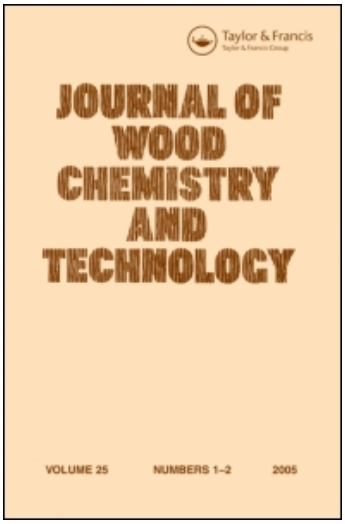

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SYNTHESIS OF A CONDENSED TANNIN MODEL COMPOUND, 4-(2,4,6-TRIHYDROXYPHENYL)FLAVAN-3,3',4',5,7-PENTAOL

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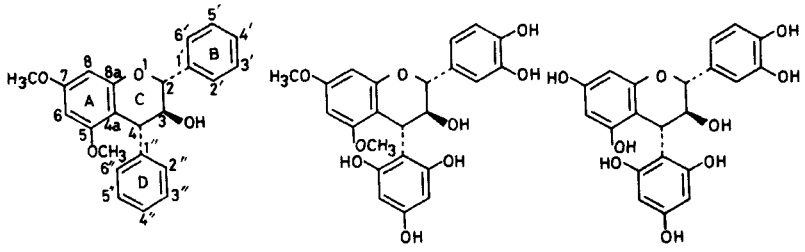
ABSTRACT

A free phenolic condensed tannin model compound, 4-(2,4,6-trihydroxyphenyl)flavan-3,3',4',5,7-pentaol, was synthesized in high yield from phloroacetophenone dibenzyl ether and protocatechualdehyde dibenzyl ether. Condensation of the 2,3-trans-3,4-cis-flavan-3,4-diol with phloroglucinol in the presence of a Lewis acid, $TiCl_4$, proceeded with high stereoselectivity, to give only the 2,3-trans-3,4-trans isomer in over 90% yield. The reactivity of this model compound might be compared with those of other model compounds to determine the effect of the hydroxyl groups in the A, B, and D rings on the reactivity of the C ring. Furthermore, this synthetic route might be applied to the synthesis of artificial tannin derivatives.

INTRODUCTION

In the previous paper,[1] we reported the synthetic route for a simple condensed tannin model compound, 5,7-dimethoxy-4-phenylflavan-3-ol(**1**), starting from dimethoxyphloroglucinol and benzalacetophenone. This model has no free hydroxyl groups in the B and D rings. In order to investigate the effect of free hydroxyl groups on the reactivity of the C ring, it was necessary to synthesize a new model compound with free hydroxyl groups in the A, B and D rings. For this reason, 4-(2,4,6-trihydroxyphenyl)-



1 2 3

flavan-3,3',4',5,7-pentaol(**3**) was selected as a new model compound.

Several synthetic routes for the 4-phenylflavan-3-ol structure have already been reported including the condensation of 3',4',5,7,-tetramethoxyflavan-3,4-diol[2,3] or 3',4',5,7-tetrahydroxyflavan-3,4-diol[4] with a large excess of phloroglucinol in the presence of a protic acid. However, with the former route, it is difficult to remove the methyl groups; the latter route suffers from low yield (32.1%) and low stereoselectivity (3,4-trans isomer : 3,4-cis isomer = 5:1) for the synthesis of the desired model compound with free hydroxyl groups in the A, B and D rings. Moreover, because (+)-taxifolin, a natural product, was used for the starting material, both of the above routes are thought to be unsuitable for the synthesis of model compounds with a variety of substituents.

In this paper we report the synthesis of model compound **3**, starting from commercially available phloroglucinol and protocatechualdehyde. In the key intermediate, flavan-3,4-diol, the phenolic hydroxyl groups are protected by benzyl ethers, which may be removed conveniently under mild (i.e. neutral) conditions.

RESULTS AND DISCUSSION

The synthetic route for model compounds **2** and **3**, starting from a diprotected phloroacetophenone **4** or **5** and protocatechuardehyde dibenzyl ether (**6**), is shown in Fig. 1.

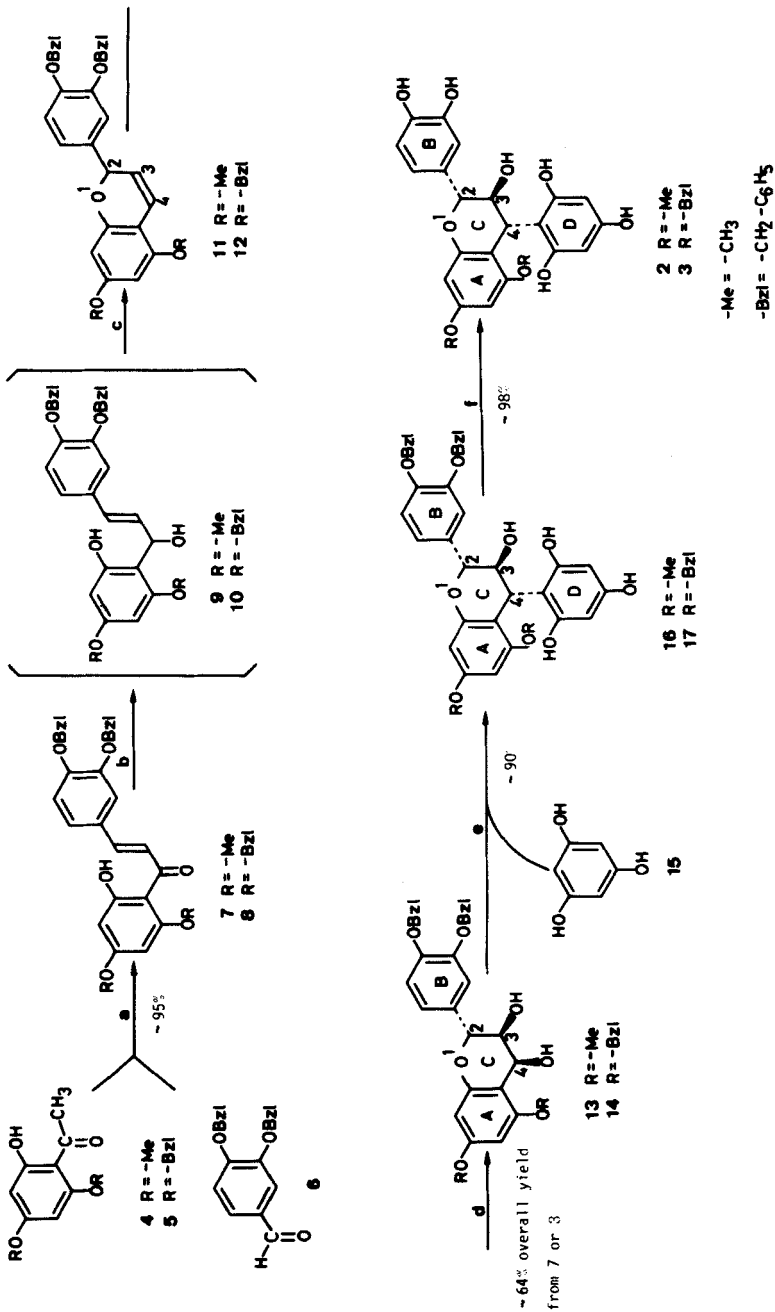


FIGURE 1. Synthetic route for model compounds 2 and 3.

For the synthesis of the key intermediate, flavan-3,4-diol, two methods have been reported. One method[4,5] is based on the reduction of taxifolin (dihydroflavonol) with sodium borohydride; the other[6,7] is based on the oxidation of flavan-3-ene with osmium tetroxide. To obtain compound **3** in high yield by the former method, it is necessary to obtain taxifolin derivatives that have phenolic hydroxyl groups protected with benzyl groups. However, methods for the benzylation of taxifolin and the synthesis of the benzylated taxifolin derivatives from commercially available compounds could not be found. Thus, in this paper, we selected the synthetic route based on the conversion of the flavan-3-ene to the corresponding flavan-3,4-diol. However, the high yield synthesis of flavan-3,4-diol, with phenolic hydroxyl groups protected by benzyl ethers, has not been reported so far.

1. Synthesis of model compound **2**.

For the synthesis of model compound **3** via the route shown in Fig.1, it is necessary to obtain phloroacetophenone dibenzyl ether (**5**). However, in the benzylation of phloroglucinol-type compounds, the desired O-benzyl derivatives are generally otained in low yield.[8,9] Purification is also difficult, because the high electron density of the aromatic rings lead to C-benzylation along with O-benzylation.

For this reason, to examine the applicability of the synthetic route shown in Fig. 1, we first attempted to synthesize model compound **2**, starting from phloroacetophenone dimethyl ether (**4**), which was obtained in 82.1% yield from commercially available phloroglucinol trimethyl ether via a two-step reaction.

The aldol condensation of acetophenone derivatives with benzaldehyde derivatives is usually carried out using sodium hydroxide or potasium hydroxide[10] as a base and affords a chalcone in low yield. However, when sodium hydride was used in DMF, the aldol condensation proceeded rapidly and the expected chalcone **7** was obtained quantitatively. A similar result has been reported by Mishima et al.[11].

Chalcone **7** was converted to flavan-3-ene **11** according to the procedure of Clark-Lewis *et al.*,[6] which involves reductive cyclization using sodium borohydride. The carbonyl group of chalcone **7** was selectively reduced to intermediate **9** using sodium borohydride in methyl cellosolve at 90°C. This transformation could be confirmed by the disappearance of the deep yellow color from the reaction solution. Because intermediate **9** is highly labile, subsequent cyclization proceeded rapidly upon the addition of a catalytic amount of boron trifluoride, to give flavan-3-ene **11** in about 70% overall yield based on TLC analysis. This flavan-3-ene **11** rapidly degraded when exposed to acids or silica gel, so it was necessary to carry out the subsequent glycolization without any purification.

Two methods were considered for the preparation of flavan-3,4-diol **13** from flavan-3-ene **11**.[12] One method utilizes an epoxide intermediate, which may be obtained by oxidation of the double bond with *m*-chloroperbenzoic acid. The other method involves a direct glycolization of the double bond with osmium tetroxide. As an example of the latter method, the oxidation of flavan-3-ene to flavan-3,4-diol using one equivalent of osmium tetroxide has been reported by Clark-Lewis *et al.*.[6] However, the high cost of osmium tetroxide, coupled with its high toxity, make it impractical to carry out a large scale glycolization using this method.

Preparation of the diol was first attempted using the former method (i.e. oxidation using *m*-chloroperbenzoic acid or peracetic acid), but the desired flavan-3,4-diol **13** was obtained in only 20% yield. The instability of the epoxide and the diol under acidic conditions is thought to be the reason for such a low yield. On the other hand, catalytic osmylation using an oxidyzing agent, such as chlorate,[13] hydrogen peroxide,[14] etc., has been reported. The desired glycolization was found to proceed smoothly by using *N*-methylmorpholine-*N*-oxide[15] and two mole percent of osmium tetroxide; flavan-3,4-diol **13** was obtained quantitatively and the ratio of the 2,3-cis-3,4-trans isomer to the 2,3-cis-3,4-cis isomer was 10:1. The identity of each isomer

was confirmed by inspection of the ^{1}H-NMR spectra of the respective acetates. The main product ($J_{2,3}$=11cps, $J_{3,4}$=3.5cps) was the 2,3-trans-3,4-cis isomer; the minor product ($J_{2,3}$=1.7cps, $J_{3,4}$=5.4cps) was the 2,3-cis-3,4-cis isomer.[16] This result may be predicted from consideration of the reaction mechanism, in which the cis-dihydroxylation occurs preferentially from the less hindered side of the double bond, the opposite side of the C-2 phenyl group.[17] Pure 2,3-trans-3,4-cis flavan-3,4-diol **13** was obtained in about 90% yield upon recrystallization.

With five equivalents of phloroglucinol in the presence of Lewis acid (titanium tetrachloride), exclusively 2,3-trans-3,4-trans-4-arylflavan-3-ol **16** was rapidly formed from flavan-3,4-diol **13** in about 90% yield. The identity of this condensation product was confirmed by ^{1}H-NMR analysis. The relatively large coupling constants of the C ring ($J_{2,3}$=8.7cps, $J_{3,4}$=9.5cps) indicate a completely trans configulation.[4] In addition to compound **16**, a mixture of higher condensation products was also obtained. Similar results using a protic acid instead of a Lewis acid have been reported.[3] However, if a protic acid is used, the reaction is very sensitive to the pH of the reaction solution; a slight alteration in pH leads to the formation of both the 3,4-trans and the 3,4-cis isomers. For this reason, the present procedure using a Lewis acid was thought to be simpler and more reproducible. The reaction mechanism shown in Fig.2 is conceivable to explain the complete inversion of configuration at the C-4 position in this condensation reaction. The bulky titanium tetrachloride molecule coordinates with the oxygen of the C-3 hydroxyl group and with the ring oxygen, as well as with the oxygen of the C-4 hydroxyl group. Consequently one side of the C ring is blocked, so that phloroglucinol is able to preferentially attack flavan-3,4-diol from the other side.

Finally, debenzylation of compound **16** was carried out quantitatively by the usual hydrogenolysis using Pd-C/H_2.

Thus, the synthetic route for the model compound proposed in Fig. 1 was justified by the high yield synthesis of compound **2**. Next, we considered the synthesis of model compound **3**, which has free hydroxyl groups in the A ring.

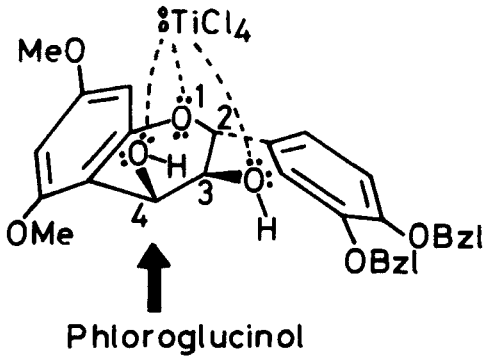


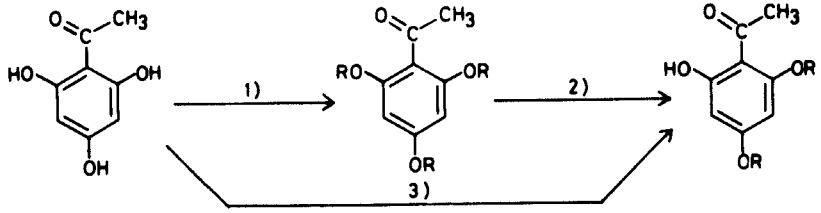
FIGURE 2. Reaction mechanism for condensation.

2.Examination of the protecting groups of the A ring and the synthesis of model compound 3.

As described previously, O-benzylation of phloroglucinol-type compounds was thought to be difficult. Therefore, we examined various protecting groups to be used instead of the benzyl ether (Table 1). It was possible to introduce methoxymethyl groups, benzyloxymethyl groups, tosyl groups and benzensulfonyl groups into phloroacetophenone to yield diprotected phloroacetophenones in moderate yield. We attempted to synthesize model compound **3**, starting from these resulting phloroacetophenone derivatives, according to the synthetic route in Fig.1. Each reaction sequence proceeded without any problems up to the stage of the condensation reaction with phloroglucinol, but in the final step it was impossible to remove these protecting groups without degrading the model compound. Removal of these protecting groups is usually carried out in the presence of an acid or a base.[18] Instability of the model compound structure under acidic or basic conditions was thought to be the reason for the degradation of the model. It was expected that hydrogenolysis would be effective for debenzyloxymethylation, but, even under neutral

TABLE 1.
Examination of the protecting groups of phloroacetophenone.

R	Reaction Conditions	overall yield (%)
$-CH_2-O-CH_3$	1) CH_3-O-CH_2-Cl / NaH / DMF / r.t. / 30 min 2) 2N-AcOH / 50°C / 2hr	62
$-CH_2-O-Bzl$	1) $Bzl-O-CH_2Cl$ / NaH / DMF / 0°C / 15 min 2) 95%-AcOH / THF / 80°C / 17 hr	61
$-SO_2-C_6H_4-CH_3$	3) tosyl-Cl / K_2CO_3 / acetone / 35°C / 5 hr	75
$-SO_2-C_6H_5$	1) $C_6H_5-SO_2-Cl$ / K_2CO_3 / acetone / 35°C / 4 hr 2) 1N-NaOH / MeOH/THF / 0°C / 15 min	71



conditions with hydrogen pressure (8 kg/cm^2), complete debenzyloxymethylation was not achieved. In acetic acid solution the expected compound decomposed. From these results, it was concluded that the benzyl ether, which may be removed successfully under neutral conditions, was the most appropriate protecting group for the synthesis of condensed tannin model compounds.

After examination of several benzylation routes, crystalline phloroacetophenone dibenzyl ether (**5**) was easily obtained, although in low yield (18.3%), from phloroglucinol via three reaction steps (Fig. 3). It is interesting to note that Friedel-Crafts acetylation of the C-benzylated derivatives proceeded to only a very limited extent under the mild conditions employed for reaction b. Thus, the C-benzylated derivatives could be removed easily at this stage.

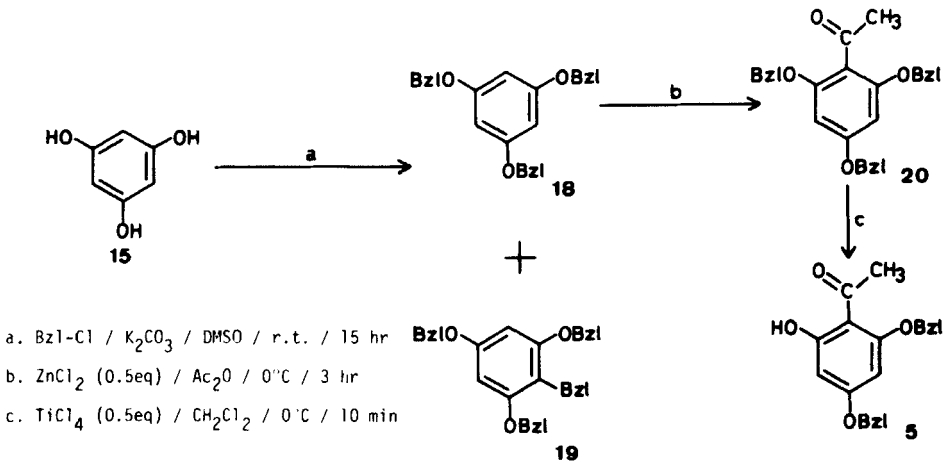


FIGURE 3. Synthetic route for compound 5.

Next, we synthesized model compound **3** using phloroacetophenone dibenzyl ether (**5**) and protocatechualdehyde dibenzyl ether (**6**) as starting materials (Fig. 1).

Each reaction proceeded rapidly with no problems, to give the target material (model compound **3**) in 55% overall yield. Roux et al.[4] have reported that a mixture of the 3,4-trans isomer and the 3,4-cis isomer of 4-arylflavan-3-ol was obtained from the free phenolic flavan-3,4-diol (obtained by reduction of (+)-taxifolin with sodium borohydride) and that separation of these isomers was possible only by methylation of the free phenolic hydroxyl groups. In the present investigation, considerable tailing of model compounds **2** and **3** with polyhydroxyl groups during purification by TLC was found to hinder the complete purification. However, such tailing was not detected for condensation products **16** and **17**, in which all of the phenolic hydroxyl groups were protected; the latter compounds could be purified easily. Moreover, the final step, debenzylation, was carried out quantitatively. According to this synthetic route, model com-

pounds **2** and **3** with polyhydroxyl groups could be obtained easily and with high purity.

In this way, the synthetic route for model compounds with polyhydroxyl groups in the A, B and D rings was established. Comparision of the reactivity of model compound **1** with that of model compound **2** or **3** will reveal the effect of the hydroxyl groups in the A, B and D rings on the reactivity of the C ring. Furthermore, it is expected that this synthetic route may be applied to investigate the relationship between tannin structure and tannin properties, for example astringency, because it is possible using this synthetic route to synthesize several artificial tannin derivatives with different substituents.

EXPERIMENTAL

The melting points are uncorrected. A SHIMADZU UV-365 ultraviolet spctrometer and a Shimadzu FT IR-4000 infrared spectrometer were used for UV and IR spectra, respectively. ^{1}H- and ^{13}C-NMR spectra were taken with a Varian XL-200 FT-NMR (200MHz) spectrometer and a JEOL FX-90Q FT-NMR (90MHz) spectrometer, respectively, with TMS as an internal standard. Chemical shifts and coupling constants are given in δ-values (ppm) and Hz, respectively. Mass spectra (MS) were obtained by the use of a SHIMADZU GCMS-QP1000 (70eV) spectrometer; the relative abundance of each peak is designated in parentheses. Preparative TLC was done on silica gel plates (Kieselgel 60 F_{254}, Merck). The standard work-up involved diluting with EtOAc, washing with water, with a saturated $NaHCO_3$ solution, and with brine, drying over Na_2SO_4 and evaporating *in vacuo*.

1. Synthesis of model compound **2**.

2,4,6-trimethoxyacetophenone. To a stirred solution of phloroglucinol trimethyl ether (1.68 g, 10 mM) in 15 ml of 1,2-dichloroethane, acetyl chloride (3.54 ml, 50 mM) and $TiCl_4$ (1.1

ml, 10 mM) were added at 0°C. After stirring for 9 hr, the reaction mixture was worked-up using the standard method to yield a colorless oil. The product was crystallized from ether to give colorless crystals (2.02 g, 96.3% yield). Mp 100-101°C (Lit.[19] 110°C).

Compound 4. To a stirred solution of 2,4,6-trimethoxyacetophenone (2.10 g, 10 mM) in 40 ml of benzene, $TiCl_4$ (3.30 ml, 30 mM) was added at room temperature (hereafter r.t.) and the resulting red-brown solution was stirred for 24 hr under reflux. The reaction mixture was worked-up using the standard method to yield a slightly brown oil. The product was purified by TLC (CH_2Cl_2) and crystallized from ether to give colorless crystals (1.67 g, 85.3% yield). Mp 80°C (Lit.[20] 80-81°C).

Compound 7. To a stirred solution of compound **4** (1.57 g, 8.0 mM) in 30 ml of DMF, 60% NaH dispersed in mineral oil (384 mg, 9.6 mM) was added and then compound **6** (2.53 g, 8.0 mM) in 5 ml of DMF was added dropwise over a period of 5 min at 0°C. After stirring for 1 hr at r.t., the reaction mixture was diluted with 300 ml of CH_2Cl_2 and washed with a 1N-HCl solution, with a saturated $NaHCO_3$ solution and with brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to yield a yellow solid. The product was crystallized from ether/n-hexane (3:1, v/v) to give yellow crystals (3.82 g, 96.1% yield). Mp 115.5°C; UV λ max (CH_3OH) nm (log ε): 369 (4.55); IR ν max (KBr) cm^{-1}: 1625 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 3.83, 3.84 (6H, two s), 5.22 (4H, s, $-CH_2-C_6H_5$, hereafter -Bzl), 5.95, 6.11 (2H, two d, J=2.0, $C_{3'}$-H, $C_{5'}$-H), 6.93-7.54 (13H, m), 7.70 (2H, s, C_α-H, C_β-H).

Compound 13. A suspension of compound **7** (1.48 g, 3.0 mM) in 40ml of methyl cellosolve was heated at 90°C to afford a clear solution. To the resulting solution, $NaBH_4$ (114 mg, 3.0 mM) was added. After stirring at 90°C for 5 min, the reaction mixture was diluted with 60 ml of EtOAc and then successively washed with brine until the washings became neutral. The organic layer was transferred to another flask and 1.0 ml (0.2mM) of 47% BF_3-Et_2O in CH_2Cl_2 (260 µl/5 ml) was added dropwise over a period of 10 min. The resulting solution was then stirred at r.t. for 15 min.

The reaction mixture was worked-up using the standard method to yield a yellow oil, which consisted of crude flavan-3-ene (**11**) (about 70% purity based on TLC analysis) (1.43 g). Compound **11**: UV λmax (CH_3CN) nm (log ε): 232 (4.44), 235 (sh, 4.45), 238 (4.46), 287 (4.07); ^{1}H-NMR ($CDCl_3$) δ: 3.73, 3.80 (6H, two s), 5.13, 5.14 (4H, two s, -Bzl), 5.52 (1H, dd, J=10.0, 3.5, C_3-H), 5.70 (1H, dd, J=3.5, 1.8, C_2-H) 6.00, 6.02 (2H, two d, J=2.4, C_6-H, C_8-H), 6.79 (1H, collapsed dd, J=10.0, 3.5, C_4-H), 6.88-7.58 (13H, m).

To a mixture of 153 μl (0.06 mM) of OsO_4 in t-BuOH (100 mg/1.0 ml), 1.19 ml (3.3 mM) of N-methylmorpholine-N-oxide in H_2O (769 mg/2.0 ml) and 25 ml of THF, the above yellow oil (1.43 g) in 10 ml of THF was added. The solution was stirred at r.t. for 1 hr, diluted with 100 ml of CH_2Cl_2 and then washed with 1M $Na_2S_2O_3$ solution and brine. The organic layer was dried over Na_2SO_4 and evaporated in vacuo to yield a greenish yellow solid, which consisted of compound **13** and the 2,3-cis-3,4-cis isomer of compound **13** (10:1 ratio). Pure compound **13** was obtained by crystallization from CH_2Cl_2/ether as colorless crystals (975 mg, 63.2% yield based on compound **7**). Compound **13**: mp 170°C; UV λmax (CH_3OH) nm(log ε): 276 (3.56), 279 (3.55); ^{1}H-NMR($CDCl_3$) δ: 2.50 (1H, d, J=7.2, C_3-OH), 2.77 (1H, d, J=2.5, C_4-OH), 3.75, 3.86 (6H, two s), 3.91 (1H, ddd, J=10.2, 7.2, 5.5, C_3-H), 4.88 (1H, d, J=10.2, C_2-H), 5.00 (1H, dd, J=5.5, 2.5, C_4-H), 5.18 (4H, s, -Bzl), 6.09, 6.13 (2H, two d, J=2.5, C_6-H, C_8-H), 6.98-7.53 (13H, m); MS m/z (%): 514 (M^+, 0.2), 496 (2.9), 377 (5.6), 92 (8.9), 91 (100). Anal. Calcd. for $C_{31}H_{30}O_7$: C, 72.4; H, 5.9. Found: C, 72.2; H, 5.7. Acetate of compound **13**: ^{1}H-NMR ($CDCl_3$) δ: 1.77, 2.11 (6H, two s), 3.75, 3.78 (6H, two s), 5.06 (1H, d, J=11.0, C_2-H), 5.16, 5.17 (4H, two s, -Bzl), 5.34 (1H, dd, J=11.0, 3.5, C_3-H), 6.08, 6.10 (2H, two d, J=2.2, C_6-H, C_8-H), 6.43 (1H, d, J=3.5, C_4-H), 6.94-7.55 (13H, m). 2,3-cis-3,4-cis isomer of compound **13**: ^{1}H-NMR ($CDCl_3$) δ:2.91 (1H, s, -OH) 3.76, 3.78 (6H, two s), 4.20 (2H, d, J=4.8, C_3-H, -OH), 4.88 (1H, s, C_2-H), 5.15 (1H, d, J=4.8, C_4-H), 5.16, 5.19 (4H, two s, -Bzl), 6.13, 6.18 (2H, two d, J=2.0, C_6-H, C_8-H), 6.87-7.56 (13H,

m). Acetate of 2,3-cis-3,4-cis isomer of compound **13**: ^{1}H-NMR ($CDCl_3$) δ: 1.91, 1.94 (6H, two s), 3.75, 3.79 (6H, two s), 5.11 (1H, d, J=1.7, C_2-H), 5.16 (4H, s, -Bzl), 5.55 (1H, dd, J=5.4, 1.7, C_3-H), 6.12, 6.18 (2H, two d, J=2.4, C_6-H, C_8-H), 6.45 (1H, d, J=5.4, C_4-H), 6.90-7.62 (13H, m).

Compound 16. To a stirred solution of compound **13** (514 mg, 1.0 mM) in 25 ml of THF/CH_2Cl_2 (2:3, v/v), first, phloroglucinol (**15**) (810 mg, 5.0 mM) in 1.0 ml of THF and then $TiCl_4$ (110 μl, 1.0 mM) in 1.5 ml of CH_2Cl_2 were added at 0°C. After stirring for 15 min, the reaction mixture was worked-up using the standard method to yield a yellow oil. After a separation of phloroglucinol (**15**) by short column chromatography (silica gel 10 g, 5 cm x 2.5 cm, CH_3OH/CH_2Cl_2 = 5:95, v/v) as a eluent, the resulting yellow oil was purified by TLC (CH_3OH/CH_2Cl_2 = 7.5:92.5, v/v) to give compound **16** as a light yellow solid (573 mg, 92.2% yield based on compound **13**). UV λmax (CH_3OH) nm (log ε): 259 (sh, 3.31), 276 (3.62), 280 (3.62); ^{1}H-NMR ($CDCl_3$) δ: 3.42, 3.72 (6H, two s), 4.11 (1H, t, J=9.0, C_3-H), 4.40 (1H, d, J=8.7, C_2-H), 4.52 (1H, d, J=9.5, C_4-H), 5.09 (4H, s, -Bzl), 5.80, 5.92 (2H, two broad s, $C_{3''}$-H, $C_{5''}$-H), 6.06, 6.17 (2H, two d, J=2.0, C_6-H, C_8-H), 6.80-7.60 (13H, m); MS m/z (%): 622 (M^+, 0.2), 496 (2.0), 377 (2.8), 167 (3.3), 126 (7.7), 92 (8.9), 91 (100). Anal. Calcd. for $C_{37}H_{34}O_9$ 0.5H_2O: C, 70.3; H, 5.6. Found: C, 70.6; H, 5.9. Acetate of compound **16**: ^{1}H-NMR ($CDCl_3$) δ: 1.60 (3H, s), 1.88, 2.23, 2.34 (9H, three s), 3.36, 3.79 (6H, two s), 4.56 (1H, d, J=9.5, C_2-H), 4.72 (1H, d, J=9.6, C_4-H), 5.15 (4H, s, -Bzl), 5.71 (1H, t, J=9.5, C_3-H), 5.99, 6.11 (2H, two d, J=2.0, C_6-H, C_8-H), 6.70-7.50 (15H, m).

Compound 2. To a stirred solution of compound **16** (248.8 mg, 0.40 mM) in 5 ml of CH_3OH, 10% Pd-C (125 mg) was added and the solution was stirred under hydrogen at r.t. for 2 hr. The reaction mixture was filtered and evaporated in vacuo. The resulting light brown oil was purified by TLC (CH_3OH/CH_2Cl_2 = 1:9, v/v) to give compound **2** as a light yellow solid (171 mg, 97.0% yield). UV λmax (CH_3OH) nm (log ε): 279 (3.65). ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ: 3.34, 3.59 (6H, two s), 3.53 (1H, d, J=4.4, C_3-OH), 4.18 (1H,

dt, J=9.0, 4.4, C_3-H), 4.30 (1H, d, J=7.8, C_2-H), 4.34 (1H, d, J=9.2, C_4-H), 5.66, 5.87 (2H, two broad s, $C_{3''}$-H, $C_{5''}$-H), 5.88, 5.96 (2H, two d, J=2.2, C_6-H, C_8-H), 6.70-6.90 (3H, m), 7.51, 8.05, 8.13, 8.28, 8.31 (5H, five s, phenolic-OH); ^{13}C-NMR (DMSO-d_6) δ: 54.7, 55.5 (-OCH_3), 71.2 (C-3), 82.6 (C-2), 92.8, 93.5, 93.8, 94.4 (C-6, C-8, C-3", C-5"), 108.2 (C-4a), 110.0 (C-1"), 114.7 (C-2'), 115.2 (C-5'), 119.3 (C-6'), 130.5 (C-1'), 144.6, 144.8 (C-3', C-4'), 155.2, 155.4, 157.0, 157.3, 158.0, 158.8 (C-5, C-7, C-8a, C-2", C-4", C-6"); MS m/z (%): 442 (M^+, 3.6), 424 (5.8), 316 (6.4), 288 (17.8), 273 (23.5), 154 (100), 126 (45.7), 125 (79.8), 123 (61.3), 94 (34.4). Anal. Calcd. for $C_{23}H_{22}O_9$ H_2O: C, 60.0; H, 4.4. Found: C, 60.4; H, 5.2. Acetate of compound **2**: ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H,s), 1.92, 2.22, 2.28, 2.35 (15H, four s), 3.36, 3.72 (6H, two s), 4.58 (1H, d, J=9.2, C_2-H), 4.80 (1H, d, J=10.0, C_4-H), 5.70 (1H, t, J=10.0, C_3-H), 6.00, 6.13 (2H, two d, J=2.5, C_6-H, C_8-H), 6.74, 6.88 (2H, two d, J=2.5, $C_{3''}$-H, $C_{5''}$-H), 7.19-7.50 (3H, m).

2. Synthesis of model compound 3.

Compound 5 from phloroglucinol (**15**). To a stirred solution of compound **15** (3.24 g, 20 mM) in 100 ml of DMSO, K_2CO_3 (50.0 g, 360 mM) and benzyl chloride (8.3 ml, 72 mM) were added and the resulting suspension was vigorously stirred at r.t. for 15 hr. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4 and evaporated *in vacuo* to yield a red-brown solid, which was crystallized from ether/n-hexane (1:4, v/v). Crude compound **18**, which included about 30% of compound **19**, was obtained as colorless crystals (6.66 g) by recrystallization from ethanol. Compound **18**: mp 93-94°C (Lit.[21] 86-87°C).

To a stirred solution of compound **18** (6.66.g) in 40ml of acetic anhydride, $ZnCl_2$ (1.28 g, 8.5 mM) in 5 ml of acetic anhydride was added dropwise over a period of 5 min. The resulting red-brown solution was stirred at 0 °C for 3 hr. The reaction mixture was worked-up using the standard method to yield a red

oil. The product was purified by column chromatography (silica gel 100 g, 11 cm x 5 cm) eluted first with CH_2Cl_2/n-hexane (1:1, v/v) and then with CH_2Cl_2 to give compound **20** as a colorless oil (2.80 g, 32% yield based on compound **15**).

To a stirred solution of compound **20** (2.63 g, 6.0 mM) in 40 ml of CH_2Cl_2, $TiCl_4$ (330 µl, 3.0 mM) in 2 ml of CH_2Cl_2 was added at 0°C. After stirring for 10 min, the reaction mixture was worked-up using the standard method to yield a red-brown oil, which was purified by a short column chromatography (CH_2Cl_2) to remove high polar products. The product was crystallized from ether to give compound **5** as colorless crystals (1.19 g, 56.8% yield). Mp 103°C (Lit.[8] 101-102°C).

Compound 3. The aldol condensation of compound **5** and compound **6** and subsequent reactions were carried out under the same conditions as described for the synthesis of model compound **2**. For this reason, only data of these compounds are presented as follows.

Compound 8 was obtained in 94.6% yield from compound **5** and compound **6**. Mp 140°C; UV λmax (CH_3OH) nm (log ε): 252 (4.19), 258 (4.18),268 (sh, 4.12), 362 (4.63); IR ν max (KBr) cm^{-1}: 1625 (C=O); ^{1}H-NMR ($CDCl_3$) δ: 4.93, 5.06, 5.09, 5.21 (8H, four s, -Bzl), 6.16, 6.22 (2H, two d, J=1.6, $C_{3'}$-H, $C_{5'}$-H), 6.62-7.56 (23H, m), 7.63 (1H, d, J=15, C_β-H), 7.76 (1H, d, J=15, C_α-H).

Compound 12. UV λmax (CH_3CN) nm (log ε): 238(4.44), 287 (4.09); ^{1}H-NMR ($CDCl_3$) δ:4.95, 5.02, 5.12, 5.14 (8H, four s, -Bzl), 5.53 (1H, dd, J=10.0, 2.0, C_4-H), 5.71 (1H, dd, J=3.5, 2.0, C_2-H), 6.09, 6.17 (2H, two d, J=2.4, C_6-H, C_8-H), 6.87 (1H, dd, J=10.0, 2.0, C_4-H), 6.88-7.66 (23H, m).

Compound 14 was obtained in 64.8% overall yield from compound 8. Mp 181-182°C; UV λmax (CH_3OH) nm (log ε): 259 (3.45), 266 (sh, 3.54), 270 (sh, 3.61), 276 (3.65), 280 (sh, 3.65); ^{1}H-NMR ($CDCl_3$) δ: 2.51 (1H, d, J=7.4, C_3-OH), 2.73 (1H, d, J=2.5, C_4-OH), 3.90 (1H, ddd, J=10.0, 7.4, 4.0, C_3-H), 4.84 (1H, d, J=10.0, C_2-H), 4.98 (2H, s, -Bzl), 5.07 (3H, d, J=2.4, C_4-H, -Bzl), 5.16 (4H, s, -Bzl), 6.17, 6.27 (2H, two d, J=2.2, C_6-H, C_8-

H), 6.95-7.57 (23H, m). Anal. Calcd. for $C_{43}H_{38}O_7$ $0.8H_2O$: C, 75.8; H, 5.9. Found: C, 75.9; H, 5.6. Acetate of compound **14**: ^{1}H-NMR ($CDCl_3$) δ: 1.77, 2.04 (6H, two s), 5.00, 5.06, 5.17, 5.18 (8H, four s, -Bzl), 5.07 (1H, d, J=11.0, C_2-H), 5.40 (1H, dd, J=11.0, 3.5, C_3-H), 6.18, 6.26 (2H, two d, J=2.0, C_6-H, C_8-H), 6.51 (1H, d, J=3.5, C_4-H), 6.88-7.60 (23H, m).

Compound 17 was obtained in 90.4% yield from compound **14**. UV λ max (CH_3CN) nm (log ε): 258 (3.46), 266 (sh, 3.53), 276 (3.65), 280 (3.65); ^{1}H-NMR ($CDCl_3$) δ: 4.03 (1H, t, J=9.0, C_3-H), 4.44 (1H, d, J=8.8, C_2-H), 4.50 (1H, d, J=10.0, C_4-H), 4.72, 2.79 (2H, two d, J=14, -Bzl (A ring)), 4.94 (2H, s, -Bzl (A ring)), 5.09 (4H, s, -Bzl (B ring)), 5.87, 5.89 (2H, two s, C_3"-H, C_5"-H), 6.25 (2H, broad s, C_6-H, C_8-H), 6.80-7.60 (23H, m); MS m/z (%): 774 (M^+, 0.1), 181 (3.2), 126 (2.6), 92 (8.8), 91 (100). Anal. Calcd. for $C_{49}H_{42}O_9$ H_2O: C, 74.2; H, 5.7. Found: C, 74.5; H, 5.5. Acetate of compound **17**: ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, s), 1.81, 2.15, 2.25 (9H, three s), 4.54 (1H, d, J=9.4, C_2-H), 4.55, 4.74 (2H, two d, J=11.0, -Bzl(A ring)), 4.70 (1H, d, J=10.5, C_4-H), 4.94, 5.01 (2H, two d, J=11.0, -Bzl (A ring)), 5.15 (4H, s, -Bzl (B ring)), 5.70 (1H, t, J=10.0, C_3-H), 6.15, 6.17 (2H, two d, J=2.4, C_6-H, C_8-H), 6.56, 6.79 (2H, two d, J=2.4, C_3"-H, C_5"-H), 6.86-7.60 (23H, m).

Compound 3 was obtained in 99.3% yield from compound **17**. UV λ max (CH_3OH) nm (log ε): 280 (3.66); ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ: 4.25 (3H, broad s, C_2-H, C_3-H, C_4-H), 5.63-5.89 (4H, m, C_6-H, C_8-H, C_3"-H, C_5"-H), 6.66, 6.87 (3H, two s), 8.28, 8.60 (7H, two broad s, phenolic-OH); ^{13}C-NMR (DMSO-d_6) δ: 37.1 (C-4), 71.1 (C-3), 82.5 (C-2), 94.3, 95.1, 95.9 (C-6, C-8, C-3", C-5"), 105.8, 107.2 (C-4a, C-1"), 114.7 (C-2'), 115.1 (C-5'), 119.3 (C-6'), 130.8 (C-1'), 144.6, 144.7 (C-3', C-4'), 155.5, 155.8, 156.2, 156.7, 157.1 (C-5, C-7, C-8a, C-2", C-4", C-6"). Anal. Calcd. for $C_{21}H_{18}O_9$ $1.5H_2O$: C, 57.2; H, 4.8. Found: C, 57.1; H, 5.1. Acetate of compound **3**: ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s), 1.94, 1.98, 2.23, 2.25, 2.28, 2.29, 2.35 (21H, seven s), 4.59 (1H, d, J=9.2, C_2-H), 4.90 (1H, d, J=10.0, C_4-H), 5.88 (1H, t, J=10.0, C_3-H), 6.51, 6.70 (2H, two d, J=2.4, C_6-H, C_8-H), 6.91 (2H, s, C_3"-H, C_5"-H), 7.19-7.45 (3H, m).

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