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New Flavones by a Novel Synthetic Route

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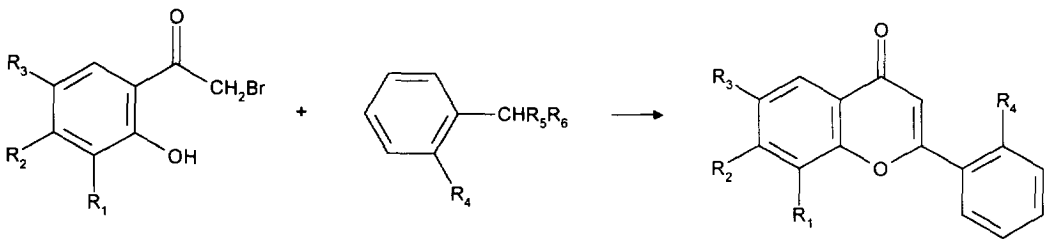
Abstract: Twelve new flavones (**3**) were prepared by the reaction of 2-hydroxy-α-bromoacetophenones (**1**) with piperidine or morpholine aminals of benzaldeydes (**2**) in refluxing methanol. The products (**3**) were fully characterised by ^{1}H NMR and IR spectroscopy and MS spectrometry. © 1997 Elsevier Science Ltd.

In view of the natural,[1, 2] pharmacological[3, 4] and chemical[5, 6] widespread importance of compounds having the flavone framework, we deemed it of interest to make an addition to the synthetic methods of preparation of flavones, which is the subject of the present report.

RESULTS AND DISCUSSION

The availability of 2-hydroxy-α-bromoacetophenones (**1**)[7] and benzaldehyde aminals (**2**)[8] prompted us to attempt to introduce a novel flavone synthesis[9] (Fig. 1). The results of the interaction of these substances in refluxing methanol with very short contact times are collected in Table 1 together with some properties of the new flavones (**3**) obtained according to this method, which appears of quite general application. The likely mechanism of the process is outlined in Fig. 2. Of course, the S_Ni reaction of the ring closure to **4** may follow a carbenium ion instead of the indicated displacement mechanism.

All of the new flavones were fully characterised by elemental analysis, mass spectrometry, ^{1}H NMR and IR spectroscopy. Continuous monitoring of the mass spectrum pattern of the material evaporated into the ion source from the solid phase allowed us to ascertain the homogeneity of the individual products.



1 2 3

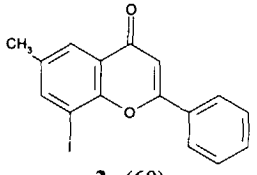
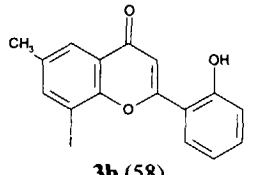
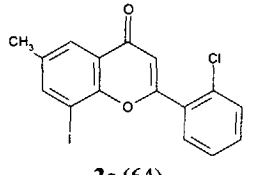
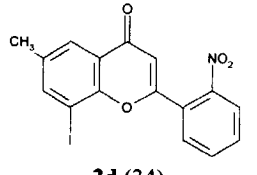
	R_1	R_2	R_3
1a	I	H	CH_3
1b	I	H	I
1c	H	CH_3	Br
1d	Br	H	CH_3
1e	CH_3	H	Br
1f	Br	H	Br

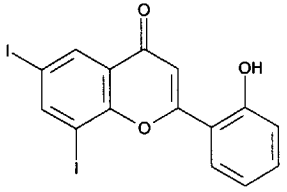
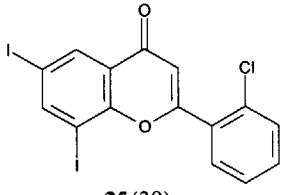
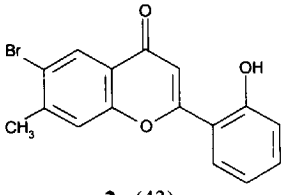
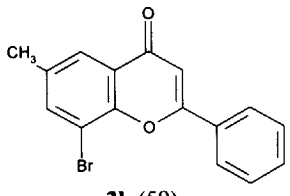
	R_4	$R_5 = R_6$
2a	H	piperidino
2b	H	morpholino
2c	OH	morpholino
2d	Cl	piperidino
2e	NO_2	morpholino

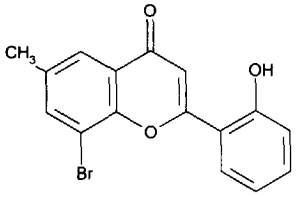
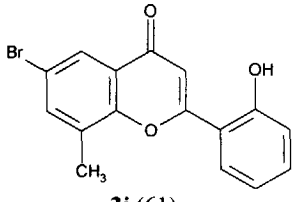
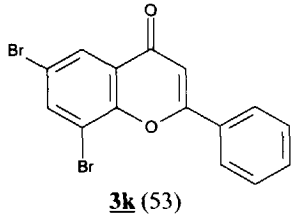
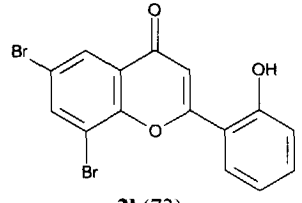
	R_1	R_2	R_3	R_4	Elemental analysis					
					Calcd.			Found		
					C	H	N	C	H	N
3a	I	H	CH_3	H	53.06	3.06		53.10	3.07	
3b	I	H	CH_3	OH	50.82	2.93		50.84	3.05	
3c	I	H	CH_3	Cl	48.45	2.54		48.51	2.48	
3d	I	H	CH_3	NO_2	47.18	2.48	3.44	47.24	2.49	3.48
3e	I	H	I	OH	36.75	1.65		36.82	1.68	
3f	I	H	I	Cl	35.45	1.39		35.51	1.40	
3g	H	CH_3	Br	OH	58.18	3.36		58.12	3.35	
3h	Br	H	CH_3	H	61.15	3.35		60.98	3.42	
3i	Br	H	CH_3	OH	58.18	3.36		57.95	3.37	
3j	CH_3	H	Br	OH	58.18	3.36		57.90	3.36	
3k	Br	H	Br	H	47.63	2.13		47.44	2.16	
3l	Br	H	Br	OH	45.49	2.04		45.42	2.09	

Fig. 1

Table 1. Results of reaction between 2-hydroxy-α-bromoacetophenones (**1**) and benzaldehydes aminals (**2**) to give flavones (**3**).

Product **3**	Properties of **3**				
(yield %)	$R_5 = R_6$ of aminals **2**	mp (°C)[a]	IR (KBr) ν (cm^{-1})[b]	^1H NMR δ, J (Hz)	MS (70 eV) m/z (%)[b]
 **3a** (60)	piperidino	164	1717vs, 1653vs, 1609vs, 1479vs, 1297s, 1236s, 1142vs, 920s, 783vs, 670s, 559s	2.38 (s, 3H, CH_3), 6.92 (s, 1H, H_3), 7.38-7.55 (m, 4H, H_5 + H_{14} + H_{15} + H_{13}), 7.78-7.84 (m, 1H, H_7), 7.95 (*app* dd, 2H, J_1=8.2, J_2=1.8, H_{16} + H_{12})[d]	362 (M^+, 80), 361 (100), 316 (11), 315 (20), 313 (20), 260 (10), 235 (27), 234 (10), 181 (M^{2+}, 4)
 **3b** (58)	morpholino	244	1682vs, 1634vs, 1597vs, 1482s, 1462vs, 1387s, 1268vs, 1240vs, 1147vs, 781s, 755s	2.35 (s, 3H, CH_3), 6.93-7.04 (m, 2H, H_{13} + H_{15} or H_{14}), 7.25-7.38 (m, 2H, H_3 + H_{14} or H_{15}), 7.55-7.65 (m, 1H, H_5), 8.00-8.05 (m, 1H, H_7), 8.22 (*app* d, 1H, J=7.7, H_{16})[e]	378 (M^+, 34), 260 (100), 214 (24), 212 (23), 189 (M^{2+}, 4), 118 (16)
 **3c** (64)	piperidino	203	1714vs, 1652vs, 1610s, 1482vs, 1147vs, 1121vs, 1100s, 781vs	2.40 (s, 3H, CH_3), 7.28-7.67 (m, 5H, H_3 + H_{13}+ H_5 + H_{14} + H_{15}), 7.80-7.86 (m, 1H, H_7), 8.46 (*app* dd, 1H, J_1=7.3, J_2=1.5, H_{16})[d]	398 (M^+, 4), 396 (M^+, 12), 361 (100), 315 (19), 313 (19), 234 (13)
 **3d** (34)	morpholino	218	1712vs, 1659vs, 1607vs, 1525vs, 1476vs, 1354vs, 1140vs, 922s, 790s	2.40 (s, 3H, CH_3), 7.33 (s, 1H, H_3), 7.48-7.64 (m, 2H, H_5 + H_{14} or H_{15}), 7.75 (*app* t, 1H, J=7.7, H_{14} or H_{15}), 7.82-7.88 (m, 1H, H_7), 8.03 (*app* dd, 1H, J_1=7.8, J_2 =1.2, H_{13}), 8.39 (*app* dd, 1H, J_1=7.8, J_2=1.2, H_{16})[d]	407 (M^+, 0.28), 377 (3), 361 (2), 260 (100), 232 (5), 214 (23), 212 (24), 133 (16)

 **3e** (61)	morpholino	272	1672s, 1620vs, 1578vs, 1459vs, 1442vs, 1259s, 1170s, 1156vs, 781s	6.90-7.05 (m, 2H, H_{13} + H_{14} or H_{15}), 7.26-7.38 (m, 2H, H_3 + H_{14} or H_{15}), 8.04 (d, 1H, J=1.6, H_5), 8.18 (*app* d, 1H, J=7.6, H_{16}), 8.44 (d, 1H, J=1.6, H_7)[e]	490 (M^+, 35), 473 (4), 372 (100), 245 (21), 118 (43)
 **3f** (39)	piperidino	203	1718vs, 1651vs, 1594vs, 1441vs, 1288s, 1152vs, 1116s, 779vs	7.32-7.55 (m, 4H, H_3 + H_{13}+ H_{14} + H_{15}), 8.08 (d, 1H, J=1.8, H_5), 8.30 (d, 1H, J=1.5, H_7), 8.43 (*app* dd, 1H, J_1=7.6, J_2=0.8, H_{16})[d]	510 (M^+, 7), 508 (M^+, 21), 473 (100), 346 (11), 254 (M^{2+}, 0.7), 245 (9), 237 (18), 219 (37)
 **3g** (43)	morpholino	251[c]	1679vs, 1643vs, 1588vs, 1460vs, 1413s, 1267vs, 1202s, 1177vs, 1142vs, 755s	2.50 (s, 3H, CH_3), 6.90-7.00 (m, 2H, H_{13} + H_{14} or H_{15}), 7.20-7.35 (m, 2H, H_3 + H_{14} or H_{15}), 7.61 (s, 1H, H_8), 7.93 (s, 1H, H_5), 8.08 (*app* d, 1H, H_{16}, J=7.3), 10.31 (broad s, 1H, O-H)[e]	332 (M^+, 55), 330 (M^+, 59), 315 (19), 313 (18), 214 (86), 212 (89), 165 (M^{2+}, 19), 118 (100)
 **3h** (59)	piperidino	180	1712vs, 1655vs, 1480s, 1241s, 1146vs, 779s	2.40 (s, 3H, CH_3), 6.93 (s, 1H, H_3), 7.39-7.55 (m, 4H, H_{14} + H_{13} + H_{15} + H_5), 7.61-7.65 (m, 1H, H_7), 7.92-8.00 (m, 2H, H_{16} + H_{12})[d]	316 (M^+, 54), 315 (100), 314 (M^+, 52), 313 (100), 214 (10), 212 (11), 133 (14)

 **3i** (63)	morpholino	244[c]	1681s, 1635vs, 1597vs, 1460vs, 1270s, 1247vs, 1153vs, 752m	2.47 (s, 3H, CH_3), 2.61 (s, 1H, O-H), 7.00-7.15 (m, 2H, H_{13} + H_{14} or H_{15}), 7.33-7.48 (m, 2H, H_3 + H_{15} or H_{14}), 7.66 (s, 1H, H_5), 7.94 (s, 1H, H_7), 8.25 (*app* d, 1H, J=6.7, H_{16})[e]	332 (M^+, 20), 330 (M^+, 21), 315 (6), 313 (5), 215 (12), 214 (97), 213 (14), 212 (100), 166 (M^{2+}, 7), 165 (M^{2+}, 16), 133 (20), 118 (32)
 **3j** (61)	morpholino	272[c]	1686vs, 1642vs, 1588vs, 1457vs, 1236vs,1140vs, 766s	2.42 (s, 3H, CH_3), 6.90-7.03 (m, 2H, H_{13}+ H_{14} or H_{15}), 7.22-7.35 (m, 2H, H_3 + H_{14} or H_{15}), 7.70-7.75 (m, 1H, H_5 or H_7), 7.79-7.83 (m, 1H, H_5 or H_7), 8.10 (*app* dd, 1H, J_1=9.5, J_2=1.6, H_{16}), 10.42 (broad s, 1H, O-H)[e]	332 (M^+, 34), 330 (M^+, 35), 315 (10), 313 (10), 215 (12), 214 (100), 213 (12), 212 (98), 186 (37), 184 (39), 166 (M^{2+}, 8), 165 (M^{2+}, 17), 118 (61)
 **3k** (53)	morpholino	170	1707vs, 1651vs, 1591s, 1454vs, 1168s, 782vs	6.89 (s, 1H, H_3), 7.35-7.49 (m, 3H, H_{13} + H_{14} + H_{15}), 7.76 (*app* d, 1H, J=2.1, H_5), 7.81-7.90 (m, 3H, H_7 + H_{16}+ H_{12})[d]	382 (M^+, 30), 381 (58), 380 (M^+, 57), 379 (100), 377 (45), 300 (2), 278 (7), 102 (5)
 **3l** (73)	morpholino	255[c]	1678s, 1623vs, 1584vs, 1458vs, 1265vs, 1236vs, 1158vs, 1143vs, 779s, 745s	6.90-7.03 (m, 2H, H_{13} + H_{15} or H_{14}), 7.25-7.40 (m, 2H, H_3 + H_{15} or H_{14}), 7.95 (d, 1H, J=1.9, H_5), 8.13 (*app* d, 1H, J=7.6, H_{16}), 8.26 (d, 1H, J=2.0, H_7), 10.61 (broad s, 1H, O-H)[e]	398 (M^+, 5), 396 (M^+, 9), 394 (M^+, 5), 280 (8), 278 (17), 276 (8), 199 (M^{2+}, 2), 197 (M^{2+}, 2), 118 (100)

[a]Uncorrected. [b]The more intense peaks are reported together with other peaks of significance. [c]Decomposed.[d] Solvent $CDCl_3$. [e]Solvent DMSO-d_6

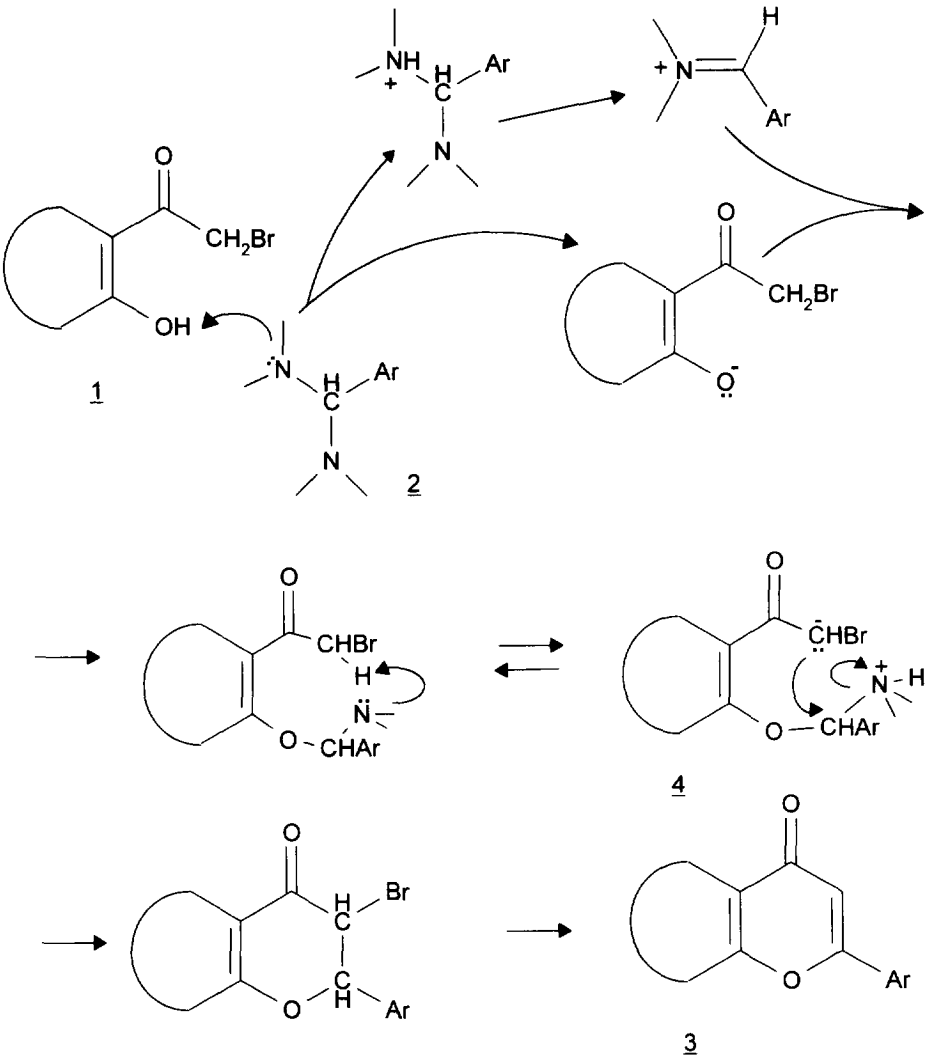
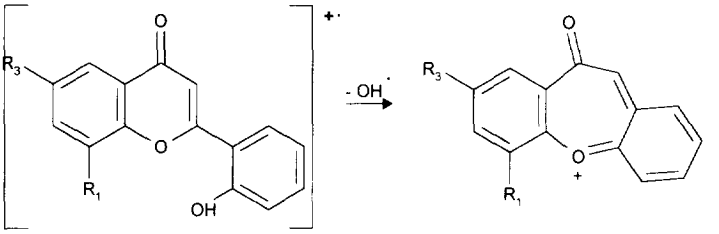


Fig. 2

The parent ion in the mass spectra of these flavones was hardly discernible only for **3d**, which underwent a powerful retro-Diels Alder type fragmentation[10] in order to loose the electronegative fragment $O_2NPhC{\equiv}CH$, to yield the base peak for **3g** and **3l**. The expected retro Diels Alder fragmentation was very frequently a dominant process, even when it was preceded by a more favourable cleavage, like in **3f**. Furthermore, many compounds showed the doubly charged parent ion. Interestingly, the halogen present in the condensed aromatic ring appeared firmly held, whereas the *ortho*-chlorine in the side phenyl ring was the trigger point of the observed

fragmentations in **3c** and **3f**. The presence of an *ortho*-hydroxyl group in the phenyl substituent (**3b**, **3e**, **3g**, **3i**, **3j** and **3l**) induced the loss of an OH group from the parent ion, likely to yield a ring expanded charged structures **5** (Fig. 3).

Occasionally, e.g. for **3a**, **3b**, **3c** and **3d**, somewhere along the fragmentation pathway we observed a loss of 46 u ($CO + H_2O$) followed by the sequentially rapid loss of two hydrogen atoms.



3 5

Fig. 3

Accurate analysis of ^1H NMR spectra confirmed the purity of compounds **3**. In the assignment of NMR signals, protons were identified by a subscript, which is the number identifying the carbon center to which they are attached (Fig. 4).

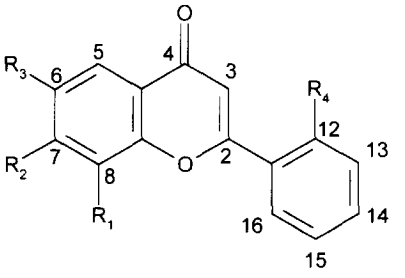


Fig. 4

A proton on the 5th-position with respect to the hydroxy group (H_{16}) of the non condensed aromatic ring (**3b**, **3e**, **3g**, **3i**, **3j** and **3l**) appeared constantly as a more or less resolved doublet in the range 8.08-8.25 ppm, showing some further finer splittings. When the OH group was not present in the ring, the two *ortho* protons (H_{12} and H_{16}) showed up in the close range 7.85-7.96 ppm (**3a**, **3h** and **3k**). Finally when a chlorine atom replaced the OH group (**3c** and **3f**), a doublet of doublets appeared at *ca.* 8.4 ppm for H_{16}. In the nitro derivative **3d** a similar doublet appeared at 8.39 ppm for the same proton. Since the resonances of the proton *ortho* to the hydroxy group (H_{13}) of compounds **3b**, **3e**, **3g**, **3i**, **3j** and **3l** was located in the range *ca.* 6.90-7.15

ppm and in the chloro derivatives **3c** and **3f** somewhere near 7.50 ppm, we believe that it is this resonance which moved downfield to 8.03 ppm for **3d**. The location of the isolated proton singlet of the heterocyclic ring (H_3) ranged from *ca.* 6.9 and 7.5 ppm. The two vicinal protons H_{14} and H_{15} far away from the two substituents in the non condensed aromatic ring consistently appeared well separated as pseudo-triplets centred at about 6.97 and 7.30 ppm when the heteroatomic substituent was the hydroxyl oxygen (**3b**, **3e**, **3g**, **3i**, **3j** and **3l**). When chlorine was this substituent (**3c** and **3f**) the two resonances merged inextricably at a slightly lower field downfield of the chloroform proton resonance. The nitro group exhibited a similar effect to a larger degree (**3d**). In the compounds **3a**, **3h** and **3k** the two *ortho* protons (H_{12} and H_{16}) quite consistently were found as doublets of doublets at *ca.* 7.9 ppm.

Finally the two protons of the benzo moiety (H_5 and H_7 or H_5 and H_8) of the flavone rings were sometimes conspicuous for exhibiting doublets ($J \cong 1.8$ Hz) which fell in the range 7.28-8.44 ppm with locations and variations of chemical shifts well in agreements with expectations.

The stretching frequency associated with the carbon double bond, which is likely conjugated in a permanent *trans* C=C–C=C and *cis* C=C–O fashion in the condensed ring and possibly cross conjugated with an aryl group, showed up at 1620-1643 cm^{-1} for the *ortho*-hydroxyphenyl substituted flavones **3** (R_4= OH), but at higher frequency (1651-1659 cm^{-1}) for the phenyl substituted (**3a**, **3h** and **3k**) or when an electron withdrawing group was present in the *ortho*-position of the phenyl group (**3c**, **3d** and **3f**). These values are in good agreement with literature compilations for similar system.[11] The carbonyl stretching mode was found confined in the narrow range 1707-1718 cm^{-1} which is in closer agreement with the locations expected[11] for aryl esters than aryl and α,β-unsaturated ketones. The presence of the phenolic hydroxyl group in **3** (R_4= OH) was made evident by a very broad and intense band peaking at 3150 cm^{-1}, well in agreement with reported values for the internally hydrogen bonded phenols (Fig. 5).[11]

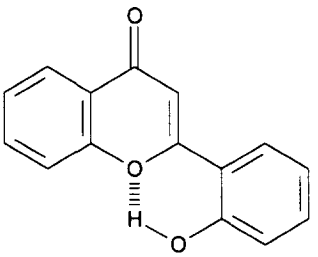


Fig. 5

This is a valuable structural confirmation because not always the hydrogen connected to an oxygen atom can be detected in the ^1H NMR spectra.

EXPERIMENTAL SECTION

Materials. 2-Hydroxy-α-bromo-acetophenones **1**[7] and aminals **2**[8] were prepared according to described procedures. Other common reagents and solvents were purchased from commercial sources and used as received.

Equipment. MS analyses were performed with a Fisons Trio 2000 mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 18-600 u. The samples were fully evaporated into the ion source at the lowest possible temperature with continuous spectral recording. The spectra obtained were carefully inspected to monitor material homogeneity.

IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using KBr technique for solids and recorded in the range 4000-400 cm^{-1}.

^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, depending on solubility, at room temperature on a Bruker AC-F 200 spectrometer at 200 MHz. NMR peak locations are reported as δ-values from TMS. Some ^1H multiplets are characterised by the term *app* (apparent): this refers only to their appearance and may be an oversimplification.

General procedure for the preparation of ***3***. A 1:1 mol/mol mixture of the appropriate 2-hydroxy-α-bromo-acetophenone (**1**) and aminal (**2**) was refluxed in methanol during *ca.* 10 minutes. After solvent removal in vacuo, the reaction product was obtained by crystallisation from ethanol.

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This work is dedicated to Prof. Hartmut Seliger on his 60th anniversary.

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