Regioselectivity of methylation of *O*-demethylangolensin [1-(2,4-dihydroxyphenyl)-2-(4-hydroxyphenyl)propan-1-one]. An expedient synthesis of angolensin

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1-(2,4-Dihydroxyphenyl)-2-(4-hydroxyphenyl)propan-1-one (**1**), also known as 2′,4′,4″-trihydroxy-α-methyldeoxybenzoin or *O*-demethylangolensin (ODMA), is regioselectively 4-*O*-alkylated at ring B *via* the triphenolate anion by one equivalent of methyl iodide in DMF to give angolensin **2** in good yield. Appropriate adjustments of the substrate : base : electrophile ratios allow the synthesis of the regioisomer **3** or the bis(methyl ether) **4**.

Recently, compounds of the 1,2-diarylpropan-1-one type, including angolensin **2**, have been discovered in human urine.[1] It is assumed that they originate from isoflavonoids present in food by metabolic action of the alimentary system microflora. Studies on the biological effects and role in steroid biosynthesis of 1,2-diarylpropan-1-ones are presently underway.[2]

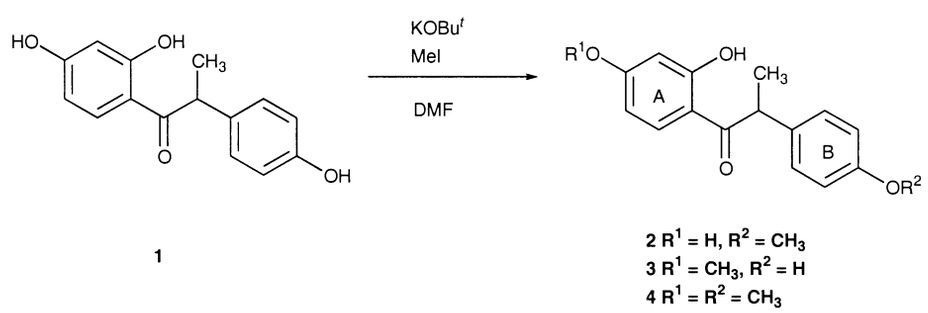
Angolensin has been previously prepared from resorcinol dibenzyl ether and 2-methoxypropionic acid chloride, overall in 5 steps in unspecified yield.[3] Angolensin has also been prepared in 11% yield by 2-methylation and deprotection of 1-[2,4-bis(benzyloxy)phenyl]-2-(4-methoxyphenyl)propan-1-one.[4] In another report, 2-methylation of 1-(4-benzyloxy-2-hydroxyphenyl)-2-(4-methoxyphenyl)propan-1-one, followed by acidic debenzylation, gave angolensin in about 60% yield.[5] Obviously the preparation of these starting materials requires further synthetic steps. We have recently reported the synthesis of angolensin by the reduction of 7-hydroxy-4′-methoxyisoflavone with lithium aluminium hydride in 42% yield.[6] Here we describe an efficient synthesis of angolensin **2** by regioselective ring B 4-*O*-alkylation of the triphenolate anion of unprotected, commercially available *O*-demethylangolensin **1** by methyl iodide in 63% yield (Scheme 1). We also show that appropriate adjustments of the substrate : base : electrophile ratio allow the synthesis of the regioisomer **3** or the bis(methyl ether) **4** (Table 1).

We have shown earlier that in dihydroxyisoflavones such as daidzein (4′,7-dihydroxyisoflavone) and genistein (4′,5,7-trihydroxyisoflavone), the 7-OH exhibits a hundredfold greater acidity compared to the 4′-hydroxy group, which can be exploited in selective mono-*O*-alkylations[7] or acylations[8] of these isoflavones. A study of the acidity of phenolic hydroxy groups in *O*-demethylangolensin **1** by the reaction-simulating computer program CAMEO[9] gives a pK_a value of 14 in DMSO for the ring A 2-hydroxy group, 15 for the ring A 4-OH and 18 for the ring B 4-OH, thus suggesting that a sufficient difference in acidity indeed exists to allow the selective di-deprotonation of the ring A hydroxy groups and subsequent alkylation of the resulting phenolates. Chelation effects would presumably obstruct *O*-alkylation at C-2 thus favouring *O*-alkylation at C-4. Furthermore, selective 4-*O*-alkylation at ring B should also be possible by allowing *O*-demethylangolensin triphenolate to react with just one equivalent of the alkylating reagent. Accordingly, ODMA **1** was converted to the triphenolate using an excess of base (KOBu′) in dry DMF and then reacted with 1 eq. of methyl iodide at 40 °C under Ar to produce the ring B 4-*O*-methylated derivative of ODMA, *i.e.* angolensin **2**. In terms of yield (63%) and number of steps (2) from a commercially available starting material, the present synthesis of angolensin compares very well with the previous routes.[3–6]

As anticipated above, the use of just one eq. of base and a small excess of methyl iodide (80 °C, 2 d) led to the ring A 4-*O*-

Table 1 Regioselective alkylation of ODMA

Amount of KOBu′/mol equiv.	Amount of MeI/mol equiv.	Reaction time/ days	Reaction temp./ °C	Product	Yield (%)
3	1	3.5	+40	**2**	63
1	1	2	+80	**3**	60
3	2.6	2	+40	**4**	70



1

2 $R^1 = H, R^2 = CH_3$
3 $R^1 = CH_3, R^2 = H$
4 $R^1 = R^2 = CH_3$

Scheme 1

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Table 2 ^{1}H NMR δ values of **2**, **3** and **4** in $CDCl_3$ and in d_6-acetone solutions (in parentheses). Assignments were unequivocally confirmed by HMBC spectra

	2		**3**		**4**	
Proton	δ (ppm)	*J*/Hz	δ (ppm)	*J*/Hz	δ (ppm)	*J*/Hz
Chain 2	4.59q	6.9	4.60q	6.9	4.59q	6.9
Chain 3	1.50d	7.0	1.51d	6.9	1.50d	6.9
Ring A 3	6.35d (6.30)	2.4	6.41d (6.39)	2.5	6.39d (6.40)	2.5
Ring A 5	6.30dd (6.37)	8.8	6.37dd (6.41)	9.0	6.35dd (6.42)	9.0
		2.4		2.5		2.5
Ring A 6	7.70d	8.8	7.71d	9.0	7.70d	9.0
Ring B 2	7.22d	8.6[a]	7.18d	8.6	7.21d	8.7
Ring B 3	6.83d	8.8[a]	6.80d	8.6	6.84d	8.7
Ring B 5	6.83d	8.8[a]	6.80d	8.6	6.84d	8.7
Ring B 6	7.22d	8.6[a]	7.18d	8.6	7.21d	8.7
Ring A 4-OMe			3.79s		3.80s	
Ring B 4-OMe	3.77s				3.77s	
Ring A 2-OH	12.85s		12.91s		12.93s	

[a] These are not true *J* values but apparent couplings as measured from the spectra (first order approximation). Simulating and iterating these spectra as AA′BB′-systems using the PERCH software[10] gave the following results for ring B: for **2**, δ(H2) = δ(H6) = 7.217, δ(H3) = δ(H5) = 6.857, $J_{2,3} = J_{5,6}$ = 8.52 Hz, $J_{2,6}$ = 2.43 Hz, $J_{3,5}$ = 2.74 Hz; for **3**, δ(H2) = δ(H6) = 7.158, δ(H3) = δ(H5) = 6.774, $J_{2,3} = J_{5,6}$ = 8.37 Hz, $J_{2,6}$ = 2.36 Hz, $J_{3,5}$ = 2.75 Hz; for **4**, δ(H2) = δ(H6) = 7.211, δ(H3) = δ(H5) = 6.844, $J_{2,3} = J_{5,6}$ = 8.54 Hz, $J_{2,6}$ = 2.82 Hz, $J_{3,5}$ = 2.50 Hz.

methylated isomer (**3**) in 60% yield. The bis(methyl ether) **4** is available from **1** in 70% yield by the reaction of 2.6 eq. of methyl iodide with the dianion of **1** (48 h at 40 °C). No ring A 2-*O*-alkylation was observed in any of these reactions, as judged by the presence in the products of a strong carbonyl absorption at *ca.* 1620 cm^{-1} which is some 50 cm^{-1} lower than the value expected for an *o*-methoxyaryl ketone.

The above reaction products were identified by direct comparison with known compounds,[6] ascertaining the identity of the respective UV, IR, NMR and mass spectra. The regiochemistry of monomethylation, to give **2** or **3**, is immediately apparent in the mass spectra, showing *inter alia* the diagnostic ions *m*/*z* 135 ($MeOC_6H_4CHMe^+$) and 137 (2,4-di$OHC_6H_3CO^+$) for **2**, or *m*/*z* 121 ($HOC_6H_4CHMe^+$) and 151 (2-OH-4-$MeOC_6H_3CO^+$) for **3**. In **2**, **3** and **4** there is an interesting reversal of the ring A H-3 and H-5 chemical shifts on changing the NMR solvent from $CDCl_3$ to d_6-acetone (see Table 2). In fact, the $CDCl_3$ shifts may be considered anomalous in that H-3 appears slightly *downfield* of H-5 although the former is *ortho* to two oxygens while H-5 is *ortho* to just one oxygen atom. This is suggested to be due to the existence of a hydrogen bond between the C-2-OH and the carbonyl which will increase the electron withdrawing effect of the latter, thus making the H-3 more paramagnetic. The acetone solvent presumably intervenes in the formation of the intramolecular hydrogen bond. The non-hydrogen bonded aryl carbonyl is then less strongly electron withdrawing, with a rather modest effect on the *meta* hydrogen, and the more typical chemical shift relationship of H-3 and H-5 is thus restored. Similar effects do not appear in the ^{13}C NMR spectra, as confirmed by GHSQC measurements, because carbonyl substituents of any kind have a very weak effect on a *meta* ring carbon atom.

Experimental

Melting points were determined in open capillary tubes with an Electrothermal apparatus and are uncorrected. UV spectra were recorded in 94% ethanol solution with a CARY 5E UV–VIS spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 Avance spectrometer or a Varian Inova 300 VB spectrometer (chemical shifts in ppm). LR and HR mass spectra were obtained with a JEOL JMS SX102 mass spectrometer operating at 70 eV. IR spectra were obtained with a Perkin-Elmer Universal ATR sampling accessory apparatus. TLC was conducted on Merck silica gel 60 F_{254} plates, and Merck silica 60 (0.040–0.063 mm, 230–400 mesh) was used for flash chromatography. Dimethylformamide (DMF) was dried by distillation over CaH_2 before use.

General procedure

Table 1 shows the amounts of base (KOBu^t) and alkylating agent (MeI) used, and the reaction temperature and time needed for the completion of regioselective alkylation of ODMA as judged by TLC monitoring. MeI (0.0137 g for **2** and **3** and 0.0357 g for **4**) was added to a solution of ODMA (**1**, 0.025 g), base (0.011 g for **3** and 0.033 g for **2** and **4**) and dry DMF under argon. The solution was stirred until the alkylation was complete. The mixture was then poured into water and extracted with ether, washed with water and dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (elution with CH_2Cl_2–EtOAc 7 : 2). For ^{1}H NMR spectra of **2**, **3** and **4**, see Table 2.

Angolensin (2) [1-(2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)-propan-1-one]

Pale yellow crystals, mp 83–84 °C (from benzene) (lit.,[5] 86–87 °C); UV, IR, MS and ^{13}C NMR as reported;[6] *m*/*z* 272 (M^+, 40%) (Found: M^+, 272.1039. $C_{16}H_{16}O_4$ requires *M*, 272.1049).

1-(2-Hydroxy-4-methoxyphenyl)-2-(4-hydroxyphenyl)propan-1-one (3)

White crystals, mp 142 °C (from *n*-hexane–diethyl ether) (lit.,[6] 142 °C); UV, IR, MS and ^{13}C NMR as reported;[6] *m*/*z* 272 (M^+, 40%) (Found: M^+ 272.1055. $C_{16}H_{16}O_4$ requires *M*, 272.1049).

4′-*O*-Methylangolensin (4) [1-(2-hydroxy-4-methoxyphenyl)-2-(4-methoxyphenyl)propan-1-one]

White crystals, mp 67 °C (from *n*-hexane–Et_2O) (lit.,[5] 69–70 °C); UV, IR, MS and ^{13}C NMR as reported; [6] *m*/*z* 286 (M^+, 45%) (Found: M^+ 286.1216. $C_{17}H_{18}O_4$ requires *M*, 286.1205).

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