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Determination of the Absolute Configuration of Optically Active 2,2-Dimethyl-3,4-epoxychromans Prepared by the Catalytic Enantioselective Epoxidation with the Dimethyldioxirane/Jacobsen Mn(III)salen System

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Abstract: Enantioselective epoxidation of 2,2-dimethyl-2*H*-chromenes **1a-d** by using Mn(III)salen complexes (*R,R*)-**3** and (*S,S*)-**3** as catalysts and dimethyldioxirane (DMD) as oxygen donor afforded optically active 2,2-dimethyl-3,4-epoxychromans **2a-d** in good yields and high enantioselectivities (up to 93% e.e.). The absolute configuration of the (*3S,4S*)-6,7-bis(tosyloxy)-2,2-dimethyl-3,4-epoxychroman (*3S,4S*)-**2d** has been determined by X-ray diffraction. The absolute configurations of the other nonracemic epoxychromans were assigned by circular dichroism (CD) measurements relative to the (*3S,4S*)-**2d** epoxide as reference compound.

INTRODUCTION

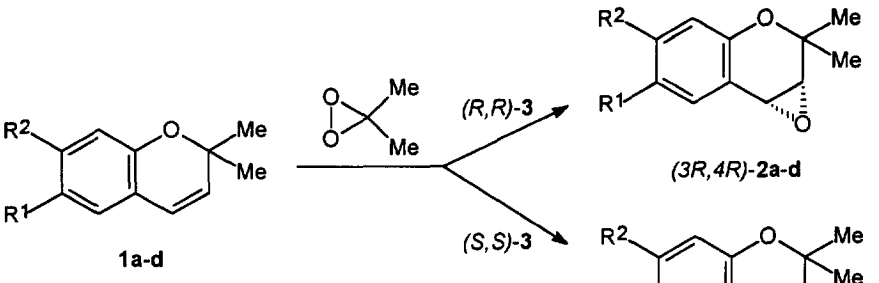
2,2-Dimethyl-3,4-epoxychromans are convenient and useful intermediates for the synthesis of chromakalim and related potassium channel openers.[1] Such labile epoxides were prepared by alkaline dehydrobromination of 3-bromo-2,2-dimethyl-4-hydroxychromans[1,2] and used for further chemical transformations without isolation. The first direct epoxidation of 2,2-dimethyl-2*H*-chromenes by dimethyldioxirane (DMD) at subambient temperature afforded racemic epoxides.[3] Since chromakalim-type drugs are enantiomerically pure substances, the availability of optically active intermediates is essential for their synthesis. The first enantioselective epoxidation of 2,2-dimethyl-2*H*-chromenes by using Mn(III)salen complexes together with NaOCl as oxygen donor was reported by Jacobsen et al.[4] Combinations of Mn(III)salen complexes and iodosylbenzene, H_2O_2 or nBu_4IO_4 as oxygen sources have also been used for such

enantioselective epoxidations.[5] Alternatively, optically active epoxides of 2,2-dimethyl-2*H*-chromenes have been prepared with molecular oxygen and an aldehyde as co-factor in the presence of Mn(III)salen complexes and N-alkylimidazoles as axial ligands.[6] Moreover, enantioselective microbial epoxidation of the 6-cyano-2,2-dimethyl-2*H*-chromene (**1a**) has been reported recently.[7] Since the 2,2-dimethyl-3,4-epoxychromans are quite sensitive and unstable compounds, strictly neutral reaction conditions are necessary for their preparation. Dioxiranes offer such advantages since they are effective oxidants under neutral and mild conditions;[8] however, the direct use of optically active dioxiranes for enantioselective epoxidations has met only with modest success.[9] Good results have been obtained in the DMD oxidation of nonracemic titanium enolates of the TADDOL type to afford an optically active α-hydroxy ketone presumably through enantioselective epoxidation.[10] For this reason, our aim was to investigate the utility of the dimethyldioxirane together with Jacobsen's Mn(III)salen complexes[4] for the enantioselective epoxidation of 2,2-dimethyl-2*H*-chromenes. In a preliminary report[11] we demonstrated the feasibility of this approach to afford epoxychromans in high enantiomeric excess (e.e.), now we present the full experimental details together with the rigorous configurational assignment of the resulting epoxides.

RESULTS AND DISCUSSION

As mentioned, most of the 2,2-dimethyl-3,4-epoxychromans are unstable at ambient temperature. Therefore, first we needed to find substrates for our planned enantioselective epoxidation experiments whose epoxides are sufficiently persistent at this temperature to allow detailed studies of the structure and configuration by means of a variety of physical and spectroscopic methods. Detailed screening of the dimethyldioxirane oxidation of numerous 2,2-dimethyl-2*H*-chromenes revealed that derivatives with strong electron-acceptor substituent(s) in their aromatic moiety afford stable enough epoxides at ambient temperature to serve our purpose. The oxidation procedure has been optimized in the case of the 6-cyano-2,2-dimethyl-2*H*-chromene (**1a**) as described in our preliminary communication.[11]

Enantioselective epoxidations of 2,2-dimethyl-2*H*-chromenes **1a-d** were performed with complexes (*R,R*)-**3** and (*S,S*)-**3** by using isolated DMD (ca. 0.1 M acetone solution)[12] as oxygen source (Scheme 1). For chromenes **1a-d** 10-20 mol% catalyst without any additive was applied for their complete conversion to the corresponding epoxides **2a-d** within 24 h. The enantiomeric purity of epoxides **2a-d** (Scheme 1) has been determined by chiral HPLC analysis, which revealed enatioselectivities between 83 and 93% e.e. These values are comparable with those reported previously for other oxygen donors.[4,5] The high e.e.'s unequivocally show that the DMD oxidizes first the Mn(III)salen complex and not the chromene. This finding makes the combination of the DMD and the Mn(III)salen complexes a most promising reagent for the enantioselective oxidation of suitable substrates under mild conditions.



1a, *(3R,4R)*-**2a**, *(3S,4S)*-**2a**: R^1=CN, R^2=H
1b, *(3R,4R)*-**2b**, *(3S,4S)*-**2b**: R^1=R^2=$PhSO_2O$
1c, *(3R,4R)*-**2c**, *(3S,4S)*-**2c**: R^1=R^2=4-Br-$C_6H_4SO_2O$
1d, *(3R,4R)*-**2d**, *(3S,4S)*-**2d**: R^1=R^2=4-Me-$C_6H_4SO_2O$

(R,R)-**3**: *(R,R)*-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese chloride
(S,S)-**3**: *(S,S)*-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino manganese chloride

Scheme 1

The structural assignment of the epoxides **2a-d** rests on microanalyses and NMR spectroscopy (cf. Experimental). In their ^{1}H NMR spectra the two doublets at δ ca. 3.5 (3-H) and 3.9 (4-H) with a coupling constant of ca. 4.3 Hz unambiguously indicate the presence of a *cis*-epoxide moiety. This is further corroborated by the δ ca 50.0 (C-3) and 62-63 (C-4) doublet signals in their ^{13}C NMR spectra.

Although the synthesis of optically active 2,2-dimethyl-3,4-epoxychromans has been performed by several research groups,[4-7,11] no direct determination of their absolute configuration has hitherto been published. The absolute configuration of the (1*S*)-camphanate of an optically active 2,2-dimethyl-3-hydroxychroman derivative determined by X-ray diffraction[13] served as reference in two studies[4b,5g] by comparing the sign of the specific rotation of the 2,2-dimethyl-3,4-epoxychromans or their ring-opened products.[4a,5g] In many cases, the absolute configuration of the optically active epoxides has not been determined.[5a-f,6] Fortunately, the absolute configurations of the persistent optically active epoxides **2a-d** prepared in our present study were directly and unambiguously determined by the combined utilization of X-ray diffraction analysis and circular dichroism (CD) measurements.

X-ray diffraction analysis of the (-)-enantiomer of **2d** obtained in the epoxidation of **1d** with DMD and (*S,S*)-**3** catalyst was successful, which provided for the first time a reliable structural reference point. A full set of Friedel pair reflections were measured for the determination of the absolute configuration. The structure was refined against F^2 by using the SHELXL93 program,[14] the absolute structure parameter[15] was refined to 0.00(2) for the correct enantiomer. This X-ray diffraction analysis revealed a (*3S,4S*) absolute configuration (Fig.1) for the (-)-enantiomer of **2d**.

Table 1. Crystal data and structure refinement for epoxide (*3S,4S*)-**2d**.[a]

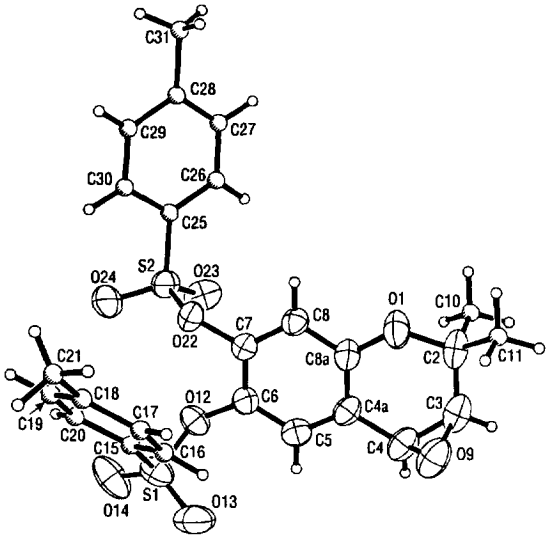
Empirical formula	$C_{25}H_{24}O_8S_2$
M_r	516.56
T (K)	293(2)
Radiation, λ (Å)	1.54184
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions,	
a (Å), b (Å), c (Å)	11.896(2), 12.160(2), 17.197(2)
V (Å^3)	2487.6(7)
Z	4
D_c (Mg/m^3)	1.379
Absorption coefficient, μ (mm^{-1})	2.353
F(000)	1080
Crystal size (mm)	0.40 x 0.25 x 0.20
θ range for data collection (°)	4.45 to 75.70
Index ranges	$-14 \le h \le 14$, $-15 \le k \le 15$, $-21 \le l \le 21$
Reflections collected	5828
Independent reflections	5162 [R(int) = 0.0129]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4733/0/323
Goodness-of-fit on F^2	1.067
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0419, $wR2$ = 0.1080
R indices (all data)	$R1$ = 0.0642, w$R2$ = 0.1195
Absolute structure parameter	0.00(2)
Extinction coefficient	0.0013(2)
Largest diff. peak and hole	0.249 and -0.325 e.Å^{-3}

[a] Intensity data were collected on an Enraf-Nonius CAD4 diffractometer.

The crystal data and collection details are given in Table 1.

Utilization of circular dichroism (CD) spectroscopy for the determination of the absolute configuration of 2,2-dialkyl-3,4-epoxychromans has hitherto been mentioned only by Jacobsen et al.[16] No details were given how the CD data were correlated with the configuration of the epoxides; however, the CD spectra deposited as supplementary material[16] are quite similar to those measured by us.

In the UV spectra of the epoxides **2a-d** in acetonitrile displayed two intense maxima with some shoulders in the wavelength regions 200-210 nm and 240-260 nm (Fig. 2), which indicates the complexity of the chromophore and renders difficult and precarious the assignment of the UV and CD maxima to particiular electronic transitions. Nonetheless, with the knowledge of the absolute configuration of the (*3S,4S*)-**2d**



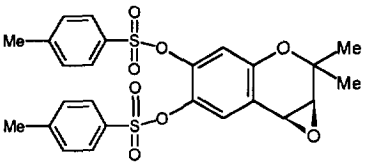


Figure 1. Molecular diagram of (*3S,4S*)-**2d** with the numbering of the atoms; thermal ellipsoids are drawn at 40% probability.

determined by X-ray diffraction analysis (Fig. 1), the stereochemistry and chiroptical properties of these epoxides can be definitively correlated. Thus, a very intense positive CD maximum ($\Delta\varepsilon$ +10-18) at ca. 210 nm and two distinct negative CD maxima at approx. 250-260 nm and 280-290 nm belong to the (*3R,4R*) absolute configuration, while in the same wavelength regions a similarly intense negative CD maximum ($\Delta\varepsilon$ -11-17) and two positive CD maxima have been measured for the (*3S,4S*) enantiomer. Thus, the CD spectra of the enantiomeric pairs are enantiomorphous (Fig. 3). Correlation of the CD data and the absolute configuration of these optically active 2,2-dimethyl-3,4-epoxychromans **2a-d** are in harmony with those found for the related 4-hydroxychroman derivatives, *viz.* 2,2-dimethyl-4-hydroxychromans[17] and 4-hydroxyflavans.[18] The sector rules introduced by Snatzke et al.[19] for the prediction of the signs of the CD maxima for the aromatic chromophore of the related tetralins and tetrahydroisoquinolines seem to be valid for these chroman derivatives as well.

In summary, optically active 2,2-dimethyl-3,4-epoxychromans **2** have been synthesized in good yields and high enantioselectivities by the catalytic epoxidation with the DMD/Mn(III)salenoxydation system. This is the first example for the utilization of a dioxirane as oxygen donor with Jacobsen's catalysts, which demonstrates that the combination of achiral dioxiranes and transition metal complexes may be advantageously used for enantioselective oxyfunctionalization. Since the DMD/Mn(III)salen oxidation is performed under strictly neutral conditions, it may offer an excellent opportunity for the enantioselective epoxidation of acid- or

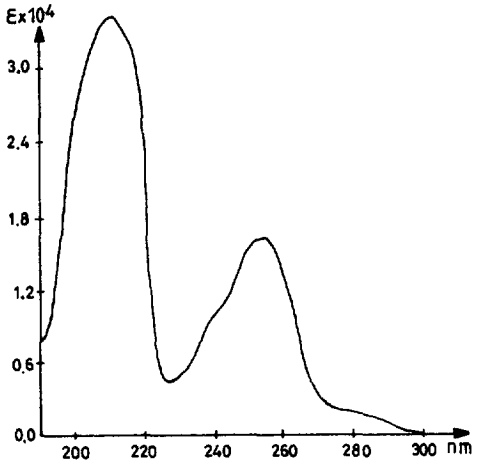


Figure 2. UV spectrum of **2a** in MeCN.

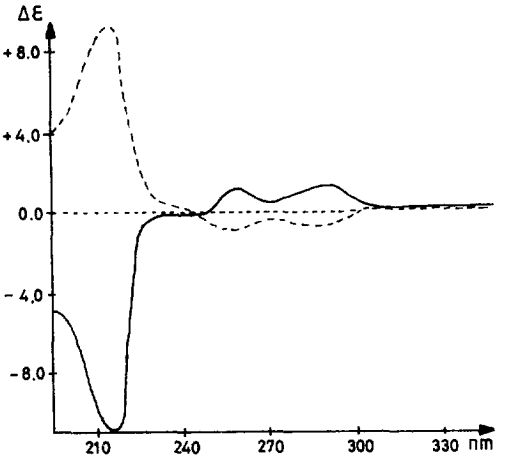


Figure 3. CD spectra of (*3R,4R*)-**2a** (-----) and (*3S,4S*)-**2a** (——) in MeCN

base-sensitive substrates. In our present study, the combined application of X-ray diffraction analysis and CD spectroscopy serves as powerful structural tool for the direct determination of the absolute configuration of optically active 2,2-dimethyl-3,4-epoxychromans. Our present results may serve as reference data for the configurational assignment of related 3,4-epoxychromans by CD measurements or even on the basis of the sign of their specific rotation.

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EXPERIMENTAL

All reagents and catalysts were of commercial purity. Caroate (potassium monoperoxosulfate), the triple salt $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, was used as received as a generous gift from the Peroxid-Chemie GmbH (München, Germany). Analytical TLC plates and silica gel for column chromatography were purchased from

Merck. Melting points were taken on a Reichert Thermovar hot-stage apparatus and are uncorrected. Microanalyses were performed in-house on a Carlo-Erba 1106 CHN Analyzer. ^{1}H and ^{13}C NMR spectra were acquired on Bruker WP 200 SY and Varian Gemini-200 spectrometers at 200/50 MHz in $CDCl_3$ (TMS, δ 0.0) at room temperature (ca. 20 °C). Optical purity was determined by HPLC on Chiradex [250 x 4.0 mm, 5 μm (Merck)] and Chiral-AGP [100 x 4.0 mm, 5 μm (Chrom Tech)] columns with MeOH-H_2O (4:6-1:1 v/v) as mobile phase. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in $CHCl_3$ (c = ca. 1). UV-VIS and CD spectra were recorded in MeCN on a Jobin-Yvon VI dichrograph calibrated with epiandosterone. Measurements were performed at room temperature in 0.02-cm and 0.1-cm cells in 1 mM concentration. X-ray diffraction analysis of compound (*3S,4S*)-**2d** has been performed with an Enraf-Nonius CAD4 diffractometer.

Dimethyldioxirane (as acetone solution) was prepared as described[12] and its peroxide content was determined iodometrically. Starting materials **1a-d** were synthesized according to published procedures.[20]

Since the measured UV, ^{1}H and ^{13}C NMR spectra of the respective enantiomeric pairs are identical, only those of the (*3S,4S*) enantiomers have been included in the description of the physical and spectral data of compounds synthesized.

General procedure for the enantioselective epoxidation of 2,2-dimethyl-2*H*-chromenes 1a-d

Dimethyldioxirane (ca. 0.1 M acetone solution) was added rapidly to a stirred solution of the particular 2,2-dimethyl-2*H*-chromene **1** (1.00-1.50 mmol) and Mn(III)salen complex **3** (ca. 10-20 mol%) in anhydrous CH_2Cl_2 (5.0 ml) and the stirring was continued at room temperature (ca. 20 °C). The progress of the reaction was monitored by TLC and new batches of DMD were added in several hour intervals until complete consumption of the starting material (ca. 24 h). The solvent was evaporated (ca. 25 °C/15 Torr) and the residue was purified by column chromatography on silica gel to afford epoxides **2a-d** (Scheme 1).

(*3R,4R*)-6-Cyano-2,2-dimethyl-3,4-epoxychroman [(*3R,4R*)-**2a**]

Reaction time 20 h, 2.2 equiv. DMD and 10 mol% (*R,R*)-**3**; yield 62%, m.p. 138-139 °C (hexane), $[\alpha]_D^{25}$ = +58.1 (c = 1, $CHCl_3$, 85% e.e.). Anal. Calcd for $C_{12}H_{11}NO_2$: C 71.62, H 5.51, N 6.95; found C 71.60, H 5.57, N 6.96%. CD [MeCN, λ (nm), Δε]: 210.0 sh (+8.91), 216.0 (+10.42), 258.6 (-0.98), 286.0 (-0.90), 289.6 (-0.92).

(*3S,4S*)-6-Cyano-2,2-dimethyl-3,4-epoxychroman [(*3S,4S*)-**2a**]

Reaction time 22 h, 2.5 equiv. DMD and 10 mol% (*S,S*)-**3**; yield 78%, m.p. 138-139 °C (hexane) (Lit.[7] m.p. 142-144 °C), $[\alpha]_D^{25}$ = -55.8 (c = 1, $CHCl_3$, 93% e.e.). Anal. Calcd for $C_{12}H_{11}NO_2$: C 71.62, H 5.51, N 6.95; found C 71.98, H 5.55, N 6.97%. ^{1}H NMR (δ): 1.31 (s, 3H), 1.61 (s, 3H), 3.56 (d, *J* = 4.3 Hz, 1H), 3.93 (d, *J* = 4.3 Hz, 1H), 6.88 (d, *J* = 8,3 Hz, 1H), 7.54 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.68 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (δ): 22.9, 25.4, 49.7, 62.2, 74.6, 104.2, 118.6, 118.9, 121.1, 133.7, 134.3, 156.4. UV [MeCN, λ (nm),

ε]: 210.0 (34400), 240.0 sh (9540), 254.6 (16300), 283.0 sh (1860), 292.6 sh (1150); CD [MeCN, λ (nm), Δε]: 209.6 sh (-10.08), 216.2 (-10.98), 258.4 (+1.08), 285.8 (+1.04), 290.8 (+1.00).

(*3R,4R*)-6,7-Bis(benzenesulfonyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3R,4R*)-2b]

Reaction time 24 h, 5.0 equiv. DMD and 16 mol% (*R,R*)-**3**; yield 64%, m.p. 73-74 °C (hexane), $[\alpha]_D^{25}$ = +27.6 (c = 1, $CHCl_3$, 84% e.e.). Anal. Calcd for $C_{23}H_{20}O_8S_2$: C 56.54, H 4.13; found C 56.73, H 4.17%. CD [MeCN, λ (nm), Δε]: 206.6 (+12.85), 241.5 (-2.22), 287.5 (-0.68).

(*3S,4S*)-6,7-Bis(benzenesulfonyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3S,4S*)-2b]

Reaction time 24 h, 5.2 equiv. DMD and 16 mol% (*S,S*)-**3**; yield 61%, m.p. 75-76 °C (hexane), $[\alpha]_D^{25}$ = -31.3 (c = 1, $CHCl_3$, 88% e.e.). Anal. Calcd for $C_{23}H_{20}O_8S_2$: C 56.54, H 4.13; found C 56.38, H 4.11%. ^{1}H NMR (δ): 1.24 (s, 3H), 1.54 (s, 3H), 3.50 (d, *J* = 4.3 Hz, 1H), 3.83 (d, *J* = 4.3 Hz, 1H), 6.69 (s, 1H), 7.29 (s, 1H), 7.42-7.74 (m, 10 arom. H); ^{13}C NMR (δ): 22.6, 25.3, 49.8, 62.1, 74.1, 113.8, 119.5, 124.9, 128.3, 128.4, 129.1, 134.4, 134.9, 135.0, 142.1, 151.6. UV [MeCN, λ (nm), ε]: 207.0 (51200), 219.6 (35000), 264.0 (3000), 272.0 (3640), 290.0 (2840); CD [MeCN, λ (nm), Δε]: 207.0 (-13.35), 241.5 (+2.25), 287.5 (+0.75).

(*3R,4R*)-6,7-Bis(4-bromobenzenesulfonyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3R,4R*)-2c]

Reaction time 24 h, 5.5 equiv. DMD and 20 mol% (*R,R*)-**3**; yield 85%, m.p. 142-143 °C (hexane), $[\alpha]_D^{25}$ = +32.7 (c = 1, $CHCl_3$, 83% e.e.). Anal. Calcd for $C_{23}H_{18}Br_2O_8S_2$: C 42.74, H 2.80; found C 42.76, H 2.81%. CD [MeCN, λ (nm), Δε]: 207.4 (+16.88), 231.8 (-2.25), 247.6 (+1.11), 288.0 (-0.58).

(*3S,4S*)-6,7-Bis(4-bromobenzenesulfonyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3S,4S*)-2c]

Reaction time 20 h, 5.4 equiv. DMD and 20 mol% (*S,S*)-**3**; yield 73%, m.p. 140-141 °C (hexane), $[\alpha]_D^{25}$ = -31.7 (c = 1, $CHCl_3$, 84% e.e.). Anal. Calcd for $C_{23}H_{18}Br_2O_8S_2$: C 42.74, H 2.80; found C 42.67, H 2.78%. ^{1}H NMR (δ): 1.29 (s, 3H), 1.60 (s, 3H), 3.51 (d, *J* = 4.2 Hz, 1H), 3.88 (d, *J* = 4.2 Hz, 1H), 6.70 (s, 1H), 7.32 (s, 1H), 7.53-7.68 (m, 8 arom. H); ^{13}C NMR (δ): 22.7, 25.5, 29.8, 31.3, 31.6, 49.9, 62.6, 75.4, 114.2, 122.0, 126.2, 130.5, 130.6, 131.0, 133.7, 135.1, 135.2, 142.6, 152.9. UV [MeCN, λ (nm), ε]: 200.4 (82300), 237.0 (42700), 278.0 (4040), 292.2 (3240); CD [MeCN, λ (nm), Δε]: 206.8 (-17.21), 231.0 (+2.30), 247.0 (-1.09), 287.5 (+0.69).

(*3R,4R*)-6,7-Bis(tosyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3R,4R*)-2d]

Reaction time 24 h, 4.8 equiv. DMD and 14 mol% (*R,R*)-**3**; yield 68%, m.p. 147-148 °C (hexane), $[\alpha]_D^{25}$ = +38.9 (c = 1, $CHCl_3$, 84% e.e.). Anal. Calcd for $C_{25}H_{24}O_8S_2$: C 58.14, H 4.68; found C 58.09, H 4.70%. CD [MeCN, λ (nm), Δε]: 207.5 (+17.59), 231.0 (-3.84), 243.6 (+0.84), 293.0 (-0.75).

(*3S,4S*)-6,7-Bis(tosyloxy)-2,2-dimethyl-3,4-epoxychroman [(*3S,4S*)-2d]

Reaction time 24 h, 5.2 equiv. DMD and 17 mol% (*S,S*)-**3**; yield 69%, m.p. 148-149 °C (hexane), $[\alpha]_D^{25}$ = -33.6 (c = 1, $CHCl_3$, 86% e.e.). Anal. Calcd for $C_{25}H_{24}O_8S_2$: C 58.14, H 4.68; found C 58.17, H 4.70%. ^{1}H NMR (δ): 1.27 (s, 3H), 1.58 (s, 3H), 2.47 (s, 6H), 3.49 (d, *J* = 4.1 Hz, 1H), 3.84 (d, *J* = 4.1 Hz, 1H), 6.71 (s, 1H), 7.25-7.66 (m, 9 arom. H); ^{13}C NMR (δ, ppm): 21.6, 22.7, 25.6, 29.8, 31.3, 50.6, 62.6, 74.9, 113.9, 121.5, 126.0, 129.3, 130.8, 133.1, 133.2, 135.4, 143.0, 146.9, 147.1, 152.5. UV [MeCN, λ (nm), ε]: 195.2 (96200), 208.4 sh (55100), 227.6 (38100), 289.0 (3700); CD [MeCN, λ (nm), Δε]: 207.8 (-16.99), 244.8 (+1.11), 292.4 (+0.71).

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