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Synthetic studies on Sch 202596, an antagonist of the galanin receptor subtype GalR1: an efficient synthesis of (±)-geodin, the spirocoumaranone part of Sch 202596

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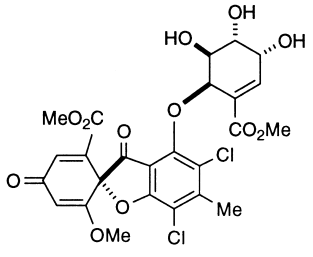
Abstract—An efficient and facile synthesis of (±)-geodin [(±)-**2**] corresponding to the spirocoumaranone part of Sch 202596 (**1**) was accomplished in a convergent manner. The synthetic method features (i) a coupling reaction of the aryl aldehyde **6** with the aryl lithium **7** generated in situ from the aryl bromide **8** to deliver the highly substituted diaryl methanol **24** (**6**+**7**→**24**) and ii) oxidative spirocyclization reaction of the benzophenone **4** to construct the requisite spirocoumaranone skeleton [**4**→(±)-**2**] as the key steps. The aromatic segments **6** and **8** were prepared from commercially available methyl 3,5-dihydroxybenzoate (**9**) and 5-methylresorcinol (**10**), respectively.

1. Introduction

Sch 202596 (**1**, Fig. 1), isolated from a fungal fermentation broth of *Aspergillus* sp. by the Schering–Plough research group in 1997, is a potent antagonist of galanin receptor subtype GalR1.[1] This natural product represents the only small non-peptidic molecule to date shown to inhibit [^{125}I]-galanin binding to GalR1-containing membranes prepared from human melanoma cells using a radioligand competition assay (IC_{50}=1.7 μM).[1,2] Galanin is a 29 amino acid neuropeptide (30 amino acids in humans) which is widely distributed in the central and peripheral nervous systems in mammals.



1 : Sch 202596

Figure 1. Structure of Sch 202596 (**1**).

So far, three galanin receptor subtypes, denoted GalR1, GalR2, and GalR3, have been cloned and characterized, all of which contain the seven-transmembrane domain motif typical of the G-protein coupled receptor superfamily.[2a,3] Galanin has been shown to inhibit secretion of insulin, acetylcholine, serotonin and noradrenaline, while it stimulates prolactin and growth hormone release; therefore, **1** is anticipated to be a promising therapeutic agent for feeding disorders involving overeating and obesity, Alzheimer's disease, pain and depression.[4]

The gross structure of **1** was revealed by extensive spectroscopic studies to have a novel spirocoumaranone skeleton incorporated with a highly oxygenated cyclohexene ring via an ether linkage.[1] Since **1** belongs to the griseofluvin family of compounds, the absolute configuration of the chiral center in the spirocoumaranone moiety was determined by comparing its circular dichroic (CD) spectrum with that of griseofluvin.[1] The relative stereochemistry of the cyclohexene ring moiety of **1** was revealed by analysis of 2D NMR spectra including COSY, NOESY, HETCOR, and HMBC experiments, while its absolute stereochemisty has not been established.[1]

Its promising biological profiles as well as unique structural features make **1** an exceptionally intriguing and timely target for total synthesis, which, however, has not been achieved to date. We embarked on a project directed at the synthesis of **1** and its congeners with the aim of exploring the structure–activity relationships. As depicted in Scheme 1, the structure of **1** can be retrosynthetically divided into two segments, namely, the spirocoumaranone part **2** and the cyclohexene part **3**.

Keywords: antibiotics; biomimetic reactions; coupling reactions; cyclization; spiro compounds.

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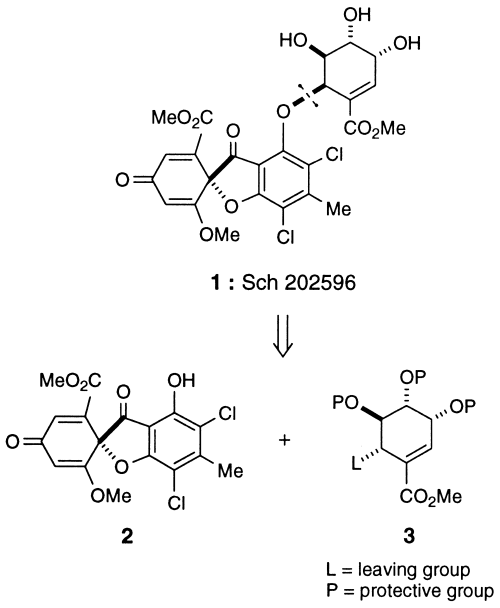
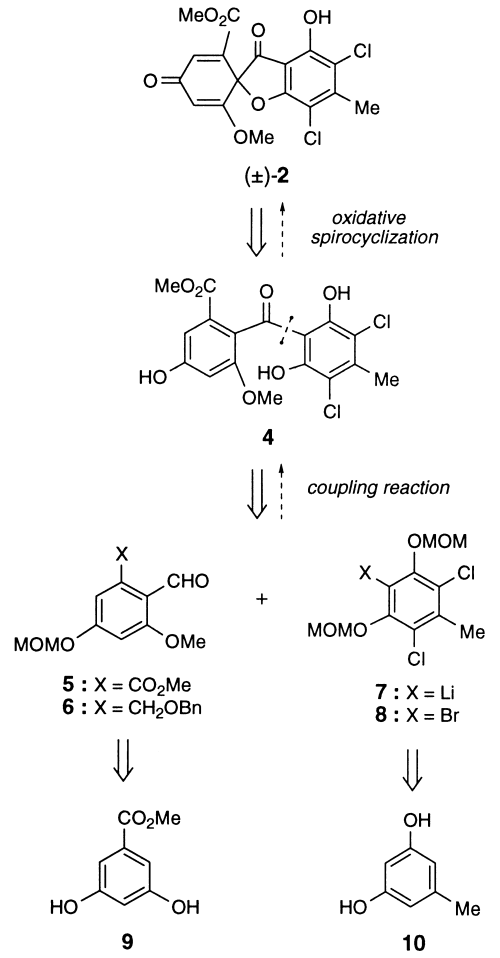
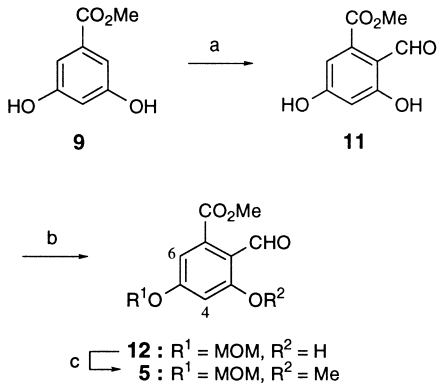


Scheme 1. Synthetic strategy for Sch 202596 (**1**).

Incidentally, **2** is identical with the known antifungal antibiotic geodin,[5] which was originally isolated from *Aspergillus terreus* Thom.[6] Quite recently, it was reported that geodin enhances fibrinolytic activity of vascular endothelical cells.[7] This finding strongly suggests that **2** may provide novel treatments for atherosclerotic cardiovascular diseases.[7] Taking into account those mentioned earlier, the development of a synthetic route to geodin is of great importance from a pharmaceutical standpoint. Recently, we communicated the total synthesis of (±)-geodin [(±)-**2**],[8] which, to the best of our knowledge, represents the first and only synthetic work of this natural product. In this paper, we wish to disclose the full details of our total synthesis of (±)-**2**.



Scheme 2. Synthetic plan for (±)-geodin [(±)-**2**].

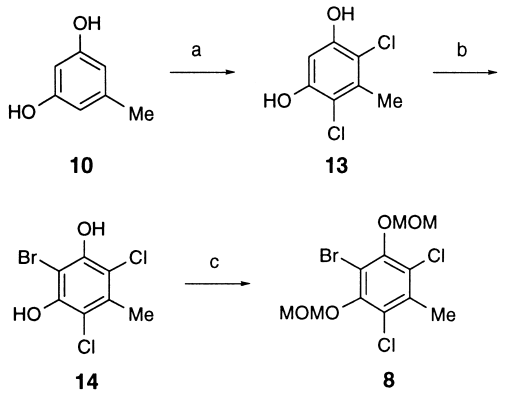


Scheme 3. Synthesis of the aryl aldehyde segment **5**. (a) $Zn(CN)_2$, HCl (gas), $AlCl_3$, Et_2O, rt, 46%; (b) MOMCl, K_2CO_3, acetone, rt, 85%; (c) MeI, Cs_2CO_3, DMF, rt, 95%.

2. Results and discussion

2.1. Synthetic strategy

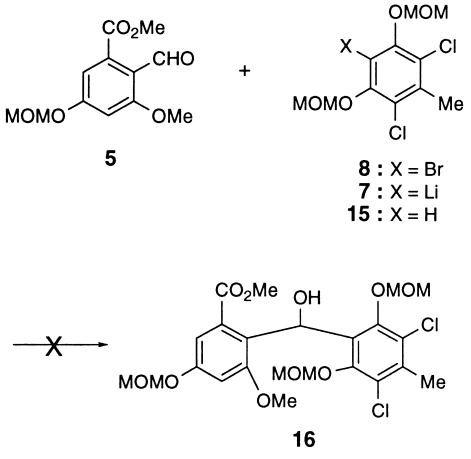
The retrosynthetic plan for (±)-geodin [(±)-**2**] is outlined in Scheme 2. The most crucial step is envisaged to be the biogenetic-type oxidative spirocyclization reaction[9] of the benzophenone **4** to construct the requisite spirocoumaranone skeleton in a single step [**4**→(±)-**2**]. Although related oxidative phenolic coupling reactions have been previously reported for the total synthesis of antifungal antibiotic (±)-griseofluvin and its related compounds,[10] to our knowledge, the spirocyclization of the highly substituted benzophenone derivative such as **4** to obtain (±)-**2** is unprecedented. The key spirocyclization precursor **4**, which possesses the highly sterically constrained tetra-*ortho*-substituted benzophenone arrangement, is envisioned to be elaborated through the coupling reaction of the tetra-substituted aryl aldehyde **5** or **6** with the fully substituted aryl lithium **7** generated in situ from the corresponding aryl bromide **8** (**5** or **6**+**7**→**4**). Analogous coupling reaction using less substituted substrates has been disclosed in the synthesis of the benzophenone part of a potent protein kinase C inhibitor balanol,[11] while the coupling reaction of **5** or **6** with **7** involves an interesting possibility at a synthetic chemical level because all of these compounds have much more substituted patterns. The two aryl aldehydes **5** and **6**, in turn, could be derived from commercially available methyl 3,5-dihydroxybenzoate (**9**). The aryl bromide **8** would be accessible from commercially available 5-methylresorcinol (**10**).



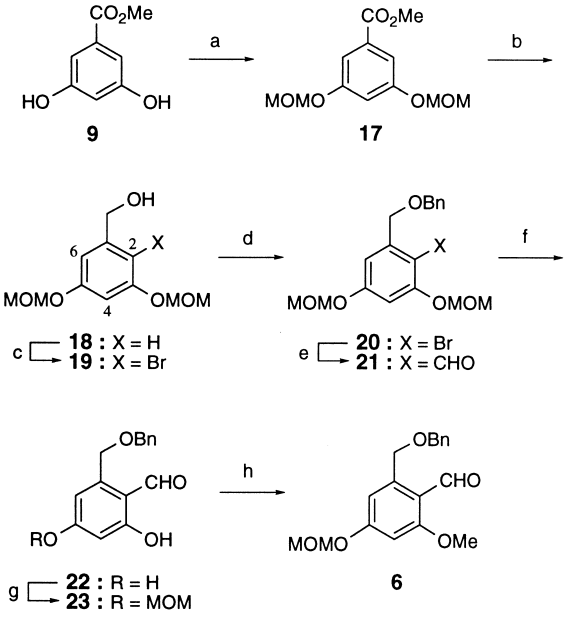
Scheme 4. Synthesis of the aryl bromide segment **8**. (a) SO_2Cl_2, $CHCl_3$, 0°C→rt, 59%; (b) Br_2, DMF, rt, 88%; (c) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 100%.

2.2. Synthesis of the aryl aldehyde segment 5

At first, as shown in Scheme 3, we pursued the synthesis of the aryl aldehyde segment **5** starting from the known 1,2,3,5-tetrasubstituted aryl aldehyde **11**,[12] which was prepared from **9** according to the literature.[12] Subsequent regioselective monoprotection of **11** was carried out under standard conditions, furnishing the methoxymethyl (MOM) ether **12** in 85% yield. The structure of **12** was determined by spectroscopic analysis including NOESY experiment in the 500 MHz ^{1}H NMR spectrum; thus, clear NOE interactions between the signals due to the methylene protons (δ 5.24) of the MOM protecting group and the C-6 aromatic proton (δ 7.12) were observed. In this reaction, reactivity of the hydroxy group adjacent to the formyl group in **11** would be precluded by the formation of an intramolecular hydrogen bond. In the 250 MHz ^{1}H NMR spectrum of **11**, a singlet signal at 12.36 ppm due to a phenolic hydroxy proton was observed, which strongly indicates the formation of an intramolecular hydrogen bond. Finally, methylation of the remaining hydroxy group in **12** was performed by treatment with iodomethane in the presence of cesium carbonate in *N*,*N*-dimethylformamide (DMF), giving rise to the requisite aryl aldehyde segment **5** in 95% yield.



Scheme 5. Initial attempts for the coupling reaction of the aryl aldehyde **5** with the aryl bromide **8**.



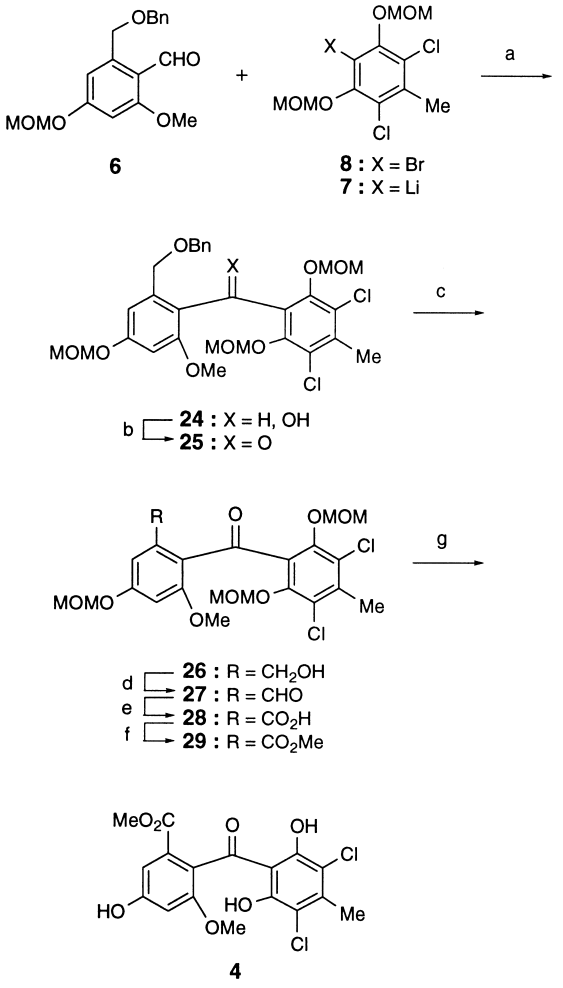
Scheme 6. Synthesis of the aryl aldehyde segment **6**. (a) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0°C→rt, 87%; (b) $LiAlH_4$, Et_2O, 0°C→rt, 98%; (c) NBS, DMF, 0°C, 93%; (d) BnBr, NaH, DMF, rt, 95%; (e) *n*-BuLi, Et_2O, −78°C; DMF, −78°C→rt, 95%; (f) 6 M HCl, THF, rt, 94%; (g) MOMCl, K_2CO_3, acetone, rt, 72%; (h) MeI, Cs_2CO_3, DMF, rt, 90%.

2.3. Synthesis of the aryl bromide segment 8

Next, the synthesis of the aryl bromide segment **8**, the coupling partner of **5**, was achieved starting from the known dichlororesorcinol **13**[13] (Scheme 4). Originally, compound **13** was derived from the commercially available 5-methylresorcinol (**10**) by the use of tedious gaseous chlorine as a chlorinating reagent in carbon tetrachloride.[13] We carried out the preparation of **13** according to the reported procedure[13a] with some improvements in the reaction conditions. Thus, exposure of **10** to sulfuryl chloride (2.1 equiv.) in chloroform at 0°C→rt afforded **13** in 59% yield. Subsequent bromination of **13** using bromine in DMF followed by protection of the two hydroxy groups in the resulting resorcinol **14** as its bis(MOM ether) provided the desired aryl bromide segment **8** in 88% yield for the two steps.

2.4. Initial attempts for the coupling reaction of the aryl aldehyde segment 5 with the aryl bromide segment 8

Having obtained both the aryl aldehyde segment **5** and the aryl bromide segment **8**, we next focused our attention on the critical coupling reaction of these two segments **5** and **8**. As depicted in Scheme 5, unfortunately, initial attempts to realize this coupling reaction turned out to be fruitless. When the aryl lithium **7**, generated in situ from **8** by bromine/lithium exchange with *n*-butyllithium at −78°C in THF, was allowed to react with **5**, none of the desired coupling product **16** was obtained and the starting material **5** and the debrominated product **15** were recovered. We assumed that the failure of this coupling reaction was due to the very low reactivity of the formyl group, which may be attributed to the steric hindrance of the methoxycarbonyl group present in **5**. In order to circumvent this problem, we decided to look at the aryl aldehyde segment **6** (see,



Scheme 7. Synthesis of the substrate **4** for the key spirocyclization. (a) **8**, *n*-BuLi, THF, −78°C; **6**, −78°C→rt, 86%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 98%; (c) H_2 (1 atm), 10% Pd–C, EtOH, rt, 79%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF/*t*-BuOH/H_2O (2:5:1), rt; (f) CH_2N_2, Et_2O, 96% (2 steps); (g) *p*-TsOH, MeOH, reflux, 81%.

Scheme 2), in which the methoxycarbonyl group in **5** is replaced with the synthetically equivalent *O*-protected hydroxymethyl group. We anticipated that **6** would behave as a promising substrate for the crucial coupling reaction. Further investigations concerning the synthesis of **6** and subsequent coupling reaction of **6** with **8** are the subjects of the following sections.

2.5. Synthesis of the aryl aldehyde segment 6

The synthesis of the aryl aldehyde segment **6** was conducted as shown in Scheme 6. Thus, the known benzyl alcohol **18**[11,14] could be readily prepared from **9** via the bis[methoxymethyl (MOM) ether] **17** according to the reported procedure.[11] Regiospecific monobromination of the symmetrical benzyl alcohol **18** was successfully carried out by exposure to 1.0 equiv. of *N*-bromosuccinimide (NBS) in DMF at 0°C, providing the unsymmetrical monobromobenzyl alcohol **19** in 93% yield. The structure of **19** was proven by the 500 MHz ^{1}H NMR spectrum; thus, distinguishable two signals [δ 6.82 (d, J=2.7 Hz) and δ 6.91 (d, J=2.7 Hz)] due to the C-4 and C-6 aromatic protons were observed. The regioselectivity observed for the monobromination of **18** probably caused by the presence of the *para*-directing group such as MOM protected hydroxy group. Conventional benzylation of the hydroxy group in **19** afforded the benzyl ether **20** in 95% yield. For introducing a formyl group, **20** was initially treated with *n*-butyllithium at −78°C to furnish the corresponding aryl lithium, which was then quenched with excess amount (10 equiv.) of DMF, affording the 1,2,3,5-tetrasubstituted aryl aldehyde **21** in 95% yield. Direct conversion of **21** to the MOM ether **23** by selective deprotection of the MOM protecting groups met with failure. Therefore, **21** was transformed to **23** via a two-step sequence of reactions including complete deprotection of the two MOM groups in **21** (94%) and regioselective monoprotection of the resulting resorcinol **22** (72%). At last, methylation of the hydroxy group in **23** provided the requisite aryl aldehyde segment **6** in 90% yield.

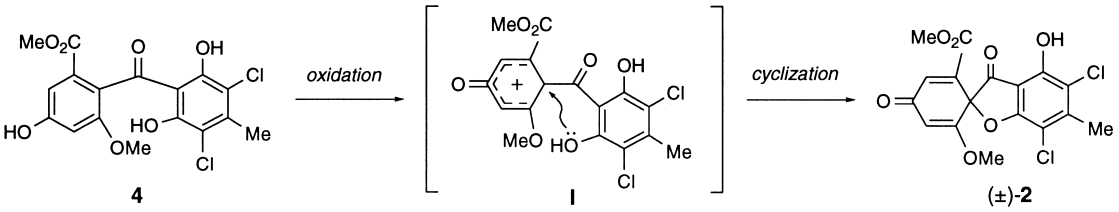
2.6. Synthesis of the substrate 4 for the key spirocyclization reaction via the coupling reaction of the aryl aldehyde segment 6 with the aryl bromide segment 8

With the aryl aldehyde segment **6** in hand, our next efforts were directed toward the crucial coupling reaction of **6** with the aryl bromide **8**, as well as elaboration of the substrate **4** for the key spirocyclization reaction as shown in Scheme 7. To our delight, the critical coupling reaction of **6** with **8** was successfully achieved by initial bromine/lithium exchange of **8** followed by reaction with **6** at −78°C→rt, which led to the formation of the desired coupling product **24** in 86% yield. Subsequent Dess–Martin oxidation[15] of **24** furnished the tetra-*ortho*-substituted benzophenone **25** in 95% yield. After removal of the benzyl protecting group in **25** by standard method, the resulting benzyl alcohol **26** was further converted to the methyl ester **29** in 91% overall yield via the aldehyde **27** and the carboxylic acid **28** by sequential two-step oxidation followed by methyl esterification. Finally, complete deprotection of the three MOM groups in **29** was conducted by exposure to *p*-toluenesulfonic acid (*p*-TsOH) in refluxing methanol, providing the key cyclization precursor **4** in 81% yield.

2.7. Synthesis of (±)-geodine [(±)-2] via the key spirocyclization reaction of the phenol 4

We next focused our attention on the crucial oxidative spirocyclization reaction to complete the synthesis of the targeted (±)-geodin [(±)-**2**]. As depicted in the scheme in Table 1, this spirocyclization event may proceed via the phenoxonium ion intermediate[16,17] such as **I**, which would be trapped by the inner phenolic hydroxy group to provide the requisite spirocyclized product (±)-**2**. After several experiments (see, Table 1), it was found that the desired oxidative spirocyclization reaction was best achieved by applying the Büchi protocol[18] with some improvements of the reaction conditions. Thus, the phenol **4** was treated with 3.0 equiv. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichlorormethane/ethanol (1:1) at room temperature for 1 h, leading to the formation of the requisite (±)-**2** in 57% yield (entry 1). Despite the presence of a nucleophilic polar protic solvent such as ethanol, none of the *para*-ethoxy-substituted cyclohexadienone derivative was obtained from this reaction. This observation strongly indicates that

Table 1. The key spirocyclization reaction of **4** to (±)-geodin [(±)-**2**] via phenolic oxidation



4 **I** **(±)-2**

Entry	Reagent (equiv.)	Solvent	Temperature	Time	Isolated yield of (±)-**2**
1	DDQ (3.0)	CH_2Cl_2/EtOH (1:1)	rt	1 h	57%
2	DDQ (3.0)	CH_2Cl_2	rt	8 h	25%
3	DDQ (2.0)	CH_2Cl_2	rt	8 h	8%
4	DDQ (3.0)	MeCN	rt	8 h	25%
5	$PhI(OCOCF_3)_2$ (1.1)	MeCN	rt	10 min	40%
6	$PhI(OCOCF_3)_2$ (1.1)	CF_3CH_2OH	−50→−30°C	2 h	Decomposition
7	$PhI(OAc)_2$ (1.1)	MeCN	rt	10 min	Decomposition
8	$C_6F_5I(OCOCF_3)_2$ (1.1)	MeCN	rt	4 h	Decomposition

the phenoxonium ion intermediate **I** having phenolic hydroxy groups is rapidly cyclized in an intramolecular manner rather than trapped by external ethanol. The ^{1}H NMR spectrum of the synthetic material (±)-**2** was identical with that reported[9a] for natural (+)-geodin [(+)-(**2**)]. The other experiments using DDQ as an oxidizing reagent deserve some comments. When the reaction was carried out in only dichloromethane, the yield of the product decreased to 25% (entry 2); this is probably due to the poor solubility of the substrate in the solvent. On employing less amount of DDQ (e.g. 2.0 equiv.), lower yield (8%) of the product was observed (entry 3). A reaction in polar nucleophilic solvent such as acetonitrile (MeCN) gave the product (±)-**2** in 25% yield (entry 4). We further examined the spirocyclization reaction of **4** by the use of hypervalent iodine reagents such as phenyliodine(III) bis(trifluoroacetate) (PIFA), phenyliodine(III) diacetate (PIDA), and pentafluorophenyliodine(III) bis(trifluoroacetate) (FPIFA). These reagents have been extensively used for various oxidative phenolic coupling reactions.[19] The results are also summarized in Table 1 (entries 5–8). When the phenol **4** was treated with PIFA (1.1 equiv.) in MeCN at room temperature according to the method reported by Kita et al.[16a] the desired (±)-(**2**) was obtained in 40% yield (entry 5). In a polar and poorly nucleophilic solvent such as 2,2,2-trifluoroethanol (CF_3CH_2OH) using the same oxidizing reagent, the requisite cyclized product was not formed and unidentified decomposition products were generated even at lower temperature (−50→−35°C) (entry 6). The use of PIDA or FPIFA as an oxidizing reagent resulted in complete decomposition of the products (entries 7 and 8). In all experiments shown in Table 1, any dimerized products generated by an intermolecular phenolic coupling reaction of **4**, were not obtained.

3. Conclusion

We have succeeded in developing a facile and efficient synthetic pathway to (±)-geodin [(±)-**2**] corresponding to the spirocoumaranone part of Sch 202596 (**1**) in a convergent manner starting from commercially available methyl 3,5-dihydroxybenzoate (**9**) and 5-methylresorcinol (**10**). The explored synthetic method features a coupling reaction of the aryl aldehyde **6** with the aryl lithium **7** derived from the aryl bromide **8** as well as an oxidative spirocyclization reaction of the benzophenone **4** to construct the spirocoumaranone ring system. Further investigation toward the total synthesis of **1** and analogues is now in progress and will be reported in due course.

4. Experimental

4.1. General methods

All reactions involving air- and moisture-sensitive reagent were carried out using oven-dried glassware and standard syringe-septum cap techniques. Routine monitoring of reaction were carried out using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40–50 μm) with indicated solvents.

All solvents and reagents were used as supplied with the following exceptions. Tetrahydrofuran (THF) and ether were freshly distilled from sodium/benzophenone under argon. Dichloromethane and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride under argon.

Melting points were taken on a Yanaco MP-3 micro melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were measured with a Brucker DRX-500 (500 MHz) spectrometer or a Brucker DRX-250 (250 MHz). Chemical shifts were expressed in ppm using tetramethylsilane (δ=0) as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HRMS) spectra were obtained on a Hitachi M-80A spectrometer.

4.1.1. Methyl 2-formyl-3,5-dihydroxybenzoate (11). This preparation was carried out according to the reported

method.[12] Anhydrous zinc cyanide (1.56 g, 13 mmol) was added to a stirred solution of methyl 3,5-dihydroxybenzoate (**9**) (1.06 g, 6.3 mmol) in dry Et_2O (10 ml) at 0°C, and a solution of anhydrous aluminum chloride (1.71 g, 13 mmol) in dry Et_2O (7.0 ml) was added at the same temperature. Dry hydrogen chloride (gas) was bubbled into the mixture at 0°C for 10 min, and the reaction mixture was further stirred at room temperature for 18 h. The reaction was quenched with water (30 ml) at 0°C, and the resulting mixture was extracted with ethyl acetate (3×50 ml). The combined extracts were washed with brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **11** (560 mg, 46%) as a white solid. Recrystallization from water afforded an analytical sample of **11** as colorless needles, mp 169.5–171°C (lit.[12] mp 163.5°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (s, 3H, OMe), 6.20 (s, 1H, C_5–OH), 6.53 (d, J=2.5 Hz, 1H, C_4–H), 6.97 (d, J=2.5 Hz, 1H, C_6–H), 10.43 (s, 1H, CHO), 12.62 (s, 1H, C_3–OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.64, 104.54, 109.62, 112.04, 136.30, 164.22, 164.28, 167.29, 191.52; IR (KBr) 3295, 1723, 1454, 1626, 1433, 1223, 1389, 1277, 1213, 1175, 1028, 862, 820, 783, 747, 675, 570 cm^{-1}; EI-MS (*m*/*z*) 196 (M^+), 181 [$(M-Me)^+$], 137 [$(M-CO_2Me)^+$]; Anal. calcd for $C_9H_8O_5$: C, 55.11; H, 4.11. Found: C, 54.76; H, 4.09.

4.1.2. Methyl 2-formyl-3-hydroxy-5-(methoxymethoxy)-benzoate (12). Chloromethyl methyl ether (0.32 ml, 4.0 mmol) was added to a stirred suspension of **11** (524 mg, 2.7 mmol) and potassium carbonate (630 mg, 4.5 mmol) in acetone (10 ml) at room temperature under argon. After 6 h, the reaction mixture was diluted with ether (50 ml). The organic layer was washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **12** (543 mg, 85%) as a pale yellow solid. Recrystallization from Et_2O afforded an analytical sample of **12** as colorless needles, mp 81.0–82.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (s, 3H, *Me*OCH_2), 3.95 (s, 3H, MeOCO), 5.24 (2H, s, OCH_2O), 6.76 (d, J=2.4 Hz, 1H, C_4–H), 7.12 (d, J=2.4 Hz, 1H, C_6–H), 10.46 (s, 1H, CHO), 12.59 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.80, 56.49, 94.08, 106.81, 112.28, 113.43, 135.22, 162.74, 165.84, 165.93, 195.62; IR (KBr) 2961, 1725, 1678, 1198, 1155, 1441, 1343, 1312, 1229, 1155, 1136, 1084, 1063, 1003, 936, 828 cm^{-1}; EI-MS (*m*/*z*) 240 (M^+), 225 [$(M-Me)^+$], 209 [$(M-OMe)^+$]; Anal. calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.74; H, 5.06.

4.1.3. Methyl 2-formyl-3-methoxy-5-(methoxymethoxy)-benzoate (5). Iodomethane (39.0 μl, 0.63 mmol) was added to a stirred suspension of **12** (101 mg, 0.42 mmol) and cesium carbonate (165 mg, 0.50 mmol) in dry DMF (5 ml) at room temperature. After 2 h, the reaction mixture was diluted with ether (40 ml). The organic layer was washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **5** (101 mg, 95%) as a white solid. Recrystallization from Et_2O/hexane (1:2) afforded an analytical sample of **5** as colorless prisms, mp 62.5–64°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (s, 3H, *Me*OCH_2), 3.91 (s, 3H, MeO), 3.92 (s, 3H, MeO), 5.23 (s, 2H, OCH_2O), 6.68 (d, J=1.9 Hz, 1H, C_4–H), 6.72 (d, J=1.9 Hz, 1H, C_6–H), 10.31 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.85, 56.05, 56.42, 94.27, 100.96, 107.68, 117.28, 136.34, 162.65, 163.07, 169.28, 187.80; IR (KBr) 2961, 1725, 1678, 1198, 1155, 1441, 1343, 1312, 1229, 1155, 1136, 1084, 1063, 1003, 936, 828 cm^{-1}; EI-MS (*m*/*z*) 254 (M^+), 239 [$(M-Me)^+$]; Anal. calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.61; H, 5.59.

4.1.4. 4,6-Dichloro-5-methylresorcinol (13). Sulfuryl chloride (6.58 ml, 82 mmol) was added to a stirred suspension of 5-methylresorcinol (**10**) (5.00 g, 40 mmol) in $CHCl_3$ (200 ml) at 0°C, and stirring was continued at rt for 1.5 h. The reaction mixture was poured into water (100 ml), which was extracted with ethyl acetate (2× 150 ml). The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **13** (4.59 g, 59%) as a white solid. Recrystallization from benzene afforded an analytical sample of **13** as colorless needles, mp 170.5–171°C (lit.[13a] mp 165.5–167°C, lit.[13b] 163.5–164°C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3H, Me), 5.99 (s, 2H, OH×2), 6.63 (s, 1H, Ar*H*); ^{13}C NMR (125 MHz, CD_3OD) δ 17.72, 101.67, 111.18, 134.47 (two carbons), 152.11 (two carbons); IR (KBr) 3443, 1602, 1454, 1360, 1325, 1223, 1140, 1092, 1072, 835, 718, 615, 544 cm^{-1}; EI-MS (*m*/*z*) 194 [$(M+2)^+$], 192 (M^+), 176 [$(M+2-H_2O)^+$], 174 [$(M-H_2O)^+$], 159 [$M+2-Cl]^+$], 157 [$(M-Cl)^+$]; Anal. calcd for $C_7H_6Cl_2O_2$: C, 43.56; H, 3.13. Found: C, 43.56; H, 3.11.

4.1.5. 2-Bromo-4,6-dichloro-5-methylresorcinol (14). Bromine (0.38 M solution in CH_2Cl_2, 16.6 ml, 6.3 mmol) was added dropwise to a stirred solution of **13** (1.00 g, 5.2 mmol) in dry DMF (25 ml) at room temperature. After 3 h, the reaction mixture was diluted with Et_2O (200 ml). The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **14** (1.26 g, 88%) as a white solid. Recrystallization from hexane afforded an analytical sample of **14** as colorless needles, mp 107–108°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3H, Me), 5.95 (s, 2H, OH×2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.97, 95.52, 112.78, 133.94 (two carbons), 147.95 (two carbons); IR (KBr) 3400, 1582, 1455, 1412, 1367, 1322, 1252, 1210, 1082, 743, 720, 662, 595 cm^{-1}; EI-MS (*m*/*z*) 274 [$(M+4)^+$], 272 [$(M+2)^+$], 270 (M^+), 239 [$(M+2-Cl)^+$], 237 [$(M-Cl)^+$]; Anal. calcd for $C_7H_5BrCl_2O_2$: C, 30.92; H, 1.85. Found: C, 31.11; H, 1.87.

4.1.6. 3,5-Bis(methoxymethoxy)-4-bromo-2,6-dichlorotoluene (8). Chloromethyl methyl ether (0.74 ml, 9.7 mmol) was added dropwise to a stirred solution of **14** (1.20 g, 4.4 mmol) in CH_2Cl_2 (30 ml) containing *N*,*N*-diisopropylethylamine (2.68 ml, 15 mmol) at 0°C under argon, and stirring was continued for 1 h at room temperature. The reaction mixture was diluted with ether (200 ml), and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$. Concentration of the

solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **8** (1.59 g, 100%) as a white solid. Recrystallization from hexane afforded an analytical sample of **8** as colorless needles, mp 63–64°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.48 (s, 3H, Ar*Me*), 3.71 (s, 6H, MeO×2), 5.16 (s, 4H, OCH_2O×2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.53, 58.38 (two carbons), 99.54 (two carbons), 112.58, 125.98, 135.62 (two carbons), 150.33 (two carbons); IR (KBr) 3452, 2950, 2905, 2840, 2098, 1775, 1655, 1542, 1478, 1460, 1412, 1398, 1375, 1340, 1304, 1212, 1177, 1098, 1042, 1005, 935, 920, 890, 760, 740, 719, 588 cm^{-1}; EI-MS (*m/z*) 362 [$(M+4)^+$], 360 [$(M+2)^+$], 358 (M^+), 302 [$(M+4-MeO-OMe+2H)^+$], 300 [$(M+4-MeO-OMe+2H)^+$]; Anal. calcd for $C_{11}H_{13}BrCl_2O_4$: C, 36.70; H, 3.60. Found: C, 36.59; H, 3.61.

4.1.7. An attempt for the coupling reaction of 5 with 8. *n*-BuLi (1.14 M solution in hexane, 0.29 ml, 0.34 mmol) was added to a stirred solution of **8** (110 mg, 0.30 mmol) in dry THF (2 ml) at −78°C under argon. After 15 min, a solution of **5** (50.8 mg, 0.20 mmol) in THF (0.8 ml) was added dropwise to the solution at −78°C, and the resulting mixture was stirred for 15 min at the same temperature. The mixture was allowed to warm up to 0°C over 1 h, and then stirring was continued for 1 h at 0°C. After additional stirring at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (0.6 ml). The mixture was extracted with Et_2O (2×40 ml), and the combined extracts were washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **15** (83.4 mg, 97%) along with **5** (46.7 mg, 92% recovery). Recrystallization of **15** from hexane/$CHCl_3$ (1:1) afforded an analytical sample as a colorless needles, mp 72–73°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H, Ar*Me*), 3.52 (s, 6H, MeO×2), 5.22 (s, 4H, OCH_2O×2), 6.96 (s, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.07, 56.50 (two carbons), 95.59 (two carbons), 103.00, 118.10, 136.24 (two carbons), 151.77 (two carbons); IR (KBr) 2966, 1581, 1479, 1452, 1402, 1323, 1226, 1163, 1095, 1041, 931, 918, 841, 742 cm^{-1}; EI-MS (*m/z*) 284 [$(M+4)^+$], 282 [$(M+2)^+$], 280 (M^+); Anal. calcd for $C_{11}H_{14}Cl_2O_4$: C, 46.99; H, 5.02. Found: C, 46.60; H, 4.99.

4.1.8. Methyl 3,5-bis(methoxymethoxy)benzoate (17). This preparation was carried out according to the reported procedure.[11] Chloromethyl methyl ether (11.3 ml, 0.15 mol) was added dropwise to a stirred solution of methyl 3,5-dihydroxybenzoate (**9**) (10.0 g, 60 mmol) and *N*,*N*-diisopropylethylamine (31.0 ml, 0.18 mol) in dry CH_2Cl_2 (100 ml) at 0°C under argon. After the solution was stirred at room temperature for 5 h, the reaction mixture was diluted with dichloromethane (500 ml). The organic layer was washed successively with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **17** (13.3 g, 87%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.48 (s, 6H, *Me*OCH_2×2), 3.90 (s, 3H, MeOCO), 5.19 (s, 4H, OCH_2O×2), 6.92 (t, *J*=2.3 Hz, 1H, C_4–H), 7.37 (d, *J*=2.3 Hz, 2H, C_2–H+C_6–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.13, 56.04 (two carbons), 94.36 (two carbons), 109.58, 110.56 (two carbons), 132.07, 158.03 (two carbons), 166.44; IR (neat) 3108, 2955, 2830, 2074, 2000, 1724, 1599, 1439, 1400, 1302, 1238, 1148, 1084, 1030, 923, 879, 709, 680, 553, 449 cm^{-1}; EI-MS (*m/z*) 256 (M^+), 225 [$(M-OMe)^+$] HREIMS (*m/z*) calcd for $C_{12}H_{16}O_6$ (M^+): 256.0946, found 256.0955. The ^{1}H NMR spectrum of this sample accorded well with that reported.[11,14c]

4.1.9. 3,5-Bis(methoxymethoxy)benzyl alcohol (18). This preparation was carried out according to the reported method.[11] A solution of **17** (13.0 g, 51 mmol) in dry THF (100 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (2.89 g, 76 mmol) in dry THF (100 ml) at 0°C, and the reaction mixture was stirred at room temperature for 2 h. Water (3 ml), 15% aqueous NaOH (3 ml), and water (3 ml) were sequentially added to the mixture, and stirring was continued for 1 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate was dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **18** (11.3 g, 98%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2,89 (br s, 1H, OH), 3.44 (s, 6H, MeO×2), 4.56 (s, 2H, ArCH_2), 5.12 (s, 4H, OCH_2O×2), 6.62 (br s, 1H, C_4–H), 6.68 (br s, 2H, C_2–H+C_6–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.86 (two carbons), 64.65, 94.21 (two carbons), 103.82, 107.77 (two carbons), 143.61, 158.19 (two carbons); IR (neat) 3402, 2920, 2432, 2072, 2000, 1613, 1462, 1402, 1290, 1215, 1145, 1086, 1022, 924, 844, 700 cm^{-1}; EI-MS (*m/z*) 228 (M^+), 198 [$(M-CH_2OH+H)^+$], 168 [$(M-CH_2OH-OMe+2H)^+$]; HREI-MS (*m/z*) calcd for $C_{11}H_{16}O_5$ (M^+): 228.0096, found: 228.1000.

4.1.10. 2-Bromo-3,5-bis(methoxymethoxy)benzyl alcohol (19). *N*-Bromosuccinimide (NBS) (8.59 g, 48 mmol) was added in small portions to a stirred solution of **18** (11.0 g, 48 mmol) in dry DMF (220 ml) at 0°C. After 2 h, the reaction mixture was diluted with ethyl acetate (400 ml). The organic layer was washed successively with 10% aqueous $Na_2S_2O_3$, water, and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **19** (13.8 g, 93%) as a white solid. Recrystallization from *i*-Pr_2O/hexane (1:1) afforded an analytical sample of **19** as a white powder, mp 56–57°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (t, *J*=6.5 Hz, 1H, O*H*), 3.48 (s, 3H, OMe), 3.52 (s, 3H, OMe), 4.73 (d, *J*=6.5 Hz, 2H, ArCH_2), 5.17 (s, 1H, OCH_2O), 5.23 (s, 1H, OCH_2O), 6.82 (d, *J*=2.7 Hz, 1H, C_3–H or C_5–H), 6.91 (d, *J*=2.7 Hz, 1H, C_3–H or C_5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.18, 56.48, 65.34, 94.57, 95.26, 104.21, 104.78, 109.48, 141.88, 154.44, 157.44; IR (KBr) 3410, 2920, 1454, 1400, 1318, 1215, 1148, 1080, 1019, 922, 853, 583 cm^{-1}; EI-MS (*m/z*) 308 [$(M+2)^+$], 306 (M^+); Anal. calcd for $C_{11}H_{15}BrO_5$: C, 43.02; H, 4.92. Found: C, 42.84; H, 4.95.

4.1.11. 2-Benzyloxymethyl-4,6-bis(methoxymethoxy)-bromo benzene (20). NaH (60% dispersion in mineral oil, 1.95 g, 49 mmol) was added in small portions to a stirred solution of **19** (10.0 g, 33 mmol) in dry DMF (50 ml) at 0°C. After 20 min, benzyl bromide (4.65 ml, 44 mmol) was

added dropwise to the solution at 0°C, and stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the resulting mixture was diluted with Et_2O (500 ml). The organic layer was washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **20** (12.2 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (s, 3H, MeO), 3.50 (s, 3H, MeO), 4.60 (s, 2H, ArCH_2O), 4.63 (s, 2H, ArCH_2O), 5.15 (s, 2H, OCH_2O), 5.22 (s, 2H, OCH_2O), 6.81 (d, J=2.8 Hz, 1H, C_3–H or C_5–H), 6.97 (d, J=2.7 Hz, 1H, C_3–H or C_5–H), 7.29 (t, J=7.3 Hz, 1H, $C_{4'}$–H), 7.35 (t, J=7.3 Hz, 2H, $C_{3'}$–H+$C_{5'}$–H), 7.39 (d, J=7.3 Hz, 2H, $C_{2'}$–H+$C_{6'}$–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.05, 56.34, 71.63, 72.72, 94.50, 95.17, 103.98, 105.02, 109.71, 127.64, 127.72 (two carbons), 128.34 (two carbons), 137.94, 139.73, 154.27, 157.18; IR (neat) 2953, 2828, 1956, 1599, 1460, 1400, 1377, 1294, 1213, 1146, 1082, 1036, 924, 847, 741, 698 cm^{-1}; EI-MS (m/z) 398 [(M+2)$^+$], 396 (M$^+$), 292 [(M+2−OBn+H)$^+$], 290 [(M−OBn+H)$^+$]; HREIMS (m/z) calcd for $C_{18}H_{21}BrO_5$ (M$^+$): 396.0561, found: 396.0566.

4.1.12. 2-Benzyloxymethyl-4,6-bis(methoxymethoxy)-benzaldehyde (21). *n*-BuLi (0.96 M solution in hexane, 26.6 ml, 26 mmol) was added dropwise to a stirred solution of **20** (6.76 g, 17 mmol) in dry Et_2O (70 ml) at −78°C under argon, and stirring was continued at the same temperature for 1 h. Dry DMF (13.2 ml, 0.17 mol) was added slowly to the solution at −78°C, and the reaction mixture was allowed to warm up to room temperature over 3 h. The reaction was quenched with saturated aqueous NH_4Cl (15 ml), and the resulting mixture was diluted with Et_2O (400 ml). The organic layer was washed successively with saturated aqueous NH_4Cl, water, and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 4:1) to give **21** (5.60 g, 95%) as a light yellow solid. Recrystallization from *i*-Pr_2O/hexane (1:1) afforded an analytical sample of **21** as a light yellow powder, mp 60–60.5°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.49 (s, 3H, MeO), 3.51 (s, 3H, MeO), 4.67 (s, 2H, ArCH_2O), 4.97 (s, 2H, ArCH_2O), 5.23 (s, 2H, OCH_2O), 5.27 (s, 2H, OCH_2O), 6.77 (d, J=2.1 Hz, 1H, C_3–H or C_5–H), 7.17 (br s, 1H, C_3–H or C_5–H), 7.29 (t, J=7.2 Hz, 1H, $C_{4'}$–H), 7.36 (t, J=7.4 Hz, 2H, $C_{3'}$–H+$C_{5'}$–H), 7.40 (d, J=7.4 Hz, 2H, $C_{2'}$–H+$C_{6'}$–H), 10.48 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.42, 56.54, 70.33, 72.94, 94.02, 94.84, 100.80, 107.47, 116.80, 127.55, 127.61 (two carbons), 128.36 (three carbons), 138.32, 145.55, 162.76, 190.19; IR (KBr) 3393, 2922, 1723, 1674, 1601, 1576, 1453, 1399, 1352, 1283, 1211, 1143, 1082, 1026, 925, 858, 812, 738, 698, 596 cm^{-1}; CI-MS 347 [(M+1)$^+$], 315 [(M−OMe)$^+$], 255 [(M−Bn)$^+$], 239 [(M−OBn)$^+$]; Anal. calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.66; H, 6.40.

4.1.13. 2-Benzyloxymethyl-4,6-dihydroxybenzaldehyde (22). 6 M HCl (65 ml, 0.39 mol) was added slowly to a stirred solution of **21** (5.38 g, 16 mmol) in THF (80 ml) at room temperature. After 2 h, the reaction mixture was diluted with ethyl acetate (400 ml). The organic layer was washed successively with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **22** (3.77 g, 94%) as a white solid. Recrystallization from $CHCl_3$/hexane (1:1) afforded an analytical sample of **22** as a white powder, mp 130.5–131.5°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.58 (s, 2H, ArCH_2O), 4.70 (s, 2H, ArCH_2O), 6.32 (d, J=2.3 Hz, 1H, C_3–H or C_5–H), 6.41 (d, J=2.3 Hz, 1H, C_3–H or C_5–H), 6.48 (br s, 1H, C_4–OH), 7.23–7.46 (m, 5H, *Ph*CH_2O), 10.10 (s, 1H, CHO), 12.36 (s, 1H, C_6–OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.0, 72.6, 103.1, 110.1, 112.7, 128.0 (two carbons), 128.1, 128.6 (two carbons), 137.1, 143.8, 163.4, 166.4, 193.5; IR (KBr) 3420, 2930, 2855, 1640, 1460, 1380, 1225, 1170, 740, 700 cm^{-1}; CI-MS (m/z) 259 [(M+1)$^+$]; 167 [(M−Bn)$^+$], 152 [(M−OBn)$^+$]; HREIMS (m/z) calcd for $C_{15}H_{14}O_4$ (M$^+$): 258.0891, found: 258.0916.

4.1.14. 2-Benzyloxymethyl-6-hydroxy-4-(methoxymethoxy)benzaldehyde (23). Chloromethyl methyl ether (1.04 ml, 14 mmol) was added to a stirred suspension of **22** (3.20 g, 12 mmol) and potassium carbonate (1.71g, 12 mmol) in acetone (60 ml) at room temperature under argon. After 1 h, the reaction mixture was diluted with ether (350 ml). The organic layer was washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 6:1) to give **23** (2.70 g, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (s, 3H, *Me*O), 4.57 (s, 2H, ArCH_2), 4.71 (s, 2H, ArCH_2), 5.20 (s, 2H, OCH_2O), 6.55 (s, 2H, C_3–H+C_5–H), 7.35 (m, 5H, *Ph*CH_2), 10.14 (s, 1H, CHO), 12.33 (s, 1H, C_6–OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.48, 69.32, 72.61, 94.04, 103.32, 110.67, 113.35, 127.97 (two carbons), 128.04, 128.57 (two carbons), 137.33, 154.06, 163.73, 166.21, 193.92; IR (neat) 3651, 3063, 3030, 2903, 1650, 1634, 1578, 1495, 1454, 1408, 1369, 1325, 1298, 1224, 1152, 1080, 1001, 937, 854, 804, 737 cm^{-1}; CI-MS (m/z) 303 [(M+1)$^+$], 211 [(M−Bn)$^+$], 211 [(M−OBn)$^+$]; HREIMS (m/z) calcd for $C_{17}H_{18}O_5$ (M$^+$): 302.1154, found: 302.1159.

4.1.15. 2-Benzyloxymethyl-6-methoxy-4-(methoxymethoxy)benzaldehyde (6). Iodomethane (0.621 ml, 9.9 mmol) was added to a stirred suspension of **23** (1.86 g, 6.2 mmol) and cesium carbonate (2.31 g, 7.1 mmol) in dry DMF (18 ml) at room temperature. After 1 h, the reaction mixture was diluted with ether (250 ml). The organic layer was washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **6** (1.75 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (s, 3H, *Me*OCH_2), 3.89 (s, 3H, *Me*OAr), 4.67 (s, 2H, ArCH_2), 4.97 (s, 2H, ArCH_2), 5.25 (s, 2H, MeOCH_2O), 6.55 (d, J=2.2 Hz, 1H, C_3–H or C_5–H), 7.11 (d, J=1.3 Hz, 1H, C_3–H or C_5–H), 7.29 (br d, J=7.3 Hz, 1H, $C_{4'}$–H), 7.35 (ddd, J=1.7, 7.3, 7.3 Hz, 2H, $C_{3'}$–H+$C_{5'}$–H), 7.40 (br d, J=7.2 Hz, 2H, $C_{2'}$–H+$C_{6'}$–H), 10.45 (s, 1H, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.91, 56.40, 70.40, 72.95, 94.06, 97.70, 106.16, 116.19, 127.54, 127.61 (two carbons), 128.36 (two carbons), 138.37, 145.81, 163.01, 165.08, 190.22; IR (neat) 3063, 3030, 2940, 2903, 2787, 2612, 2000, 1728, 1672, 1601, 1456, 1437, 1408, 1350, 1267, 1233, 1198,

1146, 1071, 1020 cm^{-1}; CI-MS (*m/z*) 317 [$(M+1)^+$], 225 [$(M-Bn)^+$], 209 [$(M-OBn)^+$]; HRCI-MS (*m/z*) calcd for $C_{18}H_{20}O_5$ [$(MH)^+$]: 317.1388, found: 317.1418.

4.1.16. 4-{[2-Benzyloxymethyl-6-methoxy-4-(methoxymethoxy)phenyl]hydroxymethyl}-3,5-bis(methoxymethoxy)-2,6-dichlorotoluene (24). *n*-BuLi (1.14 M solution in hexane, 0.58 ml, 0.66 mmol) was added to a stirred solution of **8** (214 mg, 0.60 mmol) in dry THF (4 ml) at −78°C under argon. After 15 min, a solution of **6** (126 mg, 0.40 mmol) in THF (1.5 ml) was added dropwise to the solution at −78°C, and the resulting mixture was stirred for 15 min at the same temperature. The mixture was allowed to warm up to 0°C over 1 h, and stirring was continued at the same temperature for 1 h. After additional stirring at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (1 ml). The mixture was extracted with Et_2O (2×70 ml), and the combined extracts were washed with water and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 7:1) to give **24** (204.1 mg, 86%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H, Ar*Me*), 3.47 (s, 3H, MeO), 3.51 (s, 6H, *Me*OCH_2×2), 3.70 (s, 3H, MeO), 4.55 (s, 2H, ArCH_2O), 4.63 (d, *J*=12.3 Hz, 1H, Ar*CH*O), 4.72 (d, *J*=11.8 Hz, 1H, Ar*CH*O), 4.73 (d, *J*=5.0 Hz, 2H, O*CH*H′O×2), 4.92 (d, *J*=5.0 Hz, 2H, OCH*H*′O×2), 5.14 (d, *J*=8.3 Hz, 1H, CHO*H*), 5.15 (s, 2H, MeOCH_2), 6.46 (d, *J*=8.3 Hz, 1H, *CH*OH), 6.54 (d, *J*=2.4 Hz, 1H, C_3–H or C_5–H), 6.81 (d, *J*=2.4 Hz, 1H, C_3–H or C_5–H), 7.26 (m, 1H, $C_{4'}$–H), 7.34 (m, 4H, $C_{2'}$–H+$C_{3'}$–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.47, 55.67, 56.07, 57.89 (two carbons), 66.83, 70.52, 72.47, 94.49, 99.72 (two carbons), 100.11, 108.84, 122.55, 125.26 (two carbons), 127.46, 127.71 (two carbons), 128.27 (two carbons), 132.14, 135.18, 138.27, 138.65, 150.14 (two carbons), 157.13, 158.57; IR (neat) 3436, 2938, 1605, 1454, 1383, 1333, 1213, 1153, 1082, 1032, 922, 698 cm^{-1}; EI-MS (*m/z*) 598 [$(M+2)^+$], 596 (M^+), 491 [$(M+2-OBn)^+$], 489 [$(M-OBn)^+$], 429 [$(M+2-OBn-2×OMe)^+$], 427 [$(M-OBn-2×OMe)^+$]; HREIMS (*m/z*) calcd for $C_{29}H_{34}Cl_2O_9$ (M^+): 596.1580, found: 596.1590.

4.1.17. 2′-Benzyloxymethyl-6′-methoxy-2,4′,6-tris(methoxymethoxy)-3,5-dichloro-4-methylbenzophenone (25). Dess–Martin periodinane (189 mg, 0.52 mmol) was added to a stirred solution of **24** (204 mg, 0.34 mmol) in CH_2Cl_2 (12 ml) at room temperature under argon. After 45 min, the reaction mixture was diluted with Et_2O (60 ml). The organic layer was washed with 5% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, Concentration of the solvent in vacuo afforded a residue, which was purified by silica gel column chromatography (hexane/ethyl acetate, 4:1) to give **25** (199 mg, 98%) as a colorless oil. ^1H NMR (250 MHz, $CDCl_3$) δ 2.53 (s, 3H, Ar*Me*), 3.33 (s, 6H, *Me*OCH_2×2), 3.48 (s, 3H, MeO), 3.49 (s, 3H, MeO), 4.67 (s, 2H, ArCH_2O), 4.88 (s, 4H, MeOCH_2×2), 4.91 (s, 2H, ArCH_2O), 5.22 (s, 2H, MeOCH_2), 6.46 (d, *J*=2.3 Hz, 1H, C_3–H or C_5–H), 7.17 (d, *J*=2.4 Hz, 1H, C_3–H or C_5–H), 7.25–7.50 (m, 5H, *Ar*CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.53, 55.99, 56.34, 57.97 (two carbons), 70.59, 72.89, 94.08, 98.59, 100.16 (two carbons), 106.99, 119.81, 124.96 (two carbons), 127.63, 127.91 (two carbons), 128.34 (two carbons), 133.55, 136.21, 138.41, 145.61, 148.61 (two carbons), 161.72, 162.17, 190.46; IR (neat) 3436, 2855, 1651, 1599, 1454, 1371, 1260, 1159, 1069, 1040, 922 cm^{-1}; EI-MS (*m/z*) 596 [$(M+2)^+$], 594 (M^+), 505 [$(M+2-Bn)^+$], 503 [$(M-Bn)^+$], 490 [$(M+2-OBn+H)^+$], 488 [$(M-OBn+H)^+$], HREIMS (*m/z*) calcd for $C_{29}H_{32}Cl_2O_9$ (M^+): 594.14234, found: 594.1411.

4.1.18. 2-[2,6-Bis(methoxymethoxy)-3,5-dichloro-4-methylbenzoyl]-3-methoxy-5-(methoxymethoxy)benzyl alcohol (26). A mixture of **25** (89.6 mg, 0.151 mmol) and 10% Pd/C (16.0 mg) in EtOH (5 ml) was stirred under H_2 (1 atm) at room temperature for 1 h. The reaction mixture was diluted with EtOH (30 ml), and the catalyst was filtered off. Concentration of the filtrate in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **26** (60.3 mg, 79%) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.55 (s, 3H, Ar*Me*), 3.36 (s, 6H, *Me*OCH_2O), 3.48 (s, 3H, MeO), 3.48 (s, 3H, MeO), 4.03 (t, *J*=7.3 Hz, 1H, OH), 4.62 (d, *J*=7.0 Hz, 2H, ArCH_2O), 4.92 (s, 4H, MeOCH_2O×2), 5.22 (s, 2H, MeOCH_2O), 6.50 (d, *J*=2.2 Hz, 1H, C_3–H or C_5–H), 6.79 (d, *J*=2.2 Hz, 1H, C_3–H or C_5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.63, 56.08, 56.39, 57.84 (two carbons), 65.34, 94.16, 99.76, 100.22 (two carbons), 110.82, 121.59, 125.07 (two carbons), 133.13, 136.74, 146.64, 148.76 (two carbons), 162.03, 162.68, 192.40; IR (neat) 3433, 2920, 2851, 1647, 1599, 1575, 1404, 1373, 1261, 1211, 1159, 1086, 1034, 914, 818, 606 cm^{-1}; EI-MS (*m/z*) 490 [$(M+4-H_2O)^+$], 488 [$(M+2-H_2O)^+$], 486 [$(M-H_2O)^+$], 442 [$(M-2×OMe)^+$]; HREIMS (*m/z*) calcd for $C_{22}H_{24}Cl_2O_8$ [$(M-H_2O)^+$]: 486.0848, found: 486.0826.

4.1.19. 2-[2,6-Bis(methoxymethoxy)-3,5-dichloro-4-methylbenzoyl]-3-methoxy-5-(methoxymethoxy) benzaldehyde (27). Dess–Martin periodinane (39.1 mg, 0.11 mmol) was added to a stirred solution of **26** (38.6 mg, 76 μmol) in CH_2Cl_2 (2 ml) at room temperature under argon. After 1 h, the reaction mixture was diluted with Et_2O (50 ml). The organic layer was washed successively with 5% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$, Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **27** (36.4 mg, 95%) as a white solid. Recrystallization from *i*-Pr_2O/hexane (1:1) afforded an analytical sample of **27** as a white solid, mp 112–113°C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 3H, Ar*Me*), 3.32 (s, 6H, *Me*OCH_2×2), 3.49 (s, 3H, MeO), 3.56 (s, 3H, MeO), 4.97 (s, 4H, OCH_2O×2), 5.25 (s, 2H, OCH_2O), 6.70 (d, *J*=2.3 Hz, 1H, C_3–H or C_5–H), 7.09 (d, *J*=2.3 Hz, 1H, C_3–H or C_5–H), 10.12 (s, 1H, Ar*CH*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.71, 56.35, 56.51, 57.85 (two carbons), 94.31, 100.42 (two carbons), 103.84, 107.54, 121.82, 125.15 (two carbons), 134.00, 137.43, 138.77, 149.26 (two carbons), 160.30, 161.14, 172.42, 192.41; IR (KBr) 3452, 1683, 1630, 1594, 1459, 1371, 1300, 1276, 11160, 1082, 1019, 909 cm^{-1}; EI-MS (*m/z*) 504 [$(M+2)^+$], 502 (M^+), 413 [$(M-CHO-2×OMe+2H)^+$]; Anal. calcd for $C_{22}H_{24}Cl_2O_9$: C, 52.05; H, 4.81. Found: C, 51.90; H, 4.60.

4.1.20. Methyl 2-[2,6-bis(methoxymethoxy)-3,5-dichloro-4-methylbenzoyl]-3-methoxy-5-(methoxymethoxy)benzoate (29). Sodium hydrogenphosphate (140 mg, 0.90 mmol),

2-methyl-2-butene (233 μl, 2.2 mmol), and sodium chlorite (163 mg, 1.8 mmol) were sequentially added to a stirred solution of **27** (200 mg, 0.40 mmol) in THF/*t*-BuOH/H_2O (2:5:1) (8 ml) at room temperature. After 1 h, the reaction mixture was diluted with ethyl acetate (50 ml). The organic layer was washed with 5% aqueous $Na_2S_2O_3$ and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded the carboxylic acid **28** (202 mg), which was directly used for the next reaction without further purification. CH_2N_2 (0.8 M solution in Et_2O, 1.0 ml, 0.80 mmol) was added to a stirred solution of the crude carboxylic acid **28** (202 mg) in MeOH (3 ml) at room temperature. After 10 min, the reaction was quenched with AcOH (0.1 ml). The resulting mixture was diluted with Et_2O (50 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **29** (203 mg, 96%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.55 (s, 3H, Ar*Me*), 3.39 (s, 6H, *Me*OCH_2O×2), 3.48 (s, 3H, MeO), 3.53 (s, 3H, MeO), 3.88 (s, 3H, CO_2Me), 4.96 (s, 4H, MeOCH_2O×2), 5.21 (s, 2H, MeOCH_2O), 6.60 (d, J=2.1 Hz, 1H, C_3–H or C_5–H), 6.74 (d, J=2.1 Hz, 1H, C_3–H or C_5–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.68, 52.75, 56.32, 56.44, 57.76 (two carbons), 94.30, 100.66 (two carbons), 101.57, 108.42, 119.82, 125.24 (two carbons), 131.85, 137.05, 138.33, 149.13 (two carbons), 161.50, 161.90, 169.85, 187.83; IR (neat) 3649, 2951, 2831, 2361, 1778, 1734, 1655, 1597, 1456, 1373, 1329, 1240, 1215, 1157, 1067, 1040, 1015, 923 cm^{-1}; CI-MS (*m*/*z*) 533 [$(M+1)^+$], 501 [$(M-OMe)^+$]; HRCI-MS (*m*/*z*) calcd for $C_{23}H_{26}Cl_2O_{10}$ [$(MH)^+$]: 532.0901, found: 532.0901.

4.1.21. Methyl 2-[3,5-dichloro-2,6-dihydroxy-4-methylbenzoyl]-5-hydroxy-3-methoxybenzoate (4). A solution of **29** (45.1 mg, 85 μmol) and *p*-toluenesulfonic acid (15.7 mg, 91 μmol) in MeOH (5 ml) was refluxed for 4 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (40 ml). The organic layer was washed with brine, then dried over $MgSO_4$, Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (hexane/acetone, 1:1) to give **4** (26.6 mg, 81%) as a light yellow solid. Recrystallization from EtOAc/hexane (1:1) afforded an analytical sample of **4** as a light yellow powder, mp 227–230°C (decomposed); ^{1}H NMR (500 MHz, CD_3OD) δ 2.48 (s, 3H, Ar*Me*), 3.70 (s, 3H, OMe), 3.71 (s, 3H, OMe), 6.69 (d, J=2.1 Hz, 1H, C_4–H), 7.00 (d, J=2.1 Hz, 1H, C_6–H); ^{13}C NMR (125 MHz, CD_3OD) δ 17.48, 51.16, 55.08, 102.85, 107.48, 110.93, 112.20 (two carbons), 126.10, 128.35, 141.59, 155.41 (one or two carbons), 157.12 (one or two carbons), 158.58 (one or two carbons), 166.31, 200.70; IR (KBr) 3420, 3213, 2920, 1725, 1647, 1541, 1400, 1261, 1097 cm^{-1}; EI-MS (*m*/*z*) 402 [$(M+2)^+$], 400 (M^+), 368 [$(M-OMe-H)^+$], 339 [$(M-CO_2Me-2H)^+$]; Anal. calcd for $C_{17}H_{14}Cl_2O_7$: C, 50.89: H, 3.52. Found: C, 50.74; H, 3.56.

4.1.22. (±)-Geodin [(±)-(2)]. *(a) Method using DDQ* (entry 1 in Table 1). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (44.8 mg, 0.20 mmol) was added to a stirred solution of **4** (26.4 mg, 66 μmol) in CH_2Cl_2/EtOH (1:1) (2 ml). After 1 h, the reaction mixture was passed through silica gel (ethyl acetate). Concentration of the eluent in vacuo afforded a residue, which was purified by preparative TLC (hexane/ethyl acetate, 1:1) to give (±)-geodin [(±)-**2**] (15.1 mg, 57%) as a light yellow solid. Recrystallization from $CHCl_3/Et_2O$ (1:1) afforded an analytical sample of (±)-**2** as a light yellow powder, mp 247–249°C (lit.[5] 227–231°C for natural (+)-geodin [(+)-**2**]); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.58 (s, 3H, Ar*Me*), 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 5.82 (s, 1H, C_4–H), 7.15 (s, 1H, C_6–H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.58, 52.81, 57.34, 84.58, 103.58, 108.02, 118.42, 119.56, 135.61, 139.10, 141.60, 163.08, 163.63, 165.91, 170.07, 185.03, 188.97; IR (KBr) 3434, 2924, 1720, 1655, 1610, 1522, 1458, 1335, 1233 cm^{-1}; EI-MS (*m*/*z*): 400 [$(M+2)^+$], 398 (M^+), 339 [$(M-CO_2Me)^+$], HREIMS (*m*/*z*) calcd for $C_{17}H_{12}Cl_2O_7$ (M^+): 397.9960. Found: 397.9956. The ^{1}H NMR spectrum of this sample was identical with that reported for natural (+)-geodin [(+)-(**2**)].[9a]

(b) Method using PIFA (entry 5 in Table 1). Phenyliodine(III) bis(trifluoroacetate) (PIFA), (24.6 mg, 57 μmol) was added to a stirred solution of **4** (20.8 mg, 52 μmol) in MeCN (1.6 ml) at room temperature. After 10 min, the reaction mixture was passed through silica gel (ethyl acetate). Concentration of the eluent in vacuo afforded a residue, which was purified by preparative TLC (hexane/ethyl acetate, 1:1) to give (±)-geodin [(±)-**2**] (8.3 mg, 40%) as a light yellow solid. The IR, ^{1}H NMR (250 MHz), mass spectra of this sample were identical with those recorded in (a).

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