Synthesis and Cyclization of 1-(2-Hydroxyphenyl)-2-propen-1-one Epoxides: 3-Hydroxychromanones and -flavanones *versus* 2-(1-Hydroxyalkyl)-3-coumaranones

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Competitive α and *β* cyclization of 2′-hydroxychalcone epoxides affords 2-(α-hydroxybenzyl)-3-coumaranone and/or 3-hydroxyflavanones, which depends on the conditions employed. Epoxidation of 2′-hydroxychalcones by dimethyldioxirane followed by either base- or acid-catalyzed ring closure provides a novel, general, and efficient method for the synthesis of *trans*-3-hydroxyflavanones, which includes also the naturally occurring derivatives. Extension of this two-step procedure to 1-(2-hydroxyphenyl)-2-alken-1-ones was also accomplished. A strong preference for α cyclization was observed in the case of *β*-unsubstituted or -monoalkylated α,*β*-enones, while both 2,2-dimethyl-3-hydroxychromanones and 2-(1-hydroxy-1-methylethyl)-3-coumaranones were obtained from the *β*,*β*-dimethylated substrates.

Introduction

trans-3-Hydroxyflavanones (*trans*-2,3-dihydro-2-aryl-3-hydroxy-4*H*-1-benzopyran-4-ones) and their 3-*O*-substituted derivatives are important intermediates in the synthesis of a wide variety of flavonoid compounds and also play a significant role in the biogenesis of naturally occurring flavonoid-type derivatives.[1] Some of these show considerable biological activity;[2] among others silybin and related flavanolignans are marketed as hepatoprotective agents.[3]

A great number of synthetic methods have been developed,[1] which include alkaline hydrogen peroxide oxidation of 2′-hydroxychalcones[4] (called the Algar−Flynn−Oyamada reaction in flavonoid chemistry), base-induced cyclization of 2′-hydroxychalcone dibromides and bromohydrins (Rasoda reaction),[5] or simultaneous deprotection and ring-closure of 2′-hydroxy-protected chalcone epoxides.[6,7] Common limiting factors of these methods entail side reactions, strong solvent, temperature, and substitution pattern dependence. Very recently a highly diastereoselective oxidation of enolate derivatives of flavanone by dimethyldioxirane (DMD) to *trans*-3-hydroxyflavanones as major diastereomer has also been reported.[8]

2′-Hydroxychalcone epoxides have been postulated[9] as intermediates in the Algar−Flynn−Oyamada reaction, although their role in the formation of 3-hydroxyflavanones was strongly disputed.[4,6] Their intermediacy was also proposed in the Rasoda reaction.[5c] For a long time the parent compound, 2′-hydroxychalcone epoxide, was the only known representative of the family, prepared in low yield by *m*-chloroperbenzoic acid (*m*CPBA) oxidation of 2′-hydroxychalcone.[10,11] A few years ago we reported[12] a general and high-yield synthesis of these

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Table 1. Cyclization of 2′-Hydroxychalcone Epoxide (2a)[a]

				product composition (%)[c]						
entry	reagent[b]	solvent	time	**2a**	*trans*-**3a**	*cis*-**3a**	**4a**[d]	**5a**	**6**	**7**
1[e]	–	EtOH−H_2O (95:5, v/v)	9 h	18	55	0	14 (40:60)	0	13	3
2	TEA	CH_2Cl_2	24 h	19	35	0	43 (43:57)	3	0	0
3	DMAP	CH_2Cl_2	25 h	49	24	0	21 (26:74)	12	1	4
4	DBU	CH_2Cl_2	1 h	0	39	0	15 (40:60)	10	36	6
5	DBU	CH_2Cl_2	2 min	7	40	2	44 (48:52)	4	3	3
6	TBAH	CH_2Cl_2−H_2O (97:3, v/v)	5 min	0	74	5	0 (−)	8	12	0
7[f,g]	$HClO_4$ (0.01 M)	H_2O	2.75 h	5	82	0	0 (−)	0	0	0
8	HCl (0.12 M)	EtOH−H_2O (1:1, v/v)	2.75 h	0	>95	0	0 (−)	0	0	0

[a] Reactions were performed at room temperature (20 °C) unless otherwise stated, 0.25 equiv of base was added in entries 2−6. [b] Abbrevations used: TEA: triethylamine, DMAP: 4-(dimethylamino)pyridine, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, TBAH: tetrabutylammonium hydroxide. [c] Product ratios were determined by ^{1}H NMR spectroscopy. [d] In parentheses is given the *erythro*/*threo* ratio. [e] Performed at reflux temperature [f] Performed at 55 °C. [g] Also 2,3-dihydroxy-1-(2-hydroxyphenyl)-3-phenyl-1-propanone (13%) was also formed.

epoxides directly from chalcones without protection of the phenolic hydroxy functionality by using DMD.[13] Parallel to our work, Adams and Main[14] developed a multistep methodology for the synthesis of 2′-hydroxychalcone epoxides based on the selective deprotection of tetrahydropyranylated derivatives, but their protocol was limited to 6′-substituted compounds without electron-releasing substituent at C-4. The efficiency and convenience of the dimethyldioxirane route[12] prompted us to investigate the cyclization of 2′-hydroxychalcone epoxides in the interest of providing a new and general synthetic method for the preparation of 3-hydroxyflavanones, the feasibility of which was demonstrated in a preliminary communication.[15] We now report in detail our results on the cyclization of 2′-hydroxychalcone epoxides and the exploitation of this reaction for the synthesis of various *trans*-3-hydroxyflavanones.

In contrast with the widely studied 3-hydroxyflavanones, much less has been published on the synthesis of the related 3-hydroxychromanones (2,3-dihydro-3-hydroxy-4*H*-1-benzopyran-4-ones). Although the 3-hydroxychromanone skeleton is also a frequent structural unit of various natural products,[16] only a few synthetic methods have hitherto been developed. Lead tetraacetate-mediated acetoxylation of chromanones[17] offers a useful approach but occasional difficulties in the hydrolysis of the resulting 3-acetoxychromanones have been reported.[17a] A more elegant and enantioselective hydroxylation of 3-substituted chromanone enolates by sulfonyloxaziridines was published recently by Davis and co-workers.[16] The above-mentioned ease of the preparation of chalcone epoxides and their successful cyclization encouraged us to extend our investigations to the DMD oxidation of other 1-(2-hydroxyphenyl)-2-propen-1-ones without an aryl moiety at C-3, which provides a new and useful access to 3-hydroxychromanones.

Results and Discussion

Cyclization of 2′-hydroxychalcone epoxide (**2a**) to *trans*-3-hydroxyflavanone (*trans*-**3a**) has already been reported in the very first papers,[10,11] but somewhat controversial data were published on its stability. To survey the reaction paths and to optimize the cyclization conditions, epoxide **2a** was synthesized by using DMD according to the literature procedure[12a] and was allowed to react with various reagents. The reaction mixture was analyzed by ^{1}H NMR spectroscopy and the product data are summarized in Table 1.

The results clearly show that, in contrast with previous claims,[11] epoxide **2a** is remarkably stable. In an ethanol−water mixture at elevated temperature (Table 1, entry 1) or in the presence of weaker bases such as triethylamine (Table 1, entry 2) or 4-(dimethylamino)-pyridine (Table 1, entry 3), considerable amounts of unreacted starting material **2a** could be detected even after a prolonged reaction period. This contradicts the half-life of 2.5 s (for pH 7) reported[11] earlier, although this value refers to aqueous, buffered condions. Another important finding is that under basic or even neutral conditions not only β cyclization to *trans*-**3a** but also α cyclization to 2-(α-hydroxybenzyl)-3-coumaranone (**4a**) takes place (Scheme 1).

Similar competitive pathways were found[18] and kinetically analyzed in the cyclization of 6′-alkoxy-2′-hydroxychalcone epoxides, but exclusive β cyclization was proposed for 6′-*unsubstituted* species, such as epoxide **2a**. In our preparative scale experiment coumaranone **4a** was isolated as a mixture of *erythro* and *threo* diastereomers by silica gel chromatography and fully characterized by spectroscopic methods and elemental analysis.

The ^{1}H and ^{13}C NMR spectra of the mixture of **4a** diastereomers displayed two series of signals with different intensities, which allowed easy differentiation of the two isomers. These diastereomers were characterized by their ^3J(2-H, α-H) coupling constants, namely 2.7 Hz for the major and 6.4 Hz for the minor isomer. These values are in good agreement with the coupling constants (2.4 and 6.3 Hz) reported for the *erythro,threo* pair of 2-(α-hydroxybenzyl)-4-methoxy-3-coumaranone by Adams and Main,[18a] who assigned the diastereomer with the smaller ^3J(2-H, α-H) coupling constant to the *threo* isomer. Their assignment is based on the postulated existence of one exclusive conformation for each isomer, which is fixed by intramolecular hydrogen bonding between the α-hydroxyl

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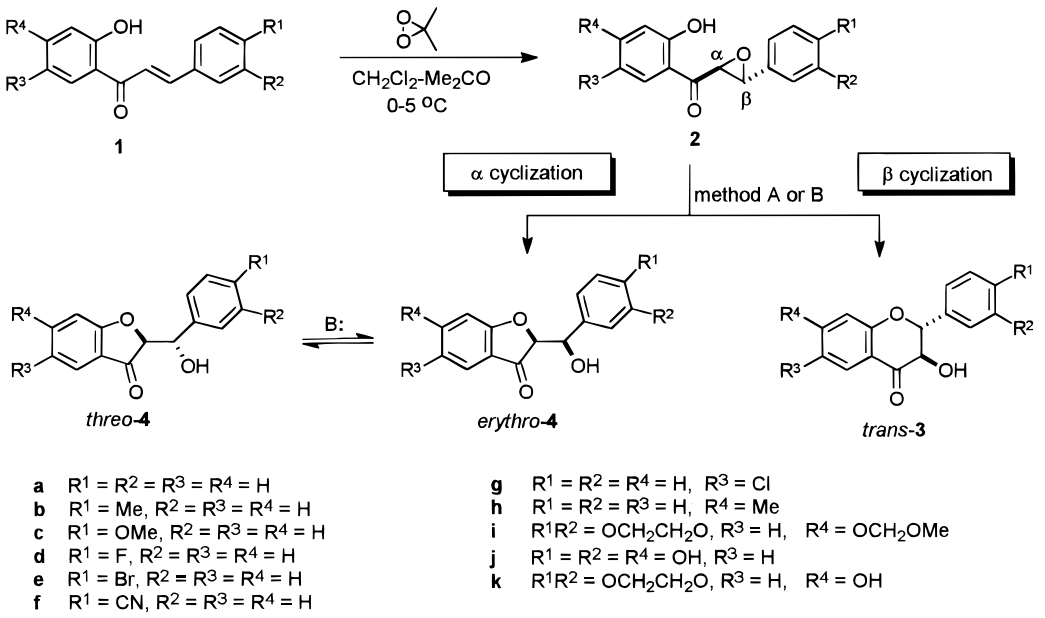
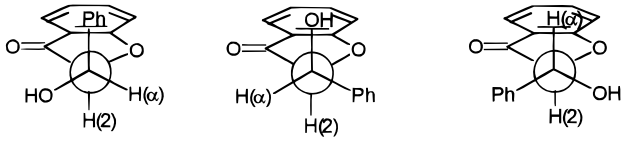
Scheme 1



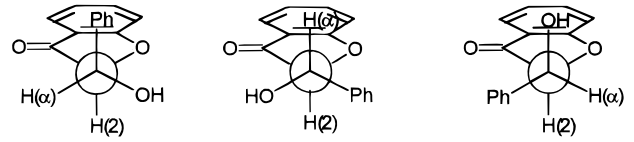
a $R^1 = R^2 = R^3 = R^4 = H$
b $R^1 = Me$, $R^2 = R^3 = R^4 = H$
c $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
d $R^1 = F$, $R^2 = R^3 = R^4 = H$
e $R^1 = Br$, $R^2 = R^3 = R^4 = H$
f $R^1 = CN$, $R^2 = R^3 = R^4 = H$
g $R^1 = R^2 = R^4 = H$, $R^3 = Cl$
h $R^1 = R^2 = R^3 = H$, $R^4 = Me$
i $R^1R^2 = OCH_2CH_2O$, $R^3 = H$, $R^4 = OCH_2OMe$
j $R^1 = R^2 = R^4 = OH$, $R^3 = H$
k $R^1R^2 = OCH_2CH_2O$, $R^3 = H$, $R^4 = OH$

and the carbonyl oxygen. However, in the spectra of the **4a** isomers, neither the O—H and C═O stretchings (ν_{OH} 3460 and ν_{CO} 1712 cm^{-1}) nor the chemical shifts of the α-hydroxy protons ($\delta = 3.68$ for the minor and $\delta = 2.84$ ppm for the major isomer) indicate the existence of any strong hydrogen bonding. On the basis of the somewhat higher chemical shift value for the major isomer ($\Delta\delta =$ 0.84 ppm), weak bonding between the hydroxyl group and the carbonyl oxygen *or* O-1 ether oxygen may be assumed. Therefore, we deemed it necessary to search for additional NMR evidence to assign the stereochemistry unambiguously.

For *erythro*- and *threo*-**4a**, the equilibrium of the following conformers **A**, **B**, and **C** may be considered.



threo-**A** *threo*-**B** *threo*-**C**



erythro-**A** *erythro*-**B** *erythro*-**C**

Significant populations of both the *threo*-**C** and *erythro*-**C** can be excluded on the basis of the unfavorable steric interaction between the carbonyl and phenyl groups. Since the conformer *threo*-**A** also suffers from steric crowding of the phenyl group and the C-3 and O-1 atoms, the conformer **B** is expected to dominate one for the *threo*-**4a** isomer. Furthermore, to the conformer *threo*-**C,** a coupling constant of 10—12 Hz would be expected between 2-H and α-H protons; thus, the measured low value (2.7 Hz) also supports the low population of this conformer. However, the same dihedral angle (ca. 60°) of 2-H and α-H in both *threo*-**A** and *threo*-**B** does not allow these conformers to be distinguished on the basis of ^3J(2-H, α-H) constant. For this differentiation the vicinal ^3J(H,C) coupling constants between the 2-H and α-H protons were determined by the 2D semiselective INEPT method.[19] On the basis of the Karplus-type dependence of ^3J(H,C) on the dihedral angle, the observed values of 1.8 Hz for both ^3J(α-H, C-3) and ^3J(2-H, C-1′) strongly support conformer *threo*-**B** since the antiperiplanar position of these atoms in conformer *threo*-**A** should give coupling constants of ca. 7—8 Hz. We conclude that the major diastereomer of **4a** with the characteristic coupling constant ^3J(2-H, α-H) of 2.7 Hz is the *threo* isomer with dominance of the *threo*-**B** conformer. Moreover, on the basis of our earlier studies,[20] the value of 4.0 Hz for the coupling constant ^3J(α-H, C-2′,6′) suggests a dihedral angle of ca. 30° between the $H_\alpha—C_\alpha$ bond and the plane of the phenyl ring.

On the basis of coupling constant ^3J(2-H, α-H) of 6.4 Hz measured for the minor diastereomer of **4a**, we can conclude that both conformers *erythro*-**A** and *erythro*-**B** are extensively populated in the conformational equilibrium. The previously postulated *weak* hydrogen bonding for this diastereomer is in agreement with both these conformations as well as the observed ^3J(α-H, C-3) coupling constant of 1.9 Hz. The marked increase (ΔJ = 2.0 Hz) of ^3J(2-H, C-1′) coupling constant of 3.8 Hz compared to that of *threo*-**4a** isomer shows unequivocally the increased population of conformer *erythro*-**A** in which C-1′ and 2-H atoms are located in the antiperiplanar position.

Irreversible formation of the 3-hydroxyflavanone (*trans*-**3a**) was verified by a control experiment. Due to the *trans* stereochemistry of the oxirane ring opening, the primary product in the α cyclization of 2′-hydroxychalcone epoxide (**2a**) is the *erythro*-**4a**, which equilibrates with its *threo*-**4a** diastereomer by the deprotonation—enolization—reprotonation sequence.[18a,21] Besides the flavanone *trans*-**3a** and the isomeric coumaranones **4a** formed in the cyclization step, a number of secondary

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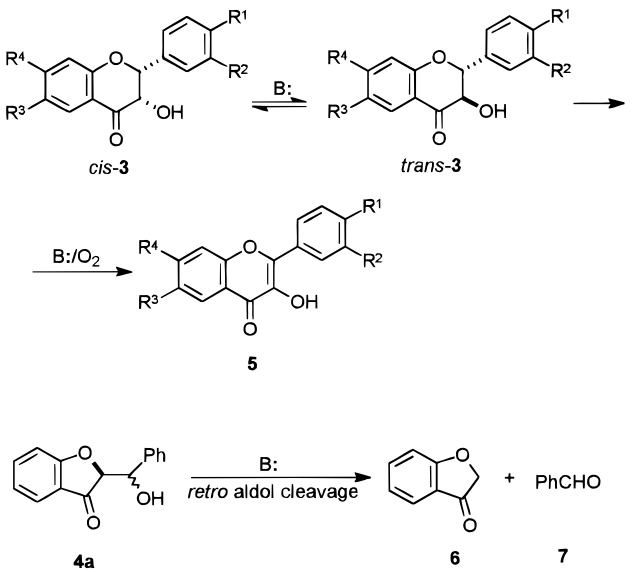
Scheme 2



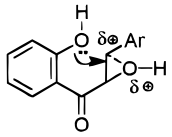
products thereof were also observed. Thus, the *cis*-3-hydroxyflavanone (*cis*-**3a**) derived from the *trans*-**3a** by base-catalyzed epimerization in the presence of strong bases (Table 1, entries 5, 6), and 3-hydroxyflavone (**5a**), the product from *trans*-**3a** by dehydrogenation in the basic medium in the presence of air,[10] were obtained as well (Scheme 2, Table 1, entries 2−6). 3-Coumaranone (**6**) and benzaldehyde (**7**), which are the products of the *retro* aldol cleavage of *erythro,threo*-**4a**, were also detected.

The significant shift in the product ratio in favor of the *retro* aldol products **6** and **7** (Table 1, entries 4, 5) in the DBU-catalyzed transformations at the longer reaction time clearly confirms this cleavage. Adams and Main[18] have also observed the formation of 4-methoxycoumaranone during the cyclization of 2′-hydroxy-6′-methoxychalcone epoxide under strongly basic conditions.

We also tested basic ion-exchange resins such as Amberlyst 21 or Amberlite IRA410 (OH^- form) to produce the cyclization but, surprisingly, no reaction took place at all. On the other hand, the use of tetrabutylammonium hydroxide (TBAH) (Table 1, entry 6) resulted in a slight shift in the competitive primary reactions in favor of β cyclization and in the fast and complete *retro* aldol cleavage of the coumaranone **4a**. These advantageous changes were exploited to develop a new and general two-step procedure for the synthesis of *trans*-3-hydroxyflavanones **3**. In the first step, the 2′-hydroxychalcones **1a**−**d,g**−**i** were oxidized with DMD (as acetone solution)[22] and after removal of the solvent, the crude epoxides **2a**−**d,g**−**i** were treated with TBAH (0.3 equiv) in dichloromethane−water mixture as medium to give the desired *trans*-3-hydroxyflavanones **3a**−**d,g**−**i** in good overall yield (Scheme 1, Table 2, method A).

The main advantage of this methodology over the previous syntheses is that the yield of isolated product *trans*-**3** is independent of the substitution pattern for a wide range of substituents. The only factor which limits the yield of the flavanones *trans*-**3** is the competitive α cyclization.

The possibility for further improvement was offered by the cyclization of epoxides **2** under acidic conditions, for which the product data (Table 1, entries 7, 8) revealed almost exclusive β cyclization. This advantage may be rationalized in terms of a change in the mechanism of the ring closure. In contrast with the attack of a phenolate anion on the oxirane ring under basic or neutral conditions (S_N2 mechanism), in the presence of strong acids the attack of the phenolic hydroxy group occurs on a protonated epoxide (S_N1-like mechanism). Thus, the β carbon atom of this protonated intermediate possesses considerable cationic character at the resonance-stabilized benzylic position and, therefore, the more pronounced reactivity at this position.



D

This enhanced regioselectivity was utilized synthetically by replacing the second step of the former base-catalyzed protocol (method A) by acid treatment (method B). Comparison of yields collected in Table 2 establishes the superiority of the acid-catalyzed cyclization. Incorporation of electron-withdrawing R^1 groups in the C-4 position (Table 2, entries 8, 9) required longer reaction times for the acid-catalyzed cyclization, which is in agreement with the destabilization of the protonated species **D**.

The determining role of the stabilizing/destabilizing effect of ring B substituents on the rate of cyclization was also utilized for the synthesis of naturally occurring *trans*-3-hydroxyflavanones **3**. The common feature of these derivatives is that most of them have at least one but typically two or three hydroxy or alkoxy functionalities on the aromatic ring attached to the C-2. Due to the activating effect of the electron-donating hydroxy groups, when 2′,4′,3,4-tetrahydroxychalcone or butein (**1j**) was treated with DMD, the corresponding *trans*-3,7,3′,4′-tetrahydroxyflavanone or (±)-fustin[1a] (*trans*-**3j**) was obtained directly in 50% yield. Besides **3j**, only highly polar, colored products with low R_f values could be detected by TLC. The probable side reaction, which lowered the yield of **3j**, is the formation of quinone-type derivatives[23] from both the starting material **1j** and the cyclization product *trans*-**3j**. In spite of this drawback, the direct DMD oxidation offers an exceptionally simple and efficient method for the preparation of naturally occurring polyhydroxylated 3-hydroxyflavanones.

The synthesis of natural 3-hydroxyflavanones with less activating substituents in their ring B was accomplished by using protecting groups. To demonstrate this approach, methoxymethylated *trans*-**3i**, synthesized either by the method A or B (Table 2, entries 14, 15), was deprotected to the *trans*-3,7-dihydroxy-3′,4′-ethylenedioxyflavanone (*trans*-**3k**), a model compound of silybin and its derivative (Scheme 3).

As a logical extension, we also examined the oxidation of α,β-unsaturated ketones *without* an aryl group at the β position to assess whether 3-hydroxychromanones and/or 2-(1-hydroxyalkyl)-3-coumaranones are formed. Surprisingly little has been published in this area so far, *e.g.*

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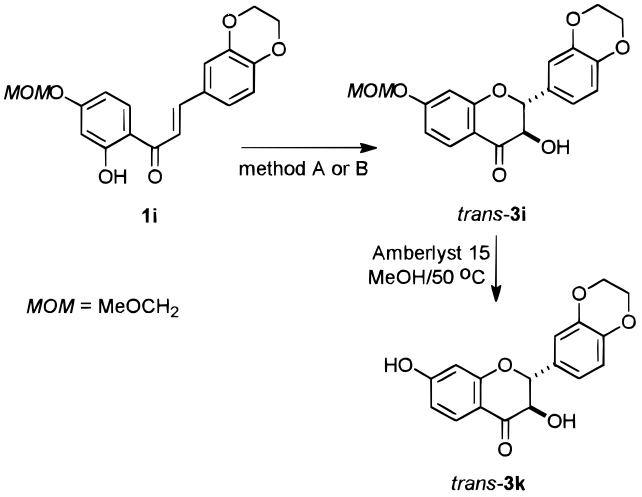
Table 2. Synthesis of 3-Hydroxyflavanones *trans*-3

entry	*trans*-**3**	R^1	R^2	R^3	R^4	method[a]	DMD (equiv)	yield[b] (%)
1	a	H	H	H	H	A	6.1	55
2						B	6.8	67
3	b	Me	H	H	H	A	3.6	44
4						B	3.2	67
5	c	OMe	H	H	H	A	2.4	51
6						B	3.6	57[c]
7	d	F	H	H	H	A	4.8	47
8	e	Br	H	H	H	B	6.5	72
9	f	CN	H	H	H	B	16.5[d]	53[e,f]
10	g	H	H	Cl	H	A	7.2	53
11						B	8.5	72
12	h	H	H	H	Me	A	4.4	40
13						B	6.5	57[g]
14	i	OCH_2CH_2O		H	OCH_2OMe	A	4.8	44
15						B	4.9	36
16	j	OH	OH	H	OH	h	4.0	50
17	k	OCH_2CH_2O		H	OH	h	–	76

[a] Method A: 1. DMD/CH_2Cl_2–Me_2CO/0 °C, 2. TBAH (0.3 equiv)/CH_2Cl_2–H_2O/rt (ca. 20 °C); method B: 1. DMD/CH_2Cl_2–Me_2CO/0 °C, 2. 0.12 M HCl–EtOH (1:1, v/v)/rt (ca. 20 °C) [b] Yields refer to isolated pure products. [c] Also 3-hydroxy-4′-methoxyflavone (**5c**) was isolated, 16%, mp 235–237 °C (lit.[40] mp 236 °C). [d] Extent of epoxidation was ca. 78% on the basis of ^{1}H NMR of the crude epoxide. [e] Cyclization was performed at reflux temperature, no reaction occurred at room temperature (ca. 20 °C). [f] Yield corrected for the extent of conversion. [g] Small amount of unreacted chalcone **1h** was also detected by TLC. [h] See text.

Scheme 3



Donnelly and Maloney[24] reported the failure of the oxidation of **8a** with alkaline hydrogen peroxide in methanolic medium because of the greater propensity of the substrate for conjugate addition of methanol. In the presence of a weaker base such as potassium carbonate, the desired 3-hydroxychromanone (**10a**) was obtained in poor yield (6.4%) beside catechol as the major product, which was generated by the concurrent Baeyer–Villiger reaction. On the contrary, 1-(2-hydroxy-4,6-dimethoxyphenyl)-2-propen-1-one failed to react under the same conditions.

As starting materials **8a,b,d,f** were prepared by literature methods,[25–28] the 6-tosyloxy derivative **8e** was obtained by tosylation of **8f**. The parent dimethyl derivative **8c** was isolated as a byproduct of the Fries rearrangement[29] of phenyl 3-methylcrotonate in low yield. Treatment of the propenones **8a–e** with DMD (Table 3, entries 2–5 and 8) revealed that the epoxides **9a–e** are much more labile than the corresponding chalcone epoxides **2**. TLC monitoring showed a component with intermediate character but only the cyclization products **10** and **11** were isolated after workup and column chromatography (Scheme 4).

The yield data in Table 3 establish that α cyclization dominates to afford 2-(1-hydroxyalkyl)-3-coumaranones **11a,b** in the case of substrates **8a,b**, which are unsubstituted or monosubstituted at carbon β. On the contrary, the dimethyl enones **8c–e** furnish both the coumaranones[30] **11c–e** and 2,2-dimethyl-3-hydroxychromanones **10c–e**, for which the regioselectivity is usually low with a slight preference of β cyclization. A possible explanation for this trend is that the incorporation of alkyl groups increases the stability of the partially positively charged carbon β in the transition state of β cyclization. On the basis of yield data in Table 3, we can conclude that the epoxide route has synthetic value only for the preparation of 2,2-dialkylated 3-hydroxychromanones.

1-(2,5-Dihydroxy-4-methoxyphenyl)-3-methyl-2-buten-1-one (**12d**), an interesting byproduct hydroxylated in its aromatic moiety, was also isolated from the dioxirane oxidation of enone **8d** (Table 3, entry 5). Such aromatic hydroxylation has already been reported in the preparation of hydroquinones[31] or methoxybenzenes from their *p*-methoxyphenol intermediates,[32] but this is the first example to proceed in competition with alkene oxidation. No hydroxylation-type product **12** was observed in the DMD oxidation of substrates **8a–c,e**. This difference indicates that both the presence of the activating 4′-methoxy group and the trisubstituted double bond is a prerequisite for the formation of the arene epoxide intermediate **13** (Scheme 4).

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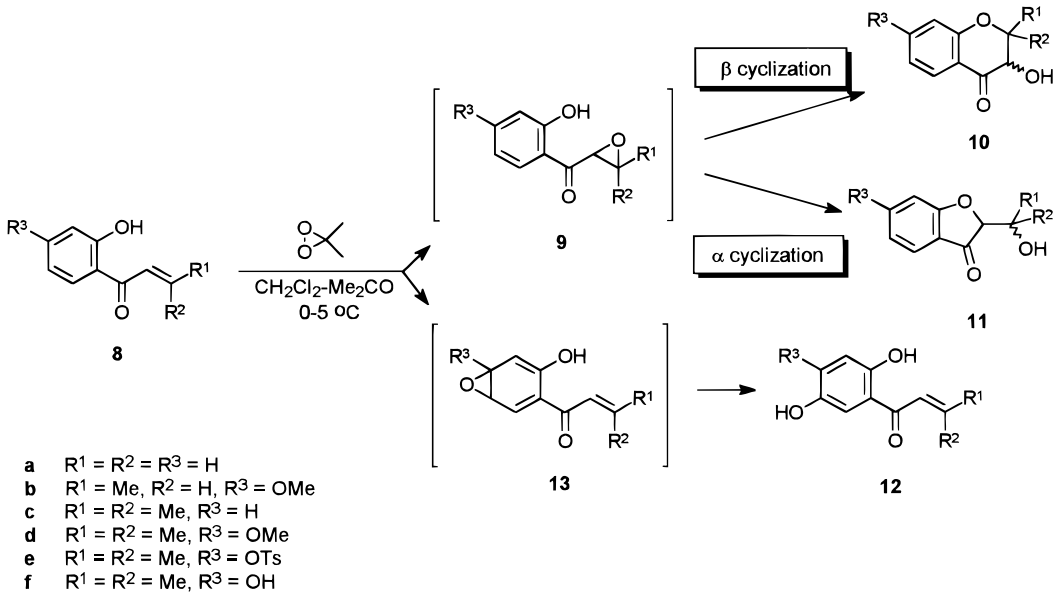
(25) Turbina, A. I.; Sinyavskii, V. G. *Metody Poluch. Khim. Reakt. Prep.* **1964**, 86; *Chem. Abstr.* **1966**, *65*, 8807g.
(26) Miranda, M. A.; Primo, J.; Tormos, R. *Heterocycles* **1988**, *27*, 673.
(27) Timár, T.; Hosztafi, S.; Jászberényi, J. Cs.; Kövér, K. E.; Batta, Gy. *Acta Chim. Hung.* **1988**, *125*, 303.
(28) Sebök, P.; Jekö, J.; Timár, T.; Jászberényi, J. Cs. *Heterocycles* **1994**, *38*, 2099.
(29) Baker, W.; Floyd, A. J.; McOmie, J. F. W.; Pope, G.; Weaving, A. S.; Wild, J. H. *J. Chem. Soc.* **1956**, 2010.
(30) The only example of this family that appears to be reported[5c] previously is the 7-bromo-4,6-dimethoxy-2-(1-hydroxy-1-methylethyl)-2-coumaranone, which was isolated from the reaction of 2′-acetoxy-3′-bromo-4′,6′-dimethoxychalcone epoxide with sodium hydroxide in aqueous acetone. The pathway postulated by the authors involves an α cyclization of the chalcone epoxide, a subsequent *retro* aldol cleavage of the 2-(α-hydroxybenzyl)-3-coumaranone (*vide supra*) and attack of the ketone solvent on the coumaranone enolate.
(31) Altamura, A.; Fusco, C.; D'Accolti, L.; Mello, R.; Prencipe, T.; Curci, R. *Tetrahedron Lett.* **1991**, *32*, 5445.
(32) Adam, W.; Shimizu, M. *Synthesis* **1994**, 560.

Table 3. Oxidation of 1-(2-Hydroxyphenyl)-2-propen-1-ones 8

		substrate						yield[a] (%)		
entry		R^1	R^2	R^3	amount (mmol)	oxidant [equiv]	conversion (%)	**10**	**11**	**12**
1[b]	a	H	H	H	18.9	H_2O_2/K_2CO_3 [1.3]	100	6.4	0	0
2					2.50	DMD [3.6]	100	5.1	53	0
3	b	Me	H	MeO	2.00	DMD [6.3]	84	4.9	37[c]	0
4	c	Me	Me	H	2.04	DMD [5.2]	84	47	31	0
5	d	Me	Me	MeO	2.00	DMD [5.3]	83	26	5.6	7.3
6					2.25	H_2O_2-NaOH [2.75]	100	48	7.2	0
7					2.25	*m*CPBA [3.3]	88	33	27	9.8
8	e	Me	Me	TsO	0.78	DMD [10.1]	81	68	17	0

[a] Yields refer to isolated products and are corrected for the extent of conversion. [b] Data from ref 24; also catechol (32%) was isolated. [c] As a 3:2 mixture of *erythro* and *threo* diastereomers.

Scheme 4



The oxidation of enone **8d** by other oxidants such as alkaline hydrogen peroxide (Table 3, entry 6) and *m*CPBA (Table 3, entry 7) revealed that in comparison with derivative **8a**, dimethyl substitution of the β carbon lowers its reactivity for the conjugate addition of the solvent methanol under basic conditions and allows the synthesis of 3-hydroxychromanone. *m*CPBA was found to react very sluggishly and yielded also a considerable amount of the hydroxylated product **12d,** presumably through the epoxide **13** (Scheme 4). Previously the oxidation of the 2′-hydroxy-4′,6′-dimethoxychalcone to the 2′,5′-dihydroxy-4′,6′-dimethoxychalcone was reported[24] in 7.6% yield upon treatment with *m*CPBA, which supports the electrophilic arene oxide for the aromatic hydroxylation of activated substrates.

In summary, 1-(2-hydroxyphenyl)-2-alken-1-one epoxides, available by DMD oxidation of the corresponding enones, are useful intermediates for the synthesis of 3-hydroxychromanones and 2-(1-hydroxyalkyl)-2-coumaranones in good yield. The formation of coumaranones by α cyclization is a general pathway in the ring closure of these epoxides although its participation strongly depends on the substitution of the β carbon and on the oxidation conditions.

Experimental Section

General. Melting points were determined with a Boetius hot-stage apparatus and are uncorrected. Elemental analysis were performed in-house. IR spectra were measured for KBr discs unless otherwise specified. ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ solution with TMS as internal reference unless otherwise stated. EI mass spectra were run at 70 eV. All commercial reagents were used as purchased. $MgSO_4$ served as drying agent. TLC's were developed on Kieselgel 60 F_{254} sheets (Merck), column chromatography was performed on silica gel 60 (0.063−0.2 mm). The 2′-hydroxychalcones **1** were synthesized according to literature procedures.[33] Dimethyldioxirane (DMD) (0.08−0.1 M acetone solution) was prepared as described in the literature[22] and its peroxide content was determined by iodometric titration. DMD solutions were stored over molecular sieve (4 Å) at −20 °C.

Cyclization of 2′-Hydroxychalcone Epoxide (2a). Characterization of Products and Determination of Product Ratios. 2′-Hydroxychalcone epoxide (**2a**)[12a] (112 mg, 0.50 mmol) was treated with the reagents and under the conditions given in Table 1. The reaction mixture was poured into water (50 mL), extracted with CH_2Cl_2 (3 × 15 mL), and dried. The solvent was removed under reduced pressure, and the composition of the residue was determined by means of ^{1}H NMR spectroscopy. For characterization of the major products *trans*-**3a**, *erythro*- and *threo*-**4a**, pure analytical samples were obtained from the reaction mixture of entry 5 (started from 3.00 mmol of **2a**) by column chromatography (eluent: hexane−acetone = 4:1, v/v). Yields of isolated materials were 43% for *trans*-**3a** and 20% for *erythro,threo*-**4a** (as a mixture of diastereomers).

***trans*-3-Hydroxyflavanone (*trans*-3a)**: mp 186−190 °C (lit.[34] mp 183−184 °C, lit.[35] mp 188 °C), colorless needles. ^{1}H

(33) Dhar, D. N. *The Chemistry of Chalcones and Related Compounds*; Wiley: New York,1981.
(34) Oyamada, T. *Bull. Chem. Soc. Jpn.* **1941**, *16*, 411; *Chem. Abstr.* **1947**, *41*, 3797.
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NMR δ 7.94 (dd, J = 7.6, 1.9 Hz, 1H), 7.40−7.62 (m, 6H), 7.0−7.15 (m, 2H), 5.16 (d, J = 12.4 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 3.67 (s, 1H, D_2O exchangeable).

***erythro,threo*-2-(α-Hydroxybenzyl)-3-coumaranone (*erythro,threo*-4a)**: Yellow oil. IR (neat) 3436, 2924, 1712, 1612, 1460, 1322, 1192, 1144, 1124, 1102, 1070, 1048, 1022, 880, 758, 698 cm^{-1}. MS (*m/z*, rel int): 240 ($M^{+\cdot}$, 22%), 238 (4), 222 (74), 221 (16), 220 (17.5), 195 (7), 183 (3), 165 (4.5), 134 (100), 121 (13), 105 (51), 91 (7), 79 (19), 77 (32). Anal. Calcd for $C_{15}H_{12}O_3$ (240.26): C, 74.99; H, 5.03. Found: C, 74.71; H, 5.12.

***erythro*-4a**:[36] ^{1}H NMR δ 7.63 (dd, J = 7.2, 1.0 Hz, 1H), 7.57 (ddd, 1H), 7.49 (m, 2H), 7.25−7.45 (m, 3H), 7.13 (d, J = 8.3 Hz, 1H), 7.02 (ddd, 1H), 4.99 (d, J = 6.4 Hz, 1H), 4.73 (d, J = 6.4 Hz, 1H), 3.68 (s, 1H, D_2O exchangeable). ^{13}C NMR δ 200.7, 173.0, 138.3, 138.1, 128.5, 128.2, 127.0, 124.3, 122.2, 121.0, 113.3, 86.3, 73.6.

***threo*-4a**:[36] ^{1}H NMR δ 7.63 (dd, J = 7.3, 1.0 Hz, 1H), 7.58 (ddd, 1H), 7.49 (m, 2H), 7.38 (m, 2H), 7.31 (m, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.04 (ddd, 1H), 5.32 (d, J = 2.7 Hz, 1H), 4.75 (d, J = 2.7 Hz, 1H), 2.84 (s, 1H, D_2O exchangeable). ^{13}C NMR δ 200.1, 173.4, 139.5, 138.1, 128.5, 128.2, 126.4, 124.2, 122.0, 121.5, 113.4, 87.4, 73.1.

For the identification of the minor products *cis*-**3a**,[37] **5a**,[38] **6**,[39] and **7**,[39] ^{1}H NMR spectra were compared with those of the literature.

When 2′-hydroxychalcone epoxide (**2a**) (114 mg, 0.51 mmol) was treated with a mixture of ethanol (5 mL) and 0.12 M hydrochloric acid solution (5 mL, ca. 0.59 mmol) at rt (ca. 20 °C) for 3 h and worked up as given for method B (*vide infra*), 86.0 mg (71%) of *trans*-**3a** was obtained, as colorless crystals, mp 188−191 °C.

Treatment of *trans*-3-Hydroxyflavanone (*trans*-3a) with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). When *trans*-**3a** (120 mg, 0.50 mmol) was treated with DBU under the conditions of entry 5 (Table 1) and worked up according to the procedure given for the cyclization of **2a** (*vide supra*), a product ratio *trans*-**3a**:*cis*-**3a**:**5a** = 89:7:4 was established by ^{1}H NMR analysis.

General Procedures for the Preparation of 3-Hydroxyflavanones *trans*-3a−i. Method A. To a cooled (0−5 °C) solution of 2′-hydroxychalcone (**1**) (2.00 mmol) in CH_2Cl_2 (10 mL) was added DMD as acetone solution (20 mL, 0.08−0.10 M). After 12 h the next batch of DMD solution was added. Additions were repeated until total consumption of the starting chalcone was detected by TLC (hexane−acetone = 4:1, v/v). The solvent was removed *in vacuo* (bath temperature = 25 °C), and the residue was dissolved in CH_2Cl_2 (15 mL). The solution was stirred under nitrogen at room temperature and 0.4 mL of 1.5 M aqueous tetrabutylammonium hydroxide (TBAH) (0.60 mmol) was added. After a structure-dependent stirring period, the reaction mixture was poured into 4% hydrochloric acid solution (25 mL) and separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (3 × 15 mL), dried, and concentrated. The residue was treated with cold hexane−absolute EtOH or hexane-acetone mixture (10−20:1, v/v), the solid crystalline residue was collected by filtration to give pure *trans*-**2** (>95% by ^{1}H NMR).

Method B. 2′-Hydroxychalcone (**1**) (2.00 mmol) was epoxidized by using DMD, and the reaction mixture was worked up as given for method A. The crude epoxide was dissolved in ethanol (20 mL), and 0.12 M hydrochloric acid solution (20 mL, ca. 2.34 mmol) was added and stirred until the completion of the cyclization. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (3 × 15 mL), dried, and concentrated. The residue was treated with cold hexane−absolute EtOH or hexane−acetone mixture (10−20:1, v/v), and the solid crystalline residue was collected to give pure *trans*-**2** (>95% by ^{1}H NMR).

***trans*-3-Hydroxyflavanone (*trans*-2a)**: Yields: 55% (method A, stirring period: 5 min), 67% (method B, stirring period: 2.5 h); mp 188−191 °C (lit.[34] mp 183−184 °C, lit.[35] mp 188 °C), colorless needles.

***trans*-3-Hydroxy-4′-methylflavanone (*trans*-2b)**: Yields: 43% (method A, stirring period: 5 min), 67% (method B, stirring period: 5 h); mp 174−176 °C (EtOH), colorless crystals. IR 3464, 3022, 2918, 2856, 1700, 1608, 1576, 1462, 1384, 1272, 1228, 1214, 1184, 1142, 1104, 1008, 812, 760 cm^{-1}. ^{1}H NMR δ 7.93 (dd, J = 8.0, 2.3 Hz, 1H), 7.57 (ddd, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.01−7.17 (m, 2H), 5.11 (d, J = 12.5 Hz, 1H), 4.66 (dd, J = 12.5, 1.9 Hz, 1H), 3.62 (d, J = 1.9 Hz, 1H, D_2O exchangeable), 2.40 (s, 3H). Anal. Calcd for $C_{16}H_{14}O_3$ (254.29): C, 75.57; H, 5.55. Found: C, 75.85; H, 5.67.

***trans*-3-Hydroxy-4′-methoxyflavanone (*trans*-2c)**: Yields: 51% (method A, stirring period: 3 min), 57% (method B, stirring period: 8 h); mp 166−170 °C (lit.[40] mp 168 °C), colorless needles. ^{1}H NMR δ 7.94 (dd, J = 7.8, 1.6 Hz, 1H), 7.57 (ddd, 1H), 7.56 (d, J = 8.7 Hz, 2H), 6.98−7.15 (m, 2H), 7.05 (d, J = 8.7 Hz, 2H), 5.11 (d, J = 12.4 Hz, 1H), 4.65 (d, J = 12.4 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 1H, D_2O exchangeable).

***trans*-4′-Fluoro-3-hydroxyflavanone (*trans*-2d)**: Yield: 47% (method A, stirring period: 2 min); mp 167−170 °C (EtOH), colorless needles. IR 3464, 3076, 2900, 2832, 1698, 1606, 1576, 1512, 1472, 1462, 1296, 1274, 1228, 1212, 1158, 1136, 1106, 1010, 832, 768 cm^{-1}. ^{1}H NMR δ 7.94 (dd, J = 8.1, 1.8 Hz, 1H), 7.51−7.62 (m, 3H), 7.02−7.28 (m, 4H), 5.13 (d, J = 12.5 Hz, 1H), 4.60 (dd, J = 12.5, 1.8 Hz, 1H), 3.69 (d, J = 1.8 Hz, 1H, D_2O exchangeable). Anal. Calcd for $C_{15}H_{11}FO_3$ (258.25): C, 69.76; H, 4.29. Found: C, 69.49; H, 4.00.

***trans*-4′-Bromo-3-hydroxyflavanone (*trans*-2e)**: Yield: 72% (method B, stirring period: 122 h); mp 173−175 °C (EtOH), colorless needles. IR 3460, 1705, 1695, 1608, 1472, 1462, 1293, 1283, 1228, 1213, 1143, 1108, 1075, 1009, 819, 769 cm^{-1}. ^{1}H NMR δ 7.93 (dd, J = 7.9, 1.7 Hz, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.58 (ddd, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.13 (ddd, 1H), 7.06 (d, J = 8.4 Hz, 1H), 5.11 (d, J = 12.3 Hz, 1H), 4.56 (d, J = 12.3 Hz, 1H), 3.68 (s, 1H, D_2O exchangeable). Anal. Calcd for $C_{15}H_{11}BrO_3$ (319.17): C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.78; H, 3.51; Br, 25.30.

***trans*-4′-Cyano-3-hydroxyflavanone (*trans*-2f)**: Yield: 41% (method B, stirring period: 5 h at reflux temperature), isolated by column chromatography (toluene−ethyl acetate = 6:1, v/v); mp 161−162.5 °C (EtOH), pale yellow crystals. IR 3474, 2222, 1692, 1604, 1576, 1464, 1276, 1222, 1194, 1138, 1106, 1020, 826, 770 cm^{-1}. ^{1}H NMR δ 7.95 (dd, J = 7.8, 1.6 Hz, 1H), 7.75 (A_2B_2, 4H), 7.61 (ddd, 1H), 7.16 (ddd, 1H) 7.08 (d, J = 8.4, 1.1 Hz, 1H), 5.20 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.2 Hz, 1H), 3.75 (s, 1H, D_2O exchangeable). Anal. Calcd for $C_{16}H_{11}NO_3$ (265.27): C, 72.45; H, 4.18; N, 5.28. Found: C, 72.15; H, 4.08; N, 4.92.

***trans*-6-Chloro-3-hydroxyflavanone (*trans*-2g)**: Yields: 53% (method A, stirring period: 10 min), 72% (method B, stirring period: 22 h); mp 130−132 °C. (EtOH), colorless needles. IR 3468, 3462, 3076, 2892, 2844, 1698, 1600, 1470, 1456, 1424, 1286, 1260, 1224, 1196, 1142, 1122, 1086, 1016, 980, 878, 838, 766, 708 cm^{-1}. ^{1}H NMR δ 7.89 (d, J = 2.6 Hz, 1H), 7.41−7.61 (m, 6H), 7.02 (d, J = 8.8 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 4.63 (d, J = 12.4 Hz, 1H), 3.56 (br s, 1H, D_2O exchangeable). Anal. Calcd for $C_{15}H_{11}ClO_3$ (174.71): C, 65.59; H, 4.04; Cl, 12.91. Found: C, 65.48; H, 3.86; Cl, 13.22.

***trans*-3-Hydroxy-7-methylflavanone (*trans*-2h)**: Yields: 40% (method A, stirring period: 5 min), 57% (method B, stirring period: 5.5 h); mp 198−201 °C (EtOH), colorless crystals. IR 3468, 2906, 1686, 1614, 1570, 1458, 1420, 1280, 1236, 1154, 1116, 1024, 994, 770, 700 cm^{-1}. ^{1}H NMR δ 7.82 (d, J = 8.0 Hz, 1H), 7.59 (m, 2H), 7.48 (m, 3H), 6.94 (dd, J = 8.3, 1.7 Hz, 1H), 6.86 (d, J = 1.7 Hz, 1H), 5.12 (d, J = 12.3 Hz,

(36) ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively.

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1H), 4.60 (d, J = 12.3 Hz, 1H), 3.68 (br s, 1H, D_2O exchangeable), 2.39 (s, 3H). Anal. Calcd for $C_{16}H_{14}O_3$ (254.29): C, 75.57; H, 5.55. Found: C, 75.33; H, 5.61.

***trans*-3′,4′-(Ethylenedioxy)-3-hydroxy-7-methoxymethoxyflavanone (*trans*-2i)**: Yields: 44% (method A, stirring period: 3 min), 36% (method B, stirring period: 21 h); mp: 153−155 °C (EtOH), colorless crystals. IR 3448, 2928, 2880, 1682, 1610, 1658, 1512, 1446, 1434, 1296, 1254, 1208, 1154, 1114, 1094, 1064, 1034, 1012, 856, 800 cm^{-1}. ^1H NMR δ 7.86 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 1.4 Hz, 1H), 7.05 (dd, J = 8.1, 1.4 Hz, 1H), 6.94 (d, J = 8.1 Hz), 6.76 (dd, J = 8.4, 1.5 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 5.20 (s, 2H), 5.01 (d, J = 12.1 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.29 (s, 4H), 3.70 (s, 1H, D_2O exchangeable), 3.70 (s, 3H). Anal. Calcd for $C_{19}H_{18}O_7$ (358.35): C, 63.68; H, 5.06. Found: C, 63.82; H, 5.03.

***trans*-3,7,3′,4′-Tetrahydroxyflavanone or (±)-Fustin (*trans*-2j).** A sample of 545 mg (2.00 mmol) of 2′,4′,3,4-tetrahydroxychalcone (**1j**) was treated with DMD (20 mL) in acetone solution. Fresh batches of dioxirane were added repeatedly until complete consumption of the starting chalcone, and the reaction mixture was concentrated (bath temperature = 25 °C) and submitted to silica gel chromatography (toluene−absolute methanol = 5:1, v/v) to give 291 mg (50%) of dihydroflavonol **2j**; mp 210−220 °C dec (lit.[41] mp 211 °C), brownish powder. IR 3412 br, 3260 br, 1676, 1610, 1522, 1464, 1322, 1266 br, 1160, 1108, 1016, 992, 806 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.60 (s, 1H, D_2O exchangeable), 9.00, 8.96 (2 × s, 2H, D_2O exchangeable), 7.92 (d, J = 8.7 Hz, 1H), 6.89 (m, 1H), 6.75 (m, 2H), 6.53 (dd, J = 8.7, 2,2 Hz, 1H), 6.30 (d, J = 2.2 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H, D_2O exchangeable), 4.97 (d, J = 11.4 Hz, 1H), 4.41 (dd, J = 11.4, 5.5 Hz, 1H).

***trans*-3,7-Dihydroxy-3′,4′-(ethylenedioxy)flavanone (*trans*-2k).** A mixture of 156 mg (0.435 mmol) *trans*-3′,4′-(ethylenedioxy)-3-hydroxy-7-(methoxymethoxy)flavanone (*trans*-**2i**), Amberlyst 15 (0.3 g) and methanol (10 mL) was stirred at 50 °C for 3.5 h. The resin was removed by filtration and washed with hot methanol (3 × 10 mL), and the combined filtrate was concentrated under reduced pressure. The residue was crystallized from diisopropyl ether to afford 104 mg (76%) brownish powder, mp 227−230 °C. IR 3446, 2938, 2878, 1676, 1654, 1612, 1510, 1466, 1436, 1384, 1310, 1260, 1156, 1106, 1064, 1008, 924, 890, 808 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.62 (br s, 1H, D_2O exchangeable), 7.53 (d, J = 9.1 Hz, 1H), 7.05 (d, J = 1.4 Hz, 1H), 6.99 (dd, J = 9.1, 1.4 Hz, 1H), 6.88 (d, J = 9.1 Hz, 1H), 6.53 (dd, J = 9.3, 2.4 Hz, 1H), 6.32 (d, J = 2.4 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H). Anal. Calcd for $C_{17}H_{14}O_6$ (314.30): C, 64.97; H, 4.49. Found: C, 64.95; H, 4.43.

1-(2-Hydroxyphenyl)-2-propen-1-one (8a). A mixture of 2′-hydroxyacetophenone (6.0 mL, 49.8 mmol), dimethylammonium chloride (5.55 g, 68.0 mmol), paraformaldehyde (2.01 g), 2-propanol (10 mL), and concd hydrochloric acid (0.2 mL) was refluxed for 1 h and was allowed to stand in the refrigerator overnight. The colorless precipitate was collected by filtration, washed with diethyl ether (4 × 30 mL), dissolved in water (750 mL), and steam-distilled. The distillate was extracted with CH_2Cl_2 (3 × 150 mL), dried, and concentrated under reduced pressure. Silica gel chromatography (eluent: toluene) of the residue afforded 1.20 g (16%) of enone **8a** as a yellow oil (lit.[25] bp 67−68 °C/1−2 Torr). IR (neat) 3046 br, 1644, 1634, 1614, 1592, 1486, 1446, 1410, 1358, 1288, 1240, 1208, 1158, 1000, 976, 832, 752, 716 cm^{-1}. ^1H NMR δ 12.53 (s, 1H, D_2O exchangeable), 7.80 (dd, J = 8.0, 1.5 Hz, 1H), 7.55 (ddd, 1H), 7.50 (dd, J = 16.9, 10.5 Hz, 1H), 6.87−7.03 (m, 2H), 6.56 (dd, J = 16.9, 1.6 Hz, 1H), 5.96 (dd, J = 10.5, 1.6 Hz, 1H). Anal. Calcd for $C_9H_8O_2$ (148.16): C, 72.96; H, 5.44. Found: C, 73.11; H, 5.19.

1-(2-Hydroxyphenyl)-3-methyl-2-buten-1-one (8c). Phenyl 3-methyl-2-butenoate (6.20 g, 35.18 mmol) was treated with $AlCl_3$ (6.51 g, 48.82 mmol) according to the literature procedure.[29] After workup and removal of the diethyl ether the residue was submitted to column chromatography (eluent: toluene) to yield 0.40 g (6.5%) enone **8c** as a yellow oil and 2,2-dimethylchromanone (2.7 g, 44%) as main product.

8c: IR (neat) 2976, 2913, 1641, 1583, 1466, 1444, 1363, 1293, 1242, 1222, 1158, 1014, 796, 756 cm^{-1}. ^1H NMR δ 12.82 (s, 1H, D_2O exchangeable), 7.87 (dd, J = 8.0, 1.7 Hz, 1H), 7.34 (ddd, 1H), 6.97 (dd, J = 8.4, 1.2 Hz, 1H), 6.87 (ddd, 1H), 6.79 (m, 1H), 2.21 (d, J = 1.3 Hz, 1H), 2.04 (d, J = 1.3 Hz, 1H). ^{13}C NMR δ 196.6, 163.5, 158.0, 135.9, 135.8, 130.0, 120.7, 120.1, 118.7, 118.5, 28.0. 21.2. MS 176 ($M^{+\bullet}$, 4), 161 (100), 131 (3). 121 (31), 120 (6), 89 (9), 83 (14), 65 (20).

1-[2-Hydroxy-4-(tosyloxy)phenyl]-3-methyl-2-buten-1-one (8f). A mixture of 1-(2,4-dihydroxyphenyl)-3-methyl-2-propen-1-one (**8e**)[27] (956 mg, 5.00 mmol), *p*-toluenesulfonyl chloride (1.35 g, 7.08 mmol), powdered anh K_2CO_3 (800 mg, 5.79 mmol), and absolute acetone (50 mL) was stirred at room temperature for 18 h, poured into water (500 mL), extracted with CH_2Cl_2 (3 × 150 mL), and dried. After concentration under reduced pressure the obtained residue was submitted to silica gel chromatography (eluent: hexane−acetone = 2:1, v/v) to give 391 mg (23%) of tosylate **8f** as pale yellow crystals, mp 109−111 °C (hexane−absolute EtOH). IR 3060, 3040, 2932, 1640, 1578, 1504, 1494, 1446, 1366, 1308, 1294, 1228, 1192, 1176, 1122, 1092, 976, 868, 850, 834, 812, 728 cm^{-1}. ^1H NMR (Me_2CO-d_6) δ 13.00 (s, 1H, D_2O exchangeable), 8.02 (dd, J = 9.3, 1.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 6.99 (m, 1H), 6.63 (dd, J = 9.3, 2.4 Hz, 1H), 6.61 (d, J = 1.0 Hz, 1H), 2.47 (s, 3H), 2.22 (d, J = 2.3 Hz, 3H), 2.06 (d, 3H, overlaps with the solvent signal). Anal. Calcd for $C_{18}H_{18}O_5S$ (346.41): C, 62.41; H, 5.24; S, 9.26. Found: C, 62.19; H, 5.27; S, 9.38.

General Procedure for the Oxidation of 1-(2-Hydroxyphenyl)-2-propen-1-ones 8 by Dimethyldioxirane. To a solution of enone **8** (2.00−2.50 mmol) in CH_2Cl_2 (10 mL) was added DMD (20 mL) as acetone solution (0.08−0.10 M) and allowed to stand at 0−5 °C. Addition of DMD was repeated in 12 h intervals, and the reaction was monitored by TLC (hexane−acetone = 4:1, v/v). The solvent was removed *in vacuo* (bath temperature = 25 °C), and the residue was submitted to silica gel chromatography. Further experimental details are given in Table 3.

3-Hydroxychromanone (10a) and 2-(hydroxymethyl)-3-coumaranone (11a), cf. Table 3, entry 2, were obtained from **8a** (370 mg, 2.50 mmol) according to the above general procedure with 8:1 (v/v) toluene−ethyl acetate mixture as eluent.

10a: Yield: 5.1%; mp 56−57.5 °C (lit.[24] mp 57−58 °C); R_f = 0.24. ^1H NMR δ 7.88 (dd, J = 7.8, 1.7 Hz, 1H), 7.53 (ddd, 1H), 7.07 (t, 1H), 6.91 (d, J = 8.3 Hz), 5.65 (**AB**X m, 2H), 4.15 (AB**X** dd, 1H), 3.65 (s, 1H, D_2O exchangeable).

11a: Yield: 53%; mp 95−98 °C (hexane−ethyl acetate); R_f = 0.10. IR 3424, 2922, 1712, 1616, 1478, 1326, 1310, 1196, 1146, 1092, 1022, 758 cm^{-1}. ^1H NMR δ 7.59−7.68 (m, 2H), 7.06−7.19 (m, 2H), 4.68 (AB**X** dd, 1H), 4.10 (**AB**X m, 2H), 2.24 (s, 1H, D_2O exchangeable). ^{13}C NMR δ 184.2, 173.0, 138.1, 123.9, 121.8, 121.0, 113.3, 85.9, 61.5. Anal. Calcd for $C_9H_8O_3$ (164.16): C, 65.85; H, 4.91. Found: C, 65.67; H, 4.79.

***cis,trans*-3-Hydroxy-7-methoxy-2-methylchromanone (10b) and *erythro,threo*-2-(1-hydroxyethyl)-6-methoxy-3-coumaranone (11b), cf. Table 3, entry 3**, were obtained from **8b**[26] (384 mg, 2.00 mmol) according to the above general procedure with 4:1 (v/v) hexane−acetone mixture as eluent.

***cis,trans*-10b**: Yield: 4.9%; colorless crytals; mp 126−148 °C (lit.[17a] mp 152 °C for *trans*-**10b** diastereomer, but stereochemistry based only on chemical properties); R_f = 0.24. IR 3410, 2986, 2942, 2844, 1668, 1616, 1574, 1446, 1384, 1252, 1198, 1164, 1102, 1070, 996, 980, 840 cm^{-1}. ^1H NMR: *trans*-**10b** δ 4.12 (d, J = 11.8 Hz, 1H), 3.84 (s, 3H), 1.64 (d, J = 6.1 Hz, 3H); *cis*-**10b** δ 3.91 (d, J = 3.7 Hz, 1H), 3.81 (s, 3H), 1.51 (d, J = 5.2 Hz, 3H). Unassigned signals: δ 7.81 (d, J = 8.8 Hz, 1H), 6.63 (dd, J = 8.8, 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 4.22 (m, 1H). The diastereomeric ratio *trans*-**10b**:*cis*-**10b** = 85:15 was determined by ^1H NMR analysis of the 7-MeO and 2-Me signals. Anal. Calcd for $C_{11}H_{12}O_4$ (208.22): C, 63.45; H, 5.81. Found: C, 63.27; H, 5.90.

(41) Fourie, T. G.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 125.

***erythro,threo*-11b:** Yield: 37%; yellowish oil; $R_f = 0.12$. IR (neat) 3440 br, 2976, 2936, 2844, 1710, 1694, 1614, 1504, 1454, 1446, 1340, 1258 br, 1150, 1102, 1016, 984, 946, 830 cm^{-1}. ^{13}C NMR δ 198.5, 198.0, 175.6, 168.5, 168.4, 125.3, 125.1, 114.8, 114.28, 111.9, 111.7, 96.1, 96.0, 88.6, 87.9, 67.8, 67.3, 55.8, 18.9, 18.0. ^1H NMR: *erythro*-**11b** δ 7.54 (d, $J = 8.6$ Hz, 1H), 6.64 (dd, $J = 8.6$, 1.7 Hz, 1H), 6.57 (br s, 1H), 4.48 (overlapping doublet, 1H), 4.13 (m, 1H), 3.88 (s, 3H), 3.26 (br s, 1H, D_2O exchangeable), 1.32 (d, $J = 6.3$ Hz, 3H); *threo*-**11b** δ 7.52 (d, $J = 8.5$ Hz, 1H), 6.63 (dd, $J = 8.5$, 1.7 Hz, 1H), 6.57 (br s, 1H), 4.48 (overlapping doublet, 1H), 4.30 (m, 1H), 3.87 (s, 3H), 2.60 (br s, 1H, D_2O exchangeable), 1.41 (d, $J = 6.5$ Hz, 3H). *erythro*-**11b**: *threo*-**11b** = 3:2. The diastereomeric ratio was determined by ^1H NMR analysis of the 6-MeO and 2′-H signals. Anal. Calcd for $C_{11}H_{12}O_4$ (208.22): C, 63.45; H, 5.81. Found: C, 63.49; H, 5.54.

2,2-Dimethyl-3-hydroxychromanone (10c) and 2-(1-hydroxy-1-methylethyl)-3-coumaranone (11c), cf. Table 3, entry 4, were obtained from **8c** (360 mg, 2.04 mmol) according to the above general procedure with 4:1 (v/v) hexane−acetone mixture as eluent.

10c: Yield: 47%; mp 49−51 °C (hexane); colorless crystals. IR 3484, 2974, 2934, 2834, 1702, 1606, 1474, 1460, 1320, 1290, 1252, 1232, 1144, 1120, 1100, 1012, 924, 772, 764 cm^{-1}. ^1H NMR δ 7.81 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.50 (ddd, 1H), 6.92−7.05 (m, 2H), 4.44 (s, 1H), 4.08 (br s, 1H, D_2O exchangeable), 1.65, 1.22 (2 × s, 6H). ^{13}C NMR δ 190.4, 159.7, 136.8, 126.6, 121.0, 118.7, 118.4, 83.4, 77.0, 26.8, 17.2. Anal. Calcd for $C_{11}H_{12}O_3$ (192.22): C, 68.73; H, 6.34. Found: C, 68.55; H, 6.39.

11c: Yield: 31%; yellowish oil. IR (neat) 3478, 2976, 2934, 1712, 1692, 1620, 1614, 1474, 1462, 1378, 1324, 1310, 1212, 1194, 1176, 1144, 1020, 984, 856, 756. ^1H NMR δ 7.65 (d, $J = 7.0$ Hz, 1H), 7.63 (ddd, 1H), 7.05−7.17 (m, 2H), 4.37 (s, 1H), 2.88 (br s, 1H, D_2O exchangeable), 1.35, 1.23 (2 × s, 6H). ^{13}C NMR δ 210.2, 172.8, 138.3, 124.2, 122.1, 121.7, 113.3, 89.1, 72.4, 25.6, 24.2. Anal. Calcd for $C_{11}H_{12}O_3$ (192.22): C, 68.73; H, 6.34. Found: C, 68.53; H, 6.21.

2,2-Dimethyl-3-hydroxy-7-methoxychromanone (10d) and 1-(2,5-dihydroxy-4-methoxyphenyl)-3-methyl-2-buten-1-one (12d), cf. Table 3, entry 5, were obtained from **8d**[28] (465 mg, 2.25 mmol) according to the above general procedure with 4:1 (v/v) hexane−acetone mixture as eluent.

10d: Yield: 26%; mp 112−113.5 °C (hexane) (lit.[17a] mp 110 °C); colorless crystals. IR 3472, 1672, 1614, 1576, 1444, 1268, 1246, 1204, 1098, 1028, 1010, 820, 798 cm^{-1}. ^1H NMR δ 7.74 (d, $J = 8.8$ Hz, 1H), 6.57 (dd, $J = 8.8$, 2.2 Hz, 1H), 6.38 (d, $J = 2.2$ Hz, 1H), 4.36 (s, 1H), 3.84 (s, 4H), 1.63, 1.22 (2 × s, 6H). ^{13}C NMR δ 192.5, 166.9, 161.9, 128.35, 112.4, 109.8, 101.4, 83.6, 76.6, 55.6, 26.9, 17.4.

12d: Yield: 7.3%; mp 116−120 °C (hexane−ethyl acetate); orange leaflets. IR 3364, 1632, 1576, 1512, 1498, 1450, 1398, 1254, 1208, 1180, 1156, 992, 878, 798 cm^{-1}. ^1H NMR δ 13.09 (s, 1H, D_2O exchangeable), 7.26 (s, 1H), 6.63 (t, $J = 1.3$ Hz, 1H), 6.45 (s, 1H), 5.23 (s, 1H, D_2O exchangeable), 3.92 (s, 3H), 2.18 (d, $J = 1.3$ Hz, 3H), 2.01 (d, $J = 1.3$ Hz, 3H). ^{13}C NMR δ 189.9, 159.7, 156.2, 153.2, 137.7, 120.3, 113.5, 113.4, 99.9, 56.1, 28.0, 21.1. Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 65.08; H, 6.29.

2,2-Dimethyl-3-hydroxy-7-(tosyloxy)chromanone (10e) and 2-(1-hydroxy-1-methylethyl)-6-(tosyloxy)-3-coumaranone (11e), cf. Table 3, entry 8, were obtained from **8e** (270 mg, 0.78 mmol) according to the above general procedure with 3:1 (v/v) hexane−acetone mixture as eluent.

10e: Yield: 68%; mp 122−124.5 (hexane−ethyl acetate), colorless crystals; $R_f = 0.18$. IR 3356, 2972, 1692, 1610, 1440, 1378, 1254, 1442, 1192, 1172, 1088, 984, 866, 818, 810, 794, 728, 714 cm^{-1}. ^1H NMR δ 7.75 (overlapping doublets, 3H), 7.34 (d, $J = 7.8$ Hz, 2H), 6.70 (d, $J = 1.9$ Hz, 1H), 6.62 (dd, $J = 7.5$, 1.9 Hz, 1H), 4.39 (s, 1H), 3.72 (s, 1H, D_2O exchangeable), 2.46 (s, 3H), 1.63, 1.19 (2 × s, 6H). ^{13}C NMR δ 193.4, 160.9, 155.9, 146.1, 132.4, 130.2, 128.6, 128.4, 117.5, 115.5, 112.4, 84.5, 77.0, 26.9, 21.9, 17.5. Anal. Calcd for $C_{18}H_{18}O_6S$ (362.40): C, 59.66; H, 5.01; S, 8.85. Found: C, 59.81; H, 4.83; S, 8.80.

11e: Yield: 17%; yellowish oil; $R_f = 0.13$. IR 3430, 2971, 2927, 1709, 1603, 1449, 1371, 1233, 1210, 1188, 1150, 990, 795 cm^{-1}. ^1H NMR δ 7.76 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 9.4$ Hz, 1H), 7.36 (d, $J = 8.4$ Hz, 2H), 6.91 (d, $J = 2.0$ Hz, 1H), 6.70 (dd, $J = 9.4$, 2.0 Hz, 1H), 4.41 (s, 1H), 3.60 (br s, 1H, D_2O exchangeable), 2.47 (s, 3H), 1.34, 1.25 (2 × s, 6H). Anal. Calcd for $C_{18}H_{18}O_6S$ (362.40): C, 59.66; H, 5.01; S, 8.85. Found: C, 59.55; H, 5.19; S, 8.73.

Oxidation of 1-(2-Hydroxy-4-methoxyphenyl)-3-methyl-2-propen-1-one (8d) by Alkaline Hydrogen Peroxide, cf. Table 3, Entry 6. A solution of enone **8d** (465 mg, 2.25 mmol), 21% H_2O_2 (1.0 mL, ca. 6.18 mmol), and 2 N NaOH (1.0 mL, 4.0 mmol) in methanol (20 mL) was stirred at rt (ca. 20 °C) for 8 h. The reaction mixture was neutralized with acetic acid, diluted with water (300 mL), extracted with CH_2Cl_2 (3 × 50 mL), dried and concentrated. Silica gel chromatography (eluent: hexane−acetone = 4:1, v/v) of the residue afforded 238 mg (48%) of 2,2-dimethyl-3-hydroxy-7-methoxychromanone (**10d**) and 36.0 mg (7.2%) of 2-(1-hydroxy-1-methylethyl)-6-methoxy-3-coumaranone (**11d**), mp 71−75 °C (hexane), colorless crystals.

11d: IR 3462, 2980, 1692, 1614, 1500, 1446, 1370, 1272, 1246, 1188, 1150, 1108, 1016, 932, 828 cm^{-1}. ^1H NMR δ 7.56 (d, $J = 8.6$ Hz, 1H), 6.66 (dd, $J = 8.6$, 2.0 Hz, 1H), 6.58 (d, $J = 2.0$ Hz, 1H), 4.39 (s, 1H), 3.89 (s, 3H), 3.34 (s, 1H, D_2O exchangeable), 1.37, 1.25 (2 × s, 6H). Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.63; H, 6.41.

Oxidation of 1-(2-Hydroxy-4-methoxyphenyl)-3-methyl-2-propen-1-one (8d) by *m*-Chloroperbenzoic Acid (*m*CPBA) cf. Table 3, Entry 7. A solution of enone **8d** (465 mg, 2.25 mmol) and mCPBA (432 mg, 2.50 mmol) in CH_2Cl_2 (20 mL) was allowed to stand at 0 °C for 6 d, and a new portion of *m*CPBA (432 mg, 2.50 mmol) was added, which was repeated after 2 d. After 19 d, the precipitate was removed by filtration and washed with CH_2Cl_2 (2 × 10 mL) and the solvent evaporated under reduced pressure. The residue was submitted to silica gel chromatography (eluent: toluene−ethyl acetate = 8:1, v/v) to give 55.0 mg of unreacted **8d**, 146 mg (33%) of 2,2-dimethyl-3-hydroxy-7-methoxychromanone (**10d**), 43.0 mg (9.8%) of 1-(2,5-dihydroxy-4-methoxyphenyl)-3-methyl-2-buten-1-one (**12d**), and 120 mg (27%) of 2-(1-hydroxy-1-methylethyl)-6-methoxy-3-coumaranone (**11d**).

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Supporting Information Available: Table with characteristic coupling constants of *erythro*- and *threo*-**4a** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any masthead page for ordering information.

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