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Solvent influence in the Rh-catalyzed intramolecular 1,6 C–H insertions: a general approach to the chromane and flavanone skeletons

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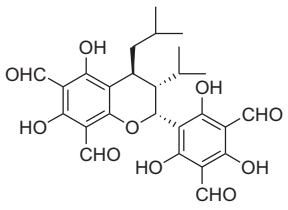
ABSTRACT

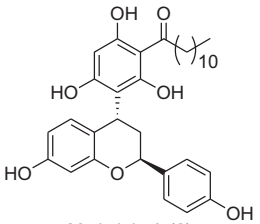
Solvent polarity and nature of the ligands on the catalyst are crucial factors that control the regioselectivity of the Rh(II) promoted intramolecular 1,6 C–H insertions versus the β-elimination. We have explored the best conditions for the preparation of flavanones and chromenes through this approach. The procedure is also an excellent way of preparing stereochemically pure *Z* aryl-alkenes.

1. Introduction

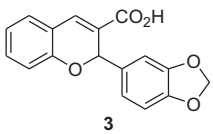
One of the most challenging reactions in organic synthesis is the functionalization of nonactivated C–H bonds. The efforts to achieve this goal have led to the development of carbon–carbon bond forming reactions that rely on catalytic activation of a C–H bond in a saturated hydrocarbon. Most of them have become standard synthetic protocols, mainly the intramolecular versions of the reactions, which lead to cyclic products. Oxygenated heterocycles with five or six members are present in many natural and bioactive molecules, and have been the target of many synthetic efforts, like the homolytic radical fragmentation of alkoxy-titanocenes,[1,2] the Sakurai condensation of benzaldehydes with benzoxasilepins,[3–5] or the palladium-catalysed cascade carbonylation–allene insertion.[6] Among them, the reaction of an α-diazoester catalyzed by a dirhodium tetracarboxylate or a related catalyst is a reaction widely used as a practical synthetic method.[7–12] In an ideal case, a new C–C bond between two sp^3 carbon centres is created through activation of the C–H bond of a saturated hydrocarbon in a regio-, diastereo- and enantio-selective manner. In this way, McKervey et al. have reported the asymmetric synthesis of substituted chromanes from α-carbonyl diazocompounds and rhodium catalysts.[13–15] This reaction offers excellent yields and good stereocontrol, although with the drawback of a competing sigmatropic rearrangement.[16] δ-Butyrolactones have also been prepared using a similar methodology.[17]



Sideroxylonal B (**1**)



Myristinin A (**2**)



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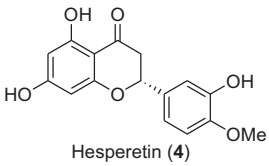

Hesperetin (**4**)

The rhodium catalyzed intramolecular 1,5 C–H insertion process is an excellent approach for the synthesis of five-membered ring oxygenated heterocycles,[18,19] as preferential formation of five-membered rings is observed,[20] being selectivity governed by both steric and electronic considerations.[21,22] The generally accepted mechanism involves the direct insertion between the carbenoid

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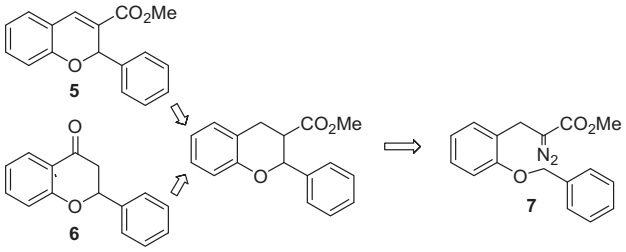
and the C–H bond by means of a three-membered transition state.[23,24] Kinetic studies suggest that the rate-determining step is the generation of the rhodium carbenoid.[25] Theoretical studies on the diastereo- and enantio-selectivity of the process show that the C–H activation/C–C formation proceeds in a single step through a three-centred hydride transfer-like transition state with a small activation energy.[26–28]

Many natural and synthetic biologically active compounds have a core skeleton of chromane or flavanone.[29,30] Thus, sideroxylonal B (**1**) is a racemic flavanoid isolated from extracts of *Eucalyptus sideroxylon*, which show, among others, bactericidal and cytotoxic biological activities.[31] Myristinin A (**2**), isolated from *Myristica cinnamomea* and *Knema elegans*, has remarkable properties because it is a potent DNA-damaging agent and DNA polymerase β inhibitor.[32] On the other hand, the benzylated chromene **3** is a strong endothelin receptor.[33] Hesperetin (**4**), a flavanone present in citrus fruits, has a broad profile of biological activity, such as antioxidant, cholesterol-lowering and antiinflammatory properties.[34]

In this paper we present the study of the influence of the solvent and catalyst in the 1,6-insertions promoted by Rh(II) salts, and the application of this synthetic approach to the preparation of six-membered ring oxygenated heterocycles.

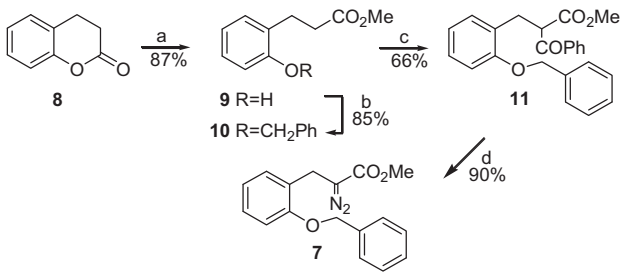
2. Result and discussion

Our strategy used in the preparation of the above mentioned compounds is depicted in the Scheme 1.



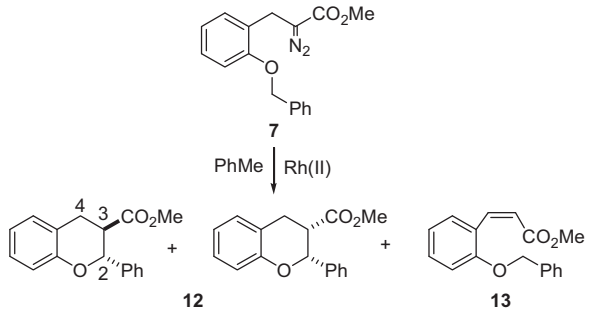
Scheme 1. Retrosynthetic analysis for chromene **5** and flavanone **6** from the diazocompound **7**.

Preparation of diazocompound **7** was achieved using the dihydrocoumarin **8** as starting material (Scheme 2). Thus, transesterification of **8** with MeOH in the presence of catalytic amounts of DDQ, following the procedure described by Turner,[35] afforded **9**, which was benzylated to afford **10**. To facilitate the introduction of the diazo function, the alpha to ester position was activated through benzoylation to afford **11**.[36] Treatment of this product with *p*-nitrobenzenesulfonyl azide gave the desired diazocompound **7** in a 44% overall yield from **8**.



Scheme 2. (a) MeOH, DDQ; (b) $PhCH_2Cl$, NaI, K_2CO_3, Me_2CO; (c) $PhCO_2Me$, NaH, DME; (d) *p*-nitrobenzenesulfonyl azide, DBU, DCM.

Diazocompound **7** was subjected to decomposition in toluene under the influence of several rhodium catalysts. In all cases, a mixture of three products was obtained (Scheme 3). Yields and conditions are given in Table 1. While chromanes **12** are the expected 1,6 C–H insertion products, **13** could arise from a β-elimination. The relative stereochemistry in each diastereomer of **12** can be easily deduced from H2–H3 coupling constants in their ^{1}H NMR spectra (8.9 Hz for **12**-*trans* and 3.6 Hz for **12**-*cis*), while alkene **13** is formed only in its *Z* form (12.5 Hz for the coupling of both olefin hydrogens).



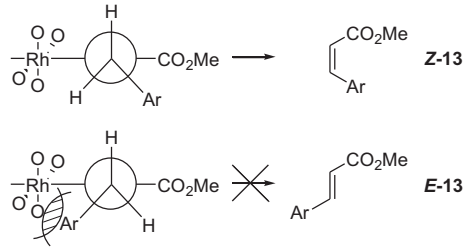
Scheme 3. Products formed in the treatment of **7** with Rh(II) catalysts (see Table 1).

Table 1
Treatment of **7** with several Rh(II) catalysts[a]

Entry	Catalyst[b]	Combined yield (%)	Relative yields (%)	
			12 (*trans*/*cis*)	**13**
1	$Rh_2(OAc)_4$	96	59 (77:33)	41
2	$Rh_2(Oct)_4$	96	60 (63:37)	41
3	Rh_2(R-MEPY)$_4$	94	20 (25:75)	81
4	Rh_2(*S*-DOSP)$_4$	95	30 (30:60)	70
5	$Rh_2(O_2CCF_3)_4$	97	3 (67:33)	97

[a] Toluene, 0 °C, 90 min. Relative yields as deduced from the integrals of signals in ^{1}H NMR of the crude mixtures and confirmed after CC isolation of products.
[b] 0.05 mol %.

The formation of this thermodynamically less stable *Z*-isomer has been attributed to steric constraints associated with the orientation of the aryl group for hydride migration in the metal carbene intermediate (Scheme 4).[37–39] Side product **13** can be recycled by hydrogenation (H_2 Pd/C) into **10**.



Scheme 4. Preferential formation of the *Z*-isomer in the β-elimination process.

From the results in Table 1 it can be concluded that when the electron withdrawing ability of the ligands on rhodium increases, the ratio of 1,6-insertion products (**12**-*cis* and **12**-*trans*) decreases, while there is a higher ratio of the β-elimination product (**13**). Similar results have been reported previously for cyclizations in which there was a C–H bond α to the diazo group, as competing side reactions either with 1,5 C–H insertions,[40,41] with intramolecular cyclopropanations[42] or with intermolecular reactions.[43] However this is the first time, that is, reported that an adequate selection of the ligands on the rhodium catalyst is needed for the exclusive formation of stereochemically pure *Z* aryl-alkenes through this procedure. On the other hand, it can also be concluded

that bulky ligands favour the formation of the *cis* isomer (Table 1, entries 3 and 4). Concerning the mechanism of the process, it has been proposed that the reaction proceeds through an intermediate Rh/carbene complex, that is, highly electron deficient at carbon and that this complex is further destabilized by electron-withdrawing ligands. With a less stable (more reactive) intermediate, the entropically less demanding pathway (earlier transition state), β-elimination, will be favoured.[44]

The main drawback for the use of the rhodium catalyzed C–H insertion process in the synthesis of six-membered heterocycles is the tendency of the rhodium carbenoids to coordinate the oxygen and rearrange into five-membered systems.[13–16] It is specially interesting that under the reaction conditions here described, no rearranged products were formed.

Next we proceeded to check whether the solvent polarity has any influence on the outcome of the insertion process, an aspect of the reaction that had not been previously studied, although the behaviour of several reactions promoted by rhodium catalysts on α-diazoesters in different solvents has been reported,[45–47] and the effect of solvents on the rates of organic chemical reactions is well documented.[48] The results of the treatment of diazocompound **7** with $Rh_2(OAc)_4$ in several solvents are summarized in Table 2.

Table 2
Treatment of **7** with $Rh_2(OAc)_4$ in several solvents[a]

Entry	Solvent	μ[b]	Combined yield (%)	Ratio	
				12 (*trans*/*cis*)	**13**
1	Cyclohexane	0	97	70 (81:19)	30
2	Benzene	0	97	54 (76:24)	46
3	Toluene	0.38	98	59 (78:22)	41
4	Dichloromethane	1.60	93	23 (74:27)	77
5	Dimethoxyethane	1.71	95	13 (77:23)	87
6	Tetrahydrofurane	1.75	89	0	100
7	Acetonitrile	2.92	90	0	100

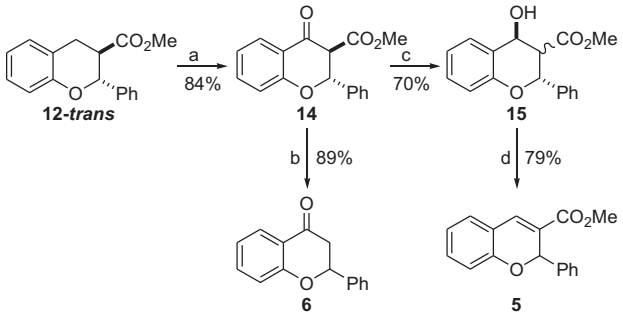
[a] Catalyst (0.05 mol %), 0 °C, 90 min. Relative ratios as deduced from the integrals of signals in ^{1}H NMR of the crude mixtures and confirmed after CC isolation of products.
[b] Dipole moment (D).

The data in Table 2 suggest that the more polar solvents favour the β-elimination process, while apolar solvents favour the cyclization (**12**). Cyclohexane is the solvent, which gives the better yields for 1,6 C–H insertion products (entry 1, 70% global). On the other hand, polar solvents (entries 6 and 7) give quantitatively the β-elimination product. These results show, for the first time, that the polarity of the solvent exerts a crucial influence on the chemoselectivity of the Rh(II) catalyzed insertion processes. Again the high electron-deficiency of the carbon in the Rh/carbene complex can be used to rationalize the results. The more polar solvents would stabilize the more polar transition state, which in our case should be that one, which leads to the β-elimination product, as it is less entropically demanding and therefore earlier in the reaction pathway, more similar to the starting Rh complex.

On the other hand, the transition state leading to the 1,6 C–H insertion product, needing a higher degree of arrangement, should be latter in the reaction pathway and possibly with a lower dipolar moment.[27,44] Once more, the correct choice of solvent can advantageously be used to prepare stereochemically pure *Z* aryl-alkenes or chromanes.

Once prepared **12**-*trans*, the total synthesis of the flavanone skeleton **6** was completed through benzylic oxidation,[49] which gave **14**, and final decarboxylation[50] as depicted in Scheme 5.

In addition, the compound with chromene skeleton **5** was prepared from **12**-*trans* through benzylic oxidation followed by reduction with $NaBH_4$, which afforded the alcohol **15** (partial epimerization was observed). This mixture of alcohols was dehydrated by treatment with *p*-TsOH.



Scheme 5. (a) H_5IO_6, CrO_3(0.05 equiv); (b) NaCl, H_2O, DMSO, Δ; (c) $NaBH_4$, MeOH; (d) *p*-TsOH, MePh.

3. Conclusions

As a conclusion, we have studied the role played by the polarity of rhodium ligands and reaction solvent as the factors that can control the competition between the 1,6-insertion and the β-elimination. We have found the best conditions for the preparation of flavanones and chromanes through this approach. In addition, through an adequate selection of the reaction conditions this procedure could also be an excellent way of preparing stereochemically pure *Z* aryl-alkenes.

We are now applying the described synthetic procedure to the synthesis of compounds **1**–**3**, as we are also engaged in the seek of rhodium complexes with apolar chiral ligands in order to explore the asymmetric version of the procedure.

4. Experimental section

4.1. General

Infrared spectra were recorded in liquid film between NaCl plates on an FT-IR Mattson Genesis II. NMR spectra were determined on a Bruker Avance DPX 300 and Bruker Avance-500. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated solvent and are reported to tetramethylsilane. Carbon substitution degrees were established by DEPT multipulse sequence. HRMS were registered on an Autospec-Q VG Analytical (FISONS) mass spectrometer. All solvents were purified and dried following standard procedures.

4.2. Methyl 3-[2-(benzyloxy)phenyl]propanoate (10)

To a solution of **9** (1.63 g, 12.95 mmol) in anhydrous acetone (25 mL), K_2CO_3 (2.27 g, 16.48 mmol) and NaI (2.54 g, 15.31 mmol) were added under N_2 atmosphere. The mixture was stirred at room temperature for 5 min and then, benzyl chloride (1.63 g, 12.95 mmol) was added. The resulting solution was heated at 65 °C for 24 h, then diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over anhyd Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane/Et_2O 9:1), affording **10** (1.98 g, 11.0 mmol, 85%), as colourless oil: IR (film) ν_{max} 3063, 3031, 2948, 2864, 1737, 1600, 1494, 1451, 1240, 1158, 1110, 1021, 751, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.37 (5H, m), 7.27 (2H, d, J=7.3 Hz), 6.99 (1H, dd, J=7.3, 6.9 Hz), 6.99 (1H, d, J=8.0 Hz), 5.16 (2H, s), 3.72 (3H, s), 3.11 (2H, t, J=8.1 Hz), 2.75 (2H, t, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.75 (C), 156.59 (C), 137.31 (C), 130.11 (CH), 129.19 (C), 128.59 (CH), 127.81 (CH), 127.63 (CH), 127.06 (CH), 120.80 (CH), 111.63 (CH), 69.76 (CH_2), 51.49 (CH_3), 34.08 (CH_2), 26.24 (CH_2). HREIMS (m/z) calcd for $C_{17}H_{18}O_3$ 270.1256 [M]$^+$, found 270.1249.

4.3. Methyl 2-[2-(benzyloxy)benzyl]-3-oxo-3-phenylpropanoate (11)

To a stirred solution of NaH (60% dispersion in mineral oil) (1.54 g, 38 mmol) in anhydrous dimethoxyethane (20 mL) at 0 °C under N_2 atmosphere, compound **10** (2.6 g, 9.63 mmol) in DME (20 mL) was added. The mixture was stirred at room temperature for 10 min, then methyl benzoate (1.79 mL, 14.44 mmol) was added. The resulting solution was heated to reflux for 6 h, and quenched by the addition of H_2O (5 mL) dropwise. Then, the mixture was diluted with water 50 (mL) and extracted with Et_2O. After washing with brine, the dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with hexane/Et_2O 8:2, to give product **11** (2.83 g, 6.35 mmol, 66%) as a white solid: mp 108–110 °C, IR (film) ν_{max} 3062, 3031, 2948, 1745, 1682, 1597, 1493, 1449, 1271, 1238, 1156, 1111, 1015, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.89 (2H, dd, J=8.1, 1.2 Hz), 7.53–7.36 (6H, m), 7.31–7.17 (4H, m), 6.94 (1H, d, J=8.1 Hz), 6.90 (1H, ddd, J=7.6, 7.2, 1.2 Hz), 5.16 (1H, d, J=11.7 Hz), 5.11 (1H, d, J=11.7 Hz), 4.91 (1H, dd, J=8.5, 6.1 Hz), 3.63 (3H, s), 3.38 (1H, dd, J=13.7, 6.1 Hz), 3.31 (1H, dd, J=8.5, 13.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.54 (C), 169.98 (C), 156.75 (C), 136.91 (C), 135.88 (C), 133.36 (CH), 131.80 (CH), 128.72 (CH), 128.57 (CH), 128.19 (CH), 128.10 (CH), 127.69 (CH), 126.50 (C), 120.86 (CH), 111.44 (CH), 70.10 (CH_2), 53.60 (CH), 52.23 (CH_3), 31.12 (CH_2). HREIMS (m/z) calcd for $C_{24}H_{22}O_4$ 374.1518 $[M]^+$, found 374.1525.

4.4. 3-[2-(Benzyloxy)phenyl]-1-methoxy-1-oxopropane-2-diazonium (7)

To a solution of **11** (180 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C, DBU (0.14 mL, 0.96 mmol) was added, and the mixture was stirred for 10 min. Then, *p*-nitrobenzenesulfonyl azide (220 mg, 0.96 mmol) was added and the resulting solution was stirred at room temperature for 3 h. The mixture was then diluted with Et_2O and washed with NaOH (1 M). The organic layer was dried over anhyd Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane/Et_2O 85:15), affording **7** (128 mg, 0.43 mmol, 90%) as a yellow liquid: IR (film) ν_{max} 3067, 3033, 2948, 2084, 1691, 1492, 1435, 1349, 1239, 1121, 751, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.36 (5H, m), 7.29–7.22 (2H, m), 6.95 (1H, ddd, J=7.3, 7.7, 1.3 Hz), 6.94 (1H, dd, J=7.3, 0.8 Hz), 5.10 (2H, s), 3.75 (3H, s), 3.67 (2H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.78 (C), 156.77 (C), 136.92 (C), 130.48 (CH), 128.61 (CH), 128.53 (CH), 128.02 (CH), 127.52 (CH), 126.05 (C), 120.89 (CH), 111.69 (CH), 70.09 (CH_2), 53.56 (C, CN_2), 51.78 (CH_3), 24.75 (CH_2).

4.5. General procedure for the synthesis of *trans*-methyl 2-phenylchromane-3-carboxylate (12-*trans*), *cis*-methyl 2-phenylchromane-3-carboxylate (12-*cis*) and methyl 3-[2-(benzyloxy)phenyl]-2-propenoate (13)

Compound **7** was placed in a Schlenck flask with 4 Å molecular sieves under Ar atmosphere. The anhydrous solvent (12 mL/mmol of **7**) was added (see manuscript, Tables 1 and 2). The solution was cooled to 0 °C and the rhodium salt (0.05 mmol/mmol of **7**) was added (see manuscript, Table 1). The mixture was stirred at 0 °C for 1.5 h, then diluted with Et_2O and washed with brine. The organic layer was dried over anhyd Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane/Et_2O 95:5), affording **12**-*trans*, **12**-*cis* and **13** (yields in manuscript). Compound **12**-*trans* could be isolated pure, but compounds **12**-*cis* and **13** were obtained as a mixture.

Procedure to isolate compound **12**-*cis*: 5% Pd/C (144 mg) was added to a mixture of **12**-*cis* and **13** (32:68) (140 mg) in AcOH (30 mL), and the suspension was bubbled with H_2 and stirred at room temperature for 3 h. The mixture was filtered and diluted with Et_2O, then the organic layer washed with brine, dried over anhyd Na_2SO_4, and the solvent removed in vacuo. The residue was purified by chromatography over silica gel, eluting with hexane/Et_2O 9:1, to give products **10** (90 mg) and **12**-*cis* (43 mg).

*4.5.1. Compound **12**-trans.* Solid foam, IR (film) ν_{max} 3031, 2947, 1733, 1584, 1487, 1454, 1434, 1235, 1165, 1038, 754, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.36 (5H, m), 7.18–7.14 (2H, m), 6.97–6.93 (2H, m), 5.14 (1H, d, J=8.9 Hz, H-2), 3.51 (3H, s), 3.34 (1H, dd, J=15.4, 10.5 Hz, H-4ax), 3.12 (1H, ddd, J=10.5, 8.9, 4.8 Hz, H-3), 3.04 (1H, dd, J=15.4, 4.8 Hz, H-4eq); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.94 (C), 154.26 (C), 138.79 (C), 129.31 (CH), 128.61 (CH), 128.53 (CH), 127.71 (CH), 126.89 (CH), 120.89 (CH), 120.06 (C), 116.85 (CH), 78.89 (CH), 51.82 (CH_3), 45.81 (CH), 28.85 (CH_2). HREIMS (m/z) calcd for $C_{17}H_{16}O_3$ 268.1099 $[M]^+$, found 268.1090.

*4.5.2. Compound **12**-cis.* White solid, mp=66–68 °C; IR (film) ν_{max} 3026, 2948, 1737, 1582, 1488, 1435, 1248, 1231, 1200, 1110, 753, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.12 (7H, m), 7.00–6.92 (2H, m), 5.64 (1H, d, J=3.6 Hz, H-2), 3.63 (3H, s), 3.37 (1H, ddd, J=8.1, 5.6, 3.6 Hz, H-3), 3.07 (1H, dd, J=16.6, 5.6 Hz, H-4eq), 2.98 (1H, dd, J=16.6, 8.1 Hz, H-4ax); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.43 (C), 154.08 (C), 138.72 (C), 129.49 (CH), 128.26 (CH), 127.92 (CH), 127.75 (CH), 125.81 (CH), 120.68 (CH), 120.15 (C), 116.51 (CH), 76.53 (CH), 51.65 (CH_3), 43.24 (CH), 24.76 (CH_2). HREIMS (m/z) calcd for $C_{17}H_{16}O_3$ 268.1099 $[M]^+$, found 268.1106.

*4.5.3. Compound **13**.* Colourless oil, IR (film) ν_{max} 3031, 2947, 1723, 1628, 1597, 1450, 1248, 1194, 1160, 1012, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.64 (1H, dd, J=7.5, 1.4 Hz), 7.41–6.26 (7H, m), 6.97 (2H, m), 6.00 (1H, d, J=12.5 Hz), 5.12 (2H, s), 3.69 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.67 (C), 156.37 (C), 139.38 (CH), 136.84 (C), 130.74 (CH), 130.36 (CH), 128.49 (CH), 127.86 (CH), 127.19 (CH), 124.41 (C), 120.22 (CH), 119.34 (CH), 111.86 (CH), 706.23 (CH_2), 51.14 (CH_3). HREIMS (m/z) calcd for $C_{17}H_{16}O_3$ 268.1099 $[M]^+$, found 268.1108.

4.6. *trans*-Methyl 4-oxo-2-phenylchromane-3-carboxylate (14)

To a solution of H_5IO_6 (62 mg, 0.27 mmol) in anhydrous CH_3CN (1 mL), CrO_3 (1 mg, 0.097 mmol) was added. The mixture was stirred until CrO_3 was dissolved. Then, **12**-*trans* (40 mg, 0.13 mmol) in CH_3CN (0.5 mL) was added, and the resulting solution was stirred at room temperature for 1 h. The mixture was then diluted with Et_2O and filtered through a pad of Celite. The solvent was removed, and **14** (84%, 64 mg, 0.23 mmol) was obtained: oil, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (1H, dd, J=8.1, 1.6 Hz), 7.42 (6H, m), 7.11 (1H, d, J=8.1 Hz), 7.06 (1H, d, J=8.4 Hz), 5.71 (1H, d, J=12.1 Hz, H-2), 4.12 (1H, d, J=12.1 Hz, H-3), 3.65 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.67 (C), 167.48 (C), 161.05 (C), 136.77 (C), 136.51 (CH), 129.41 (CH), 128.82 (CH), 127.46 (CH), 127.16 (CH), 122.02 (CH), 119.79 (C), 118.10 (CH), 81.15 (CH), 59.67 (CH_3), 52.40 (CH). HREIMS (m/z) calcd for $C_{17}H_{14}O_4$ 282.0892 $[M]^+$, found 282.0884.

4.7. Methyl 4-hydroxy-2-phenylchromane-3-carboxylate (15)

To a solution of **14** (40 mg, 0.13 mmol) in anhydrous MeOH (2 mL), $NaBH_4$ (8 mg, 0.21 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h, then diluted with Et_2O and washed with brine. The organic layer was dried over anhyd Na_2SO_4, and the solvent was removed. The residue was submitted to flash chromatography (hexane/Et_2O 7:3), affording (2*R**,3*R**,4*S**)-methyl 4-hydroxy-2-phenylchromane-3-carboxylate (**15a**) (22 mg,

0.071 mmol, 55%) and its 3-epimer (2*R**,3*S**,4*S**)-methyl 4-hydroxy-2-phenylchromane-3-carboxylate (**15b**) (8 mg, 0.019 mmol, 15%).

*4.7.1. Compound **15a**.* White solid, mp 167–169 °C; IR (film) ν_{max} 3358, 1731, 1581, 1483, 1429, 1232, 1189, 1008, 759, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57 (1H, br d, *J*=7.7 Hz), 7.42 (5H, m), 7.24 (1H, br d, *J*=7.7 Hz), 7.05 (1H, dt, *J*=0.8, 7.3 Hz), 6.92 (1H, d, *J*=8.1 Hz), 5.36 (1H, dd, *J*=10.0, 8.5 Hz, H-3), 5.16 (1H, d, *J*=10.5 Hz, H-2), 3.48 (3H, s), 3.11 (1H, dd, *J*=10.5, 10.0 Hz, H-4), 2.39 (1H, d, *J*=8.5 Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.89 (C), 153.70 (C), 137.41 (C), 129.33 (CH), 128.97 (CH), 128.58 (CH), 126.95 (CH), 126.80 (CH), 124.35 (C), 121.42 (CH), 116.51 (CH), 78.75 (CH), 68.42 (CH), 55.20 (CH)*, 52.01 (CH_3)*. *May be interchanged. HREIMS (*m*/*z*) calcd for $C_{17}H_{16}O_4$ 284.1049 $[M]^+$, found 284.1040.

*4.7.2. Compound **15b**.* White solid, mp 199–201 °C; IR (film) ν_{max} 3433, 1730, 1483, 1168, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (1H, br d, *J*=7.7 Hz), 7.42 (4H, m), 7.37 (1H, m), 7.25 (1H, br d, *J*=7.7 Hz), 7.07 (1H, dt, *J*=1.2, 7.7 Hz), 6.97 (1H, br d, *J*=8.1 Hz), 5.43 (1H, d, *J*=2.4 Hz), 5.30 (1H, dd, *J*=10.5, 6.1 Hz), 3.54 (1H, dd, *J*=6.1, 2.4 Hz), 3.46 (3H, s), 2.80 (1H, d, *J*=10.5 Hz, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.02 (C), 154.13 (C), 138.32 (C), 129.03 (CH), 128.27 (CH), 127.95 (CH), 127.13 (CH), 125.40 (CH), 124.58 (C), 121.69 (CH), 116.28 (CH), 77.19 (CH), 66.64 (CH), 51.41 (CH_3)*, 50.87 (CH)*. *May be interchanged. HREIMS (*m*/*z*) calcd for $C_{17}H_{16}O_4$ 284.1049 $[M]^+$, found 284.1062.

4.8. Methyl 2-phenyl-2*H*-chromene-3-carboxylate (5)

Compounds **15a** (16 mg, 0.05 mmol) and **15b** (6 mg, 0.019 mmol) were dissolved in toluene (2.5 mL), and *p*-TsOH (6 mg, 0.03 mmol) was added. The mixture was refluxed for 50 min, then diluted with Et_2O and washed with brine. The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with hexane/Et_2O 9:1, to give compound **5** (16 mg, 0.054 mmol, 79%): white solid, mp=82–84 °C; IR (film) ν_{max} 3029, 2949, 1709, 1637, 1602, 1434, 1289, 1255, 1210, 1118, 997, 758, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (1H, s), 7.40 (2H, m), 7.29 (3H, m), 7.21 (2H, d, *J*=7.3 Hz), 6.92 (1H, dt, *J*=7.7, 1.2 Hz), 6.82 (1H, dd, *J*=7.7, 0.8 Hz), 6.31 (1H, s), 3.79 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.24 (C), 153.60 (C), 139.08 (C), 133.34 (CH), 132.28 (CH), 128.80 (CH), 128.57 (CH), 128.45 (CH), 127.12 (CH), 124.23 (C), 121.49 (CH), 120.30 (C), 116.80 (CH), 75.17 (CH), 51.93 (CH_3). HREIMS (*m*/*z*) calcd for $C_{17}H_{14}O_3$ 266.0943 $[M]^+$, found 266.0952.

4.9. Flavanone (6)

A mixture of **14** (40 mg, 0.13 mmol), NaCl (10 mg, 0.16 mmol) and water (0.1 mL) in DMSO (2 mL) was heated at 155–165 °C for 4 h, cooled, poured into water (15 mL), and extracted with hexane/Et_2O (1:1). The organic layer was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography (Et_2O) of the residue gave flavanone **6** (32 mg, 0.12 mmol, 89%).[35]

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