2,5,6,7,8-Pentasubstituted (*S*)- and (*R*)-[2-chroman-2-yl]ethanols as intermediates for the synthesis of α-tocopherol and its chiral analogs

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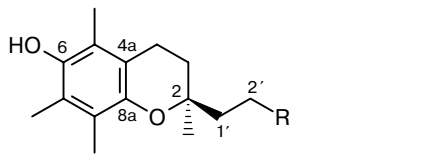
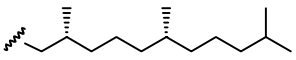
In the presence of lipase from the yeast *Candida cylindracea*, partial acetylation of (±)-2-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanol with vinyl acetate gives *S*-(+)-acetate whose alkaline hydrolysis affords (*S*)-(−)-alcohol. Repeated enzymatic acetylation of the "residual" alcohol up to ~39% conversion afforded the *R*-enantiomer. The enantiomeric alcohols were oxidized to (*S*)- or (*R*)-aldehydes having the same sign of $[\alpha]_D$ as the original alcohols. These alcohols were converted into *S*-(+)- and *R*-(−)-enantiomers of the antioxidant MDL-73404, a hydrophilic analog of α-tocopherol.

Key words: (*S*)- and (*R*)-2-[6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanols; (*S*)- and (*R*)-[6-benzyloxy-2,5,7,8-tetramehylchroman-2-yl]acetaldehydes; (*S*)-2-[6-hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethanol; lipase from *Candida cylindracea*, enantioselective acylation; 2-{[6-hydroxy-2,5,7,8-tetramethylcroman-2-yl]ethy}trimethylammonium *p*-toluenesulfonate, *S*- and *R*-enantiomers.

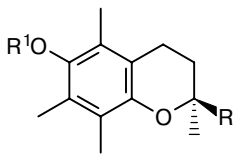
Natural α-tocopherol ((2*R*,4′*R*,8′*R*)-6-hydroxy-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman, (*R*)-**1**) is an important inhibitor of lipid peroxidation *in vivo* and a powerful cytoprotector.[1,2] Although the activity of (*R*)-**1** is only ~1.4 times as high as that of synthetic vitamin E (a racemic mixture of all stereoisomers possible for this structure), the understanding of the importance of this lipophilic vitamin as a therapeutic and preventive drug and a food additive, which has grown rapidly during the last three decades, has led to intensive search for industrially viable methods of the total synthesis of enantiopure α-tocopherol (for reviews, see Refs 3 and 4). In particular, many effective and/or elegant pathways to chroman derivatives of the type **2** containing a functionalized substituent at C(2) appropriate for construction of side chains of α-tocopherol and related compounds have been developed.[3—11] (*S*)-(6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl)acetaldehyde ((*S*)-**3**),[10,12] 2-(*S*)-2-[6-hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((*S*)-**4**),[10,13] and (*S*)-2-[6-ben-



(*R*)-**1:** R =



(*S*)-**10:** R = $[N^+Me_3]TsO^-$



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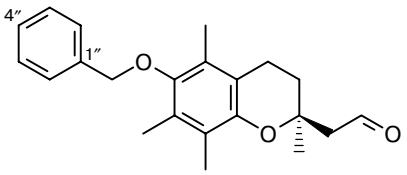
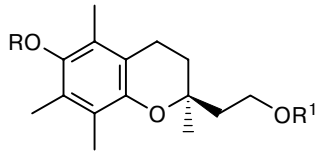
2: R = CHO, Cl, OMe, CH_2CO_2H, CH_2CH_2OTs, *etc.*
R^1 = H, Ac, H_2NCOCO, *etc.*



(*S*)-**3**



(*S*)-**4**, (*S*)-**5**, (*S*)-**6**, (*S*)-**7**

(*S*)-**4:** R = H, R^1 = H
(*S*)-**5:** R = H, R^1 = Ac
(*S*)-**6:** R = Bn, R^1 = H
(*S*)-**7:** R = Bn, R^1 = Ac

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Table 1. Acylation of alcohol (±)-**6** with vinyl acetate in the presence of lipase from the yeast *Candida cylindracea* (CCL)

Run	*T*/°C	(±)-**6** : CCL ratio, (w/w)	*C* (%)[a]	(+)-**7**		(+)-**6**	
				Yield (%)	$[\alpha]_D$ ($CHCl_3$)	Yield[b] (%)	$[\alpha]_D$ ($CHCl_3$)
1	22±2	1 : 1	50—52	50	+5.9	43.5	+4.4
2	22±2	2 : 1	~32	32	+6.8	66.5	Not determined
3	4±1	1 : 1	≥ 32	31	+18.5	65.4	Not determined
4	4±1	1 : 1	≥ 47.5	47.5	+17.1	49.7	+16.2
5	4±1	1 : 1	≥ 50.5	50.5	+16.3	44.8	+16.4

[a] Determined from the chemical yield of isolated pure (TLC, ^{1}H NMR) acetate (+)-**7**.
[b] Recovery of the pure scalemic alcohol.

zyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((*S*)-**6**)[14] are among the most promising intermediates for the synthesis of (*R*)-**1** and its biologically active analogs.

Homochiral intermediates (S)-**3**, (S)-**4**, and (S)-**6** were first synthesized from the corresponding (*S*)-acid (**2**, R = CH_2CO_2H, R^1 = H), which in turn was obtained from the corresponding racemate by classical resolution of diastereomeric salts.[12] A rational alternative to this approach is the synthesis of racemic phenolic alcohol **4** ((±)-**4**) and its kinetic resolution into enantiomers using lipases, because simple methods are known[9,10] for the conversion of the "wrong" enantiomer (*R*)-**4** into (*S*)-**4**. Compound (±)-**4** is easily obtained by C-alkylation of trimethylhydroquinone (**8**) with 4-methyl-5,6-dihydro-2*H*-pyran (**9**),[15] which is a side product in the production of isoprene by the Prins reaction.[16] Phenol (±)-**4** has already been used for the synthesis of the racemic antioxidant MDL-73404, which displays cardioprotective activity,[17] and later, for the synthesis of an optically active form of MDL-73404, to which the *S*-configuration at C(2) was assigned ((*S*)-**10**).[10]

Results and Discussion

We have developed a chemo-enzymatic synthesis of aldehyde (*S*)-**3** from compounds **8** and **9** using the most readily available microbial lipase, the lipase from the yeast *Candida cylindracea* (CCL). It had been shown previously[18] that (±)-3,7-dimethyloctanol and (±)-7-methoxy-3,7-dimethyloctanol where, alike with alcohol **6**, the reaction center and asymmetric center are separated by two methylene groups, can be converted, on treatment with vinyl acetate in the presence of CCL, into the corresponding (*S*)-acetates and "residual" (*R*)-alcohols with high enantioselectivity (*ee* 92—98%) and good yields. This served as the basis for the present study.

***Chemo-enzymatic synthesis of enantiomeric chirons* 6 *and* 3.** The reaction of dihydropyran **9** with trimethylhydroquinone **8** in the presence of $AlCl_3$ [15] gave compound (±)-**4**, the phenolic hydroxyl of which was selectively protected by benzylation ($PhCH_2Cl$ in the K_2CO_3 (solid)/DMF system). The resulting compound (±)-**6** was acylated with vinyl acetate in Et_2O in the presence of CCL (no reaction occurs in acetone at 0 or 22 °C, Scheme 1), and the reaction products were separated by column chromatography (Table 1). No products other than (+)-acetate and the "residual" (+)-alcohol were detected.

At both 22±2° and 4±1 °C, dextrorotatory acetate and dextrorotatory "residual" alcohol were obtained. Judging by the sign and the magnitude of $[\alpha]_D$ (for (*S*)-**6** and (*R*)-**6** the $[\alpha]_D^{25}$ values are −16.2 ($CHCl_3$) [12] and +15.7 ($CHCl_3$),[19] respectively), the latter was assumed to be alcohol (*R*)-**6**. Hence, *S*-configuration should be assigned to the isolated acetate (+)-**7**.

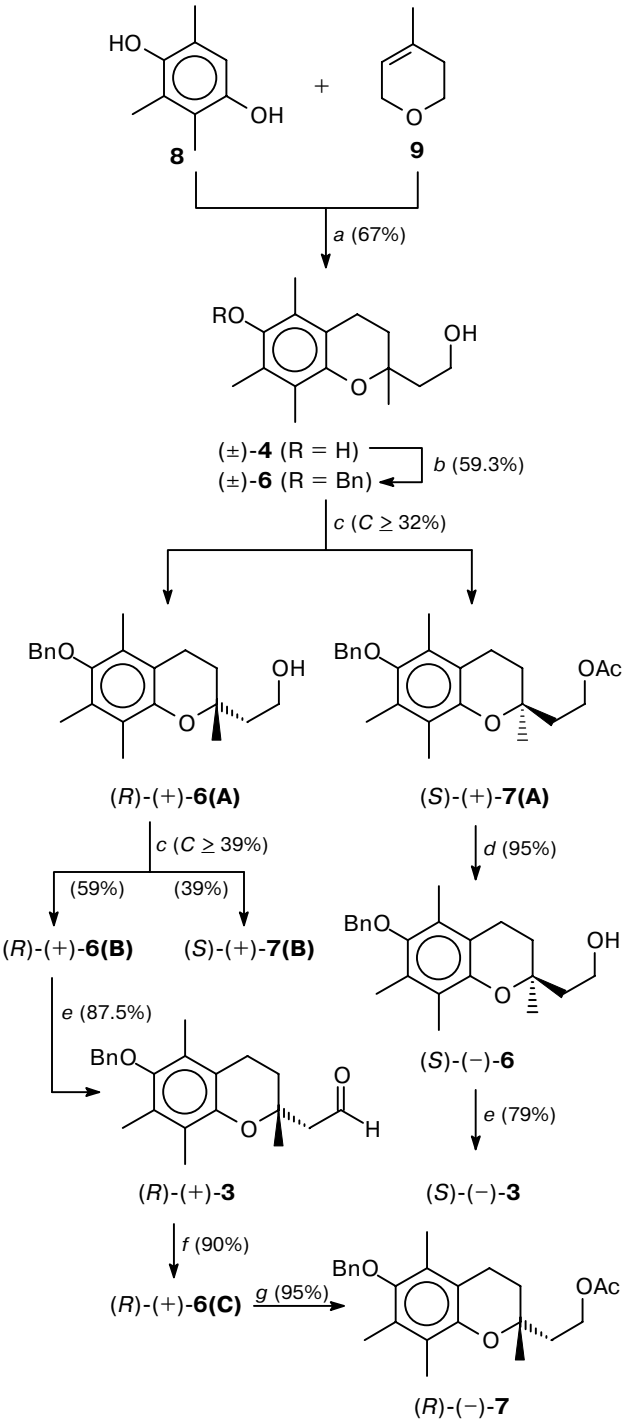
Enzymatic acylation of alcohol (±)-**6** at 4±1 °C up to the conversion $C \geq 32\%$ followed by chromatographic separation of the product mixture afforded acetate **7** with $[\alpha]_D^{22}$ +18.5 ($CHCl_3$) (specimen (*S*)-**7(A)**, Table 1, run *3*). Alkaline hydrolysis of this acetate (LiOH in aqueous MeOH) gave rise to alcohol (*S*)-**6** with $[\alpha]_D^{22}$ −17.1 ($CHCl_3$). The total yield of (*S*)-**6** over two steps was 30.4% based on (±)-**6**, or, in other words, 60.8% of its content in the racemate.

Upon oxidation with pyridinium chlorochromate, the resulting specimen of alcohol (*S*)-**6** was converted into aldehyde (*S*)-**3** with $[\alpha]_D^{22}$ −15.1 ($CHCl_3$). Although this configuration has previously been assigned[12] to an aldehyde with $[\alpha]_D^{22}$ +15.16 or +16.2 ($CHCl_3$), prepared by treating precursor **2** (R = CH_2CO_2Me, R′ = Bn)* with Bu^i_2AlH, the above transformations suggest that dextrorotatory acetate **7** has most probably *S* configuration.

The scalemic alcohol fraction isolated upon enzymatic acylation of (±)-**6** at 4±1 °C (specimen (*R*)-**6(A)**, run *3*) was purified from unconsumed alcohol (*S*)-**6** by repeated enzymatic acylation under the same condi-

* Previously,[14] a specimen of (*R*)-**1** with the same characteristics (including $[\alpha]_D$) as natural α-tocopherol had been prepared from alcohol (*S*)-(−)-**6** by a reliable route; therefore, the true configuration at C(2) in the chroman fragment in both compounds is beyond doubt. However, aldehyde (+)-**3** was used only in the synthesis of α-tocotrienol,[12] whose identification with a specimen of natural origin was less certain due to the absence of reliable $[\alpha]_D$ values for this compound.

Scheme 1



Reagents and conditions:
a. $AlCl_3$/DCE, Δ; *b*. BnCl—K_2CO_3/DMF, ~20 °C;
c. H_2C=CHOAc—CCL (cat.)/Et_2O 3—5 °C, 10 h;
d. LiOH/MeOH—H_2O, ~20 °C; *e*. PCC/CH_2Cl_2, ~20 °C;
f. $NaBH_4$/MeOH; *g*. Ac_2O—DMAP/Py—Et_2O, ~20 °C.

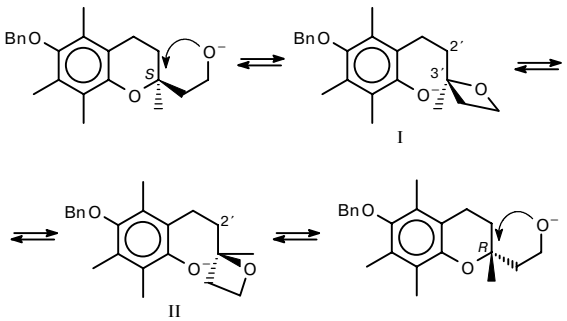
Note. The chemical yields for enzymatic reactions are given in weight percent relative to the introduced substrate ((±)-**4** for the first resolution and scalemic alcohol (*R*)-**4(A)** for the second one).

tions. The yield of the acetate fraction ((*S*)-**7(B)**) was 39% calculated in relation to alcohol (*R*)-**6(A)** and the yield (recovery) of the enantiomerically enriched alcohol (*R*)-**6(B)** with $[\alpha]_D^{22}$ +17.35 ($CHCl_3$) was 59%. The total yield of this alcohol (specimen (*R*)-**6(B)**) from (±)-**6** after two operations of enzymatic kinetic resolution was 38.5% (77% of the content of the *R*-enantiomer in the racemate).

Oxidation of alcohol (*R*)-**6(B)** with PCC smoothly resulted in the dextrorotatory aldehyde with $[\alpha]_D^{21}$ +16.0 ($CHCl_3$), whose ^1H and ^{13}C NMR spectra were the same as the spectrum of aldehyde (*S*)-**3** synthesized by us (see above). In order to exclude any probability of inversion of configuration at C(2) during oxidation of the alcohol, the dextrorotatory aldehyde ((*R*)-**3,** by its origin) was reduced by $NaBH_4$. The resulting alcohol (*R*)-**6** (specimen **C**) had $[\alpha]_D^{21}$ +16.0 ($CHCl_3$).* Obviously, neither inversion at C(2), nor considerable loss of *ee* took place in the oxidation of (*R*)-**6**. Standard acetylation of specimen (*R*)-**6(C)** furnished acetate (*R*)-**7** with $[\alpha]_D^{22}$ −15.5 ($CHCl_3$).

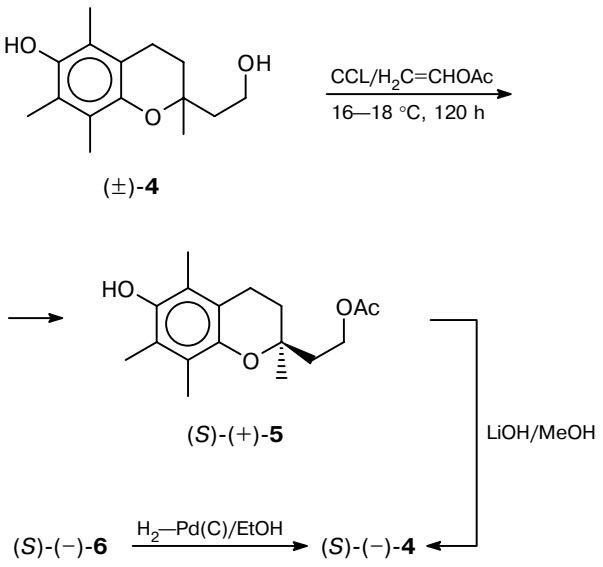
These correlations between enantiomeric alcohols **6**, their acetates **7**, and aldehydes **3** showed that the acetylation of alcohols (*R*)-**6** and (*S*)-**6** is accompanied *by inversion of the sign of the specific rotation of the product.* An analogous effect has been observed previously in the replacement of the OH group of (*S*)-**6** by a more electronegative OTs group;[14] this might also be mani-

* Both in this case and in the case of alkaline hydrolysis of acetate (*S*)-**7** with LiOH in aqueous MeOH, the $[\alpha]_D$ for the resulting specimens of alcohol (*S*)-**6** was somewhat lower than it might be expected on the basis of $[\alpha]_D$ of the initial acetate. The $[\alpha]_D$ value of alcohol is also affected by the duration of the contact of (*S*)-**7** with the base. Alkaline hydrolysis of a specimen of (*S*)-**7** with $[\alpha]_D^{22}$ +18.5 carried out for 1 h gave a specimen of alcohol (*S*)-**6** with $[\alpha]_D^{22}$ −17.1, whereas a specimen of (*S*)-**7** with $[\alpha]_D$ +17.1 was converted into specimen (*S*)-**6** with $[\alpha]_D^{23}$ −16.85 after alkaline hydrolysis for 0.5 h; alkaline hydrolysis of (*S*)-**7** with $[\alpha]_D$ +16.3 for 1 h gave alcohol (*S*)-**6** with $[\alpha]_D$ −15.5. Although the deviation from proportionality for the $[\alpha]_D^{20}$ values of the initial acetate and the corresponding alcohol differ little from the standard error of measurements, the noted tendency may point to possible alkaline racemization at C(2) in chroman (*S*)-**6**. Its driving forces are probably the energy difference between the bicyclic alkoxide anion and delocalized phenoxide anion and the ease of formation and opening of the oxetane ring in rotamers **I** and **II** caused by spatial proximity.



fested to a minor extent in the transition from alcohol **6** to aldehyde **3**. The difference between molecular rotations of the acetate and the alcohol $\{\Delta[M]_D = [\alpha]_{D(ace)} \cdot MW_{ace}/100 - [\alpha]_{D(alc)} \cdot MW_{alc}/100\}$ is 126.8° in the (*S*)-series and −114.8° in the (*R*)-series, *i.e.*, the average $|\Delta[M]_D|$ value is ~120°. So great $|\Delta[M]_D|$ values are usually found in molecules with heteroatoms at the asymmetric C-atom.[20]

Enzymatic acylation of phenol (±)-**4** with vinyl acetate in Et_2O at 4 °C occurs slowly, unlike that of alcohol (±)-**6**. The only reaction product obtained at 16—18 °C (yield 17%) had an $[\alpha]_D$ of +17.2 ($CHCl_3$) and was identified as (*S*)-**5** based on ^1H and ^{13}C NMR spectra. The alkaline hydrolysis of (*S*)-**5** yielded levorotatory alcohol (*S*)-**4**, which was identical with phenol (±)-**4** as regards the NMR and UV spectra and TLC data, while the sign of $[\alpha]_D$ was the same as that of a specimen of (*S*)-**4** synthesized from (*R*)-mevalonolactone[13] and with that of the product of hydrogenolytic debenzylation of alcohol (*S*)-**6** prepared in this study.* This confirmed the correctness of the configuration assigned to levorotatory phenol (*S*)-**4**. Since the synthesis of chiron (*S*)-**5** using this method was ineffective, we did not investigate the synthetic application of (*S*)-**5**.



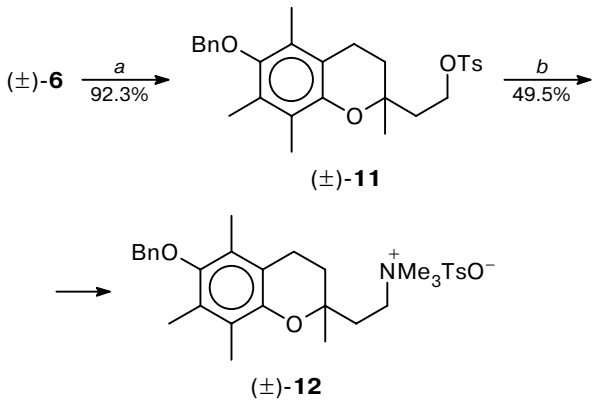
In a previous study,[10] the acylation of (±)-**4** in the presence of lipase from *Pseudomonas* sp. up to a ~64% conversion gave the dextrorotatory "residual" alcohol, which was assumed to have the *S* configuration. This assignment was based on the conversion of the alcohol (after 6-*O*-benzylation and oxidation) into aldehyde with $[\alpha]_D^{25}$ +16.2 ($CHCl_3$). It has been taken for granted[12] that this aldehyde was (*S*)-**3**. However, as follows from our work, this is most likely (*R*)-**3.***

Synthesis of both enantiomers of the antioxidant MDL-73404. Both enantiomers of (±)-**10** were synthesized from chirons (*R*)-**6** and (*S*)-**6**, prepared by a single acylation of alcohol (±)-**6** to a conversion of ≥ 50.5% (see Table 1, run *5*). The starting alcohol (*S*)-**6** used in this synthesis had $[\alpha]_D^{23}$ −15.5 ($CHCl_3$).

At the beginning, the synthesis was performed in four steps by analogy with the route described previously[17] for the transformation of synthon (±)-**4** into (±)-**10**. The overall yield of (*R*)-{2-[6-hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate (*R*)-**10** from (*R*)-**6** was only 8%, because of the low yield of (*R*)-2,5,7,8-tetramethyl-2-(2-bromoethyl)chroman in the first step of the synthesis, *i.e.*, in the reaction of alcohol (*R*)-**6** with $Ph_3P \cdot Br_2$, which yielded benzyl bromide as the major product. Similar transformations of alcohol (*S*)-**6** gave salt (*S*)-(+)-**10** in an overall yield of 6.5%.

The synthesis comprising the conversion of alcohols (*R*)-**6** or (*S*)-**6** into the corresponding toluenesulfonates ((*R*)-**11**, (*S*)-**11**) and their reaction with trimethylamine appeared to be more efficient. Indeed, the modeling of this route using (±)-**6** gave racemic (±)-**12** in an overall yield of 40.6% (Scheme 2). However, a combination of the two above approaches proved to be the method of choice for the synthesis of MDL-73404 enantiomers.

Scheme 2



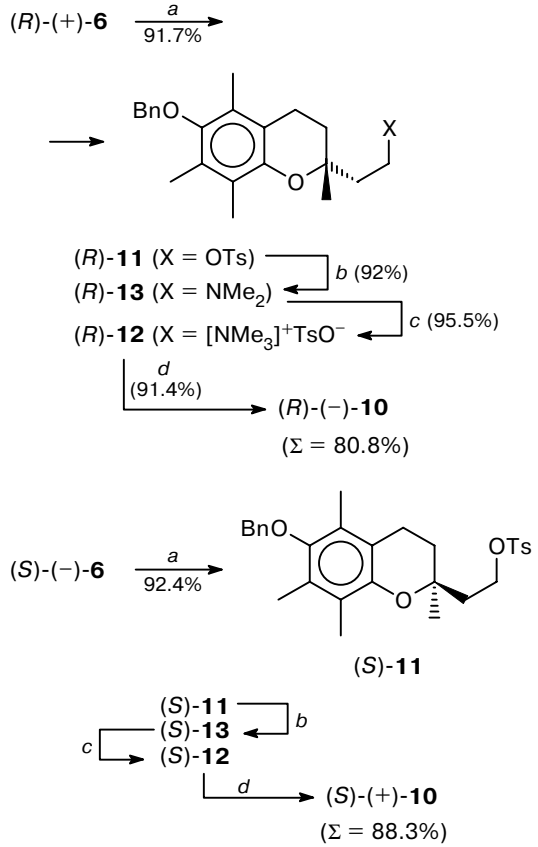
Reagents and conditions:
a. TsCl/Py, 8—10 °C, 48 h;
b. NMe_3 (10 equiv.)/DMF, 20 °C, 48 h.

* The specimen of (*S*)-**4** obtained by a stereocontrolled route from (*R*)-mevalonic acid had $[\alpha]_D^{27}$ −4.06 (MeOH)[13]. Alcohol (*S*)-**4** that we prepared by alkaline hydrolysis of monoacetate (*S*)-(+)-**5** had $[\alpha]_D^{20}$ −10.4 (*c* 0.3, MeOH).

* Paradoxically, the reference compounds (*S*)-(+)-**3** [12] and (*S*)-(−)-**6** [14] were first synthesized from a common chiral precursor (**2**, R = CH_2CO_2H, R′ = H) by pathways that rule out, in all probability, the inversion at C(2) in the chroman nucleus. However, to the best of our knowledge, to the exclusion of one ambiguous work,[10] direct oxidation of (*S*)-(−)-**6** [14] or (*R*)-(+)-**6** [19] to aldehydes has not been reported.

Tosylation of alcohol (*R*)-**6**, the subsequent reaction of *p*-toluenesulfonate (*R*)-**11** with Me_2NH in DMF, and quaternization of the resulting amine (*R*)-**13** by methyl *p*-toluenesulfonate proceeded with more than >90% yields to produce the *O*-benzyl derivative of (*R*)-**10** ((*R*)-**12**). Hydrogenolysis of (*R*)-**12** yielded crystalline salt (*R*)-**10**, $[\alpha]_D^{23}$ −5.23 (MeOH), in an overall yield of 80.8% (Scheme 3).

Scheme 3



Reagents and conditions: *a*. TsCl/Py, 8—10 °C, 48 h; *b*. $HNMe_2$ (10 equiv.)/DMF, 20 °C, 24 h; *c*. TsOMe/DMF, 20 °C, 24 h; *d*. H_2—Pd(C)/EtOH, ~20 °C.

The ^{1}H NMR spectroscopic data for (*R*)-**10** were in qualitative agreement with the data published for optically active[10] and racemic[17] compounds with structure **10**. The same route was used to transform alcohol (*S*)-**6** into crystalline salt (*S*)-**10**, $[\alpha]_D^{23}$ +5.25 (MeOH), in an overall yield of 88.3%.

Previously, the dextrorotatory enantiomer of MDL-73404 with $[\alpha]_D^{25}$ −5.8° (MeOH) has been prepared from the dextrorotatory enantiomer of alcohol **4** with *ee* 99% (data from enantioselective GLC).[10] Comparison of the $[\alpha]_D$ of our specimens of (*R*)-**10** and (*S*)-**10** with the above $[\alpha]_D$ shows that our (−)- and (+)-MDL-73404 specimens and, correspondingly, the initial alcohols (*R*)-**6** and (*S*)-**6** had *ee* of ~90%.

It is noteworthy that Mizuguchi and coworkers attributed the *S* configuration to the dextrorotatory enantiomer of phenol **4** {$[\alpha]_D^{23}$ +19.2 ($CHCl_3$) for *ee* >99%[10] or $[\alpha]_D^{26}$ +14.3 ($CHCl_3$) for *ee* 71%[9]}. The *S* configuration was also assigned to the levorotatory enantiomer of MDL-73404 prepared therefrom.[10] The chemical correlation of chirons (*S*)-**4** and (*S*)-**6** synthesized in the present work does not support this assignment.

* * *

The CCL-catalyzed acetylation of alcohols (±)-**6** and (*R*)-**6(A)** allows one to obtain enantiomeric 2-(6-benzyloxy-2,5,7,8-tetramethylchroman-2-yl)ethanols having *ee* of ~90%, *i.e.*, at the same level as in the case of previously synthesized specimens of (*S*)-**6** [14] and (*R*)-**6**.[19] The correlation of the signs of $[\alpha]_D$ to configurations of enantiomeric 2-(chroman-2-yl)ethanols, their acetates, and the corresponding aldehydes as well as the inversion of $[\alpha]_D$ upon the transitions of (*R*)-**6** to (*R*)-**10** and (*S*)-**6** to (*S*)-**10** attest to the necessity of careful approach to the determination of absolute configurations of this type of compounds. Preparation of both enantiomers of the antioxidant MDL-73404 is a prerequisite for the study of the dependence of their biological activities on the absolute configuration.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (operating at 300.13 and 75 MHz for ^{1}H and ^{13}C, respectively) using $CDCl_3$ as the solvent (unless stated otherwise). The UV spectra (λ/nm; ε) were recorded on a Specord UV-VIS instrument (Karl Zeiss) in EtOH. The $[\alpha]_D$ values were determined on a JASCO-DIP 360 polarimeter. Column chromatography was carried out using SiO_2 (Silica gel 60, Fluka) and TLC analysis was done with Silica gel/TLC cards (Fluka). The specific activity of the lipase from *Candida cylindracea* (CCL, Fluka) was 2.3—2.4 u mg^{-1}.

2-[(±)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((±)-4). Alkene **9** (706 mg, 7.2 mmol) was slowly added to a mixture of trimethylhydroquinone **8** (906 mg, 6 mmol) and anhydrous $AlCl_3$ (0.8 g, 6 mmol) in 6 mL of anhydrous 1,2-dichloroethane. The mixture was stirred under reflux for 15 min, cooled, poured into ice water, and allowed to stand in the cold for 12 h. The crystals that precipitated were filtered off and washed with cold Et_2O to give 1 g (67%) of alcohol (±)-**4**, m.p. 135—136 °C (from a CH_2Cl_2—hexane mixture). ^{1}H NMR (DMSO-d_6), δ: 1.10 (s, 3 H, 2-C$\underline{H}_3$); 1.55—1.75 (m, 4 H, C(3)H_2, C(1′)H_2); 1.91 (s, 3 H, Ar—C$\underline{H}_3$); 1.94 (s, 3 H, Ar—C$\underline{H}_3$); 1.98 (s, 3 H, Ar—C$\underline{H}_3$); 2.42 (t, 2 H, C(4)H_2, J = 6.3 Hz); 3.43—3.63 (m, 2 H, C(2′)H_2). ^{13}C NMR (DMSO-d_6), δ: 12.11, 12.18, 13.17 (3 Ar—$\underline{C}H_3$); 20.68 (C(4)); 24.48 (2-$\underline{C}H_3$); 32.15 (C(3)); 41.60 (C(1′)); 57.40 (C(2′)); 73.75 (C(2)); 117.30 (C(8a)); 120.97 (C(5)); 121.63 (C(8)); 123.23 (C(7)); 144.94 (C(4a)); 145.58 (C(6)). UV, λ_{max}/nm (ε): 225 (11000) and 287 (3100).

2-[(±)-6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((±)-6). Calcined K_2CO_3 (2.72 g, 19.7 mmol) and

benzyl chloride (2.6 mL, 20.6 mmol) were added to a solution of phenol (±)-**4** (1.86 g, 7.44 mmol) in 15.3 mL of anhydrous DMF. The reaction mixture was stirred for 36 h and poured into ice water, the products were extracted with EtOAc, the extract was washed with brine, dried ($MgSO_4$), concentrated, and chromatographed on a column (elution with Et_2O—hexane, 1 : 10) to give 1.5 g (59.3%) of alcohol (±)-**6**, m.p. 64—69 °C (from an Et_2O—hexane mixture). ^{1}H NMR, δ: 1.35 (s, 3 H, 2-C$\underline{H}_3$); 1.78—2.50 (m, 4 H, C(3)H_2 and C(1′)H_2); 2.14 (s, 3 H, Ar—C$\underline{H}_3$); 2.23 (s, 3 H, Ar—C$\underline{H}_3$); 2.27 (s, 3 H, Ar—C$\underline{H}_3$); 2.67 (t, 2 H, C(4)H_2, J = 7.1 Hz); 3.86—4.02 (m, 2 H, C(2′)H_2); 4.74 (s, 2 H, PhC$\underline{H}_2$O); 7.35—7.50 (m, 5 H, Ar—$\underline{H}$). ^{13}C NMR, δ: 11.89 (Ar—$\underline{C}H_3$); 11.95 (Ar—$\underline{C}H_3$); 12.79 (Ar—$\underline{C}H_3$); 20.36 (C(4)); 23.24 (2-$\underline{C}H_3$); 31.62 (C(3)); 41.91 (C(1′)); 58.98 (C(2′)); 74.63 (C(2)); 75.41 (Ph$\underline{C}H_2$O); 117.38 (C(8a)); 122.61 (C(8)); 126.18 (C(7)); 127.63 (C(2″)/C(6″)); 127.72 (C(4″)); 128.09 (C(5)); 128.35 (C(3″)/C(5″)); 137.74 (C(1″)); 147.10 (C(4a)); 148.52 (C(6)).

(*S*)-(+)-2-(2-Acetoxyethyl)-6-benzyloxy-2,5,7,8-tetramethylchroman ((*S*)-7). Freshly distilled vinyl acetate (85 μL, 0.92 mmol) and CCL powder (260 mg) were added to a solution of alcohol (±)-**6** (260 mg, 0.76 mmol) in 3 mL of anhydrous Et_2O. The reaction mixture was magnetically stirred in a sterilized two-neck flask at 4±1 °C, the course of the reaction was monitored by TLC (system I: benzene—EtOAc, 5 : 1). After 10 h, the reaction mixture was filtered through a porous glass filter No. 3, the precipitate was washed with anhydrous Et_2O, and the combined organic filtrate was concentrated at 40 °C (30 Torr). The residue (a mixture of the acetate with nonconsumed alcohol) was fractionated on a column with SiO_2 with an adsorbent : adsorbate ratio of 40 : 1 (w/w) using a benzene—EtOAc gradient (100 : 0 → 50 : 50) as the eluent to give pure acetate (*S*)-**7** (specimen **(7A)**) as a colorless solid with m.p. 55—59 °C, R_f 0.77 (system I) and $[\alpha]_D$ +18.5 (*c* 0.8, $CHCl_3$). Yield 93.5 mg (32%). Further elution gave 170 mg (65.4%) of a chromatographically pure fraction of the nonconsumed alcohol. No other products were detected by either TLC or ^{1}H NMR; the material balance of the reaction corresponded to a degree of conversion of about 31—33%.

On trituration with a drop of EtOH, acetate (*S*)-**7** was transformed into fine crystals with the same m.p. ^{1}H NMR, δ: 1.35 (s, 3 H, 2-CH_3); 1.85—1.95 (m, 4 H, C(3)H_2, C(1′)H_2); 2.08 (s, 3 H, $COCH_3$); 2.13 (s, 3 H, Ar—C$\underline{H}_3$); 2.18 (s, 3 H, Ar—C$\underline{H}_3$); 2.24 (s, 3 H, Ar—C$\underline{H}_3$); 2.65 (t, 2 H, C(4)H_2, J = 6.5 Hz); 4.32 (m, 2 H, C$\underline{H}_2$OAc); 4.75 (s, 2 H, PhC$\underline{H}_2$O); 7.40—7.55 (m, 5 H, Ar—$\underline{H}$). ^{13}C NMR (δ: 11.90 (Ar—$\underline{C}H_3$); 12.01 (Ar—$\underline{C}H_3$); 12.88 (CO$\underline{C}H_3$); 12.90 (Ar—$\underline{C}H_3$); 20.42 (C(4)); 24.81 (2-$\underline{C}H_3$); 31.95 (C(3)); 52.34 (C(1′)); 73.59 ($\underline{C}H_2$OAc); 74.73 (C(2)); 117.02 (C(8a)); 123.12 (C(8)); 126.21 (C(7)); 127.69 (C(2″)/C(6″)); 127.81 (C(4″)); 128.44 (C(5), C(3″)/C(5″)); 146.90 (C(4a)); 148.77 (C(6)); 201.75 ($\underline{C}OCH_3$). UV, λ_{max}/nm (ε): 230 (11400), 280 (2100), 287 (2350).

Acylation of alcohol (±)-**6** (0.5 g, 1.46 mmol) in Et_2O (10 mL) with vinyl acetate (2 mmol) at 4 °C over a period of 17 h gave products whose yields and $[\alpha]_D$ values are given in Table 1 (run *5*).

(*S*)-(−)-2-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((*S*)-6). A solution of acetate (*S*)-**7(A)** (93 mg, 0.24 mmol) in 1.2 mL of MeOH was added to a solution of LiOH (6.2 mg, 0.26 mmol) in 0.8 mL of water. The reaction mixture was stirred for 1 at 20 °C until the initial acetate completely disappeared (TLC monitoring, system I) and neutralized to pH 7.0 with glacial AcOH. The solvent was evaporated *in vacuo*, 1.5 mL of water was added to the viscous residue, and the emulsion was extracted with EtOAc (4×5 mL). The extract was dried (Na_2SO_4) and concentrated *in vacuo* (40 °C, 25 Torr), and the oily residue (86 mg) was chromatographed on a column with 12 g of SiO_2 in a benzene—EtOAc gradient. Elution with a benzene—EtOAc mixture (50 : 50) gave a pure (TLC, system I) colorless oil with R_f 0.36, which solidified on storage into a finely crystalline mass with m.p. 55—58 °C and $[\alpha]_D^{22}$ −17.1 (*c* 0.65, $CHCl_3$) (Ref. **14**: $[\alpha]_D$ −16.2 ($CHCl_3$)). Yield 79 mg (95% based on acetate (*S*)-**7(A)**, 30.4% based on the starting alcohol (±)-**6** and, correspondingly, 60.8% of the theoretical content in the racemate). The ^{1}H and ^{13}C NMR spectra of the resulting specimen of (*S*)-**6** were almost indistinguishable from the corresponding spectra of alcohol (±)-**6**.

Similar hydrolysis of a specimen of (*S*)-**7** with $[\alpha]_D^{23}$ +16.3 (*c* 0.4, $CHCl_3$) prepared in run *5* (Table 1) resulted in alcohol (*S*)-**6** with $[\alpha]_D^{23}$ −15.5 (*c* 0.4, $CHCl_3$), yield 96%.

(*R*)-(+)-2-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((*R*)-6). The alcohol fraction recovered from enzymatic acetylation of (±)-**6** at 4 °C (specimen (*R*)-**6(A)**, 170 mg, 0.5 mmol)) was dissolved in 2 mL of anhydrous Et_2O. Vinyl acetate (56 μL, 0.6 mmol) and CCL powder (170 mg) were added to the solution. The mixture was stirred for 10 h at 4 °C, the degree of conversion being monitored by TLC, and worked up as described for the synthesis of acetate (*S*)-**7**. Column chromatography on SiO_2 using a benzene—EtOAc gradient gave initially 74.6 mg (39% based on (*R*)-**6(A)**) of TLC-pure acetate (scalemic mixture of *S*- and *R*-enantiomers, specimen (*S*)-**7(B)**) and then pure "residual" alcohol (*R*)-**6(B)**, a colorless oil with R_f 0.36 (system I) and $[\alpha]_D^{22}$ +17.35 (*c* 0.7, $CHCl_3$), which gradually transformed into fine crystals with m.p. 52—55 °C; Ref. 19: m.p. 51—56 °C, $[\alpha]_D^{25}$ +15.68 ($CHCl_3$). The yield was 100 mg (59% based on (*R*)-**6(A)**, 38.5% based on the initial alcohol (±)-**6** and, correspondingly, 77% of the content in the racemate).

(*R*)-(+)-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]acetaldehyde ((*R*)-3). Alcohol (*R*)-**6(B)** (100 mg, 0.294 mmol) was added in one portion at 20 °C under argon to a vigorously stirred suspension of PCC (88.5 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was stirred for 2 h, then, without dilution with Et_2O, the supernatant was decanted from the black precipitate and filtered through a pad of SiO_2 (3×1.7 cm), which was washed with anhydrous CH_2Cl_2 (9 mL) and Et_2O (3×5 mL). The combined solutions were filtered and concentrated (40 °C (bath), 25 Torr) to give 90 mg of a TLC-homogeneous light-colored oil with R_f 0.78 (system I). Column chromatography on SiO_2 using a benzene—EtOAc gradient (10 : 0 → 8 : 2) gave aldehyde (*R*)-**3** as a colorless oil, which slowly solidified on storage to give an amorphous material, m.p. 76—81 °C and $[\alpha]_D^{21}$ +16.0 (*c* 0.9, $CHCl_3$). Yield 87 mg (87.5%). ^{1}H NMR, δ: 1.45 (s, 3 H, 2-CH_3); 1.90—2.0 (m, 2 H, C(3)H_2); 2.12 (s, 3 H, Ar—C$\underline{H}_3$); 2.20 (s, 3 H, Ar—C$\underline{H}_3$); 2.25 (s, 3 H, Ar—C$\underline{H}_3$); 2.55—2.80 (m, 4 H, C(4)H_2 and C(1′)H_2); 4.75 (s, 2 H, PhC$\underline{H}_2$O); 7.35—7.60 (m, 5 H, Ar—$\underline{H}$); 9.96 (t, 1 H, C$\underline{H}$=O, J = 1.5 Hz). ^{13}C NMR, δ: 11.90 (Ar—$\underline{C}H_3$); 12.01 (Ar—$\underline{C}H_3$); 12.90 (Ar—$\underline{C}H_3$)); 20.43 (C(4)); 24.81 (2-$\underline{C}H_3$); 31.95 (C(3)); 52.34 (C(1′)); 73.58 (C(2)); 74.73 (Ph$\underline{C}H_2$O); 117.02 (C(4a)); 123.11 (C(8)); 127.69 (C(7)); 127.83 (C(2″)/C(6″)); 128.45 (C(4″)); 128.09 (C(5)); 128.35 (C(3″)/C(5″)); 137.81 (C(1″)); 146.05 (C(8a)); 148.77 (C(6)); 201.78 ($\underline{C}$H=O). UV, λ_{max}/nm (ε): 230 (sh, 11200), 360 (sh, 890). The spectroscopic data and the characteristics of the resulting aldehyde (*R*)-**3** are similar to those reported for the dextrorotatory aldehyde having the same

structure (Ref. 12: m.p. 85—90 °C, $[\alpha]_D^{25}$ from +16.2 ($CHCl_3$) to +15.16 ($CHCl_3$) for the analytical specimen) but prepared by a different route.

(*S*)-(−)-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]acetaldehyde ((*S*)-3). Levorotatory aldehyde (*S*)-**3** was prepared from 50 mg of alcohol (*S*)-**6** using the above-described procedure as a finely crystalline white material with m.p. 70—80 °C and $[\alpha]_D^{25}$ −15.1 (*c* 0.65, $CHCl_3$). Yield 39.3 mg (79%). The spectroscopic data of (*S*)-**3** virtually coincided with those of the specimen of (*R*)-**3** described above.

(*R*)-(−)-2-(2-Acetoxyethyl)-6-benzyloxy-2,5,7,8-tetramethylchroman ((*R*)-7). A solution of aldehyde (*R*)-**3** (82 mg, 0.25 mmol) in 2 mL of MeOH was added at 0 °C to a solution of $NaBH_4$ (4.9 mg, 0.128 mmol) in 1.5 mL of MeOH chilled to 0 °C, and the reaction mixture was magnetically stirred for 1.5 h without further cooling until the initial (*R*)-**3** disappeared (TLC). Methanol was evaporated *in vacuo*, the residue was partitioned between 0.2 mL of water and 0.3 mL of Et_2O, and the aqueous layer was additionally extracted with ether (3×0.5 mL). The combined extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on a column with SiO_2 to isolate pure alcohol (*R*)-**6(C)** with R_f 0.36 and $[\alpha]_D^{20}$ +15.99 (*c* 0.6, $CHCl_3$). Yield 74.3 mg (90%). This specimen did not differ, judging by ^{1}H NMR spectra, from specimens (*R*)-**6(B)** and (*S*)-**6**; however, according to TLC data (system I), it contained traces of an impurity with a greater R_f.

Freshly distilled Ac_2O (29 μL 0.28 mmol), pyridine (23 μL, 0.28 mmol), and DMAP (3 mg) were added to a solution of alcohol (*R*)-**6(C)** (70 mg, 0.21 mmol) in 2.5 mL of anhydrous Et_2O. The reaction mixture was stirred for 2 h at ~20 °C, allowed to stand for 16 h, washed with saturated aqueous solutions of $CuSO_4$ and $NaHCO_3$ and with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue (oil, 76 mg) was chromatographed on a column with SiO_2 in a benzene—EtOAc gradient. Elution with benzene—EtOAc (9 : 1) gave TLC-pure (R_f 0.77) acetate (*R*)-**7** as a colorless oil, which slowly became a solid with m.p. 50—55 °C and $[\alpha]_D^{22}$ −15.33 (*c* 0.55, $CHCl_3$). Yield 74.3 mg (95%). The ^{1}H and ^{13}C NMR spectra of this compound virtually coincided with the spectra of acetate (*S*)-**7**.

(*S*)-(+)-2-(2-Acetoxyethyl)-6-hydroxy-2,5,7,8-tetramethylchroman ((*S*)-5). Vinyl acetate (36 μL, 0.4 mmol) and CCL powder (0.1 g) were added to a solution of phenol (±)-**4** (0.1 g, 0.294 mmol) in 2 mL of anhydrous Et_2O. The mixture was stirred at 16—18 °C, the degree of conversion being monitored by TLC. In a benzene—EtOAc mixture (5 : 2, system II), the starting (±)-**4** had R_f 0.36, and the only product had R_f 0.83. The product accumulated over the reaction time from 7 to 24 h, no changes being observed during the subsequent 96 h. The reaction mixture was worked-up as described in the synthesis of acetate (*S*)-**7**. Elution of the column with benzene—EtOAc (4 : 1) gave pure monoacetate (*S*)-**5** as a colorless oil, which slowly solidified into an amorphous mass with $[\alpha]_D^{21}$ +17.20 (*c* 0.18, $CHCl_3$). Yield 19.9 mg (17%). ^{1}H NMR, δ: 1.35 (s, 3 H, 2-CH_3); 1.80—2.02 (m, 4 H, C(3)H_2, C(1′)H_2); 2.07 (s, 3 H, Ar—C$\underline{H}_3$); 2.12 (s, 6 H, Ar—C$\underline{H}_3$, COCH_3); 2.18 (s, 3 H, Ar—C$\underline{H}_3$); 2.65 (t, 2 H, C(4)H_2 *J* = 6); 4.38 (m, 2 H, C$\underline{H}_2$OAc). ^{13}C NMR, δ: 11.04 (Ar—$\underline{C}H_3$); 11.35 (Ar—$\underline{C}H_3$); 11.86 (Ar—$\underline{C}H_3$); 11.90 (Ar—$\underline{C}H_3$); 12.28 (CO$\underline{C}H_3$); 20.63 (C(4)); 23.81 (2-$\underline{C}H_3$); 32.08 (C(3)); 37.86 (C(1′)); 60.98 ($\underline{C}H_2$OAc); 73.24 (C(2)); 118.67 (C(8a)); 121.35 (C(8)); 128.88 (C(7)); 144.94 (C(4a)); 145.05 (C(6)); 171.27 ($\underline{C}OCH_3$). UV, λ_{max}/nm (ε): 230 (10900), 280 (2010), 286 (2210).

Subsequent elution with benzene—EtOAc (1 : 1) and pure EtOAc resulted in the recovery of 75 mg of nonconsumed compound **4** (R_f 0.36 in system II) containing no visible impurities (TLC). The ^{1}H NMR spectrum practically coincided with that of (±)-**4**.

(*S*)-(−)-2-[6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethanol ((*S*)-4). ***A.*** A solution of LiOH (4 mg) in a mixture of 0.2 mL of water and 0.8 mL of MeOH was added at 20 °C to a solution of acetate (*S*)-**5** (17 mg) in 0.2 mL of MeOH. After 30 min, the reaction mixture was neutralized with glacial AcOH to pH 7.0. Subsequent work-up was the same as described for the synthesis of alcohol (*S*)-**6**. Column chromatography on SiO_2 in a benzene—EtOAc gradient gave compound (*S*)-**4** as a colorless oil with R_f 0.36 (system II) and $[\alpha]_D$ −10.4 (*c* 0.4, MeOH) or −14.1 (*c* 0.3, $CHCl_3$), *cf.* Ref. 13: $[\alpha]_D^{20}$ −4.06 (MeOH). On prolonged storage under argon, the oil turned into a solid with m.p. 126—131 °C (lit.: m.p. 137 **[13]** or 153 °C**[15]**). Yield 13.2 mg (90%). The ^{1}H NMR spectrum of alcohol (*S*)-**4** was virtually identical with that of (±)-**4**.

B. Hydrogenolysis of alcohol (*S*)-**6** (34 mg, 0.1 mmol) in 5 mL of EtOH over 5% Pd/C (50 mg) was carried out for 4 h. The catalyst was filtered off and washed with EtOH (2 mL), and the filtrates were combined and concentrated *in vacuo*. The residue was chromatographed twice on a column with SiO_2. Elution with benzene—EtOAc (1 : 1) gave 23 mg of compound (*S*)-**4** as a colorless oil with R_f 0.36 (system II) and $[\alpha]_D^{20}$ −10.9 (*c* 0.25, MeOH) or −16.4 (*c* 0.2, $CHCl_3$). The ^{1}H NMR spectrum of the product was identical with those of (±)-**4** and the above-mentioned specimen of (*S*)-**4**.

(*R*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-[2-tosyloxyethyl]chroman ((*R*)-11). Alcohol (*R*)-**6** (31.2 mg, 0.09 mmol) and TsCl (39 mg, 0.21 mmol) were dissolved in 0.3 mL of pyridine and the solution was allowed to stand for 48 h at 4 °C. The reaction mixture was worked up by a known procedure,**[14]** and the residue (45 mg) was chromatographed on a column with SiO_2. Elution with a benzene—EtOAc mixture (4 : 1) gave 42.5 mg (93%) of a chromatographically pure thick oil with R_f 0.73 (system I). ^{1}H NMR, δ: 1.25 (s, 3 H, 2-C$\underline{H}_3$); 1.81 (t, 2 H, C(3)H_2); 1.97, 2.15, 2.20 (all s, 3×3 H, Ar—C$\underline{H}_3$); 2.05 (m, 2 H, C(1′)H_2); 2.45 (s, 3 H, Ar—C$\underline{H}_3$); 2.57 (t, 2 H, C(4)H_2, *J* = 6.5 Hz); 4.30 (m, 2 H, C(2′)H_2); 4.71 (s, 2 H, ArOC$\underline{H}_2$Ph); 7.3—7.5 (m, 7 H, Ar—H); 7.78 (d, 2 H, *J* = 8 Hz, a part of an A_2B_2 system of toluenesulfonate).

(*S*)-6-Benzyloxy-2,5,7,8-tetramethyl-2-[2-tosyloxyethyl]-chroman ((*S*)-11) was prepared in the same way as toluenesulfonate (*S*)-**11** from 62.4 mg of alcohol (*S*)-**6** and 78 mg of TsCl. The yield of the toluenesulfonate characterized by R_f (0.73, system I) was 92.4%.

(*R*)-6-Benzyloxy-2-(2-dimethylaminoethyl)-2,5,7,8-tetramethylchroman ((*R*)-13). A flow of Me_2NH generated by treating a saturated aqueous solution of $[Me_2NH_2]Cl$ with KOH and dried successively with BaO and Na_2SO_4 was bubbled into a tared flask with anhydrous DMF (10 mL) at 5 °C When the weight gain reached 0.38 g, 1.0 mL (~37.5 mg of Me_2NH, 0.83 mmol) of the resulting solution was withdrawn, and *p*-toluenesulfonate (*R*)-**11** (41.2 mg, 0.083 mmol) in anhydrous DMF (0.2 mL) was added to the solution. The reaction mixture was kept at 4 °C for 48 h. Excess Me_2NH and the solvent were removed *in vacuo* (60 °C, 10 Torr), the poorly soluble residue was suspended in 1 mL of water, the suspension was acidified with HCl to pH 2, and the organic impurities were extracted with Et_2O (3×3 mL). The aqueous phase was brought to pH 11 at 10 °C by adding solid NaOH and extracted with Et_2O (5×3 mL). The extract was dried (Na_2SO_4)

and concentrated *in vacuo* to give amine (*R*)-**13** as a colorless oil. Yield 29 mg (92%). ^{1}H NMR, δ: 1.27 (s, 3 H, 2-C$\underline{H}_3$); 1.85 (m, 4 H, C(3)H$_2$, C(1′)H$_2$); 2.10, 2.17, 2.22 (all s, 3×3 H, Ar—C$\underline{H}_3$); 2.29 (s, 6 H, N(C$\underline{H}_3$)$_2$); 2.60 (m, 2 H, C(2′)H$_2$); 2.57 (m, 2 H, NCH$_2$); 2.61 (t, 2 H, C(4)H$_2$, J = 6.5 Hz); 4.70 (s, 2 H, OC$\underline{H}_2$Ph); 7.4—7.5 (m, 5 H, Ph).

(*S*)-6-Benzyloxy-2-(2-dimethylaminoethyl)-2,5,7,8-tetramethylchroman ((*S*)-13) was prepared in the same way as amine (*R*)-**13** from *p*-toluenesulfonate (*S*)-**11** (61.3 mg) and Me$_2$NH (55.8 mg) in DMF. Yield 43.5 mg (95.5 mg). The ^{1}H NMR spectrum coincided with that of (*R*)-**13**.

(*R*)-{2-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate ((*R*)-12). A mixture of amine (*R*)-**13** (28 mg, 0.076 mmol) and methyl *p*-toluenesulfonate (28.2 mg, 0.152 mmol) in 2.5 mL of freshly distilled DMF was allowed to stand for 24 h at 20—22 °C, DMF and the main portion of the methylating reagent were evaporated *in vacuo* (70 °C (bath), 3 Torr), the residue was triturated and washed with anhydrous Et$_2$O (5×3 mL) to remove traces of TsOMe. The white precipitate was crystallized from a MeCN—Et$_2$O mixture to give pure salt (*R*)-**12** with m.p. 218—220 °C (dec.). Yield 40.5 mg (96.5%). ^{1}H NMR, δ: 1.25 (s, 3 H); 1.80 (m, 2 H, C(3)H$_2$); 2.06—2.08 (coalescence of s, 3 H + m, 2 H, Ar—C$\underline{H}_3$, C(1′)H$_2$); 2.12 (s, 3 H); 2.18 (s, 3 H); 2.35 (s, 3 H, SO$_2$C$_6$H$_4$C$\underline{H}_3$); 2.60 (t, 2 H, C(4)H$_2$, J = 6.5 Hz); 3.32 (s, 9 H, N$^+$CH$_3$); 3.52 (m, 2 H, C(2′)H$_2$); 4.72 (s, 2 H, OC$\underline{H}_2$Ph); 7.12 (d, 2 H, J_{AB} = 8 Hz); 7.25—7.55 (m, 5 H, Ph); 7.73 (d, 2 H, J_{AB} = 8 Hz, —C$_6$H$_4$—).

(*S*)-{2-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate ((*S*)-12) was prepared in the same way as the *R*-enantiomer from amine (*S*)-**13** (43.5 mg, 0.188 mmol) and methyl toluenesulfonate (44 mg, 0.24 mmol) in 3 mL of DMF. Yield 64 mg (97.7%). M.p. 219—221 °C (MeCN—Et$_2$O, dec.). The ^{1}H NMR spectrum was identical with that described above. Found (%): C, 69.23; H, 7.92; S, 5.59. C$_{32}$H$_{43}$NO$_5$S. Calculated (%): C, 69.4; H, 7.8; S, 5.8.

(*R*)-{2-[6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate ((*R*)-10). Salt (*R*)-**12** (40.5 mg, 0.073 mmol) was dissolved in 3 mL of EtOH and subjected to hydrogenolysis over 5% Pd/C (60 mg) (22 °C, 750 Torr) for 5 h until visible absorption of H_2 ceased. The catalyst was filtered off and washed with EtOH, and the filtrates were concentrated *in vacuo* to give 31 mg (91.4%) of a white powder with m.p. 181—184 °C (dec.). recrystallization from MeCN—Et$_2$O (~4 : 1) gave crystals with m.p. 204—208 °C (dec.) and $[\alpha]_D^{23}$ −5.23 (*c* 0.21, MeOH), lit[10]: m.p. 205—208 °C, $[\alpha]_D^{23}$ −5.8 (MeOH). ^{1}H NMR (DMSO-d$_6$) δ: 1.20 (s, 3 H, 2-CH$_3$); 1.76 (m, 2 H, C(3)H$_2$); 2.00 (s, 3 H); 2.02 (signal overlap s, 3 H, and m, 2 H); 2.06 (s, 3 H); 2.35 (s, 3 H, SO$_2$C$_6$H$_4$C$\underline{H}_3$); 2.55 (m, 2 H, C(4)H$_2$); 2.70 (narr.s, 1 H, OH); 3.05 (s, 9 H, N$^+$CH$_3$); 3.45 (m, 2 H, C(2′)H$_2$); 7.12 and 7.45 (both d, 2 H, C$_6$H$_4$, J_{AB} = 8 Hz).

(*S*)-{2-[6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate ((*S*)-10) was prepared by hydrogenolysis of salt (*S*)-**12** (34 mg, 0.06 mmol) over 5% Pd/C (52 mg) in 4 mL of EtOH for 5 h. Recrystallization from MeCN—Et$_2$O gave crystals of (*S*)-**12** with m.p. 207—208 °C and $[\alpha]_D^{23}$ +5.25 (*c* 0.2, MeOH). Yield 27.1 mg (96%). Found (%): C, 64.63; H, 7.83. C$_{25}$H$_{37}$NO$_5$S. Calculated (%): C, 64.8; H, 8.0.

(±)-{2-[6-Benzyloxy-2,5,7,8-tetramethylchroman-2-yl]ethyl}trimethylammonium *p*-toluenesulfonate ((±)-12). *p*-Toluenesulfonate (±)-**11** was prepared by the reaction of alcohol (±)-**6** (2.17 g, 6.38 mmol) with TsCl (1.37 g, 7.15 mmol) in 20 mL of anhydrous Py (0—4 °C, 48 h). The usual work-up gave 2.32 g (74%) of *p*-toluenesulfonate (±)-**11** (oil), whose ^{1}H NMR and R_f coincided with those for (*R*)- and (*S*)-**11**.

A flow of trimethylamine generated by treatment of a saturated aqueous solution of [Me$_3$NH]Cl with KOH and dried by passing over BaO and Na$_2$SO$_4$ was bubbled into a tared flask with anhydrous DMF (10 mL) at 0—5 °C. When the weight gain reached 1.07 g, 1.0 mL (~106 mg Me$_3$N, ~1.8 mmol) of the resulting solution was withdrawn and *p*-toluenesulfonate (±)-**11** (110 mg, 0.83 mmol) in dry DMF (2 mL) was added to the solution. The mixture was kept at 4 °C for 44 h. Excess Me$_3$N and DMF were removed *in vacuo*, and the residue (colorless oil) was triturated and washed with anhydrous Et$_2$O (5×4 mL); concentration of the extract gave nonconsumed sulfonate (±)-**11** (51 mg, 0.41 mmol). On trituration with 2 or 3 drops of Et$_2$O, the reaction product (60 mg, 49.5%) turned into crystals with m.p. 205—208 °C (dec.). The ^{1}H NMR spectrum of salt (±)-**12** virtually coincided with the spectra of (*R*)-**12** and (*S*)-**12**.

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