An Effective Method for the Synthesis of ^{13}C-Labeled Polyprenylhydroxybenzoic Acids

Martin Lang,[1] Wolfgang Steglich*

Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5–13 (F), 81377 München, Germany
Fax +49(89)218077756; E-mail: wolfgang.steglich@cup.uni-muenchen.de

Received 12 January 2005

Abstract: The synthesis of side-chain ^{13}C-labeled geranylgeranyl-4-hydroxybenzoic acids and geranylgeranyl-3,4-dihydroxybenzoic acids is described. The synthesis starts from *O*-protected methyl hydroxyiodobenzoates, which are transformed into Grignard reagents by low-temperature iodine–magnesium exchange according to Knochel's procedure. Copper catalyzed cross-coupling with labeled geranylgeranyl bromide followed by deprotection affords the products with good yields and full retention of stereochemistry.

Key words: allylations, copper, coupling, Grignard reactions, organometallic reagents

In the course of our studies on the biosynthesis of meroterpenoids from larger fungi, we required side-chain ^{13}C-labeled polyprenylhydroxybenzoic acids for feeding experiments. Unfortunately, known methods for the polyprenylation of hydroxybenzoic acids appeared to be unsuitable for the preparation of the valuable isotope-labeled compounds due to lack of generality, unreliable yields or loss of stereochemical integrity in the side chain. In this publication we describe an effective method for the introduction of polyprenyl side chains into hydroxybenzoic acids that circumvents these problems.

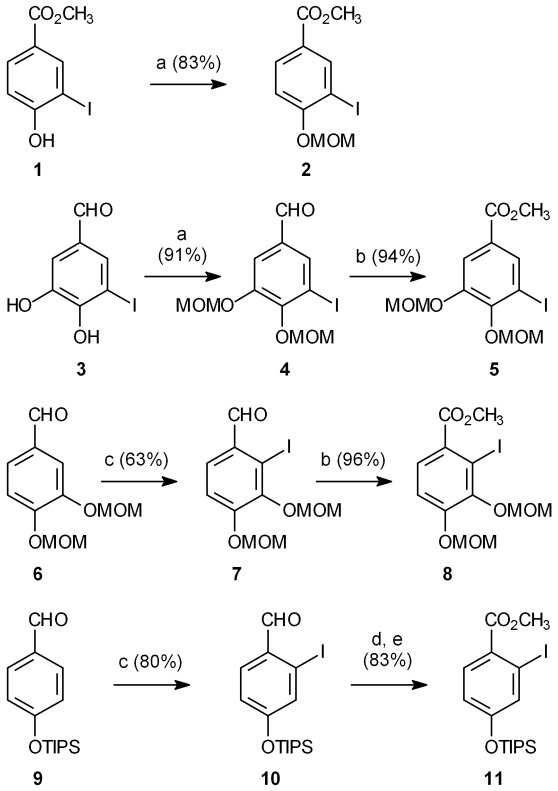
The Claisen alkylation[2] of 4-alkoxycarbonylphenolates with (poly)prenyl bromides[3] represents the most common method for the synthesis of 4-hydroxy-3-(poly)prenylbenzoic acids. The reported yields, however, are generally low, covering a range between 7%[3b] and 37%.[3c] Recently, Wessjohann[4] developed an enzymatic method for the transfer of polyprenyl pyrophosphates to the *meta*-position of 4-hydroxy- and 4-aminobenzoic acids using a prenyltransferase isolated from an overproducing strain of *E. coli*.

The syntheses of (2′*E*,6′*E*)-3-farnesyl-4-hydroxybenzoic acid and 3-farnesyl-4,5-dihydroxybenzoic acid were accomplished by the Stille coupling.[5] This methodology, however, suffers from the problem of removing toxic[6a] traces of organotin compounds.[6b] In the course of the Stille coupling of methyl 4,5-diacetoxy-3-[(tri-*n*-butyl)stannyl]benzoate with polyprenyl bromides, we also observed the formation of a 3:1 *E*/*Z* mixture at C-2′.[7–10]

Methods based on the formation of lithiated intermediates use silyl-protected benzyl alcohols[11] or oxazolines[12] instead of the corresponding ester derivatives. In these cases additional protection/deprotection steps, as well as changes of the oxidation state, are required.

In recent years, important progress in Grignard methodology has been contributed by Knochel and coworkers.[13] They demonstrated that halogen–magnesium exchange in (hetero)aryl or alkenyl halides can be performed with *i*-PrMgBr at low temperatures, thereby avoiding reaction of the resulting Grignard reagents with sensitive functionalities such as amide, cyano, halogen, or carboxylic ester groups. We believed that this technique would allow us to introduce the valuable ^{13}C-labeled side chain into iodobenzoic acid derivatives at a later stage of the synthesis. The preparation of the desired O-protected hydroxyiodobenzoates is depicted in Scheme 1.

In the synthesis of iodoester **2**, methyl 4-hydroxybenzoate was treated with NaI and chloramine-T[14] and the resulting



Scheme 1 *Reagents and conditions*: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 or DMF, r.t.; (b) I_2, KOH, MeOH, 0 °C; (c) LTMDA, –20 °C; then *n*-BuLi (excess), –20 °C; then 1,2-diiodoethane, –40 °C → r.t.; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O, r.t.; (e) MeI, DBU, DMF, r.t.

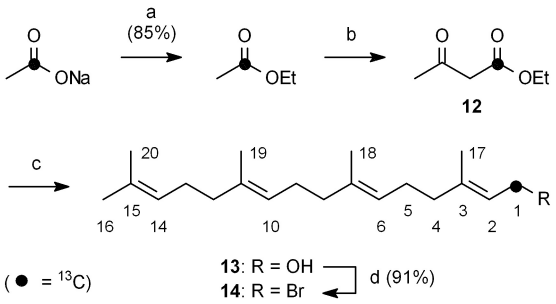
SYNTHESIS 2005, No. 6, pp 1019–1027
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-861863; Art ID: Z01205SS

iodo derivative **1** was converted into the methoxymethyl (MOM) ether **2**.[15]

The synthesis of ester **5** started from 4,5-dihydroxy-3-iodobenzoic acid (**3**),[16] which can be easily prepared by demethylation of 5-iodovanillin with BBr_3. Protection of **3** with MOM chloride[15] and oxidation of the resulting diether **4** with iodine and KOH in MeOH[17] afforded **5** in excellent yield.

For the synthesis of regioisomer **8**, 3,4-dihydroxybenzaldehyde was methoxymethylated[15] and the resulting diether **6** was treated with the lithium salt of *N*,*N*,*N*′-trimethylethylenediamine (LTMDA).[18] *Ortho*-lithiation with *n*-butyl lithium followed by treatment with 1,2-diiodoethane afforded a mixture of 2-iodo-3,4-bis(methoxymethoxy)benzaldehyde (**7**) and its 6-iodo isomer in 63% and 3% yield, respectively. This reflects the cooperative anion stabilizing effect of the neighboring α-amino alkoxide[18] and methoxymethyl[19] groups favoring the predominant formation of the 2-iodo isomer. Alkaline iodine oxidation[17] of the crude aldehyde mixture and chromatographic purification of the product yielded the methyl ester **8**.

Methyl 2-iodo-4-(triisopropylsilyloxy)benzoate (**11**) was prepared from aldehyde **9**.[20] Treatment of **9** with LTMDA and *n*-BuLi,[18] followed by addition of 1,2-diiodoethane yielded exclusively the 2-iodo derivative **10**, which was oxidized with sodium chlorite in the presence of 2-methyl-2-butene.[21] Treatment of the resulting carboxylic acid with MeI and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[22] afforded the desired ester **11**.



Scheme 2 *Reagents and conditions*: (a) Me_2SO_4 (excess), 155 °C to 165 °C;[25] (b) See ref.[24]; (c) See ref.[23]; (d) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 2 h. The atom numbering indicates the system used for NMR assignments of all geranylgeranyl compounds.

(2*E*,6*E*,10*E*)-[1-^{13}C]Geranylgeraniol (**13**) was prepared from (2*E*,6*E*)-farnesyl bromide and ethyl [1-^{13}C]acetoacetate (**12**) applying the four-step procedure of Schmalz[23] (Scheme 2). Compound **12** was obtained by acetylation[24] of ethyl [1-^{13}C]acetate, which was in turn prepared by alkylation of sodium [1-^{13}C]acetate with diethyl sulfate.[25] For the conversion of polyprenyl alcohols

Biographical Sketches

Martin Lang was born in 1972 in Weilheim, Germany. He studied chemistry in Munich and obtained his diploma in 1997. He received his PhD under the guidance of Prof. Wolfgang Steglich in 2002 and is currently working as a medicinal chemist at 4SC AG, Martinsried.

Wolfgang Steglich was born in 1933 in Kamenz/Sachsen. He studied chemistry at the TU Berlin and received his PhD at the TU München under the guidance of Prof. Friedrich Weygand. During his postdoctoral studies with Sir Derek H. R. Barton at the Imperial College London, he worked on the biosynthesis of morphine alkaloids. He finished his habilitation in München in 1965 and held chairs of Organic Chemistry at the TU Berlin (1971–1975), University of Bonn (1975–1991), and University of München (emeritus status since 2001). His major topic of interest is the chemistry of natural products, especially the isolation, synthesis and biosynthesis of fungal metabolites, the synthesis of marine pyrrole alkaloids and the chemistry of peptides. He introduced DMAP as a nucleophilic catalyst in organic synthesis and was involved in the development of strobilurins as a major class of fungicides. He has served as an editor of several journals and the Römpp Encyclopedia 'Natural Products'.

to the corresponding bromides (e.g. **14**), the Appel reaction[26] was preferred over the use of PBr_3.[27]

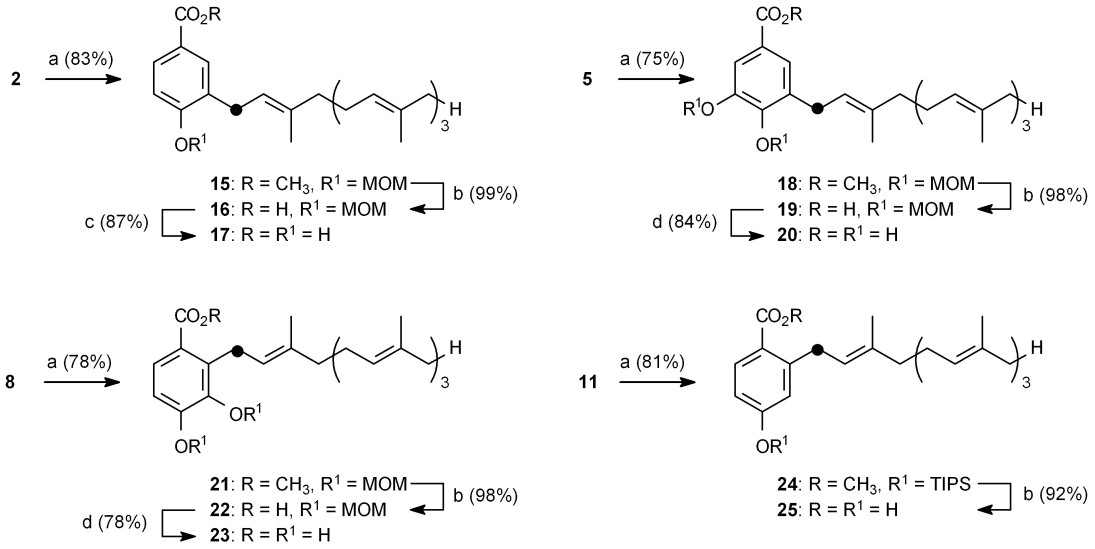
With the four aryl iodides **2**, **5**, **8**, and **11** at hand, we were able to show that the iodine–magnesium exchange under Knochel's conditions[13] was complete after 0.5 h at –20 °C without affecting the ester group.[28] Not surprisingly, the coupling of the Grignard compounds with polyprenyl bromides required catalysis.

Dilithium tetrachlorocuprate(II)[29] is a frequently used catalyst in the reaction of Grignard reagents with electrophiles.[30] The catalytically active species is most likely a copper(I) derivative[31] formed in situ on reduction of the copper(II) complex by the organomagnesium compound. In cases of intramolecular stabilization of the Grignard reagent by chelating substituents, e.g. MOM ethers, this reduction is reported to be seriously hampered, resulting in reduced coupling yields.[32] This can be prevented by the use of dilithium trichlorocuprate(I) instead of the copper(II) salt.[32] Accordingly, we used the copper(I) complex[33] as a catalyst and good coupling yields with geranyl bromide were obtained. Later, however, no significant difference between the copper(I) complex and dilithium tetrachlorocuprate(II) was noted. The latter is commercially available and can be stored in THF solution. With both copper catalysts, α (S_N2) substitution occurred exclusively, and no γ (S_N2') substitution product was detectable by NMR. *E*/*Z* isomerization of the 2′-double bond in the polyprenyl chain was negligible, and the coupling yields with geranylgeranyl bromide (**14**) were generally in the range of 70%–88%. With respect to the valuable isotope-labeled side chain, a slight excess (1.2 equivalents) of aryl iodide was employed.

The methyl ester and silyl ether groups of **24** were cleaved with LiOH to afford hydroxy acid **25**. Standard hydrolysis of the corresponding esters furnished the crude acids **16**, **19**, and **22**, respectively. The MOM groups of **19** and **22** were cleaved with 0.5 M HCl in *i*-PrOH[34] to yield **20** and **23**, respectively. Acetal hydrolysis of **16** required both higher HCl concentration and prolonged reaction time. Under these conditions, however, a significant amount of material underwent HCl addition to the terminal double bond;[35] this could not be prevented by addition of 20 equivalents of 2-methyl-2-butene. The problem was finally solved by deprotecting **16** with *p*-toluenesulfonic acid in *i*-PrOH at 60 °C.

In conclusion, we have developed a reliable method for the synthesis of stereo- and regiochemically defined polyprenylhydroxybenzoic acids. These compounds are not only potential biosynthetic precursors of meroterpenoids from larger fungi,[36] but are also intermediates in the biosynthesis of ubiquinones.[37] They have been isolated from several plants, fungi and marine sponges[38] and include acids **17**,[38f–j] **20**,[38j,k] and **23**,[38j,k] whose syntheses are reported for the first time. Their NMR and IR spectra are in good agreement with the literature data.[38k] In addition, our new method offers easy access to many other compounds of this type. To the best of our knowledge, 4-hydroxybenzoic acids carrying a polyprenyl residue at C-2 have not been prepared before.

Melting points (uncorrected): Büchi SMP 535 apparatus. IR spectra: Perkin-Elmer FT-IR Spectrum 1000. Abbreviations: s, strong; m, medium; w, weak; sh, shoulder; br, broad. Mass spectra (EI, 70 eV): Finnigan MAT 90 and Finnigan MAT 95Q. High-resolution mass spectra (EI, 70 eV): Finnigan MAT 95Q. NMR spectra: Bruker ARX 300 and Bruker AMX 600. The spectra were recorded in $CDCl_3$ or acetone-d_6 using the residual solvent peak as an internal standard ($CDCl_3$, $\delta_H = 7.26$ and $\delta_C = 77.10$; acetone-d_6, $\delta_H = 2.04$ and $\delta_C = 29.80$). For atom numbering within geranylgeranyl chains, see Scheme 2. Interchangeable NMR assignments are labeled by † and ‡ or separated by /. Elemental analyses were carried out by the Microanalytical Laboratory of the Department Chemie, Universität München. TLC: Silica gel F_{254} (Merck). Flash chromatography (FC): Merck Kieselgel 60 (0.040–0.063 mm). Solvents for chroma-



Scheme 3 *Reagents and conditions*: (a) *i*-PrMgBr, –20 °C; then Li_2CuCl_4 (4 mol%), **14**; (b) LiOH, MeOH, H_2O, 100 °C; (c) *p*-TsOH (1 equiv, 0.1 M), *i*-PrOH, 60 °C, approx. 6 h; (d) AcCl (5 equiv, 0.5 M), *i*-PrOH, r.t., approx. 5 h.

tography were distilled before use. THF was distilled under Ar from Na/benzophenone. CH_2Cl_2 was distilled under Ar from Sicapent (Merck). Dry DMF was purchased from Fluka.

n-BuLi was purchased as a solution in hexanes (Aldrich) and the actual concentration was determined using diphenylacetic acid.[39] Li_2CuCl_4 (0.2 M solution in THF) was obtained from Aldrich. Alternatively, the solution was prepared from dry LiCl und $CuCl_2$.[29] Geraniol was purchased from Fluka, (2*E*,6*E*)-farnesol from Aldrich. For every substitution pattern of the polyprenylhydroxybenzoic acids, the geranyl, (2′*E*,6′*E*,10′*E*)-geranylgeranyl, and (2′*E*,6′*E*,10′*E*)-[1-^{13}C]geranylgeranyl derivatives were synthesized. Only the data of the labeled geranylgeranyl compounds are given.

Air and moisture sensitive compounds were handled under argon using standard Schlenk techniques.

Methyl 4-Hydroxy-3-iodobenzoate (1)

To a solution of methyl 4-hydroxybenzoate (1.52 g, 10 mmol) and NaI (1.80 g, 12 mmol) in MeCN (30 mL) was added within 10 min chloramine-T trihydrate (3.38 g, 12 mmol). The mixture was stirred for 1.5 h at r.t., then slightly acidified with 2 N HCl and concentrated in vacuo. H_2O (30 mL) was added and the resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with aq $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (FC) (hexanes–EtOAc, 3:1) afforded a colorless solid (2.47 g) consisting of 8.3 mmol of **1** (83% yield) and 1.1 mmol of starting material (determined by ^{1}H NMR).[40]

^{1}H NMR (300 MHz, acetone-d_6): δ = 3.83 (s, 3 H), 7.02 (d, 1 H, ^3J = 8.5 Hz), 7.87 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.1 Hz), 8.34 (d, 1 H, ^4J = 2.1 Hz).

^{13}C NMR (75 MHz, acetone-d_6): δ = 51.7, 83.2, 114.9, 123.9, 131.6, 141.2, 161.0, 165.1.

Methyl 3-Iodo-4-(methoxymethoxy)benzoate (2)

To a solution of **1** (2.40 g, containing 8.1 mmol of **1** and 1.1 mmol of methyl 4-hydroxybenzoate) in CH_2Cl_2 (15 mL) were added *i*-PrNEt$_2$ (3.7 mL, 22.5 mmol) and a 6 M solution of MOMCl in EtOAc[15b] (2.5 mL, 15 mmol). The mixture was stirred at r.t. until the reaction was complete (5 h). 2 N NH_4OH (30 mL) was added and the resulting mixture was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo, FC (hexanes–EtOAc, 7:1) afforded a colorless solid (2.42 g) containing 6.9 mmol of **2** (83% yield) and 1.0 mmol of methyl 4-(methoxymethoxy)benzoate (determined by ^{1}H NMR).[40]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3 H, OCH_2OCH_3), 3.88 (s, 3 H, CO_2CH_3), 5.29 (s, 2 H, OCH_2OCH_3), 7.07 (d, 1 H, ^3J = 8.6 Hz, 5-H), 7.96 (dd, 1 H, ^3J = 8.6 Hz, ^4J = 2.1 Hz, 6-H), 8.45 (d, 1 H, ^4J = 2.1 Hz, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2 (CO_2CH_3), 56.7 (OCH_2OCH_3), 86.3 (C-3), 94.8 (OCH_2OCH_3), 113.5 (C-5‡), 125.3 (C-1), 131.4/141.1 (C-2‡, C-6‡), 159.6 (C-4), 165.5 (CO_2CH_3).

GC/MS: *m/z* (%) = 322 (28) [M]$^+$, 292 (5), 291 (11), 261 (6), 45 (100) [C_2H_5O]$^+$.

3-Iodo-4,5-bis(methoxymethoxy)benzaldehyde (4)

To a stirred suspension of 5-iodovanillin (1.39 g, 5.00 mmol) in dry CH_2Cl_2 (10 mL), BBr_3 (1.20 mL, 12.5 mmol) was added at 0 °C under argon. The ice bath was removed and the mixture was stirred for 4 h at r.t. After cooling to 0 °C, MeOH (10 mL) was added slowly and the solution was subsequently refluxed for 0.5 h under an argon atmosphere. The volatiles were distilled off, and H_2O (30 mL) was added to the obtained residue. The mixture was extracted with EtOAc (3 × 40 mL), and the combined organic phases were washed with brine and dried (Na_2SO_4). Concentration in vacuo yielded crude **3** which was suspended in anhyd CH_2Cl_2 (15 mL) and treated with a 6 M solution of MOMCl in EtOAc[15b] (2.5 mL, 15 mmol) and *i*-PrNEt$_2$ (2.9 mL, 17.5 mmol). The mixture was stirred for 5 h at r.t., then treated with 2 N NH_4OH (30 mL) and extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. FC (hexanes–EtOAc, 5:2) afforded **4** as a colorless oil (1.60 g, 4.53 mmol, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.50 (s, 3 H, OCH_2OCH_3), 3.66 (s, 3 H, OCH_2OCH_3), 5.24 (s, 2 H, OCH_2OCH_3), 5.31 (s, 2 H, OCH_2OCH_3), 7.62 (d, 1 H, ^4J = 1.9 Hz, 6-H), 7.95 (d, 1 H, ^4J = 1.9 Hz, 2-H), 9.81 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.6 (OCH_2OCH_3), 58.6 (OCH_2OCH_3), 92.7 (C-3), 95.3 (OCH_2OCH_3), 99.1 (OCH_2OCH_3), 116.3 (C-6), 134.0 (C-1), 135.1 (C-2), 149.9/151.7 (C-4, C-5), 189.5 (CHO).

Methyl 3-Iodo-4,5-bis(methoxymethoxy)benzoate (5)

To a solution of **4** (1.17 g, 3.33 mmol) in MeOH (40 mL) at 0 °C was added a cold solution of KOH (0.49 g, 8.65 mmol) in MeOH (11 mL), followed by rapid addition of a cold solution of iodine (1.10 g, 4.33 mmol) in MeOH (11 mL). The mixture was treated with sat. aq NH_4Cl (30 mL) and sat. aq $Na_2S_2O_3$ (10 mL) and then extracted with EtOAc (3 × 40 mL). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated. FC (hexanes–EtOAc, 5:1) afforded **5** as a yellowish oil (1.20 g, 3.13 mmol, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, OCH_2OCH_3), 3.65 (s, 3 H, OCH_2OCH_3), 3.88 (s, 3 H, CO_2CH_3), 5.22 (s, 2 H, OCH_2OCH_3), 5.27 (s, 2 H, OCH_2OCH_3), 7.76 (d, 1 H, ^4J = 2.0 Hz, 6-H), 8.14 (d, 1 H, ^4J = 2.0 Hz, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4 (CO_2CH_3), 56.6 (OCH_2OCH_3), 58.5 (OCH_2OCH_3), 92.0 (C-3), 95.3 (OCH_2OCH_3), 99.0 (OCH_2OCH_3), 117.8 (C-6), 127.6 (C-1), 134.1 (C-2), 149.1/150.5 (C-4, C-5), 165.2 (CO_2CH_3).

MS: *m/z* (%) = 382 (8) [M]$^+$, 351 (1), 306 (100), 275 (12), 255 (2), 179 (2), 45 (62) [C_2H_5O]$^+$.

Anal. Calcd for $C_{12}H_{15}IO_6$: C, 37.72; H, 3.96; I, 33.21. Found: C, 37.79; H, 3.95; I, 33.17.

3,4-Bis(methoxymethoxy)benzaldehyde (6)

To 3,4-dihydroxybenzaldehyde (3.94 g, 28.5 mmol) in anhyd DMF (30 mL) was added a 6 M solution of MOMCl in EtOAc[15b] (19 mL, 0.11 mol), followed by *i*-PrNEt$_2$ (29 mL, 0.17 mol). After stirring for 5 h at r.t., 2 N NH_4OH (30 mL) was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. FC (hexanes–EtOAc, 5:2) afforded **6** as a colorless solid (5.36 g, 23.7 mmol, 83%), mp 58 °C (Lit.[41] 60 °C).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.31; H, 6.18.

2-Iodo-3,4-bis(methoxymethoxy)benzaldehyde (7)

In a dry, argon-flushed Schlenk flask equipped with a gas inlet and rubber septum, *N*,*N*,*N*′-trimethylethylenediamine (0.57 mL, 4.4 mmol) was dissolved in anhyd THF (10 mL), and a solution of *n*-BuLi (4.2 mmol) in hexanes was added dropwise at 0 °C. After stirring for 15 min at r.t., the mixture was cooled to –20 °C, and a solution of **6** (0.91 g, 4.00 mmol) in anhyd THF (3 mL) was added slowly. The mixture was stirred for an additional 0.5 h at –20 °C and then treated with *n*-BuLi (12 mmol). After stirring at –20 °C for 3 h, the solution was cooled to –40 °C, and a solution of 1,2-diiodoethane (5.1 g, 18 mmol) in anhyd THF (5 mL) was added (caution: gas development). After 5 min, the cooling bath was removed and the mixture was allowed to reach r.t. After the addition of sat. aq NH_4Cl (30 mL) followed by sat. aq $Na_2S_2O_3$ (10 mL), the solution

was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. FC (hexanes–EtOAc, 3:1) afforded **7** as a yellowish solid (0.88 g, 2.51 mmol, 63%); mp 55–57 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 3.49 (s, 3 H, OCH_2OCH_3), 3.65 (s, 3 H, OCH_2OCH_3), 5.23 (s, 2 H, OCH_2OCH_3), 5.39 (s, 2 H, OCH_2OCH_3), 7.32 (d, 1 H, ^3J = 8.6 Hz)/7.62 (d, 1 H, ^3J = 8.6 Hz) (5-H, 6-H), 10.00 (s, 1 H, C*H*O).

^{13}C NMR (75 MHz, acetone-d_6): δ = 56.8 (OCH_2OCH_3), 58.7 (OCH_2OCH_3), 95.7 (OCH_2OCH_3), 99.8 (OCH_2OCH_3), 100.6 (C-2), 116.3 (C-5), 127.4 (C-6), 131.1 (C-1), 147.4/155.7 (C-3, C-4), 195.0 (*C*HO).

Anal. Calcd for $C_{11}H_{13}IO_5$: C, 37.52; H, 3.72; I, 36.04. Found: C, 37.28; H, 3.51; I, 35.96.[42]

Methyl 2-Iodo-3,4-bis(methoxymethoxy)benzoate (8)

To a solution of **7** (0.400 g, 1.14 mmol) in MeOH (15 mL) was added at 0 °C a cold solution of KOH (0.195 g, 2.96 mmol) in MeOH (3.5 mL), followed by rapid addition of a cold solution of I_2 (0.375 g, 1.48 mmol) in MeOH (3.5 mL). After stirring for 1 h at 0 °C, the addition of KOH and I_2 was repeated, and the stirring was continued at 0 °C until the reaction was complete (2 h). After the addition of sat. aq NH_4Cl (30 mL) and sat. aq $Na_2S_2O_3$ (10 mL), the mixture was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. FC ($CHCl_3$–acetone, 40:1) afforded pure **8** as a colorless oil [0.416 g, 1.09 mmol, 96%; R_f (TLC) = 0.32] and methyl 2-iodo-4,5-bis(methoxymethoxy)benzoate (0.01 g, 3%, R_f = 0.37).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, OCH_2OCH_3), 3.68 (s, 3 H, OCH_2OCH_3), 3.89 (s, 3 H, CO_2CH_3), 5.17 (s, 2 H, OCH_2OCH_3), 5.33 (s, 2 H, OCH_2OCH_3), 7.13 (d, 1 H, ^3J = 8.6 Hz)/7.52 (d, 1 H, ^3J = 8.6 Hz) (5-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4 (CO_2CH_3), 56.5 (OCH_2OCH_3), 58.6 (OCH_2OCH_3), 94.7 (C-2), 95.0 (OCH_2OCH_3), 99.1 (OCH_2OCH_3), 115.2 (C-5), 127.5 (C-6), 130.0 (C-1), 147.1/152.3 (C-3, C-4), 166.8 (CO_2CH_3).

MS: *m/z* (%) = 383 (2) $[M + 1]^+$, 382 (15) $[M]^+$, 351 (3), 337 (2), 307 (10), 306 (100), 275 (33), 255 (15), 179 (7), 45 (32) $[C_2H_5O]^+$.

HRMS: *m/z* calcd for $C_{12}H_{15}IO_6$: 381.9913; found: 381.9898.

4-(Triisopropylsilyloxy)benzaldehyde (9)

Following the standard procedure,[43] 4-hydroxybenzaldehyde (1.22 g, 10 mmol) was reacted with TIPSCl (2.12 g, 11 mmol), NEt_3 (1.67 mL, 12 mmol), and DMAP (0.12 g, 1 mmol) in CH_2Cl_2 (20 mL). After workup, FC (hexanes–EtOAc, 15:1) afforded **9** as a colorless oil (2.68 g, 9.64 mmol, 96%).

2-Iodo-4-(triisopropylsilyloxy)benzaldehyde (10)

In a dry, argon-flushed Schlenk flask equipped with a gas inlet and rubber septum, *N*,*N*,*N*′-trimethylethylenediamine (0.56 mL, 4.40 mmol) was dissolved in anhyd THF (10 mL). At 0 °C, *n*-BuLi (4.20 mmol) in hexanes was added and the solution was stirred for 15 min at the same temperature. The mixture was cooled to –20 °C and treated slowly with a solution of **9** (1.11 g, 4.00 mmol) in anhyd THF (3 mL). After 0.5 h, *n*-BuLi (12 mmol) was added and the solution was stirred for 15 h at –20 °C. Then the mixture was cooled to –40 °C and treated with a solution of 1,2-diiodoethane (5.1 g, 18 mmol) in anhyd THF (5 mL). Workup as described for compound **7** and FC (hexanes–EtOAc, 25:1) yielded **10** as a yellow oil (1.29 g, 3.20 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07–1.13 (m, 18 H, 6 CH_3), 1.21–1.36 {m, 3 H, Si[C*H*$(CH_3)_2]_3$}, 6.93 (ddd, 1 H, ^3J = 8.6 Hz, ^4J = 2.3 Hz, ^5J = 0.8 Hz, 5-H), 7.44 (d, 1 H, ^4J = 2.3 Hz, 3-H), 7.79 (d, 1 H, ^3J = 8.6 Hz, 6-H), 9.92 (d, 1 H, ^5J = 0.8 Hz, C*H*O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 {s, Si[*C*H$(CH_3)_2]_3$}, 17.9 (s, 6 *C*H_3), 102.1 (C-2), 120.1 (C-5‡), 128.9 (C-1), 131.5 (C-3‡), 131.7 (C-6‡), 161.8 (C-4), 194.5 (*C*HO).

HRMS: *m/z* calcd for $C_{16}H_{25}IO_2Si$: 404.0669; found 404.0662.

Methyl 2-Iodo-4-(triisopropylsilyloxy)benzoate (11)

To aldehyde **10** (0.765 g, 1.89 mmol) were added *t*-BuOH (38 mL), 2-methyl-2-butene (19 mL), and a solution of $NaH_2PO_4·2H_2O$ (2.07 g, 13.3 mmol) in H_2O (5 mL). The mixture was stirred vigorously, and a solution of $NaClO_2$ (80% purity; 2.14 g, 18.9 mmol) in H_2O (5 mL) was added dropwise. After stirring for 0.5 h at r.t., H_2O (40 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with water and concentrated. The residue was agitated with $CHCl_3$ and filtered through glass wool. Concentration of the filtrate afforded the free acid as a colorless solid (0.770 g, 1.83 mmol, 97%). The crude acid (0.763 g, 1.82 mmol) was dissolved in dry DMF (3.5 mL) and treated with DBU (0.34 mL, 2.27 mmol) and MeI (0.17 mL, 2.72 mmol). After stirring for 3 h at r.t., H_2O was added and the mixture was extracted with Et_2O (3 × 40 mL). The combined extracts were washed with brine and concentrated. FC (hexanes–$CHCl_3$, 1:1) afforded **11** as a colorless oil (0.682 g, 1.57 mmol, 86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06–1.13 {m, 18 H, Si[CH(C*H*$_3)_2]_3$}, 1.19–1.34 {m, 3 H, Si[C*H*$(CH_3)_2]_3$}, 3.88 (s, 3 H, CO_2CH_3), 6.86 (dd, 1 H, ^3J = 8.6 Hz, ^4J = 2.4 Hz, 5-H), 7.53 (d, 1 H, ^4J = 2.4 Hz, 3-H), 7.79 (d, 1 H, ^3J = 8.6 Hz, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 {s, Si[*C*H$(CH_3)_2]_3$}, 17.9 {s, Si[CH(*C*H$_3)_2]_3$}, 52.2 (CO_2CH_3), 95.4 (C-2), 119.1 (C-5‡), 126.6 (C-1), 132.5 (C-3‡), 133.2 (C-6‡), 159.2 (C-4), 166.2 (CO_2CH_3).

MS: *m/z* (%) = 435 (5) $[M + 1]^+$, 434 (24) $[M]^+$, 403 (5), 392 (22), 391 (100) $[M – CH(CH_3)_2]^+$, 364 (6), 363 (33), 336 (7), 335 (52), 321 (17), 305 (5), 264 (5), 222 (3), 221 (3), 167 (5), 152 (5).

Anal. Calcd for $C_{17}H_{27}IO_3Si$: C, 47.01; H, 6.27; I, 29.21. Found: C, 47.13; H, 6.36; I, 29.18.

Ethyl [1-^{13}C]Acetoacetate (12)

12 was prepared from ethyl [1-^{13}C]acetate[25b] according to Lit.[24]; bp 65 °C/18 mbar. Yield 60% to 65%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3), 2.27 (s, 3 H, 4-H), 3.44 (d, 2 H, $^2J_{CH}$ = 7.3 Hz, 2-H), 4.20 (qd, 2 H, $^3J_{HH}$ = 7.2 Hz, $^3J_{CH}$ = 3.2 Hz, $^{13}CO_2CH_2CH_3$), 4.97 (s, ~0.06 H, 2-H, enol tautomer).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (d, $^3J_{CC}$ = 2.1 Hz, $^{13}CO_2CH_2CH_3$), 30.2 (C-4), 50.2 (d, $^1J_{CC}$ = 58.4 Hz, C-2), 61.5 (d, $^2J_{CC}$ = 2.3 Hz, $^{13}CO_2CH_2CH_3$), 167.2 (^{13}C-1), 172.7 (^{13}C-1, enol tautomer), 200.7 (d, $^2J_{CC}$ = 2.4 Hz, C-3).

(2*E*,6*E*,10*E*)-[1-^{13}C]Geranylgeraniol (13)

13 was synthesized from **12** and (2*E*,6*E*)-farnesyl bromide as described in the literature.[23]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.1 (s, br, 1 H, OH), 1.60 (s, 9 H, 18-H, 19-H, 20-H), 1.68 (s, 6 H, 16-H, 17-H), 1.90–2.18 (m, 12 H, 4-H, 5-H, 8-H, 9-H, 12-H, 13-H), 4.15 (dd, 2 H, $^1J_{CH}$ = 142 Hz, $^3J_{HH}$ = 7.0 Hz, 1-H), 5.06–5.15 (m, 3 H, 6-H, 10-H, 14-H), 5.38–5.46 (m, 1 H, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (s, 2 CH_3, C-18, C-19), 16.4 (C-17), 17.8 (C-20), 25.8 (C-16), 26.4 (C-5), 26.7 (C-9), 26.8 (C-13), 39.6 (C-4), 39.76/39.80 (C-8, C-12), 59.5 (^{13}C-1), 123.4 (d, $^1J_{CC}$ = 47.5 Hz, C-2), 123.9/124.3/124.5 (C-6, C-10, C-14), 131.3 (C-15), 135.0/135.5 (C-7, C-11), 139.9 (C-3).

(2*E*,6*E*,10*E*)-[1-^{13}C]Geranylgeranyl bromide (14)

To (2*E*,6*E*,10*E*)-[1-^{13}C]geranylgeraniol (**13**, 0.291 g, 1.00 mmol) in anhyd CH_2Cl_2 (1 mL) was added PPh_3 (0.289 g, 1.1 mmol). The

mixture was cooled to 0 °C, treated with CBr_4 (0.398 g, 1.2 mmol) in one portion, and stirred in the dark for 2 h at 0 °C. Then the solvent was removed in vacuo at r.t., sat. aq $NaHCO_3$ solution (20 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4), and concentrated at r.t. The residue was dissolved in *n*-hexane (5 mL) and the flask stored at 4 °C in the dark for several hours. After removal of the precipitated PPh_3O by filtration and washing the filter cake with cold *n*-hexane, the solvent was partly removed. The flask was stored at –20 °C overnight and the precipitate was filtered off again. When necessary, the hexane precipitation was repeated several times. After concentration at r.t. and drying under vacuum, crude **14** was obtained as a slightly brownish oil (0.322 g, 0.91 mmol, 91%). The product was used without further purification and can be stored at –20 °C for several weeks without decomposition.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 18-H, 19-H, 20-H), 1.68 (s, 3 H, 16-H), 1.73 (s, 3 H, 17-H), 1.93–2.15 (m, 12 H, 4-H, 5-H, 8-H, 9-H, 12-H, 13-H), 4.02 (dd, 2 H, $^1J_{CH}$ = 153 Hz, $^3J_{HH}$ = 8.4 Hz, 2-H), 5.05–5.15 (m, 3 H, 6-H, 10-H, 14-H), 5.48–5.58 (m, 1 H, 2-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.02/16.08/16.13 (C-17, C-18, C-19), 17.8 (C-20), 25.8 (C-16), 26.2 (C-5), 26.7/26.9 (C-9, C-13), 29.7 (^{13}C-1), 39.6 (d, $^3J_{CC}$ = 5.0 Hz, C-4), 39.75/39.80 (C-8, C-12), 120.6 (d, $^1J_{CC}$ = 47.6 Hz, C-2), 123.5/124.3/124.5 (C-6, C-10, C-14), 131.3 (C-15), 135.0/135.7 (C-7, C-11), 143.7 (C-3).

Coupling of the Iodobenzoic Acid Derivatives with Polyprenyl Bromides; General Procedure

In a dry, argon-flushed Schlenk flask equipped with a gas inlet and rubber septum, the corresponding aryl iodide (0.6 mmol) was dissolved in anhyd THF (3 mL). After cooling to –20 °C, *i*-PrMgBr[44] (0.675 mmol, approx. 1 M in THF) was added dropwise. After stirring for 0.5 h at –20 °C, a 0.2 M solution of Li_2CuCl_4 (0.1 mL, 0.02 mmol) in THF was added, and the stirring was continued for 10 min at –20 °C. Then a solution of the appropriate polyprenyl bromide (0.5 mmol) in anhyd THF (concentration, 0.2 to 0.4 M) was added dropwise over 30–45 min by means of a syringe pump. After stirring for 1.5 h at –20 °C, the cooling bath was removed and the solution was allowed to warm to r.t. Then sat. aq NH_4Cl (15 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with NH_4OH and brine and dried (Na_2SO_4). The products were purified by FC.

Methyl (2′*E*,6′*E*,10′*E*)-3-[1′-^{13}C]Geranylgeranyl-4-(methoxymethoxy)benzoate (15)

From **2** [0.140 g, containing 0.40 mmol of **2** and 0.06 mmol of methyl 4-(methoxymethoxy)benzoate[40]] and **14** (0.117 g, 0.33 mmol) according to the general procedure. FC (hexanes–EtOAc, 12:1) yielded **15** as a colorless oil (0.129 g, 0.27 mmol, 83%).

IR (KBr):[45] 2951 (s, sh), 2917 (s), 2853 (s), 1722 (s), 1606 (m), 1498 (m), 1437 (s), 1383 (w), 1326 (w), 1297 (s), 1266 (s), 1246 (s), 1193 (m), 1155 (s), 1131 (s), 1121 (s), 1080 (s), 999 (s), 925 (m), 832 (w), 771 (s), 658 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.68 (s, 3 H, 16′-H), 1.73 (s, 3 H, 17′-H), 1.92–2.17 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.37 (dd, 2 H, $^1J_{CH}$ = 127.5 Hz, $^3J_{HH}$ = 7.2 Hz, 1′-H), 3.48 (s, 3 H, OCH_2OCH_3), 3.87 (s, 3 H, CO_2CH_3), 5.05–5.16 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.25 (s, 2 H, OCH_2OCH_3), 5.27–5.36 (m, 1 H, 2′-H), 7.07 (app. d, 1 H, ^3J = 9.2 Hz, 5-H), 7.83–7.88 (m, 2 H, 2-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1 (s, 2 CH_3, C-18′, C-19′), 16.3 (d, $^3J_{CC}$ = 3.8 Hz, C-17′), 17.7 (C-20′), 25.7 (C-16′), 26.7 (2 CH_2)/26.8 (1 CH_2) (C-5′, C-9′, C-13′), 28.7 (^{13}C-1′), 39.7–40.0 (m, 3 CH_2, C-4′, C-8′, C-12′), 51.9 (CO_2CH_3), 56.2 (OCH_2OCH_3), 94.1 (OCH_2OCH_3), 112.9 (C-5), 121.8 (d, $^1J_{CC}$ = 43.7 Hz, C-2′), 123.3 (d, $^3J_{CC}$ = 2.9 Hz, C-1), 124.2/124.3/124.5 (C-6′, C-10′, C-14′), 129.2 (C-2‡), 130.8 (d, $^3J_{CC}$ = 43.7 Hz, C-3), 131.24 (C-6‡), 131.28 (C-15′), 134.9/135.2/136.7 (C-3′, C-7′, C-11′), 158.7 (C-4), 167.1 (CO_2CH_3).

MS: *m/z* (%) = 470 (2) [M + 1]$^+$, 469 (6) [M]$^+$, 438 (2) [M – OCH_3]$^+$, 424 (3) [M – C_2H_5O]$^+$, 400 (4) [M – C_5H_9]$^+$, 368 (2), 324 (6), 300 (6), 263 (6), 259 (9), 256 (11), 232 (10), 218 (13), 210 (11), 204 (23), 190 (10), 189 (10), 188 (37), 166 (19), 137 (12), 136 (15), 135 (18), 123 (14), 121 (14), 109 (12), 107 (10), 95 (13), 93 (12), 81 (40) [C_6H_9]$^+$, 69 (100) [C_5H_9]$^+$, 45 (83) [C_2H_5O]$^+$, 41 (19) [C_3H_5]$^+$.

Anal. Calcd for $C_{30}H_{44}O_4$ (unlabeled compound): C, 76.88; H, 9.46. Found: C, 76.80; H, 9.43.

Methyl (2′*E*,6′*E*,10′*E*)-3-[1′-^{13}C]Geranylgeranyl-4,5-bis(methoxymethoxy)benzoate (18)

From **5** (0.138 g, 0.36 mmol) and **14** (0.106 g, 0.30 mmol) according to the general procedure. FC (hexanes–EtOAc, 7:1) yielded **18** as a colorless oil (0.119 g, 0.23 mmol, 75%).

IR (KBr):[45] 2952 (s), 2917 (s), 2852 (m), 1723 (s), 1590 (m), 1484 (m), 1435 (s), 1401 (w), 1383 (w), 1329 (m), 1310 (m), 1298 (m), 1246 (w), 1219 (m), 1195 (m), 1180 (m), 1158 (s), 1094 (m), 1077 (m), 1037 (s), 962 (s), 927 (m), 769 (s), 595 (w, br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.67 (s, 3 H, 16′-H), 1.72 (s, 3 H, 17′-H), 1.91–2.17 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.44 (dd, 2 H, $^1J_{CH}$ = 128 Hz, $^3J_{HH}$ = 7.1 Hz, 1′-H), 3.50 (s, 3 H, OCH_2OCH_3), 3.58 (s, 3 H, OCH_2OCH_3), 3.87 (s, 3 H, CO_2CH_3), 5.04–5.17 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.18 (s, 2 H, OCH_2OCH_3), 5.22 (s, 2 H, OCH_2OCH_3), 5.27–5.36 (m, 1 H, 2′-H), 7.57 (dd, 1 H, $^3J_{CH}$ = 4.1 Hz, $^4J_{HH}$ = 2.0 Hz, 2-H), 7.64 (d, 1 H, $^4J_{HH}$ = 2.0 Hz, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.04/16.06 (C-18′, C-19′), 16.3 (d, $^3J_{CC}$ = 3.5 Hz, C-17′), 17.7 (C-20′), 25.7 (C-16′), 26.7 (2 CH_2)/26.8 (1 CH_2) (C-5′, C-9′, C-13′), 28.5 (^{13}C-1′), 39.7–39.9 (m, C-4′, C-8′, C-12′), 52.1 (CO_2CH_3), 56.4 (OCH_2OCH_3), 57.6 (OCH_2OCH_3), 95.2 (OCH_2OCH_3), 99.0 (OCH_2OCH_3), 115.2 (C-2‡), 121.9 (d, $^1J_{CC}$ = 43.7 Hz, C-2′), 124.2/124.3/124.5/125.0 (C-6‡, C-6′, C-10′, C-14′), 125.9 (d, $^3J_{CC}$ = 3.8 Hz, C-1), 131.3 (C-15′), 134.9/135.2 (C-7′†, C-11′†), 136.1 (d, $^1J_{CC}$ = 43.7 Hz, C-3), 137.0 (C-3′†), 149.0/149.3 (C-4, C-5), 166.7 (CO_2CH_3).

MS: *m/z* (%) = 529 (1) [M]$^+$, 498 (2) [M – OCH_3]$^+$, 497 (2) [M – CH_3OH]$^+$, 484 (4), 460 (2) [M – C_5H_9]$^+$, 452 (3), 428 (3), 396 (2), 384 (2), 361 (2), 360 (2), 328 (3), 316 (5), 248 (18), 234 (13), 220 (12), 216 (11), 194 (30), 182 (12), 135 (18), 121 (16), 109 (14), 107 (12), 95 (13), 93 (15), 81 (32) [C_6H_9]$^+$, 69 (71) [C_5H_9]$^+$, 45 (100) [C_2H_5O]$^+$, 41 (18) [C_3H_5]$^+$.

Anal. Calcd for $C_{32}H_{48}O_6$ (unlabeled compound): C, 72.69; H, 9.15. Found: C, 72.50; H, 9.10.

Methyl (2′*E*,6′*E*,10′*E*)-2-[1′-^{13}C]Geranylgeranyl-3,4-bis(methoxymethoxy)benzoate (21)

From **8** (0.092 g, 0.24 mmol) and **14** (0.071 g, 0.20 mmol) according to the general procedure. FC (hexanes–EtOAc, 6:1) yielded **21** as a colorless oil (83 mg, 0.157 mmol, 78%).

IR (KBr):[45] 2917 (s), 2853 (m), 1723 (s), 1596 (m), 1486 (m), 1435 (s), 1398 (w), 1383 (w), 1263 (s), 1220 (m), 1207 (m), 1192 (m), 1157 (s), 1135 (m), 1090 (m), 1033 (s), 965 (m), 931 (m), 828 (w), 792 (m), 753 (m) cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.57 (s, 3 H)/1.58 (s, 3 H)/1.59 (s, 3 H) (18′-H, 19′-H, 20′-H), 1.67 (s, 3 H, 16′-H), 1.75 (s, 3 H, 17′-H), 1.92–1.99 (m, 6 H)/2.00–2.08 (m, 6 H) (4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.49 (s, 3 H, OCH_2OCH_3), 3.60 (s, 3 H, OCH_2OCH_3), 3.81 (dd, 2 H, $^1J_{CH}$ = 129 Hz, $^3J_{HH}$ = 6.3 Hz, 1′-H), 3.83 (s, 3 H, CO_2CH_3), 5.05–5.11 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.08 (s, 2 H,

OCH_2OCH$_3$), 5.11–5.16 (m, 1 H, 2′-H), 5.23 (s, 2 H, OCH_2OCH$_3$), 7.01 (d, 1 H, ^3J = 8.7 Hz)/7.60 (d, 1 H, ^3J = 8.7 Hz) (5-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.0 (s, 2 CH_3, C-18′, C-19′), 16.5 (d, $^4J_{CC}$ = 3.8 Hz, C-17′), 17.7 (C-20′), 25.7 (C-16′), 26.1 (^{13}C-1′), 26.71/26.80/26.83 (C-5′, C-9′, C-13′), 39.7–39.9 (m, 3 CH_2, C-4′, C-8′, C-12′), 51.9 (CO_2CH_3), 56.4 (OCH$_2$OCH_3), 57.7 (OCH$_2$OCH_3), 94.8 (OCH_2OCH$_3$), 99.3 (OCH_2OCH$_3$), 112.7 (C-5‡), 123.3 (d, $^1J_{CC}$ = 42.9 Hz, C-2′), 124.28/124.35/124.48 (C-6′, C-10′, C-14′), 124.7 (C-1), 127.5 (C-6‡), 131.3 (C-15′), 134.9/135.0/135.4 (C-3′, C-7′, C-11′), 138.6 (d, $^1J_{CC}$ = 42.9 Hz, C-2), 144.9/152.9 (C-3, C-4), 167.9 (CO_2CH_3).

MS: *m/z* (%) = 530 (1) [M + 1]$^+$, 529 (2) [M]$^+$, 485 (2), 484 (7) [M – C_2H_5O]$^+$, 452 (2), 428 (2), 392 (3), 360 (5), 334 (5), 328 (4), 316 (6), 284 (7), 278 (8), 264 (15), 248 (35), 234 (20), 220 (26), 216 (27), 194 (17), 121 (23), 95 (16), 81 (34) [C_6H_9]$^+$, 69 (82) [C_5H_9]$^+$, 45 (100) [C_2H_5O]$^+$, 41 (17) [C_3H_5]$^+$.

Anal. Calcd for $C_{32}H_{48}O_6$ (unlabeled compound): C, 72.69; H, 9.15. Found: C, 72.50; H, 9.28.

Methyl (2′*E*,6′*E*,10′*E*)-2-[1′-^{13}C]Geranylgeranyl-4-(triisopropylsilyloxy)benzoate (24)

From **11** (0.209 g, 0.48 mmol) and **14** (0.142 g, 0.40 mmol) according to the general procedure. FC (hexanes–$CHCl_3$, 1:1) yielded **24** as a colorless oil (0.186 g, 0.32 mmol, 81%).

IR (KBr):[45] 2946 (s), 2926 (s), 2868 (s), 1722 (s), 1601 (s), 1566 (m), 1494 (m), 1463 (m), 1434 (s), 1384 (m), 1298 (s), 1249 (s), 1271 (s), 1189 (m), 1124 (s), 1080 (m), 990 (s), 883 (s), 838 (s), 800 (m), 779 (m), 701 (m, sh), 688 (s), 664 (m), 650 (m, sh), 598 (w, br), 451 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07–1.13 {m, 18 H, Si[CH(CH_3)$_2$]$_3$}, 1.19–1.32 {m, 3 H, Si[CH(CH$_3$)$_2$]$_3$}, 1.60 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.68 (s, 3 H, 16′-H), 1.70 (s, 3 H, 17′-H), 1.93–2.17 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.70 (dd, 2 H, $^1J_{CH}$ = 129 Hz, $^3J_{HH}$ = 7.2 Hz, 1′-H), 3.85 (s, 3 H, CO_2CH_3), 5.06–5.17 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.26–5.36 (m, 1 H, 2′-H), 6.71 (dd, 1 H, $^3J_{HH}$ = 8.6 Hz, $^4J_{HH}$ = 2.5 Hz, 5-H), 6.80 (dd, 1 H, $^3J_{CH}$ = 4.7 Hz, $^4J_{HH}$ = 2.5 Hz, 3-H), 7.83 (dd, 1 H, $^3J_{HH}$ = 8.6 Hz, $^4J_{CH}$ = 0.7 Hz, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 {s, Si[*C*H(CH$_3$)$_2$]$_3$}, 16.1 (s, 2 CH_3, C-18′, C-19′), 16.4 (d, $^3J_{CC}$ = 3.5 Hz, C-17′), 17.8 (C-20′), 18.0 {s, Si[CH(*C*H$_3$)$_2$]$_3$}, 25.8 (C-16′), 26.7 (1 CH_2)/26.9 (2 CH_2) (C-5′, C-9′, C-13′), 32.6 (^{13}C-1′), 39.7–40.0 (m, C-4′, C-8′, C-12′), 51.7 (CO_2CH_3), 117.2 (C-5), 121.4 (C-3), 122.0 (C-1), 122.5 (d, $^1J_{CC}$ = 43.5 Hz, C-2′), 124.26/124.34/124.50 (C-6′, C-10′, C-14′), 131.3 (C-15′), 132.9 (C-6), 135.0/ 135.1/136.9 (C-3′, C-7′, C-11′), 146.1 (d, $^1J_{CC}$ = 41.7 Hz, C-2), 159.5 (d, $^3J_{CC}$ = 3.8 Hz, C-4), 167.8 (CO_2CH_3).

MS: *m/z* (%) = 582 (10) [M + 1]$^+$, 581 (20) [M]$^+$, 538 (6), 512 (11) [M – C_5H_9]$^+$, 480 (11), 444 (21), 412 (45), 376 (67), 370 (37), 334 (56), 316 (52), 280 (19), 274 (19), 259 (27), 135 (27), 121 (23), 109 (29), 81 (38) [C_6H_9]$^+$, 69 (100) [C_5H_9]$^+$, 41 (31) [C_3H_5]$^+$.

HRMS: *m/z* calcd for $C_{37}H_{60}O_3Si$ (unlabeled compound): 580.4312; found 580.4286.

Ester Hydrolysis; General Procedure

A suspension of the corresponding methyl ester (up to 1 mmol) in a mixture of LiOH·H_2O (0.084 g, 2 mmol), H_2O (1 mL) and MeOH (3 mL) was heated to 100 °C until the TLC indicated completion of the hydrolysis (**16**, **19**, and **22**: 4–6 h; **25**: 40 h). Then H_2O (20 mL) was added and the mixture was slightly acidified with 2 N HCl (approx. 1 mL). After extraction of the aq phase with EtOAc (3 × 30 mL), the combined organic phases were washed twice with H_2O and concentrated in vacuo.

(2′*E*,6′*E*,10′*E*)-3-[1′-^{13}C]Geranylgeranyl-4-hydroxybenzoic Acid (17)

Hydrolysis of **15** (118 mg, 0.251 mmol) according to the general procedure afforded crude acid **16** as a colorless oil (113 mg, 0.248 mmol, 99%). **16** (63.2 mg, 0.139 mmol) was dissolved in *i*-PrOH (1.4 mL), and after addition of *p*-TsOH·H_2O (26 mg, 0.14 mmol) the solution was stirred at 60 °C until TLC indicated completion (6 h). Then H_2O (15 mL) was added and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O and concentrated. FC ($CHCl_3$–MeOH, 12:1) yielded **17** as a colorless, waxy solid (50.0 mg, 0.121 mmol, 87%).

IR (KBr):[45] 3387 (s, br), 2967 (s), 2922 (s), 2855 (s), 2664 (m), 2544 (m), 1682 (s), 1603 (s), 1506 (w), 1444 (m), 1410 (m), 1383 (m), 1276 (s), 1219 (m), 1172 (m), 1128 (m), 1096 (m), 928 (w), 833 (m), 774 (m), 636 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.68 (s, 3 H, 16′-H), 1.80 (s, 3 H, 17′-H), 1.91–2.21 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.42 (dd, 2 H, $^1J_{CH}$ = 127 Hz, $^3J_{HH}$ = 7.1 Hz, 1′-H), 5.04–5.16 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.29–5.39 (m, 1 H, 2′-H), 6.85 (d, 1 H, $^3J_{HH}$ = 9.0 Hz, 5-H), 7.88–7.93 (m, 2 H, 2-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.08/16.15 (C-18′, C-19′), 16.4 (d, $^3J_{CC}$ = 3.5 Hz, C-17′), 17.8 (C-20′), 25.8 (C-16′), 26.5/26.7/26.9 (C-5′, C-9′, C-13′), 29.8 (^{13}C-1′), 39.6–39.9 (m, C-4′, C-8′, C-12′), 115.9 (C-5), 120.9 (d, $^1J_{CC}$ = 42.3 Hz, C-2′), 121.8 (s, br, C-1), 123.6/ 124.3/124.5 (C-6′, C-10′, C-14′), 126.9 (d, $^1J_{CC}$ = 44.3 Hz, C-3), 130.6 (C-2‡), 131.3 (C-15′), 132.7 (C-6‡), 135.0/135.8 (C-7′, C-11′), 139.6 (C-3′), 159.6 (C-4), 172.2 (CO_2H).

MS: *m/z* (%) = 412 (2) [M + 1]$^+$, 411 (8) [M]$^+$, 368 (2), 342 (10) [M – C_5H_9]$^+$, 287 (4), 259 (7), 232 (6), 218 (6), 205 (12), 204 (13), 192 (10), 190 (13), 162 (15), 152 (56), 137 (19), 136 (27), 135 (26), 123 (24), 121 (19), 109 (20), 107 (18), 95 (21), 93 (21), 81 (55) [C_6H_9]$^+$, 69 (100) [C_5H_9]$^+$, 55 (12), 41 (31) [C_3H_5]$^+$.

HRMS: *m/z* calcd for $C_{27}H_{38}O_3$ (unlabeled compound): 410.2821; found 410.2834.

(2′*E*,6′*E*,10′*E*)-3-[1′-^{13}C]Geranylgeranyl-4,5-dihydroxybenzoic Acid (20)

18 (137 mg, 0.26 mmol) was hydrolyzed according to the general procedure to yield acid **19** as a colorless oil (130 mg, 0.25 mmol, 98%). To a solution of crude **19** (83.3 mg, 162 μmol) in *i*-PrOH (1.6 mL) was added AcCl (57 μL, 0.80 mmol), and the solution was stirred at r.t. under argon. The reaction was monitored by TLC to avoid prolonged reaction times. After completion (5 h), H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with H_2O and concentrated. FC ($CHCl_3$–MeOH, 9:1) afforded **20** as a colorless solid (59 mg, 137 mmol, 84%).

IR (KBr):[45] 3433 (s), 3289 (s, br), 2967 (s), 2922 (s), 2854 (s), 1688 (s), 1603 (m), 1444 (s), 1376 (m), 1293 (s), 1234 (s), 1099 (m), 987 (m), 775 (m), 707 (m), 566 (w), 551 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.68 (s, 3 H, 16′-H), 1.78 (s, 3 H, 17′-H), 1.92–2.20 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.41 (dd, 2 H, $^1J_{CH}$ = 128 Hz, ^3J = 7.1 Hz, 1′-H), 5.04–5.15 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.30–5.39 (m, 1 H, 2′-H), 7.53 (s, 2 H, 2-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.07/16.14 (C-18′, C-19′), 16.3 (d, $^3J_{CC}$ = 2.9 Hz, C-17′), 17.8 (C-20′), 25.8 (C-16′), 26.5/26.7/26.8 (C-5′, C-9′, C-13′), 29.3 (^{13}C-1′), 39.7–39.9 (m, 3 CH_2, C-4′, C-8′, C-12′), 115.1 (C-6), 121.01 (d, $^3J_{CC}$ = 3.2 Hz, C-1), 121.04 (d, $^1J_{CC}$ = 42.9 Hz, C-2′), 123.8/124.3/124.5/125.0 (C-2, C-6′, C-10′, C-14′), 127.5 (d, $^1J_{CC}$ = 43.5 Hz, C-3), 131.4 (C-15′), 135.1/135.7 (C-7′, C-11′), 139.2 (C-3′), 143.3/147.8 (C-4, C-5), 172.3 (CO_2H).

MS: *m/z* (%) = 428 (4) $[M + 1]^+$, 427 (12) $[M]^+$, 412 (3) $[M - CH_3]^+$, 384 (7), 358 (16) $[M - C_5H_9]^+$, 276 (10), 259 (16), 248 (12), 234 (11), 223 (14), 221 (17), 208 (23), 206 (33), 204 (23), 168 (89), 149 (18), 137 (28), 136 (32), 135 (35), 123 (36), 121 (31), 109 (32), 107 (21), 95 (29), 93 (24), 81 (68) $[C_6H_9]^+$, 69 (100) $[C_5H_9]^+$, 55 (9), 41 (16) $[C_3H_5]^+$.

HRMS: *m/z* calcd for $C_{27}H_{38}O_4$ (unlabeled compound): 426.2770; found 426.2744.

(2′*E*,6′*E*,10′*E*)-2-[1′-^{13}C]Geranylgeranyl-3,4-dihydroxybenzoic Acid (23)

21 (57.6 mg, 109 μmol) was hydrolyzed according to the general procedure to afford **22** as a colorless, waxy solid (55.1 mg, 107 μmol, 98%). The crude acid (51 mg, 99 μmol) was dissolved in *i*-PrOH (1 mL) under argon. Then AcCl (36 μL, 0.5 mmol) was added, and the solution was stirred at r.t. (TLC monitoring). After completion of the reaction (5 h), H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with H_2O and concentrated. FC ($CHCl_3$–MeOH, 10:1) afforded **23** as a brownish, waxy solid (33 mg, 77 μmol, 78%).

IR (KBr):[45] 3446 (s), 3292 (s, br), 3140 (s, br), 2966 (s), 2921 (s), 2854 (s), 1682 (s), 1621 (m), 1615 (m), 1584 (s), 1504 (m), 1494 (m), 1446 (m), 1378 (m), 1343 (s), 1296 (s), 1237 (s), 1195 (s), 1148 (m), 1009 (m), 971 (m), 874 (m), 830 (m), 788 (m), 754 (m), 706 (m), 632 (m), 536 (w), 450 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.67 (s, 3 H, 16′-H), 1.85 (s, 3 H, 17′-H), 1.90–2.18 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.92 (dd, 2 H, $^1J_{CH}$ = 131 Hz, $^3J_{HH}$ = 6.7 Hz, 1′-H), 5.01–5.14 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.23–5.32 (m, 1 H, 2′-H), 6.82 (d, 1 H, ^3J = 8.6 Hz)/7.65 (d, 1 H, ^3J = 8.6 Hz) (5-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.07/16.16 (C-18′, C-19′), 16.4 (d, $^3J_{CC}$ = 3.2 Hz, C-17′), 17.8 (C-20′), 25.8 (C-16′), 26.6 (^{13}C-1′), 26.8, 39.7–39.9 (m, C-4′, C-8′, C-12′), 112.5 (C-5‡), 120.7 (C-1), 121.7 (d, $^1J_{CC}$ = 41.4 Hz, C-2′), 123.6/124.2/124.5 (C-6′, C-10′, C-14′), 126.0 (C-6‡), 130.5 (d, $^1J_{CC}$ = 42.3 Hz, C-2), 131.3 (C-15′), 135.1/135.9 (C-7′, C-11′), 139.3 (C-3′), 142.7/149.0 (C-3, C-4), 173.0 (*C*O_2H). Two of the three signals of C-5′, C-9′, and C-13′ are hidden by the ^{13}C-1′ signal. They appear in the spectrum of the corresponding unlabeled compound at δ = 26.4, 26.6, 26.8.

MS: *m/z* (%) = 427 (5) $[M + 1]^+$, 426 (17) $[M]^+$, 411 (3) $[M - CH_3]^+$, 383 (7), 357 (17) $[M - C_5H_9]^+$, 289 (19) $[357–C_5H_8]^+$, 271 (19), 259 (39), 229 (23), 221 (49), 205 (100), 203 (57), 175 (43), 167 (44), 165 (46), 163 (45), 161 (30), 157 (32), 149 (33), 135 (36), 123 (34), 121 (37), 109 (36), 107 (33), 95 (32), 93 (28), 81 (62) $[C_6H_9]^+$, 69 (88) $[C_5H_9]^+$, 41 (19) $[C_3H_5]^+$.

HRMS: *m/z* calcd for $C_{27}H_{38}O_4$ (unlabeled compound): 426.2770; found 426.2756.

(2′*E*,6′*E*,10′*E*)-2-[1′-^{13}C]Geranylgeranyl-4-hydroxybenzoic Acid (25)

24 (120 mg, 206 μmol) was hydrolyzed according to the general procedure. FC ($CHCl_3$–MeOH, 10:1) afforded **25** as a colorless, waxy solid (78 mg, 190 μmol, 92%).

IR (KBr):[45] 3187 (s, br), 2967 (s), 2919 (s), 2854 (s), 2655 (m), 2548 (m), 1684 (s), 1603 (s), 1576 (s), 1498 (w), 1445 (m), 1407 (m), 1383 (m), 1300 (m), 1236 (s), 1141 (m), 1078 (w), 968 (w), 931 (w), 863 (m), 833 (m), 784 (m), 703 (w), 613 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 18′-H, 19′-H, 20′-H), 1.68 (s, 3 H, 16′-H), 1.71 (s, 3 H, 17′-H), 1.92–2.18 (m, 12 H, 4′-H, 5′-H, 8′-H, 9′-H, 12′-H, 13′-H), 3.78 (dd, 2 H, $^1J_{CH}$ = 129 Hz, $^3J_{HH}$ = 7.1 Hz, 1′-H), 5.06–5.18 (m, 3 H, 6′-H, 10′-H, 14′-H), 5.29–5.38 (m, 1 H, 2′-H), 6.71 (dd, 1 H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.5 Hz, 5-H), 6.78 (dd, 1 H, $^3J_{CH}$ = 4.4 Hz, $^4J_{HH}$ = 2.5 Hz, 3-H), 8.01 (d, 1 H, ^3J = 8.5 Hz, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.07/16.10 (C-18′, C-19′), 16.3 (d, $^3J_{CC}$ = 3.2 Hz, C-17′), 17.7 (C-20′), 25.8 (C-16′), 26.7 (2 CH_2)/26.8 (1 CH_2) (C-5′, C-9′, C-13′), 32.8 (^{13}C-1′), 39.75/39.78 (C-8′, C-12′), 39.9 (d, $^3J_{CC}$ = 4.1 Hz, C-4′), 112.8/117.1 (C-3, C-5), 120.5 (C-1), 122.3 (d, $^1J_{CC}$ = 43.5 Hz, C-2′), 124.2/124.4/124.5 (C-6′, C-10′, C-14′), 131.4 (C-15′), 134.5 (C-6), 135.1/135.2 (C-7′, C-11′), 137.0 (C-3′), 148.0 (d, $^1J_{CC}$ = 41.4 Hz, C-2), 159.7 (d, $^3J_{CC}$ = 3.5 Hz, C-4), 172.7 (*C*O_2H).

MS: *m/z* (%) = 411 (11) $[M]^+$, 298 (5), 259 (3), 256 (3), 214 (6), 189 (10), 162 (23), 161 (20), 160 (17), 148 (12), 147 (11), 146 (13), 137 (11), 136 (13), 135 (17), 123 (12), 121 (18), 108 (27), 107 (20), 95 (19), 93 (19), 81 (48) $[C_6H_9]^+$, 69 (100) $[C_5H_9]^+$.

HRMS: *m/z* calcd for $C_{27}H_{38}O_3$ (unlabeled compound): 410.2821; found 410.2831.

Acknowledgment

The authors would like to thank the Deutsche Forschungsgemeinschaft (SFB 369) for financial support of this work.

References

(1) New address: M. Lang, 4SC AG, Am Klopferspitz 19a, 82152 Martinsried, Germany.
(2) Claisen, L.; Kremers, F.; Roth, F.; Tietze, E. *Justus Liebigs Ann. Chem.* **1925**, *442*, 210.
(3) (a) Kaczka, E. A.; Shunk, C. H.; Richter, J. W.; Wolf, F. J.; Gasser, M. M.; Folkers, K. *J. Am. Chem. Soc.* **1956**, *78*, 4125. (b) Inouye, H.; Ueda, S.; Inoue, K.; Matsumura, H. *Phytochemistry* **1979**, *18*, 1301. (c) Blunt, S. B.; Chen, T.-B.; Wiemer, D. F. *J. Nat. Prod.* **1998**, *61*, 1400. (d) Xie, Z.; Hu, Y.; Li, Y. *J. Chem. Res., Synop.* **2002**, 293. (e) Tanada, Y.; Mori, K. *Eur. J. Org. Chem.* **2003**, 848.
(4) (a) Wessjohann, L.; Sontag, B.; Dessoy, M.-A. In *Bioorganic Chemistry*; Diederichsen, U.; Lindhorst, T. K.; Westermann, B.; Wessjohann, L. A., Eds.; Wiley-VCH: Weinheim, **1999**, 79. (b) Wessjohann, L.; Sontag, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 1697; *Angew. Chem.* **1996**, *108*, 1821.
(5) Shepherd, J. A.; Poon, W. W.; Myles, D. C.; Clarke, C. F. *Tetrahedron Lett.* **1996**, *37*, 2395.
(6) (a) Nicklin, S.; Robson, M. W. *Appl. Organomet. Chem.* **1988**, *2*, 487. (b) Fouquet, E.; Pereyre, M.; Rayez, J.-C.; Rayez, M.-T.; Roulet, T. *C. R. Acad. Sci., Ser. IIc* **2001**, 641.
(7) Reaction conditions: organotin reagent and electrophile (1:1 stoichiometric ratio), $Pd(dba)_2$ (2.5 mol%), NEt_4Cl (10 mol%), THF, 50 °C, 18 h. Yields of coupling products: 60% to 70%. Residues of organotin compounds could not be removed satisfactorily despite the fact that fluoride precipitation was applied prior to chromatography: Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449.
(8) Loss of sterochemistry in reactions that involve η^3-allyl palladium complexes: (a) Castano, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6587. (b) Takanashi, S.; Mori, K. *Lieb. Ann./Recl.* **1997**, 825. (c) Takanashi, S.; Mori, K. *Lieb. Ann./Recl.* **1997**, 1081.
(9) Monoorganostannanes were developed which allow Stille-type reactions leading to products free of organotin contamination. In a reaction of prenyl monoorganostannane with an aryl iodide, however, exclusively S_N2' substitution occurred. See: Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242.

(10) Determination of double bond stereochemistry within polyprenyl chains by NMR spectroscopy: (a) Tanaka, Y.; Sato, H.; Kageyu, A. *Polymer* **1982**, *23 (Suppl.)*, 1087. (b) Shashkov, A. S.; Grigor'eva, N. Y.; Avrutov, I. M.; Semenovskii, A. V.; Odinokov, V. N.; Ignatyuk, V. K.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 388; *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1979**, *28*, 359.
(11) (a) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718. (b) Falck, J. R.; Reddy, K. K.; Chandrasekhar, S. *Tetrahedron Lett.* **1997**, *38*, 5245.
(12) Nakano, J.; Uchida, K.; Fujimoto, Y. *Heterocycles* **1989**, *29*, 427.
(13) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; *Angew. Chem.* **2003**, *115*, 4438; and references cited therein.
(14) Kometani, T.; Watt, D. S.; Ji, T. *Tetrahedron Lett.* **1985**, *26*, 2043.
(15) (a) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275. (b) A 6 M solution of MOMCl in EtOAc was prepared according to: Amato, J. S.; Karady, S.; Sletzinger, M.; Weinstock, L. M. *Synthesis* **1979**, 970. (c) Linderman, R. J.; Jaber, M.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6499.
(16) Anhoury, M.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1015.
(17) Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329.
(18) (a) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078. (b) Comins, D. L. *Synlett* **1992**, 615.
(19) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (b) Ronald, R. C.; Winkle, M. R. *Tetrahedron Lett.* **1983**, *39*, 2031. (c) For a general review on directed *ortho* metalation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(20) Aitken, D. J.; Faure, S.; Roche, S. *Tetrahedron Lett.* **2003**, *44*, 8827.
(21) (a) Bal, S. B.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (b) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720.
(22) Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401.
(23) Eis, K.; Schmalz, H.-G. *Synthesis* **1997**, 202.
(24) Leete, E.; Bjorklund, J. A.; Couladis, M. M.; Kim, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 9286.
(25) (a) Graebe, C. *Justus Liebigs Ann. Chem.* **1905**, *340*, 244. (b) Beyer, J.; Lang-Fugmann, S.; Mühlbauer, A.; Steglich, W. *Synthesis* **1998**, 1047. (c) Lang, M.; Lang-Fugmann, S.; Steglich, W. *Org. Synth.* **2001**, *78*, 113.
(26) (a) Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139. (b) See ref. 8b (c) Takagi, R.; Sasaoka, A.; Nishitani, H.; Kojima, S.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 925.
(27) Isler, O.; Rüegg, R.; Chopard-dit-Jean, L.; Wagner, H.; Bernhard, K. *Helv. Chim. Acta* **1956**, *39*, 897.
(28) On addition of MeOH, work-up and flash chromatography, the corresponding dehalogenated compounds were isolated in nearly quantitative yields.
(29) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(30) (a) Bertz, S. H.; Fairchild, E. H. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 2; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, New York, **1995**, 1324. (b) Thompson, A. S. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, New York, **1995**, 1957. (c) Johnson, D. K.; Donohoe, J.; Kang, J. *Synth. Commun.* **1994**, *24*, 1557; and references cited therein. (d) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615. (e) Bäckvall, J.-E.; Persson, E. S. M.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126. (f) Suzuki, S.; Shiono, M.; Fujita, Y. *Synthesis* **1983**, 804.
(31) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82; *Angew. Chem.* **1974**, *86*, 50.
(32) Schlosser, M.; Bossert, H. *Tetrahedron* **1991**, *47*, 6287.
(33) A 0.2 M solution of Li_2CuCl_3 was prepared by dissolving dry LiCl (2 mmol) and CuCl (1 mmol) in anhyd THF (5 mL) under argon. The solution is only storable for a few hours. The CuCl used can be purchased in 99.995% purity from Aldrich, or purified according to: Mason, R. B.; Mathews, J. H. *J. Phys. Chem.* **1925**, *29*, 1379.
(34) HCl was generated by alcoholysis of AcCl in *i*-PrOH.
(35) (a) Brieger, G. *J. Am. Chem. Soc.* **1963**, *85*, 3783. (b) Julia, M.; Roy, P. *Tetrahedron* **1986**, *42*, 4991.
(36) (a) Mühlbauer, A.; Beyer, J.; Steglich, W. *Tetrahedron Lett.* **1998**, *39*, 5167. (b) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* **1987**, *51*, 98.
(37) Recent reviews: (a) Kawamukai, M. *J. Biosci. Bioeng.* **2002**, *94*, 511. (b) Meganathan, R. *Vitam. Horm.* **2001**, *61*, 173. (c) Szkopinska, A. *Acta Biochim. Pol.* **2000**, *47*, 469.
(38) For 3-geranyl-4-hydroxybenzoic acid: (a) Yazaki, K.; Fukui, H.; Tabata, M. *Chem. Pharm. Bull.* **1986**, *34*, 2290. (b) Seeram, N. P.; Jacobs, H.; McLean, S.; Reynolds, W. F. *Phytochemistry* **1996**, *43*, 863. (c) Baldoqui, D. C.; Kato, M. J.; Cavalheiro, A. J.; Bolzani, V. da S.; Young, M. C. M.; Furlan, M. *Phytochemistry* **1999**, *51*, 899. For 3-farnesyl-4-hydroxybenzoic acid: (d) Ampofo, S. A.; Roussis, V.; Wiemer, D. F. *Phytochemistry* **1987**, *26*, 2367. (e) Maxwell, A.; Rampersad, D. *J. Nat. Prod.* **1988**, *51*, 370. For 3-geranylgeranyl-4-hydroxybenzoic acid: (f) Cimino, G.; De Stefano, S.; Minale, L. *Experientia* **1972**, *28*, 1401. (g) Lütke-Brinkhaus, F.; Liedvogel, B.; Kleinig, H. *Eur. J. Biochem.* **1984**, 537. (h) Perez Baz, J.; Canedo, L. M.; Tapiolas, D. *J. Nat. Prod.* **1996**, *59*, 960. (i) Kang, H.-C.; Yun, B.-S.; Yu, H.; Yoo, I.-D. *Sanop Misaengmul Hakhoechi* **2001**, *29*, 149; *Chem. Abstr.* **2002**, *136*, 275806. For 3-geranylgeranyl-4,5-dihydroxybenzoic acid and 2-geranylgeranyl-3,4-dihydroxybenzoic acid: (j) Maxwell, A.; Rampersad, D. *J. Nat. Prod.* **1989**, *52*, 614. (k) Maxwell, A.; Rampersad, D. *J. Nat. Prod.* **1989**, *52*, 891.
(39) (a) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879. (b) 4-Biphenylmethanol may also be used, see: Juaristi, E.; Martínez-Richa, A.; García-Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603.
(40) Methyl 4-hydroxy-3,5-diiodobenzoate was separated from **1** by flash chromatography. Non-iodinated material could be removed neither from **1** nor from **2**. Thus, a mixture of **2** and methyl 4-(methoxymethoxy)benzoate was employed in the cross coupling reactions.
(41) Edwards, R. L.; Wilson, D. V. *J. Chem. Soc.* **1961**, 5003.
(42) Impurity: 2-iodo-4,5-bis(methoxymethoxy)benzaldehyde.
(43) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.
(44) Determination of the concentration: In a dried and argon-flushed Schlenk flask with gas inlet and rubber septum, an exactly known amount of menthol (approx. 0.8 mmol) and a few mg of 1,10-phenanthroline were dissolved in anhyd THF (2.5 mL). The *i*-PrMgBr solution was added dropwise until blue color appeared. See: Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(45) IR data of the corresponding unlabeled compound.