A General Approach for the Synthesis of Phenolic Natural Products. Facile Syntheses of Grifolin and Colletochlorins B and D

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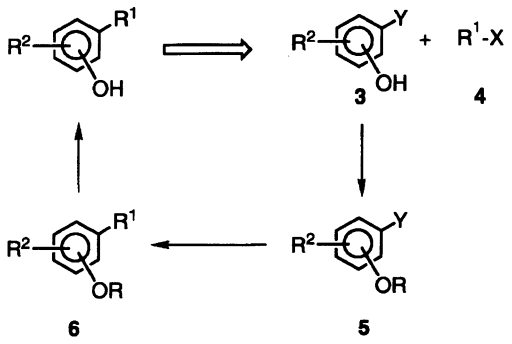
A general approach is established for the synthesis of phenolic compounds having terpenoid side chains: (1) protection of the phenolic hydroxyls in the aromatic precursor by ether formation, (2) coupling the aromatic part with a terpenoid bromide, and (3) deprotection to regenerate the hydroxyl groups. This strategy was successfully applied to the synthesis of colletochlorins B and D and grifolin. Some of the colletochlorin derivatives were found to inhibit the cell growth of P388.

Since the discovery of a variety of biological activities of phenolic natural products,[1—3] the study of this class of compounds has become an active area in the field of synthetic and pharmaceutical chemistry.[4,5] Recently phenolic compounds such as **1**, **2**, and their derivatives have been found to be potent inducers of differentiation of leukemia cells.[6,7] The phenolic compounds contain aromatic rings substituted by one or more hydroxyl groups as well as terpenoid side chains. For the convergent synthesis of these compounds, it seems rational to disconnect them into the corresponding arenes **3** and the side chains **4** (Scheme 1). Introduction of the side chain directly into the aromatic precursor **3**, however, results in poor yields.[8,9] Although the side chain moiety was known to be connected efficiently to the protected precursor **5**,[10] deprotection of the protected hydroxyl group in **6** has been the major synthetic obstacle.[11] Herein we report solutions for these problems as exemplified by the synthesis of colletochlorins B (**2**),[4,12] D (**7**),[9,13] and grifolin (**8**) (Chart 1).[14] We have found that 1-alkoxyalkyl ethers are cleaved by diphosphorus tetraiodide (P_2I_4) under neutral conditions[15] and that a counter cation of ethanethiolate affects cleavage of methyl aryl ether with ethanethiolate.[16] These findings enabled our synthetic strategy which involved (1) protection of the phenolic hydroxyl by ether formation, (2) coupling the aromatic part with a terpenoid bromide, and (3) deprotection to regenerate the hydroxyl group.

Synthesis of Hexasubstituted Benzenes and Coupling with Terpenoid Bromides. As an aryl group precursor, we chose 2,6-dialkoxyphenyl bromides **12**, **13**, and a dibromo analog **15**, because bromine–lithium exchange would supply substituted phenyllithiums. According to the Sargent's method,[17] bromides **10** and **14** were prepared from cyclohexenone **9** as shown in Scheme 2.[18] In a preliminary study, resorcinol derivative **11** was protected by triethylsilyl or *t*-butyldimethylsilyl groups, but the silyl protecting groups proved to be partially cleaved during lithiation with butyllithium in tetrahydrofuran (THF) at −78 °C. Therefore, methyl and alkoxymethyl ether, both tolerate wide range of C–C bond forming conditions, were employed. Chlorination of pentasubstituted benzene **10** gave **11**,



Scheme 1.

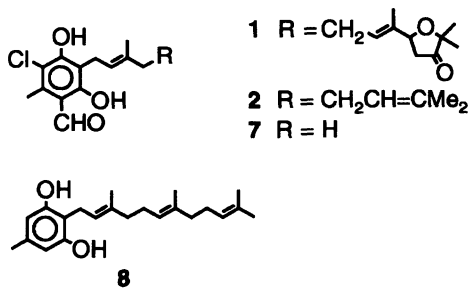
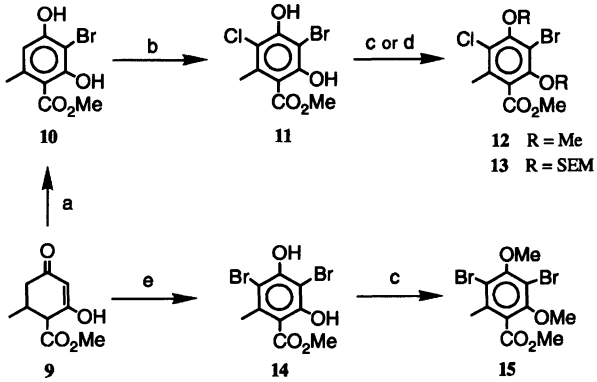


Chart 1.



a: 2 equiv Br_2, AcOH; b: SO_2Cl_2, Et_2O; c: Me_2SO_4, K_2CO_3, acetone; d: SEM-Cl, *i*-Pr_2NEt, CH_2Cl_2; e: 3 equiv Br_2, AcOH.

Scheme 2.

whose hydroxyl groups were protected by methyl or 2-(trimethylsilyl)ethoxymethyl (SEM) group to yield **12** or **13**, respectively. Methylation of dibromide **14** gave **15**.

Among various methods of the regiospecific ortho lithiation of masked phenols,[19,20] bromine–lithium exchange at low temperatures seems to be applicable for the lithiation of arenes bearing an ester group. Thus, the hexasubstituted benzene **12** was treated with butyllithium at −78 °C to give the corresponding substituted phenyllithium, which was converted into a mixed cuprate[21] and used for the coupling reaction with an allylic bromide. As shown in Table 1, reaction of (*E*)-3,7-dimethyl-2,6-octadienyl bromide (geranyl bromide) with **12**, **13**, or **15** afforded **16a**, **16c**, or **16d** in good yields, respectively. When 3-methyl-2-butenyl bromide was employed instead of geranyl bromide, **16b** and **16e** were obtained (Runs 2 and 5). Transformation of the ester function of **16** into formyl group was accomplished by reduction with $LiAlH_4$ followed by oxidation of the resulting alcohols **17** with pyridinium chlorochromate (PCC). Yields are summarized in Table 1.

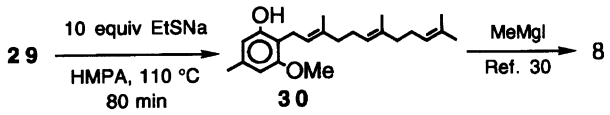
Regeneration of the Phenolic Hydroxyl Groups. The conversion of aryl methyl ether into phenols has been achieved with trimethylsilyl iodide[11] as far as one methoxyl group is involved; boron tribromide sometimes transforms formyl group to dibromomethyl.[22] Acidic conditions induce chroman or chromene ring formation.[23] Accordingly these conditions are not applicable to highly functionalized methyl ethers like **18**.

Therefore, we decided to apply the Mirrington's method (EtSNa/DMF)[24] to removal of the methyl ether of **18a** and **18b**. As shown in Table 2 (Run 1), this method afforded colletochlorin B (**2**) along with a monomethyl ether **19** and an ethylthio derivative **20**, but the yields were disappointedly low. We found that the methyl ether bonds were efficiently cleaved by EtSNa when hexamethylphosphoric triamide (HMPA) was used as a solvent (Run 2). Runs 8 and 9 in Table 2 show that the original conditions EtSNa/DMF was not useful also for the synthesis of colletochlorin D (**7**). In Run 8, only one of the methyl ether bonds was cleaved to yield monomethyl ethers **21**[11] and **22**. When the protected resorcinol **18b** was treated with EtSNa under forcing conditions (Run 9), chlorine atom attached to the benzene ring was replaced by ethylthio group to give a side product **23**. As shown in Run 10, bromomagnesium ethanethiolate in DMF was found to be suitable for the transformation of **18b** to **7** and the reaction performed in 30 min.

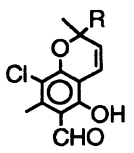
On the other hand, SEM ethers were eliminated by the novel method using P_2I_4[15,25] to afford colletochlorin B (**2**) and **11** in good yields (Runs 3 and 11). The best conditions we found were those which involve treatment of masked resorcinols with P_2I_4 in dichloromethane at 0 °C and pouring the reaction mixture onto a silica-gel column followed by elution with ether at 0 °C. Similarly methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), and 1-ethoxyethyl (EE) protecting groups as seen in **18f**, **24**, **25**, and **26** were cleaved by P_2I_4 to give the corresponding phenols in good yields (Runs 6, 12, 13, and 14). In comparison with conventional deprotection methods (Runs 4,[26] 5,[27] and 7[28]), the one with P_2I_4 proceeds under much milder conditions. This advantage was exemplified by our preliminary work on the synthesis of ascofuranone (**1**).[15]

Application for the Synthesis of Grifolin. Grifolin (**8**)[14] is reported to exhibit various antibiotic activities and appeared to be a suitable synthetic target to demonstrate the utility of our approach. As shown in Table 1 (Run 6), orcinol dimethyl ether **27** was treated with butyllithium to give the corresponding phenyllithium,[19] which was converted into a mixed cuprate and allowed to react with geranyl bromide to yield a model compound **28**. A grifolin precursor **29** was similarly prepared from **27** and (2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienyl bromide (farnesyl bromide) in a good yield (Run 7). When the hydroxyl groups of 5-methylresorcinol are not protected, the yields for introduction of the side chains are reportedly low.[29] Scheme 3 shows that a grifolin monomethyl ether **30**[30,31] was obtained in 95% yield by treatment of **29** with EtSNa in HMPA. Although treatment of **29** and **30** having no electron withdrawing substituent like a formyl group under the same reaction conditions failed to give **8**, transformation of **30** to **8** is known to be accomplished by the procedure using methylmagnesium iodide.[30]

Synthesis of Cannabichromene Analogs and Biological Activities of Colletochlorin Derivatives. In the chemistry of phenolic compounds, preparation of chromenes or chromans has attracted considerable attention in connection with their biological activities.[32,33] Colletochlorin B (**2**) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[34] in refluxing benzene to give cannabichromene derivatives **31** and **32** (Chart 2). In a similar manner, colletochlorin D (**7**) was transformed into a β-tubanol[35] analog **33** by the oxidative cyclization. The synthesized colletochlorin derivatives were subjected to in vitro test for cell growth inhibition of P388.[36,37] Although benzaldehydes



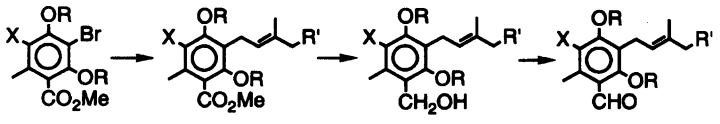
Scheme 3.



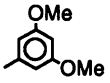
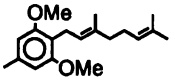
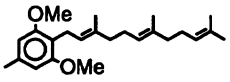
31 R = $CH_2CH_2CH{=}CMe_2$
32 R = $CH{=}CHCH{=}CMe_2$
33 R = Me

Chart 2.

Table 1. Preparation of Masked Resorcinols Having a Side Chain[a)]



12 13 15 16 17 18

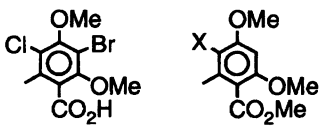
Run	Substrate			Coupling product			Aldehyde	
	R	X		R'	Yield/%		Yield/%	
1	Me	Cl	12	$CH_2CH{=}CMe_2$	**16a**	70	**18a**	99
2	Me	Cl	12	H	**16b**	92	**18b**	95
3	SEM	Cl	13	$CH_2CH{=}CMe_2$	**16c**	91	**18c**	99
4	Me	Br	15	$CH_2CH{=}CMe_2$	**16d**	62	**18d**	65
5	Me	Br	15	H	**16e**	62	**18e**	60
6	 **27**			 **28**		85		
7	**27**			 **29**		82		

a) Coupling reaction: 1) BuLi, 2) $CuC{\equiv}C{-}C(OMe)Me_2$, 3) $BrCH_2CH{=}CMeCH_2R'$, yields based on allylic bromides; preparation of **18**: 1) $LiAlH_4$, 2) PCC, yields from **16**.

18a, **18b**, **18f**, and a benzyl alcohol derivative **17a** exhibited IC_{50} (μmol cm^{-3}) 2.6—5.1×10^{-3} comparable to the cytotoxicity of prostaglandin A2 (2.8×10^{-3}), most of phenol derivatives synthesized in this study showed weak cytotoxicity. Among the derivatives, 3-bromo-5-chloro-2,4-dimethoxy-6-methylbenzoic acid (**34**) and benzoic acid esters such as **11**, **16c**, and methyl 3-chloro-4,6-dimethoxy-2-methylbenzoate (**35**) were hardly cytotoxic ($IC_{50}>1.0\times10^{-1}$) (Chart 3). As was shown in our previous report on the cytotoxicity to human promyelocytic leukemia cells (HL-60),[6)] the colletochlorin derivatives having a benzaldehyde moiety seem to be more cytotoxic than those having a benzoate moiety. On the other hand, the esters **14**, **15**, and methyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (**36**) showed antifungal activity against Trichophyton spp. and Microsporum sp.[38)]

Experimental

All the reactions were carried out under an argon atmosphere. All mps and bps were uncorrected. Microscale distillation was performed by Kugelrohr (Büchi). ^{1}H NMR spectra in $CDCl_3$ were recorded on a Hitachi R-90H or Varian XL-100A spectrometer, and IR spectra (neat liquid film samples unless otherwise noted) on a JASCO A 202 spectrometer. Mass spectra were obtained on a Hitachi RMU-6MG or Hitachi M-80A spectrometer. Preparative TLC plates were prepared using Kieselgel 60 PF_{254} (Merck). Column chromatography was performed using Kieselgel 60 (Merck). According to the reported procedure,[17)] the cyclohexenone **9** was prepared from methyl 2-butenoate and methyl acetoacetate in 67% yield or from 3-penten-2-one and dimethyl malonate in 88% yield, and then converted to **10** and **14** in 49 and 97% yield, respectively. Protected compounds **24**, **25**, and **26** were prepared from the corresponding commercially available phenols by the usual methods.[28,39,40)]



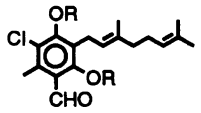
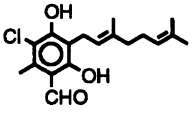
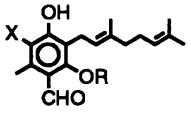
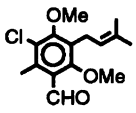
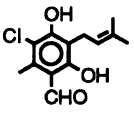
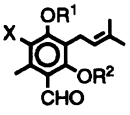
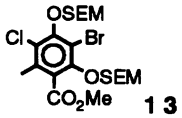
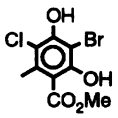
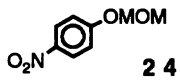
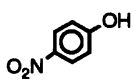
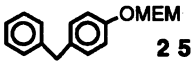
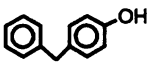
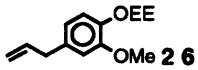
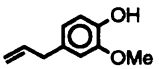
34 **35** X=Cl **36** X=Br

Chart 3.

Methyl 3-Bromo-5-chloro-2,4-dihydroxy-6-methylbenzoate (11) and Methyl 3-Bromo-5-chloro-2,4-dimethoxy-6-methylbenzoate (12). Sulfuryl chloride (3.12 g 23.1 mmol) was added to an ether (50 ml) solution of **10** (4.64 g, 17.8 mmol) and stirred for 3.5 h at room temperature. Concentration of the reaction mixture gave crude chloride **11** (5.36 g), a part of which was purified by column chromatography (hexane–dichloromethane 1 : 1—1 : 100) to give **11** (97% yield). Mp 108—109 °C (colorless plates from hexane–dichloromethane 11 : 2); IR (KBr) 3480, 1641, 1589, 1258, and 1207 cm^{-1}; ^{1}H NMR δ=2.59 (s, 3H), 3.97 (s, 3H), 6.49 (br s, 1H), 12.19 (s, 1H). MS *m/z* (%) 298 (6), 296 (23), 294 (M^+, 18). Anal. ($C_9H_8BrClO_4$) C, H.

The crude chloride **11** (1.36 g) was treated with Me_2SO_4 (1.27 g, 10.1 mmol) and K_2CO_3 (1.40 g, 10.1 mmol) in acetone (40 ml) at reflux temperature for 2.5 h. Extrac-

Table 2. Deprotection of Protected Phenolic Hydroxyl Groups[a)]

Run	Substrate	Method	Yield of product/%					
								
1	**18a** R=Me	A	**2**	45	**19** R=Me X=Cl	17	**20** R=H X=SEt	12
2	**18a**	B	**2**	81				
3	**18c** R=SEM	C	**2**	86				
4	**18c**	D	**2**	70				
5	**18c**	E	**2**	48				
6	**18f** R=MOM	C	**2**	56				
7	**18f**	F	**2**	36				
								
8	**18b**	A[b)]	**7**	19	**21** R^1=H R^2=Me X=Cl	57	**22** R^1=Me R^2=H X=Cl	13
9	**18b**	A[c)]	**7**	47	**21**	7	**23** R^1=R^2=H X=SEt	17
10	**18b**	G	**7**	51				
11	 **13**	C			 **11**		70	
12	 **24**	C					92	
13	 **25**	C					81	
14	 **26**	C					90	

a) Method A: 10 equiv EtSNa, DMF, 120 °C, 1 h, Ref. 24; B: 10 equiv EtSNa, HMPA, 120 °C, 80 min; C: 0.75 equiv P_2I_4, CH_2Cl_2, 0 °C, 30—45 min; D: 10 equiv TBAF, HMPA, 70 °C, 2.5 h, Ref. 26; E: 5 equiv TASF, THF, 25 °C, 2.5 d, Ref. 27; F: 6 mol dm^{-3} HCl, THF, 25 °C, 4.5 h, Ref. 28; G: 10 equiv EtMgBr, DMF, 120 °C, 30 min. b) 100 °C, 30 min. c) 2.5 h.

tive workup followed by column chromatography (hexane–dichloromethane 1:1—1:100) gave a colorless oil, **12** (1.41 g, 94% yield from **10**). Bp 130 °C (bath temp)/0.09 Torr (1 Torr=133.322 Pa); IR 1737, 1383, 1259, and 1100 cm^{-1}; ^{1}H NMR δ=2.27 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H); MS *m/z* (%) 326 (13), 324 (51), 322 (M^+, 40). Anal. ($C_{11}H_{12}BrClO_4$) C, H.

Methyl 3-Bromo-5-chloro-6-methyl-2,4-bis[2-(trimethylsilyl)ethoxymethoxy]benzoate (13). According to the reported methods,[26)] **11** (1.18 g, 4.0 mmol) was treated with SEM chloride (2.7 g, 16 mmol) and diisopropylethylamine (3.1 g, 24 mmol) in dichloromethane (4 ml) at room temperature for 2 h. Extractive workup followed by column chromatography (hexane–ethyl acetate 10:1) gave **13** (colorless oil, 2.2 g) quantitatively. IR 1739, 1254, and 1161 cm^{-1}; ^{1}H NMR δ=0.02 (s, 18H), 0.98 (t, J=8.6 Hz, 4H), 2.26 (s, 3H), 3.7—4.1 (m+s (δ=3.89), 7H), 5.13 (s, 2H), 5.20 (s, 2H); MS *m/z* (%) 427 (16), 425 (48), 423 (M^+−SEM, 35). Anal. ($C_{21}H_{36}BrClO_6Si_2$) C, H.

Methyl 3,5-Dibromo-2,4-dimethoxy-6-methylbenzoate (15). The dibromide **14** (1.11 g, 3.27 mmol) was converted into **15** (colorless oil, 1.17 g, 97% yield) by the same procedure as preparation of **12**. IR 1735, 1380, 1258, and 1093 cm^{-1}; ^{1}H NMR δ=2.32 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H); MS *m/z* 366 (M^+) with an isotopic pattern of dibromine. Anal. ($C_{11}H_{12}Br_2O_4$) C, H.

Coupling of Bromobenzenes with Allylic Bromide. Methyl 3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-2-methyl-4,6-bis[2-(trimethylsilyl)ethoxymethoxy]-benzoate (16c). (A Typical Procedure). Butyllithium (1.71 mol dm^{-3} in hexane, 0.79 ml, 1.35 mmol) was added to a THF (8 ml) solution of **13** (0.68 g, 1.23 mmol) at

−78 °C. Consumption of **13** was confirmed by TLC analysis. After 15 min, a THF (4 ml)–HMPA (0.34 ml)–hexane (0.87 ml) solution of 3-methoxy-3-methyl-1-butynylcopper[21] (1.35 mmol) was added to the reaction mixture over a period of 5 min, and the whole was stirred for 30 min at −78 °C followed by addition of a THF (2 ml) solution of geranyl bromide (0.21 g, 0.98 mmol). The mixture was stirred for 18 h and warmed to room temperature. Workup in the usual manner and purification by preparative TLC (hexane–ethyl acetate 5:1) gave **16c** as a syrup (0.55 g, 91% yield from geranyl bromide, R_f 0.61—0.66) along with methyl 3-chloro-2-methyl-4,6-bis[2-(trimethylsilyl)ethoxymethoxy]benzoate (**37**) (29 mg, 5% yield from **13**, R_f 0.53—0.57). The coupling product **16c** showed IR 1738, 1261, 1250, 1156, 1057, 941, 861, and 837 cm^{-1}; ^1H NMR δ=0.05 (s, 18H), 0.99 (t, J=8.6 Hz, 4H), 1.59 (s, 3H), 1.66 (s, 3H), 1.75 (s, 3H), 1.9—2.1 (m, 4H), 2.31 (s, 3H), 3.48 (d, J=6.3 Hz, 2H), 3.6—4.1 (m+s (δ=3.91), 7H), 4.9—5.3 (m+s (δ=5.00)+s (δ=5.11), 6H); MS m/z (%) 483 (11), 481 (M^+, 24). Anal. ($C_{31}H_{53}ClO_6Si_2$) C, H, Cl.

37: IR 1736, 1595, 1259, and 1042 cm^{-1}; ^1H NMR δ=−0.01 (s, 18H), 0.93 (t, J=8.3 Hz, 4H), 2.28 (s, 3H), 3.6—3.9 (m+s (δ=3.87), 7H), 5.0—5.4 (m+s (δ=5.17)+s (δ=5.26), 6H), 6.95 (s, 1H); MS m/z (%) 478 (trace), 476 (M^+, 1). Anal. ($C_{21}H_{37}ClO_6Si_2$) C, H, Cl.

In a similar manner, **16a**, **16b**, **16d**, **16e**, **28**, and **29** together with side products **35** and **36** were obtained.

Methyl 3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-dimethoxy-2-methylbenzoate (16a) and Methyl 3-Chloro-4,6-dimethoxy-2-methylbenzoate (35). **16a**: IR 1735, 1584, 1321, 1263, 1158, and 1095 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.64 (s, 3H), 1.77 (s, 3H), 1.9—2.2 (m, 4H), 2.69 (s, 3H), 3.39 (d, J=6.6 Hz, 2H), 3.77 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.9—5.3 (m+t (δ=5.17, J=6.6), 2H); MS m/z (%) 382 (4), 380 (M^+, 10). Anal. ($C_{21}H_{31}ClO_4$) C, H, Cl.

35: IR (KBr) 1733, 1596, 1339, 1272, 1216, and 1089 cm^{-1}; ^1H NMR δ=2.28 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.37 (s, 1H); MS m/z (%) 246 (17), 244 (M^+, 53). Anal. ($C_{11}H_{12}ClO_4$) C, H, Cl.

Methyl 3-Chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzoate (16b). Mp 80.5—81.5 °C (colorless prisms from hexane); IR (KBr) 1736, 1584, 1264, 1158, and 1091 cm^{-1}; ^1H NMR δ=1.67 (s, 3H), 1.76 (s, 3H), 2.27 (s, 3H), 3.35 (d, J=6.5 Hz, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 5.16 (t, J=6.5 Hz, 1H); MS m/z (%) 314 (16), 312 (M^+, 45). Found: m/z 312.1147. Calcd for $C_{16}H_{21}ClO_4$: M, 312.1127.

Methyl 3-Bromo-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-dimethoxy-2-methylbenzoate (16d) and Methyl 3-Bromo-4,6-dimethoxy-2-methylbenzoate (36). **16d**: bp 195 °C (bath temp)/0.62 Torr; IR 1735, 1585, 1452, 1263, 1152, and 1081 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.63 (s, 3H), 1.76 (s, 3H), 1.9—2.1 (m, 4H), 2.33 (s, 3H), 3.39 (d, J=6.5 Hz, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 5.04 (t, J=6.0 Hz, 1H), 5.16 (t, J=6.5 Hz, 1H); MS m/z (%) 426 (23), 424 (M^+, 30). Anal. ($C_{21}H_{29}BrO_4$) C, H.

36: IR (KBr) 1728, 1590, 1340, 1268, 1215, and 1092 cm^{-1}; ^1H NMR δ=2.33 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.34 (s, 1H); MS m/z (%) 290 (55), 288 (M^+, 55). Anal. ($C_{11}H_{13}BrO_4$) C, H.

Methyl 3-Bromo-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzoate (16e). Mp 100.2—101.8 °C; IR (KBr) 1732, 1585, 1266, 1155, and 1085 cm^{-1}; ^1H NMR δ=1.68 (s, 3H), 1.76 (s, 3H), 2.32 (s, 3H), 3.37 (d, J=6.9 Hz, 2H), 3.75 (s, 3H), 3.79 (s, 3H), 3.91 (s, 3H), 5.15 (t, J=6.9 Hz, 1H); MS m/z (%) 358 (56), 356 (M^+, 59). Anal. ($C_{16}H_{21}BrO_4$) C, H, Br.

2-[(*E*)-3,7-Dimethyl-2,6-octadienyl]-1,3-dimethoxy-5-methylbenzene (28). Treatment of **27** (0.28 g, 1.82 mmol) in ether (6 ml) with butyllithium (1.60 mol dm^{-3} in hexane, 1.37 ml, 2.2 mmol) at reflux temperature for 1.5 h afforded 2,6-dimethoxy-4-methylphenyllithium,[19] which was allowed to react with geranyl bromide (0.40 g, 1.82 mmol) by the same method as preparation of **16c**. **28**: IR 1610, 1590, 1467, 1168, 1122, and 816 cm^{-1}; ^1H NMR δ=1.56 (s, 3H), 1.63 (s, 3H), 1.74 (s, 3H), 1.8—2.1 (m, 4H), 2.31 (s, 3H), 3.30 (d, J=6.8 Hz, 2H), 3.78 (s, 6H), 4.9—5.3 (m+t (δ=5.17, J=6.8 Hz), 2H), 6.36 (s, 2H); MS m/z (%) 288 (M^+, 11), 165 (100). Anal. ($C_{19}H_{28}O_2$) C, H.

1,3-Dimethoxy-5-methyl-2-[(2*E*,6*E*)-3,7,11-trimethyl-2,6,10-dodecatrienyl]benzene (29). Farnesyl bromide (0.65 g, 2.3 mmol) and **27** (0.34 g, 2.3 mmol) were transformed into **29** by the method described above. IR 1609, 1588, 1467, 1121, and 815 cm^{-1}; ^1H NMR δ=1.57 (s, 6H), 1.67 (s, 3H), 1.75 (s, 3H), 1.8—2.1 (m, 8H), 2.31 (s, 3H), 3.30 (d, J=7.1 Hz, 2H), 4.9—5.3 (m, 3H), 6.36 (s, 2H); MS m/z (%) 356 (M^+, 4), 165 (100). Anal. ($C_{24}H_{36}O_2$) C, H.

Transformation of Methyl Benzoates 16 into Benzaldehydes 18. 3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-2-methyl-4,6-bis[2-(trimethylsilyl)ethoxymethoxy]benzaldehyde (18c). (A Typical Procedure). An ethereal (4 ml) solution of **16c** (82 mg, 0.13 mmol) was added to a suspension of $LiAlH_4$ (12 mg, 0.32 mmol) in ether (3 mol) at 0 °C and stirred for 1 h. After addition of ether (10 ml) and saturated aq Na_2SO_4 (ca. 0.1 ml), the precipitate was filtered and washed with ether (3×10 ml). The combined ether solutions were dried and concentrated to give crude alcohol **17c** (77 mg), which was treated with PCC (100 mg, 0.46 mmol) in dichloromethane (5 ml) at room temperature for 40 min. After addition of the same amount of PCC, the reaction mixture was stirred for 4 h, diluted with ether (10 ml), and filtered through Celite and silica gel. The filtrate was concentrated and purified by column chromatography (ether) to give **18c** (77 mg, 99% yield). IR 1696, 1249, 1057, 939, 858, and 836 cm^{-1}; ^1H NMR δ=0.03 (s, 18H), 0.9—1.1 (m, 4H) 1.57 (s, 3H), 1.64 (s, 3H), 1.75 (s, 3H), 1.9—2.1 (m, 4H), 2.63 (s, 3H), 2.63 (s, 3H), 3.46 (d, J=4.7 Hz, 2H), 3.7—4.0 (m, 4H), 4.9—5.3 (m+s (δ=5.02)+s (δ=5.16), 6H), 10.40 (s, 1H); MS m/z (%) 451 (M^+−SEM, 4), 73 (100). Anal. ($C_{30}H_{51}ClO_5Si_2$) C, H, Cl.

3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-dimethoxy-2-methylbenzyl Alcohol (17a) and 3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-dimethoxy-2-methylbenzaldehyde (18a). **17a**: IR 3400, 1583, 1450, 1397, 1225, and 1098 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.9—2.2 (m, 5H), 2.46 (s, 3H), 3.39 (d, J=6.6 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 4.75 (s, 2H), 4.9—5.3 (m+t (δ=5.18, J=6.6 Hz 2H); MS m/z (%) 354 (3), 352 (M^+, 9). Anal. ($C_{20}H_{29}ClO_3$) C, H, Cl.

18a: IR 1695, 1553, 1450, 1377, 1308, 1226, and 1097 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.64 (s, 3H), 1.79 (s, 3H), 1.9—2.2 (m, 4H), 2.63 (s, 3H), 3.41 (d, J=6.6 Hz, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 4.9—5.3 (m+t (δ=5.16, J=6.6 Hz), 2H), 10.45 (s, 1H); MS m/z (%) 352 (1), 350 (M^+, 3). Anal. ($C_{20}H_{27}ClO_3$) C, H, Cl.

3-Chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzyl Alcohol (17b) and 3-Chloro-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (18b).[11] **17b**: IR 3440, 1227, and 1097 cm^{-1}; ^1H NMR δ=1.67 (s, 3H), 1.77 (s, 3H), 2.11 (br s, 1H), 2.42 (s, 3H), 3.36 (d, J=6.9 Hz, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 4.70 (s, 2H), 5.16 (t, J=6.9 Hz 1H); MS m/z (%) 286 (16), 284 (M^+, 50). Anal. ($C_{15}H_{21}ClO_3$) C, H, Cl.

18b: IR 1707, 1390, 1322, 1239, and 1108 cm^{-1}; ^1H NMR δ=1.70 (s, 3H), 1.79 (s, 3H), 2.62 (s, 3H), 3.39 (d, J=6.5 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 5.16 (t, J=6.5 Hz, 1H); MS m/z (%) 284 (18), 282 (M^+, 55). Anal. ($C_{15}H_{19}ClO_3$) C, H, Cl.

3-Bromo-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-dimethoxy-2-methylbenzaldehyde (18d). Bp 194 °C (bath temp)/0.6 Torr; IR 1693, 1304, 1218, 1092, 989, and 542 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.63 (s, 3H), 1.79 (s, 3H), 1.9—2.1 (m, 4H), 2.68 (s, 3H), 3.42 (d, J=6.8 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 5.04 (t, J=6.6 Hz, 1H), 5.18 (t, J=6.8 Hz, 1H), 10.39 (s, 1H). Anal. ($C_{15}H_{18}BrO_3$) C, H.

3-Bromo-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzyl Alcohol (17e) and 3-Bromo-4,6-dimethoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (18e). **17e**: IR 3340, 1587, 1451, 1315, 1223, and 1097 cm^{-1}; ^1H NMR δ=1.67 (s, 3H), 1.77 (s, 3H), 2.48 (s, 3H), 3.37 (d, J=7.1 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.74 (s, 2H), 5.17 (t, J=7.1 Hz, 1H); MS m/z (%) 330 (53), 328 (M^+, 53).

18e: Bp 158 °C (bath temp)/0.6 Torr; IR 1694, 1306, 1219, and 1091 cm^{-1}; ^1H NMR δ=1.69 (s, 3H), 1.79 (s, 3H), 2.66 (s, 3H), 3.41 (d, J=6.5 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 5.17 (t, J=6.5 Hz, 1H), 10.40 (s, 1H). Anal. ($C_{10}H_{10}BrO_3$) C, H.

3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4,6-bis(methoxymethoxy)-2-methylbenzaldehyde (18f). The MOM ether **18f** was prepared from **2** by the reported method[28] in 64% yield. IR 1694, 1163, 1046, and 928 cm^{-1}; ^1H NMR δ=1.60 (s, 3H), 1.67 (s, 3H), 1.78 (s, 3H), 1.9—2.2 (m, 4H), 2.67 (s, 3H), 3.3—3.7 (m+s (δ=3.57)+s (δ=3.67), 8H), 4.9—5.4 (m+s (δ=5.00)+s (δ=5.14), 6H), 10.39 (s, 1H); MS m/z (%) 410 (M^+, trace), 45 (100). Anal. ($C_{22}H_{31}ClO_5$) C, H, Cl.

Cleavage of Methyl Ether Bonds with Ethanethiolates. Preparation of Colletochlorin B (2). (A Typical Procedure). Ethanethiol (0.72 g, 11.5 mmol) was added to an HMPA (10.7 ml) suspension of NaH (0.29 g, 12 mmol) at 0 °C and stirred for 20 min at room temperature. This solution was added to **18a** (0.40 g, 1.15 mmol), and the resulting mixture was stirred at 120 °C for 1.3 h, and then cooled to 0 °C. Extractive workup with ether (150 ml), ice (10 g), and hydrochloric acid (6 mol dm^{-3}, 2.5 ml) afforded an organic layer, which was washed with hydrochloric acid (0.5 mol dm^{-3}, 3×4 ml) and dried over Na_2SO_4. Purification of the concentrated residue (0.64 g) by column chromatography (hexane–ethyl acetate 10:1) gave **2**[4,12] (0.30 g, 81% yield). Mp 90—91 °C (colorless needles from benzene–hexane); IR 3360, 1618, 1456, 1424, 1281, 1237, and 795 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.64 (s, 3H), 1.78 (s, 3H), 1.9—2.2 (m, 4H), 2.59 (s, 3H), 3.40 (d, J=7.1 Hz, 2H), 4.9—5.3 (m+t (δ=5.22, J=7.1 Hz), 2H), 6.40 (s, C4–OH, 1H), 10.15 (s, 1H), 12.70 (s, C6–OH, 1H); MS m/z (%) 324 (4) 322 (M^+, 12), 199 (100).

3-Chloro-5-[(*E*)-3,7-dimethyl-2,6-octadienyl]-4-hydroxy-6-methoxy-2-methylbenzaldehyde (19). IR (KBr) 3450, 1670, 1590, 1563, 1311, 1232, and 1099 cm^{-1}; ^1H NMR δ=1.57 (s, 3H), 1.64 (s, 3H), 1.78 (s, 3H), 1.9—2.2 (m, 4H), 2.65 (s, 3H), 3.41 (d, J=6.8 Hz, 2H), 3.80 (s, 3H), 4.9—5.3 (m+t (δ=5.19, J=6.8 Hz), 2H), 6.28 (br s, C4—OH, 1H), 10.38 (s, 1H); MS m/z (%) 338 (4), 336 (10), 123 (100). Anal. ($C_{19}H_{25}ClO_3$) C, H, Cl.

3-[(*E*)-3,7-Dimethyl-2,6-octadienyl]-5-ethylthio-2,4-dihydroxy-6-methylbenzaldehyde (20). This unstable compound was characterized only by ^1H NMR δ=1.20 (t, J=7.2 Hz, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.9—2.2 (m, 4H), 2.59 (q, J=7.2 Hz, 2H), 2.79 (s, 3H), 3.39 (d, J=7.2 Hz, 2H), 4.9—5.4 (m+t (δ=5.23, J=7.2 Hz), 2H), 8.02 (s, C4–OH, 1H), 10.15 (s, 1H), 12.86 (s, C2–OH, 1H).

Colletochlorin D (7).[9,13] Mp 147—149 °C (colorless needles from hexane–ether); IR (KBr) 3420, 1619, 1282, 1255, and 1232 cm^{-1}; ^1H NMR δ=1.69 (s, 3H), 1.78 (s, 3H), 2.58 (s, 3H), 3.39 (d, J=6.8 Hz, 2H), 5.23 (t, J=6.8 Hz, 1H), 6.41 (s, C4–OH, 1H), 10.13 (s, 1H), 12.71 (s, C6–OH, 1H); MS m/z (%) 256 (13), 254 (M^+, 35), 199 (100).

3-Chloro-4-hydroxy-6-methoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (21).[11] ^1H NMR δ=1.71 (s, 3H), 1.80 (s, 3H), 2.69 (s, 3H), 3.41 (d, J=6.3 Hz, 2H), 3.82 (s, 3H), 5.21 (t, J=6.3 Hz, 1H), 6.29 (s, C4–OH, 1H), 10.40 (s, 1H).

3-Chloro-6-hydroxy-4-methoxy-2-methyl-5-(3-methyl-2-butenyl)benzaldehyde (22) and 3-Ethylthio-4,6-dihydroxy-2-methyl-5-(3-methyl-2-butenyl)-benzaldehyde (23). These unstable compounds were characterized by only spectrometric data. **22**: IR 3450, 1634, 1605, 1400, and 1243 cm^{-1}; ^1H NMR δ=1.68 (s, 3H), 1.78 (s, 3H), 2.62 (s, 3H), 3.38 (d, J=6.9 Hz, 2H), 3.86 (s, 3H), 5.22 (t, J=6.9 Hz, 1H); 10.28 (s, 1H), 12.53 (s, C6–OH, 1H).

23: IR (KBr) 3440, 3290, 1630, 1565, 1424, 1286, 1249, and 1110 cm^{-1}; ^1H NMR δ=1.20 (t, J=8.2 Hz, 3H), 1.68 (s, 3H), 1.79 (s, 3H), 2.59 (q, J=8.2 Hz, 2H), 2.78 (s, 3H), 3.36 (d, J=7.1 Hz, 2H), 5.22 (t, J=7.1 Hz, 1H), 8.20 (s, C4–OH, 1H), 10.16 (s, 1H), 12.87 (s, C6–OH, 1H); MS m/z (%) 280 (M^+, 67), 225 (100).

3-Methoxy-5-methyl-2-[(2*E*,6*E*)-3,7,11,-trimethyl-2,6,10-dodecatrienyl]phenol (30).[30,31] IR 3450, 1616, and 1511 cm^{-1}; ^1H NMR δ=1.57 (s, 6H), 1.66 (s, 3H), 1.78 (s, 3H), 1.8—2.1 (m, 8H), 2.25 (s, 3H), 3.36 (d, J=7.1 Hz, 2H), 3.76 (s, 3H), 4.9—5.3 (m, 3H), 6.29 (s, 2H); MS m/z (%) 342 (M^+, 5), 151 (100).

Cleavage of Alkoxymethyl Aryl Ethers with P_2I_4. Transformation of 18c into 2. (A Typical Procedure). P_2I_4 (15 mg, 0.027 mmol) was added to a dichloromethane (0.5 ml) solution of **18c** (21 mg, 0.036 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 25 min and at room temperature for 5 min. The reaction mixture was directly charged on the top of a short silica-gel column and eluted at 0 °C with ether to afford a crude product (11

mg), which was purified by preparative TLC (hexane–ethyl acetate 5:1) to give rise to **2** (10 mg, 86% yield). This procedure applies to the transformation of **13**, **18f**, **24**, **25**, and **26**.

Preparation of 8-Chloro-5-hydroxy-2,7-dimethyl-2-(4-methyl-3-pentenyl)-2*H*-1-benzopyran-6-carbaldehyde (31) and 8-Chloro-5-hydroxy-2,7-dimethyl-2-[(*E*)-4-methyl-1,3-pentadienyl)-2*H*-1-benzopyran-6-carbaldehyde (32). (A Typical procedure). DDQ (67 mg, 0.28 mmol) was added to a benzene (5 ml) solution of **2** (32 mg, 0.099 mmol) at room temperature. After stirring for 10 min at 80 °C, the reaction mixture was concentrated and purified by column chromatography (hexane–ethyl acetate 20:1) to give **31** (16 mg, 50% yield) along with **32** (3 mg, 9% yield). **31**: Mp 76 °C; IR (KBr) 3100—3700, 1638, 1619, 1253, 1242, 1126, and 723 cm^{-1}; ^1H NMR δ=1.4—1.9 (m+s (δ=1.48)+s (δ=1.57)+s (δ=1.65), 11H), 1.9—2.3 (m, 2H), 2.58 (s, 3H), 5.10 (t, J=6.8 Hz, 1H), 5.54 (d, J=10.1 Hz, 1H), 6.14 (d, J=10.1 Hz, 1H), 10.11 (s, 1H), 12.64 (s, C5–OH, 1H); MS m/z (%) 322 (3), 320 (M^+, 8), 237 (100). Anal. ($C_{18}H_{21}ClO_3$) C, H, Cl. The unstable compound **32** was characterized spectrometrically. IR (CH_2Cl_2) 2500—3600, 1643, 1620, 1375, 1255, and 1146 cm^{-1}; ^1H NMR δ=1.63 (s, 3H), 1.74 (s, 6H), 2.59 (s, 3H), 5.57 (d, J=15.2 Hz, 1H), 5.58 (d, J=10.1 Hz, 1H), 5.78 (d, J=10.8 Hz, 1H), 6.48 (dd, J=10.8, 15.2 Hz, 1H), 6.77 (d, J=10.1 Hz, 1H), 10.12 (s, 1H), 12.65 (s, C5–OH, 1H); MS m/z (%) 320 (24), 318 (M^+, 63), 303 (100).

8-Chloro-5-hydroxy-2,2,7-trimethyl-2*H*-1-benzopyran-6-carbaldehyde (33). Mp 98—99 °C; IR (KBr) 3200—3700, 1636, 1369, 1299, 1258, and 1161 cm^{-1}; ^1H NMR δ=1.47 (s, 6H), 2.56 (s, 3H), 5.55 (d, J=10.0 Hz, 1H), 6.64 (d, J=10.0 Hz, 1H), 10.09 (s, 1H), 12.63 (s, C5–OH, 1H); MS m/z (%) 254 (5), 252 (M^+, 16), 237 (100). Anal. ($C_{13}H_{13}ClO_3$) C, H, Cl.

3-Bromo-5-chloro-2,4-dimethoxy-6-methylbenzoic Acid (34). An ethanol (1 ml) solution of **12** (0.30 g, 0.94 mmol) was treated with aq KOH (5 mol dm^{-3}, 1 ml) for 2 h at reflux temperature. After washing with ether (3×10 ml), the aqueous solution was adjusted to pH 1 with hydrochloric acid (6 mol dm^{-3}) and extracted with ether (5×10 ml). The combined extracts were dried over Na_2SO_4 and concentrated to give **34** (0.28 g, 98% yield). Mp 131—132 °C (colorless needles from hexane–dichloromathane); IR (Nujol) 2400—3600, 1693, 1384, 1297, and 1100 cm^{-1}; ^1H NMR δ=2.42 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 7.86 (br s, 1H); MS m/z (%) 312 (12), 310 (M^+, 46), 292 (100). Anal. ($C_{10}H_{10}BrClO_4$) C, H.

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