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Tetrahedron 59 (2003) 7345–7355

TETRAHEDRON

Synthetic analogues of the antibiotic pestalone

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Received 2 June 2003; revised 22 July 2003; accepted 22 July 2003

Abstract—The first synthetic study towards the natural product pestalone (**1**) is described culminating in the preparation of selected $n-1$ analogues. Pestalone is a chlorinated and prenylated benzophenone antibiotic, which is of interest due to a strong activity against methicillin-resistant *staphylococcus aureus* strains (MRSA). Key step of the synthesis is the nucleophilic addition of a highly functionalized aryllithium building block to a 2-prenylated 3,5-dialkoxy-benzaldehyde followed by oxidation. For the introduction of the prenyl sidechain by aryl-allyl coupling, different procedures were evaluated, among them the Stille reaction and a nickel π-allyl complex coupling.

1. Introduction

Today several classes of antibiotics are clinically used to fight infectious diseases, for example the β-lactames, glycopeptides, tetracyclines, macrolides, rifamycines and quinolones. However, due to the emergence of resistance to antimicrobial agents[1] and the fact that time for resistance to develop against new drugs if often short, the search for new antibiotics[2] remains an important goal for medicinal chemistry. Especially the introduction of completely new classes of antibiotics (for example the oxazolidinone linezolid[3]) are important. Recently, Fenical and coworkers discovered a new marine natural product, the prenylated and chlorinated tetra-*ortho*-substituted benzophenone[4] pestalone[5] (**1**) (Fig. 1). Pestalone showed potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MIC=37 ng/mL) and vancomycin-resistant *Enterococcus faecium* (MIC=78 ng/mL). Thus, pestalone was recommended to be evaluated in advanced animal models of infectious diseases. Pestalone was obtained from the mixed fermentation of a marine derived deuteromycete of the genus *Pestalotia* together with a marine bacterium. The structure of **1** was established by NMR analysis and X-ray diffraction. The new compound shows a structure which significantly differs to that of other natural products,[6] mostly because the two rings have a substitution pattern different from each other. While the aromatic ring B with its dichloroorcine structure shows similarities with the fungal metabolites geodin and erdin[7] and many lichen xanthones,[8] the A-ring of the benzophenone with its prenyl and formyl *o*-substituents is somewhat related to fungal and plant-derived benzophenones[9] and xanthones. Among the family of the benzophenone natural products, the tetra-*ortho*-substituted benzophenones form only a small subgroup, with the PKA inhibitor balanol[10] and the G6Pase inhibitor mumbaistatin[11] being the most prominent members. As known for other natural benzophenones, it can be assumed that pestalone is biosynthetically derived from oxidative cleavage of a corresponding anthracenone generated by either a mixed shikimate-acetate or a pure polyketide pathway with subsequent prenylation and chlorination.

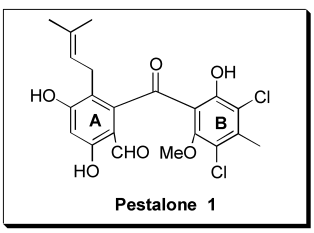

Figure 1. Structure of pestalalone (**1**).

The biological activity of pestalone (**1**) makes it an interesting target for total synthesis. A short and flexible synthetic approach to this new antibiotic lead structure would also pave the way for the synthesis of (possibly simplified) analogs, which could then be screened in order to study structure activity relationships and possibly to identify new useful antimicrobials.

Despite the seemingly simple appearance (pestalone carries no stereochemical information and has a molecular weight of only 440), pestalone (**1**) features several challenging structural elements, namely the densely functionalized aromatic core (11 out of the 12 aromatic carbons are

Keywords: pestalone; benzophenones; antibiotics; synthesis; natural products.
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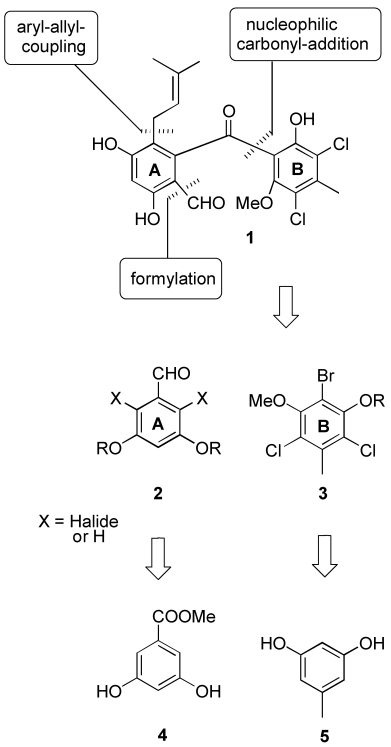
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)01136-0



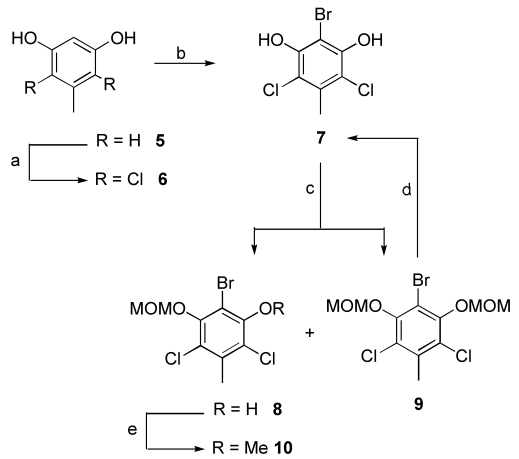
Scheme 1. Retrosynthetic analysis for pestalone and simplified analogs.

substituted), the possible acid-labile *o*-prenylphenol-substructure and, most importantly, the sterically crowded benzophenone. Beside the anionic homo-Fries rearrangement,[12] the nucleophilic carbonyl-addition of a lithiated arene to a benzaldehyde followed by oxidation is the most important method for the setup of such hindered benzophenones.[13] For our synthetic study towards pestalone and analogs we intended to utilize the latter method (Scheme 1) by reacting a benzaldehyde of type **2** with an aryllithium-nucleophile generated from a bromide **3**. The attachment of the prenyl sidechain should be achieved by an organometallic reaction, using either alkylation of an aryl cuprate, a Pd-catalyzed Stille cross- coupling or, alternatively, a nickel-(π-allyl) complex as a coupling reagent.

The final CC bond connection, i.e. the introduction of the formyl group, could possibly be achieved by an electrophilic aromatic substitution reaction (Vilsmeier or a related formylation) in a late stage of the synthesis; this would be especially attractive due to the fact that the key nucleophilic coupling of the two aromatic segments would be facilitated with only three *ortho*-substituents. Alternatively, an anionic formylation or Pd-catalyzed carbonylation starting from a suitable benzophenone halide could be considered. In the beginning of the project, the order and the exact timing for the three CC bond formations was not obvious. In any case, the two aromatic building blocks should be prepared from the (commercial) symmetric resorcine derivatives **4** and **5**.

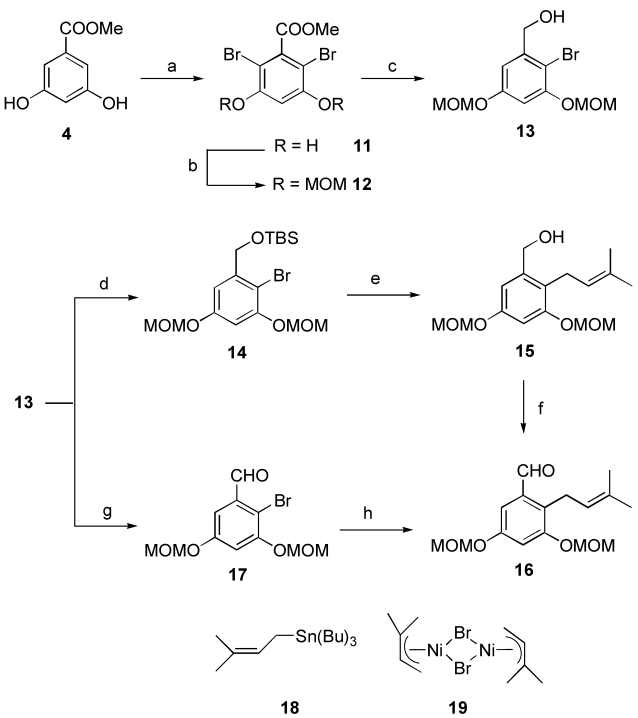
2. Results and discussion

Our approach started with the preparation of suitable functionalized aromatic building blocks for the anticipated



Scheme 2. Synthesis of the B-ring building block (a) $SOCl_2$, $CHCl_3/CH_3CN$ 5:1, rt, 3 h, 90%; (b) Br_2, CH_3CN, 0°C, 3 h, 99%; (c) DIPEA, MOMCl, CH_2Cl_2, rt, overnight, 46% of **9**, 31% of **8**; (d) 6N HCl, THF, rt, 12 h, 99%; (e) NaH, Me_2SO_4, DMF, rt, overnight, 97%.

benzophenone coupling. The preparation of the B-ring precursor **10** (Scheme 2) began with the literature-known double chlorination of orcinol **5** using sulfuryl chloride.[14] Optimization of the solvent system greatly increased the selectivity of the reaction, and in a 5:1 mixture of chloroform/acetonitrile, dichlororcinol **6** was obtained in 90% yield. Subsequent bromination of the last free aromatic position using bromine in acetonitrile gave the bromide **7**[15] almost quantitatively. The following desymmetrisation by mono-protection of the diphenol gave mono MOM-protected **8** only in 31% together with 46% of the



Scheme 3. Synthesis of the A-ring building block (a) Br_2, $CHCl_3/CH_3CN$ 6:1, rt, 5 h, 96%; (b) DIPEA, MOMCl, CH_3CN, rt, overnight, 95%; (c) $LiAlH_4$, THF, rt, 24 h, 91%; (d) imidazole, DMAP, TBSCl, CH_2Cl_2, rt, overnight, 87%; (e) (i) *t*-BuLi, THF, −78°C, (ii) CuCN·2LiCl, −15°C, 1 h, (iii) prenyl bromide, HMPT, −78°C rt, overnight, (iv) TBAF, THF, rt, 8 h, 60% (2 steps); (f) IBX, DMSO, rt, 5 h, 91%; (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78°C rt, overnight, 95%; (h) see Table 1.

Table 1. Introduction of the prenyl sidechain via Pd- or Ni-mediated coupling reactions (Scheme 3)

Entry	Complex	Reaction conditions	Yield
1	**18**	$Pd(Ph)_4$ (0.1 equiv.), CsF, DMF, 70°C, 20 h	22%
2	**18**	Pd_2dba_3 (0.05 equiv.), $As(Ph)_3$ (0.2 equiv.), CsF, NMO, 70°C, 20 h	40%
3	**18**	Pd_2dba_3 (0.05 equiv.), $As(Ph)_3$ (0.2 equiv.), CsF, NMO, 20°C, 48 h	38%
4	**18**	Pd_2dba_3 (0.05 equiv.), $P(tBu)_3$ (0.2 equiv.), CsF, NMO, 70°C, 20 h	68%
5	**19**	**19** (3 equiv.), DMF, 50°C, 10 h	35%
6	**19**	**19** (3 equiv.), benzene, $h\nu$, *N*-methy-limidazole, 20°C, 20 h	Traces

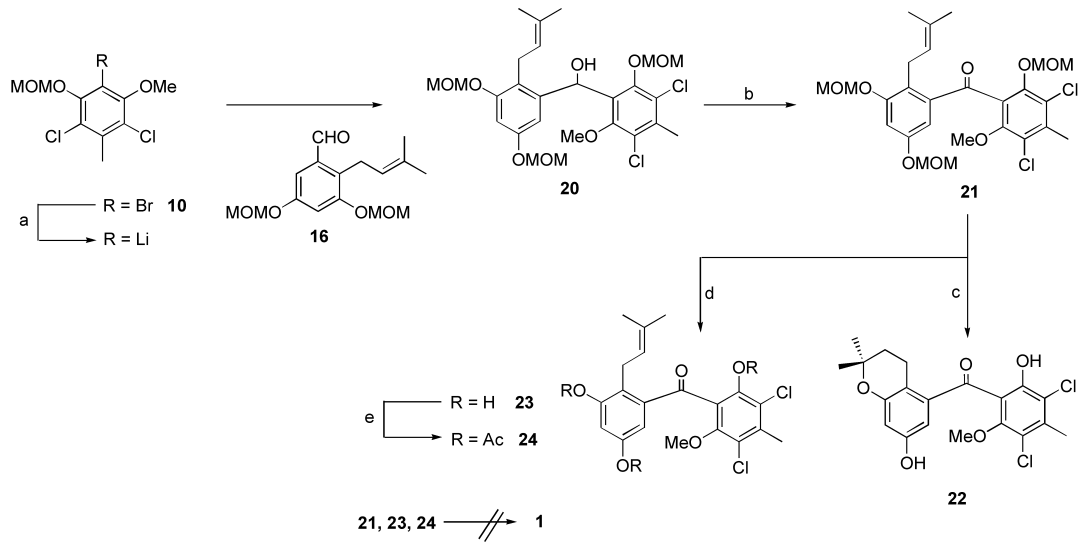
di-alkylated compound **9**. However, due to the fact that **9** and all mixture fractions could be quantitatively recycled by deprotection using 6N HCl in THF, the yield of **8** based on recovered starting material was almost 85%.

The synthesis of the B-ring building block **10** was completed by methylation of the remaining phenolic OH-group of **8** using NaH/dimethyl sulfate (97% yield).

The synthesis of the anticipated A-ring benzaldehydes of type **2** is shown in Scheme 3. Double halogenation of 3,5-dihydroxymethyl benzoate **4** using bromine in acetonitrile/chloroform gave the symmetric bromide **11**. After MOM-protection of the two phenolic OH groups, treatment of the *o*,*o*-dibromoester **12** with an excess of $LiAlH_4$ led to ester reduction under simultaneous loss of one of the halides and cleanly gave the benzylic alcohol **13**.[16] Compound **13** was the starting point for the preparation of prenylated benzaldehyde **16**.

One part of the synthetic project was to test and compare common methods for the introduction of isoprenoid allyl-sidechains (like the dimethylallyl group in pestalone) onto the aromatic nucleus.[17] In a first approach, the benzylic alcohol **13** was protected (TBSCl, imidazole, DMAP, 87% yield) to give the silyl ether **14**.[18] After bromine–lithium exchange using *t*-BuLi followed by transmetallation with CuCN·2LiCl,[19] the resulting cuprate was treated with prenylbromide to afford the allylated product, which was directly desilylated (TBAF) to give the *o*-prenylbenzylic alcohol **15** in 60% yield (two steps).[20] Subsequent IBX-oxidation[21] furnished the benzaldehyde **16** (Scheme 3).

A different procedure for aromatic prenylation, which has become popular in the recent past, is the Pd-catalyzed Stille cross-coupling[22,23] of a prenylstannane with an aryl-halide. In contrast to most other allylmetallic reagents, the 3,3-disubstituted allylstannanes tend to react without allylic inversion or rearrangement in coupling reactions. First, alcohol **13** was oxidized to the corresponding benzaldehyde **17** under Swern conditions[24] in order to reduce the electron-richness of the arylbromide for the following coupling reaction. The Stille reaction between **17** and prenyl tributyltin (**18**)[25] was attempted under various conditions (Table 1). Soon it became obvious that the anticipated cross coupling between the *o*,*o*-disubstituted bromide and the tin reagent proceeds only sluggishly and was hampered by long reaction times and unproductive side reactions. While $PdCl_2$dppf, $Pd(Ph)_4$ or $PdCl_2/P(o\text{-tol})_3$ proved to be less successful (in terms of conversion and the ratio of coupling product vs. debromination), $Pd_2dba_3/As(Ph)_3$[26] in NMO or DMF gave the coupling product **16**, albeit only in a moderate yield of 40% due to partial degradation, regardless if the reaction was run for 48 h at rt or 20 h at 70°C. CsF was added as promoter in all the reactions. Application of Fu's catalyst system ($Pd_2dba_3/P(tBu)_3$)[27] gave an improved yield of 68% (NMO, 20 h for 70°C). Interestingly, when Fu's catalyst was employed at rt, the dehalogenated product was obtained almost exclusively. Last, we examined the coupling of bromide **17** with the π-allyl nickel bromide



Scheme 4. Synthesis of the pestalone analogues **22**–**24** (a) (i) **10**, *n*-BuLi, THF, −78°C, (ii) **16**, THF, −78°C rt, overnight, 86%; (b) DMP, CH_2Cl_2, rt, 3 h, 88%; (c) *p*-TsOH, MeOH, 60°C, 3 h, 50%; (d) CSA, MeOH, rt, 24 h, 91%; (e) Ac_2O, pyridine, rt, overnight, 90%.

complex **19**.[28,29] This complex was prepared in situ from prenyl bromide and $Ni(COD)_2$ and used without isolation. Coupling under the standard conditions (stirring for 24 h at 60°C in DMF) gave the prenylated product **16** only in 35% yield, while the Schugar-modification[30] for the nickel-promoted allylation (irridation, use of *N*-methylimidazole as a ligand in a non-coordinating solvent like benzene) produced only traces of the product. In summary, the Stille coupling came out to be the method of choice for the preparation of the prenylated benzaldehyde **16**, which was synthesized in five steps and an overall yield of more than 50% (Scheme 3).

With both the benzaldehyde **16** and the aryl bromide **10** in our hands, we next focused on the anticipated nucleophilic coupling to form the sterically hindered benzophenone. Bromine–lithium exchange of **10** employing *n*-BuLi at −78°C followed by reaction with **16** at −78°C→rt cleanly gave the benzhydrol **20** in 86% yield (Scheme 4). Subsequent oxidation employing the Dess–Martin periodinane[31] (88% yield) or, alternatively, Jones-reagent[32] (87% yield) furnished the benzophenone **21**. As foreseen, the following deprotection turned out to be challenging: The use of reagents like 6N HCl, TMSBr or BF_3 only resulted in decomposition or crude product mixtures. Heating of **21** together with *p*-toluenesulphonic acid in methanol produced the chromane **22**. Under the acidic conditions, complete deprotection had occured with concomitant cyclization of the *o*-prenylphenol system.[33] In contrast, use of campfor-sulfonic acid in methanol at rt[33b] gave the corresponding prenyl-benzophenone **23** (deformyl-pestalone).

Our attempts to prepare the natural product itself from the deformyl derivative **23** were not successful, so far. The anticipated introduction of the formyl group by a S_EAr reaction failed under a variety of conditions: The classical Vilsmeier formylation,[34] dichloro-methylation using $TiCl_4$ or $SnCl_4/CHCl_2OMe$,[35] or the Casiraghi formylation[36] only resulted in either no conversion of **23** or complete decomposition of the starting material at higher temperatures. Likewise, formylation attempts employing the MOM-protected derivative **21** or the acetylated compound **24** did not lead to success.

3. Conclusion

In this article, we described the first synthetic studies towards the highly substituted benzophenone antibiotic pestalone. While having elaborated an efficient access to deformyl-derivatives thus demonstrating the power of the selected approach, we could identify the final formylation as a surprisingly difficult task. Nevertheless, a series of selected $n-1$ analogues of the natural product have been synthesized, which will be used for preliminary SAR studies.

To open an entry to the natural product itself (and other *o*-formylated benzophenone derivatives), prenylated benzaldehydes of type **16** bearing a second *o*-substituent, either a protected benzylic alcohol, an ester or, alternatively, a halide may be used as building blocks in the central carbonyl addition step. The extension of the approach described herein towards the synthesis of further analogs and the natural product itself is a subject of current investigations in these laboratories.

4. Experimental

4.1. General information

Melting points (Mp) were determined in open capillary tubes measured on a Büchi Melting Point B-545 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker 250, 300 or 500 MHz instruments and are referenced to the non-deuterated impurities of the used solvents ($CDCl_3$, CD_3OD, d_6-DMSO) as internal standard. The spectra are reported in ppm using the following abbreviations to express the multiplicities: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; b=broad. ^{13}C chemical shifts were determined using ^1H-decouplet spectra, the number of protons bound directly was determined employing the DEPT sequence (q=CH_3; t=CH_2; d=CH; s=quarternary carbon) Some of the assignments are based on 2-dimensional spectra additionally recorded. IR-spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer using the ATR-technique. Gas-chromatography (GC) and low-resolution mass spectra (EI, 70 eV) were recorded on an Agilent HP 6890 GC-MS system using an Optima 1 MS column with H_2 as carrier-gas (flow 10 psi). Temperature programs are presented as following: starting temperature$_{\text{length of stay [min]}}$→[°C/min]→end temperature$_{\text{length of stay [min]}}$. Given are the retention times and the purities calculated from the uncorrected FID-integrations. High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 900S (ESI). Analytical thin-layer chromatography (TLC) was performed on silica coated alumina plates. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Reagents were supplied by Aldrich, Merck, Fluka, Acros and Chemetall and were used without further purification unless otherwise noted. THF and toluene were freshly distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2. Other solvents (acetonitrile, benzene, hexane, DMF, DMSO) were purchased in HPLC-pure quality and stored under argon over molecular sieves. Bulk solvents for chromatography and extraction, such as ethyl acetate, cyclohexane, dichloromethane and methyl *tert*butyl ether (MTBE), were distilled prior to use. All reactions with organometallic reagents were carried out under a positive atmosphere of dry argon in oven-dried glassware by using Schlenk techniques. Solvents and solutions were added with syringes through rubber septa.

4.1.1. 2,6-Dichloro-3,5-dihydroxytoluene (6). 12.41 g (100 mmol) of orcinol **5** was dissolved in a mixture of 450 mL of chloroform and 100 mL of acetonitrile. At 0°C a solution of 16.2 mL (200 mmol) of sulfuryl chloride in 50 mL of chloroform was added dropwise over 30 min. After stirring for further 3 h at rt, 50 mL of a 1 M aqueous solution of NaOH was added. After stirring for 15 min, the mixture was acidified with 200 mL of 1 M aqueous HCl, and the phases were separated. The aqueous layer was extracted with dichloromethane (3×200 mL). The combined

organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue, a white-yellow solid, was purified by flash chromatography (400 g of silica, cyclohexane/ethyl acetate 4:1) to give 17.37 g (90 mmol, 90%) of dichlororcinol **6** as a white crystalline solid. The compound showed analytical data in accordance to those described in literature.[13d] Mp: 170°C (lit. 170.5–171°C). TLC (cyclohexane/ethyl acetate 5:1) R_f=0.18. ^{1}H NMR (250 MHz, d_6-DMSO): δ [ppm]=2.33 (s, 3H, C7), 3.39 (br s, 2H, OH), 6.55 (s, 1H, C4). ^{13}C NMR (63 MHz, d_6-DMSO): δ [ppm]=17.7 (q, C7), 101.6 (d, C4), 111.1 (s, C2/C6), 134.4 (s, C1), 152.1 (s, C3/C5). HR-MS (EI): calcd 191.9745 for $C_7H_6O_2Cl_2$, found 191.975. Anal. calcd for $C_7H_6O_2Cl_2$: C 43.56; H 3.13; found: C 43.60; H 3.14.

4.1.2. 2,6-Dichloro-4-bromo-3,5-dihydroxytoluene (7). 8.98 g (46.5 mmol) of **6** was dissolved in 300 mL of acetonitrile. At 0°C a solution of 2.5 mL (48.8 mmol) of bromine in 50 mL of acetonitrile was added dropwise over a period of 30 min, and the resulting mixture was stirred for 2 h at 0°C. After full conversion was ensured by GC-analysis, 200 mL of a saturated $Na_2S_2O_3$ solution was added. After addition of 100 mL of ethyl acetate and subsequent phase separation, the aqueous layer was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solution was concentrated to 100 mL and passed through a pad of silica. After evaporation of the solvent, the resulting fawn solid was washed with hexane and dried in vacuo to give 12.517 g (46 mmol, 99%) of bromine **7** as a white crystalline solid. The compound showed analytical data in accordance to those described in literature.[13d] Mp: 107°C (lit. 107–108°C). TLC (cyclohexane/dichloromethane 1:1) R_f=0.25. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3570 (m), 3470 (s), 3270 (br, m), 1724 (w), 1613 (w), 1575 (m), 1444 (s), 1425 (s), 1404 (s), 1362 (m), 1309 (s), 1206 (s), 1086 (s), 1017 (w), 739 (s), 713 (m), 662 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm]=2.35 (s, 3H, C7), 9.85 (br s, OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm]=18.2 (q, C7), 100.1 (s, C4), 113.5 (s, C2, C6), 133.1 (s, C1), 149.5 (s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.95 min, 96% purity. MS (EI): (the peaks showed the typical isotopic pattern of a monobromo-dichloro compound) 274 (46, [M]$^+$), 272 (100, [M]$^+$), 270 (61, [M]$^+$), 254 (4, [M−H_2O]$^+$), 239 (14, [M−Cl]$^+$), 237 (57, [M−Cl]$^+$), 235 (44, [M−Cl]$^+$), 219 (4, [M−Cl−H_2O]$^+$), 207 (3), 192 (9, [M−Br]$^+$), 179 (3), 157 (8, [M−Br−Cl]$^+$), 145 (6), 127 (8), 99 (10), 87 (8), 73 (10), 63 (15), 51 (6), 39 (7). HR-MS (EI): calcd 269.8850 for $C_7H_5O_2BrCl_2$, found 269.885. Anal. calcd for $C_7H_5O_2BrCl_2$ C 30.92; H 1.85; found: C 30.74; H 1.90.

4.1.3. 2,6-Dichloro-4-bromo-3-methoxymethoxy-5-hydroxytoluene (8) and 2,6-dichloro-4-bromo-3,5-dimethoxymethoxytoluene (9). 21.91 g (80.5 mmol) of **7** was dissolved in 600 mL of dry dichloromethane under argon. At 0°C 18.3 mL (105 mmol) of diisopropylethylamine (DIPEA) was added. After 30 min 8.6 mL (113 mmol) of MOMCl [CAUTION: Due to the carcinogenity of MOMCl all operations involving this reagent should be performed in a well working fume hood!] was added, and the solution was stirred overnight at rt. After addition of 200 mL of a saturated NH_4Cl solution, the phases were separated, and the aqueous layer was extracted with dichloromethane (3×200 mL). The combined organic layers were washed with a saturated $CuSO_4$ solution and brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting brown oil was purified by flash chromatography to give 13.34 g (37 mmol, 46%) of 2,6-dichloro-4-bromo-3,5-dimethoxymethoxytoluene (**9**) as a white-yellow crystalline solid and 7.89 g (25 mmol, 31%) of 2,6-dichloro-4-bromo-3-methoxymethoxy-5-hydroxy-toluene (**8**) as a white crystalline solid. Analytical data of **9**. Mp: 86–88°C. TLC (cyclohexane/dichloromethane 1:1) R_f=0.3. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2951 (w), 2826 (w), 1446 (w), 1414 (m), 1368 (s), 1328 (w), 1209 (m), 1159 (s), 1096 (m), 1042 (s), 1008 (s), 897 (s), 763 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm]=2.45 (s, 3H, H at C7), 3.67 (s, 2×3H, CH_3 of C3-OMOM, C5-OMOM), 5.12 (s, 2×2H, CH_2 of C3-OMOM, C5-OMOM). ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm]=18.5 (q, C7), 58.5 (q, CH_3 of C3-OMOM, C5-OMOM), 99.4 (t, CH_2 of C3-OMOM, C5-OMOM), 112.6 (s, C4), 125.9 (s, C2, C6), 135.6 (s, C1), 150.0 (s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.94 min, 95% purity. MS (EI): (the peaks showed the typical isotopic pattern of a momobromo-dichloro compound) 360 (8, [M$^+$]), 329 (1–2, [M−OCH_3]$^+$), 300 (2), 191 (5), 145 (5), 111 (3), 87 (3), 75 (6), 63 (4), 45 (100). HR-MS (EI): calcd 357.9374 for $C_{11}H_{13}O_4BrCl_2$, found 357.937. Analytical data of **8**. Mp: 110–112°C. TLC (cyclohexane/dichloromethane 1:1) R_f=0.1. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3336 (br, s), 2978 (w), 1558 (m), 1452 (m), 1432 (s), 1388 (s), 1347 (s), 1276 (s), 1205 (s), 1157 (s), 1099 (m), 1076 (s), 1017 (m), 934 (s), 913 (s), 753 (s), 733 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm]= 2.43 (s, 3H, H at C7), 3.69 (s, 3H, CH_3 of C3-OMOM), 5.14 (s, 2H, CH_2 of C3-OMOM), 6.00 (s, 1H, C5-OH). ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm]=18.2 (q, C7), 58.4 (q, CH_3 of C3-OMOM), 99.6 (t, CH_2 of C3-OMOM), 104.1 (s, C4), 117.3, 121.2 (each s, C3, C5), 134.9 (s, C1), 148.1, 149.8 (each s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.44 min, 95% purity. MS (EI): (the peaks showed the typical isotopic pattern of a momobromo-dichloro compound) 316 (19, [M]$^+$), 286 (7), 272 (4), 243 (5), 206 (3), 179 (5), 162 (6), 127 (5), 111 (5), 87 (5), 63 (7), 45 (100). HR-MS (EI): calcd 313.9112 for $C_9H_9O_3BrCl_2$, found 313.911.

4.2. Recovery of 2,6-dichloro-4-bromo-3,5-dihydroxytoluene (7) from 2,6-dichloro-4-bromo-3,5-dimethoxymethoxytoluene (9)

15.83 g (44 mmol) of **9** was dissolved in 200 mL of THF. 50 mL of a 6N HCl solution was added, and the resulting solution was stirred for 12 h at rt. After addition of each 100 mL of water and ethyl acetate the phases were separated. The aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After the solution was passed through a pad of silica, the solvent was evaporated to give 11.85 g (43.6 mmol, 99%) of **7** as a white solid which was free of impurities (GC, ^{1}H NMR).

4.2.1. 2,6-Dichloro-4-bromo-3-methoxymethoxy-5-methoxytoluene (10). 1.19 g of a 60% dispersion of sodium

hydride in oil were placed in a flask under argon. After washing with dry hexane, the NaH was suspended in 60 mL of dry DMF. The cooled (0°C) suspension was slowly treated with a solution of 7.12 g (22.8 mmol) of phenol **8** in 40 mL of dry DMF. After the emission of hydrogen had ceased, the mixture was stirred for 1 h at rt. The cooled (0°C) reaction mixture was treated with 4.3 mL (45.6 mmol) of dimethylsulfate. Stirring was continued overnight at rt, before 200 mL of an ice cold NH_4Cl solution was added. The mixture was extracted with MTBE (4×100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash-chromatography (200 g of silica, cyclohexane/ethyl acetate 15:1) to give 7.39 g (22.2 mmol, 97%) of **10** as a white solid with a low melting point. Mp: 20–25°C. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.2. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2931 (m), 1542 (w), 1448 (m), 1412 (m), 1369 (s), 1328 (m), 1209 (m), 1159 (s), 1067 (s), 1011 (s), 945 (s), 901 (s), 756 (m), 713 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=2.45 (s, 3H, H an C7), 3.69 (s, 3H, CH_3 of C3-OMOM), 3.85 (s, 3H, CH_3 at C5-OMe), 5.13 (s, 2H, CH_2 of C3-OMOM). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=18.3 (q, C7), 58.4 (q, *C*H_3 of C3-OMOM), 60.5 (q, *C*H_3 of C5-OMe), 99.6 (t, *C*H_2 of C3-OMOM), 112.2 s, C4), 125.7, 125.9 (each s, C2, C6), 135.6 (s, C1), 150.0, 152.7 (each s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.3 min, 96% purity. MS (EI): (the peaks showed the typical isotopic pattern of a momobromo-dichloro compound) 330 (12, $[M]^+$), 300 (8), 285 (2), 257 (4), 242 (4), 189 (3), 133 (3), 111 (3), 75 (3), 45 (100). HR-MS (EI): calcd 327.9268 for $C_{10}H_{11}O_3BrCl_2$, found 327.927. Anal. calcd for $C_{10}H_{11}O_3BrCl_2$: C 36.40; H 3.36; found: C 36.15; H 3.34.

4.2.2. 2,6-Dibromo-3,5-dihydroxymethyl benzoate (11). 16.82 g (100 mmol) of 3,5-dihydroxymethyl benzoate (**4**) was dissolved in 800 mL of 6:1 mixture of chloroform and acetonitrile. At rt a solution of 11 mL (215 mmol) of bromine in 50 mL of chloroform was added dropwise over 30 min, and the resulting solution was stirred for 5 h at rt. After addition of 200 mL of a saturated $Na_2S_2O_3$ solution the phases were separated. The aqueous layer was extracted with dichloromethane (3×200 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in 100 mL of ethyl acetate and filtrated through a pad of silica. The solvent was evaporated to give a yellow oil, which crystallized overnight at 4°C. 31.26 g (97 mmol, 97%) of **11** were obtained as an ocher solid. Mp: 93–94°C. TLC (cyclohexane/ethyl acetate 2:1) R_f=0.15. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3386 (br, s), 2951 (m), 2842 (m), 2709 (m), 2618 (m), 2358 (w), 2339 (w), 2291 (w), 2258 (m), 2141 (w), 1715 (s), 1651 (m), 1579 (s), 1539 (m), 1525 (m), 1512 (m), 1461 (s), 1425 (s), 1368 (s), 1249 (s), 1049 (s), 993 (s), 902 (m), 844 (s), 768 (s), 721 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=3.96 (s, 3H, CH_3 of C7-OMe), 6.73 (s, 1H, H at C4). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=53.3 (q, C8), 98.6 (s, C2, C6), 104.1 (d, C4), 137.0 (s, C1), 153.2 (s, C3, C5), 166.2 (s, C7). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=10.36 min, 99% purity. MS (EI): (the peaks showed the typical isotopic pattern of a dibromo compound) 328 (43, $[M]^+$), 326 (88, $[M]^+$), 324 (47, $[M]^+$), 297 (50, $[M-OCH_3]^+$), 295 (100), 293 (54), 267 (11, $[M-COOCH_3]^+$), 246 (10, $[M-Br]^+$), 230 (6), 215 (19), 188 (25), 186 (25), 168 (9), 160 (8), 137 (12), 129 (11), 123 (4), 109 (5), 93 (4), 78 (8), 69 (25), 62 (5), 50 (20). HR-MS (EI): calcd 326.8646 for $C_8H_6O_4Br_2$, found 326.864. Anal. calcd for $C_8H_6O_4Br_2$: C 29.48; H 1.86; found: C 29.36; H 1.88.

4.2.3. 2,6-Dibromo-3,5-dimethoxymethoxymethyl benzoate (12). 34.00 g (104 mmol) of **11** was dissolved in each 250 mL of dichloromethane and acetonitrile under argon. The solution was cooled to 0°C, and 54.5 mL (312 mmol) of diisopropyl-ethylamine was added dropwise via syringe. After 30 min 24.7 mL (325 mmol) of MOMCl [CAUTION: Due to the carcinogenity of MOMCl all operations involving this reagent should be performed in a well working fume hood!] was added via syringe, and the resulting solution was stirred at rt overnight. After addition of 200 mL of saturated NH_4Cl solution the flask was opened and the mixture was stirred for 1 h. After phase separation the aqueous layer was extracted with ethyl acetate (3×200 mL). After concentration, the combined organic layer was washed with K_2CO_3 solution and brine and dried over $MgSO_4$. The solution was passed through a pad of silica, and the solvent was evaporated to give 40.70 g (98.3 mmol, 95%) of a yellow oil which solidified upon standing. Mp: 62–63°C. TLC (cyclohexane/dichloromethane 1:2) R_f=0.15. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2950 (m), 1737 (s), 1571 (s), 1434 (s), 1397 (m), 1324 (s), 1220 (s), 1149 (s), 1087 (s), 1009 (s), 957 (s), 918 (s), 876 (s), 788 (m), 700 (m). ^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm]=3.47 (s, 2×3H, CH_3 of C3-OMOM, C5-OMOM), 3.96 (s, 3H, CH_3 of C7 (O)OMe), 5.21 (s, 2×2H, CH_2 of C3-OMOM, C5-OMOM), 7.04 (s, H at C4). ^{13}C NMR (63 MHz, $CDCl_3$): δ [ppm]=53.1 (q, CH_3 of C7OOMe), 56.6 (q, 2C, CH_3 of C3-OMOM, C5-OMOM), 95.4 (t, 2C, CH_2 of C3-OMOM, C5-OMOM), 102.4 (s, 2C, C2, C6), 104.7 (d, C4), 139.2 (s, C1), 153.9 (s, 2C, C3, C5), 166.4 (s, C7). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=11.78 min, 96% purity. MS (EI): (the peaks showed the typical isotopic pattern of a dibromo compound) 414 (13, $[M]^+$), 383 (5, $[M-OCH_3]^+$), 354 (2), 336 (3), 29 (3), 140 (4), 77 (3), 61 (3), 45 (100). HR-MS (EI): calcd 413.9137 for $C_{12}H_{14}O_6Br_2$, found 413.914.

4.2.4. 2-Bromo-3,5-dimethoxymethoxybenzylic alcohol (13). 4.74 g (125 mmol) of $LiAlH_4$ was suspended in 400 mL of dry THF under argon. At 0°C a solution of 20.675 g (50 mmol) of the ester **12** in 100 mL of dry THF was added slowly via syringe. The resulting mixture was stirred for 20 h. The flask was cooled to 0°C, and acetone was added carefully to destroy the excess of $LiAlH_4$, followed by addition of 200 mL of a 10% NaOH solution. After filtration of the mixture through a sintered funnel and addition of ethyl acetate, the phases were separated. The aqueous layer was extracted with ethyl acetate (3×200 mL). The combined organic layers were concentrated, washed with brine and dried over $MgSO_4$. The solution was passed through a pad of silica, and the solvent was evaporated to give 14.05 g (46 mmol, 91%) of the bromo benzylic alcohol **13** as a white solid. The compound showed analytical data in accordance to those described in literature.[16] Mp: 62–63°C. TLC (cyclohexane/ethyl acetate 2:1) R_f=0.3. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3405 (br, s), 2903 (s), 2824 (s), 1585 (s), 1447 (s),

1396 (s), 1356 (s), 1315 (s), 1211 (s), 1150 (s), 1083 (s), 844 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=3.44, 3.49 (each s, 3H, CH_3 of C3-OMOM, C5-OMOM), 4.68 (s, 2H, H at C7), 5.13, 5.20 (each s, 2H, CH_2 of C3-OMOM, C5-OMOM), 6.77 (d, 1H, ^4J=3 Hz, C3 or C5), 6.88 (d, 1H, ^4J=3 Hz, C3 or C5). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]= 56.6, 56.9 (each q, CH_3 of C3-OMOM, C5-OMOM), 65.6 (t, C7), 94.9, 95.6 (each t, CH_2 of C3-OMOM, C5-OMOM), 104.5 (d, C4 o. C6), 105.2 (s, C2), 109.7 (d, C4 o. C6), 142.3 (s, C1), 154.8, 157.7 (each s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.82 min, 99% purity. MS (EI): 308/306 (13/12, $[M]^+$), 276/278 (3), 246/248 (4), 232 (2), 212 (3), 77 (4), 63 (5), 45 (100). HR-MS (EI): calcd 306.0103 for $C_{11}H_{15}O_5Br$, found 306.011.

4.2.5. 2-Bromo-1-[(*tert*-butyldimethylsilyl)oxymethyl]-3,5-dimethoxy-methoxybenzene (14). 5.49 g (17.8 mmol) of the alcohol **13** was dissolved in 180 mL of dry dichloromethane under argon. After addition of 6.079 g (89.3 mmol) of imidazole and 110 mg (0.9 mmol) of DMAP, the resulting solution was cooled to 0°C. 5.381 g (35.7 mmol) of TBSCl was added in portions over a period of 30 min. The milky reaction mixture was stirred at rt overnight. After addition of 50 mL of a saturated NH_4Cl solution the layers were separated. The aqueous layer was extracted with dichloromethane (3×100 mL). The combined organic layer was washed with a saturated $CuSO_4$ solution and brine and dried over $MgSO_4$. After evaporation of the solvent, the residue, a yellow oil, was purified by flash-chromatography (300 g of silica, cyclohexane/ethyl acetate 10:1) to give 6.53 g (15.5 mmol, 87%) of the silylated alcohol **14** as a white solid. The compound showed analytical data in accordance to those described in literature.[18] TLC (cyclohexane/ethyl acetate 10:1) R_f=0.3. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2948 (s), 2929 (s), 1587 (s), 1469 (m), 1447 (s), 1395 (m), 1365 (m), 1316 (s), 1296 (s), 1252 (s), 1143 (s), 1084 (s), 1013 (s), 923 (s), 835 (s), 775 (s). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=0.11 (s, 6H, CH_3 of Si(*Me*)$_2$*t*Bu), 0.95 (s, 9H, CH_3 of Si(Me)$_2$C(*CH*$_3$)$_3$), 3.45, 3.50 (each s, 3H, CH_3 of C3-OMOM, C5-OMOM), 4.75 (s, 2H, H at C7), 5.14, 5.20 (each s, 2H, CH_2 of C3-OMOM, C5-OMOM), 6.70, 6.70 (each d, 1H, ^4J=3 Hz, H at C4, C6). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=−5.4 (q, Si(*C*H$_3$)$_2$), 18.3 (s, Si*C*), 25.9 (q, SiC(*C*H$_3$)$_3$), 56.0, 56.4 (q, *C*H$_3$ of C3-OMOM, C5-OMOM), 64.8 (t, C7), 94.6, 95.3 (each t, *C*H$_2$ of C3-OMOM, C5-OMOM), 103.2 (s, C2), 103.5, 108.5 (each d, C4, C6), 142.6 (s, C1), 153.9, 157.3 (each s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=10.55 min, 98% purity. MS (EI): 365/636 (6, [M−*t*Bu]$^+$), 335/333 (5), 318 (1), 303 (5), 239 (6), 209 (4), 179 (3), 137 (4), 89 (15), 73 (6), 45 (100). HR-MS (EI): calcd 363.0263 for $C_{13}H_{20}O_5SiBr$ (M−*t*Bu), found 363.026.

4.2.6. 1-[*tert*-Butyldimethylsilyl)oxy]-2-(3-methylbut-2-enyl)-3,5-dimethoxy-methoxybenzene. 1.264 g (3 mmol) of the bromide **14** was dissolved in 20 mL of dry THF under argon. At −78°C, 3.55 mL of *t*-BuLi (1.7 M solution in pentane) was added. After 15 min 3 mL of a 1 M solution of CuCN·2LiCl was added, and the resulting brown solution was stirred for 1 h at −15°C. After recooling to −78°C, 2.65 mL (15 mmol) of dry HMPA and 5 min later 1.75 mL (15 mmol) of freshly distilled prenyl bromide was added. After being stirred fo 1 h at −78°C, the solution was allowed to slowly come to rt while stirring was continued overnight. After addition of 20 mL of saturated NH_4Cl solution and subsequent phase separation, the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting yellow oil was placed on top of a silica pad and eluted with cyclohexane/ethyl acetate 10:1 to give 1.125 g of the prenylated silyl ether, which was still unpure charged by GC. The crude product was directly desilylated in the next step without further purification. TLC (cyclohexane/ethyl acetate 15:1) R_f=0.25. GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=10.55 min, 75% purity. MS (EI): 379 (1, $[M-OCH_3]^+$), 354 (3), 309 (3), 278 (57, [M−OTBDMS]$^+$), 263 (17), 247 (5), 233 (18), 217 (10), 202 (15), 187 (8), 89 (12), 69 (21), 45 (100).

4.2.7. 2-(3-Methylbut-2-enyl)-3,5-di-(methoxymethoxy)-benzylic alcohol (15). 1.125 g of the crude silyl ether (prepared as decribed above) was dissolved in 10 mL of THF. After addition of 12 mL of a 1 M tetrabutyl-ammonium fluoride solution in THF, the resulting solution was stirred for 8 h at rt. Then the reaction mixture was poured into 20 mL of a saturated NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate (4×25 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the resulting yellow oil was purified by flash-chromatography (100 g of silica, cyclohexane/ethyl acetate 3:1) to give 531 mg (1.8 mmol, 60% for 2 steps) of benzylic alcohol **15** as a solidified, colorless oil. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.2. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3422 (br, m), 2955 (m), 2902 (m), 1604 (s), 1587 (s), 1476 (s), 1436 (s), 1397 (s), 1308 (s), 1284 (s), 1214 (s), 1149 (s), 1134 (s), 1079 (s), 1020 (s), 936 (s), 920 (s), 893 (s), 850 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=1.65 (d, 3H, ^4J=2 Hz, H at C12), 1.76 (d, 3H, ^4J=2 Hz, H at C11), 3.35 (d, 2H, ^3J=7 Hz, H at C8), 3.45 (s, 2×3H, CH_3 of C3-OMOM, C5-OMOM), 4.62 (s, 2H, H at C7), 5.08 (m, 1H, H at C9), 5.13, 5.15 (each s, 2H, CH_2 of C3-OMOM, C5-OMOM), 6.73 (d, 1H, ^4J=2.5 Hz, H at C4), 6.78 (d, 1H, ^4J=2.5 Hz, H at C6). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=17.8 (q, C11), 24.3 (t, C8), 25.7 (q, C12), 56.0 (q, 2C, *C*H$_3$ of C3-OMOM, C5-OMOM), 63.3 (t, C7), 94.4, 94.6 (each t, *C*H$_2$ of C3-OMOM, C5-OMOM), 103.0 (d, C4), 108.8 (d, C6), 122.3 (s, C2), 123.5 (d, C9), 131.4 (s, C10), 140.8 (s, C1), 155.9, 156.3 (each s, C3, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=10.5 min, 99% purity. MS (EI): 296 (11, $[M]^+$), 278 (13), 251 (10), 233 (9), 217 (4), 189 (11), 161 (5), 91 (4), 69 (3), 45 (100). HR-MS (EI): calcd 296.1624 for $C_{16}H_{24}O_5$, found 296.162.

4.2.8. 2-Bromo-3,5-dimethoxymethoxybenzaldehyde (17). 12.29 g (40 mmol) of alcohol **13** was dissolved in 500 mL of dry dichloromethane. At −78°C 10.4 mL (160 mmol) of dry DMSO was added, followed by 6.8 mL (40 mmol) of oxalyl chloride 10 min later. After stirring was continued at −78°C for 90 min, 27.5 mL (400 mmol) of triethylamine was added. The reaction mixture was stirred overnight while the temperature was allowed to slowly come to rt. After the reaction was quenched by addition of

300 mL of brine, the phases were separated. The aqueous layer was extracted with dichloromethane (3×200 mL). The combined organic layer was dried over $MgSO_4$, filtrated through a pad of silica and evaporated. The resulting brown solid was purified by flash chromatography (400 g of silica, cyclohexane/ethyl acetate 3:1) to give 11.60 g (38 mmol, 95%) of the benzaldehyde **17** as a yellow crystalline solid. Mp: 72°C. TLC (cyclohexane/ethyl acetate 3:1) R_f=0.32. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2903 (br, w), 1691 (s), 1583 (s), 1446 (m), 1381 (m), 1282 (s), 1225 (m), 1142 (s), 1084 (s), 1007 (s), 904 (s), 852 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=3.38, 3.44 (each s, 3H, CH_3 of C3-OMOM, C5-OMOM), 5.10, 5.18 (each s, 2H, CH_2 of C3-OMOM, C5-OMOM), 7.01 (d, 1H, ^4J=3 Hz, H at C4), 7.18 (d, 1H, ^4J=3 Hz, H at C6). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=56.3, 56.5 (each q, CH_3 of C3-OMOM, C5-OMOM), 94.5, 95.3 (each t, CH_2 of C3-OMOM, C5-OMOM), 109.0 (d), 110.4 (s), 110.6 (d), 134.9 (s), 155.0, 157.3 (each s, C3, C5), 191.6 (d, C7). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=10.05 min, 99% purity. MS (EI): (the peaks showed the typical isotopic pattern of a bromo compound) 306 (10), 274 (2), 63 (59, 45 (100). HR-MS (EI): calcd 303.9946 for $C_{11}H_{13}O_5Br$, found 303.994. Anal. calcd for $C_{11}H_{13}O_5Br$: C 43.30; H 4.29; found: C 43.45; H 4.19.

4.2.9. 2-(3-Methylbut-2-enyl)-3,5-dimethoxymethoxybenzaldehyde (16). *Method A*. From 2-(3-Methylbut-2-enyl)-3,5-dimethoxymethoxybenzylic alcohol (**15**). 125 mg (0.42 mmol) of benzylic alcohol **15** was dissolved in 4 mL of dry DMSO. After addition of 178 mg (0.63 mmol) of IBX, the resulting solution was stirred at rt for 5 h. After addition of 10 mL of water, the mixture was filtered through a sintered funnel and subsequently extracted with MTBE (5×10 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (10 g of silica, cyclohexane/ethyl acetate 5:1) to give 112 mg (0.38 mmol, 91%) of the benzaldehyde **16** as a colorless oil. TLC (cyclohexane/ethyl acetate 5:1) R_f=0.15. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2955 (m), 2904 (m), 1687 (s), 1600 (s), 1476 (s), 1449 (m), 1392 (m), 1306 (m), 1277 (s), 1210 (s), 1150 (s), 1137 (s), 1079 (s), 1020 (s), 956 (s), 937 (s), 921 (s), 896 (m), 854 (m). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=1.63 (s, 3H, H at C12), 1.74 (s, 3H, H at C11), 3.44, 3.45 (each s, 3H, CH_3 of C3-OMOM, C5-OMOM), 3.68 (d, 2H, ^3J=7 Hz, H at C8), 5.08 (m, 1H, H at C9), 5.14, 5.17 (each s, 2H, CH_2 of C3-OMOM, C5-OMOM), 7.00 (d, 1H, ^4J=2.5 Hz, H at C4), 7.16 (d, 1H, ^4J=2.5 Hz, H at C6), 10.22 (s, 1H, H at C7). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=17.8 (q, C12), 23.0 (t, C8), 25.5 (q, C11), 56.0 (q, 2C, CH_3 of C3-OMOM, C5-OMOM), 94.5, 94.6 (each t, CH_2 of C3-OMOM, C5-OMOM), 109.0, 109.2 (each d, C4, C6), 123.2 (d, C9), 127.8 (s, C2), 131.6 (s, C10), 135.2 (s, C1), 156.2, 156.2 (each s, C3, C5), 191.5 (s, C7). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): t_{Ret}=9.97 min, 98% purity. MS (EI): 294 (25, [M]$^+$), 279 (7), 251 (10), 236 (3), 217 (7), 202 (5), 189 (5), 175 (6), 161 (4), 115 (5), 91 (4), 77 (5), 45 (100). HR-MS (EI): calcd 294.1467 for $C_{16}H_{22}O_5$, found 294.147.

Method B. From 2-bromo-3,5-dimethoxymethoxy-benzaldehyde (**17**) via Stille coupling. 611 mg (2 mmol) of the bromobenzaldehyde **17**, 911 mg (6 mmol) of cesium fluoride and 92 mg (0.1 mmol) of Pd_2dba_3 were placed in a Schlenk flask under argon. 15 mL of NMP was added, followed by 0.1 mL (0.4 mmol) of P(tBu)$_3$ and 1.440 g (4 mmol) of prenyltributyl stannane **18**. The solution was degassed, flushed with argon and stirred for 20 h at 70°C. After filtration through a pad of celite, the reaction mixture was poured into a saturated KF solution (20 mL). The aqueous mixture was extracted with methyl *tert*butyl ether (3×20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and filtrated through a pad of silica. After evaporation of the solvent, the residue was purified by flash chromatography (100 g of silica, 750 mL of hexane/ether 20:1, then cyclohexane/ethyl acetate 6:1) to give 398 mg (1.36 mmol, 68%) of the prenylated benzaldehyde **16** as a pale oil.

Method C. From 2-bromo-3,5-dimethoxymethoxy-benzaldehyde **17** via coupling with the nickel-π-allyl complex **19**. In a glovebox, 550 mg (2 mmol) of Ni(COD)$_2$ was placed in a Schlenk flask under argon. After transfer to a Schlenk line, 10 mL of dry and degassed benzene was added. The resulting yellow solution was cooled to 5°C, and a degassed solution of 0.35 mL (3 mmol) of freshly destilled prenyl bromide in 5 mL of benzene was added dropwise. The resulting red solution was stirred for 1 h. Then the benzene was carefully evaporated. The deep red complex **19** was dissolved in 5 mL of dry and degassed DMF. A degassed solution of 152 mg (0.5 mmol) of bromo benzaldehyde **17** in 10 mL of dry DMF was added. The resulting mixture was stirred at 50°C, until the solution had completely changed the color from red to green (10 h). The mixture was filtered through a pad of celite. After evaporation of the solvent, the residue was purified by flash chromatography (20 g of silica, cyclohexane/ethyl acetate 6:1) to give 51 mg (0.17 mmol, 35%) of the prenylated benzaldehyde **16** as a pale oil.

4.2.10. [3,5-Bis-methoxymethoxy-2-(3-methylbut-2-enyl)-phenyl]-(3,5-dichloro-2-methoxy-6-methoxymethoxy-4-methyl-phenyl]-methanol (20). 858 mg (2.6 mmol) of bromide **10** was dissolved in 20 mL of dry THF under argon. At −78°C 1.69 mL (2.7 mmol) of a 1.6 M solution of n-BuLi was added, and the resulting solution was stirred for 15 min. A solution of 590 mg (2.0 mmol) of aldehyde **16** in 10 mL of dry THF was added dropwise. The resulting solution was allowed to slowly warm up to rt while being stirred overnight. After addition of 20 mL of a saturated NH_4Cl solution, the mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (100 g of silica, cyclohexane/ethyl acetate 6:1) to give 940 mg (1.72 mmol, 86%) of the benzhydrol **20** as a brown oil. TLC (cyclohexane/ethyl acetate 6:1) R_f=0.15. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=3446 (br, m), 2928 (m), 1604 (s), 1448 (s), 1379 (s), 1283 (s), 1209 (m), 1150 (s), 1021 (s), 919 (s), 850 (m), 780 (w). ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=1.36 (d, 3H, ^4J=1.5 Hz, H at C17), 1.55 (d, 3H, ^4J=1.5 Hz, H at C18), 2.45 (s, 3H, H at C19), 2.97/3.12 (each d, 1H, J=5.5 Hz, H at C14), 3.37 (s, 3H, CH_3 of C3-OMOM), 3.47 (s, 3H, CH_3 of C5-OMOM), 3.51 (s, 3H, CH_3 of C8-OMe), 3.59 (s, 3H, CH_3 of C12-OMOM), 4.25 (m, 1H, H at C15),

4.99/5.13 (each d, 1H, ^3J=5.5 Hz, CH_2 of C12-OMOM), 5.10 (s, 2H, CH_2 of C3-OMOM), 5.17/5.21 (each d, 1H, ^3J=7 Hz, CH_2 of C5-OMOM), 6.29 (s, 1H, H at C13), 6.70 (d, 1H, ^4J=2.5 Hz, H at C4), 7.27 (d, 1H, ^4J=2.5 Hz, H at C6). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=18.0 (q, C18), 18.4 (q, C19), 25.2 (t, C14), 25.5 (q, C17), 56.15 (q, CH_3 of C5-OMOM), 56.2 (q, CH_3 of C3-OMOM), 58.3 (q, CH_3 of C12-OMOM), 61.6 (q, CH_3 of C8-OMe), 67.3 (d, C13), 95.5 (t, CH_2 of C3-OMOM), 95.7 (t, CH_2 of C5-OMOM), 101.5 (t, CH_2 of C12-OMOM), 103.0 (d, C4), 108.8 (d, C6), 122.5 (s, C2), 124.3 (d, C15), 126.2 (s, C9), 126.8 (s, C11), 131.4 (s, C16), 132.5 (s, C7), 137.0 (s, C10), 145.0 (s, C1), 152.3 (s, C12), 155.8 (s, C8), 157.1 (s, C3), 157.15 (s, C5). GC-MS (Optima 1 MS, 10 psi, 50°$_2$→[25°C/min]→300°$_{10}$): broad signal, t_{Ret}=13.5–14.4 min, 94% purity. MS (EI): (the peaks showed the typical isotopic pattern of a dichloro compound) 544 (5, $[M]^+$), 526 (15), 481 (38), 458 (15), 413 (22), 405 (25), 369 (16), 339 (15), 263 (11), 233 (22), 219 (27), 189 (20), 149 (27), 115 (22), 91 (42), 69 (100). HR-MS (EI): calcd 544.1630 for $C_{26}H_{34}O_8Cl_2$, found 544.163.

4.2.11. [3,5-Bis-methoxymethoxy-2-(3-methylbut-2-enyl)-phenyl]-(3,5-dichlor-2-methoxy-6-methoxy-methoxy-4-methyl-phenyl]-methanon (21). 927 mg (1.70 mmol) of the benzhydrol **20** was dissolved in 15 mL of dry dichloromethane. 1.42 g (3.44 mmol) of Dess–Martin periodinane was added. The resulting orange solution was stirred for 3 h at rt. Then the reaction mixture was concentrated and filtered through a pad of celite. After evaporation of the solvent, the residue was purified by flash chromatography to give 820 mg (1.50 mmol, 88%) of the benzophenone **21** as a yellow oil, which slowly solidified upon standing at 4°C. TLC (cyclohexane/ethyl acetate 6:1) R_f=0.2. IR (ATR) $\tilde{\nu}$ [cm^{-1}]=2954 (m), 2065 (w), 1674 (s), 1600 (s), 1572 (s), 1448 (m), 1371 (s), 1282 (s), 1210 (s), 1152 (s), 1064 (s), 1024 (s), 977 (s), 916 (s). ^{1}H NMR (300 MHz, CD_3OD): δ [ppm]=1.59 (s, 3H, H at C17), 1.55 (s, 3H, H at C18), 2.49 (s, 3H, H at C19), 3.29 (s, 2×3H, CH_3 of C3-OMOM, C5-OMOM), 3.40 (s, 3H, CH_3 of C8-OMe), 3.55 (s, 3H, CH_3 of C12-OMOM), 3.61 (d, 2H, J=6.5 Hz, H at C14), 4.95 (s, 2H, CH_2 of C12-OMOM), 4.99 (s, 2H, CH_2 of C3-OMOM), 5.10–5.15 (m, 1H, H at C15), 5.17 (s, 2H, CH_2 of C5-OMOM), 6.72 (d, 1H, ^4J=2.5 Hz, H at C4), 6.97 (d, 1H, ^4J=2.5 Hz, H at C6). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=18.5 (q, C18), 18.9 (q, C19), 26.3 (t, C14), 26.3 (q, C17), 56.5 (q, CH_3 of C5-OMOM), 56.7 (q, CH_3 of C3-OMOM), 58.4 (q, CH_3 of C12-OMOM), 62.7 (q, CH_3 of C8-OMe), 95.9 (t, CH_2 of C3-OMOM), 96.0 (t, CH_2 of C5-OMOM), 101.7 (t, CH_2 of C12-OMOM), 108.7 (d, C4), 113.8 (d, C6), 124.9 (s, C2), 126.4 (d, C15), 126.8 (s, C9), 131.9 (s, C11), 132.1 (s, C16), 139.5 (s, C7), 140.1 (s, C10), 150.6 (s, C1), 153.8 (s, C12), 157.2 (s, C8), 157.2 (s, C3), 158.2 (s, C5), 195.7 (s, C13). GC-MS (Optima 1 MS, 10 psi, 200°$_2$→[25°C/min]→300°$_{10}$): broad signal, t_{Ret}=7.35–7.7 min, 99% purity. MS (EI): (the peaks showed the typical isotopic pattern of a dichloro compound) 542 (3, $[M]^+$), 513 (10), 497 (25), 481 (27), 467 (33), 411 (10), 367 (5), 291 (7), 271 (52), 247 (87), 215 (20), 189 (7), 99 (58), 73 (100). HR-MS (EI): calcd 542.1474 for $C_{26}H_{32}O_8Cl_2$, found 542.145.

4.2.12. [3,5-Bishydroxy-2-(3-methylbut-2-enyl)phenyl]-(3,5-dichloro-2-methoxy-6-hydroxy-4-methyl-phenyl]-methanon (deformyl-pestalone) (23). 217 mg (0.4 mmol) of the benzophenone **21** was dissolved in 10 mL of dry methanol under argon. After addition of 93 mg (0.4 mmol) of camphorsulphonic acid (CSA), the resulting solution was stirred for 24 h at rt, until TLC-showed complete conversion to one final product. After the solvent was evaporated under reduced pressure, the residue was purified by flash chromatography (30 g of silica, cyclohexane/ethyl acetate 4:1) to give 150 mg (0.36 mmol, 91%) of the deprotected benzophenone **23** (deformyl-pestalone). TLC (cyclohexane/ethyl acetate 4:1) R_f=0.1. ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=1.57 (s, 3H, H at C18), 1.61 (s, 3H, H at C 17), 2.50 (s, 3H, H at C19), 3.18 (d, 2H, J=6.5 Hz, H at C14), 3.31 (s, 3H, CH_3 of C8-OMe), 5.12 (t, 1H, J=6.5 Hz, H at C15), 5.92 (br s, 1H, C3-OH), 6.18 (s, 1H, C5-OH), 6.23 (d, 1H, J=2.5 Hz, H at C6), 6.36 (d, 1H, J=2.5 Hz, H at C4), 12.15 (s, 1H, C12-OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=17.7 (q, C18), 19.0 (q, C19), 25.6 (q, C17), 26.1 (t, C14), 61.8 (q, CH_3 of C8-OMe), 105.2 (d, C4), 106.2 (d, C6), 115.4 (s, C7), 116.4 (s, C2), 119.0 (s, C11), 119.8 (s, C9), 121.9 (d, C15), 134.8 (s, C16), 142.6 (s, C1), 144.1 (s, C10), 154.3 (s, C5), 155.5 (s, C8), 155.8 (s, C3), 156.5 (s, C12), 201.6 (s, C13). MS (EI): (the peaks showed the typical isotopic pattern of a dichloro compound) 410 (23, $[M]^+$), 396 (8), 381 (65), 379 (100), 367 (22), 323 (50), 297 (20), 235 (20), 233 (32), 218 (35), 189 (20), 161 (40), 115 (20), 77 (37), 69 (70), 54 (82). HR-MS (EI): calcd 410.0688 for $C_{20}H_{20}O_5Cl_2$, found 410.069.

4.2.13. [7-Hydroxy-2,2-dimethyl-chroman-5-yl]-(3,5-dichloro-6-methoxy-2-hydroxy-4-methyl-phenyl]-methanon (22). 109 mg (0.2 mmol) of the benzophenone **21** was placed in a flask equipped with a reflux condenser and dissolved in 5 mL of dry methanol. After addition of 40 mg (0.2 mmol) of *p*-toluenesulphonic acid the solution was stirred at 60°C for 3 h. After evaporation of the solvent, the residue was purified by flash chromatography (10 g of silica, cyclohexane/ethyl acetate 4:1) to give 40 mg (0.1 mmol, 50%) of the chromane **22** as a yellow crystalline solid. TLC (cyclohexane/ethyl acetate 4:1) R_f=0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm]=1.31 (s, 6H, H at C17, C18), 1.72 (t, 2H, J=7 Hz, H at C15), 2.53 (s, 3H, H at C19), 2.62 (t, 2H, J=7 Hz, H at C14), 3.36 (s, 3H, CH_3 of C8-OMe), 6.30 (d, 1H, J=2.5 Hz, H at C6), 6.36 (d, 1H, J=2.5 Hz, H at C4), 11.57 (s, 1H, C12-OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm]=18.9 (q, C19), 19.9 (t, C14), 26.6 (q, C17, C18), 32.5 (t, C15), 61.8 (q, CH_3 of C8-OMe), 74.5 (s, C16), 106.3 (d, C4), 106.8 (d, C6), 111.3 (s, C2), 115.9 (s, C7), 118.8 (s, C11), 119.9 (s, C9), 141.6 (s, C1), 143.4 (s, C10), 154.1 (s, C5), 155.1 (s, C3), 155.3 (s, C8), 155.7 (s, C12), 200.9 (s, C13). MS (EI): (the peaks showed the typical isotopic pattern of a dichloro compound) 410 (35, $[M]^+$), 396 (10), 381 (65), 379 (100), 367 (25), 341 (24), 323 (55), 297 (24), 261 (2), 235 (20), 233 (37), 218 (32), 189 (24), 177 (32), 161 (45), 115 (25), 91 (27), 77 (37), 69 (68), 54 (77). HR-MS (EI): calcd 410.0687 for $C_{20}H_{20}O_5Cl_2$, found 410.069.

Acknowledgements

This work was supported by Aventis Pharma GmbH and the Fonds der Chemischen Industrie. We thank Dr Hans Schmickler for NMR spectroscopic support and Dr Mathias

Schäfer for MS spectroscopic measurements. Generous gifts of chemicals from Chemetall AG are also highly appreciated.

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