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# Enantioselective Synthesis of 3-Methylisochromans and Determination of Their Absolute Configurations by Circular Dichroism

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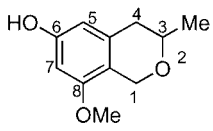
*Dedicated to Prof. András Lipták on the occasion of his 70th birthday*

**Keywords:** Chirality / Configuration determination / Kinetic resolution

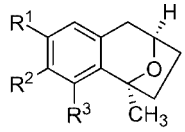
Seven (*S*)-3-methylisochromans with different substitution patterns on their aromatic rings, and hence with different directions of their sum electric transition moments, were synthesized by ring-closure of optically active (*S*)-1-arylpropan-2-ol derivatives. The (*S*)-1-arylpropan-2-ols were obtained by kinetic resolution and their absolute configurations were determined with the aid of a zinc porphyrin tweezer and by Mosher's method. A systematic CD study of substituted isochroman derivatives revealed that, unlike in the cases of chiral tetralin and 2,3-dihydrobenzo[*b*]furan chromophores, the presence of achiral substituents of large spectroscopic moment (e.g., OMe) on the aromatic ring does not change the helicity rule of the "unsubstituted" isochroman chromophore: (*P*)/(*M*) helicity of the isochroman heteroring resulted in *positive/negative* $^1L_b$ band Cotton effects (CE) regardless of the nature(s) and position(s) of the substituent(s). (*S*)-3-Methylisochromans were oxidized at C-1, allowing access to the corresponding dihydroisocoumarins, in which positive CE of the n→π* transitions were correlated with (*P*) helicity and (*S*) absolute configuration. On DDQ-assisted oxidation, two *trans*-1-methoxy-3-methylisochroman derivatives were prepared and used to study the effect of the *axial* benzylic C-1 methoxy group on the conformation of the heteroring and the $^1L_b$ band CE.


## Introduction

Thanks to semiempirical helicity rules, the chiroptical properties of benzene-fused cyclic compounds such as tetralins,[1] chromans,[2] or dihydrobenzo[*b*]furans[2a,3] are widely used for the determination of the absolute configurations of natural or synthetic derivatives containing these chromophores. In contrast, there is no such rule – which would allow direct configurational assignment by a simple CD measurement – available for the isochroman chromophore. There are several natural 3-alkylisochromans possessing remarkable biological activities in which the absolute configurations have not yet been determined: the absolute configurations of, for instance, the anticoccidial optically active 3-methylisochroman derivative **1**,[4] isolated from *Penicillium sp.*, and the tricyclic derivatives **2a**–**c**[5] have not been

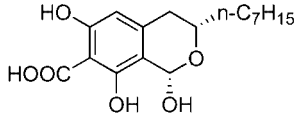



**1**

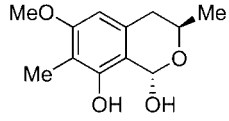



**2**

| **2** | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **a** | OH | H | H |
| **b** | OH | OH | H |
| **c** | OH | H | OH |




*cis*-**3**




*trans*-**4**

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reported, while the absolute configurations of the topoisomerase II inhibitor CJ-12,373 (*cis*-**3**)[6] and the isochroman toxin *trans*-**4**,[7] natural products containing benzylic hydroxy groups, have also not been determined.

The sign of the benzene $^1L_b$ CD band can be correlated with the conformation or helicity of the fused heteroring of the isochroman chromophore by a helicity rule. Since the relative steric orientations of the substituents on the heteroring can be determined by NMR, the measurement of its CD spectrum allows elucidation of ring helicity and hence of the absolute configuration.

A relationship between the helicity of the heteroring and the $^1L_b$ CD band, based on the synthetic steroid model compounds **5** and **6** (Figure 1, a), had previously been proposed for the isochroman chromophore with no aromatic substituents: (*P*) helicity of the heteroring gives rise to a positive Cotton effect (CE) for the $^1L_b$ band while (*M*) helicity is manifested in a negative one (Figure 1, b).[8] However, a negative $^1L_b$ band CE was measured for the 6aβ-H, 12aβ-H derivative **7**, in which the heteroring should adopt (*P*) helicity provided that ring A of the cholestane skeleton has the chair conformation. This discrepancy could be attributed to the contribution of a conformer with the boat conformation in ring A, but it made the application of the above helicity rule ambiguous for the configurational assignment of natural isochromans, and so enantioselective synthesis and CD study of further isochroman derivatives of known absolute configurations are required in order to make the helicity rule suitable for the configurational assignment of chiral isochromans. Moreover, it had previously been shown for tetralin,[1a] phenylcarbinamine, and carbinol[9] – and recently for 2,3-dihydrobenzo[*b*]furan[2a] derivatives – that the presence on the fused aromatic ring of achiral substituents with large spectroscopic moments, such as hydroxy, alkoxy, or alkenyl, can change the sign of the $^1L_b$ CE, even though the absolute configurations of the stereogenic centers remain the same. This has been explained by the conjecture that achiral substituents with large spectroscopic moments can change the direction of the sum electric transition moment vector and hence the polarization directions of the aromatic transitions by more than 30°, resulting in inversion of the measured $^1L_b$ CE.[1a] Since natural or synthetic isochroman derivatives of pharmacological interest often contain achiral substituents of large spectroscopic moment (alkoxy, hydroxy) on their fused aromatic rings, their configurational assignment by CD spectroscopy would thus require a systematic study of whether the different substitution patterns would affect the helicity rule proposed for the unsubstituted isochroman chromophore.[8] In order to achieve this goal, enantioselective syntheses of 3-methylisochroman derivatives with different substitution patterns on their aromatic rings were carried out and their absolute configurations were determined independently prior to the formation of the heteroring.

Since isochroman derivatives can readily be oxidized[10] at their benzylic carbons, to afford dihydroisocoumarins, the synthesis of substituted isochromans also allows access

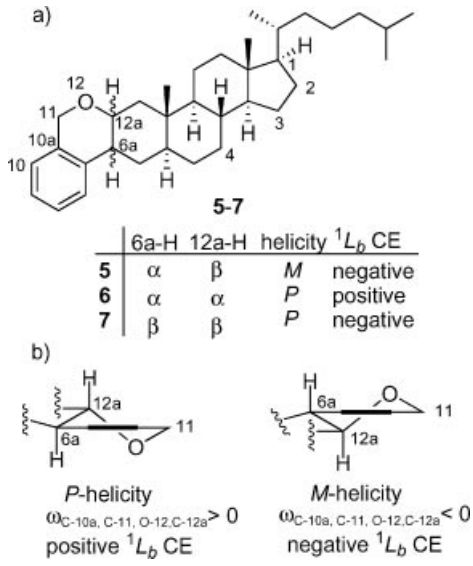



Figure 1. a) Structures of isochroman model compounds **5**–**7** with the helicity of their heterorings and the signs of the measured $^1L_b$ CE bands. b) Helicity rule for the isochroman chromophore with no substituents on the aromatic ring represented by the examples of **5** and **6**.

to optically active substituted dihydroisocoumarins such as (*S*)-mellein. For the configurational assignment of 1-alkoxy- or 1-hydroxyisochromans such as *cis*-**3** and *trans*-**4**, the effect of axial benzylic C-1 methoxy groups both on the conformation of the heteroring and on the $^1L_b$ band CE was studied and compared with those relating to the corresponding flavan-4-ols.

## Results and Discussion

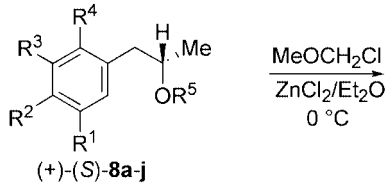
### Arylpropanols and Isochromans

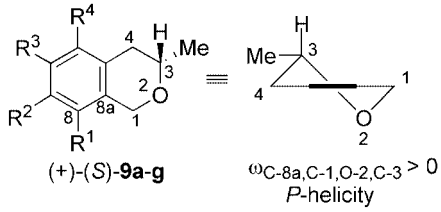
3-Methylisochroman derivatives (+)-(*S*)-**9a**–**e** with different substitution pattern on their aromatic rings were synthesized by ring-closure of the (+)-(*S*)-1-arylpropan-2-ols **8a**–**e** (Scheme 1), in turn prepared by kinetic resolution.

Since *Pseudomonas* lipases have been found to be very effective enzymes in the kinetic transesterification of numerous racemic secondary alcohols with remarkable enantiopreference and tolerance for a great variety of substrates,[11] the lipase from *Pseudomonas cepacia* (PCL) was used for the kinetic resolution of *rac*-**8a**–**c**. PCL-catalyzed acylations of *rac*-**8a**–**c** were carried out with vinyl acetate (VA), the reactions were terminated at approximately 50% conversion as monitored by TLC (Scheme 2), and the unreacted alcohols (+)-(*S*)-**8a**–**c** and the acetates (–)-(*R*)-**8a**–**c**-Ac were separated by column chromatography.

As the chirality of the C-2 stereogenic center should be preserved during the ring-closure of each optically active alcohol (+)-(*S*)-**8a**–**c**, the absolute configurations of isochromans **9a**–**c** can be determined readily, provided that the absolute configurations of the arylpropanols **8a**–**c** are

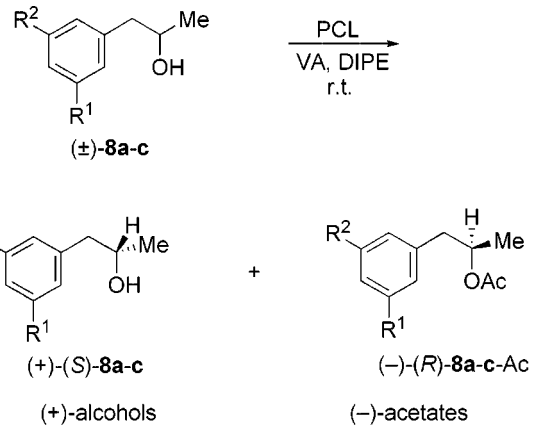
  




| 8,9 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|---|
| **a** | H | H | H | H | H |
| **b** | OMe | H | OMe | H | H |
| **c** | OMe | H | H | H | H |
| **d** | H | OMe | OMe | H | H |
| **e** | H | -$OCH_2O$- | | H | H |
| **f** | OMe | H | H | Br | H |
| **9g** | H | H | OMe | H | H |
| **8h** | OMe | H | H | Br | MOM |
| **8i** | OMe | H | OMe | H | (*R*)-MPA |
| **8j** | OMe | H | H | H | (*R*)-MPA |

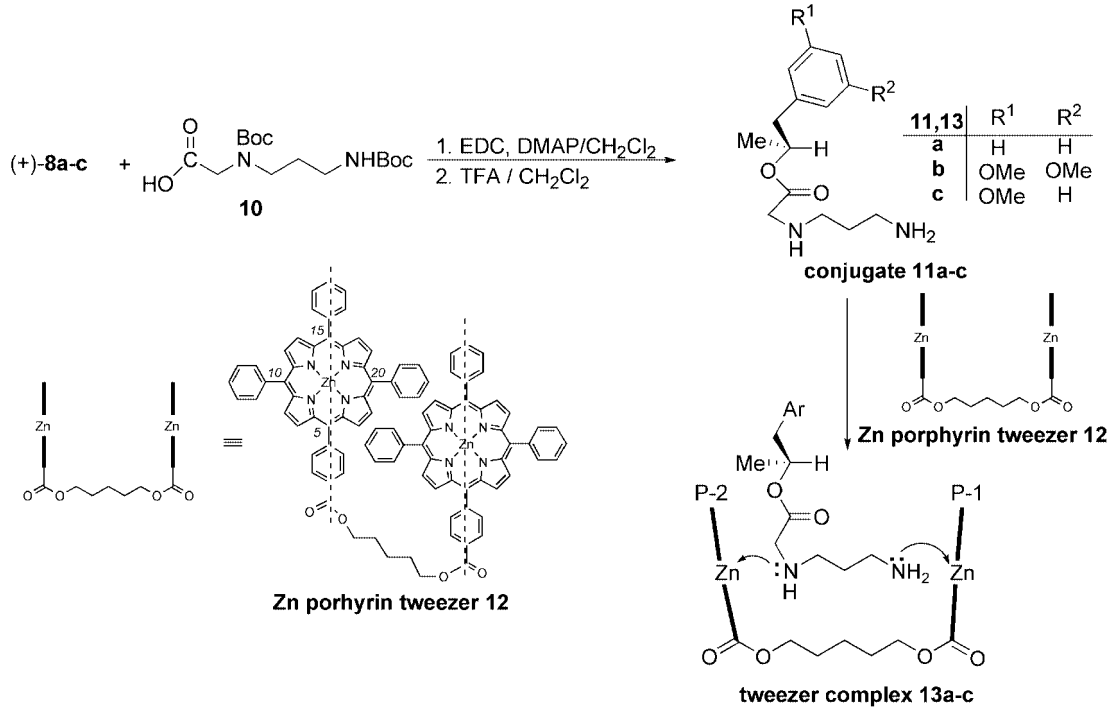
Scheme 1. Ring-closure to give the (*S*)-isochromans **9a**–**g** and their helicities. MOM: methoxymethyl, (*R*)-MPA: acyl group of (*R*)-(–)-α-methoxyphenylacetic acid.




| 8 | $R^1$ | $R^2$ | Conv. (%) | Time (h) | $[\alpha]_D^{25}$ | *ee*% | $[\alpha]_D^{25}$ |
|---|---|---|---|---|---|---|---|
| **a** | H | H | 52 | 4 | 32.2 | >95 | –3.35 |
| **b** | OMe | OMe | 53 | 16 | 23.1 | >95 | –2.34 |
| **c** | OMe | H | 53 | 166 | 32.6 | >95 | –2.48 |

Scheme 2. Kinetic resolution of alcohols (*rac*)-**8a**–**c** with lipase from *Pseudomonas cepacia* (PCL).

known. For this purpose we envisaged the employment of the zinc porphyrin tweezer exciton chirality method.[12] By this method, the chiral secondary alcohols (+)-(*S*)-**8a**–**c** were each directly linked to the di-Boc-protected achiral carrier molecule **10** and then deprotected with trifluoroacetic acid (TFA) to produce the bidentate conjugates **11a**–**c**, each capable of forming a 1:1 host–guest complex with dimeric zinc porphyrin host **12** (Scheme 3). Because of the steric differentiation between the substituents flanking the stereogenic center (the larger group protrudes from the porphyrin binding pocket), the formation of the host–guest complex occurs with a preferred porphyrin helicity, which




Scheme 3. Preparation of tweezer complex **13a**–**c**.

produces intense exciton split spectra. The conformational A values are generally used to decide which substituent is treated as larger by the zinc porphyrin tweezer.[12] More recently, a Merck Molecular Force Field (MMFF) molecular modeling approach has been developed,[13] and since the conformational A value of the methyl group was reported to be very close to that of the benzyl group (methyl: 1.74 kcal mol$^{-1}$, benzyl: 1.68 kcal mol$^{-1}$),[14] the CD measurement was complemented by this calculation protocol (i.e., conformational analysis of the tweezer complex (*S*)-**13a**). The calculation allowed us to estimate the most probable projection angle between longitudinal (C5–C15) porphyrin axes, which is the geometrical parameter responsible for the sign of the measured CD couplet.[15]

This revealed that the C5–C15 oriented longitudinal effective electric transition moments[15] of the two tetraphenylporphyrin rings have an 84% preference for the positive projection angle in (*S*)-**13a** (Figure 2), and hence it should give a positive exciton couplet in the Soret region. The front and side views of the most probable conformation belonging to the most probable cluster are shown in Figure 3. According to these results, the zinc porphyrin tweezer treats the benzyl group as larger than the methyl group, and since positive exciton couplets (positive CE at longer wavelength) were measured for **13a**–**c** {CD for **13a** [nm ($\Delta\varepsilon$)]: 430 (+44), 420 (–36); **13b**: 430 (+58), 420 (–41); **13c**: 430 (+34), 420 (–39)}, the initial alcohols **8a**–**c** all have (*S*) configurations.

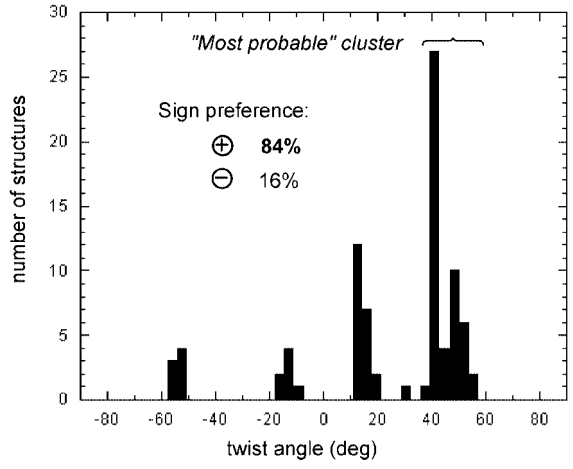



Figure 2. Distribution of the twist angles of the MC/MMFFs-calculated host–guest complex **13a** within 10 kJ mol$^{-1}$ of the lowest-energy conformation. The sum probabilities of the conformers with negative and positive twist angles are reported as percentages and the most probable cluster is indicated.

The enantiomeric excesses (*ee* values) of (*S*)-**8b** and (*S*)-**8c** were determined from the $^1$H NMR signals of the aromatic OMe(s) in their corresponding Mosher's ester derivatives (*S*)-**8i** and (*S*)-**8j** prepared with (*R*)-(–)-α-methoxyphenylacetic acid [(–)-(*R*)-MPA] as described in the literature.[16] Since the (*R*)-MPA esters of *rac*-**8b** and *rac*-**8c** were also prepared, the separate chemical shifts of (*S*)-**8i** and (*S*)-**8j** can be compared with those of (*R*)-**8i** and (*R*)-**8j**, which also allowed the configurational assignment of (*S*)-**8b** and (*S*)-**8c** by Mosher's method. Since the $^1$H NMR signals of the aryl protons and the aromatic OMe(s) of (*S*)-**8i** and (*S*)-**8j** were shifted downfield while those of the methyl groups were shifted upfield in relation to the corresponding signals of (*R*)-**8i** and (*R*)-**8j**, Mosher's method also gave (*S*) absolute configurations for **8i** and **8j**, consistently with the zinc porphyrin tweezer method. The *ee* of (*S*)-**8a** was determined by comparing its specific rotation with the literature data.[17]

The secondary alcohols (+)-(*S*)-**8d** and (+)-(*S*)-**8e** were prepared in optically pure form (*ee* > 99.5%) by chiral bioreduction of the corresponding arylacetone derivatives **14a** and **14b** as described in the literature[18] and shown in Scheme 4.

The ring closures of (+)-(*S*)-**8a**, (+)-(*S*)-**8b**, (+)-(*S*)-**8d**, and (+)-(*S*)-**8e** each took place smoothly on treatment with monochloromethyl methyl ether in the presence of the Lewis acid $ZnCl_2$ at 0 °C, producing the corresponding isochromans (*S*)-**9a**, (*S*)-**9b**, (*S*)-**9d**, and (*S*)-**9e**. While the cyclizations of (+)-(*S*)-**8d** and (+)-(*S*)-**8e** were regioselective and hence each provided a single product in good yield (94% and 77%, respectively), the ring-closure of **8c** resulted in a mixture of (+)-(*S*)-**9c** and **9g** (1:4 ratio), although they

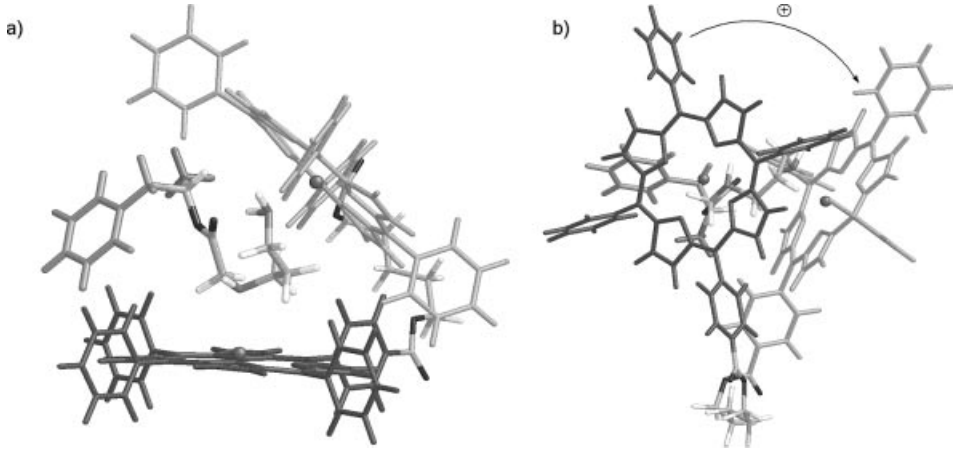
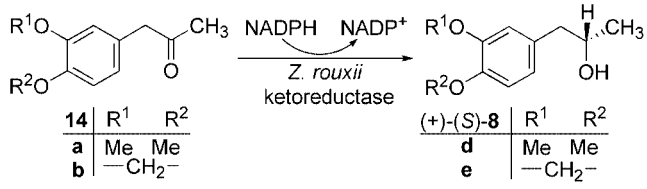



Figure 3. Top (**a**) and front (**b**) views of the most probable MC/MMFFs-calculated structure of **13a** belonging to the most probable cluster in Figure 2.

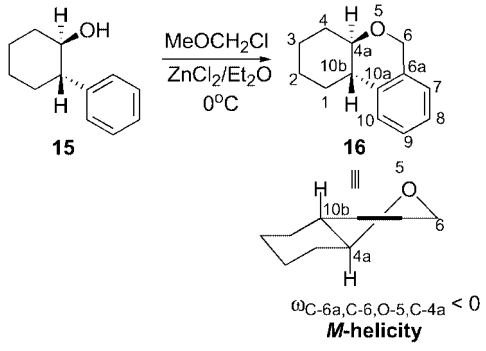



Scheme 4. Chiral bioreduction of **14a** and **14b**.

could readily be separated by column chromatography. In order to prepare (+)-**9c**, the precursor of the natural product (+)-mellein, in a better yield, the $R^4$ position of the alcohol (+)-(*S*)-**8c** was blocked by bromination to give (+)-(*S*)-**8f**, treatment of which with monochloromethyl methyl ether and $ZnCl_2$ provided (+)-(*S*)-**9f**, together with the methoxymethyl ether intermediate **8h**.

The transformation of (+)-(*S*)-**9f** into (+)-(*S*)-**9c** could be achieved in high yield (73%) by treatment with *n*BuLi in THF at –70 °C, followed by quenching with water. It is also noteworthy that the ring-closure of the 1-arylpropan-2-ol **8d** could be also performed in high yield (81%) by treatment with formaldehyde dimethyl acetal in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$).

In order to study the influence of a benzylic substituent on the chiroptical properties of the isochroman chromophore and to prepare an analogue of the model compound **5**, the cyclization of the commercially available (–)-(1*R*,2*S*)-2-phenylcyclohexanol (**15**) was also carried out under the conditions described above to afford the *trans*-fused ring system **16** in 76% yield (Scheme 5).




Scheme 5. Preparation and helicity of (–)-(4a*R*,10b*S*)-**16**.

The helicity of and CD data for the isochromans (*S*)-**9a**–**g** and (4a*R*,10b*S*)-**16** are tabulated in Table 1. Compounds (*S*)-**9a** and (4a*R*,10b*S*)-**16**, bearing no substituents on their aromatic rings, have heterorings of (*P*) and (*M*) helicity (see Scheme 1 and Scheme 5 for definition and representation), respectively, in which the C-3 methyl group of **9a** is oriented *equatorially* ($J_{3H,4H}$ = 10.9 and 3.1 Hz) while the 4a,10b hydrogens of the *trans*-annulated **16** have a *trans-diaxial* configuration.

## CD Analysis

As the $^1L_b$ bands of (*S*)-**9a** (see Scheme 1) of (*P*) helicity and (4a*R*,10b*S*)-**16** of (*M*) helicity show positive and negative CEs, respectively, it follows that the unsubstituted isochroman chromophore obeys the helicity rule established for unsubstituted chiral tetralins:[1b] (*P*)/(*M*) helicity of the heteroring results in a *positive/negative* $^1L_b$ *band CE*.

Smith applied empirical sector rules to describe the vibronic contribution to the $^1L_b$ CE in benzene compounds possessing contiguous stereogenic centers and without any additional ring substituents (phenylcarbinamines, phenylcarbinols, 1-substituted indans and tetralins).[19] With additional achiral ring substituents there is an induced rotatory contribution to the $^1L_b$ CE, characterized by a chirality rule, which can override the former vibronic contribution depending on the spectroscopic moment and ring position(s) of the substituent(s). The spectroscopic moment, introduced by Platt[20] and studied in more detail by Petruska,[21] was successfully used to predict or explain the effect of achiral substituents of the benzene chromophore on the $^1L_b$ CE.[1a,22] In chiral tetralins, the chirality of the stereogenic center(s) determines the helicity of the fused cyclohexane ring, which was correlated with the $^1L_b$ CE by a helicity rule [(*P*)/(*M*) helicity → *positive/negative* $^1L_b$ CE, respectively; see Figure 4].[1] However, it was also shown that achiral ring substituents of large spectroscopic moment – such as a methoxy group {$g_{OMe}$ = 33 [(cm mol)/L]$^{-1/2}$}[22b] – in specific positions inverted the helicity rule, which was attributed to the change of the direction of the sum spectroscopic moment vector. 6-Methoxy- and 5,7-dimethoxy-substituted chiral tetralins thus obeyed the opposite helicity rule [i.e., (*P*) helicity resulted in nega-

Table 1. Helicity of and CD data for isochromans (*S*)-**9a**–**g** and (4a*R*,10b*S*)-**16** measured in acetonitrile.

| Compound | Helicity | CD: $\lambda_{max}$ [nm] ($\Delta\varepsilon$) $^1L_b$ | $^1L_a$ | $^1B$ |
|---|---|---|---|---|
| (*S*)-**9a** | (*P*) | 272 sh (+0.06), 2.68 (+0.11) 261 sh (+0.09) | 221 (+0.24) | n.d. |
| (*S*)-**9b** | (*P*) | 279 sh (+0.45), 277 (+0.47), 275 sh (+0.45) | 237 (+0.78), 219 sh (+0.40) | 209.5 (–3.04) |
| (*S*)-**9c** | (*P*) | 277 (+0.29), 270 sh (+0.21), 269 sh (+0.21) | 228 (–0.27) 215 (+1.98) | 205 (–4.58) |
| (*S*)-**9d** | (*P*) | 288 sh (+0.65), 282 (+0.71) 271 sh (+0.41) | 230 (+3.44) | 208 (+6.49) |
| (*S*)-**9e** | (*P*) | 295 (+0.98), 287 sh (+0.91), 270 sh (+0.27) | 243 (–1.78), 226 (+2.38) | 204 (+4.75) |
| (*S*)-**9f** | (*P*) | 284 (+0.24), 278 (+0.23) | 234 (+0.49), 228 (+0.38) | 210 (–1.14) |
| (*S*)-**9g** | (*P*) | 284 sh (+0.35), 278 sh (+0.40), 275 (+0.40) | 230 (+1.34), 224 sh (+1.06), 218 sh (+0.93) | n.d. |
| (4a*R*,10b*S*)-**16** | (*M*) | 273 sh (–0.05), 268 (–0.09), 262 sh (–0.08) | 222 (+0.86) | 204 (+3.20) |

tive $^1L_b$ CE (Figure 4)], so the effect of similar achiral ring substituents of the isochroman chromophore also needs to be studied.

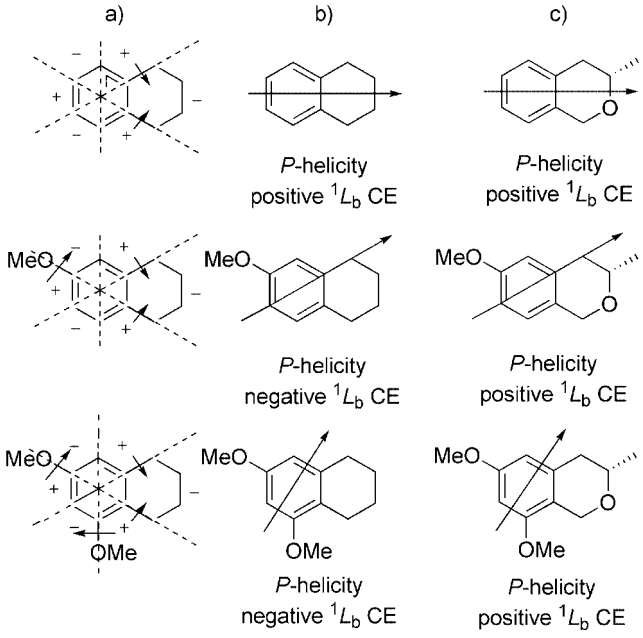
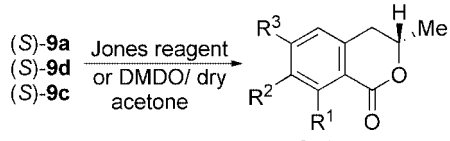



Figure 4. a) Polarization diagram of the $^1L_b$ bands for tetralin, 6-methoxytetralin, and 5,7-dimethoxytetralin (signs chosen arbitrarily), b) Direction of the overall spectroscopic moment and helicity rule for substituted chiral tetralins, c) Direction of the overall spectroscopic moment and helicity rule for 3-methylisochroman, 6-methoxy-3-methylisochroman, and 6,8-dimethoxy-3-methylisochroman.

In the substituted isochromans (*S*)-**9b**–**g**, the different substitution patterns given by the methoxy, methylenedioxy, and bromine ring substituents provide different directions of the sum spectroscopic moment vectors, which allows the effect on the $^1L_b$ CE of achiral isochroman chromophore ring substituents to be studied and compared with the corresponding data for the substituted chiral tetralins (Figure 4). The CD data for **9b** and **9g** (Table 1) revealed that, unlike in the case of the tetralin chromophore, 6-methoxy or 6,8-dimethoxy substitution did not invert the sign of the $^1L_b$ CE, while the same was also found for **9c**–**f**. This showed that the presence of achiral substituents of large spectroscopic moment in different positions on the benzene moiety did not change the isochroman helicity rule, and hence that the $^1L_b$ band can safely be used for the configurational assignment of isochromans such as **1** and **2a**–**c**, substituted with groups of large spectroscopic moment (alkoxy, OH, halogen) on their aromatic rings. In contrast, the signs of the CEs in the shorter-wavelength aromatic transitions – namely, the $^1L_a$ and $^1$B regions of (*S*)-**9b**–**g** – varied with the positions and natures of the substituents, making this region less useful for the determination of configuration.

### Dihydroisocoumarins and 1-Methoxyisochroman Derivatives

Optically active isochromans can be converted into the corresponding dihydroisocoumarins by oxidation with Jones reagent[10a] or dimethyldioxirane (DMDO),[10b] as demonstrated in the preparation of **17a**–**c** (Scheme 6). The dihydroisocoumarin **17c**, the 8-*O*-methyl derivative of the natural product (*S*)-mellein, can be transformed into (*S*)-mellein by demethylation with $AlCl_3$ as described in the literature.[23] The (*S*)-dihydroisocoumarins **17a**–**c** have very similar CD patterns: positive π→π* and n→π* transitions at 278–307 nm and 252–268 nm, respectively, followed by a negative and a positive band in the high-energy region. Since the n→π* transition is not sensitive to the substitution pattern of the aromatic ring, the positive n→π* transition of 3-alkyldihydroisocoumarins corroborates (*P*) helicity of the heteroring and thus (*S*) absolute configuration, in accordance with previous results (Table 2).[8,24]




(*S*)-**17a**-**c**

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **17a** | H | H | H |
| **17b** | H | OMe | OMe |
| **17c** | OMe | H | H |

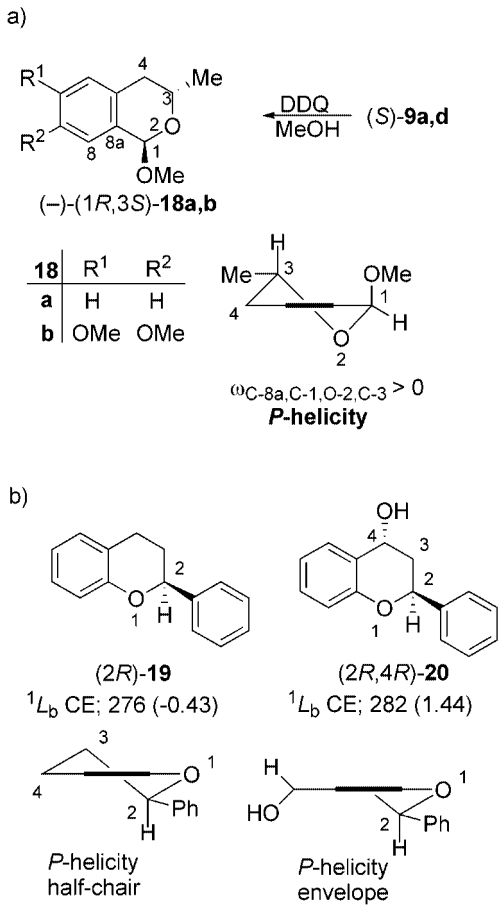
Scheme 6. Oxidation of (*S*)-**9a**, **-9c**, and **-9d** to the corresponding dihydroisocoumarins **17a**–**c**.

Snatzke and co-workers[25] had reported earlier that the introduction of an axial benzylic hydroxy group into the chroman chromophore of a flavan-4-ol [(2*R*)-**19**→(2*R*,4*R*)-**20**] could invert the sign of the CEs of the $^1L_b$ band while the absolute configuration of C-2 remained the same (Scheme 7, b).

Table 2. CD data for dihydroisocoumarins (*S*)-**17a**–**c** and isochromans (1*R*,3*S*)-**18a** and (1*R*,3*S*)-**18b** in acetonitrile.

| Compound | CD: $\lambda_{max}$ [nm] ($\Delta\varepsilon$) |
|---|---|
| (*S*)-**17a** | π→π*: 289 sh (+1.08), 278 sh (+2.00); n→π*: 252 (+4.19); 230 (–4.73), 204 (+13.83) |
| (*S*)-**17b** | π→π*: 307 sh (+1.10), 300 (+1.28), 294 sh (+1.20); n→π*: 268 (+7.62); 244 (–4.64), 226 (+10.48), 204 (–6.22) |
| (*S*)-**17c** | π→π*: 304 sh (+2.44), 296 (+2.48); n→π*: 258 (+4.17); 239 (–1.29), 229 sh (+0.67), 206 (+11.21) |
| (1*R*,3*S*)-**18a** | 266 (+0.03), 260 (+0.02), 255 sh (+0.01), 252 sh (+0.01), 213 (+1.41), 208 sh (1.20) |
| (1*R*,3*S*)-**18b** | 287 sh (+0.59), 282 (+0.69), 275 sh (+0.63), 234 (+4.77), 204 (+8.44) |




Scheme 7. a) Treatment of (*S*)-**9a** and (*S*)-**9d** with DDQ in MeOH and the helicity of the product. b) Structure, helicity, and $^1L_b$ band CE of (*R*)-**19** and (2*R*,4*R*)-**20**.

The reason for this – of whether this effect is due to the participation of the nonbonding electron pairs of the axial benzylic oxygen or distortion of the half-chair conformation of the heteroring – remained unclear. In order to test this effect on the isochroman chromophore, the 1-methoxy derivatives (–)-(1*R*,3*S*)-**18a** and (–)-(1*R*,3*S*)-**18b** were prepared by oxidation of (+)-(*S*)-**9a** and (+)-(*S*)-**9d** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol (Scheme 7, a) and the relative configuration of the C-1 methoxy group in (–)-(1*R*,3*S*)-**18b** was studied. The three-bond carbon–proton coupling constants in (–)-(1*R*,3*S*)-**18b** ($^3J_{C8,1H}$ = 2.2 Hz, $^3J_{C3,1H}$ = 6.0 Hz, $^3J_{C1,3H}$ = 1–2 Hz) were measured, and showed that the C-8, 1-H, and C-1, 3-H atoms have a *gauche* orientation (small coupling constant), while C-3 and 1-H have an *anti* orientation (large coupling constant).[26] This showed that the introduction of the methoxy group had taken place diastereoselectively and that, due to the anomeric effect, only the *trans* product (–)-(1*R*,3*S*)-**18b**, in which the methoxy group is axially oriented while the heteroring has a half-chair conformation, had been formed (Scheme 7).[27]

The heterorings of (1*R*,3*S*)-**18a** and (1*R*,3*S*)-**18b** have (*P*) helicity and their $^1L_b$ CEs [287 sh (+0.59), 282 (+0.69), 275 sh (+0.63) for **18b** (Table 2)] are practically the same as those of (*S*)-**9a** and (*S*)-**9d**, which confirmed that, unlike in flavan-4-ols [such as (2*R*,4*R*)-**20**; see Scheme 7, b], the introduction of an axial benzylic alkoxy group should not change the isochroman helicity rule as long as the conformation or helicity of the heteroring remains the same. In contrast, in the case of the chroman chromophore, the introduction of an axial benzylic hydroxy group [(2*R*)-**19** → (2*R*,4*R*)-**20**] inverted the sign of the $^1L_b$ CE, which was attributed to a conformational change in the heteroring even though its helicity had not changed.[25] This result allows the configurational assignment of 1-alkoxy- or 1-hydroxyisochromans such as *cis*-**3** and *trans*-**4** from their CD spectra.

## Conclusions

The synthesis of (*S*)-3-methylisochromans with different substitution patterns on their aromatic rings has allowed a helicity rule for the unsubstituted isochroman chromophore to be set up: (*P*)/(*M*) helicity of the heteroring resulted in a *positive/negative* $^1L_b$ *band CE*. CD study of isochromans substituted with OMe, Br, and methylenedioxy substituents revealed that, unlike in the case of chiral tetralins, a change in the direction of the sum electric transition moment induced by achiral substituents of large spectroscopic moment did not influence the helicity rule.

*trans*-1-Methoxy-3-methylisochroman derivatives were prepared by DDQ-assisted oxidation, after which the effects of the *axial* benzylic C-1 heteroatoms on the conformation of the heteroring and the $^1L_b$ band CE were studied. This showed that the *axial* benzylic C-1 heteroatoms, again unlike in the cases of flavan-3-ols, neither distorted the half-chair conformation nor changed the $^1L_b$ band CE, allowing the configurational assignment of analogous natural 1-hydroxy or 1-alkoxyisochromans.

## Experimental Section

**General Experimental Procedures:** Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined with a Carlo–Erba Tpy 1106 analyzer. The NMR spectra were recorded on a Bruker AMX 500 ($^1$H: 500 MHz; $^{13}$C: 125 MHz), a Bruker WP 200 SY ($^1$H: 200 MHz, $^{13}$C: 50 MHz), or a Bruker Aspect 3000 ($^1$H: 360 MHz) spectrometer with TMS as internal standard; chemical shifts are reported in ppm. Optical rotations were determined with a Perkin–Elmer 241 polarimeter and CD spectra were recorded on a J-810 spectropolarimeter; the CD spectra were measured in millidegrees and normalized into $\Delta\varepsilon_{max}$ [l mol$^{-1}$ cm$^{-1}$]/$\lambda$ [nm] units. In the UV spectra, a red shift of the tweezer Soret band indicated that complexation had taken place. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer and absorption bands are reported in cm$^{-1}$. Precoated silica gel plates (Kieselgel 60 $F_{254}$, 0.25 mm, Merck) were

used for analytical and preparative TLC. High-resolution FAB mass spectra were measured on a JEOL JMS-DX303 HF mass spectrometer with use of a glycerol matrix and Xe as ionizing gas, while ESI-TOF MS measurements were performed on a Micro-TOF-Q instrument (Bruker Daltonik GmbH, Bremen, Germany).

**General Procedure for the Preparation of 9a–g, 8h, and 16. (+)-(3*S*)-3-Methyl-3,4-dihydro-1*H*-isochromene (9a):** Anhydrous $ZnCl_2$ (41 mg, 0.30 mmol) was added under nitrogen at room temperature to a solution of **8a** (94 mg, 0.69 mmol) in methoxymethyl chloride (1.4 mL, 18 mmol) and the mixture was stirred at room temperature for 15 min. Water was added, the mixture was stirred for 15 min and extracted with diethyl ether (3·10 mL), and the combined organic layer was washed with a solution of $NaHCO_3$ and water, dried ($CaCl_2$), filtered, and concentrated in vacuo. The residue was purified by preparative TLC (hexane/ethyl acetate 7:1) to give a colorless oil (76 mg, 74%): $[\alpha]_D^{20}$ = +134.6 ($c$ = 2.20, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.36 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.71 (d, $J$ = 6.8 Hz, 2 H, $CH_2$–CH), 3.74–3.87 (m, 1 H, CH), 4.83 (s, 2 H, $OCH_2$), 6.97–7.18 (m, 4 H, Ar-H) ppm.

**(+)-(3*S*)-6,8-Dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromene (9b) by Ring-Closure of 8b:** White crystal (90%): m.p. 54–56 °C. $[\alpha]_D^{20}$ = +82.5 ($c$ = 0.40, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.33 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.63 (d, $J$ = 6.8 Hz, 2 H, $CH_2$–CH), 3.66–3.88 (m, 1 H, CH), 3.76 (s, 6 H, 2 × Ar–$OCH_3$), 4.57 (d, $J$ = 15.3 Hz, 1 H, $OCH_2$a), 4.86 (d, $J$ = 15.3 Hz, 1 H, $OCH_2$b), 6.22 (d, $J$ = 2.2 Hz, 1 H, Ar-H), 6.28 (d, $J$ = 2.2 Hz, 1 H, Ar-H) ppm. $C_{12}H_{16}O_3$ (208.25): calcd. C 69.21, H 7.74; found C 69.32, H 7.72.

**(+)-(3*S*)-6,7-Dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromene (9d) by Ring-Closure of (*S*)-8d:** [(*S*)-**8d**: $[\alpha]_D^{20}$ = +26.8 ($c$ = 1.85, $CH_2Cl_2$); lit. for (*R*)-**8d**: $[\alpha]_D^{22}$ = –21.7 ($c$ = 0.40, $CHCl_3$)].[28] White crystals (94%): m.p. 57–59 °C. $[\alpha]_D^{20}$ = +111.0 ($c$ = 1.29, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.35 (d, $J$ = 6.1 Hz, 3 H, $CH_3$), 2.63 (d, $J$ = 6.65 Hz, 2 H, $CH_2$–CH), 3.71–3.81 (m, 1 H, CH), 3.85 (s, 6 H, 2 × Ar-$OCH_3$), 4.76 (s, 2 H, $OCH_2$), 6.49 (s, 1 H, Ar-H), 6.58 (s, 1 H, Ar-H) ppm. $C_{12}H_{16}O_3$ (208.25): calcd. C 69.21, H 7.74; found C 69.15, H 7.75.

**(+)-(7*S*)-7-Methyl-7,8-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]isochromene (9e) by Ring-Closure of 8e:** [**8e**: $[\alpha]_D^{20}$ = +28.2 ($c$ = 1.17, $CH_2Cl_2$); lit. $[\alpha]_D^{20}$ = +34.0 ($c$ = 1.00, $CHCl_3$)].[29] White crystals (77%): m.p. 101–104 °C. $[\alpha]_D^{20}$ = +123.3 ($c$ = 1.27, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.32 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.61 (d, $J$ = 6.6 Hz, 2 H, $CH_2$–CH), 3.68–3.84 (m, 1 H, CH), 4.72 (s, 2 H, $OCH_2$), 5.89 (s, 2 H, $OCH_2O$), 6.46 (s, 1 H, Ar-H), 6.55 (s, 1 H, Ar-H) ppm. $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.64, H 6.30.

**(+)-(3*S*)-5-Bromo-8-methoxy-3-methyl-3,4-dihydro-1*H*-isochromene (9f) and (2*S*)-1-Bromo-4-methoxy-2-(2-methoxymethoxy-propyl)benzene (8h) by Ring-Closure of 8f**

**Compound 9f:** White crystals (73%): m.p. 41–43 °C. $[\alpha]_D^{20}$ = +92.2 ($c$ = 1.56, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.38 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.47 (dd, $J$ = 17.0, 10.7 Hz, 1 H, $CH_2$a), 2.76 (dd, $J$ = 17.0, 1.8 Hz, 1 H, $CH_2$b), 3.70–3.74 (m, 1 H, CH), 3.78 (s, 3 H, $OCH_3$), 4.57 (d, $J$ = 16.0 Hz, 1 H, $OCH_2$a), 4.90 (d, $J$ = 16.0 Hz, 1 H, $OCH_2$b), 6.59 (d, $J$ = 8.7 Hz, 1 H, 7-H), 7.37 (d, $J$ = 8.7 Hz, 1 H, 6-H) ppm. $C_{11}H_{13}BrO_2$ (257.12): calcd. C 51.38, H 5.10; found C 51.49, H 5.12.

**Compound 8h:** Colorless oil (15%): $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.22 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.81 (dd, $J$ = 13.4, 6.1 Hz, 1 H, $CH_2$a), 2.97 (dd, $J$ = 13.4, 6.1 Hz, 1 H, $CH_2$b), 3.21 (s, 3 H, $OCH_3$), 3.78 (s, 3 H, Ar–$OCH_3$), 3.99–4.09 (m, 1 H, CH), 4.52 (d, $J$ = 6.8 Hz, 1 H, $OCH_2$a), 4.63 (d, $J$ = 6.8 Hz, 1 H, $OCH_2$b), 6.64 (dd, $J$ = 8.7, 3.1 Hz, 1 H, 5-H), 6.82 (d, $J$ = 3.1 Hz, 1 H, 3-H), 7.40 (d, $J$ = 8.7 Hz, 1 H, 6-H) ppm. Calcd mass for $C_{12}H_{17}BrO_3$ $[M + Na]^+$ 311.0253; found 311.0264.

**(+)-(3*S*)-6-Methoxy-3-methyl-3,4-dihydro-1*H*-isochromene (9g) and (+)-(3*S*)-8-Methoxy-3-methyl-3,4-dihydro-1*H*-isochromene (9c) by Ring-Closure of 8c**

**Compound 9g:** Solid (71%): m.p. 44–46 °C. $[\alpha]_D^{20}$ = +103.9 ($c$ = 1.36, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.35 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.68 (d, $J$ = 7.0 Hz, 2 H, $CH_2$–CH), 3.78 (s, 3 H, $OCH_3$), 3.71–3.87 (m, 1 H, CH), 4.78 (s, 2 H, $OCH_2$), 6.62–6.93 (m, 3 H, Ar-H) ppm. $C_{11}H_{12}O_3$ (178.23): calcd. C 74.13, H 7.92; found C 74.05, H 7.94.

**Compound 9c:** Colorless oil (19%): $[\alpha]_D^{20}$ = +133.6 ($c$ = 1.38, $CH_2Cl_2$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.34 (d, $J$ = 6.1 Hz, 3 H, $CH_3$), 2.67 (d, $J$ = 6.6 Hz, 2 H, $CH_2$), 3.74–3.78 (m, 1 H, CH), 3.78 (s, 3 H, $OCH_3$), 4.64 (d, $J$ = 15.9 Hz, 1 H, $OCH_2$a), 4.93 (d, $J$ = 15.9 Hz, 1 H, $OCH_2$b), 6.67 (d, $J$ = 7.9 Hz, 1 H, Ar-H), 6.70 (d, $J$ = 7.9 Hz, 1 H, Ar-H), 7.13 (t, $J$ = 7.9 Hz, 1 H, 6-H) ppm.

**(–)-(4a*R*,10b*S*)-2,3,4,4a,6,10b-Hexahydro-1*H*-benzo[*c*]chromene (16) by Ring-Closure of 15:** Colorless oil (76%): $[\alpha]_D^{20}$ = –123.5 ($c$ = 1.49, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.36–1.54 (m, 4 H, 2 × $CH_2$), 1.89 (t, $J$ = 11.9 Hz, 2 H, $CH_2$), 2.07 (dd, $J$ = 12.2, 3.1 Hz, 1 H, $CH_2$), 2.45 (d, $J$ = 13.2, Hz, 1 H, $CH_2$), 2.57 (t, $J$ = 9.9 Hz, 1 H, 4-H), 3.27 (dt, $J$ = 10.3, 3.8 Hz, 1 H, 3-H), 4.86 (d, $J$ = 15.0 Hz, 1 H, 1-$CH_2$a), 4.93 (d, $J$ = 15.0 Hz, 1 H, 1-$CH_2$b), 6.97 (d, $J$ = 7.3 Hz, 1 H, Ar-H), 7.16 (t, $J$ = 7.3 Hz, 1 H, Ar-H), 7.20 (t, $J$ = 7.3 Hz, 1 H, Ar-H), 7.27 (d, $J$ = 7.3 Hz, 1 H, Ar-H) ppm.

**(+)-(3*S*)-3-Methyl-3,4-dihydro-1*H*-isochromen-1-one (17a):** Jones reagent (6 drops) was added dropwise at 16 °C to a solution of **9a** (17 mg, 0.12 mmol) in glacial acetic acid (0.6 mL). After the mixture had been stirred for 2 h, water (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layer was washed twice with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated, and the residue was purified by preparative TLC with hexane/acetone (19:1) as eluent to give **17a** (13.8 mg, 74%) as a yellow oil: $[\alpha]_D^{20}$ = +90.2 ($c$ = 0.55, $CH_2Cl_2$) [lit. $[\alpha]_D^{26}$ = +280.0 ($c$ = 0.23, $CHCl_3$)].[30] $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.52 (d, $J$ = 6.3 Hz, 3 H, $CH_3$), 2.94–2.98 (m, 2 H, $CH_2$), 4.64–4.74 (m, 1 H, CH), 7.23 (dd, $J$ = 7.6, 1.4 Hz, 1 H, 5-H), 7.39 (dt, $J$ = 7.6, 1.4 Hz, 1 H, 7-H), 7.54 (dt, $J$ = 7.6, 1.4 Hz, 1 H, 6-H), 8.1 (dd, $J$ = 7.6, 1.4 Hz, 1 H, 8-H) ppm.

**(+)-(3*S*)-6,7-Dimethoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one (17b):** A solution of DMDO in acetone (0.08 M, 43 mL) was added to the solution of **9d** (70 mg, 0.34 mmol) in acetone (10 mL), and the mixture was stirred for 24 h, washed with $NaHCO_3$ solution, and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo, and the residue was purified by preparative TLC (hexane/ethyl acetate 2:5) to give **17b** (49.5 mg, 66%). The product was crystallized from hexane to afford white crystals: m.p. 92–93 °C. $[\alpha]_D^{20}$ = +109.5 ($c$ = 0.58, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.50 (d, $J$ = 6.3 Hz, 3 H, $CH_3$), 2.76–2.93 (m, 2 H, $CH_2$), 3.90 (s, 3 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$), 4.57–4.74 (m, 1 H, 3-H), 6.65 (s, 1 H, 5-H), 7.54 (s, 1 H, 8-H) ppm. IR (KBr): 2970, 2940, 2838, 1712, 1268, 1134 $cm^{-1}$. $C_{12}H_{14}O_4$ (222.24): calcd. C 64.85, H 6.35; found C 64.97, H 6.33.

**(+)-(3*S*)-8-Methoxy-3-methyl-3,4-dihydro-1*H*-isochromen-1-one (17c):** Compound **9c** (26 mg, 0.15 mmol) was dissolved in acetic

acid/acetone (2:1, 3 mL) and the system was cooled to 0 °C. A solution of Jones reagent (1 mL) in acetic acid/acetone (2:1, 3 mL) was added dropwise, the solution was stirred for 20 min and then allowed to warm to room temperature, water (10 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic layer was washed with saturated $NaHCO_3$ (3 × 20 mL) and brine, dried ($MgSO_4$), and concentrated, and the residue was purified by column chromatography (toluene/ethyl acetate 1:1) to give **17c** (14.5 mg, 52%) as a white solid: m.p. 81–83 °C. $[a]_D^{20}$ = +238.1 ($c$ = 0.58, $CHCl_3$) [lit. $[a]_D^{26}$ = +261.0 ($c$ = 0.52, $CHCl_3$)].[28] $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.48 (d, $J$ = 6.3 Hz, 3 H, $CH_3$), 2.85 (dd, $J$ = 16.0, 3.2 Hz, 1 H, $CH_2$a), 2.89 (dd, $J$ = 16.0, 10.9 Hz, 1 H, $CH_2$b), 3.95 (s, 3 H, $OCH_3$), 4.54–4.58 (m, 1 H, CH), 6.79 (d, $J$ = 8.0 Hz, 1 H, Ar-H), 6.91 (d, $J$ = 8.0 Hz, 1 H, Ar-H), 7.45 (t, $J$ = 8.0 Hz, 6-H) ppm. $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.81, H 6.30.

**(–)-(1*R*,3*S*)-1-Methoxy-3-methyl-3,4-dihydro-1*H*-isochromene (18a) and (+)-(3*S*)-3-Methyl-3,4-dihydro-1*H*-isochromen-1-one (17a):** MeOH (5 drops) and DDQ (150 mg, 0.66 mmol) were added to a solution of **9a** (73 mg, 0.50 mmol) in $CH_2Cl_2$ (8 mL), and the mixture was stirred at room temperature for 20 h, treated with $NaHCO_3$ solution, and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layer was dried over $Na_2SO_4$, filtered, and concentrated in vacuo, and the residue was purified by preparative TLC (hexane/ethyl acetate 19:1) to give **18a** (42 mg, 48%) and **17a** (18 mg, 27%) as colorless oils.

**Compound 18a:** $[a]_D^{20}$ = –2.5 ($c$ = 1.59, $CHCl_3$). $^1$H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.37 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.67 (d, $J$ = 7.4 Hz, 2 H, $CH_2$), 3.54 (s, 3 H, $OCH_3$), 4.18–4.28 (m, 1 H, 3-H), 5.48 (s, 1 H, 1-H), 7.06–7.11 (m, 1 H, Ar-H), 7.19–7.25 (m, 3 H, Ar-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta$ = 20.48 ($CH_3$), 34.84 (C-4), 54.49 ($OCH_3$), 62.39 (C-3), 97.89 (C-1), 125.62 (C-Ar), 126.62 (C-Ar), 127.47 (C-Ar), 127.61 (C-Ar), 132.98 (C-Ar), 133.57 (C-Ar) ppm. IR (KBr): 2978, 2934, 1728, 1280, 1238, 1122 cm$^{-1}$. $C_{10}H_{10}O_2$ (178.23): calcd. C 74.06, H 6.21; found C 74.01, H 6.22.

**Compound 17a:** $[a]_D^{20}$ = +128.5 ($c$ = 0.71, $CHCl_3$). (See $^1$H NMR spectroscopy data earlier.) $^{13}$C NMR (50 MHz, $CDCl_3$, 25 °C): $\delta$ = 20.83 ($CH_3$), 34.80 (C-4), 75.02 (C-3), 124.97 (C-Ar), 127.26 (C-Ar), 127.58 (C-Ar), 130.20 (C-Ar), 133.61 (C-Ar), 139.07 (C-Ar), 165.56 (C-1) ppm. IR (KBr): 2978, 2934, 1728, 1280, 1238, 1122 cm$^{-1}$.

**(–)-(1*R*,3*S*)-1,6,7-Trimethoxy-3-methyl-3,4-dihydro-1*H*-isochromene (18b):** MeOH (4 mL) and DDQ (50 mg, 0.22 mmol) were added to a solution of **9d** (40 mg, 0.19 mmol) in $CH_2Cl_2$ (5 mL), and the mixture was stirred at room temperature for 5 h, treated with $NaHCO_3$ solution, and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layer was dried on $Na_2SO_4$, filtered, and concentrated in vacuo, and the residue was purified by preparative TLC (hexane/ethyl acetate 3:2) to give **18b** (31 mg, 68%). The product was crystallized from hexane: m.p. 91–92 °C. $[a]_D^{20}$ = –16.1 ($c$ = 0.33, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.36 (d, $J$ = 6.2 Hz, 3 H, $CH_3$), 2.58–2.61 (m, 2 H, $CH_2$), 3.54 (s, 3 H, $OCH_3$), 3.85 (s, 3 H, Ar-$OCH_3$), 3.87 (s, 3 H, Ar-$OCH_3$), 4.15–4.25 (m, 1 H, 3-H), 5.42 (s, 1 H, 1-H), 6.56 (s, 1 H, 5-H), 6.72 (s, 1 H, 8-H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$, 25 °C): $\delta$ = 20.51 ($CH_3$), 34.42 (C-4), 54.61 ($OCH_3$), 55.12 (2 × Ar-$OCH_3$), 62.83 (C-3), 98.05 (C-1), 109.83 (C-8), 110.06 (C-5), 124.53 (C-8a), 126.08 (C-5a), 145.91 (C-6), 148.12 (C-7) ppm. $^3J_{C3,1H}$ = 6.0 Hz, $^3J_{C1,3H}$ = 1–2 Hz, $^3J_{C8,1H}$ = 2.2 Hz. IR (KBr): 2966, 2928, 2834, 1260, 1078 cm$^{-1}$. $C_{13}H_{18}O_4$ (238.28): calcd. C 65.53, H 7.61; found C 65.65, H 7.58.

**Supporting Information** (see also the footnote on the first page of this article): Experimental data for **8a**–**c**, **8a**–**c-Ac**, **8i**, *rac*-**8i**, **8j**, *rac*-**8j**, **9c**, **9d**, *bis*-Boc derivatives of **11a**–**c**, **11a**–**c**, **13a**–**c**. $^1$H NMR spectra of **8a**–**h**, **8j**, **8a**–**c-Ac**, *rac*-**8j**, **9a**, **9c**–**g**, **16**, **17a**–**c**, **18b**. CD spectra of **13a**–**c**, (*S*)-**9a**–**g**, (4a*R*,10b*S*)-**16**, (*S*)-**17a**–**c**, (1*R*,3*S*)-**18b**.

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