Full Paper

CSIRO PUBLISHING

Aust. J. Chem. **2008**, *61*, 122–130

www.publish.csiro.au/journals/ajc

Studies Towards the Stereoselective α-Hydroxylation of Flavanones. Biosynthetic Significance

Zola-Michéle Border,[A,B] *Charlene Marais,*[A] *Barend C. B. Bezuidenhoudt,*[A,C] *and Jacobus A. Steenkamp*[A]

[A]Department of Chemistry, University of the Free State, PO Box 339, Bloemfontein 9300, South Africa.

[B]Dedicated to the husband and close family of Z.-M. Border who passed away tragically at the age of 31 before she could fully complete this project and her PhD.

[C]Corresponding author. Email: bezuidbc.sci@ufs.ac.za

The enolates of various propiophenones, chromanones, and also analogues of naturally occurring flavanones were stereoselectively hydroxylated at the α-position, by employing commercially available enantiopure oxaziridines, to afford the desired α-hydroxylated target molecules in good to exceptional stereoselectivities and in moderate to good chemical yields. A mechanistic rationale is presented to account for the stereoselectivities achieved. These in vitro results were tentatively related to the stereoselective biosynthesis of enantio-enriched dihydroflavonols while questions were raised about the authenticity of certain natural compounds.

Manuscript received: 12 September 2007.
Final version: 11 January 2008.

Introduction

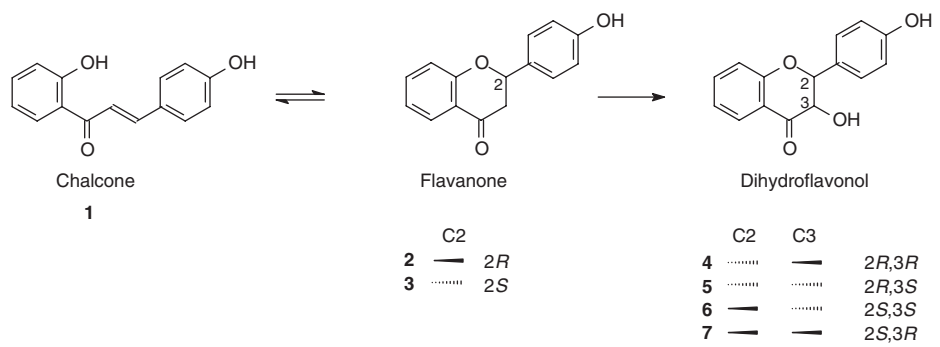
The synthesis of α-hydroxy carbonyl compounds of preselected stereochemistry is of considerable interest, as this structural array is featured in many bioactive molecules, such as vast numbers of flavonoids. Noteworthy in the structural assembly of these flavonoids is that the stereochemistry of the majority of flavonoids resides mainly in C2, C3, and C4 of the heterocyclic C_3-moiety (pyran ring). Emphasis in the present article is, however, placed on the stereochemistry of the C3 carbon bearing the hydroxyl functionality, because the absolute configuration of only this carbon atom is likely to be preserved under mild reaction conditions.

Although the source of the C_{15}-skeleton of flavonoids has been beyond dispute for decades,[1–3] the sequence of changes that result in the formation of a relatively diverse group of compounds based on variation in the oxidation level of the C_3-moiety of the molecule remains a source of uncertainty despite impressive progress in the understanding of flavonoid biosynthesis.[4]

Although the central role of the chalcone–flavanone pair has gained general acceptance, the biogenetic origin of the 3-hydroxyflavonoids (Scheme 1) may conceivably be attributed to more than one route, the possibilities considered being via chalcone epoxides, α-hydroxychalcones, or 3-hydroxylation of flavanones.

It was suggested decades ago that chalcone epoxides may play an important role in the stereoselective biosynthesis of dihydroflavonols[5] and the success that has been achieved by the in vitro mimicking of the chalcone epoxide route[6–10] has understandably and justifiably created expectations that this is indeed the reactive and biosynthetic intermediate towards the synthesis of the abundant natural dihydroflavonols.

Although evidence to unequivocally corroborate the existence of the elusive natural chalcone epoxides remains outstanding, it is likely that revealing and irrefutable evidence is lacking because of the high reactivity and hence short-lived existence of such a proposed and unprotected epoxide.



Scheme 1.

10.1071/CH07325 0004-9425/08/020122

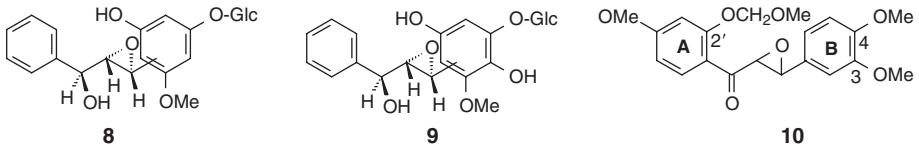


Fig. 1. Isolated chalconol glucosides and a typical chalcone epoxide.

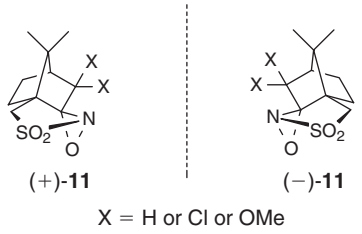


Fig. 2. Available chiral *N*-sulfonyloxazindines.

Notable, however, is the recent isolation from *Trifolium alexandrinum* by Mohamed et al.[11] of the analogous chalcanol glucosides, 2-methoxy-4,6-dihydroxy-α′-chalcanol-α,β-epoxide-4-*O*-β-D-glucopyranoside **8** and 2-methoxy-3,4,6-trihydroxy-α′-chalcanol-α,β-epoxide-4-*O*-β-D-glucopyranoside **9**, which is plausibly formed via the enzymatic reduction of the corresponding chalcone epoxides (e.g. **10**) (Fig. 1).[12]

Roux and Ferreira[13] suggested that α-hydroxychalcones, of which only three have been isolated to date,[14–17] offer a viable alternative route to 2,3-*trans*- as well as 2,3-*cis*-dihydroflavonols. More recent evidence, however, indicates that these are presumably not intermediates representing a first step in the biological oxygenation of either a flavanone or chalcone, but rather compounds resulting from the isomerisation and/or ring contraction of already formed dihydroflavonols.[18]

The stereoselective biosynthetic C3 hydroxylation of flavanones by 2-oxoglutarate-dependent dioxygenases (2-ODDs) has been conclusively evaluated and reported on.[4,19–23] This preferred enzymatic conversion of the abundant 2*S*-flavanones **3** into the 2*R*,3*R*-*trans* isomers **4**,[24] and to a lesser extent the 2*R*,3*S*-*cis* isomers **5**,[22] is reflected by the preference for these configurations in nature and is also corroborated by the exclusive isolation of the 2*R*,3*S*-*cis* isomers **5** of certain dihydroflavonols.[25–30]

Although we, like the majority of chemists, take cognisance of the complexity of biochemical transformations, an investigation into the chemical 3-hydroxylation of flavanones, utilizing modern synthetic methodologies such as powerful chiral reagents or catalysts seems desirable. The general applicability of *N*-sulfonyloxaziridines in the hydroxylation of enolates to afford α-hydroxy compounds[31] offered a promising opportunity to shed more light on this intriguing biosynthetic question. Moreover, with non-racemic oxaziridines **11** (Fig. 2), these hydroxylations can be carried out with high asymmetric induction and predictable stereochemistry.[31]

In the present paper, we describe details of a comprehensive study of the asymmetric hydroxylation of propiophenone analogues, 4-chromanones, and also of flavanones using non-racemic (camphorylsulfonyl)oxaziridines. In addition, these results will be related to an outstanding issue concerning the biosynthetic route to C3-hydroxylated flavonoids.

Results and Discussion

Various oxidative methods have been developed for the synthesis of α-hydroxy carbonyl compounds from ketones.[31–35] The versatility of metal enolates, the aprotic nature of *N*-sulfonyloxaziridines, and their availability in enantiopure form (e.g. **11**) made this protocol ideally suited to the stereoselective hydroxylation of flavanone analogues (Scheme 2).

Hence, the propiophenone analogues (Scheme 3, **12**–**19**), reminiscent of the flavanone structural array, were exposed to an appropriate base (lithium diisopropyl amide (LDA)), the kinetic enolates oxidized by an oxaziridine **11** (X = Cl), and the products separated and identified. The absolute configuration and % enantiomeric excesses (% ees) were determined by derivatization of the non-racemic α-hydroxy carbonyl compounds with the (*R*)-(+)-Mosher acid chloride, utilizing a modified Mosher's method.* These results are summarized in Tables 1 and 2.

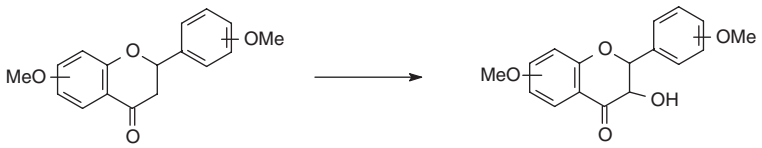
It is clear from the results that utilization of the dichloro(camphorylsulfonyl)oxaziridine, (+)-**11** (X = Cl), led to a good stereochemical outcome, while the chemical yields of the desired products were satisfactory.

Notable, however, is the erosion of the stereogenic integrity as the hydroxylation of the aromatic ring is increased. Although the yields (chemical and ees) of compounds **12** and **13** (Table 1, entries 1 and 2) were good, a decline in % ee for compounds **14** and **15** (Table 1, entries 3 and 4) was evident. Not only were the yield and % ee disappointingly low for compound **15**, but the absolute configuration was *R* compared with the *S* absolute configuration of the other oxidation products. The most obvious argument to account for this inversion of configuration is to embrace the notion that the opposite geometry (*E*-isomer) of the enolate is operational under the prevailing conditions (Scheme 4). It is, however, clear from an investigation by Davis et al.[36] on the geometry of various enolates that it is highly likely that the enolate of **15** is in the *Z*-configuration. In the absence of evidence to the contrary, it is conceivable that the *Z*-isomer is the kinetically favoured product at the prevailing low temperature, whereas the *E*-isomer predominates at higher temperatures.

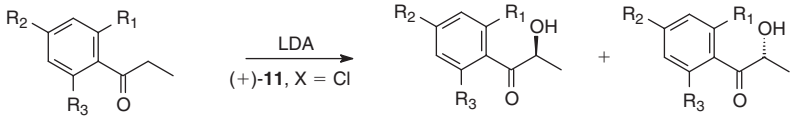
Davis et al.[36] proposed both planar (A_S and C_R) and spiro (B_S and D_R) transition states for the attack of (+)-**11** (X = Cl) on either the *Si*- or *Re*-faces of *Z*-enolates with the transition state that is more favourable under each unique circumstance resulting in the major product.

The prevailing protocol was extended to include the 4-chromanones (Scheme 5, **20**–**24**, Table 3). Although no obvious discernible pattern emerged, it is worthwhile to note that substitution at the α-carbon (cf. **24**) had a positive influence on the

* As both alcohol isomers are present in the reaction mixture, both of them are esterified with the (*R*)-(+)-Mosher acid chloride, which enables comparison of the chemical shifts of corresponding protons of these isomers and thus allocation of the absolute configuration according to the established model. By the same token, the % ee is conveniently calculated by the comparison of the integration values of the relevant protons (A. F. Hundt, J. F. W. Burger, J. P. Steynberg, J. A. Steenkamp, D. Ferreira, *Tetrahedron Lett.* **1990**, *31*, 5073).



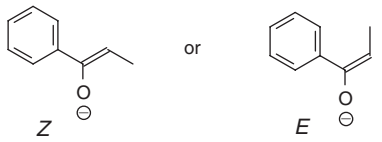
Scheme 2.



S *R*

12	$R_1 = R_2 = R_3 = H$	**16**
13	$R_1 = R_3 = H$, $R_2 = OMe$	**17**
14	$R_1 = H$, $R_2 = R_3 = OMe$	**18**
15	$R_1 = R_2 = R_3 = OMe$	**19**

Scheme 3.



Scheme 4.

enantioselectivity of the reaction (ee > 95%). Further, little or no substitution on the aromatic ring seemed to negatively impact on the enantioselectivity as well as the yield of the reaction (cf. **20** and **21**). In contrast to the propiophenones (see above), chromanones can only form the enolates with the *E*-geometry. The stereochemistry of the stereogenic centres was confirmed by the Mosher protocol (Table 4) and that, together with the various yields, can be rationalized in terms of the transition states proposed by Davis et al.[36] and Davis and Chen.[31]

Noteworthy is the very satisfactory outcome of the hydroxylation of chromanone **24**, which may conceivably be attributed to, among others, the greater stability of the more substituted enolate compared with the enolate of chromanone **20**.

Flavanones (e.g. **2** and **3**) represent a small but salient group of compounds in the flavonoid family. They are considered to be the biogenetic precursors of the C3 hydroxylated analogues (dihydroflavonols, e.g. **4**–**7**). Hence, stereoselective hydroxylation of those flavanones via their respective enolates and the utilization of a chiral oxidant could possibly shed some light on this biosynthetic pathway.

Indeed, oxidation of the enolate of racemic **30** (Scheme 6) with chiral oxaziridine (+)-**11** (X = Cl), afforded the expected dihydroflavonol **32**, in 26% yield, with the 2,3-*trans*-2*R*,3*R* configuration dominating (57% ee) as established by the Mosher protocol (Table 5). Extension of the established protocol to the racemic substituted flavanone **31** led to the expected dihydroflavonol **33** in 13% yield, with the 2,3-*trans*-2*R*,3*R* isomer in excess (63% ee). Conspicuous is the absence of the diastereomeric 2,3-*cis* isomers, reflecting a truly amazing 100% diastereoselectivity in favour of the 2,3-*trans* isomers. The absence of the thermodynamically less stable 2,3-*cis* isomers is likely explicable in terms of a strong and supporting synergism between a preferred fit of the oxaziridine and the formed enolate and a dynamic stereo-directing effect of the C2 phenyl ring. Such a transitional spatial arrangement would govern a biased electrophilic attack of the oxaziridine such that the 'oxygen' is delivered to the opposite side of the bulky phenyl ring, hence the exclusive formation of the 2,3-*trans* products. This notable ability of the C2 phenyl group to direct selected reagents to the 'opposite' side of itself (2,3-*trans*-type intermediate) is a structural feature in certain flavonoids that plays a pivotal role in many of their reactions, details of which will be discussed elsewhere.

Table 1. Oxidation of propiophenones
ee, enantiomeric excess

Entry	Substrate	Product	Yield [%]	ee [%]	Absolute configuration
1	**12**	**16**	89	88	*S*
2	**13**	**17**	95	91	*S*
3	**14**	**18**	91	70	*S*
4	**15**	**19**	45	28	*R*

A disappointing feature of these reactions was the low yields. This is, however, explicable in terms of a competitive base-catalyzed opening of the heterocyclic ring to afford the corresponding chalcones, the intermediate shifting progressively from an enolate (**34**) to a carbanion (**35**) (Scheme 7) with increasing base concentration.[37]

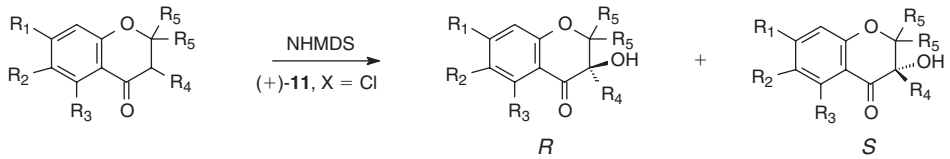
Based on these observations, it was envisaged that the selection of a suitable substrate could lead to an outstanding degree of stereoselection. Indeed, oxidation of enantiopure flavanone **37** afforded the expected dihydroflavonol **32** (Scheme 8) in 56% yield, and only the *trans*-2*R*,3*R* stereoisomer in 100% diastereomeric excess (de), but also in 100% ee. Although the likelihood of scrambling of the established chirality of the enantiopure products via ring-opening or enolization is possible under the prevailing conditions, the high % ee attained is an unmistakable indication of a highly successful stereoselective α-hydroxylation.

Conclusion

In conclusion, it was established (see above) that the enolate of flavanones are stable under mild conditions and that the stereochemistry of the formed enantioenriched dihydroflavonol remained intact under mild workup and separation conditions.

Table 2. ^{1}H NMR data for the (*S*)-(−)-MTPA esters of 16–19 in $CDCl_3$ (*J* values in Hz)
(*R*) and (*S*) notation refers to the configuration of the newly formed chiral centre. MTPA, α-methoxy-α-(trifluoromethyl)phenyl acetic

Proton	**16**	**17**	**18**	**19**
ArH	7.96–7.36 (10H, m)			
H2′, H6′ (*R*)		7.93 (2H, d, *J* 9.0)		
H2′, H6′ (*S*)		7.89 (2H, d, *J* 9.0)		
H3′, H5′ (*R*)		6.95 (2H, d, *J* 9.0)		6.07 (2H, s)
H3′, H5′ (*S*)		6.95 (2H, d, *J* 9.0)		6.01 (2H, s)
H6′ (*R*)			7.90 (1H, d, *J* 8.8)	
H6′ (*S*)			7.87 (1H, d, *J* 8.8)	
H5′ (*R*)			6.56 (1H, dd, *J* 2.5, 8.8)	
H5′ (*S*)			6.54 (1H, dd, *J* 2.5, 8.8)	
H3′ (*R*)			6.44 (1H, d, *J* 2.5)	
H3′ (*S*)			6.43 (1H, d, *J* 2.5)	
MTPA ArH		7.68–7.56 (2H, m)	7.71–7.59 (2H, m)	7.59–7.48 (2H, m)
		7.42–7.38 (3H, m)	7.42–7.37 (3H, m)	7.54–7.30 (3H, m)
H2		6.09 (1H, q, *J* 7.0)		5.96 (1H, q, *J* 7.0)
H2 (*R*)	6.13 (1H, q, *J* 7.0)		6.17 (1H, q, *J* 7.0)	
H2 (*S*)	6.13 (1H, q, *J* 7.0)		6.19 (1H, q, *J* 7.0)	
H3 (*S*)	1.62 (3H, d, *J* 7.0)	1.61 (3H, d, *J* 7.0)	1.53 (3H, d, *J* 6.8)	1.52 (3H, d, *J* 7.5)
H3 (*R*)	1.55 (3H, d, *J* 7.0)	1.53 (3H, d, *J* 7.0)	1.45 (3H, d, *J* 6.8)	1.42 (3H, d, *J* 7.5)
MTPAOMe (*R*)	3.64 (3H, m)	3.66 (3H, m)	3.65 (3H, m)	3.53 (3H, m)
MTPAOMe (*S*)	3.57 (3H, m)	3.58 (3H, m)	3.58 (3H, m)	3.48 (3H, m)
OMe (*S*)		3.85 (3H, s)	3.89 (3H, s), 3.84 (3H, s)	3.81 and 3.80 (9H, 2 × s)
OMe (*R*)		3.86 (3H, s)	3.89 (3H, s), 3.85 (3H, s)	3.74 and 3.73 (9H, 2 × s)



20	$R_1 = R_2 = R_3 = R_4 = R_5 = H$	**25**
21	$R_1 = OMe, R_2 = R_3 = R_4 = R_5 = H$	**26**
22	$R_1 = R_3 = OMe, R_2 = R_4 = R_5 = H$	**27**
23	$R_1 = OEt, R_2 = OMe, R_3 = R_4 = H, R_5 = Me$	**28**
24	$R_1 = R_2 = R_3 = R_5 = H, R_4 = Me$	**29**

Scheme 5.

Table 3. Oxidation of chromanones

Entry	Substrate	Product	Yield [%]	ee [%]	Absolute configuration
1	**20**	**25**	61	20	*S*
2	**21**	**26**	74	3.4	*R*
3	**22**	**27**	82	69	*R*
4	**23**	**28**	23	62	*R*
5	**24**	**29**	74	>95	*R*

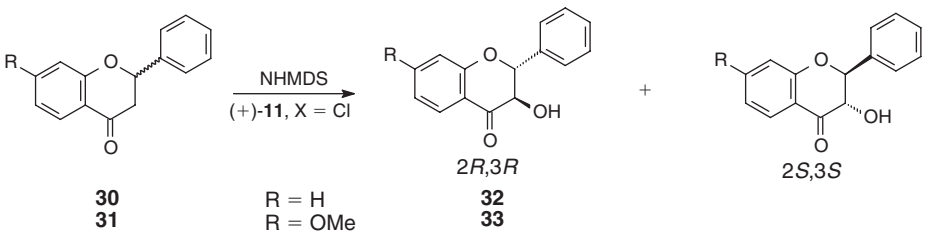
Furthermore, it was confirmed that there exists a preferential facial attack on the enolate by the enantiopure oxazaridine (+)-**11** and that if such a propensity is synergistically supported by the crucial and dominating directing effect of the bulky B-ring towards a hydroxylation step to the 'opposite' side, the stereochemical induction is amplified to an exceptionally high level with the overwhelming dominance of the *trans* isomers. Moreover, this investigation culminated in the successful C3 hydroxylation of an enantiopure flavanone to yield the enantiopure dihydroflavonol in acceptable yield.

The influence of the 'fit' of the substrate and oxidizing agent, as well as the influence of the stereochemistry of the B-ring and the proximity of the oxidizing agent, find a precedent in the stereoselective C3 hydroxylation of flavanones by biosynthetic enzymes. Different mechanisms of oxidation are applicable although, as an S_N2 mechanism is presumably applicable in the case of the *N*-sulfonyloxaziridines,[31] whereas a radical mechanism prevails in the case of the Fe^{II} 2-ODDs[20] (which utilize 2-oxoglutarate as co-substrate to achieve the two-electron oxidation of the substrate).

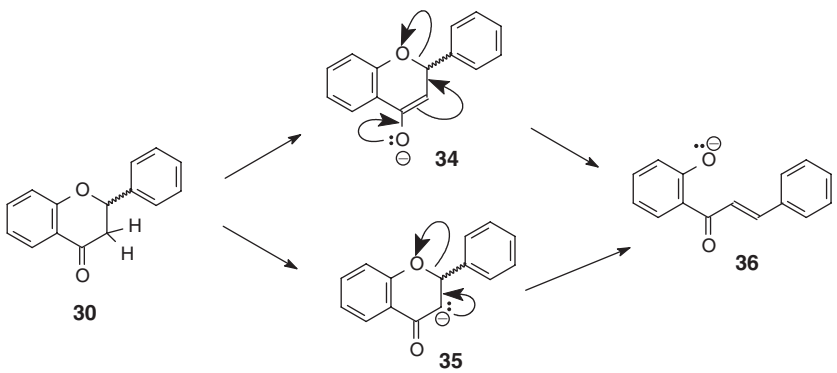
Scrutiny of a dihydroflavonol (DHF) structure (e.g. **38** in Scheme 9) reveals the presence of labile bonds, the cleavage of which can have a significant effect on the stereochemistry of a particular compound. It is conceivable that the cleavage of the O1–C2 bond, ably assisted by the inductive effect of the 4′-OH group (as the phenoxide), is more likely than the competing removal of H3 (C), which, in turn, is synchronized with the departure of the relatively good leaving A-ring (benzoyl moiety) to afford the conjugated C2–C3 double bond. For the H3 (C) to act as the counterpart for the A-ring for elimination of these two groups with the formation of the α-hydroxychalcone (e.g. **42**), they must be able to form an antiperiplanar-type transition state to accomplish the favourable orbital alignment – a prerequisite that will not be satisfied in all the cases under discussion. In contrast, it is clear that the formation of the quinone methide (e.g. **39**)

Table 4. ^{1}**H NMR data of the (*S*)-(−)-MTPA esters of 25–29 in $CDCl_3$ (*J* values in Hz)**
(*R*) and (*S*) notation refers to the configuration of the newly formed chiral centre. MTPA, α-methoxy-α-(trifluoromethyl)phenyl acetic

Proton	**25**	**26**	**27**	**28**	**29**
ArH	7.90–6.98 (9H, m)	7.83–6.40 (8H, m)	7.68–7.64 (2H, m) 7.45–7.37 (3H, m) 6.08–6.04 (2H, m)	7.80–7.73 (2H, m; 3*S*-isomer) 7.69–7.62 (2H, m, 3*R*-isomer) 7.47–7.39 (3H, m) 7.18 (1H, s) 6.39 (1H, s)	7.97–6.96 (9H, m)
H3				5.73 (1H, s)	
H3 (3*S*)	5.92 (1H, dd, *J* 6.0, 12.5)	5.86 (1H, dd, *J* 6.0, 11.5)	5.74 (1H, dd, *J* 6.0, 10.5)		
H3 (3*R*)	5.84 (1H, dd, *J* 6.0, 12.5)	5.78 (1H, dd, *J* 6.0, 11.5)	5.68 (1H, dd, *J* 6.0, 11.0)		
H2					5.04 (1H, d, *J* 10.5) 4.10 (1H, d, *J* 10.5)
$H2_{eq}$ (3*R*)	4.62 (1H, dd, *J* 6.0, 11.0)	4.59 (1H, dd, *J* 6.0, 11.0)	4.54 (1H, dd, *J* 6.0, 11.0)		
$H2_{ax}$ (3*R*)	4.53 (1H, dd, *J* 11.0, 12.5)	4.51 (1H, dd, *J* 11.0, 11.5)	4.47 (1H, t, *J* 11.0)		
$H2_{eq}$ (3*S*)	4.49 (1H, dd, *J* 6.0, 11.0)	4.47 (1H, dd, *J* 6.0, 11.0)	4.40 (1H, dd, *J* 6.0, 11.0)		
$H2_{ax}$ (3*S*)	4.36 (1H, dd, *J* 11.0, 12.5)	4.34 (1H, dd, *J* 11.0, 11.5)	4.39 (1H, dd, *J* 10.5, 11.0)		
MTPAOMe (3*S*)	3.69 (3H, m)	3.68 (3H, m)	3.70 (3H, m)	3.66 (3H, m)	3.67 (3H, m)
MTPAOMe (3*R*)	3.58 (3H, m)	3.60 (3H, m)	3.55 (3H, m)	3.59 (3H, m)	3.59 (3H, m)
OMe		3.83 (3H, s)	3.86 (3H, s) 3.82 (3H, s)	3.83 (3H, s)	
CH_2CH_3				4.11 (2H, q, *J* 7.0)	
CH_2CH_3				1.48 (3H, t, *J* 7.0)	
2-CH_3				1.56 (3H, s) 1.35 (3H, s)	
3-CH_3					2.15 (3H, s)



Scheme 6.



Scheme 7.

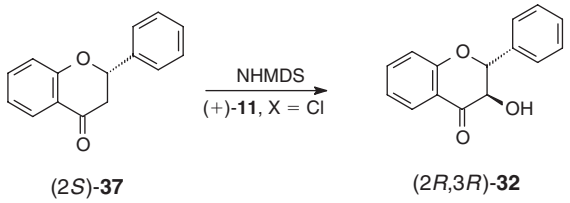
is accomplished in a relatively facile mode as the free rotation of the B-ring assists the formation of a transition state in which the obligatory orbital arrangement is possible. It is also worth mentioning the presence of the relatively strong intramolecular H-bond between the carbonyl functionality and the α-hydroxyl group. The planar character of this formed five-membered ring must have an influence on the preferred conformation of the C-ring, hence exerting an influence on the necessary orbital overlap to influence significantly the formation of the enol tautomer (cf. the H3 (C) of *trans*- and *cis*-DHF). The structural features mentioned (see above) act to abate the probable scrambling of the formed stereogenic centres of those natural DHFs. On the contrary, when the C-ring has opened to form the open-chain analogue, most of the conformational restrictions mentioned lapse, hence enabling the optimal orbital overlap to afford in thermodynamic ratios *E*- and *Z*-α-hydroxychalcones and hence

all the possible stereoisomers of the DHF, whereas the same α-hydroxychalcones may lead to the diketone **43** and hence the coumaranone **44** (Scheme 9).

These arguments are corroborated by in vitro retention of configuration at C3[18] and the absence of deuterium incorporation at C3[38] under mild conditions, as well as the co-occurrence of non-racemic *cis*- and *trans*-dihydroflavonol isomer pairs with similar C3 absolute configurations in nature,[18,39] which suggests the formation of a quinone methide intermediate **39** for *cis–trans* isomerization[40] of 3-hydroxyflavanols under mild conditions. 2-Benzyl-2-hydroxy-3-coumaranone **44**, however, forms only on harsh treatment,[18] which suggests the formation of an α-hydroxychalcone **42** as intermediate under those circumstances.

A few α-hydroxychalcones[13–17] and 2-benzyl-2-hydroxy-3-coumaranones[14,16,41–43] have been reported to be isolated from plants, but as the conditions under which flavonoids are isolated (Soxhlet extraction, high temperature, acid content of EtOAc, evaporation under reduced pressure at ∼50°C, etc.) are comparable with the harsh conditions considered above, the authors feel modestly confident to suggest that a distinct probability exists that compounds such as α-hydroxychalcones and 2-benzyl-2-hydroxy-3-coumaranones are artefacts rather than natural products.

The authors thus feel confident to suggest that the most probable biosynthetic route towards *trans*- and *cis*-dihydroflavonols entails the 2-ODD-catalyzed hydroxylation of flavanones, whereas in vivo isomerization of dihydroflavonols via the quinone methide and especially via the α-hydroxychalcone still need to be confirmed.

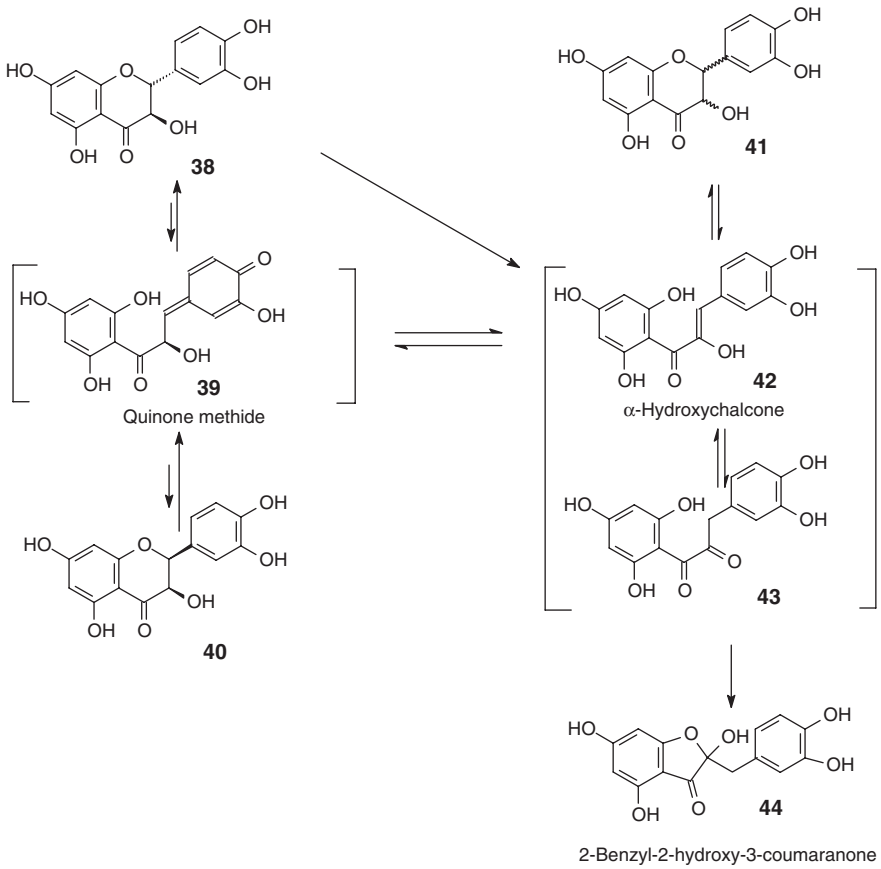


Scheme 8.

Table 5. ^{1}H NMR data of the (*S*)-(−)-MTPA esters of 32 and 33 in $CDCl_3$ (*J* values in Hz)

(*R*) and (*S*) notation refers to the configurations of the chiral centres at C2 and C3. MTPA, α-methoxy-α-(trifluoromethyl)phenyl acetic

Proton	**32**	**33**
ArH	7.94–7.04 (14H, m)	7.63–7.20 (10H, m)
H-8 (2*R*,3*R*)		6.53 (1H, d, *J* 2.5)
H-8 (2*R*,3*S*)		6.50 (1H, d, *J* 2.5)
H-6 (2*R*,3*R*)		6.71 (1H, dd, *J* 2.5, 9.0)
H-6 (2*R*,3*S*)		6.713 (1H, dd, *J* 2.5, 9.0)
H-5 (2*R*,3*R*)		7.89 (1H, d, *J* 9.0)
H-5 (2*R*,3*S*)		7.90 (1H, d, *J* 9.0)
H-3 (2*R*,3*R*)	6.04 (1H, d, *J* 12.5)	6.04 (1H, d, *J* 12.5)
H-3 (2*R*,3*S*)	6.15 (1H, d, *J* 12.5)	6.13 (1H, d, *J* 12.5)
H-2 (2*R*,3*R*)	5.50 (1H, d, *J* 12.5)	5.51 (1H, d, *J* 12.5)
H-2 (2*R*,3*S*)	5.42 (1H, d, *J* 12.5)	5.40 (1H, d, *J* 12.5)
7-OMe		3.87 (3H, s)
MTPAOMe (2*R*,3*R*)	3.33 (3H, m)	3.38 (3H, m)
MTPAOMe (2*R*,3*S*)	3.55 (3H, m)	3.57 (3H, m)



Scheme 9.

Experimental

General

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions as indicated with Me_4Si as internal standard. *J* values are given in Hz. Mass spectra were obtained with a VG 70-70 instrument. TLC was performed on precoated Merck plastic sheets (silica gel 60 PF_{254}, 0.25 mm) and the plates were sprayed with H_2SO_4–HCHO (40:1 v/v) after development. Preparative plates (PLC), 20 × 20 cm, Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Column chromatography was on silica (Merck Kieselgel 60, 230–400 mesh) in various columns, solvent systems, and flow rates (to be specified in each instance) under the influence of gravity or pressure from a nitrogen cylinder in the case of flash column chromatography. Diazomethane methylations were performed with an excess of diazomethane in MeOH/diethyl ether over 48 h at −15°C. Evaporations were done under reduced pressure at ambient temperatures in a rotary evaporator. 3-Methoxyphenol, 2,5-dimethoxyphenol, 2′,4′,6′-trihydroxyacetophenone, 2′,4′-dimethoxyacetophenone, propiophenone **12**, 4′-methoxypropiophenone **13**, 4-chromanone **20**, 7-ethoxy-6-methoxy-2,2-dimethyl-4-chromanone **23**, 7-methoxyflavanone **31**, and flavanone **30** were obtained from Aldrich, whereas (+)-(8,8-dichlorocamphorylsulfonyl) oxaziridine (+)-**11** was obtained from Merck. 2′,4′,6′-Trimethoxyacetophenone[36] was prepared by the methylation of 2′,4′,6′-trihydroxyacetophenone with dimethylsulfate in dry acetone. 2′-Hydroxy-4′-methoxyacetophenone was prepared by the regioselective diazomethane methylation of 2′,4′-dihydroxyacetophenone.

Preparation of Propiophenones *14* and *15*

LDA was prepared by standard procedure from equivalent amounts of dry diisopropylamine and butyllithium (BuLi) in freshly distilled anhydrous tetrahydrofuran (THF) at 0°C over ∼10 min under argon and subsequently cooled to −78°C, whereafter a solution of the appropriate acetophenone, in dry THF, was slowly transferred to the base and stirred for ∼30 min in an argon atmosphere to form an enolate. MeI was added and the temperature kept at −78°C for 0.5 h, then at −40°C for 1 h and finally at 0°C for 2–6 h. Following completion of the reaction according to TLC, NH_4Cl was added and the reaction mixture extracted with diethyl ether (×3). The organic layer was concentrated under vacuum and the products purified to afford 2′,4′-dimethoxypropiophenone **14** with NMR data entirely consistent with those published[44] and 2′,4′,6′-trimethoxypropiophenone **15**. δ_H ($CDCl_3$) 6.08 (2H, s, H3′ and H5′), 3.80 (3H, s, 1 × OMe), 3.75 (6H, s, 2 × OMe), 2.72 (2H, q, *J* 7, H2) and 1.11 (3H, t, *J* 7, H3) in acceptable yields.

7-Methoxychroman-4-one *21*

Exposure of 3-(3′-methoxyphenoxy)propionitrile (5.0 g, 28 mmol), prepared in 66% yield from 3-methoxyphenol, acrylonitrile, and Triton (40% benzyltrimethylammonium hydroxide in methanol), to Hoesch reaction conditions[45] afforded the *title compound*[46] **21** as an amorphous solid (3.6 g, 24 mmol, 70%), the ^{1}H NMR data completely consistent with those published.[47] Found: [M^+] *m/z* 178.0633. Calc. for $C_{10}H_{10}O_3$ 178.0630.

5,7-Dimethoxychroman-4-one *22*

Exposure of 3-(3′,5′-dimethoxyphenoxy)propionitrile (7.4 g, 36 mmol), prepared in 70% yield from 3,5-dimethoxyphenol, acrylonitrile and Triton (40% benzyltrimethylammonium hydroxide in methanol), to Hoesch reaction conditions[45] afforded the *title compound*[46] **22** as an amorphous solid (3.8 g, 18 mmol, 52%). δ_H (C_3D_6O) 6.15 (1H, s, H6 or H8), 6.08 (1H, s, H6 or H8), 4.43 (2H, t, *J* 6.2, H2), 3.83 (3H, s, 1 × OMe), 3.79 (3H, s, 1 × OMe), 2.58 (2H, t, *J* 6.2, H3). Found: [M^+] *m/z* 208.0740. $C_{11}H_{12}O_4$ requires M 208.0736.

3-Methylchroman-4-one *24*

An enolate of chroman-4-one (2.0 g, 13 mmol) in anhydrous THF (75 mL) was prepared by transferring the chroman-4-one solution to freshly prepared LDA (1.2 equiv.) in dry THF (20 mL) at −78°C, whereafter MeI (1.2 equiv.) was added. After 0.5 h, the reaction temperature was increased to −40°C for 1 h and finally to 0°C for 2–6 h. Following completion of the reaction according to TLC, NH_4Cl was added and the reaction mixture extracted three times with ethyl acetate. The organic layer was concentrated under vacuum and the product purified by means of column chromatography with hexane/ethyl acetate/acetone (9:0.5:0.5, v/v) to yield the title compound **24** as an amorphous solid (1.53 g, 9.43 mmol, 73%) and ^{1}H NMR data consistent with those published.[48] Found: [M^+] *m/z* 162.0679. $C_{10}H_{10}O_2$ requires M 162.0681.

General Oxidation Procedure[36]

The appropriate base (LDA or 0.88 M N-sodiohexamethyldisilazane (NHMDS)) in freshly distilled dry THF was cooled to −78°C, whereafter a solution of the ketone in THF was slowly transferred to the base and the mixture stirred for ∼30 min in an argon atmosphere. The mixture was warmed to −40°C, kept at this temperature for 0.5 h, and cooled to −78°C, whereafter a solution of (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine (+)-**11** (1.2 equiv. propiophenones, 1.5 equiv. chromanones and 7-methoxyflavanone **31**, or 1.7 equiv. flavanone **30**) in dry THF was added slowly over 20 min. The reaction was subsequently quenched by the addition of a saturated NH_4Cl solution, diluted with diethyl ether at −78°C, and allowed to reach room temperature. The aqueous layer was extracted with diethyl ether (3 × 25 mL) and the combined organic layers were washed with saturated aq. $Na_2S_2O_3$ (2 × 20 mL) and brine solutions (2 × 20 mL). The organic layer was dried with Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure.

Silylation and Desilylation[49,50]

To facilitate the separation of the substrate chromanone (except **25**) and 7-methoxyflavanone **31** from the respective reaction products, silylation was performed after workup of the oxidation mixture. The residue of the oxidation mixture was dried in benzene, after which 4-(dimethylamino)pyridine (DMAP; 5 mg), imidazole (2 equiv.), *tert*-butyldimethylsilyl chloride (TBDMSCl; 1.2 equiv. for the chromanones and 1.5 for the flavanone), and dry THF (2 mL) were added. The reaction mixture was stirred for 12 h, after which ether (50 mL) was added. Filtration, followed by concentration under vacuum and flash chromatography with hexane/acetone (9:1, v/v) yielded the pure silyl ether. This derivative was dissolved in a minimum volume of dry THF (∼2 mL), whereafter tetrabutylammonium fluoride (TBAF; 1.5 equiv.) was added. After 5 min, a saturated aq. NH_4Cl solution was added and the reaction mixture extracted with ether (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to afford the α-hydroxy ketone.

Absolute Configuration and ee Determinations

The (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenyl acetic derivatives ((*S*)-(−)-MTPA) of the α-hydroxy compounds were prepared according to the standard procedure[51] and separated. Analysis of the NMR spectra of these MTPA esters not only established their structures, but also gave unambiguously the percentage ee as well as the absolute configuration of the dominant stereoisomer.[52]

(S)-α-Hydroxypropiophenone ***16***

Application of the oxidation procedure to propiophenone **12** (201.3 mg, 1.50 mmol), in anhydrous THF (8 mL), with LDA (1.2 equiv.) in dry THF (2 mL) afforded, after flash chromatography purification with hexane/ethyl acetate/acetone (8:1:1, v/v), the *title compound* **16** as an amorphous solid (200.5 mg, 1.335 mmol, 89.00% yield and 88% ee), with ^{1}H NMR data consistent with those published.[53] Found: [M$^+$] *m*/*z* 150.0682. $C_9H_{10}O_2$ requires M 150.0681.

(S)-α-Hydroxy-4′-methoxypropiophenone ***17***

Application of the oxidation procedure to 4′-methoxypropiophenone **13** (98.9 mg, 0.602 mmol) in anhydrous THF (5 mL) with LDA (1.2 equiv.) in dry THF (2 mL) afforded, after flash chromatography purification with hexane/ethyl acetate/acetone (8:1:1, v/v), the title compound **17** as an amorphous solid (103.3 mg, 0.5732 mmol, 95.2% yield and 91% ee). δ_H ($CDCl_3$) 7.90 (2H, d, *J* 7.0, H2′), 6.95 (2H, d, *J* 7.0, H3′), 5.09 (1H, q, *J* 7.0, H2), 3.83 (3H, s, 1 × OMe), 1.42 (3H, d, *J* 7.0, H3). Found: [M$^+$] *m*/*z* 180.0782. $C_{10}H_{12}O_3$ requires M 180.0786.

(S)-α-Hydroxy-2′,4′-dimethoxypropiophenone ***18***

Application of the oxidation procedure to 2′,4′-dimethoxypropiophenone **14** (100.0 mg, 0.5149 mmol) in anhydrous THF (5 mL) with LDA (1.2 equiv.) in dry THF (2 mL) afforded, after flash chromatography purification with hexane/ethyl acetate/acetone (7:2:1, v/v), the *title compound* **18** as an amorphous solid (98.7 mg, 0.469 mmol, 91.1% yield and 70% ee). δ_H ($CDCl_3$) 7.89 (1H, d, *J* 8.9, H6′), 6.56 (1H, dd, *J* 8.9 and 2.8, H5′), 6.44 (1H, d, *J* 2.8, H3′), 5.10 (1H, q, *J* 7.0, H2), 3.88 (3H, s, 1 × OMe), 3.85 (3H, s, 1 × OMe), 1.30 (3H, d, *J* 7.0, H3). Found: [M$^+$] *m*/*z* 210.0889. $C_{11}H_{14}O_4$ requires M 210.0892.

(R)-α-Hydroxy-2′,4′,6′-trimethoxypropiophenone ***19***

Application of the oxidation procedure to 2′,4′,6′-trimethoxypropiophenone **15** (84.4 mg, 0.376 mmol) in anhydrous THF (5 mL) with LDA (1.2 equiv.) in dry THF (2 mL) afforded, after flash chromatography purification with hexane/ethyl acetate/acetone (7:2:1, v/v), the *title compound* **19** as an amorphous solid (40.5 mg, 0.169 mmol, 44.9% yield and 28% ee). δ_H ($CDCl_3$) 6.12 (2H, s, H3′ and H5′), 4.79 (1H, q, *J* 7.0, H2), 3.84 (3H, s, 1 × OMe), 3.78 (3H, s, 1 × OMe), 1.28 (3H, d, *J* 7.0, H3). Found: [M$^+$] *m*/*z* 240.1001. $C_{12}H_{16}O_5$ requires M 240.0998.

(R)-3-Hydroxychroman-4-one ***25***

Application of the oxidation procedure to chroman-4-one **20** (100.0 mg, 0.6749 mmol) in anhydrous THF (2.5 mL) with 0.88 M NHMDS (1.5 equiv.), afforded, after flash chromatography purification with hexane/acetone (9:1, v/v), the *title compound* **25** as colourless needles (67.3 mg, 0.410 mmol, 60.7% yield and 20% ee). mp 58–60°C (lit.[54] 57–58°C) with ^{1}H NMR data consistent with those published.[54] Found: [M$^+$] *m*/*z* 164.0476. $C_9H_8O_3$ requires M 164.0474.

(R)-3-Hydroxy-7-methoxychroman-4-one ***26***

Application of the oxidation procedure to 7-methoxychroman-4-one **21** (219.1 mg, 1.230 mmol) in anhydrous THF (2.5 mL) with 0.88 M NHMDS (1.5 equiv.) in dry THF afforded, after silylation and desilylation purification, the *title compound* **26** as colourless needles (176.7 mg, 0.910 mmol, 73.98% yield and 3.4% ee). mp 104–106°C. δ_H ($CDCl_3$) 7.78 (1H, d, *J* 9.0, H5), 6.60 (1H, dd, *J* 9.0 and 2.8, H6), 6.39 (1H, d, *J* 2.8, H8), 4.62 (1H, dd, *J* 10.0 and 6.5, H3), 4.52 (1H, dd, *J* 13.0 and 6.5, H2$_{eq}$), 4.08 (1H, dd, *J* 13.0 and 10.0, H2$_{ax}$), 3.82 (3H, s, 1 × OMe). Found: [M$^+$] *m*/*z* 194.0584. $C_{10}H_{10}O_4$ requires M 194.0579.

(R)-5,7-Dimethoxy-3-hydroxychroman-4-one ***27***

Application of the oxidation procedure to 5,7-dimethoxychroman-4-one **22** (256.0 mg, 1.230 mmol) in anhydrous THF (2.5 mL) with 0.88 M NHMDS (1.5 equiv.) in dry THF afforded, after silylation and desilylation purification, the *title compound* **27** as colourless needles (226.4 mg, 1.01 mmol, 82.11% yield and 69% ee). mp 121–123°C. δ_H ($CDCl_3$) 6.04 (1H, d, *J* 2.0, H6 or H8), 6.02 (1H, d, *J* 2.0, H6 or H8), 4.56 (1H, dd, *J* 7.1 and 4.8, H3), 4.39 (1H, dd, *J* 9.8 and 4.8, H2$_{eq}$), 3.99 (1H, dd, *J* 9.8 and 7.1, H2$_{ax}$), 3.86 (3H, s, 1 × OMe), 3.80 (3H, s, 1 × OMe). Found: [M$^+$] *m*/*z* 224.0684. $C_{11}H_{12}O_5$ requires M 224.0685.

(R)-7-Ethoxy-3-hydroxy-6-methoxy-2,2-dimethylchroman-4-one ***28***

Application of the oxidation procedure to 7-ethoxy-6-methoxy-2,2-dimethylchroman-4-one **23** (307.7 mg, 1.229 mmol) in anhydrous THF (2.5 mL) with 0.88 M NHMDS (1.5 equiv.) in dry THF afforded, after silylation and desilylation purification, the *title compound* **28** as colourless needles (75.3 mg, 0.283 mmol, 23.0% yield and 62% ee). mp 119–121°C. δ_H ($CDCl_3$) 7.15 (1H, s, H5 or H8), 6.35 (1H, s, H5 or H8), 4.33 (1H, s, H3), 4.10 (2H, q, *J* 7.0, CH_3CH_2O), 3.84 (3H, s, 1 × OMe), 1.60 (3H, s, 2-CH_3), 1.47 (3H, t, *J* 7.0, CH_3CH_2O), 1.19 (3H, s, 2-CH_3). Found: [M$^+$] *m*/*z* 266.1152. $C_{14}H_{18}O_5$ requires M 266.1154.

(R)-3-Hydroxy-3-methylchroman-4-one ***29***

Application of the oxidation procedure to 3-methylchroman-4-one[55] **24** (216.7 mg, 1.336 mmol) in anhydrous THF (2.5 mL) with 0.88 M NHMDS (1.5 equiv.) in dry THF afforded, after silylation and desilylation purification, the *title compound* **29** as an amorphous solid (177 mg, 0.995 mmol, 74.48% yield and >95% ee). δ_H ($CDCl_3$) 7.90–7.84 (1H, m, ArH), 7.55–7.47 (1H, m, ArH), 7.09–6.95 (2H, m, ArH), 4.29 (2H, d, *J* 11.2, H2), 4.18 (2H, d, *J* 11.2, H2), 2.15 (3H, s, 1 × OMe). Found: [M$^+$] *m*/*z* 178.0636. $C_{10}H_{10}O_3$ requires M 178.0630.

(2R,3R)-Dihydroflavonol ***32***

Application of the oxidation procedure to flavanone **30** (200.0 mg, 0.8918 mmol) in anhydrous THF (5 mL) with 0.88 M NHMDS (1.2 equiv.) in dry THF afforded, after flash chromatography purification with hexane/ethyl acetate/acetone (90:5:5, v/v), the title compound **32** as an amorphous solid (55.6 mg, 0.231 mmol, 25.9% yield, 57% ee) and ^{1}H NMR data consistent with those published.[56] Found: [M$^+$] *m*/*z* 240.0786. $C_{15}H_{12}O_3$ requires M 240.0787.

In a similar procedure, oxidation of (2*S*)-flavanone **37**[57] (200.0 mg, 0.8918 mmol) afforded the *title compound* **32** as white needles[56] (119.7 mg, 0.4982 mmol, 55.86% yield, 100% ee).

(2R,3R)-7-Methoxydihydroflavonol ***33***

Application of the oxidation procedure to 7-methoxyflavanone **31** (254.3 mg, 1.00 mmol) in anhydrous THF (5 mL) with 0.88 M NHMDS (1.5 equiv.) in dry THF, afforded, after silylation and desilylation purification, the title compound **33** as an amorphous solid (35.1 mg, 0.130 mmol, 13.0% yield, 63% ee), with ^{1}H NMR data completely consistent with those published.[58] Found: [M^+] *m/z* 270.0893. $C_{16}H_{14}O_4$ requires M 270.0892.

Acknowledgements

Support from the Sentrale Navorsingsfonds, of this University, and the Foundation for Research and Development, Pretoria, is acknowledged. We are also grateful to Professor D. Ferreira, formerly from this University, for financial support to Z.-M.B. and fruitful discussions during the execution of the work leading to the present manuscript.

References

[1] J. B. Harborne, *Comparative Biochemistry in Flavonoids* **1967**, p. 251 (Academic Press: London).
[2] H. Pacheco, *Bull. Soc. France Physiol. Vegetale* **1969**, *15*, 3.
[3] H. Grisebach, W. Barz, *Naturwissenschaften* **1969**, *56*, 538. doi:10.1007/BF00597256
[4] W. Heller, G. Forkmann, *The Flavonoids. Advances in Research since 1986* (Ed. J. B. Harborne) **1994**, pp. 499–535 (Chapman & Hall: London).
[5] E. Wong, *Chemistry and Biochemistry of Plant Pigments* (Ed. T. W. Goodwin) **1976**, pp. 464–526 (Academic Press: New York, NY).
[6] J. A. N. Augustyn, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron* **1990**, *46*, 2651. doi:10.1016/S0040-4020(01)82043-3
[7] H. van Rensburg, P. S. van Heerden, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron* **1997**, *53*, 14141. doi:10.1016/S0040-4020(97)00916-2
[8] D. Enders, S. Nakai, *Chem. Ber.* **1991**, *124*, 219. doi:10.1002/CBER.19911240133
[9] W. Adam, J. Bialas, L. Hadjiarapoglou, T. Patonay, *Synthesis* **1992**, 49. doi:10.1055/S-1992-34184
[10] T. Patonay, G. Tóth, W. Adam, *Tetrahedron Lett.* **1993**, *34*, 5055. doi:10.1016/S0040-4039(00)60674-3
[11] K. M. Mohamed, H. A. Hassanean, K. Ohtani, R. Kasai, K. Yamasaki, *Phytochemistry* **2000**, *53*, 401. doi:10.1016/S0031-9422(99)00547-6
[12] R. J. J. Nel, P. S. van Heerden, H. van Rensburg, D. Ferreira, *Tetrahedron Lett.* **1998**, *39*, 5623. doi:10.1016/S0040-4039(98)01064-8
[13] D. G. Roux, D. Ferreira, *Phytochemistry* **1974**, *13*, 2039. doi:10.1016/0031-9422(74)85001-6
[14] J. P. van der Merwe, D. Ferreira, E. V. Brandt, D. G. Roux, *J.C.S. Chem. Comm.* **1972**, 521. doi:10.1039/C39720000521
[15] E. Malan, D. G. Roux, *Phytochemistry* **1974**, *13*, 1575. doi:10.1016/0031-9422(74)80331-6
[16] F. du R. Volsteedt, G. J. H. Rall, D. G. Roux, *Tetrahedron Lett.* **1973**, *14*, 1001. doi:10.1016/S0040-4039(00)72473-7
[17] Z. P. Pakudina, *Khim. Prir. Soedin*. **1969**, *5*, 126.
[18] E. Kiehlmann, E. P. M. Li, *J. Nat. Prod.* **1995**, *58*, 450. doi:10.1021/NP50117A018
[19] Y. Gebhardt, S. White, G. Forkmann, R. Lukačin, U. Matern, S. Martens, *Phytochemistry* **2005**, *66*, 1273.
[20] R. W. D. Welford, I. J. Clifton, J. J. Turnbull, S. C. Wilson, C. J. Schofield, *Org. Biomol. Chem.* **2005**, *3*, 3117. doi:10.1039/B507153D
[21] J. J. Turnbull, J. Nakajima, R. W. D. Welford, M. Yamazaki, K. Saito, C. J. Schofield, *J. Biol. Chem.* **2004**, *279*, 1206. doi:10.1074/JBC.M309228200
[22] A. G. Prescott, N. P. J. Stamford, G. Wheeler, J. L. Firmin, *Phytochemistry* **2002**, *60*, 589. doi:10.1016/S0031-9422(02)00155-3
[23] F. Wellmann, M. Griesser, W. Schwab, S. Martens, W. Eisenreich, U. Matern, R. Lukačin, *FEBS Lett.* **2006**, *580*, 1642. doi:10.1016/J.FEBSLET.2006.02.004
[24] D. Slade, D. Ferreira, J. P. J. Marais, *Phytochemistry* **2005**, *66*, 2177. doi:10.1016/J.PHYTOCHEM.2005.02.002
[25] S. Öksüz, G. Topçu, *Phytochemistry* **1992**, *31*, 195. doi:10.1016/0031-9422(91)83034-I
[26] L. Y. Foo, *J. Chem. Soc. Chem. Commun.* **1986**, 675. doi:10.1039/C39860000675
[27] L. Y. Foo, *Phytochemistry* **1987**, *26*, 813. doi:10.1016/S0031-9422(00)84793-7
[28] F. Bohlmann, C. Zdero, *Phytochemistry* **1983**, *22*, 2877. doi:10.1016/S0031-9422(00)97725-2
[29] X. A. Dominguez, *J. Nat. Prod.* **1986**, *49*, 143. doi:10.1021/NP50043A019
[30] Md. Tofazzal Islam, S. Tahara, *Phytochemistry* **2000**, *54*, 901. doi:10.1016/S0031-9422(00)00048-0
[31] F. A. Davis, B.-C. Chen, *Chem. Rev.* **1992**, *92*, 919. doi:10.1021/CR00013A008
[32] G. M. Rubottom, M. A. Vazquez, D. R. Pelegrina, *Tetrahedron Lett.* **1974**, *15*, 4319. doi:10.1016/S0040-4039(01)92153-7
[33] L. A. Paquette, H.-S. Lin, M. J. Coglan, *Tetrahedron Lett.* **1987**, *28*, 5017. doi:10.1016/S0040-4039(00)96684-X
[34] B. Plietker, *Tetrahedron Asymmetry* **2005**, *16*, 3453. doi:10.1016/J.TETASY.2005.08.057
[35] M. Engqvist, J. Casas, H. Sundén, I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2053. doi:10.1016/J.TETLET.2005.01.167
[36] F. A. Davis, A. C. Sheppard, B.-C. Chen, M. S. Haque, *J. Am. Chem. Soc.* **1990**, *112*, 6679. doi:10.1021/JA00174A035
[37] E. A. González, M. A. Nazareno, C. D. Borsarelli, *J. Chem. Soc., Perkin Trans. 2* **2002**, 2052. doi:10.1039/B207663B
[38] R. W. D. Welford, J. J. Turnbull, T. D. W. Claridge, A. G. Prescott, C. J. Schofield, *Chem. Commun.* **2001**, 1828. doi:10.1039/B105576N
[39] J. L. Ingham, S. Tahara, S. Z. Dziedzic, *J. Nat. Prod.* **1986**, *49*, 631. doi:10.1021/NP50046A012
[40] L. N. Lundgren, O. Theander, *Phytochemistry* **1988**, *27*, 829. doi:10.1016/0031-9422(88)84101-3
[41] J. Mathew, A. V. S. Rao, *Phytochemistry* **1983**, *22*, 794. doi:10.1016/S0031-9422(00)86994-0
[42] T. G. Fourie, I. C. du Preez, D. G. Roux, *Phytochemistry* **1972**, *11*, 1763. doi:10.1016/0031-9422(72)85034-9
[43] K. Yoshikawa, K. Eiko, N. Mimura, Y. Kondo, S. Arihara, *J. Nat. Prod.* **1998**, *61*, 786. doi:10.1021/NP9800396
[44] X. Chen, M. Yu, M. Wang, *J. Chem. Res.* **2005**, *2*, 80.
[45] E. A. Jeffery, D. P. N. Satchell, *J. Chem. Soc. B* **1966**, 579. doi:10.1039/J29660000579
[46] D. M. X. Donnelly, J. P. Finet, B. A. Rattigan, *J. Chem. Soc., Perkin Trans.* **1993**, *1I*, 1729. doi:10.1039/P19930001729
[47] N. Srikanth, O. L. Kon, S. C. Ng, K. Y. Sim, *J. Chem. Res.* **1997**, *6*, 1412.
[48] D. Crich, X. Hao, *J. Org. Chem.* **1997**, *62*, 5982. doi:10.1021/JO970500J
[49] S. Banerjee, A. Nayek, S. Sinha, T. Bhaumik, S. Ghosh, *J. Mol. Catal. Chem.* **2006**, *254*, 85. doi:10.1016/J.MOLCATA.2006.03.023
[50] R. F. de la Pradilla, M. V. Buergo, C. Montero, A. Viso, *Tetrahedron* **2006**, *62*, 2684. doi:10.1016/J.TET.2005.12.024
[51] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512. doi:10.1021/JA00783A034
[52] A. F. Hundt, J. F. W. Burger, J. P. Steynberg, J. A. Steenkamp, D. Ferreira, *Tetrahedron Lett.* **1990**, *31*, 5073. doi:10.1016/S0040-4039(00)97809-2
[53] K. Harada, S. Shiono, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1040. doi:10.1246/BCSJ.57.1040
[54] A. S. Demir, A. Aybey, O. Sesenoglu, F. Polat, *Tetrahedron Asymmetry* **2003**, *14*, 1489. doi:10.1016/S0957-4166(03)00214-3
[55] F. A. Davis, M. C. Weismiller, *J. Org. Chem.* **1990**, *55*, 3715. doi:10.1021/JO00299A007
[56] T. Todoroki, A. Saito, A. Tanaka, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1772. doi:10.1271/BBB.66.1772
[57] This optically pure compound was obtained via chiral derivatization and subsequent restoration of the carbonyl functionality. The details of this protocol will be published elsewhere.
[58] J. W. Clark-Lewis, P. G. Tucker, *Aust. J. Chem.* **1976**, *29*, 1397. doi:10.1071/CH9761397