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# ANTIBIOTICS FROM ALGAE—XXVIII†

## CLEAVAGE OF HIGH MOLECULAR PHLOROTANNIN DERIVATIVES FROM THE BROWN ALGA *FUCUS VESICULOSUS L*[1]

K. -W. GLOMBITZA* and G. LENTZ‡
Institut für Pharmazeutische Biologie, University of Bonn, D-5300 Bonn, Federal Republic of Germany

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**Abstract**—A mixture of various high molecular weight phenols containing phlorotannins was extracted from the brown alga *Fucus vesiculosus*, and phase transfer catalytically methylated in the presence of Adogen 464. Aromatic ether chains of permethylated phlorotannins and of a few low molecular weight model compounds were cleaved with sodium in liquid ammonia. A number of methoxylated phenols, biphenyls, diphenyl ethers and phenoxybiphenyls were isolated from the mixture of cleavage products. Analysis of these cleavage products proves the occurrence of the substitution patterns already known for low molecular weight phlorotannins consisting of polyhydroxyphenols derived from phloroglucinol and indicates the presence of additional substitution patterns in high molecular phlorotannins.

In addition to free phloroglucinol,[2] dehydropolymerisation products such as oligoaryls (fucols)[3-5] or compounds with one diaryl element and one or more aryl ether groups (fucophlorethols)[3,5-7] have been isolated from *Fucus vesiculosus*. The largest compound yet to be clearly identified contains five phloroglucinol moieties.[6] The alga, however, contains a little-studied mixture of considerably higher molecular representatives of this class (phlorotannins).[5] Spectroscopic analysis as well as the more or less complete decomposition of the compounds give an insight into the structure of this polymer.

Phloroglucinol was the only identifiable product in all but one[14] cleavage experiments using a concentrated alkaline solution or an alkaline fusion to investigate either polyphenol-containing extracts from *F. vesiculosus*,[8] *Cystophyllum hakodatense*,[9] *Ecklonia cava*,[10] *Sargassum ringgoldianum*[11] or pure substances from *Halidrys siliquosa*[12] and *Bifurcaria bifurcata*.[13]

Extensive examinations conducted by Fretheim[15] utilizing a variety of reagents to study cleavage of a polyphenol mixture from Ascophyllum nodosum had no better results. Only a few of the numerous methods described in literature for the cleavage of ethers are applicable to the cleavage of diaryl ethers and of these few, sodium in liquid ammonia[16-18] appeared to be the most suitable for this case.

The advantage of this method was that, under favorable reaction conditions, only diaryl ethers were cleaved and neither alkyl aryl ether nor diaryl compounds were attacked.

If the phlorotannin mixture is quantitatively methylated in advance, OH groups liberated by cleavage show the positions of the diphenyl ether bridges in the natural compounds.

### RESULTS

*Methylation of the phlorotannins*

Previous work has shown that quantitative methylation of the phenolic OH groups of phlorotannins is relatively hard to achieve without, at the same time, substituting the nucleus with a methyl group. However, this problem has been solved by phase transfer catalysed methylation using dimethylsulphate in the presence of Adogen 464§ in a benzene/$H_2O$ system and by carefully maintaining the pH between 7.5 and 9. After treating the methylated phlorotannins with $Ac_2O$/Py, $^1H$ NMR spectrum showed a small signal around 2.0 ppm, caused by an acetate group, which was indicative of a previously incomplete methylation. Thus, the mixture had to be remethylated in a subsequent reaction. Since then, it has been possible to achieve the quantitative methylation in a one course reaction.[19]

*Cleavage of model substances*

Sowa's group[16] laid down rules for the cleavage of mono- and dimethoxylated diphenyl ethers. These rules had to be examined in experiments on simple model substances to test whether they were also valid for highly substituted phlorotannins. As expected, 2,4,6,2',4',6'-hexamethoxybiphenyl (**1**) could be quantitatively recollected from the reaction mixture unchanged. 2,4,6,3',5'-Pentamethoxydiphenyl ether (diphloretholpentamethyl ether) yielded (in mol % related to the material used) 44.6% phloroglucinol trimethyl- (**2**) and 54.6% phloroglucinol dimethyl ether (**3**). 2,4,6,3',4',5'-Hexamethoxydiphenyl ether (**4**, bifuhalol hexamethyl ether) yielded 39.7% **2**, 50.3% 3,4,5-trimethoxy phenol (**5**), 6.8% **3** and small amounts of unidentified, often coloured impurities. Surprisingly, trifuhalol octamethyl ether (**6**) was not degraded quantitatively but did, as expected, yield **2**, **3** and **5** as well as diphenyl ethers with one (**7**) or two free OH groups (**8**, Fig. 1). A number of impurities were also found in small quantities. Thus, it is clear that the ether bridges of highly substituted phlorotannin precursors were specifically cleaved beside the ortho-positioned methoxyls so that the ether oxygen remained with the meta- and not the ortho-substituted ring. Demethylated derivatives also arose (e.g. **8** from **6** and considerable amounts of **3** from **4**) to some extent.

Previous studies by Weber and Sowa[16c] and Tomita *et al.*[20] indicated that it is difficult to cleave diphenyl ethers having free OH groups. This was confirmed by the formation of **7** and **8**. The detection of these multi-ringed

†Part XXVII see Ref. 1.

‡From the thesis by G. Lentz, Bonn, D5, 1980.

§We thank Prof. Dehmlow, Berlin, for valuable information about this reaction.

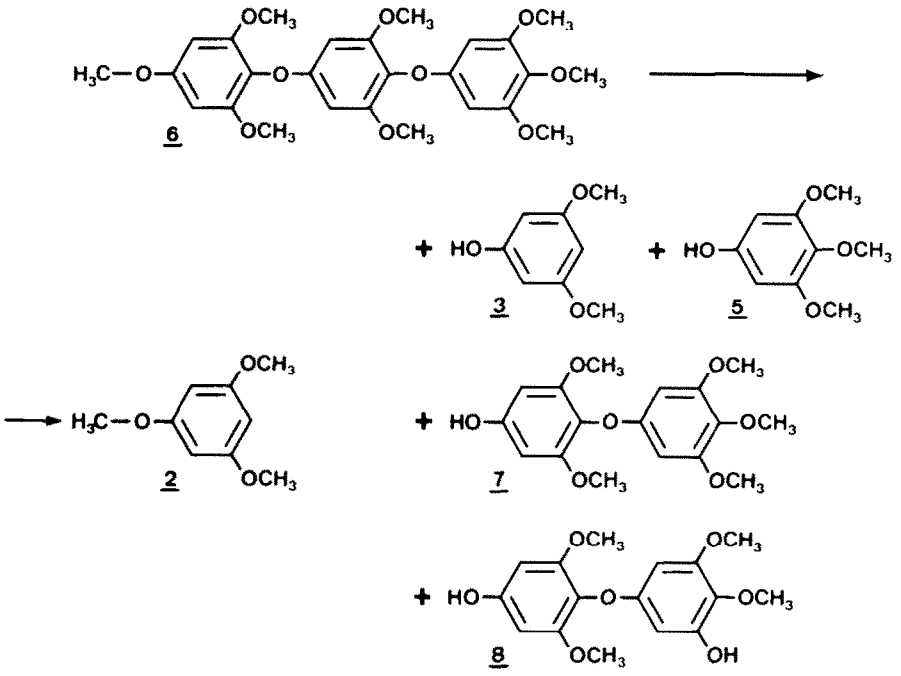

Fig. 1. Cleavage of trifuhalol octamethyl ether (6).

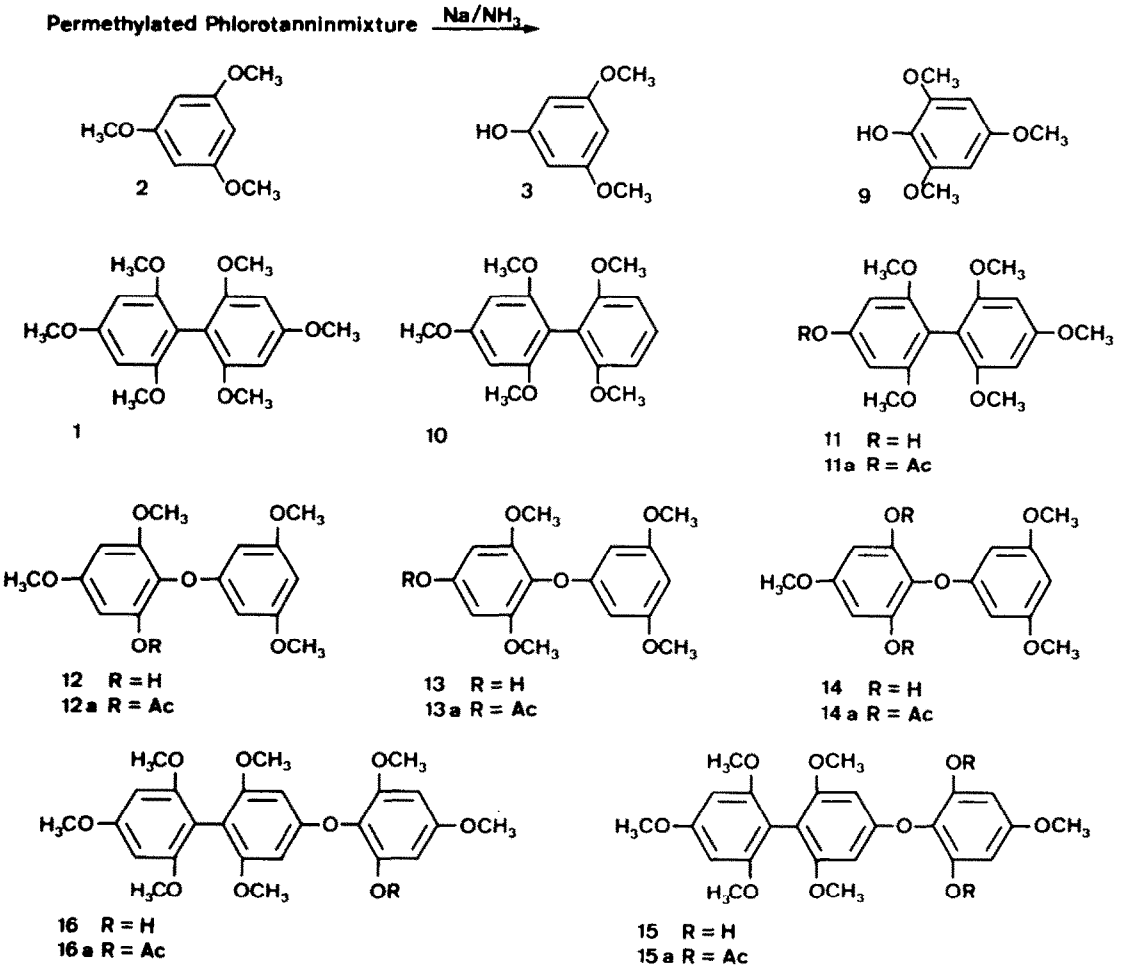


Fig. 2. Identified cleavage products of the methylated phlorotannins from Fucus vesiculosus.

fragments, arising after phlorotannins were cleaved from *Fucus vesiculosus*, greatly facilitates the reconstruction of definite partial structures.

*Cleavage of the permethyl phlorotannins from Fucus vesiculosus*

Lyophilized *Fucus vesiculosus* was extracted[6] in the usual manner with 80% ethanol. A particularly high molecular weight phlorotannin fraction was precipitated with caffeine before the extract was partitioned with ethyl acetate. However, since precipitable and non-precipitable fractions gave rise to identical degradation products after cleavage, fractionation could be left out and the whole mixture of ethyl acetate soluble, medium- to high- molecular weight phlorotannins could be phase transfer catalytically methylated. The Adogen was subsequently washed out and with it, the minute amounts of 2–3 ring low molecular weight phlorotannins were also quantitatively removed. When necessary, the mixture was remethylated and then cleaved with sodium in liquid ammonia following the method described by Yamaguchi.[18] After the ammonia was removed, the reaction products were extracted with ethyl acetate. The ethyl acetate phase was evaporated and the residue dissolved in diethyl ether and separated into an ether soluble and an ether-insoluble fraction. The latter fraction was not further investigated. The soluble fraction was separated into 4 fractions (SC1–SC4) on a silica gel column with $CHCl_3$/EtOH. The three more strongly lipophilic fractions (SC1–SC3) were further separated with various gradient elution programs of $CCl_4$, $CHCl_3$ and EtOH through HPLC on Lichrosorb Si 60 and examined by spectroscopic and chemical methods. A total of 11 compounds (**1–3**; **9–16**), all shown in Fig. 2, were clearly identified. The structures for all of the substances with free OH groups were positively established by spectroscopic examination of the acetates **11a–16a**. A large number of other compounds were visible on the TLC plates, but only in small amounts. The fraction SC4 contained free hydrophilic phenols which have not as yet been further analysed.

## DISCUSSION

Based upon the rules presented by Sowa *et al.*[16] and the data obtained by examining model substances in this paper, cleavage products could be derived from the already known structures of phlorotannins in *Fucus vesiculosus* and new combinations of the phloroglucinol rings could be proposed.

Structure elements characteristic for fuhalols which should have resulted in 3,4,5-trimethoxy phenol were not found. This coincides with the results obtained by Rauwald[21] through $^1$H NMR spectra correlation.

The mixture of high molecular phenols from *Fucus vesiculosus* evidently contains a partial structure with a difucol moiety phenoxylated para to the biaryl bond.

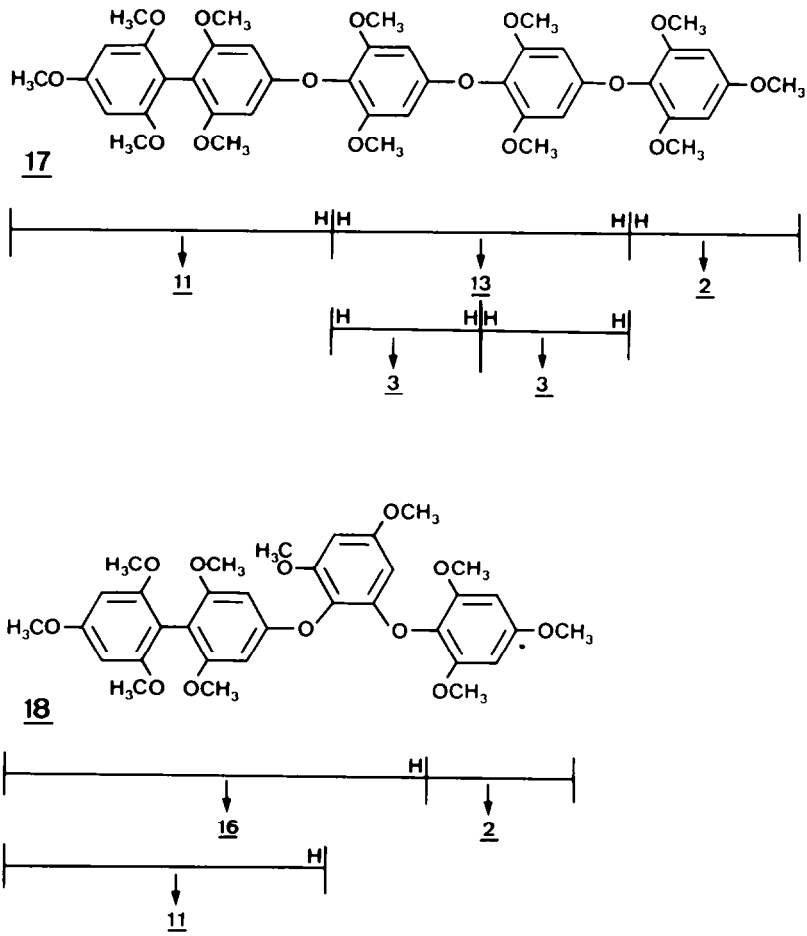


Fig. 3. Correlation of the detected cleavage products with structure elements of known fucophlorethols from Fucus vesiculosus.

Such a structure is already known for permethylfucotriphlorethol A (17)[3,6] and also exists in the permethylfucodiphlorethol (18) described by Craigie *et al.*[7] These may lead to the degradation products 11, 13, 3, 2 and 11, 16, 2, respectively (Fig. 3).

The appearance of 15 implies that the phenyl connected to the biaryl element by an oxygen atom could also be phenoxylated twice as shown in the structure element 21 (Fig. 4). In this case, it is also conceivable that the splitting of the ether bridge to the biaryl element could result in 10 (Fig. 4).

Structural elements with a difucol substituted meta to the biaryl bond appear to be present. Such compounds were previously found in *Cystoseira baccata*[1] (e.g. permethylfucodiphlorethol B, 19) but not in *Fucus vesiculosus*. These structures might result in the formation of 1, 12 and 2 (Fig. 4).

The formation of 14 implies that polymers with partial

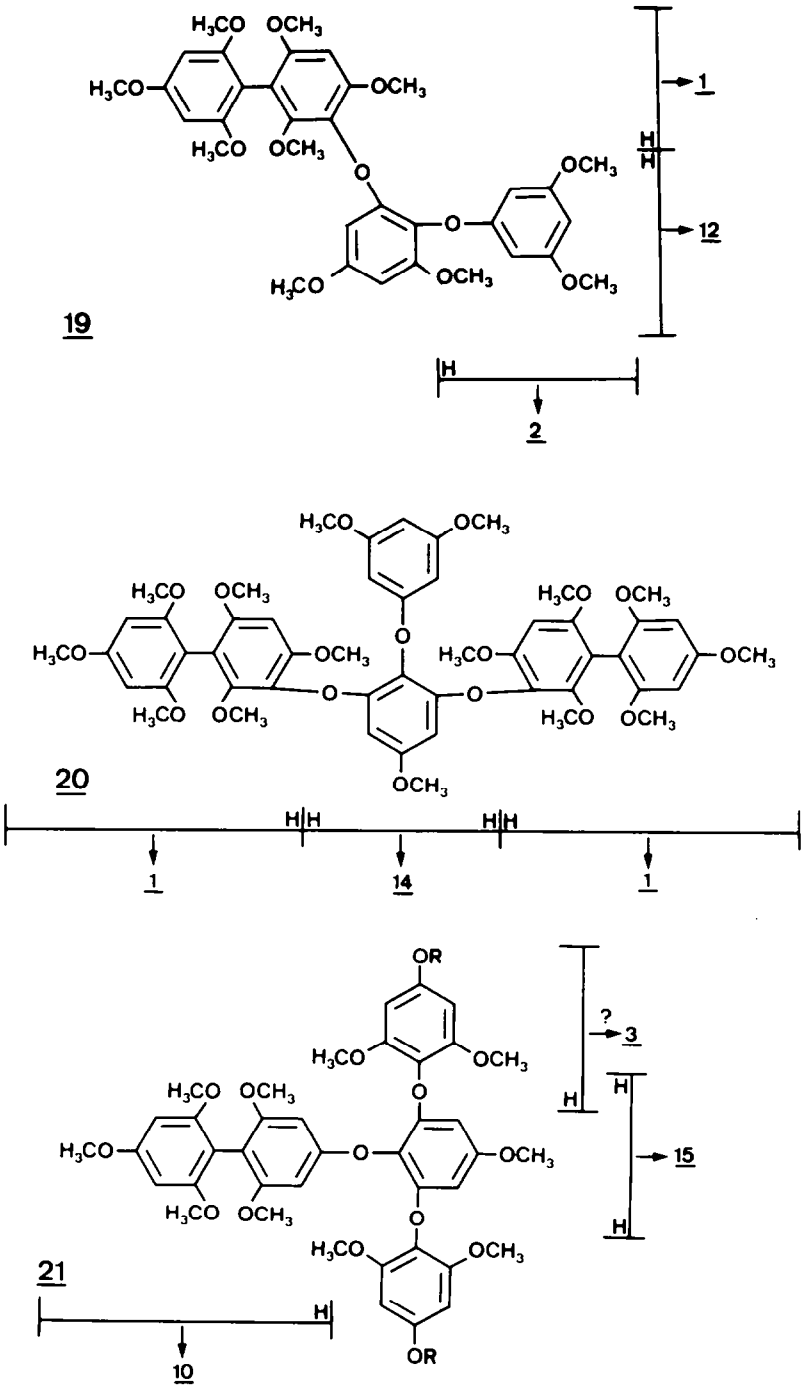


Fig. 4. Correlation of the detected cleavage products with structure elements of known permethylated fucophlorethols from Cystoseira baccata (19, 20) and with a partial structure (21) which up until now has not been detected.

structure of a 5-hydroxyphen-1,2,3-trioxyl unit such as have been recently found in Cystoseira baccata (**20**, Fig. 4)[1] also appear in *Fucus vesiculosus*. These proposed correlations are of course only valid if no single OH groups are set free by the cleavage of the alkyl aryl ethers.

Cleavage product **9** cannot be derived directly from any of the discussed structure elements. It might have arisen from a cleavage of **21** (Fig. 4) in contradiction to the rules discussed above or could have resulted from other compounds.

## EXPERIMENTAL

### *Materials and Methods*

MS were taken with a MS 30 or MS 50 (AEI) in combination with the DS 50 data system. Only the fragments that were most important for the interpretation are presented. $^1$H NMR spectra, elucidating structure, were taken with an WH 90 (FT) instrument (Bruker), all others with a EM 360 A (CW Varian).

### *Synthesis of model substances*

2,4,6,2',4',6'-Hexamethoxybiphenyl (**1**) was prepared according to Ragan and Craigie;[5] 45.6% theoretical yield, m.p. 155–156°C (lit 156°).

2,4,6,3',5'-Pentamethoxydiphenyl ether was prepared according to Glombitza *et al*;[22] but from 2,4,6-trimethoxyphenol and 5-bromo-1,3-dimethoxybenzene 64.0% of theoretical yield, m.p. 103°C (lit 102–103°).

2,4,6,3',4',5'-Hexamethoxydiphenyl ether (**4**, bifuhalol hexamethyl ether) was prepared according to Sattler and Glombitza;[23] 47.0% of theoretical yield, m.p. 121–122° (lit 124.5°).

Trifuhalol-A-octamethyl ether (**6**) was also prepared according to ref. 23 by 6-stage synthesis.

### *Extraction and methylation of the phlorotannins from Fucus vesiculosus*

1 kg lyophilized Fucus vesiculosus (France, Brittany, La Corniche) was extracted in the usual manner with 80% ethanol. After evaporation of most of the solvent, the phlorotannin mixture was extracted with EtOAc.[6] Yield 15 g. If the higher molecular portion was precipitated with 5% caffeine solution before the extraction with EtOAc, the EtOAc extract contained only the lower oligomers (yield 4.5 g). The caffeine could be desorbed from the high molecular weight phlorotannins with 200 ml $CHCl_3$/$Me_2CO$ (9:1) by two or three 1 hr digestions of the caffeine-containing precipitate. 5.0 g of the total mixture, or the lower oligomers or the high molecular fraction were mixed with 50.2 g Adogen 464, 200 g $NaHCO_3$ and 300 ml benzene plus 300 ml $H_2O$, respectively, and heated to 50° in a $N_2$ atmosphere with intensive stirring from a vibromixer (Chemap E1). 114 ml $Me_2SO_4$ were added dropwise over a period of 3.5 hr so that the pH value remained between 7 and 9. After 2.5 hr more, the mixture was heated to boiling for 30 min, cooled and then the organic phase was separated. The water phase was shaken twice, each time with 200 ml benzene. The purified benzene phases were dried and then evaporated in vacuo. The residue was digested with 300 ml petrol ether, filtered, the filter cake washed with 200 ml petrol ether, then dissolved in benzene, refiltered and once again the benzene was evaporated in vacuo. To test for free OH groups, the mixture was acetylated with $Ac_2O$/Py. $^1$H NMR spectra were taken before and after acetylation. If necessary, the residue was further treated with 84 g $NaHCO_3$ and 300 ml $Me_2CO$ to complete methylation. 47.5 ml $Me_2SO_4$ were added dropwise over 3 hr with constant stirring in a $N_2$ atmosphere at ≦40° with pH constant between 7 and 9. 2 hr later, 200 ml MeOH/$H_2O$ (1:1) were added and the mixture heated to boiling for 30 min. The organic solvent was withdrawn in vacuo at ≦40°. The water phase was shaken thrice, each time with 250 ml $CHCl_3$ and evaporated in vacuo at ≦40° to dryness. The residue was digested five times with 100 ml MeOH to remove Adogen remains. Yield 3.5 g.

### *Cleavage and isolation of cleavage products*

Apparatus and method were essentially the same as those described by Yamaguchi.[18] Dried $NH_3$ was condensed at −70°. 100 mg of **1** or **6**, 200 mg of **4** or diphloretholpentamethyl ether or 1 g of permethylated phlorotannins were dissolved or suspended in 100 ml liquid $NH_3$. Na was added in small pieces, continuously stirred and cooled until the mixture retained an intensive blue colour. The coolant was withdrawn after 1 hr (model substances) or two (phlorotannins). The mixture was then stirred for 1-2 hr more in a Dewar container without any additional cooling. A surplus of $NH_4Cl$ (compared to the Na used) was added and the $NH_3$ allowed to evaporate in a stream of $N_2$. The residue was dried and treated several times with a total of up to 150 ml EtOAc (model substances) or up to 400 ml EtOAc after suspending in 75 ml water (phlorotannins). The organic solvent was removed. Yield: 93–103% with the model substances and 80% with the phlorotannins. **1** was quantitatively collected. The residue from diphloretholmethyl ether was separated into **2** and **3** by extracting the $Et_2O$ soln with N NaOH. Concentrations were either determined gravimetrically or through a TLC method analogous to that used for bifuhalolhexamethyl ether (Silica gel, $CHCl_3$/EtOH (97:3) and then spectrophotometrically measured in either MeOH or MeOH plus NaOMe (relative to **2** and **3**). The residue of **6** was separated by HPLC in a method analogous to that given for the phlorotannin derivatives. The residue of these derivatives was digested twice with 50 ml $Et_2O$, evaporated (yield 600 mg) and separated on a silica gel column (ø 3.0 cm, length 30 cm) with a mixture of $CHCl_3$ and EtOH (the EtOH was added in increasing amounts 0.5, 1.3, 50.0%) into the fractions SC1 (60 mg), SC2 (225 mg), SC3 (75 mg) and SC4 (225 mg). Further separation was achieved by HPLC: 2 Knauer-HPLC-pumps FR 30, gradient programs of $CCl_4$/($CHCl_3$/EtOH, 90:10), Lichrosorb Si 60, 7 μm (ø 10 mm, length 25 cm), detection UV (270 nm).

### *Substances isolated after cleavage*

$R_f$ value when not specified: Silica gel 60 $F_{254}$ $CHCl_3$/EtOH (96:4); colour specification after detection with vanillin/$H_2SO_4$, 5', 120°. $^1$H NMR, when not specifically stated, in $CDCl_3$ with reference to TMS and given in ppm on the δ-scale. The C atom ($C^x$), on which the resonance-producing substituant was located, was marked whenever an assignment was possible.

2,4,6,2',4',6'-Hexamethoxybiphenyl (**1**), $R_f$ 0.61, red. MS: *m/e* = 334 ($M^+$, 100%), 303, 288. $^1$H NMR: 6.23 (4H), 3.84 (6H), 3.71 (12H) Phloroglucinol trimethyl ether (**2**), $R_f$ 0.68, red-orange. $^1$H NMR: 6.08 (3H), 3.76 (9H). UV $\lambda_{max}^{MeCN}$: S227, 229 nm. Phloroglucinol dimethyl ether (**3**), $R_f$ 0.27, orange. $^1$H NMR: 6.07 (1H), 6.01 (2H, $AB_2$ system, $J_{AB}$ = 2 Hz), 4.81 (1H), 3.76 (6H). UV $\lambda_{max}^{MeCN}$: S 226, 260 nm. 4-Hydroxy-2,6,3',4',5'-pentamethoxydiphenyl ether (**7**), $R_f$ 0.30 ($CHCl_3$/EtOH (97:3)), red. MS: *m/e* 336 ($M^+$), 321, 293, 205, 184, 169, (100%), 154, 141, 125, 111, 89, 71, 69. $^1$H NMR: 6.17 (2H, $C^{3,5}$), 6.12 (2H, $C^{2',6'}$), 4.85 (1H, $C^4$), 3.78 (3H, $C^4$), 3.76, 3.75 (each 6H). Acetate (**7a**) $^1$H NMR: 6.45 (2H, $C^{3,5}$), 6.13 (2H, $C^{2',6'}$), 3.78 (9H), 3.76 (6H), 2.32 (3H, $C^4$). 4,3'-Dihydroxy-2,6,4',5'-tetramethoxydiphenyl ether (**8**), $R_f$ 0.23 ($CHCl_3$/EtOH (97:3)). MS: *m/e* = 322 ($M^+$), 307 (100%), 293, 279, 181, 167, 155, 111, 69. $^1$H NMR: 6.24 ($C^6$), 5.94 (each 1H, $C^2$, AB system, $J_{AB}$ = 2.8 Hz), 6.15 (2H, $C^{3,5}$), 5.71 (1H, $C^3$), 4.78 (1H, $C^4$), 3.83, 3.82 (each 3H), 3.75 (6H, $C^{2,6}$). Diacetate (**8a**) $^1$H NMR: 6.57 ($C^6$), 5.96 (each 1H, $C^2$, AB system, $J_{AB}$ = 2.85 Hz), 6.42, (2H, $C^{3,5}$), 3.83 (3H, $C^5$), 3.77 (3H, $C^4$), 3.76 (6H, $C^{2,6}$), 2.32 (3H, $C^4$), 2.26 (3H, $C^3$). 2,4,6-Trimethoxyphenol (**9**), $R_f$ 0.47, yellow-brown. MS: *m/e* = 184 ($M^+$). $^1$H NMR: 6.19 (2H), 5.09 (1H), 3.87 (6H), 3.77 (3H). 2,4,6,2',6'-Pentamethoxybiphenyl (**10**), $R_f$ 0.63, violet. MS: *m/e* = 304 ($M^+$, 100%), 273, 258, 243, 168, 151, 91, 69. $^1$H NMR: 7.26 (1H, $C^4$), 6.64 (2H, $C^{3',5'}$, $AB_2$ system, $J_{AB}$ = 7.5 Hz), 6.24 (2H, $C^{3,5}$), 3.84 (3H, $C^4$), 3.72, 3.71 (each 6H). $Me_2CO$-$d_6$: 7.18 (1H, $C^4$), 6.63 (2H, $C^{3',5'}$, $AB_2$ system, $J_{AB}$ = 8.7 Hz), 6.25 (2H, $C^{3,5}$), 3.83 (3H, $C^4$), 3.65, 3.64 (each 6H). 4-Hydroxy-2,6,2',4',6'-pentamethoxybiphenyl (**11**), $R_f$ 0.21, red. MS: *m/e* = 320 ($M^+$, 100%), 274, 259, 181, 167, 160, 154, 69. $^1$H NMR, $Me_2CO$-$d_6$: 8.15 (1H, $C^4$), 6.23 (2H, $C^{3',5'}$), 6.15 (2H, $C^{3,5}$), 3.82 (3H, $C^4$), 3.63 (6H, $C^{2',6'}$), 3.58 (6H, $C^{2,6}$). Acetate (**11a**) $^1$H NMR: 6.40 (2H, $C^{3,5}$), 6.23 (2H, $C^{3',5'}$), 3.84 (3H, $C^4$), 3.69 (12H),

2.30 (3H, $C^4$). 2-Hydroxy-4,6,3',5'-tetramethoxydiphenyl ether (**12**), $R_f$ 0.52, red. MS: *m/e* = 306 ($M^+$, 100%), 290, 275, 259, 244, 193, 181, 169, 151, 141, 69. $^1$H NMR: 6.24 ($C^5$), 6.14 (each 1H, $C^3$, AB system, $J_{AB}$ = *ca.* 3 Hz), 6.19 (1H, $C^{4'}$), 6.13 (2H, $C^{2',6'}$, $AB_2$ system, $J_{AB}$ = 2 Hz), 5.36 (1H, $C^2$), 3.79 (3H, $C^4$), 3.74 (9H). Acetate (**12a**) $^1$H NMR $CDCl_3$: 6.45 ($C^5$), 6.31 (each 1H, $C^3$, AB system, $J_{AB}$ = 2.9 Hz), 6.13 (1H, $C^{4'}$), 6.05 (2H, $C^{2',6'}$, $AB_2$ system, $J_{AB}$ = 2.4 Hz), 3.80 (3H, $C^4$), 3.78 (3H, $C^6$), 3.72 (6H, $C^{3',5'}$), 2.11 (3H, $C^2$). 4-Hydroxy-2,6,3',5'-tetramethoxydiphenyl ether (**13**), $R_f$ 0.27, red. MS: *m/e* = 306 ($M^+$, 100%), 275, 169, 155, 152, 151, 141, 69. $^1$H NMR: 6.14 (2H, $C^{3,5}$), around 6.09 (3H, m), 4.72 (1H, $C^4$), 3.75, 3.73 (each 6H). Acetate (**13a**) $^1$H NMR: 6.42 (2H, $C^{3,5}$), 6.13 (1H, $C^{4'}$), 6.08 (2H, $C^{2',6'}$, $AB_2$ system, $J_{AB}$ = 3 Hz), 3.76, 3.74 (each 6H), 2.31 (3H, $C^4$). 2,6-Dihydroxy-4,3',5'-trimethoxydiphenyl ether (**14**), $R_f$ 0.27, red. MS: *m/e* = 292 (100%; $M^+$), 277, 275, 259, 155, 138, 127. $^1$H NMR: 6.18 (2H, $C^{3,5}$), 6.18 (1H, $C^{4'}$), 6.14 (2H, $C^{2',6'}$, $AB_2$ system, $J_{AB}$ = 2.4 Hz), 5.09 (2H, $C^{2,6}$), 3.76 (3H, $C^4$), 3.75 (6H, $C^{3',5'}$). Diacetate (**14a**) $^1$H NMR: 6.63 (2H, $C^{3,5}$), 6.13 (1H, $C^{4'}$), 6.06 (2H, $C^{2',6'}$, $AB_2$ system, $J_{AB}$ = 2.7 Hz), 3.80 (3H, $C^4$), 3.71 (6H, $C^{3',5'}$), 2.07 (6H, $C^{2,6}$). 2,6,2',4',6'-Pentamethoxy-4-(2,6-dihydroxy-4-methoxyphenoxy) biphenyl (**15**), $R_f$ 0.25, red. MS: *m/e* = 458 ($M^+$, 100%), 443, 412, 304, 282, 273, 258, 254, 243, 229, 155, 127. $^1$H NMR: biphenyl part: 6.23, 6.22 (each 2H), 3.84 (3H, $C^4$), 3.71, 3.64 (each 6H); phenoxyl part: 6.27 (2H, $C^{3,5}$), 5.23 (2H, $C^{2,6}$), 3.78 (3H, $C^4$). Diacetate (**15a**) $^1$H NMR: biphenyl part: 6.24 (4H), 3.84 (3H, $C^4$), 3.70, 3.62 (each 6H); phenoxyl part: 6.66 (2H, $C^{3,5}$), 3.81 (3H, $C^4$), 2.06 (6H, $C^{2,6}$). 2,6,2',4',6'-Pentamethoxy - 4 - (2-hydroxy-4, 6-dimethoxyphenoxy) biphenyl (**16**), $R_f$ 0.50, red. $^1$H NMR: biphenyl part: 6.22 (4H), 3.84 (3H, $C^4$), 3.70, 3.62 (each 6H); phenoxyl part: 6.26 (1H, $C^5$), 6.16 (1H, $C^3$, AB system, $J_{AB}$ = 3.6 Hz), 5.47 (1H, $C^2$), 3.81 (3H, $C^4$), 3.78 (3H, $C^6$). Acetate (**16a**) MS: *m/e* 514 ($M^+$, 100%), 472, 457, 441, 434, 426, 317, 236, 181, 169, 167. $^1$H NMR: biphenyl part: 6.22, 6.18 (each 2H), 3.83 (6H, $C^{4'}$ + $C^4$ phenoxyl), 3.68, 3.61 (each 6H); phenoxyl part: 6.48 (1H, $C^5$), 6.34 (1H, $C^3$), 3.81 (3H, $C^6$), 2.05 (3H, $C^2$).

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