Selective demethylation and debenzylation of aryl ethers by magnesium iodide under solvent-free conditions and its application to the total synthesis of natural products†

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An efficient selective demethylation and debenzylation method for aryl methyl/benzyl ethers using magnesium iodide under solvent-free conditions has been developed and applied to the synthesis of natural flavone and biphenyl glycosides. A variety of functional groups including glycoside were tolerated under the reaction conditions. Experimental results indicated that the removal of an *O*-benzyl group was easier than that of an *O*-methyl group, regardless of wherever they were *meta* or *para* to the carbonyl. Thus selective debenzylation can be achieved for substrates bearing both benzyloxy and methoxy groups.

Introduction

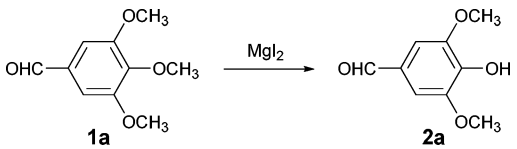
Demethylation and debenzylation of aryl methyl/benzyl ethers is a common strategy for the unmasking of Ar–OH functional groups in synthetic chemistry. Of the several conventional approaches for demethylation or debenzylation, Lewis acid-promoted methods are among the most widely used.[1,2] However, removal of aryl methyl/benzyl groups is not possible for compounds with labile groups using these methods, as they often result in undesired reactions and low yields. Thus, it is necessary to develop a new and efficient procedure for selective demethylation and debenzylation in the presence of functional groups under relatively mild conditions.

Magnesium iodide is an efficient Lewis acid that has been applied in various functional transformations and C–C bond-forming reactions.[3–5] MgI_2 in ether, ether–tetrahydrofuran, ether–benzene or ether–toluene is a mild and efficient reagent to remove phenolic *O*-methyl groups. This method works particularly well when the methyl ether is *ortho* to a carbonyl group.[6–10] To the best of our knowledge, however, there are only a few reports on the selective cleavage of *O*-methyl and *O*-benzyl groups at other positions with MgI_2. Herein, we wish to report a facile and selective demethylation and debenzylation of aryl methyl/benzyl ethers with MgI_2 under solvent-free conditions.

Results and discussion

The conventional synthesis of MgI_2 often requires several hours.[7] Considering that the preparation of MgI_2 is a biphasic liquid–solid process, we believed that the use of ultrasound should promote the reaction, and we found this to be correct. Taking care to protect the reaction from light, it only took a few minutes for the reaction between magnesium powder and iodine in dry ether to be complete under ultrasound irradiation. Thus, a rapid and efficient method for the synthesis of MgI_2 was developed.

Table 1 Selective demethylation of **1a** with MgI_2



1a **2a**

Entry	MgI_2 (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	1.5	Ether	Reflux	2.5	71
2	2	Ether–THF 1:3	Reflux	5	64
3	2	Ether–toluene 1:4	Reflux	2.5	60
4	2	THF	50	5	48
5	2	Toluene	50	0.5	59
6	2	Toluene	50	5	82
7	2	—	50	0.5	77
8	2	—	50	5	90
9	1.5	—	80	0.5	76
10	2	—	80	0.5	92
11	2	—	80	2.5	81
12	2	—	100	0.5	88
13	3	—	80	0.5	85

3,4,5-Trimethoxyphenyl and 4-hydroxy-3,5-dimethoxyphenyl groups are common structural motifs in both natural products and synthetic pharmaceuticals.[11,12] It has been reported that direct transformation of the former to the latter can be performed in the presence of demethylating agents such as BBr_3 and CH_3MgI.[13,14] Following these previously reported methods, a model reaction of **1a** with MgI_2 under conventional reflux conditions in various solvents was performed to give the demethylation product **2a** in moderate yields (60–71%, Table 1, entries 1–3). Based on the proposed demethylation mechanism, we presumed that the coordination of MgI_2 with the oxygen atoms of the solvent was interfering with the chelate formed between MgI_2 and the substrate. This interference may have a detrimental effect on yield. We therefore proceeded to repeat this reaction under

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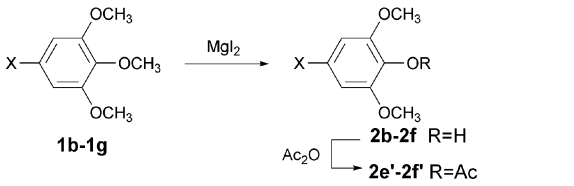
† Electronic supplementary information (ESI) available: Data for known compounds (**2b–2d**, **2f′**, **4a–4f**, **4h**, **6a** and **6c**), and copies of NMR spectra of all compounds. See DOI: 10.1039/b916969e

Table 2 Selective demethylation of pyrogallol trimethyl ethers with MgI_2



1b-1g

Entry	Substrate	Time (h)	Product	Yield (%)
1	**1b**, X = $COCH_3$	0.5	**2b**	90
2	**1c**, X = COOH	0.5	**2c**	86
3	**1d**, X = $COOC_2H_5$	0.5	**2d**	86
4	**1e**, X = H	3	**2e′**	78
5	**1f**, X = CH_3	2.5	**2f′**	83
6	**1g**, X = $CHOHCH_3$	0.5	—	—

different conditions (entries 4–8) and found that: (1) only 48% of demethylation product **2a** was obtained when THF was used as the solvent; (2) the use of toluene could improve the yield of **2a** significantly; (3) the reaction of **1a** with MgI_2 proceeded successfully at 50 °C under solvent-free conditions, in 5 h, to give **2a** in good yield.

In order to optimize the conditions, we examined the influence of stoichiometry, reaction time and temperature on the yield (entries 9–13). The optimal conditions provided **2a** in 92% yield when **1a** was reacted with MgI_2 (2 equiv.) under solvent-free conditions at 80 °C for 0.5 h. These results indicated that ether solvents such as ether and THF were unfavorable to the reactions. Furthermore, by avoiding the coordination of MgI_2 with the oxygen atoms of the solvent, the use of toluene or solvent-free conditions could not only improve the yield but also accelerate the reaction significantly, and indeed, the best result was obtained when the reaction was carried out under solvent-free conditions.

With these optimized conditions, we investigated the reaction of diverse pyrogallol trimethyl ethers with MgI_2. A variety of functional groups including $COCH_3$, COOH and $COOC_2H_5$ were tolerated under the reaction conditions. Substrates **1b–1d** were efficiently transformed to give **2b–2d**, respectively (Table 2 entries 1–3). For substrates **1e** and **1f**, the unstable demethylated products **2e–2f** were trapped by acylation with acetic anhydride to give **2e′** and **2f′** respectively. Unfortunately, attempts at demethylation of **1g** led to complex mixtures.

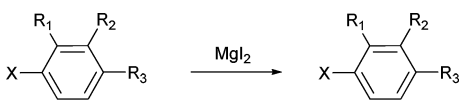
To demonstrate the utility of this method, we then extended the substrate scope to include aryl methyl ethers **3a–3f**, bearing one to three methoxy groups, and found that the reactions proceeded readily under the standard conditions. As shown in Table 3, the methyl groups *ortho*, *meta* or *para* to the carbonyl group of monomethoxy-substituted substrates could be readily cleaved, although more time was required (entries 1–3). As for dimethoxy- and trimethoxy-substituted aryl ethers **3d–3f** (entries 4–6), the methyl group *ortho* or *para* to the carbonyl group could be selectively removed.

Methyl and benzyl ethers have been widely used as stable protecting groups for the hydroxyl groups in organic synthesis. Some demethylation methods such as BBr_3 and piperazine/DMA[15,16] are also suitable for removal of benzyl groups. However, mild debenzylation conditions that tolerate labile groups are still needed. Thus, we further investigated the reactions of several aryl benzyl ethers **3g–3j** under the standard conditions, and the results are summarized in Table 3 (entries 7–10). Substrates with *ortho*-, *meta*- or *para*-substituted benzyloxy groups worked well to give the debenzylated products in excellent yields.

In view of the results obtained, we were interested in exploring the relative reactivity of benzyl and methyl groups when both functional groups were present in one molecule. For this purpose, aryl ethers **5a–5c** were investigated. As shown in Table 4, the removal of the *O*-benzyl group was easier than that of the *O*-methyl group, regardless of wherever they were *meta* or *para* to the carbonyl. These observations were consistent with the experiments in entry 4. Treatment of an equimolar mixture of **3c** and **3j** with MgI_2 at 80 °C led to a 76% conversion of **3j** to its debenzylation product **4j**, while the unreacted starting material **3c** was recovered. These observations suggested that under our conditions, selective debenzylation could be realized for substrates bearing both benzyloxy and methoxy groups.

Encouraged by these interesting results, investigation of more complicated structures such as biphenyl compounds **7a–7c** was

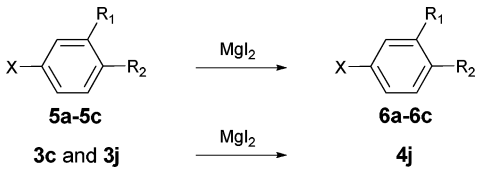
Table 3 Demethylation/debenzylation of aryl methyl/benzyl ethers with MgI_2



3a-3j 4a-4j

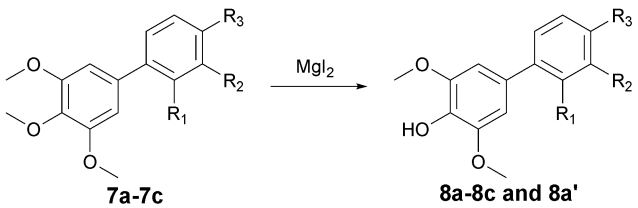
Entry	Substrate	X	R_1	R_2	R_3	Time (h)	Product	X	R_1	R_2	R_3	Yield (%)
1	**3a**	CHO	OCH_3	H	H	5	**4a**	CHO	OH	H	H	93
2	**3b**	CHO	H	OCH_3	H	5	**4b**	CHO	H	OH	H	89
3	**3c**	CHO	H	H	OCH_3	10	**4c**	CHO	H	H	OH	77
4	**3d**	$COCH_3$	OCH_3	OCH_3	OCH_3	10	**4d**	$COCH_3$	OH	OCH_3	OCH_3	84
5	**3e**	CHO	OCH_3	OCH_3	H	10	**4e**	CHO	OH	OCH_3	H	80
6	**3f**	CHO	H	OCH_3	OCH_3	8	**4f**	CHO	H	OCH_3	OH	87
7	**3g**	CHO	OBn	H	H	6	**4g (4a)**	CHO	OH	H	H	90
8	**3h**	COOH	OBn	H	H	6	**4h**	COOH	OH	H	H	92
9	**3i**	CHO	H	OBn	H	5	**4i (4b)**	CHO	H	OH	H	93
10	**3j**	CHO	H	H	OBn	7	**4j (4c)**	CHO	H	H	OH	88

Table 4 Selective debenzylation of aryl ethers with MgI_2



Entry	Substrate	X	R_1	R_2	Time (h)	Product	X	R_1	R_2	Yield (%)
1	**5a**	CHO	OBn	OCH_3	10	**6a**	CHO	OH	OCH_3	87
2	**5b**	CHO	OCH_3	OBn	10	**6b** (**4f**)	CHO	OCH_3	OH	83
3	**5c**	COOH	OCH_3	OBn	10	**6c**	COOH	OCH_3	OH	80
4	**3c** and **3j**				5	**4j**				76

Table 5 Demethylation/debenzylation of biphenyl compounds with MgI_2



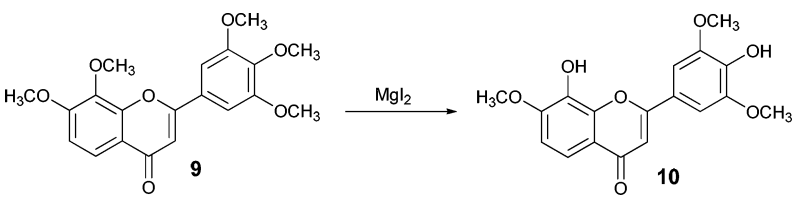
Entry	Substrate	R_1	R_2	R_3	MgI_2 (equiv.)	Time (h)	Product	R_1	R_2	R_3	Yield (%)
1	**7a**	F	OCH_3	H	2	4	**8a**	F	OCH_3	H	67
2	**7a**	F	OCH_3	H	4	4	**8a′**	F	OH	H	58
3	**7b**	H	OBn	H	4	6	**8b**	H	OH	H	76
4	**7c**	H	OBn	CHO	4	8	**8c**	H	OH	CHO	84

carried out (Table 5). It was found that 2.0 equiv. MgI_2 led to selective removal of the *O*-methyl group at the 4-position of **7a** (entries 1–2), whereas increasing the amount of MgI_2 to 4.0 equiv. resulted in formation of **8a′**. For substrates **7c** and **7d** bearing benzyloxy and methoxy groups, demethylation and debenzylation products were obtained smoothly in 76% and 84% yields, respectively.

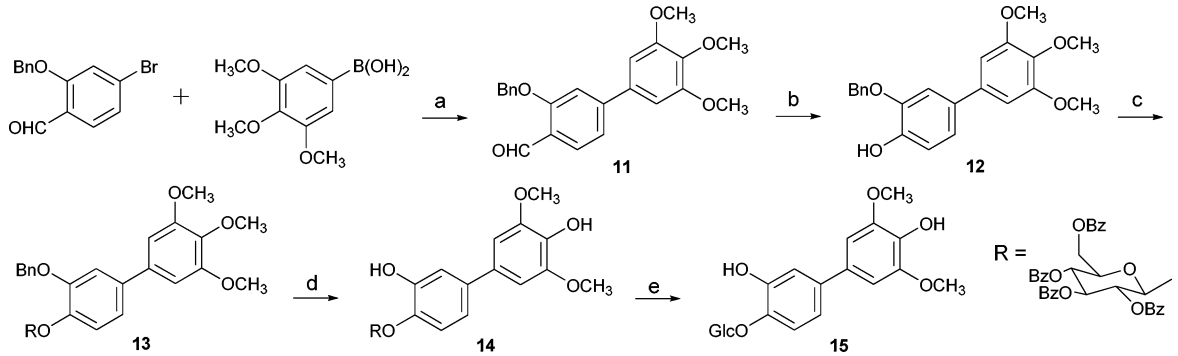
To explore the substrate diversity, this method was applied to the synthesis of natural products. 8,4′-Dihydroxy-7,3′,5′-trimethoxyflavone (**10**), a natural product isolated from the stem bark of *Muntingia calabura*, has demonstrated potential cytotoxicity against the P-338 cell line.[17] Following the procedure described above, selective demethylation of compound **9**, which was reported in our previous work,[18] with MgI_2 at 50 °C under solvent-free conditions gave **10** in 61% yield (Scheme 1). Synthetic **10** was identical in all respects (^{1}H NMR, ^{13}C NMR, MS) with the natural flavone.

In the continuation of our research, we extended our method to the synthesis of a more complex natural product. We selected fortuneanoside E (**15**) as our target. This compound was isolated from the fruit of *Pyracantha fortueana* by our group and was found to show potent *in vitro* tyrosinase inhibitory activity.[19] The structure of **15** features a β-D-glucopyranoside and a biphenyl moiety with a hydroxyl on each ring. Taking into consideration the interesting chemical structure of **15**, an efficient synthesis was designed (Scheme 2).

Our synthesis commenced with a Suzuki–Miyaura cross-coupling between commercially available 3,4,5-trimethoxyphenylboronic acid and 2-benzyloxy-4-bromobenzaldehyde to yield biphenyl **11**. Baeyer–Villiger oxidation of **11** with *m*-CPBA in the presence of Na_2HPO_4 gave the corresponding ester, which was hydrolyzed to furnish phenol **12**. Glycosylation of **12** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate[20] in the presence of $BF_3{\cdot}Et_2O$ afforded **13**. In the key step, selective



Scheme 1 Synthesis of natural flavone **10**.



Scheme 2 Synthesis of natural biphenyl glycoside **15**. *Reagents and conditions*: (a) K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (0.01 equiv.), DMF, 110 °C (72%); (b) *m*-CPBA (5.0 equiv.), Na_2HPO_4 (1.3 equiv.), CH_2Cl_2, 0 °C, then reflux; KOH (1.1 equiv.), H_2O, RT (78%); (c) 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (2.0 equiv.), $BF_3{\cdot}Et_2O$ (0.1 equiv.), CH_2Cl_2, −10 °C, 30 min, (91%); (d) MgI_2 (4.0 equiv), 50 °C (83%); (e) NaOH (4.1 equiv.), RT, (93%).

demethylation and debenzylation were achieved by treatment of **13** with MgI_2 at 80 °C under solvent-free conditions to give **14** in 83% yield. Finally, deprotection of **14** with NaOH afforded **15** in near-quantitative yield, which was characterized by MS and NMR techniques. The total synthesis of **15** was thereby accomplished with an overall yield of 39%. It was particularly noteworthy that conversion of **13** to **14** was achieved in a single step. Moreover, the sensitive glucosidic bond and benzoyl groups on the glucose moiety remained unaffected when the *O*-methyl in the 4′-position and *O*-benzyl groups of **3** were removed selectively.

Conclusions

In summary, we have developed a practical and selective demethylation/debenzylation method using MgI_2 under solvent-free conditions. The substrate scope was investigated and included several kinds of aryl ethers featuring methoxy and/or benzyloxy groups. A variety of functional groups were tolerated under the reaction conditions. Selective debenzylation could be achieved when *O*-benzyl and *O*-methyl groups were present in one molecule. Furthermore, the first total syntheses of natural products were accomplished by this method, which has been proved to be a general strategy for selective demethylation and/or debenzylation of aryl methyl/benzyl ethers.

Experimental

General

MgI_2 was prepared in an ultrasonic cleaner (KQ-400KDE, made in Kunshan Ultrasonic Equipment Co., Ltd.) with frequency of 25 kHz and a nominal power of 400 W at 20–23 °C. Unless otherwise noted, all the materials were obtained from commercially available sources and were used without purification. Thin-layer chromatography was performed on GF254 silica gel plates to monitor the reaction, and the plates were examined under UV light. The purification of the products was performed using column chromatography (60 Å, 200–300 mesh, Qingdao Ocean Chemicals or 120 Å, S-50μm, YMC Co., Ltd.), or silica gel plates (0.25 mm layer, Qingdao Ocean Chemicals) with the designated solvents. IR spectra were obtained using a JASCO FT/IR-480 plus spectrometer. ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ solution on Bruker ARX-300, Bruker AV-400 and Bruker AV-600 spectrometers with TMS as the internal reference. Chemical shifts were reported in ppm downfield from tetramethylsilane and proton–proton coupling constants (*J*) in Hz. ESI-MS spectra were performed on a Finigan LCQ Advantage MAX mass spectrometer. HR-ESI-MS spectra were acquired using a Micromass Q-TOF mass spectrometer. For data of the known compounds (**2b–2d**, **2f′**, **4a–4f**, **4h**, **6a** and **6c**), see the ESI†.

4-Hydroxy-3,5-dimethoxybenzaldehyde (2a)

To magnesium powder (0.17 g, 7.08 mmol) in dry ether (10 mL), I_2 crystals (0.86 g, 3.39 mmol) were added in small portions. The mixture was protected from light under N_2 and placed in an ultrasonic cleaner until the reaction mixture turned colorless (8 min). The resulting mixture of magnesium iodide etherate was separated from unreacted Mg. MgI_2 (0.28 g, 1.02 mmol) in dry ether (10 mL) was added to a solution of **1a** (0.10 g, 0.51 mmol) in CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure and the residual solid was heated at 80 °C for 0.5 h. Then H_2O (20 mL) and $Na_2S_2O_3$ was added and the reaction mixture was poured into 5% hydrochloric acid (10 mL). The solution was extracted with EtOAc (2 × 15 mL) and the combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and saturated brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by preparative thin layer chromatography (petrol–EtOAc 2:1) to give **2a** as a white solid (0.08 g, 92%). ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 9.82 (s, 1H, CHO), 7.16 (s, 2H, 2,6-H), 6.12 (s, 1H, OH), 3.98 (s, 6H, CH_3O); MS (ESI, *m*/*z*): 181 [M − H^-]; data consistent with the literature.[21]

2,6-Dimethoxyphenyl acetate (2e′)

To a solution of **1e** (0.10 g, 0.59 mmol) in CH_2Cl_2 (10 mL), a mixture of MgI_2 (0.33 g, 1.18 mmol) in dry ether (10 mL) was added. The solvent was removed under reduced pressure and the residual solid was heated at 80 °C for 3 h. Then acetic anhydride (15 mL) was added and stirred for 24 h under 25 °C. Then H_2O (50 mL) and $Na_2S_2O_3$ was added and the reaction mixture was poured into 5% hydrochloric acid (10 mL), and extracted with EtOAc (2 × 15 mL). The combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and

saturated brine (20 mL) before drying ($MgSO_4$) and evaporation in *vacuo*. The crude product was purified by preparative thin layer chromatography (petrol–EtOAc 2:1) to give **2e′** as a white solid (0.09 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.12 (t, 1H, J = 8.4 Hz, 4-H), 6.61 (d, 2H, J = 8.4 Hz, 3,5-H), 3.81 (s, 6H, CH_3O), 2.33 (s, 3H, CH_3CO); MS (ESI, m/z): 219 [M + Na^+]; data consistent with the literature.[22]

2′-Fluoro-3,3′,5-trimethoxybiphenyl-4-ol (8a)

IR (KBr) ν_{max}/cm^{-1} 3420, 3003, 2937, 2844, 2360, 1611, 1219, 1116; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.10 (m, 1H, 5′-H), 6.99 (m, 1H, 6′-H), 6.93 (m, 1H, 4′-H), 6.78 (s, 2H, 2,6-H), 5.57 (s, 1H, 4-OH), 3.92 (s, 6H, 3,5-CH_3O), 3.93 (s, 3H, 3′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 150.8 (C-2′), 148.4 (C-3′), 147.0 (C-3/C-5), 134.8 (C-4), 130.1 (C-1′), 126.7 (C-1), 123.8 (C-5′), 121.9 (C-6′), 112.0 (C-4′), 106.2 (C-2/C-6), 56.4 (3,5-CH_3O); MS (ESI, m/z): 301 [M + Na^+], 277 [M – H^-]; HRMS (ESI, m/z) Calcd. for $C_{15}H_{15}FO_4Na^+$ 301.0847, found 301.0853.

2-Fluoro-3′,5′-dimethoxybiphenyl-3,4′-diol (8a′)

IR (KBr) ν_{max}/cm^{-1} 3407, 2924, 2852, 2360, 1614, 1216, 1115; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.07 (m, 1H, 6-H), 6.99 (m, 2H, 4,5-H), 6.77 (s, 2H, 2′,6′-H), 3.93 (s, 6H, 3′,5′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 149.5 (C-2), 147.0 (C-3′/C-5′), 144.2 (C-3), 134.9 (C-4′), 129.7 (C-1), 126.5 (C-1′), 124.4 (C-5), 121.6 (C-6), 115.8 (C-4), 106.1 (C-2′/C-6′), 56.4 (3′, 5′-CH_3O); MS (ESI, m/z): 287 [M + Na^+], 263 [M – H^-]; HRMS (ESI, m/z) Calcd. for $C_{14}H_{23}FO_4Na^+$ 287.0690, found 287.0701.

3′,5′-Dimethoxybiphenyl-3,4′-diol (8b)

IR (KBr) ν_{max}/cm^{-1} 3419, 2924, 2852, 1712, 1613, 1217, 1114; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.29 (m, 1H, 5-H), 7.12 (m, 1H, 2-H), 7.02 (m, 1H, 6-H), 6.79 (s, 2H, 2′,6′-H), 6.78 (m, 1H, 4-H), 3.95 (s, 6H, 3′,5′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 156.7 (C-3), 147.3 (C-3′/C-5′), 143.3 (C-1), 134.7 (C-4′), 132.4 (C-1′), 129.9 (C-5), 119.6 (C-6), 114.0 (C-4), 113.8 (C-2), 104.2 (C-2′/C-6′), 56.4 (3′, 5′-CH_3O); MS (ESI, m/z): 269 [M + Na^+], 245 [M – H^-]; HRMS (ESI, m/z) Calcd. for $C_{14}H_{14}O_4Na^+$ 269.0784, found 269.0789.

3,4′-Dihydroxy-3′,5′-dimethoxybiphenyl-4-carbaldehyde (8c)

IR (KBr) ν_{max}/cm^{-1} 3451, 2925, 2852, 2359, 1645, 1210, 1107; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 11.12 (s, 1H, CHO), 9.90 (s, 1H, 3-OH), 7.58 (d, 1H, J = 8.0 Hz, 5-H), 7.20 (dd, 1H, J = 8.0 Hz, 1.5 Hz, 6-H), 7.17 (d, 1H, J = 1.5 Hz, 2-H), 6.85 (s, 2H, 2′,6′-H), 5.64 (s, 1H, 4′-OH), 3.96 (s, 6H, 3′,5′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 195.8 (CHO), 162.0 (C-3), 150.0 (C-1), 147.5 (C-3′/C-5′), 134.0 (C-4′), 130.8 (C-1′), 121.0 (C-4), 119.4 (C-5), 118.5 (C-6), 115.3 (C-2), 104.5 (C-2′/C-6′), 56.5 (3′, 5′-CH_3O); MS (ESI, m/z): 275 [M + H^+], 273 [M – H^-]; HRMS (ESI, m/z) Calcd. for $C_{15}H_{14}O_5H^+$ 275.0914, found 275.0908.

8,4′-Dihydroxy-7,3′,5′-trimethoxyflavone (10)

MgI_2 (0.60 g, 2.15 mmol) in dry ether (15 mL) was added to a solution of **9** (0.20 g, 0.54 mmol) in CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure and the residual solid was heated at 50 °C for 0.5 h. Then H_2O (20 mL) and $Na_2S_2O_3$ was added and the reaction mixture was poured into 5% hydrochloric acid (10 mL). The solution was extracted with EtOAc (2 × 15 mL) and the combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and saturated brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by preparative thin layer chromatography (petrol–EtOAc 2:1) to give **10** as a white solid (0.11 g, 61%). ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ 7.76 (d, 1H, J = 8.8 Hz, 5-H), 7.22 (s, 2H, 2′,6′-H), 7.01 (d, 1H, J = 8.8 Hz, 6-H), 6.69 (s, 1H, 3-H), 4.04 (s, 3H, 7-CH_3O), 3.99 (s, 6H, 3′,5′-CH_3O); MS (ESI, m/z): 367 [M + Na^+]; data consistent with the literature.[17]

3-Benzyloxy-3′,4′,5′-trimethoxybiphenyl-4-carbaldehyde (11)

To a solution of 2-benzyloxy-4-bromobenzaldehyde (5.24 g, 18.00 mmol) and 3,4,5-trimethoxyphenylboronic acid (2.54 g, 12.00 mmol) in DMF (20 mL), was added anhydrous K_2CO_3 (3.32 g, 24.00 mmol) and $Pd(OAc)_2$ (0.08 g, 0.36 mmol). The reaction mixture was strirred at 110 °C for 5 h, then cooled to room temperature and poured into water, filtered and recrystallized with ethyl acetate to afford **11** as a colorless solid (3.27 g, 72%). IR (KBr) ν_{max}/cm^{-1} 3432, 2921, 2852, 2361, 1678, 1604, 1132, 1004; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 10.57 (s, 1H, CHO), 7.90 (d, 1H, J = 8.0 Hz, 5-H), 7.36-7.48 (m, 5H, benzyl-H), 7.21 (d, 1H, J = 8.1 Hz, 6-H), 7.15 (s, 1H, 2-H), 6.70 (s, 2H, 2′,6′-H), 5.29 (s, 2H, CH_2Obenzyl), 3.91 (s, 6H, 3′,5′-CH_3O), 3.90 (s, 3H, 4′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 189.24 (CO), 161.2 (C-3), 153.6 (C-3′/C-5′), 149.0 (C-1), 138.9 (C-4′), 135.9 (C-1′), 136.2, 128.8, 128.3, 127.3 (C-benzyl), 129.0 (C-5), 124.1 (C-4), 120.0 (C-6), 112.0 (C-2), 104.8 (C-2′/C-6′), 70.8 (CH_2Obenzyl), 61.0 (4′-CH_3O), 56.4 (3′,5′-CH_3O); MS (ESI, m/z): 401 [M + Na^+], 779 [2M + Na^+]; HRMS (ESI, m/z) Calcd. for $C_{23}H_{22}O_5Na^+$ 401.1365, found 401.1361.

3-Benzyloxy-3′,4′,5′-trimethoxybiphenyl-4-ol (12)

m-CPBA (85%, 8.63 g, 42.50 mmol) was added in portions to a suspension of **11** (3.22 g, 8.50 mmol) and anhydrous Na_2HPO_4 (1.57 g, 11.05 mmol) in CH_2Cl_2 (50 mL) in an ice–water bath and the mixture was stirred at room temperature for 1 h. The resulting mixture was refluxed overnight, then cooled and filtered. The filter cake was washed with CH_2Cl_2 (3 × 30 mL). Evaporation of the solvent *in vacuo* gave a residue that was directly used in the next reaction. KOH (0.52 g, 9.35 mmol) in H_2O (10 mL) was added to the crude formate in MeOH (20 mL) and stirred for 2 h at room temperature. The mixture was concentrated and acidified with hydrochloric acid (5 mL of a 2 M solution). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), washed with H_2O (2 × 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (*n*-hexane–EtOAc 3:1) to give **12** (2.43 g, 78%) as a light yellow solid. IR (KBr) ν_{max}/cm^{-1} 3538, 2957, 2937, 2360, 1581, 1498, 1261, 1131, 1003; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.36-7.46 (m, 5H, benzyl-H), 6.99 (m, 1H, 2-H), 7.06-7.08 (m, 2H, 5,6-H), 6.65 (s, 2H, 2′,6′-H), 5.66 (s, 1H, OH), 5.19 (s, 2H, CH_2Obenzyl), 3.90 (s, 6H, 3′,5′-CH_3O), 3.87 (s, 3H, 4′-CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 153.4 (C-3′/C-5′), 145.9 (C-3), 145.6 (C-4), 137.2 (C-1), 137.1 (C-4′), 133.9 (C-1′), 136.4,

128.8, 128.5, 127.8 (C-benzyl), 120.5 (C-6), 114.9 (C-5), 111.6 (C-2), 104.4 (C-2′/C-6′), 71.4 (CH_2Obenzyl), 60.9 (4′-CH_3O), 56.2 (3′,5′-CH_3O); MS (ESI, *m/z*): 389 [M + Na^+], 365 [M − H^-]; HRMS (ESI, *m/z*) Calcd. for $C_{22}H_{22}O_5Na^+$ 389.1365, found 389.1370.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Benzoyloxymethyl)-6-(3-benzyloxy-3′,4′,5′-trimethoxybiphenyl-4-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (13)

A solution of the 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate (4.05 g, 5.46 mmol) and freshly activated 4 Å molecular sieves (8.20 g) in CH_2Cl_2 (80 mL) was treated at −10 °C with a solution of **12** (1.00 g, 2.73 mmol) in CH_2Cl_2 (12 mL). After being stirred for 30 min, $BF_3{\cdot}OEt_2$ (34 μL, 0.27 mmol) in CH_2Cl_2 (5 mL) was added dropwise at −10 °C. The mixture was stirred for another 30 min at the same temperature after which the reaction was quenched by slow addition of MeOH (60 mL). The solution was filtered and the residue washed carefully with CH_2Cl_2 and MeOH. The combined organic phases were washed with 15% $NaHCO_3$ solution (180 mL) and brine (180 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was subjected to silica gel flash chromatography (petrol–EtOAc 2:1), and **13** (2.35 g, 91%) was obtained as a pale white solid. IR (KBr) ν_{max}/cm^{-1} 3437, 2925, 2360, 1733, 1264, 1127, 1093, 1069, 710; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.85–8.01 (m, 8H, benzoyl-H), 7.27-7.65 (m, 15H, Ar-H), 7.00 (d, 1H, *J* = 2.1 Hz, 2-H), 6.90 (dd, 1H, *J* = 8.3 Hz, 2.1 Hz, 6-H), 6.57 (s, 2H, 2′,6′-H), 6.06 (m, 1H, Glc-3″), 5.86 (m, 1H, Glc-5″), 5.77 (m, 1H, Glc-2″), 5.58 (d, 1H, *J* = 7.8 Hz, Glc-1″), 4.66 (m, 1H, *J* = 7.8 Hz, Glc-4″), 4.59/4.41 (m, 2H, Glc-6″), 3.86 (s, 6H, 3′,5′-CH_3O), 3.83 (s, 3H, 4′-CH_3O), 4.96/4.92 (d, 2H, *J* = 12.6 Hz, CH_2Obenzyl); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 167.1, 166.8, 166.4, 166.3(CO), 154.0 (C-3′/C-5′), 150.0 (C-3), 146.9 (C-4), 138.4 (C-1), 138.1 (C-4′), 137.8, 134.4, 134.2, 134.1, 133.9, 127.8-130.5 (Ar-C), 137.5 (C-1′), 120.5 (C-2/C-5), 115.4 (C-6), 105.0 (C-2′/C-6′), 101.3 (Glc-1″), 74.0 (Glc-2″), 73.1 (Glc-3″), 72.9 (Glc-5″), 71.8 (CH_2Obenzyl), 70.7 (Glc-6″), 63.9 (Glc-4″), 61.2 (4′-CH_3O), 55.6 (3′,5′-CH_3O); MS (ESI, *m/z*): 967 [M + Na^+], 1911 [2M + Na^+]; HRMS (ESI, *m/z*) Calcd. for $C_{56}H_{48}O_{14}Na^+$ 967.2942, found 967.2931.

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Benzoyloxymethyl)-6-(3,4′-dihydroxy-3′,5′-dimethoxybiphenyl-4-yloxy)tetrahydro-2*H*-pyran-3,4,5-triyl tribenzoate (14)

MgI_2 (0.59 g, 2.12 mmol) in dry ether (10 mL) was added to a solution of **13** (0.50 g, 0.53 mmol) in CH_2Cl_2 (10 mL). The solvent was removed under reduced pressure and the residual solid was heated at 80 °C for 5 h. Then H_2O (20 mL) and $Na_2S_2O_3$ were added and the mixture was poured into 5% hydrochloric acid (10 mL), and extracted with EtOAc (2 × 15 mL). The combined organic phase was washed with saturated sodium bicarbonate solution (20 mL) and saturated brine (20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The crude product was purified by silica gel flash chromatography (petrol–EtOAc 2:1) to give **14** as a white solid (0.37 g, 83%). IR (KBr) ν_{max}/cm^{-1} 3446, 2920, 1730, 1452, 1280, 1098, 756; ^{1}H NMR (600 MHz, $CDCl_3$, TMS): δ 7.87–8.09 (m, 8H, benzoyl-H), 7.30-7.55 (m, 12H, Ar-H), 7.09 (d, 1H, *J* = 1.8 Hz, 2-H), 7.01 (d, 1H, *J* = 8.3 Hz, 5-H), 6.82 (dd, 1H, *J* = 8.3 Hz, 1.8 Hz, 6-H), 6.68 (s, 2H, 2′,6′-H), 6.20 (s, 1H, OH), 6.05 (m, 1H, Glc-3″), 5.79 (m, 1H, Glc-5″), 5.75 (m, 1H, Glc-2″), 3.92 (s, 6H, 3′,5′-CH_3O), 5.52 (s, 1H, OH), 5.29 (d, 1H, *J* = 7.9 Hz, Glc-1″), 4.75 (m, 1H, Glc-4″), 4.54/4.33 (m, 2H, Glc-6″); ^{13}C NMR (150 MHz, $CDCl_3$, TMS): δ 166.0, 165.9, 165.7, 165.2 (CO), 133.8, 133.7, 133.5, 133.3, 133.9, 128.4-132.0 (Ar-C), 147.3 (C-3), 147.2 (C-3′/C-5′), 143.4 (C-4), 138.7 (C-1), 137.0 (C-4′), 136.3 (C-1′), 118.5 (C-2), 117.5 (C-5), 114.7 (C-6), 103.8 (C-2′/C-6′), 102.0 (Glc-1″), 72.9 (Glc-2″), 72.3 (Glc-3″), 69.3 (Glc-5″), 63.7 (Glc-6″), 62.8 (Glc-4″), 56.3 (3′,5′-CH_3O); MS (ESI, *m/z*): 863 [M + Na^+], 839 [M − H^-]; HRMS (ESI, *m/z*) Calcd. for $C_{48}H_{40}O_{14}Na^+$ 863.2361, found 863.2296.

(2*S*,3*R*,4*S*,5*S*,6*R*)-2-(3,4′-Dihydroxy-3′,5′-dimethoxybiphenyl-4-yloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (15)

NaOH (0.10 g, 2.50 mmol) in H_2O (10 mL) was added to a solution of **14** (0.15 g, 0.18 mmol) in MeOH (20 mL), and the mixture was stirred for 2 h at room temperature. The mixture was concentrated, acidified with hydrochloric acid (5 mL of a 2 M solution) and extracted with EtOAc (2 × 15 mL). The combined water phase was then subjected to column chromatography on YMC S-50 gel (CH_3OH–H_2O 1:1) to give **15** as a white solid (0.70 g, 93%). ν_{max}/cm^{-1} 3433, 2921, 1630, 1608, 1453, 1065, 713; ^{1}H NMR (400 MHz, CD_3OD, TMS): δ 7.21 (d, 1H, *J* = 8.4 Hz, 5-H), 7.05 (d, 1H, *J* = 2.2 Hz, 2-H), 6.98 (dd, 1H, *J* = 8.4 Hz, 2.2 Hz, 6-H), 6.77 (s, 2H, 2′,6′-H), 3.92/3.73 (m, 2H, Glc-6″); 3.88 (s, 6H, 3′,5′-CH_3O), 3.51 (m, 1H, Glc-3″), 3.47 (m, 1H, Glc-2″), 3.43 (m, 1H, Glc-5″), 3.41 (m, 1H, Glc-4″); ^{13}C NMR (100 MHz, CD_3OD, TMS): δ 149.5 (C-3′/C-5′), 148.6 (C-3), 145.9 (C-4), 138.7 (C-1), 136.3 (C-4′), 133.2 (C-1′), 119.24 (C-5), 119.21 (C-2), 115.4 (C-6), 105.4 (C-2′/C-6′), 104.5 (Glc-1″), 78.3 (Glc-5″), 77.7 (Glc-3″), 74.9 (Glc-2″), 71.3 (Glc-4″), 62.5 (Glc-6″), 56.9 (3′,5′-CH_3O); MS (ESI, *m/z*): 447 [M + Na^+], 423 [M − H^-]; HRMS (ESI, *m/z*) Calcd. for $C_{20}H_{24}O_{10}Na^+$ 447.1267, found 447.1278.

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