMF with the expected selectivity[17] to give dibromide **10**[18] in excellent yield (Scheme 4).

In compound **10**, the two bromine substituents are *incorrectly* positioned on the aromatic rings to lead to polysiphenol (**1**) by oxidative coupling. However, this substrate was purposefully prepared for a 2-fold test of the oxidative coupling. First, would

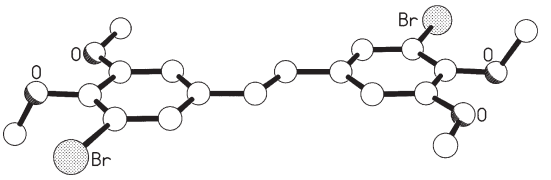
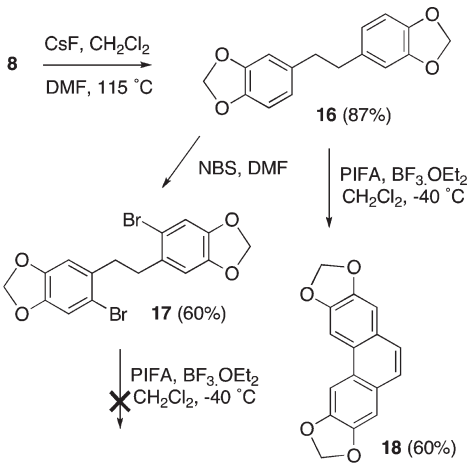


Figure 5. Molecular structure of *E*-**13** showing the now out-of-plane arrangement of the 4-methoxy groups.

Scheme 6. Regioselectivity Experiments



aromatic bromides survive the PIFA oxidative-coupling conditions? Second, with the two bromines now blocking the previously preferred positions of coupling (cf. compound **6**, Scheme 2), would coupling occur instead between the other two free *ortho* positions? An X-ray crystal structure of compound **10** (Figure 4) clearly shows the coplanar arrangement of the two pairs of methoxy groups,[19] which may be a factor in controlling regioselective coupling.

In the event, subjecting compound **10** to identical oxidative-coupling conditions as used for **6** gave complete return of unreacted starting material upon workup. This experiment thus demonstrates that (a) the aromatic bromide functionality is tolerant of these conditions and (b) that the oxidative coupling does not proceed when this position is blocked.

Having established the above, attention now turned to a synthesis of polysiphenol (**1**). Commercially available 5-bromoveratraldehyde **11** was reduced to the corresponding alcohol **12**[20] (Scheme 5). Alcohol **12** was converted into olefin **13**[21] in a telescoped one-pot reaction sequence via the bromide, phosphonium salt, ylid, and Wittig reaction with **11**. *E*-**13** proved to be crystalline, and an X-ray crystal structure was obtained (Figure 5). Although the bromine atoms buttress their adjacent methoxy groups, the remote methoxy groups maintain their preferred planar arrangement with the aromatic ring.[22]

Subsequent hydrogenation of olefin **13** afforded dibromide **14**[23] as the substrate for oxidative coupling. To our delight, oxidative coupling proceeded smoothly to dibromodihydrophenanthrene **15** in excellent yield (90%) and with perfect regioselectivity. Evidently, this dihydrophenanthrene, with the two bromine atoms preinstalled at the 4- and 5-positions (phenanthrene numbering), cannot aromatize to a planar phenanthrene. Finally, the methoxy groups were removed from

dx.doi.org/10.1021/np200596q |*J. Nat. Prod.* 2011, 74, 1980–1984

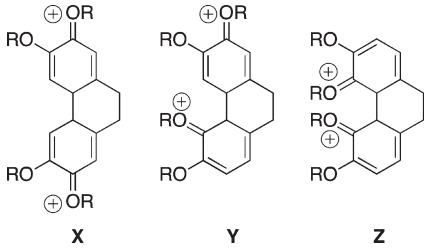


Figure 6. Intermediates **X**, **Y**, and **Z** with decreasing amounts of cross-conjugation.

15 to give (±)-polysiphenol (**1**).[1,24] Dibromide **14** could also be deprotected to provide naturally occurring dibromodihydrostilbene **2**.[9,25]

To further probe the regioselectivity of the oxidative coupling, we examined the PIFA-mediated reaction of methylenedioxy compounds **16** and **17**. Dihydrostilbene **16**[26] was prepared from tetrol **8**, and dibromide **17** was prepared by regioselective bromination of **16** (Scheme 6). While **16** underwent efficient cyclization (and aromatization) to **18**,[27] dibromide **17** returned only starting material under these conditions. These experiments prove that the regioselectivity of the oxidative coupling is not controlled by steric effects due to enforced coplanar dimethoxybenzene conformations in compounds **6**, **10**, and **14** and must instead be under electronic control. We suggest that the observed regioselectivity of coupling is such that cross-conjugation[28] is maximized in the transition state leading to intermediate **X** (via mode a, cf., Figure 2) rather than intermediates **Y** (mode c) or **Z** (mode b) (Figure 6).

In conclusion, we have reported the first total syntheses of naturally occurring (±)-polysiphenol **1**, dibromodihydrostilbene **2**, and hexabromide **9**. The synthesis of (±)-polysiphenol **1** is brought about in four steps with an overall yield of 70%. The key step involves highly regioselective oxidative coupling of a dibrominated dihydrostilbene, as inspired by the probable biogenesis of polysiphenol.

EXPERIMENTAL SECTION

General Experimental Procedures. See Supporting Information.

5,5′-(Ethane-1,2-diyl)bis(3,4,6-tribromobenzene-1,2-diol) (9).[16] To a stirred solution of tetrol **8** (0.10 g, 0.41 mmol) in acetic acid (5 mL) was added bromine (2.1 mL, 4.1 mmol, 10 equiv), and the mixture was stirred for 48 h. The mixture was diluted with CH_2Cl_2 (10 mL), quenched with saturated aqueous sodium sulfite solution (25 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 25 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated, affording title compound, **9** (0.19 g, 65%), as a yellow solid: mp 228 °C; lit.[16] 230−232 °C; IR (neat) 3550−2700 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.69 (2H, br s, ArO*H*), 8.56 (2H, br s, ArO*H*), 3.45 (4H, s, ArC_2H_4Ar); ^{13}C NMR (100 MHz, acetone-d_6) δ 144.0, 143.9, 132.5, 118.0, 113.9, 37.3; MS (EI^+) m/z 714, 716, 718, 720, 722, 724, 726 $[M]^+$; HREIMS m/z 713.5522 $[M]^+$ (calcd for $C_{14}H_8O_4{}^{79}Br_6$, 713.5523).

(±)-4,5-Dibromo-2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (15). To a stirred solution of diarylethane **14** (0.20 g, 0.43 mmol) in CH_2Cl_2 (10 mL) at −40 °C were added PIFA (0.24 g, 0.52 mmol) and $BF_3{\cdot}OEt_2$ (0.13 mL, 1.04 mmol), and the mixture was allowed to warm to room temperature (rt) and stirred for 24 h. The solution was filtered through a silica plug, and the solvent evaporated *in vacuo*. The residue was subjected to column chromatography (petroleum spirit/EtOAc, 2:1) to provide the title compound, **15** (0.18 g, 90%), as a white solid: mp 215 °C; IR (neat) 2939, 2837, 1594, 1464, 1401, 1257, 1059, 996 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (2H, s, Ar*H*), 3.94 (6H, s, $ArOCH_3$), 3.92 (6H, s, $ArOCH_3$), 2.75−2.57 (4H, m, ArC_2H_4Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 145.7, 137.9, 128.8, 119.1, 110.2, 60.7, 56.2, 31.6; MS (CI^+, NH_3) m/z 474, 476, 478 $[M + NH_4]^+$; HRCIMS (NH_3) m/z 473.9931 $[M + NH_4]^+$ (calcd for $C_{18}H_{22}{}^{79}Br_2NO_4$, 473.9916).

(±)-Polysiphenol (1).[1] To a stirred solution of tetramethoxyphenanthrene **15** (0.20 g, 0.51 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added a solution of BBr_3 in CH_2Cl_2 (1 M, 3.06 mL, 3.06 mmol) dropwise. The mixture was allowed to warm to rt and was stirred for 16 h. The reaction mixture was quenched by the addition of MeOH (25 mL), and the solvent evaporated *in vacuo*. The solid was placed under high vacuum at 60 °C for 16 h to give the title compound, **1** (0.18 g, 100%), as an off-white solid: mp 133 °C;[29] IR (neat) 3550−2800, 2942, 1608, 1578, 1520, 1471, 1421, 1261, 1232, 1199, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (2H, s, Ar*H*), 5.58 (2H, s, ArO*H*), 5.49 (2H, s, ArO*H*), 2.69−2.47 (4H, m, ArC_2H_4Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 139.3, 135.6, 127.1, 113.5, 110.1, 31.2; MS (CI^+, NH_3) m/z 400, 402, 404 $[M]^+$; HRCIMS (NH_3) m/z 399.8944 $[M]^+$ (calcd for $C_{14}H_{10}{}^{79}Br_2O_4$, 399.8946).

5,5′-(Ethane-1,2-diyl)bis(3-bromobenzene-1,2-diol) (2).[9] To a stirred solution of dihydrostilbene **14** (0.10 g, 0.22 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added a solution of BBr_3 in CH_2Cl_2 (1 M, 1.30 mL, 1.30 mmol) dropwise. The reaction mixture was allowed to warm to rt and was stirred for 16 h. The reaction mixture was quenched by the addition of MeOH (10 mL), and the solvent evaporated *in vacuo*. The solid was placed under high vacuum at 60 °C overnight to remove volatile impurities, giving the title compound, **2** (0.18 g, 100%), as an off-white solid: mp 198 °C, lit.[9] 205−206 °C; IR (neat) 3529, 3448, 3240, 2925, 2852 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.49 (2H, s, ArO*H*), 8.72 (2H, s, ArO*H*), 6.73 (2H, d, J = 2 Hz, Ar*H*), 6.54 (2H, d, J = 2 Hz, Ar*H*), 2.58 (4H, s, ArC_2H_4Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.0, 140.8, 133.5, 122.2, 114.8, 109.6, 36.1; MS (EI^+) m/z 402, 404, 406 $[M]^+$; HRCIMS (NH_3) m/z 419.9426 $[M + NH_4]^+$ (calcd for $C_{14}H_{16}{}^{79}Br_2NO_4$, 419.9946).

ASSOCIATED CONTENT

Supporting Information. General experimental procedures and characterization data for **5**−**8**, **10**, **12**−**14**, and **16**−**18**, copies of ^1H and ^{13}C NMR spectra for **15**, **1**, **2**, **9**, **17**, and **18**, a comparison of the spectroscopic data of synthetic (±)-**1** and the published data, and X-ray crystallographic details for **6**, **10**, and *E*-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: c.braddock@imperial.ac.uk.

ACKNOWLEDGMENT

We thank the EPSRC and GSK for a DTA-CASE award (to A.M.)

REFERENCES

(1) Aknin, M.; Samb, A.; Mirailles, J.; Constantino, V.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **1992**, *33*, 555–558.

(2) Reviews: (a) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335–346. (b) de Carvalho, L. R.; Roque, N. F. *Quim. Nova* **2000**, *23*, 757–764.

(3) For recent representative examples see: (a) Liu, Q.-W.; Qiao, Q.-A.; Zhang, T.; Sun, L.-X.; Wang, M.-S. *J. Mol. Struct.* **2009**, *929*, 1–5.

(b) Li, K.; Li, X.-M.; Ji, N.-Y.; Wang, B.-G. *J. Nat. Prod.* **2008**, *71*, 28–30. (c) Li, K.; Li, X.-M.; Ji, N.-Y.; Gloer, J. B.; Wang, B.-G. *Org. Lett.* **2008**, *10*, 1429–1432. (d) Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. *J. Nat. Prod.* **2007**, *70*, 337–341. (e) Li, K.; Li, X.-M.; Ji, N.-Y.; Wang, B.-G. *Bioorg. Med. Chem.* **2007**, *15*, 6627–6631. (f) Liu, Q.-W.; Tan, C.-H.; Zhang, T.; Zhang, S.-J.; Han, L.-J.; Fan, X.; Zhu, D.-Y. *J. Asian Nat. Prod. Res.* **2006**, *8*, 379–383. (g) Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. *J. Nat. Prod.* **2006**, *69*, 206–210. (h) Zhao, J.; Ma, M.; Wang, S.; Li, S.; Cao, P.; Yang, Y.; Lü, Y.; Shi, J.; Xu, N.; Fan, X.; He, L. *J. Nat. Prod.* **2005**, *68*, 691–694. (i) Zhao, J.; Fan, X.; Wang, S.; Li, S.; Yang, Y.; Xu, N.; Lü, Y.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1032–1035. (j) Fan, X.; Xu, N.-J.; Shi, J.-G. *J. Nat. Prod.* **2003**, *66*, 455–458. (k) Fan, X.; Xu, N. J.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 1045–1047. (l) Xu, N. J.; Fan, X.; Yang, Y. C.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 807–809. (m) Fan, X.; Xu, N. J.; Shi, J. G. *Chin. Chem. Lett.* **2003**, *14*, 939–941, and references therein.

(4) Assorted bromophenols have been isolated from brown algae also. See: (a) Popplewell, W. L.; Northcote, P. T. *Tetrahedron Lett.* **2009**, *50*, 6814–6817. (b) Xu, X.; Song, F.; Wang, S.; Li, S.; Xiao, F.; Zhao, J.; Yang, Y.; Shang, S.; Yang, L.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1661–1666. (c) Xu, X. L.; Fan, X.; Song, F. H.; Zhao, J. L.; Han, L. J.; Shi, J. G. *Chin. Chem. Lett.* **2004**, *15*, 661–663, and references therein.

(5) For example: (a) α-glucosidase inhibitors: Kim, K. Y.; Nam, K. A.; Kurihara, H.; Kim, S. M. *Phytochemistry* **2008**, *69*, 2820–2825. (b) Cytotoxicity: refs 4b and 3g. (c) DPPH-radical scavenging ability: refs 3b, 3c, and 3e. (d) Isocitrate lyase inhibitor: Lee, H.-S.; Lee, T.-H.; Lee, J.-H.; Chae, C.-S.; Chung, S.-C.; Shin, D.-S.; Shin, J.; Oh, K.-B. *J. Agric. Food Chem.* **2007**, *55*, 6923–6928.

(6) For a review of naturally occurring phenanthrenes see: Kovács, A.; Vasas, A.; Hohmann, J. *Phytochemistry* **2008**, *69*, 1084–1110.

(7) Whiting, D. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press, 1991; Vol. 3, pp 659−703, and references therein.

(8) An intramolecular free-radical dimerization of two phenyl radicals (as opposed to oxidative coupling) has been proposed as the key carbon−carbon bond forming step in the biogenesis of urceolatin (ref 3c).

(9) Kurata, K.; Amiya, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2020–2022.

(10) For the synthesis of halogenated bis(hydroxyphenyl)methanes see: (a) Akbaba, K.; Balaydin, H. T.; Goksu, S.; Sahin, E.; Menzek, A. *Helv. Chim. Acta* **2010**, *93*, 1127–1135. (b) Oh, K.-B.; Lee, J. H.; Lee, J. W.; Yoon, K.-M.; Chung, S.-C.; Jeon, H. B.; Shin, J.; Lee, H.-S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 945–948. (c) Li, J.; Guo, S. J.; Su, H.; Han, L. J.; Shi, D. Y. *Chin. Chem. Lett.* **2008**, *19*, 1290–1292.

(11) Biveratryl (compound **6** in this work) is known to readily aromatize during oxidative coupling using PIFA: (a) Rossiter, L. M.; Slater, L. M.; Giessert, R. E.; Sakwa, S. A.; Herr, R. J. *J. Org. Chem.* **2009**, *74*, 9554–9557. (b) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045–6047. (c) Moreno, I.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Eur. J. Org. Chem.* **2002**, 2126–2135, and references therein.

(12) For solution studies see: (a) Schaefer, T.; Laatikainen, R. *Can. J. Chem.* **1983**, *61*, 224–229. For a discussion of 32 X-ray crystal structures with this motif see:(b) Caillet, J. *Acta Crystallogr.* **1982**, *B38*, 1786–1791. For computational studies see:(c) Chein, R.-J.; Corey, E. J. *Org. Lett.* **2010**, *12*, 132–135. (d) Vande Velde, C.; Bultinck, E.; Tersago, K.; Van Alsenoy, C.; Blockhuys, F. *Int. J. Quant. Chem.* **2007**, *107*, 670–679, and references therein.

(13) CCDC 831106. The two methoxy groups are coplanar with their parent aromatic ring, the Ar−OMe twist angles being ca. 3° and 8° for the 3- and 4-methoxy groups, respectively. Given that the coplanar conformational preference of 1,2-dimethoxybenzene has also been established in solution (ref 12a), we consider that the solid-state conformation observed here should translate to solution also. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(14) One referee noted that the overall conversion of dihydrostilbene **6** to phenanthrene **7** is a four-electron oxidation, theoretically requiring 2 equivalents of PIFA to effect. In our work and other previous work (see ref 11) only 1.2 equivalents of PIFA are used. The referee suggested that in all likelihood aerial oxidation is involved in the final aromatization.

(15) Nishimura, N.; Kobayashi, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6255–6258.

(16) Duan, X.-J.; Li, X.-M.; Wang, B.-G. *J. Nat. Prod.* **2007**, *70*, 1210–1213.

(17) 3,4-Dimethoxytoluene is regioselectively monobrominated at the 2-position using NBS in DMF: Fukuda, T.; Iwao, M. *Heterocycles* **2007**, *74*, 701–720.

(18) Erdtman, H. *Ann. Chem.* **1933**, 195–202.

(19) CCDC 789908. The two methoxy units are essentially coplanar with their parent aromatic ring, the Ar−OMe twist angles being ca. 2° and 8° for the 4- and 5-methoxy groups, respectively.

(20) Srikrishna, A.; Satyanarayana, G. *Tetrahedron* **2006**, *62*, 2892–2900.

(21) Ueda, S. *Yakugaku Zasshi* **1962**, *82*, 714–718.

(22) CCDC 831197. The 4-methoxy groups (adjacent to the bromine substituent) are twisted out of the aryl ring plane, the Ar−OMe twist angle being ca. 88° (the twist angles for the 5-methoxy groups are ca. 5°).

(23) Iyoda, M.; Sakaitani, M.; Otsuka, Hi.; Oda, M. *Chem. Lett.* **1985**, 127–130.

(24) The spectroscopic data of synthetic **1** matched the published data in ref 1 (see Supporting Information).

(25) Attempted PIFA cyclization of **2** into **1** using PIFA/$BF_3 \cdot OEt_2$ in CH_2Cl_2 failed.

(26) Oh, K.-B.; Jeon, H. B.; Han, Y.-R.; Lee, T.-J.; Park, J.; Lee, S.-H.; Yang, D.; Kwon, M.; Shin, J.; Lee, H.-S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6644–6648.

(27) The moderate isolated yield of **18** is a reflection of its instability on silica gel on purification.

(28) Phelan, N. F. *J. Chem. Educ.* **1968**, *45*, 633–637.

(29) A melting point for polysiphenol was not reported in the original isolation paper (ref 1).