Synthesis and Biological Activity of the Structural Analogues of (–)-Cabenegrin A-I

Katalin Gulácsi[a], György Litkei[a], Sándor Antus*[a], Csaba Szántay[b], László L. Darkó[c], Judith Szelényi[d], György Haskó[d], and Szilveszter E. Vizi[d]

[a] Department of Organic Chemistry, University of Debrecen, P.O.Box 20, H-4010 Debrecen, Hungary

[b] Institute of Organic Chemistry, Technical University, P.O.Box 91, H-1111 Budapest, Hungary

[c] Farmacon Inc., 90 Grove Street, Suite 109 Ridgefield, Connecticut 06877-4118, USA

[d] Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O.Box 67, H-1450 Budapest, Hungary

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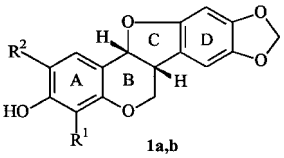
Summary

A series of phenylbutene and butanol derivatives (**6a–j**, **12**, **13**, **15**, **17**, **24b,c**, **26**, **27a,b**) were prepared from the readily available resorcinol derivatives **2a–f** and 7-hydroxy-chroman (**18**). The products were tested for inhibitory activity on the LPS-induced TNF-α production in the plasma in comparison with that of cabenegrin A-I (**1a**).

Introduction

Pterocarpans are naturally occurring plant products carrying a *cis*-fused benzofuranyl-benzopyran ring system [1], and many of them exhibit various biological effects, most particularly antifungal [2], antibacterial, and anti-HIV activity [3]. In 1982 one of us demonstrated that two representatives of these natural products, cabenegrin A-I [(–)-**1a**] and A-II [(–)-**1b**] (Figure 1) are the active components of a Brazilian folk medicine used against snake venoms [4,5]. Although the most active component, (–)-cabenegrin A-I (**1a**), is synthetically available both in racemic[6] and optically pure forms,[7] these multistep procedures are not suitable for industrial production.



1a,b

1	R^1	R^2
a		H
b	H	

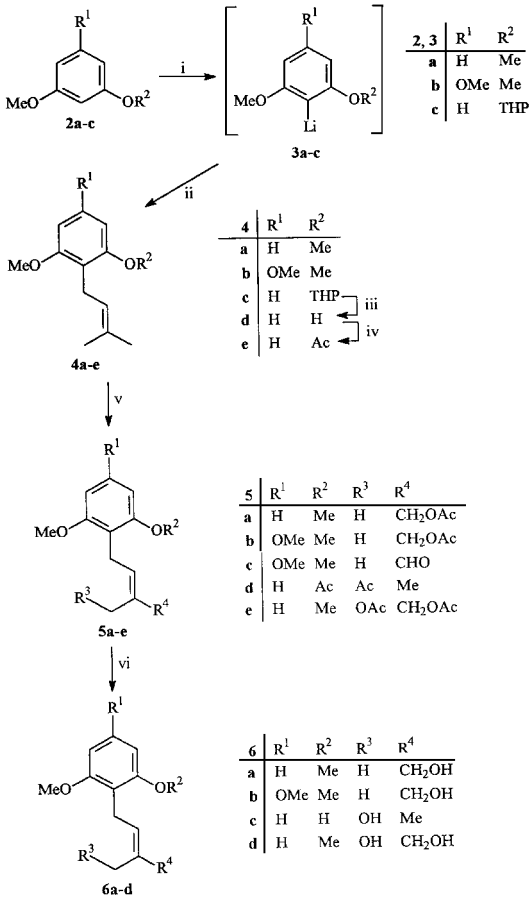
Figure 1

In order to establish the pharmacophore of this molecule, it appeared reasonable to synthesize a series of phenylbutene and butanol derivatives (**6a–j**, **12**, **13**, **15**, **17**, **24b,c**, **26**, **27a,b**) for a structure-activity relationship study, with the fact in mind that the A-ring of (–)-cabenegrin A-I [(–)-**1a**] carrying a hydroxyisoprenyl side chain with *E*-geometry, seems to be the most essential for the biological activity.

Results and Discussion

Chemistry

A simple synthesis of (*E*)-but-2-ene derivatives (**6a,b**) could be achieved from the respective resorcinol derivatives



2, 3	R^1	R^2
a	H	Me
b	OMe	Me
c	H	THP

4	R^1	R^2
a	H	Me
b	OMe	Me
c	H	THP
d	H	H
e	H	Ac

5	R^1	R^2	R^3	R^4
a	H	Me	H	CH_2OAc
b	OMe	Me	H	CH_2OAc
c	OMe	Me	H	CHO
d	H	Ac	Ac	Me
e	H	Me	OAc	CH_2OAc

6	R^1	R^2	R^3	R^4
a	H	Me	H	CH_2OH
b	OMe	Me	H	CH_2OH
c	H	H	OH	Me
d	H	Me	OH	CH_2OH

i: n-BuLi/cyclohexane, reflux; ii: $(Me)_2C{=}CH{-}CH_2Br$; iii: oxalic acid, MeOH, r.t; iv: Ac_2O/pyridine; v: SeO_2/Ac_2O, vi: NaOMe/MeOH or $LiAlH_4/Et_2O$ r.t

Scheme 1

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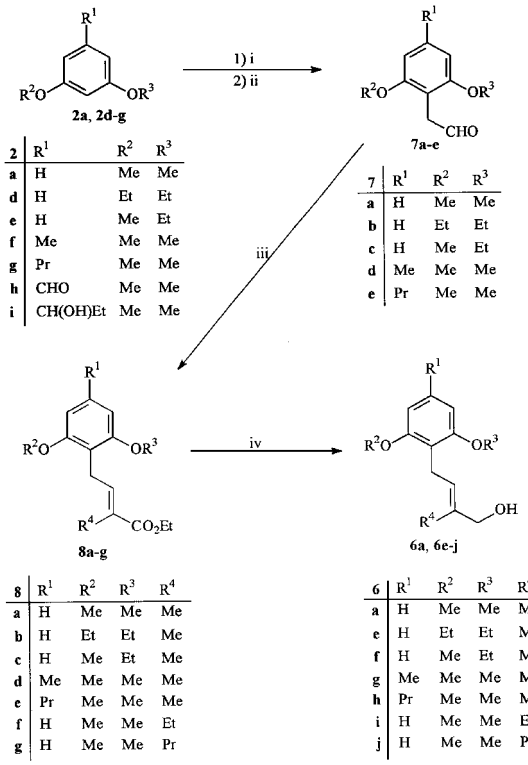
(**2a,b**). Our approach (Scheme 1) was based on the method described by Bohlmann et al. [8–10], who recognized that various C-3,3-dimethylallylphenols could be stereoselectively transformed by oxidation with selenium dioxide in acetic anhydride into the corresponding (*E*)-1-acetoxy-2-methylprop-2-en-1-yl derivatives in good yield.

Accordingly, resorcinol dimethyl ether (**2a**) was regioselectively lithiated with *n*-butyllithium in cyclohexane, followed by trapping of the formed lithium intermediate (**3a**) by addition of 3,3-dimethylallyl bromide to result **4a** in a moderate yield (51%). In a good agreement with Bohlmann's observations [8–10], oxidation of **4a** took place regioselectively in the presence of a stoichiometric amount of selenium dioxide to furnish the acetoxy derivative **5a**, whose saponification with sodium methoxide in methanol at room temperature afforded **6a** in 37% yield. As shown in Scheme 1, the same sequence (**2b** → **3b** → **4b**) was used for the preparation of **4b**. It is to be noted that oxidation of **4b** with selenium dioxide under the conditions used for **4a** resulted in a ca. 1:2 mixture of **5b** and **5c** based on the ^{1}H-NMR spectra. Although our attempts for the separation of this mixture were unsuccessful, reduction with lithium aluminium hydride yielded our target molecule (**6b**) in a good yield (70%). In the case of the dimethylallylphenol derivative **4e**, prepared from **2c** in four steps (**2c** → **3c** → **4c** → **4d** → **4e**) according to the literature [11], oxidation with selenium dioxide provided also an astonishing result. Thus, introduction of the acetoxy group into the dimethylallyl side chain took place with an opposite regioselectivity (*Z*) than found in the case of **4a** or **4b**. The *Z*-geometry of the double bond of **5d** and **6c** (prepared by simple saponification of **5d** with sodium methoxide) could be unequivocally detected by NOE experiments.

The intermediate **4a** was found to be an appropriate starting material also for the synthesis of **6d**. Thus, oxidation of **4a** with 2 molar equivalents of selenium dioxide for a fourfold prolonged period than used in the case of the transformation of **4a** or **4b**, resulted in the diacetate **5e**, which was isolated by means of column chromatography on silica gel with 14% yield. Saponification of this latter with sodium methoxide in methanol at room temperature gave **6d** in a moderate yield (41%).

Starting from **2a**, the synthesis of the (*E*)-but-2-ene derivative **6a** could also be achieved by the Wittig methodology which had been previously used for the synthesis of the racemic and optically active cabenegrin A-I (**1a**) [6,7]. In the first step, the lithium salt **3a** of **2a** was alkylated with the commercially available bromoacetaldehyde diethyl acetal, and the resulting acetal was hydrolyzed under mild acidic conditions to the aldehyde **7a** as shown in Scheme 2. According to earlier procedures [6,7], the Wittig reaction of the aldehyde **7a** with α-ethoxycarbonyltriphenylphosphonium bromide [12] in the presence of sodium ethoxide in ethanol at room temperature furnished the respective α,β-unsaturated ester **8a**. Finally, reduction of **8a** with lithium aluminium hydride in ether at room temperature resulted in the allyl alcohol derivative **6a** in a moderate yield (37%). In order to influence the lipophilicity of **6a**, and therefore to modify its pharmacological profile, its substituted derivatives (**6e–j**) were also synthesized by the Wittig methodology starting from the phenol derivatives **2d–g** as depicted in Scheme 2. Among these starting materials resorcinol diethyl ether (**2d**)



2	R^1	R^2	R^3
a	H	Me	Me
d	H	Et	Et
e	H	Me	Et
f	Me	Me	Me
g	Pr	Me	Me
h	CHO	Me	Me
i	CH(OH)Et	Me	Me

7	R^1	R^2	R^3
a	H	Me	Me
b	H	Et	Et
c	H	Me	Et
d	Me	Me	Me
e	Pr	Me	Me

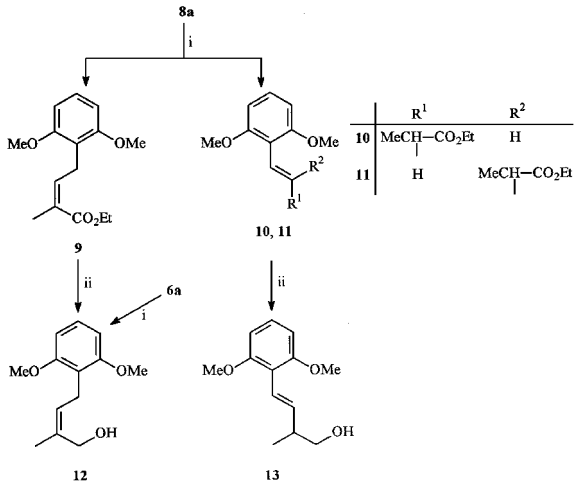
8	R^1	R^2	R^3	R^4
a	H	Me	Me	Me
b	H	Et	Et	Me
c	H	Me	Et	Me
d	Me	Me	Me	Me
e	Pr	Me	Me	Me
f	H	Me	Me	Et
g	H	Me	Me	Pr

6	R^1	R^2	R^3	R^4
a	H	Me	Me	Me
e	H	Et	Et	Me
f	H	Me	Et	Me
g	Me	Me	Me	Me
h	Pr	Me	Me	Me
i	H	Me	Me	Et
j	H	Me	Me	Pr

i: n-BuLi/cyclohexane, reflux; ii: $BrCH_2CH(OEt)_2$/cyclohexane reflux then $H^{\oplus}/H_2O$;
iii: $Ph_3P^{\oplus}CH(R_4)CO_2EtBr^{\ominus}$, NaOEt, r.t; iv: $LiAlH_4$, Et_2O, r.t

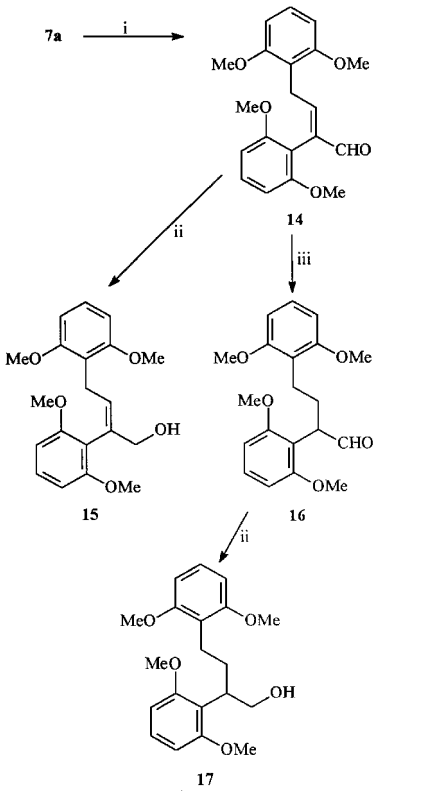
Scheme 2

was commercially available, and **2e** and **2f** were prepared from the readily available resorcinol monomethyl ether and orcinol by simple alkylation according to the literature [13,14]. In the case of **2g**, we started from the readily available 3,5-dimethoxybenzaldehyde (**2h**), whose Grignard reaction with ethylmagnesium bromide in ether at room temperature resulted in the benzyl alcohol **2i** in good yield (88%). Finally, catalytic hydrogenation of **2i** in the presence of palladium on charcoal in acetic acid at room temperature afforded **2g** in 68% yield.



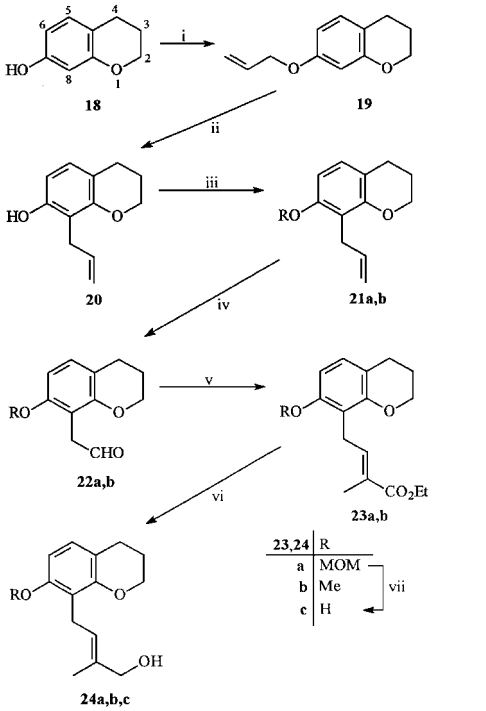
	R^1	R^2
10	MeCH–CO_2Et	H
11	H	MeCH–CO_2Et

Scheme 3



i: NaOEt/EtOH, r.t; ii: $LiAlH_4/Et_2O$, r.t; iii: $Pd(C)/H_2$

Scheme 4



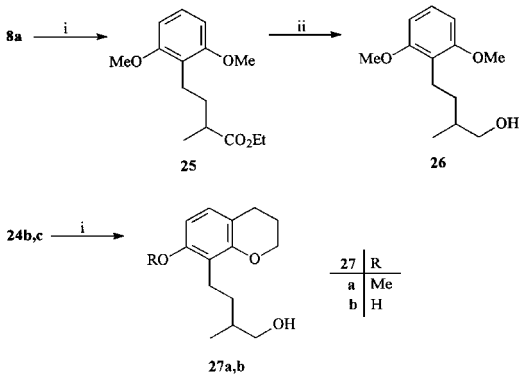
i: NaH/DMF at 0°C then allyl bromide; ii: in xylene at 200°C Δ; iii: NaH/DMF then $MeOCH_2Cl$ r.t or $DMSO_4/KOH$; iv: $OsO_4/NaIO_4$ dioxane, r.t;
v: $Ph_3P^{\oplus}CH_2(Me)CO_2Et\ Br^{\ominus}$, NaOEt/EtOH r.t; vi: $LiAlH_4/Et_2O$, r.t
vii: $H^{\oplus}/H_2O$, MeOH, r.t

Scheme 5

It seemed also to be interesting to find out the influence of the position of the double bond and the stereochemistry in the side chain of **6a** on the biological activity. Therefore, we prepared the structural analogues **12** and **13** from the ester **8a** as depicted in Scheme 3. Interconversion of the (*E*)-but-2-ene **8a** by photoisomerization in benzene at room temperature resulted in a mixture of the butene derivatives **9**, **10**, and **11**, whose separation could be achieved by column chromatography on silica gel. Reduction of the esters **9** and **10** gave the corresponding primary alcohols **12** and **13**, respectively. The allyl alcohol **12** was also formed in a moderate yield (23%) when **6a** was irradiated in benzene at room temperature.

The simple aldol condensation of the aldehyde **7a** in the presence of sodium ethoxide in ethanol at room temperature gave the α,β-unsaturated aldehyde **14** in 56% yield, whose reduction with lithium aluminium hydride under standard conditions afforded the specifically substituted but-2-ene derivative **15**. In the course of our detailed study on the structure-biological activity relationship, the chroman derivatives **24b,c**, carrying a hydroxyisoprenyl side chain at C-8, were also synthesized from 7-hydroxychroman (**18**) according to our procedure employed for the total synthesis of (–)-cabenegrin A-I (**1a**).[7] In the first step, 7-hydroxychroman (**18**) was transformed by alkylation with allyl bromide in the presence of sodium hydride in DMF into the allyl ether **19** in good yield (72%), whose thermal Claisen rearrangement in xylene at 200 °C gave the chroman derivative **20** in 50% yield. In the next step, **20** was alkylated with chloromethyl methyl ether (**20** → **21a**) and the product was reacted with osmium tetroxide, followed by oxidation with sodium metaperiodate in dioxane at room temperature to give aldehyde **22a** in an overall yield of 85%. The last two steps of the synthesis (**22a** → **23a** → **24a**) were performed as in the case of **6a** and **6e–f**, and thus **24a** could be isolated in 63% yield, whose deprotection under mild acidic conditions furnished the target molecule **24c**. Its methyl ether **24b** was also synthesized according to the same sequence (**20** → **21b** → **22b** → **23b** → **24b**) starting from the chroman derivative **20** in an overall yield of 31%.

Taking into consideration that cabenegrin A-II (**1b**) possesses a reduced antidote activity against the venom of *Bothrops atrox* as compared to cabenegrin A-I (**1a**), and also that they are different in the side chains located in ring-A, it



i: Pd(C)/MeOH, r.t; ii: $LiAlH_4/Et_2O$, r.t

Scheme 6

seemed to be reasonable to prepare some analogues of cabenegrin A-II (**1b**), as well. The synthesis of these compounds (**26**, **27a,b**) is depicted in Scheme 6. In the first step, **8a** was reduced by catalytic hydrogenation over 10% palladium on charcoal to give the saturated esters **25** in good yield, whose reduction with lithium aluminium hydride in ether at room temperature resulted in the corresponding primary alcohol **26**. The synthesis of **27a** and **27b** could be achieved by simple reduction of **24b** and **24c** over 10% palladium on charcoal in methanol, respectively.

Pharmacology

It is well known that several infections, particularly with Gram-negative bacteria, leads to septic shock [15]. Recently it has also become clear that the tumor necrosis factor (TNF-α) characterized originally by its antitumor activity and cytotoxic response[16] occupies a key role in the phytophysiology associated with diverse inflammatory states and other severe illnesses including septic and endotoxic shocks, such as cachexia, as well as non-insulin-dependent diabetes [17]. Since TNF-α neutralization in the treatment of septic shock is now well accepted [18], therefore measuring of the immune response *via* modulating the endotoxin-induced TNF-α production seems to be an appropriate model also for the characterization of the pharmacological profile of the phenylbutene derivatives **6a–c, 6e–j, 12, 13** and **24b** in comparison with that of *rac*.-cabenegrin (**1a**). The values of the TNF-α levels are given in Table 1.

Table 1. The inhibitory effects of **1a**, **6a-c**, **6e-j**, **13**, **15,** and **24b** on the LPS-induced TNF-α production in the plasma.

Compound	Dose		TNF-α level % of control
	mg/kg	mmol/kg× 10^{-4}	
1a	5	1.4	53 ± 10
	10	2.7	42 ± 8
	20	5.4	18 ± 3
6a	40	18.0	10 ± 7 **
6b	40	15.8	59 ± 8 *
6c	40	19.2	24 ± 6 *
6e	40	16.0	58 ± 10 *
6f	40	16.9	51 ± 22
6g	40	16.9	57 ± 20
6h	40	15.1	56 ± 10 *
6i	40	16.9	76 ± 15
6j	40	16.0	79 ± 18
12	40	18.0	68 ± 14
13	40	18.0	62 ± 20
15	40	11.6	37 ± 11 *
24b	40	16.1	6 ± 2 **

± Standard error of means. Significance: *p>0.05; **p>0.01.

According to our assumption, cabenegrin A-I (**1a**) inhibited significantly and dose-dependently the increase of the plasma TNF-α level, and its activity is strongly connected with its A and B rings, since the **24b** chroman derivative has been found to possess the same order of inhibitory activity as found for the *rac*.-**1a** itself. The inhibitory values of **6a, 6e, 12**, and **13** have also clearly indicated that both of the presence of the unsaturated side chain on A ring of **1a** and its *E*-geometry, as well as the position of the double bond is essential for the inhibitory activity. Since elongation of the side chain of **6a** with one or two carbon atoms (**6i, 6j**) resulted in a significant loss of the inhibitory action of the molecule, therefore it is presumable that the four carbon atom length of the side chain of **1a** may also play an important role in its activity. In this context it is to be noted that substitution of the methyl group at C-2 of **6a** with a 2,6-dimethoxyphenyl group (**6a**→**15**) gave rise to a remarkably smaller influence on the inhibition. Moreover, it is noteworthy that further analogues of **6a** (i.e. **6b, 6c, 6f–h**) possessing higher lipophilicity were found to be still less active in the inhibition of the endotoxin-induced TNF-α production, than **6a** itself.

The mechanism how cabenegrin A-I (**1a**) could suppress TNF-α synthesis is not known yet. A number of structurally unrelated compounds were reported to inhibit the endotoxin evoked TNF-α response affecting various steps of the signal transduction pathway. Inhibitors of the arachidonate metabolism like 4-aryl-5-pyridinylimidazoles[19] and acetylsalicylic acid[20] are affecting possibly the activation of the transcription factor NF-kB. There are literary data on the inhibitory effect on TNF-α production of phosphodiesterase inhibitors[21] and that of p38 MAP kinase inhibitors as well, demonstrating the effectiveness of drugs with unrelated chemical structures [22].

On the basis of these results it is presumed that the pharmacological activity of cabenegrin (**1a**) may be closely related to its chroman moiety carrying a hydroxyisoprenyl side chain with *E*-geometry. Further work on the evaluation of this influence is currently in progress.

Acknowledgement

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Experimental

Melting points were determined with a Kofler hot stage microscope and are uncorrected. The reactions and the purity of compounds were controlled by TLC using precoated Silica gel 60 F254 plates (Merck). Detection of the components was by UV light and/or treatment with molybdatophosphoric acid hydrate/EtOH. Preparative separations were performed by column or flash chromatography using Merck Silica gel 60 (0.063–0.200 nm). The 200-MHz ^{1}H-NMR spectra were recorded on a Brucker WP-200 SY spectrometer with TMS as internal standard (δ = 0) in $CDCl_3$. Coupling constants (*J*) are given in Hz. Elemental analyses were determined by Carlo-Erba analysator Tpy 1106 and given within ±0.4% unless otherwise stated.

*General Procedure for the Preparation of **4a–c***

A solution of 29.7 mmol of resorcinol derivative in 100 ml absolute cyclohexane was cooled to 0 °C under N_2 atmosphere and 41 mmol of *n*-butyllithium (solution of 15% in hexane) were added under the above conditions. The reaction mixture was boiled for 30 minutes. After cooling to room temperature, 43.3 mmol of 3,3-dimethylallylbromide were added dropwise and the mixture boiled for 2 hours. After cooling the reaction mixture was poured in a saturated solution of $NaHCO_3$, extracted with ethyl acetate, washed with water and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel.

*4-(2,6-Dimethoxyphenyl)-2-methylbut-2-ene (**4a**)*

Eluent: hexane; colourless oil; yield 70%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.65 and 1.75 (s, 6H, 2×Me), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 5.2 (t, *J* = 7.5, 1H, =CH), 6.55 (d, *J* = 10.0, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 10.0, 1H, H-4, aromat.).– Anal. $C_{13}H_{18}O_2$.

*4-(2,4,6-Trimethoxyphenyl)-2-methylbut-2-ene (**4b**)*

Eluent: hexane-acetone 9:1; colourless oil; yield 94%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.6 and 1.75 (s, 6H, 2×Me), 3.25 (d, *J* = 7.5, 2H, CH_2Ar), 3.75 (s, 9H, 3×OMe), 5.15 (t, *J* = 7.5, 1H, =CH), 6.1 (s, 2H, 3-,5-H, aromat.).– Anal. $C_{14}H_{20}O_3$.

*4-[2-(2-Tetrahydropyranyloxy)-6-methoxyphenyl]-2-methylbut-2-ene (**4c**)*

Eluent: hexane-ethyl acetate 20:1; yellow oil; yield 52%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.2, 1.55 and 1.8 (m, 6H, 3×CH_2), 1.6 and 1.8 (s, 6H, 2×Me), 3.3 (d, *J* = 7.5, 2H, CH_2Ar), 3.55 and 3.85 (m, 2H, CH_2), 3.75 (s, 3H, OMe), 5.15 (t, *J* = 7.5, 1H, =CH), 5.35 (t, 1H, -O*CH*O-), 6.5 and 6.7 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.0 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{17}H_{24}O_3$.

*2-(3-Methylbut-2-ene-1-yl)-3-methoxyphenol (**4d**)*

4c (4.85 g, 0.0175 mol), 250 ml of methanol and oxalic acid (3.7 g, 0.041 mol) dissolved in 20 ml water were stirred at room temperature, for 1 hour. The methanol was evaporated, the residue was diluted with water, extracted with dichloromethane, washed with water, dried over $MgSO_4$. After evaporation of the solvent the oily residue was sufficiently pure for further use. Yield 98%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 3.4 (d, *J* = 7.5, 2H,CH_2Ar), 3.8 (s, 3H, OMe), 5.0 (t, *J* = 7.5, 1H, =CH), 5.65 (s, 1H, Ar-*OH*), 6.4 (d, *J* = 7.5, 2H, 4-,6-H, aromat.), 7.0 (t, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{12}H_{16}O_2$.

*1-(2-Acetoxy-6-methoxyphenyl)-3-methylbut-2-ene (**4e**)*

4d (3.53 g, 0.018 mol), 20 ml of acetic anhydride and 0.5 ml abs. pyridine were kept on water bath for 1 hour. Then the mixture was poured in cold water, stirred 0.5 h, extracted with ethyl acetate, washed with $NaHCO_3$ solution, water, dried over $MgSO_4$ and evaporated. The obtained brown oil was sufficiently pure. Yield 87%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.65 and 1.75 (s, 6H, 2×Me), 2.3 (s, 3H, OAc), 3.3 (d, *J* = 7.5, 2H,CH_2Ar), 3.85 (s, 3H, OMe), 5.15 (t, *J* = 7.5, 1H, =CH), 6.7–7.2 (m, 3H, 3-,4-,5-H, aromat.).– Anal. $C_{14}H_{18}O_3$.

*General Procedure for the Preparation of **5a–e***

A mixture of 0.028 mmol prenylated compound, 70 ml of acetic anhydride and 0.68 mol SeO_2 was boiled for 30 minutes (4 days in case of **4a** → **5e**). The reaction mixture was poured in cold water, extracted with ethyl acetate, washed with water, $NaHCO_3$ solution, water, dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel.

*(E)-1-Acetoxy-4(2,6-dimethoxyphenyl)-2-methylbut-2-ene (**5a**)*

Eluent: hexane; yellow colourless oil; yield 38%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.8 (s, 3H, Me), 2.0 (s, 3H, OAc), 3.3 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 4.4 (s, 2H, CH_2O), 5.15 (t, *J* = 7.5, 1H, =CH), 6.7 and 6.8 (d, *J* = 7.5, 2H, 3-H, 5-H, aromat.), 7.2 (t, *J* = 7.5, 1H, H-4, aromat.).– Anal. $C_{15}H_{20}O_4$.

*(E)-1-Acetoxy-4-(2,4,6-trimethoxyphenyl)-2-methylbut-2-ene (**5b**) and (E)-4-(2,4,6-Trimethoxyphenyl)-2-methylbut-2-ene-1-al (**5c**)*

Eluent: hexane-ethyl acetate 5:2; colourless oil. **5b**: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.8 (s, 3H, Me), 1.9 (s, 3H, OAc), 3.35 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 9H, 3×OMe), 4.4 (s, 2H, CH_2O), 5.5 (t, *J* = 7.5, 1H, =CH), 6.15 (s, 2H, 3-,5-H, aromat.). **5c**: ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.8 (s, 3H, Me), 3.6 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 9H, 3×OMe), 6.1 (s, 2H, 3-,5-H, aromat.), 5.15 (t, *J* = 7.0, 1H, =CH), 9.35 (s, 1H, CHO).

*(Z)-1-Acetoxy-4-(2-acetoxy-6-methoxyphenyl)-2-methylbut-2-ene (**5d**)*

Eluent: hexane-ethyl acetate 4:1; colourless oil; yield 30%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.75 (s, 3H, Me), 2.10 (s, 3H, OAc), 3.3 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 3H, OMe), 4.45 (s, 2H, CH_2OAc), 5.50 (t, *J* = 7.5, 1H, =CH-), 6.65–7.30 (m, 3H, ArH).– Anal. $C_{16}H_{20}O_5$.

*1-Acetoxy-2-acetoxymethyl-4-(2,6-dimethoxyphenyl)but-2-ene (**5e**)*

Eluent: hexane-ethyl acetate 5:2; oil; yield 14%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.05 and 2.1 (s, 6H, 2×OAc), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 3.80 and 3.85 (s, 6H, 2×OMe), 4.55 and 4.9 (s, 4H, 2×OCH_2), 5.9 (t, *J* = 7.5, 1H, =CH), 6.5 and 6.6 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{17}H_{22}O_5$.

*General Procedure for the Preparation of **6a–d***

*1. Preparation of **6a**,**c**,**d** from **5a**,**d**,**e***

The mixture of 1.78 mmol of acetate, 10 ml abs. methanol and 4 ml of 1N $NaOCH_3$ was stirred under N_2 atmosphere for 20 hours at room temperature. The solvent was evaporated, the residue diluted with water, neutralized with acetic acid, extracted with ethyl acetate, washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on silica gel.

*(E)-4-(2,6-Dimethoxyphenyl)-2-methylbut-2-en-1-ol (**6a**)*

Eluent: hexane-acetone 5:2; colourless oil; yield 35%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 2.0 (brs, 1H, OH), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 3.95 (s, 2H, CH_2-O), 5.45 (t, *J* = 7.5, 1H, =CH), 6.55 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{13}H_{18}O_3$.

*(Z)-4-(2-Hydroxy-6-methoxyphenyl)-2-methylbut-2-en-1-ol (**6c**)*

Eluent: toluene-ethyl acetate 4:1; colourless oil; yield 40%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.88 (s, 3H, Me), 3.41 (d, *J* = 7.5, 2H, CH_2Ar), 3.82 (s, 3H, OMe), 4.05 (s, 2H, -CH_2OH), 5.12 (s, 1H, OH), 5.55 (t, *J* = 7.5, 1H, =CH-), 6.48 (t, *J* = 8.0, 2H, 3-,5-H), 7.05 (t, *J* = 8.0, 1H, 4-H).– Anal. $C_{12}H_{16}O_3$.

*2-Hydroxymethyl-4-(2,6-dimethoxyphenyl)but-2-en-1-ol (**6d**)*

Eluent: hexane-acetone 2:1; mp 71–73 °C; yield 41%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.15 and 2.6 (brs, 2H, OH), 3.45 (d, *J* = 8.0, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 4.2 and 4.4 (s, 4H, 2×CH_2O), 5.65 (t, *J* = 8.0, 1H, =CH), 6.6 (d, *J* = 8.0, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 8.0, 1H, 4-H, aromat.).– Anal. $C_{13}H_{18}O_4$.

*2. Preparation of **6b** from **5b**,**c***

$LiAlH_4$ (2.8 g, 0.073 mol) was suspended in 90 ml abs. ethyl ether, under N_2 atmosphere, at room temperature. 4.77 g of **5b**,**c** mixture dissolved in ether were added dropwise during 1 hour. The reaction mixture was stirred for 10 min at room temperature, then ethyl acetate was added dropwise to decompose the excess of $LiAlH_4$. Then saturated solution of NH_4Cl was added, extracted with ethyl acetate, washed with water and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel.

*(E)-4-(2,4,6-Trimethoxyphenyl)-2-methylbut-2-en-1-ol (**6b**)*

Eluent: toluene-acetone 4:1; mp 51-53 °C; yield 47%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 3.45 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 9H, 3×OMe), 3.95 (s, 2H, CH_2OH), 5.45 (t, *J* = 7.5, 1H, =CH), 6.2 (s, 2H, 3-,5-H, aromat.).– Anal. $C_{14}H_{20}O_4$.

*1-(3,5-Dimethoxyphenyl)-propane-1-ol (**2i**)*

To the ethylmagnesiumbromide [prepared freshly from magnesium (0.6 g), ethylbromide (2 ml) and anhydrous ether (20 ml)] was dropped the solution of 3,5-dimethoxybenzaldehyde (**2h**, 4.15 g, 21 mmol) in anhydrous

ether (40 ml) with stirring at room temperature during 30 min. The reaction mixture was boiled for 2 hours. To the cooled mixture NH_4Cl solution was added and then extracted with ether. The organic phase was washed, dried and evaporated yielding the crude product which was purified by flash column chromatography with hexane-ethyl acetate (5:1). 4.35 g (88%) of **2i** was obtained (R_f = 0.4).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.95 (t, *J* = 7.5, 3H, Me), 1.7 (m, 2H, CH_2), 2.2 (s, 1H, OH), 3.8 (s, 6H, 2×OMe), 4.5 (t, *J* = 7.5, 1H, CH), 6.35 (dd, *J* = 1.0 and 1.5, 1H, 4-H, aromat.), 6.5 (d, *J* = 2.0, 2H, 2-,6-H, aromat.).

*3,5-Dimethoxy-n-propylbenzene (**2g**)*

4.2 g (21.4 mmol) of **2i** was reduced with H_2 in glacial acetic acid (70 ml) in the presence of 10% Pd/C (3.5 g). After 30 hours (using 550 ml of H_2) the catalyst was filtered off, the solvent was evaporated and the residue was flash chromatographed on silica gel with hexane-ethyl acetate (5:2) as the eluent yielding 2.6 g (68%) of **2g**.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.0 (t, *J* = 7.5, 3H, Me), 1.7 (m, 2H, CH_2), 2.55 (t, *J* = 8.0, CH_2Ar), 3.8 (s, 6H, 2×OMe), 6.3–6.4 (m, 3H, 2-,4-,6-H, aromat.).

General Procedure for the Preparation of **7a–e**

To the solution of 0.05 mol resorcinol derivative in 200 ml anhydrous cyclohexane butyllithium (0.1 mol, 42 ml 15% solution in hexane) was added dropwise at 0 °C, N_2 atmosphere and stirring. The reaction mixture was boiled for 1.5 hours. After cooling, 0.0625 mol of bromoacetaldehyde diethyl acetal was added dropwise and the mixture boiled for another 1.5 hours. After cooling, the mixture was diluted with $NaHCO_3$ solution, extracted with dichloromethane, washed with water, dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in ethanol and stirred with 10% HCl at room temperature. The solvent was distilled off, water was added and the mixture extracted with CH_2Cl_2, washed, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

*2,6-Dimethoxyphenylacetaldehyde (**7a**)*

Eluent: hexane-ethyl acetate 5:1; mp 37–38 °C; yield 33%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.7 (d, *J* = 1.5, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 6.6 (d, *J* = 6.5, 2H, 3-,5-H, aromat.), 7.25 (t, *J* = 8.0, 1H, 4-H, aromat.), 9.5 (t, *J* = 1.5, 1H, CHO).– Anal. $C_{10}H_{12}O_3$.

*2,6-Diethoxyphenylacetaldehyde (**7b**)*

Eluent: hexane-ethyl acetate 10:1; colourless oil; yield 50%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.4 (t, *J* = 7.5, 6H, 2×Me), 3.7 (d, *J* = 1.0, 2H, CH_2Ar), 4.0 (q, *J* = 7.5, 4H, 2×CH_2), 6.5 (d, *J* = 5.0, 2H, 3-,5-H, aromat.), 7.2 (t, *J* = 7.5, 1H, 4-H, aromat.), 9.6 (t, *J* = 1.0, 1H, CHO).– Anal. $C_{12}H_{16}O_3$.

*2-Ethoxy-6-methoxyphenylacetaldehyde (**7c**)*

Eluent: hexane-ethyl acetate 10:1; colourless oil; yield 38%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.4 (t, *J* = 7.5, 3H, Me), 3.65 (d, *J* = 1.5, 2H, CH_2Ar), 3.85 (s, 3H, OMe), 4.05 (q, *J* = 7.5, 2H, CH_2), 6.6 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.25 (t, *J* = 8.0, 1H, 4-H, aromat.), 9.65 (t, *J* = 1.5, 1H, CHO).– Anal. $C_{11}H_{14}O_3$.

*2,6-Dimethoxy-4-methylphenylacetaldehyde (**7d**)*

Eluent: hexane-ethyl acetate 10:1; colourless oil; yield 34%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.35 (s, 3H, Me), 3.65 (d, *J* = 1.0, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 6.4 (s, 2H, 3-,5-H, aromat.), 9.5 (t, *J* = 1.0, 1H, CHO).– Anal. $C_{11}H_{14}O_3$.

*2,6-Dimethoxy-4-n-propylphenylacetaldehyde (**7e**)*

Eluent: hexane-acetone 9:1; colourless oil; yield 20%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.0 (t, *J* = 7.5, 3H, Me), 1.7 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 3.65 (d, *J* = 1.0, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 6.45 (s, 2H, 3-,5-H, aromat.), 9.6 (t, *J* = 1.0, 1H, CHO).– Anal. $C_{13}H_{18}O_3$.

General Procedure for the Preparation of ***8a–g***

The mixture of 0.05 mol of aldehyde, 0.075 mol of phosphonium salt,[23] 100 ml of anhydrous ethanol and 0.1 mol of 1N $NaOC_2H_5$ was stirred at room temperature under N_2 atmosphere for 2 hours. The solvent was partially evaporated, water was added and the solution extracted with ethyl acetate, washed with water, dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel, hexane-ethyl acetate 10:1 as eluent.

*(E)-Ethyl 4-(2,6-dimethoxyphenyl)-2-methylcrotonate (**8a**)*

Yellow oil; yield 75%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t, *J* = 7.5, 3H, Me), 3.0 (s, 2H, Me), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.15 (q, *J* = 7.5, 2H, CH_2), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 6.8 (t, *J* = 7.5, 1H, =CH), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{15}H_{20}O_4$.

*(E)-Ethyl 4-(2,6-diethoxyphenyl)-2-methylcrotonate (**8b**)*

Thick oil; yield 66%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.2 (t, *J* = 7.5, 3H, Me), 1.4 (t, *J* = 7.5, 6H, 2×Me), 2.0 (s, 3H, Me), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 4.0 (q, *J* = 7.5, 4H, 2×CH_2), 4.1 (q, *J* = 7.5, 4H, CH_2), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 6.8 (t, *J* = 7.5, 1H, =CH), 7.15 (m, 1H, 4-H, aromat.).– Anal. $C_{17}H_{24}O_4$.

*(E)-Ethyl 4-(2-ethoxy-6-methoxyphenyl)-2-methylcrotonate (**8c**)*

Colourless oil; yield 56%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.3 (t, *J* = 7.5, 3H, Me), 1.45 (t, *J* = 7.5, 3H, Me), 2.0 (s, 3H, Me), 3.55 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 3H, OMe), 4.0 and 4.15 (q, *J* = 7.5, 4H, 2×CH_2), 6.5 (d, *J* = 7.0, 2H, 3-,5-H, aromat.), 6.75 (t, *J* = 7.5, 1H, =CH), 7.1 (m, 1H, 4-H, aromat.).– Anal. $C_{16}H_{22}O_4$.

*(E)-Ethyl 4-(2,6-dimethoxy-4-methylphenyl)-2-methylcrotonate (**8d**)*

Colourless oil; yield 62%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t, *J* = 7.5, 3H, Me), 2.0 (s, 3H, Me), 2.32 (s, 3H, Me), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.15 (q, *J* = 7.5, 2H, CH_2), 6.35 (s, 2H, 3-,5-H, aromat.), 6.75 (t, *J* = 7.5, 1H, =CH).– Anal. $C_{16}H_{22}O_4$.

*(E)-Ethyl 4-(2,6-dimethoxy-4-propylphenyl)-2-methylcrotonate (**8e**)*

Eluent: dichloromethane-benzene 3:1; colourless oil; yield 40%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.9 (t, *J* = 7.5, 3H, Me), 1.3 (s, 3H, Me), 1.7 (m, 2H, CH_2), 2.0 (s, 3H, Me), 2.6 (t, *J* = 6.0, 2H, CH_2), 3.5 (d, *J* = 6.0, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.2 (q, *J* = 7.5, 2H, CH_2), 6.4 (s, 2H, 3-,5-H, aromat.), 6.8 (t, *J* = 6.0, 1H, =CH).– Anal. $C_{18}H_{26}O_4$.

*(E)-Ethyl 2-ethyl-4-(2,6-dimethoxyphenyl)crotonate (**8f**)*

Thick oil; yield 18%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.1 and 1.25 (t, *J* = 7.5, 6H, 2×OMe), 2.5 (q, *J* = 7.5, 2H, CH_2), 3.55 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.15 (q, *J* = 7.5, 2H, CH_2O), 6.55 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 6.7 (t, *J* = 7.5, 1H, =CH), 7.2 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{16}H_{22}O_4$.

*(E)-Ethyl 4-(2,6-dimethoxyphenyl)-2-propylcrotonate (**8g**)*

Thick oil; yield 15%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.95 and 1.25 (t, *J* = 7.5, 6H, 2×OMe), 1.5 (m, 2H, CH_2), 2.5 (t, *J* = 7.5, 2H, CH_2), 3.55 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.2 (q, *J* = 7.5, 2H, CH_2O), 6.0 (d, *J* = 3.5, 2H, 3-,5-H, aromat.), 6.8 (t, *J* = 7.5, 1H, =CH), 7.2 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{17}H_{24}O_4$.

General Procedure for the Preparation of **6a**,**e–j**

$LiAlH_4$ (1.0 g, 26 mmol) was suspended in 100 ml anhydrous ether and cooled at 0 °C, under N_2 atmosphere and stirring. A solution of esther (3.7 mmol) in abs. ether was added dropwise. After stirring for 2 hours at room temperature, ethyl acetate was added dropwise to decompose the excess of $LiAlH_4$. The mixture was diluted with a saturated solution of NH_4Cl, extracted with ethyl acetate, washed, dried, evaporated and purified by column chromatography on silica gel.

*(E)-4-(2,6-Diethoxyphenyl)-2-methylbut-2-en-1-ol (**6e**)*

Eluent: hexane-ethyl acetate 5:2; mp 74–76 °C; yield 71%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.35 (t, *J* = 7.5, 6H, 2×Me), 1.5 (brs, 1H, OH), 1.85 (s, 3H, Me), 3.45 (d, *J* = 7.5, 2H, CH_2Ar), 4.0 (q, *J* = 7.5, 4H, 2×CH_2), 4.05 (s, 2H, CH_2OH), 5.5 (t, *J* = 7.5, 1H, =CH), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.05 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{15}H_{22}O_3$.

*(E)-4-(2-Ethoxy-6-methoxyphenyl)-2-methylbut-2-en-1-ol (**6f**)*

Eluent: hexane-ethyl acetate 5:2; thick oil; yield 60%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.4 (t, *J* = 7.5, 3H, Me), 1.5 (brs, 1H, OH), 1.85 (s, 3H, Me), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 3H, OMe), 4.0 (m, 4H, 2×CH_2), 5.5 (t, *J* = 7.5, 1H, =CH), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.05 (t, *J* = 7.5, 1H, 4-H).– Anal. $C_{14}H_{20}O_3$.

*(E)-4-(2,6-Dimethoxy-4-methylphenyl)-2-methylbut-2-en-1-ol (**6g**)*

Eluent: hexane-ethyl acetate 5:2; thick oil; yield 30%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.5 (s, 1H, OH), 1.8 (s, 1H, Me), 2.35 (s, 3H, Me), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 4.0 (s, 2H, CH_2OH), 5.45 (t, *J* = 7.5, 1H, =CH), 6.4 (s, 2H, 3-,5-H, aromat.).– Anal. $C_{14}H_{20}O_3$.

*(E)-4-(2,6-Dimethoxy-4-propylphenyl)-2-methylbut-2-en-1-ol (**6h**)*

Eluent: hexane-acetone 4:1; colourless oil; yield 50%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.9 (t, *J* = 7.5, 3H, Me), 1.3 (brs, 1H, OH), 1.6 (m, 2H, CH_2), 1.8 (s, 3H, Me), 2.55 (t, *J* = 7.5, 2H, CH_2), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.75 (s, 6H, 2×OMe), 3.95 (s, 2H, CH_2OH), 5.5 (t, *J* = 7.5, 1H, =CH), 6.4 (s, 2H, 3-,5-H, aromat.).– Anal. $C_{16}H_{24}O_3$.

*(E)-2-Ethyl-4-(2,6-dimethoxyphenyl)but-2-en-1-ol (**6i**)*

Eluent: hexane-acetone 5:2; thick oil; yield 46%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.05 (t, *J* = 7.5, 3H, Me), 1.6 (brs, 1H, OH), 2.3 (q, *J* = 7.5, 2H, CH_2), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.75 (s, 6H, 2×OMe), 3.95 (s, 2H, CH_2OH), 5.45 (t, *J* = 7.5, 1H, =CH), 6.55 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 4.15 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{14}H_{20}O_3$.

*(E)-4-(2,6-Dimethoxyphenyl)-2-propylbut-2-en-1-ol (**6j**)*

Eluent: hexane-acetone 5:2; thick oil; yield 75%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.95 (t, *J* = 7.5, 3H, Me), 1.4 (brs, 1H, OH), 2.2 (m, 2H, CH_2), 2.2 (t, *J* = 7.5, 2H, CH_2), 3.45 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 6H, 2×OMe), 3.95 (s, 2H, CH_2OH), 5.5 (t, *J* = 7.5, 1H, =CH), 6.6 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, 1H, 4-H, aromat.).– Anal. $C_{15}H_{22}O_3$.

General Method for the Photoisomerization of **8a** *and* **6a**

1.3 g of Compound dissolved in 280 ml anhydrous benzene were placed into a quartz pot and irradiated with a mercury lamp (450 W) for 3 hours. The solvent was evaporated in vacuo and the residue was chromatographed several times on silica gel column using hexane-methyl ethyl ketone 20:1 and toluene-methyl ethyl ketone 40:1 as eluent.

*(Z)-Ethyl 4-(2,6-dimethoxyphenyl)-2-methylcrotonate (**9**)*

Colourless oil; yield 13%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.35 (t, *J* = 7.5, 3H, Me), 1.9 (s, 3H, Me), 3.85 (s, 6H, 2×OMe), 3.9 (d, *J* = 7.0, 2H, CH_2Ar), 4.3 (q, *J* = 7.5, 2H, CH_2), 5.9 (t, *J* = 7.0, 1H, =CH), 6.6 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).

*(E)-2-Ethoxycarbonyl-4-(2,6-dimethoxyphenyl)-2-methylbut-3-ene (**10**)*

Colourless oil; yield 11%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.2 (t, *J* = 6.0, 3H, Me), 1.3 (d, *J* = 6.0, 3H, Me), 3.1 (m, 1H, CH), 3.75 (s, 6H, 2×OMe), 4.15 (q, *J* = 7.5, 2H, CH_2), 5.9 (t, 1H, *J* = 10.0, H-α), 6.3 (d, 1H, *J* = 10.0, H-β), 6.6 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.3 (t, *J* = 7.5, 1H, 4-H, aromat.).

*(Z)-2-Ethoxycarbonyl-4-(2,6-dimethoxyphenyl)-2-methylbut-3-ene (**11**)*

Colourless oil ; yield 3.5%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.25 (t, *J* = 7.5, 3H, Me), 1.4 (d, 3H, Me), 3.25 (q, *J* = 7.5, 1H, CH), 3.85 (s, 6H, 2×OMe), 4.15 (q, *J* = 7.5, 2H, CH_2), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 6.55 (d, 2H, 3-,5-H, aromat.), 6.7 (d, 1H, *J* = 1.5, H-α), 6.75 (d, 1H, *J* = 1.5, H-β), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).

*(Z)-4-(2,6-Dimethoxyphenyl)-2-methylbut-2-en-1-ol (**12**)*

Prepared from **9** as described for **6b**. Eluent: hexane-acetone 5:1; colourless oil; yield 23%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 1.95 (s, 1H, OH), 3.45 (d, *J* = 7.5, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 4.25 (s, 2H, CH_2OH), 5.4 (t, *J* = 7.5, 1H, =CH), 6.55 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).

*(E)-4-(2,6-Dimethoxyphenyl)-2-methylbut-3-en-1-ol (**13**)*

Prepared from **10** as described for **6b**. Eluent: hexane-acetone 5:2; colourless oil; yield 65%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.9 (d, *J* = 7.5, 3H, Me), 2.0 (brs, 1H, OH), 3.3 (d, *J* = 8.0, 2H, OCH_2), 3.4 (m, 1H, CH), 3.75 (s, 6H, 2×OMe), 5.5 (t, *J* = 10.0, 1H, H-β), 6.2 (d, *J* = 10.0, 1H, H-α), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).

*2,4-[Bis(2,6-Dimethoxyphenyl)]but-2-ene-1-al (**14**)*

7a (1.04 g, 5.7 mmol), anhydrous ethanol (50 ml) and 1N $NaOC_2H_5$ (15 ml) were stirred at room temperature for 2 hours. The solvent was distilled off, the residue extracted with ethyl acetate, washed with water, dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography on silica gel, using hexane-ethyl acetate (5:1) as eluent, to give **14** as colourless prisms. Mp 133–134 °C; yield 56% (0.55 g).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 3.7 and 3.8 (s, 12H, 4×OMe), 6.55 and 6.7 (d, *J* = 7.5, 4H, 2×3-,5-H, aromat.), 6.95 (t, *J* = 7.5, 1H, =CH), 7.15 and 7.35 (t, *J* = 7.5, 2H, 2×4-H, aromat.), 9.6 (s, 1H, CHO). MS (m/e): 342 (75), 313 (100), 151 (95), 91 (80).– Anal. $C_{20}H_{22}O_5$.

*2,4-[Bis(2,6-Dimethoxyphenyl)]but-2-en-1-ol (**15**)*

Prepared from **14** as described for **6b**. Mp 138–140 °C; yield 80% (0.2 g).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.0 (brs, 1H, OH), 3.15 (d, *J* = 7.5, 2H, CH_2Ar), 3.65 and 3.75 (s, 12H, 4×OMe), 4.25 (s, 2H, CH_2O), 6.05 (t, *J* = 7.5, 1H, =CH), 6.45 and 6.65 (d, *J* = 7.5, 4H, 2×3-,5-H, aromat.), 7.05 and 7.2 (t, *J* = 7.5, 2H, 4-H, aromat.). MS (m/e): 344 (5), 327 (20), 313 (25), 151 (65), 91 (70).– Anal. $C_{20}H_{24}O_5$.

*2,4-[Bis(2,6-Dimethoxyphenyl)]butanal (**16**)*

The solution of **14** (0.3 g, 0.87 mmol) in glacial acetic acid (25 ml) was added to the suspension of 10% Pd/C catalyst (0.5 g) in glacial acetic acid (10 ml), previously saturated with hydrogen. The hydrogenation was continued for 20 hours using 50 ml of H_2. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel, using hexane-ethyl acetate (5:1) as eluent to give **16**. Yield 67% (0.23 g).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.8 and 2.5 (m, 4H, 2×CH_2), 3.7 and 3.75 (s, 12H, 4×OMe), 4.05 (dd, *J* = 6.0 and 4.0, 1H, CH), 6.45 and 6.55 (d, *J* = 7.5, 4H, 2×3-,5-H, aromat.), 7.1 and 7.2 (t, *J* = 7.5, 2H, 2×4-H, aromat.).– Anal. $C_{20}H_{24}O_5$.

*2,4-[Bis(2,6-Dimethoxyphenyl)]butanol (**17**)*

Prepared from **16** as described for **6b**. Mp 96–97 °C; yield 65% (0.15 g).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.8 and 2.5 (m, 4H, 2×CH_2), 2.0 (s, 1H, OH), 3.65 (d, *J* = 7.0, 2H, CH_2), 3.7 and 3.8 (s, 12H, 2×OMe), 3.95 (m, 1H, CH), 6.5 and 6.6 (d, *J* = 7.5, 4H, 2×3-,5-H, aromat.), 7.1 and 7.2 (t, *J* = 7.5, 2H, 2×4-H, aromat.).– Anal. $C_{20}H_{26}O_5$.

*7-Allyloxychroman (**19**)*

To a stirred solution of **18** (10 g, 66.6 mmol) in anhydrous dimethylformamide (130 ml), NaH (3.4 g) was added under N_2 atmosphere and at 0 °C. After 15 min allylbromide (10.5 ml) in anh. DMF (15 ml) was added dropwise, during 30 min. The reaction mixture was stirred at 0 °C 2 hours, then was diluted with water, extracted with ethyl ether, washed with 10% solution of NaOH, with water, dried over $MgSO_4$, evaporated and purified by column chromatography using toluene as eluent to afford **19** as colourless

oil, 12.2 g (72%).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.0 (m, 2H, 3-CH_2), 2.7 (t, *J* = 7.5, 2H, 4-CH_2), 4.1 (t, *J* = 7.0, 2H, 2-CH_2O), 4.5 (d, *J* = 6.0, 2H, CH_2-O), 5.35 (m, 2H, CH_2=), 6.0 (m, 1H, =CH), 6.4 (m, 2H, 6,8-H, aromat.), 6.9 (d, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{12}H_{14}O_2$.

*8-Allyl-7-hydroxychroman (***20***)*

7-Allyloxychroman **19** (6 g, 0.031 mol) in xylene (110 ml) was heated in a closed tube at 200 °C for 20 hours. The solvent was evaporated in vacuo and the residue purified by flash chromatography on silica gel, toluene as eluent, to give **20** as colourless oil, 3.12 g (50%).– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.95 (m, 2H, 3-CH_2), 2.7 (t, *J* = 7.5, 2H, 4-CH_2), 3.4 (d, *J* = 6.5, 2H, CH_2-Ar), 4.15 (t, *J* = 6.0, 2H, 2-CH_2), 5.1 (m, 2H, CH_2=), 6.0 (m, 1H, =CH), 6.45 and 6.8 (d, *J* = 7.5, 2H, 5-,6-H, aromat.).– Anal. $C_{12}H_{14}O_2$.

*8-Allyl-7-Methoxymethoxychroman (***21a***)*

To a solution of **20** (1.66 g, 8.7 mmol) in abs. DMF (20 ml), NaH (0.8 g) was added under N_2 atmosphere and at 0 °C and stirred for 15 min. Then chloromethyl methyl ether (2 ml) in abs. DMF (5 ml) was added dropwise and the mixture stirred overnight at room temperature. Then the mixture was diluted with water, extracted with ethyl ether, washed with a solution of 10% NaOH, water, dried over $MgSO_4$ and evaporated to obtain an oil, (1.95 g, 95%), wich was sufficiently pure for further use.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.95 (m, 2H, 3-CH_2), 2.75 (t, *J* = 7.0, 2H, 4-CH_2), 3.4 (d, *J* = 7.0, 2H, CH_2Ar), 3.5 (s, 3H, OMe), 4.2 (d, *J* = 6.0, 2H, 2-CH_2), 5.0 (m, 2H, CH_2=), 5.15 (s, 2H, OC*H*$_2$O), 6.0 (m, 1H, =CH), 6.6 and 6.85 (d, *J* = 7.5, 2H, 5-,6-H, aromat.).– Anal. $C_{14}H_{18}O_3$.

*8-Allyl-7-Methoxychroman (***21b***)*

To the mixture of **20** (1.9 g, 0.01 mol), water (25 ml) and KOH (2.5 g, 0.044 mol) after stirring for 15 min at room temperature, dimethyl sulphate (3.5 ml, 0.037 mol) was added dropwise. The mixture was stirred 10 hours at room temperature, extracted with dichloromethane, washed with a solution of 10% KOH, water, dried over Na_2SO_4, evaporated to give on oil, (1.8 g, 90%), which was sufficiently pure for further use.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.95 (m, 2H, 3-CH_2), 2.7 (t, *J* = 7.0, 2H, 4-CH_2), 3.4 (d, *J* = 7.5, 2H, C*H*$_2$=), 3.8 (s, 3H, OMe), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 5.0 (m, 2H, CH_2=), 5.95 (m, 1H, =CH), 6.5 and 6.9 (d, 2H, 5-,6-H, aromat.).– Anal. $C_{13}H_{16}O_2$.

General Procedure for the Preparation of **22a**,**b**

To 27.4 mmol of allyl-derivatives **21a**,**b** in 356 ml dioxane, 5.6 mmol OsO_4 in 30 ml dioxane was added and the mixture was stirred in dark for 30 min at room temperature. Then $NaIO_4$ (0.065 mol) in 1070 ml water was added dropwise during 75 min. The mixture was diluted with water (200 ml), extracted with ethyl acetate, washed with a solution of 20% sodium thiosulphate, water and dried over $MgSO_4$. Evaporation of the solution gave an oil, which was purified by column chromatography using hexane-ethyl acetate 9:1 as eluent.

*(7-Methoxymethoxychroman-8-yl)acetaldehyde (***22a***)*

Colourless oil; yield 85%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.0 (m, 2H, 3-CH_2), 2.75 (t, *J* = 7.0, 2H, 4-CH_2), 3.4 (s, 3H, OMe), 3.7 (d, *J* = 5.0, 2H, CH_2Ar), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 5.15 (s, 2H, OCH_2O), 6.7 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.95 (d, *J* = 7.5, 1H, 5-H, aromat.), 9.65 (t, *J* = 1.0, 1H, CHO).– Anal. $C_{13}H_{16}O_4$.

*(7-Methoxychroman-8-yl)acetaldehyde (***22b***)*

Colourless oil; yield 90%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 2.0 (m, 2H, 3-CH_2), 2.75 (t, *J* = 7.0, 2H, 4-CH_2), 3.65 (d, *J* = 1.0, 2H, CH_2Ar), 3.8 (s, 3H, OMe), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 6.5 (d, *J* = 7.5, 1H, 6-H, aromat.), 7.0 (d, *J* = 7.5, 1H, 5-H, aromat.), 9.65 (t, *J* = 1.0, 1H, CHO).– Anal. $C_{12}H_{14}O_3$.

*(E)-Ethyl 4-(7-methoxymethoxychroman-8-yl)-2-methylcrotonate (***23a***)*

Prepared as described for **8a**–**g**. Eluent: hexane-acetone 10:1; oil; yield 70%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.3 (t, *J* = 7.5, 3H, Me), 1.95 (m, 2H, 3-CH_2), 2.0 (s, 3H, Me), 2.75 (t, *J* = 6.0, 2H, 4-CH_2), 3.45 (s, 3H, OMe), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 4.15 (m, 4H, 2-CH_2, OCH_2), 5.2 (s, 2H, OCH_2O), 6.6 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.75 (t, *J* = 7.5, 1H, CH=), 6.9 (d, 1H, 5-H, aromat.).– Anal. $C_{18}H_{24}O_5$.

*(E)-Ethyl 4-(7-methoxychroman-8-yl)-2-methylcrotonate (***23b***)*

Prepared as described for **8a**–**g**. Eluent: hexane-acetone 10:1; oil; yield 60%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.3 (t, *J* = 7.5, 3H, Me), 1.95 (m, 2H, 3-CH_2), 2.0 (s, 3H, Me), 2.75 (t, *J* = 6.0, 2H, 4-CH_2), 3.5 (d, *J* = 7.5, 2H, CH_2Ar), 3.8 (s, 2H, OMe), 4.2 (m, 4H, 2-CH_2, OCH_2), 6.45 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.75 (t, *J* = 7.5, 1H, CH=), 6.9 (d, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{17}H_{22}O_4$.

*(E)-4-(7-Methoxymethoxychroman-8-yl)-2-methylbut-2-en-1-ol (***24a***)*

Prepared as described for **6b**. Eluent: toluene-ethyl acetate 4:1; oil; yield 63%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 2.0 (m, 2H, 3-CH_2), 2.75 (t, *J* = 6.0, 2H, 4-CH_2), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.5 (s, 3H, OMe), 3.95 (s, 2H, CH_2-O), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 5.2 (s, 2H, OCH_2O), 5.5 (t, *J* = 7.5, 1H, =CH), 6.6 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.85 (d, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{16}H_{22}O_4$.

*(E)-4-(7-Methoxychroman-8-yl)-2-methylbut-2-en-1-ol (***24b***)*

Prepared as described for **6b**. Eluent: toluene-ethyl acetate 4:1; mp 56.5–57.5 °C; yield 65%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.5 (t, 1H, OH, deuterable), 1.85 (s, 3H, Me, 2.0 (m, 2H, 3-CH_2), 2.75 (t, *J* = 6.0, 2H, 4-CH_2), 3.35 (d, *J* = 7.5, 2H, CH_2Ar), 3.75 (s, 3H, OMe), 3.95 (s, 2H, CH_2-O), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 5.5 (t, *J* = 7.5, 1H, CH=), 6.45 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.9 (d, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{15}H_{20}O_3$.

*4-(7-Hydroxychroman-8-yl)-2-methylbut-2-en-1-ol (***24c***)*

24a (0.7 g, 2.5 mmol) in methanol (20 ml) was stirred with 1:1 HCl (1 ml) at room temperature for 16 hours. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel, toluene-ethyl acetate (4:1) as eluent, to give **24c** (0.35 g, 60%), mp 84–86 °C.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.85 (s, 3H, Me), 2.0 (m, 2H, 3-CH_2), 2.75 (t, *J* = 6.0, 2H, 4-CH_2), 3.4 (d, *J* = 7.5, 2H, CH_2Ar), 3.95 (s, 2H, CH_2O), 4.2 (t, *J* = 6.0, 2H, 2-CH_2), 5.3 (brs, 1H, OH), 5.5 (t, *J* = 7.5, 1H, =CH), 6.3 (d, *J* = 7.5, 1H, 6-H, aromat.), 6.75 (d, *J* = 7.5, 1H, 5-H, aromat.).– Anal. $C_{14}H_{18}O_3$.

Procedures for Preparation of **25**, **26**, **27a**,**b**,**c**

Reduction of **8a** to **25** as well as **24b**,**c** to **27a**,**b** was carried out as described at aldehyde **14**, using methanol instead of glacial acetic acid. Reduction of **25** to **26** was carried out with $LiAlH_4$ as described for **6b**.

*Ethyl 4-(2,6-dimethoxyphenyl)-2-methylbutyrate (***25***)*

Eluent: hexane-acetone 5:2; colourless oil; yield 85%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.2 (t, *J* = 7.5, 3H, Me), 1.3 (d, *J* = 6.0, 3H, Me), 1.6, 1.9 and 2.4 (m, 3H, CH, CH_2), 2.7 (t, *J* = 7.5, 2H, CH_2Ar), 3.75 (s, 6H, 2×OMe), 4.1 (q, *J* = 7.5, 2H, CH_2), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.15 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{15}H_{22}O_4$.

*4-(2,6-Dimethoxyphenyl)-2-methylbutanol (***26***)*

Eluent: hexane-acetone 5:2; colourless oil; yield 83%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.0 (d, *J* = 7.5, 3H, Me), 1.45, 1.65 and 2.75 (m, 5H, 1-CH_2, 2-CH, 3-CH_2), 1.9 (s, 1H, OH), 3.5 (m, 2H, CH_2Ar), 3.85 (s, 6H, 2×OMe), 6.5 (d, *J* = 7.5, 2H, 3-,5-H, aromat.), 7.1 (t, *J* = 7.5, 1H, 4-H, aromat.).– Anal. $C_{13}H_{20}O_3$.

*4-(7-Methoxychroman-8-yl)-2-methylbutanol (***27a***)*

Eluent: hexane-acetone 5:2; colourless oil.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.98 (d, *J* = 5.0, 3H, Me), 1.39–2.10 (bm, 3H, CH_2-CH-), 2.75 (m, 4H, 4-CH_2 and ArCH_2), 3.61 (t, *J* = 4.0, CH_2OH), 3.85 (s, 3H, OMe), 4.18 (t, *J* = 5.0, 2H, 2-CH_2), 4.85 (s, 1H, OH), 6.45 (d, *J* = 6.0, 1H, 6-H, aromat.), 6.87 (d, *J* = 6.0, 1H, 5-H, aromat.).– Anal. $C_{15}H_{22}O_3$.

*8-(3-Hydroxymethylbutyl)chroman-7-ol (***27b***)*

Eluent: toluene-acetone 3:1; colourless oil; yield 22%.– ^{1}H-NMR ($CDCl_3$): δ (ppm) = 0.98 (d, *J* = 5.0, 3H, Me), 1.39–2.10 (bm, 3H, CH_2-CH-), 2.75 (m, 4H, 4-CH_2 and ArCH_2), 3.61 (t, *J* = 4.0, CH_2OH), 4.18 (t, *J* = 5.0, 2H, 2-CH_2), 4.85 (s, 1H, OH), 6.45 (d, *J* = 6.0, 1H, 6-H, aromat.), 6.87 (d, *J* = 6.0, 1H, 5-H, aromat.).– Anal. $C_{14}H_{20}O_3$.

Determination of TNF-α Production in the Plasma

Male BALB/c mice (20–25g) were purchased from Charles River Laboratories (Budapest) and kept in individual cages in the air conditioned room (22–24 °C) of the Animal Department at least for 7 days for adaptation before use. Animals received food and water *ad libitum*, and lightening was maintained on a 12 h cycle.

On the day of the experiment animals were injected intraperitoneally (i.p.) with the tested compounds in a volume of 0.1 ml/10g body weight, while control animals received the same amount of physiological saline completed with the solvent of the drug.

60 minutes later they were primed with 5 mg/kg LPS (055:B5 Sigma). Ninety minutes after LPS induction animals were humanly killed and their blood was collected in ice-cooled Eppendorf tubes containing heparin. After centrifugation the plasma was stored at –70 °C until assayed.

Plasma TNF-α levels were determined using solid-phase enzyme immunoassay (ELISA), employing the multiple Ab sandwich principle that specifically detects mouse TNF-α (Genzyme Cambridge MA). Absorbency was read by Bio-Rad Microplate Reader Model 450 and calculated as concentration (pg/ml) using standard curve by Microplate Manager/PC Data Analysis Software. Statistical analysis of the data were performed by one- or two-way analysis of variance. Comparison between groups were made by use of Dunett or Student's unpaired t test; *p* values less than 0.05 were considered to be statistically significant.

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