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Absolute stereochemistry of dihydrofuroangelicins bearing C-8 substituted double bonds: a combined chemical/exciton chirality protocol †

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Coumarins are associated with a variety of pharmacological activities which have led to the synthesis of numerous derivatives. However, no general method for determination of the absolute configuration of chiral coumarins is known. This has now been achieved for a series of dihydrofuroangelicins bearing a variety of C-8 substituted double bonds, synthesized in the racemic form and resolved through enantioselective chromatography. A combined chemical/chiroptical protocol has been developed in which the C=C double bonds are replaced with a styrenoid chromophore through either (i) cross metathesis, (ii) Heck reaction, or (iii) a combined method of cross metathesis and Heck reaction with about 1 mg sample under mild conditions. The coupling between the styrenoid and coumarin chromophores gives rise to clear-cut exciton coupled CD curves, suitable for assignments of absolute configurations. The solution conformation of the styrenoid derivatives is determined by NMR and DFT molecular modeling; the electronic structure of the 7-hydroxy coumarin chromophore is also clarified by semi-empirical and TDDFT methods. The conformation thus derived, in conjunction with quantitative DeVoe's coupled-oscillator CD calculation, establishes the absolute configurations of the coumarins. The theoretical study described herein justifies the straightforward approach of the current chemical/exciton chirality protocol to this type of dihydrofuroangelicins.

Introduction

Coumarins exhibit various pharmacological activities.[1] Marmesin and columbianetin derivatives are cytotoxic against KB cells,[2] inhibit cAMP[3] and mediate the action of acetylcholinesterase involved in Alzheimer's disease, while a related dihydropsoralen, from *Borstenia contrajerva*, is reported to moderate the toxicity of rattlesnake venom.[4] Warfarin is an anticoagulant (the *S* isomer is more potent) that depresses the formation of prothrombin,[5] while synthetic coumarins have been used for treating skin diseases such as psoriasis and vitiligo.[6] Such conspicuous pharmacological activities have led to numerous syntheses of chiral coumarins over the past 30 years, including the recent preparations of substituted dihydrofuroangelicins **A** and dihydrofuropsoralens **B** (Chart 1).[7] This method relies on the palladium catalyzed annulation of 1,3-dienes by *o*-iodoumbelliferones, proceeding in 70–85% yields with a variety of 1,3-dienes; many substituted furocoumarins **A** and **B** have been synthesized using this route. Although efficient enantiomeric separations of these compounds have been reported,[8] no efficient method to determine their absolute configurations (when $R_1 \neq R_2$) is known. In general, the assignment of the absolute configuration of chiral coumarin and isocoumarin derivatives has relied on chemical correlations with compounds of known configuration,[9] empirical comparisons of optical rotations and CD curves,[10] or other empirical approaches such as Horeau's or modified NMR Mosher's method.[11]

The circular dichroic (CD) exciton chirality method is a reliable non-empirical approach based on the coupled-oscillator theory, which has been widely employed for determining the absolute configuration of various organic compounds, including many natural products.[12] In the context of coumarin chemistry, the application of the exciton method has so far been limited to rigid dimers;[13] on the other hand, it is noteworthy that a coumarin-based chromophore, 7-diethylaminocoumarin-3-carboxylic acid, has been recently proposed as an exciton CD-reporter group.[14] In view of the potentiality offered by the presence of the coumarin chromophore in compounds **A** and **B** (Chart 1), it was considered that if a suitable chromophore were present at C-8, it might lead to diagnostic exciton coupling with the coumarin moiety and allow determination of the absolute configuration.

This strategy was tested with one of the synthetic chiral dihydrofuroangelicins, 4-methyl-8-(2-*E*-phenylethenyl)-8,9-dihydro-2*H*-furo[2,3-*h*]-1-benzopyran-2-one **1**.[15] This compound was already endowed with a styrenoid chromophore which coupled favorably with the coumarin moiety due to the proximity of their UV bands. In fact, the CD spectrum of **1** showed a moderately intense CD couplet in the 240–330 nm region, in correspondence with the two more intense red-shifted electronic absorptions of the styrene and coumarin chromophores. The solution conformation of **1** was elucidated by NMR and molecular modeling, and the interchromophoric arrangement turned out to be sensitive to the absolute configuration at the stereogenic center. Application of the exciton chirality approach, substantiated by quantitative CD calculations by means of DeVoe's method, afforded assignment of the absolute configuration of **1** in a non-empirical manner.[15]

† Electronic supplementary information (ESI) available: Relative energies and relevant geometrical parameters of DFT-optimized structures of **sty-2** and **sty-5** (Table ESI1). Calculated and experimental $^3J_{Me8,H9a}$ and $^3J_{Me8,H9b}$ values (in Hz) for **sty-2** and **sty-5** (Table ESI2). UV absorption spectrum of 7-hydroxy-4-methylcoumarin in CH_3CN (Fig. ESI1). Description of the procedure for estimating transition dipole moment positions from excited-states calculations. See http://www.rsc.org/suppdata/ob/b3/b312542d/

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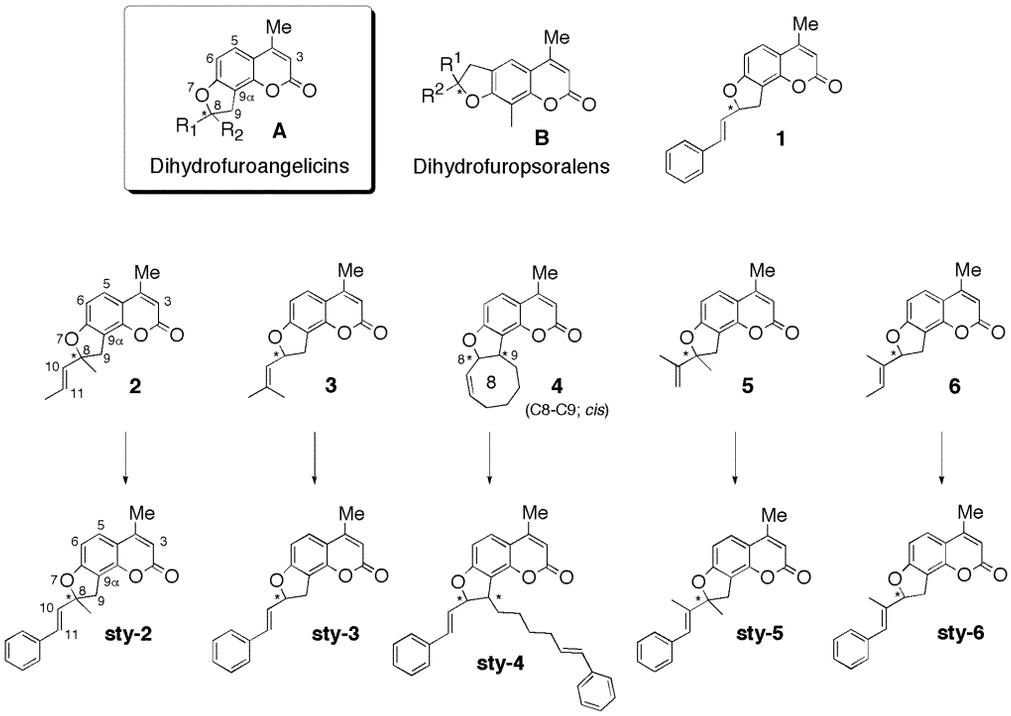


Chart 1 The structures of various C-8 alkenyl substituted dihydrofuroangelicins and their corresponding styrene derivatives.

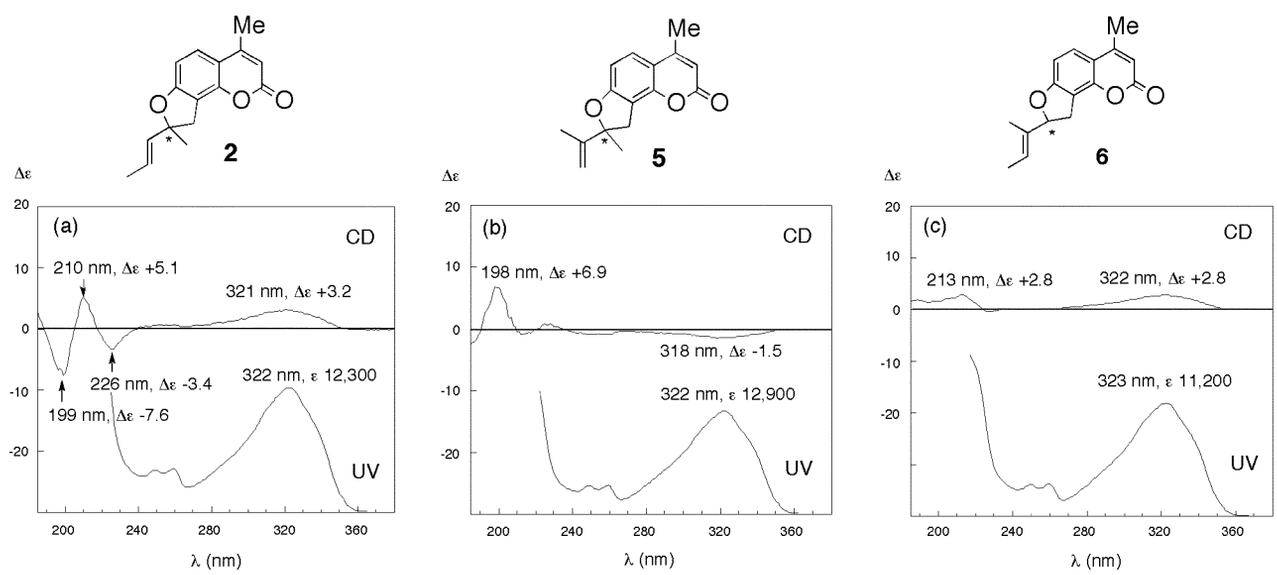


Fig. 1 UV (bottom) and CD (top) spectra of dihydrofurocoumarins **2**, **5**, and **6** in acetonitrile. Spectrum (a), first eluted enantiomer of **2** separated by chiral HPLC, 4.16×10^{-4} M; spectrum (b), first eluted enantiomer of **5** separated by chiral HPLC, 6.46×10^{-4} M; spectrum (c), first eluted enantiomer of **6** separated by chiral HPLC, 4.34×10^{-4} M. HPLC methodologies are given in reference 8.

On the basis of these results, we report herein a general protocol for the determination of absolute configurations of dihydrofuroangelicins **2**–**6** linked at C-8 to variously substituted double bonds (R_1 or R_2, Chart 1). As shown in Fig. 1 for chiral furocoumarins **2**, **5**, and **6**, these compounds have weak CD spectra above 200 nm; in particular, the intense red-shifted coumarin π–π* transition (band I at λ_{max} *ca.* 320 nm, $\varepsilon = 13000$) gives rise to only modest Cotton effects. It is conceivable that some contributions to the observed CD arise from the exciton coupling between the coumarin and the lowest energy π–π* transition of the C=C double bond (*ca.* 195 nm, ε 12000); however, the latter is clearly obscured by overlap with other transitions around 200 nm. In conclusion, the weakness of these bands and absence of a clear-cut exciton feature hampers direct application of the exciton chirality.

Therefore, it was desirable to devise a scheme that converts the side chain double bond of dihydrofuroangelicins **2**–**6** into other suitable chromophores, for example, a styrenoid (K band at λ_{max} 248 nm, $\varepsilon = 15000$),[16] that would couple more effectively with the coumarin. Moreover, considering the scarcity of such chiral coumarins either from natural sources or upon enantioselective separation of racemates, it was important to have an efficient micro-scale method to convert the variously substituted double bonds into aromatic chromophores under mild conditions, leaving the coumarin moiety intact. Once the derivatization into suitable styrenoid chromophores was achieved, the corresponding CD spectra were found to be suitable for a straightforward exciton analysis. Prior to this, the solution conformations were extensively studied by means of NMR and DFT molecular modeling. Moreover, the qualitative exciton chirality assignment was substantiated by means of quantitative CD calculations run with DeVoe's method;[17] to provide better parameters for DeVoe calculations, the electronic structure of 7-hydroxy coumarin chromophore was

also investigated with semi-empirical and time-dependent DFT techniques. The agreement between experimental and calculated CD (Boltzmann-weighted average for DFT-computed structures) allowed the absolute configuration of these furocoumarins to be established. Furthermore, the results from theoretical studies provide a sound basis for application of the combined chemical/chiroptical approach described in this paper to new C-8 alkenyl dihydrofuroangelicin analogs in a straightforward manner without extensive conformational analysis and CD calculations.

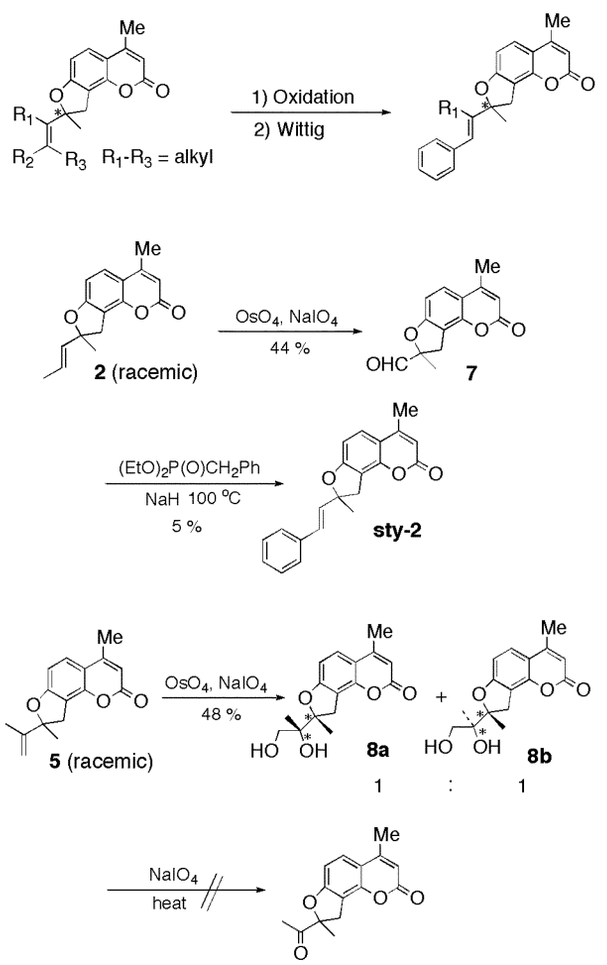
Results and discussion

Derivatization of dihydrofuroangelicins (2–6) into the styrenoid derivatives

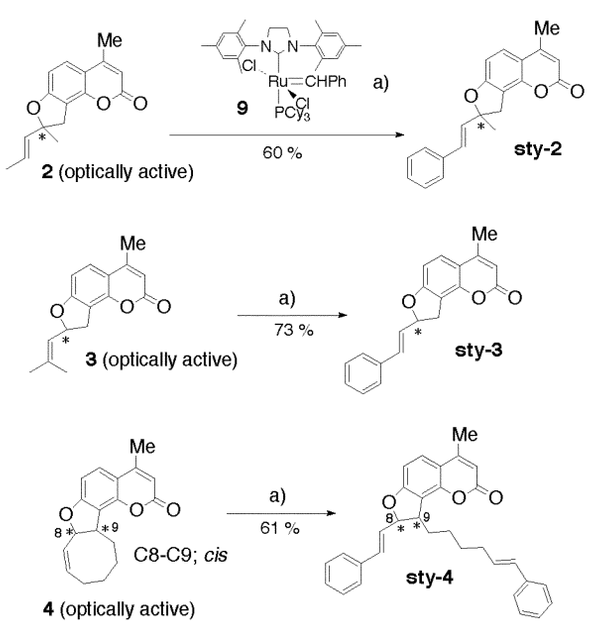
The initial strategy for the conversion of dihydrofuroangelicins **2**–**6** (Chart 1) into styrene derivatives is shown in Scheme 1. The dihydrofuroangelicins would be converted to the corresponding carbonyl compounds *via* the oxidative cleavage of the double bonds directly by ozonolysis or by the two-step procedure of dihydroxylation with osmium tetroxide (OsO_4) followed by treatment with sodium periodate ($NaIO_4$). Then, these carbonyl compounds were thought to react with Wittig reagents to provide the styrenoid derivatives. This strategy was first tested on racemic **2** and **5**, which were prepared in a large quantity according to the established method of palladium catalyzed annulation of 1,3-dienes by *o*-iodoumbelliferones.[7] Thus racemic **2** was reacted with a catalytic amount of OsO_4 in the presence of two equivalents of $NaIO_4$ for three hours at room temperature to give the corresponding aldehyde **7** in 44% yield. The employment of $OsO_4/NaIO_4$ oxidant was preferable to ozonolysis, because the exact amount of the reagent could be measured, thus avoiding over-oxidation of the coumarin double bond. When aldehyde **7** was reacted with Horner–Emmons reagent, diethyl benzylphosphonate, at 100 °C in THF, the corresponding (*E*)-styrene derivative of **2** was obtained with very low yield (less than 5% yield) and most of the starting material **7** was recovered. Presumably this was due to the sterically hindered quaternary carbon atom next to the aldehyde group in **7**.

Furthermore, the treatment of racemic **5** with $OsO_4/NaIO_4$ oxidant unexpectedly provided the diols **8a** and **8b** in 1 : 1 diastereomeric ratio in 48% yield, without any trace of the carbonyl derivative even at elevated temperatures. The resistance of these diols toward $NaIO_4$ oxidation might be related again to the steric hindrance around the two consecutive quaternary carbon centers in **8a** and **8b**. Namely, the oxidant $NaIO_4$ would fail to access the diols to form the corresponding cyclic iodoester that provides the ketone derivative. Therefore, it was concluded that conventional oxidative cleavage of the double bonds followed by Wittig chemistry is not applicable for derivatization of these sterically hindered furocoumarins such as **2** and **5**.

On the other hand, during our recent study on developing a new chemical/chiroptical method for configurational assignment of allylic alcohols and amines,[16] we found out that cross olefin metathesis[18,19] is suited for introducing the styrene chromophore as a CD reporter group. By using the recently developed Grubbs' second generation ruthenium catalyst **9**[20] (structure shown in Scheme 2), the linear allylic mono- and 1,2-disubstituted C=C double bonds can be replaced with the styrene group in high yields under mild conditions without epimerization of the substrates.[21] The styrenoid chromophore introduced then couples with the allylic acylate to yield a distinct couplet. The method overcomes the restriction of the conventional allylic benzoate method that gives rise to weak CD couplets, for which in many cases only one wing of the couplet is observable.[16] Therefore, we considered cross metathesis as an attractive alternative in the present case; it was interesting to examine how this chemistry would work in the conversion of a variety of the sterically hindered C=C double bonds, namely, 1,2-disubstituted (**2**), 1,2,2-trisubstituted (**3**), endocyclic double bond (**4**), 1,1-disubstituted (**5**), and 1,1,2-trisubstituted (**6**) double bonds into the corresponding styrenoids. If the cross metathesis did not work, combined methods with



Scheme 1 Initial trials for conversion of **2** and **5** into styrenoids *via* an oxidation–Wittig strategy.



Scheme 2 Conversion of **2**, **3**, and **4** into styrenoids *via* cross metathesis with styrene. *Reagents and conditions*: (a) 10 equiv. styrene, 10 mol% of Grubbs' catalyst **9**, CH_2Cl_2, 40 °C.

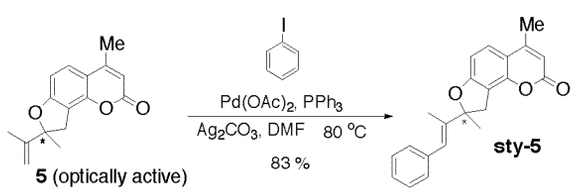
Table 1 UV and CD spectra of **sty-2**–**sty-6** in acetonitrile

Substrate	UV λ/nm (ε)[a]	CD λ/nm ($\Delta\varepsilon$)[a]	A_{CD} amplitude observed	Abs. config. at C-8
sty-2	321 (14000)	320 (+14.7)	+31.5	*S*
	251 (20000)	250 (−16.9)		
sty-3	322 (11200)	318 (−12.5)	−29.2	*R*
	251 (17400)	254 (+16.6)		
sty-4	320 (13200)	320 (−10.9)	−23.0	*R*
	251 (35100)	251 (+12.1)		
sty-5	322 (13500)	320 (−14.3)	−28.3	*R*
	247 (16900)	243 (+14.0)		
sty-6	321 (14200)	320 (+14.6)	+24.8	*S*
	249 (19900)	247 (−10.2)		

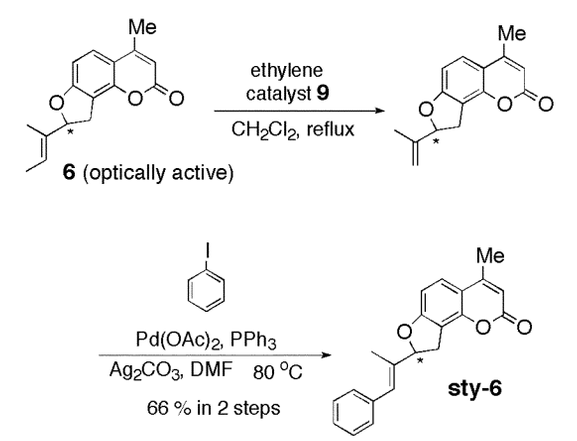
[a] In L mol^{-1} cm^{-1}.

other chemical transformations, *i.e.* Heck reaction, would be utilized.

After examination of a variety of reaction conditions, it was found that the adaptation of either cross metathesis,[18,19] Heck reaction, or combined cross metathesis and Heck reaction, satisfied the criteria of mild micro-scale reactions; all double bond substitution patterns in the dihydrofuroangelicins **2**–**6** (Chart 1) could be replaced with the styrenoid chromophore, yielding the styrene derivatives **sty-2**–**sty-6**. The final optimized results on the derivatization of the enantiopure coumarins, all of which were the first eluted enantiomers resolved by HPLC, are shown in Schemes 2–4 . The coumarins **3**–**5** were resolved by using a Chirobiotic TAG column, eluent heptane/ethanol and as first eluted enantiomers they are of (*R*)-configuration. The coumarins **2** and **6** were resolved on Chirobiotic T on the reversed phase, therefore these first eluted enantiomers **2** and **6** are of (*S*)-configuration (*cf.* Table 1). The detailed enantioselective separation of these dihydrofuroangelicins **2**–**6** is described in the Experimental section.



Scheme 3 Conversion of **5** into styrenoid *via* Heck reaction with iodobenzene.



Scheme 4 Transformation of **6** into styrenoid *via* combined cross metathesis and Heck reaction.

The chemical transformations employed for the conversion of dihydrofuroangelicins **2**–**6** into the corresponding styrenoids, depending on the substitution patterns of the C=C double bonds, are summarized as follows.

(i) *Conversion by cross metathesis with styrene* (Scheme 2): The olefin cross metathesis is successful with 1,2-disubstituted, 1,2,2-trisubstituted, and endocyclic double bonds such as **2**, **3**, and **4**, respectively. Thus the reaction of 1,2-disubstituted derivative **2** with an excess amount of styrene, using 10 mol% of Grubbs' ruthenium catalyst **9** in CH_2Cl_2 at 40 °C for 10 h, cleanly provided the corresponding (*E*)-styrenoid derivative **sty-2** in 60% yield. Similarly, the 1,2,2-trisubstituted derivative **3** was transformed into the corresponding styrenoid, **sty-3**, in 73% yield. Furthermore, the endocyclic double bond in the eight-membered ring of **4** also gave the corresponding styrenoid derivative **sty-4** in 61% yield. As Grubbs and co-workers reported,[18] the thermodynamically more stable (*E*)-isomers could be obtained exclusively by the cross metathesis reaction with styrene and no (*Z*)-stereoisomers were observed. Furthermore, enantioselective HPLC analysis demonstrated that no epimerization occurs during the cross metathesis reaction: starting from an enantiopure sample of **3**, the corresponding enantiopure **sty-3** was obtained in >99% enantiomeric excess.

(ii) *Conversion by Heck reaction with iodobenzene* (Scheme 3): The 1,1-disubstituted *exo*-methylene double bond in **5** (first eluted enantiomer) was unexpectedly inactive to the cross metathesis with styrene, and starting material was recovered. We therefore utilized Heck reaction by reaction of **5** with iodobenzene in the presence of $Pd(OAc)_2$, triphenylphosphine, and silver carbonate in DMF at 80 °C for 5 h, to give the corresponding **sty-5** in 83% yield (Scheme 3).

(iii) *Transformation by the combined method of cross metathesis and Heck reaction* (Scheme 4): In the case of 1,1,2-trisubstituted derivative **6**, the direct transformation into the styrene derivative by use of either cross metathesis with styrene or Heck reaction was unsuccessful. Therefore, we utilized the combined method of cross metathesis with ethylene and Heck reaction as shown in Scheme 4. Thus the trisubstituted double bond in **6** was first converted into an exomethylene double bond by reaction with ethylene in the presence of Grubbs catalyst **9** in almost quantitative yield. Subsequently, the obtained exomethylene intermediate was subjected to Heck reaction, by reaction with iodobenzene, $Pd(OAc)_2$, triphenylphosphine, and silver carbonate in DMF, to provide the desired styrenoid derivative of **6** in 66% yield for two steps. It is noteworthy that the intermolecular metathesis, Heck reaction, and combined chemical transformations converted all the substitution pattern of the C=C double bonds in **2**–**6** (Chart 1) into the styrenoids **sty-2**–**sty-6** with about 1 mg sample under mild conditions.[16]

Conformational analysis of styrenoid derivatives sty-2–sty-6

Inspection of molecular models of **1** and **sty-2**–**sty-6** (Chart 1) suggests strong similarity between the conformational spaces for all the styrenoid compounds. In particular, two main degrees of conformational freedom may be recognized in all cases (Fig. 2): (a) the rotamerism around the C8–C10 bond, described by the dihedral angle O7–C8–C10–C11 ($d_{8,10}$); and (b) the dihydrofuranyl ring flip, which may be described by the O7–C8–C9–C9α torsion ($d_{8,9}$). These two are especially relevant to the application of exciton chirality method because, in

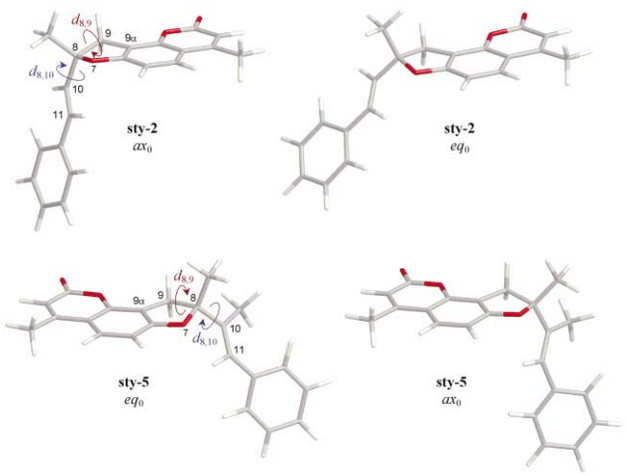


Fig. 2 The two lowest energy DFT (B3LYP/6-31G**, $CHCl_3$) optimized structures of (*S*)-**sty-2** and (*R*)-**sty-5**.

principle, the variation of both $d_{8,10}$ and $d_{8,9}$ may affect the relative arrangement of the coumarin and styrene chromophores. Our previous experience on compound **1** (which coincides with **sty-3**) confirmed that both torsional modes are effective;[15] the presence of further methyl groups at C-8 and C-10 position in **sty-2** and **sty-4**–**sty-6**, however, is likely to affect these torsions in an unpredictable way and cause some difference with respect to **1**.

Knowledge of the molecular conformation in solution is essential for applying the exciton chirality approach. It is well-known that application of the exciton chirality CD method for elucidation of absolute configuration is straightforward only in those cases where no conformational ambiguity exists.[22] In the current case, however, the solution conformations of styrenoid derivatives **sty-2** to **sty-6** are not necessarily clear since the styrene moieties are attached to five-membered rings that can adopt variable conformations depending on the substitution pattern. Therefore a completely novel conformational analysis for the compounds described in this paper, concentrating especially on **sty-2** and **sty-5**, was performed. The results for these two models may be easily transferred to the other derivatives **sty-4** and **sty-6**; as for the former, the conformational freedom of the chain at C-9 may be disregarded due to its negligible contribution to the CD (*vide infra*).

Molecular modeling of sty-2 and sty-5. The molecular conformations of **sty-2** and **sty-5** were investigated by means of DFT calculations (see Computational section for details). The dihydrofuranyl five-membered ring is capable of assuming two main conformations where the styrenyl substituent occupies a pseudo-equatorial (*eq*) or pseudo-axial (*ax*) position. For each *eq* and *ax* conformer, three energy minima (indicated with subscripts 0–2) were isolated relative to the variation around the $d_{8,10}$ dihedral, resulting in overall six conformers within 1.3–1.5 kcal mol^{-1} (that is, with non-negligible population at room temperature). The two lowest energy conformers (ax_0 and eq_0) for each compound are shown in Fig. 2; the relative energies and main geometrical parameters for all computed minima are listed in ESI† (Table ESI1). For both compounds, DFT calculations predict that *eq* and *ax* conformers are almost equally probable. The preferred value of the $d_{8,10}$ angle is around 0°, corresponding to a *syn* orientation between the C10–C11 double bond and the C8–O7 bond (Fig. 2); on the other hand, the energy barrier between the various C8–C10 rotamers is quite low (below 4–5 kcal mol^{-1}). Interestingly, such a preferred conformation is at odds with the results of DFT calculations for **1**, which favor a strongly preferred *eq* conformation with $d_{8,10} \approx 120°$ (C10–C11 double bond *syn* to C8–H8).

NMR experiments on sty-2 and sty-5. Modeling results predict that compounds **sty-2** and **sty-5** may assume multiple conformations that presumably are fast exchanging in solution, due to the low energy barriers relative to the $d_{8,10}$ and $d_{8,9}$ torsional modes. Therefore, NMR spectra represent the average conformational situation in which all conformers with significant population contribute. In fact, the ^{1}H-NMR spectra of **sty-2** and **sty-5** show a single set of signals at room temperature in $CDCl_3$.

The conformational situation about the dihydrofuranyl ring was investigated by means of NOE (Fig. 3) and long-range heteronuclear $^3J_{C,H}$ measurements (the numbering of protons (H_x) and methyl (Me_y) groups is according to Fig. 3). For both compounds **sty-2** and **sty-5**, proton H_{9a} which resonates at higher field than H_{9b} (3.27 *vs.* 3.43 ppm for **sty-2**, and 3.25 *vs.* 3.46 ppm for **sty-5**), shows an almost twofold stronger NOE with methyl Me_8 with respect to H_{9b}. On the contrary, H_{9b} shows stronger NOEs with the protons of the styrenyl group (H_{10} or Me_{10}, and H_{11}) with respect to H_{9a} (Fig. 3). It may be easily concluded that the styrenyl group is *cis* to H_{9b} and *trans* to H_{9a}. It is generally observed that axial protons are upfield shifted with respect to equatorial protons in cyclic systems.[23] This would lead to the conclusion that, in the average situation detected by NMR, proton H_{9a} and the styrenyl substituents are both pseudo-axial, while proton H_{9b} and Me_8 are both pseudo-equatorial. However, such generalization may hardly be extended to the dihydrofuranyl rings in **sty-2** and **sty-5**; effects other than the axial/equatorial position are likely to determine the chemical shifts of protons H_{9a}/H_{9b}, in particular the coumarin and styrene ring anisotropies.

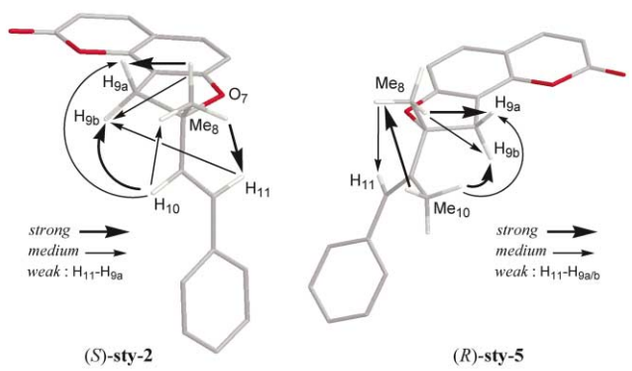


Fig. 3 Relevant ^{1}H NMR NOEs measured for (*S*)-**sty-2** and (*R*)-**sty-5** (ROESY spectra, mixing time 200 ms).

The *J*-couplings between protons H_{9a}/H_{9b} and methyl carbon at C-8 ($^3J_{Me8,H9a}$ and $^3J_{Me8,H9b}$) were expected to be informative of the respective dihedral angles, and ultimately of the $d_{8,9}$ torsion, through a specific Karplus-type relation (see Computational section).[24] We found that the experimental pairs of $^3J_{C,H}$ values fit reasonably well with those calculated as the average of all the DFT-computed minima (Boltzmann-weighted at 300 K), although experimental values are especially closer to the estimates for the *eq* conformers (see ESI, † Table ESI2).

The rotamerism around the C8–C10 bond may be depicted by means of relative NOEs (Fig. 3). For compound **sty-5**, methyl protons Me_{10} show similar NOE with Me_8 and H_{9b} protons, while proton H_{11} has twofold stronger NOE with Me_8 than H_{9b} and almost negligible with H_{9a}. The same is true for compound **sty-2**, where proton H_{10} shows relative NOEs in the order $H_{9b} > Me_8 \approx H_{9a}$ and proton H_{11} in the order $Me_8 > H_{9b} > H_{9a}$. The average situation detected is in accord with modeling results, which predict a favored conformation with *syn*-oriented C10–C11 double bond and C8–O7 bond.

In conclusion, the combination of computational and experimental techniques discloses the existence of multiple and fast-exchanging conformations for compounds **sty-2** and **sty-5**.

However, this conformational heterogeneity does not affect the following exciton chirality analysis, because molecular models suggest that the relative arrangement between the coumarin and styrene chromophores is not dramatically influenced by the possible molecular motions.

Experimental CD spectra and application of exciton chirality method

The absorption and CD spectra of the non-styrenoid compounds **2**–**6** (Fig. 1) are dominated by a strong broad band with a maximum at 322–323 nm, $\varepsilon \approx 11000$–$13000$. It is due to the electric dipole allowed HOMO–LUMO transition (band I) delocalized over the entire 7-hydroxy coumarin chromophore.[25] Instead only very weak bands are present in the 230–260 region, where the styrene chromophore undergoes a strong π–π^* transition centered around 250 nm (substituted benzene K band), which may couple favorably with the above coumarin one.

In fact, in the CD spectra in acetonitrile of compounds **sty-2**–**sty-6** (Table 1, Fig. 4a,b, and 5b,d), distinctive exciton couplets appear in the 230–350 nm region, with short wavelength maximum at 243–254 nm, crossover around 270 nm, and long wavelength maximum at 318–320 nm. These couplets mainly arise from the exciton coupling between the above styrene K and coumarin transition I; both transitions are polarized along the long axes of the respective aromatic systems[15] (see also next section). In keeping with our expectations, all compounds exhibit a split CD pattern typical for exciton chirality, namely, two opposite Cotton effects of moderate intensity (absolute amplitudes between 23–31 M^{-1} cm^{-1}) and rather symmetrical appearance (in terms of integrated areas of the two components). In particular, the exciton-coupled CD spectra of styrene derivatives are far more intense than the inherent CD of the parent coumarins above 240 nm (absolute $\Delta\varepsilon$ less than 3 M^{-1} cm^{-1} around 320 nm, Fig. 1); therefore, the contribution of optical activity mechanisms other than the coupled-oscillator one is minor. Although **sty-4** is endowed with a further styrene substituent, its CD spectrum is perfectly comparable to those of other mono-styrenoid derivatives; it is likely that, due to the long and flexible aliphatic chain attached at C-9, the second styrene makes only a small contribution to the overall CD spectrum.

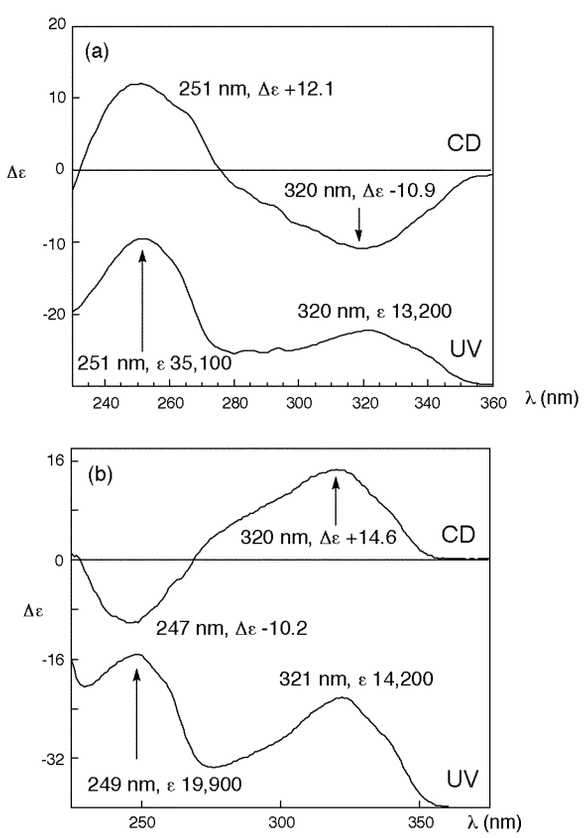


Fig. 4 UV (bottom) and CD (top) spectra of **sty-4** and **sty-6** in acetonitrile. Spectrum (a), (8*R*,9*R*)-**sty-4**, 1.17×10^{-5} M; spectrum (b), (8*S*)-**sty-6**, 3.02×10^{-5} M.

Simple inspection of the molecular models leads to the conclusion that all the styrene derivatives showing a positive exciton couplet in the 230–350 nm region, namely **sty-2** and **sty-6**, have the (8*S*) absolute configuration, while those showing a negative couplet, namely **sty-3**, **sty-4**, and **sty-5**, have the (8*R*) absolute configuration; compound **sty-4** is therefore (8*R*,9*R*). For example, in **sty-2** (Fig. 5a), in the lowest energy DFT conformer with an (8*S*) absolute configuration, a positive chirality is clearly defined by the long axes of the two aromatic chromophores; in other words, a clockwise twist is necessary to bring the transition dipole in the front in Fig. 5a (styrene K transition) onto the one in the back (coumarin transition I). For the second model compound **sty-5**, the (8*R*) absolute configuration for the lowest energy DFT conformer corresponds to a negative chirality defined by the two chromophores (Fig. 5c).

Importantly, for **sty-2** all six minimum energy conformations computed by DFT with (8*S*) absolute configuration, define similar positive chirality; this is quantitatively confirmed by DeVoe calculations (see following section). Similarly, all six DFT-computed conformations for (8*R*)-**sty-5** define a negative chirality. The same behavior has been observed for compound **sty-3** (which coincides with that previously reported for **1**),[15] and may be safely considered for the remaining derivatives **sty-4** and **sty-6**. It is apparent that, due to a favorable characteristic for this type of chiral coumarin and geometrical arrangement, *the chirality defined by the two transition dipoles responsible for the CD spectrum above 230 nm is completely dictated by the absolute configuration at C-8, independent of conformational rearrangements*. We believe that the underlying reason for this is the relative rigidity of the dihydrofurocoumarin skeleton which determines a definite orientation of the styrene substituent at the C-8 position with respect to the coumarin ring; the sense of twist between the two long-axis directions is thus unambiguous for all populated conformers.

In conclusion, the current combined chemical/chiroptical protocol based on styrene as the CD reporter group is an efficient and versatile method of assigning the absolute configuration of C-8 alkenyl substituted dihydrofuroangelicins. In particular, in the absence of substituents at C8–C10 which may revert the formal chirality, *a positive CD couplet in the 230–350 nm region is a proof of the (8S) configuration, and vice versa*.

Quantitative coupled-oscillator CD calculations

In order to test the scope and limitation of the previous qualitative application of the exciton chirality approach to coumarin derivatives **sty-2**–**sty-6**, we undertook a quantitative chiroptical analysis by means of coupled-oscillator DeVoe calculations for the two model compounds **sty-2** and **sty-5**. The DeVoe method[17] offers a means for calculating full CD spectra[26] in the approximation that the coupled-dipole mechanism makes the dominant contribution to the CD spectrum, in common with the exciton chirality method. In the current case it was especially interesting to compare calculated spectra for various possible conformations of **sty-2** and **sty-5**, given the difficulty of obtaining experimental data concerning conformer populations.

It is a necessary prerequisite for any exciton chirality application to clarify, in addition to the molecular conformation, the polarization directions of the coupled transition moments. In a previous paper,[15] we obtained such information with semi-empirical CNDO/S-CI calculations. As a matter of fact, higher level theoretical treatments seem to be lacking for 7-hydroxy coumarin,[25,27] while available for the parent

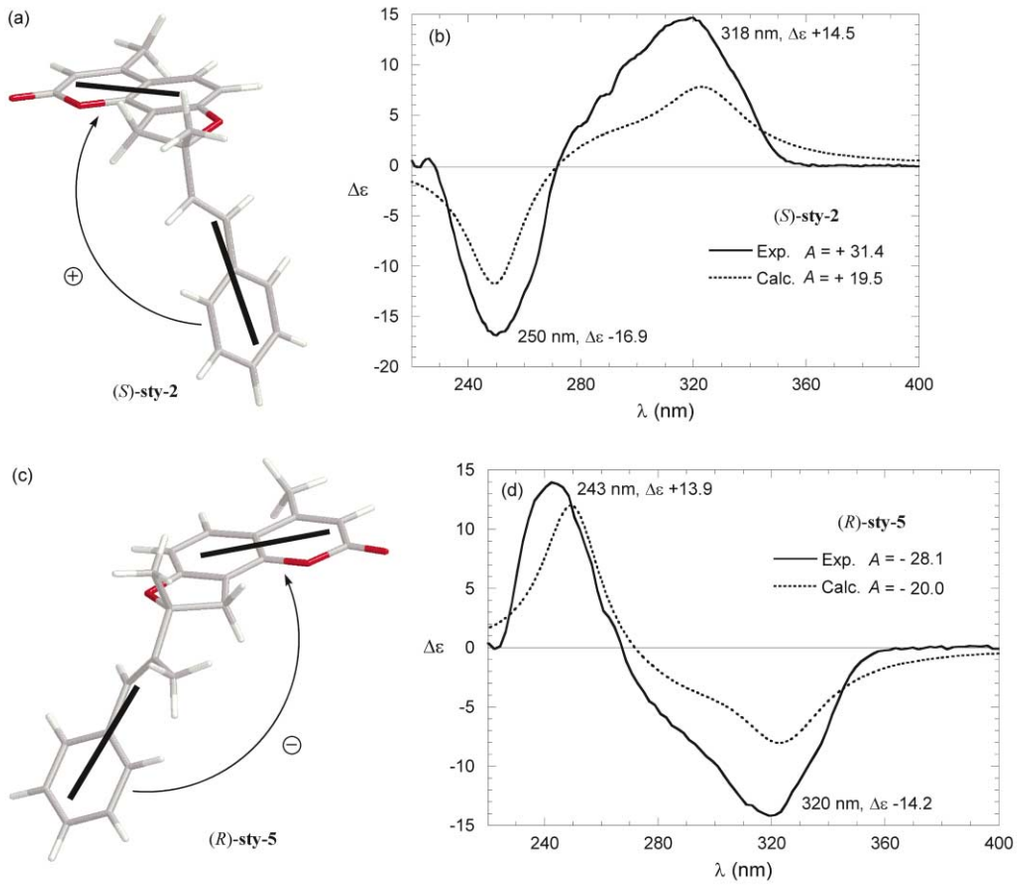


Fig. 5 (a,c) Absolute sense of twist defined by styrene K (in the front) and coumarin I transition (in the back) for the lowest energy conformers of (*S*)-**sty-2** (a) and (*R*)-**sty-5** (c). (b,d) Experimental (in acetonitrile, solid lines, $c = 4.94 \times 10^{-5}$ M (**sty-2**) and $c = 1.40 \times 10^{-5}$ M (**sty-5**)) and calculated (dotted lines) CD spectra of compounds (*S*)-**sty-2** (b) and (*R*)-**sty-5** (d). Calculated spectra were obtained with the DeVoe method as the Boltzmann-weighted average at room temperature for the six lowest energy minima computed by DFT (see text).

coumarin chromophore and some of its derivatives.[28] It is noteworthy that in some special cases, a critical geometrical situation also renders the knowledge of the exact position of the transition dipoles within the chromophore framework indispensable for application of exciton chirality.[29] While this parameter is not experimentally accessible, it can be calculated if accurate molecular orbitals are available.[30] For these reasons, the electronic properties of 7-hydroxy coumarin chromophore were newly investigated prior to DeVoe calculations.

Chromophore electronic structures. The absorption spectrum of 7-hydroxy coumarin chromophore exhibits, in addition to the above discussed band I (λ_{max} = 319 nm, ε_{max} = 13500 for 7-hydroxy-4-methylcoumarin in acetonitrile; see ESI,† Fig. ESI1), a distinctive shoulder around 290 nm, arising from a second π–π* transition (band II).[25] Weaker bands are also present in the 240–250 nm region (band III). Below 220 nm strong bands appear due to higher energy transitions.

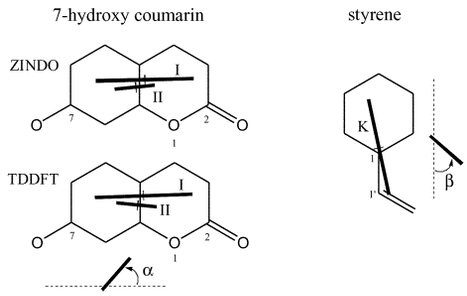
The results of our electronic structure calculations (see Computational section), with both semi-empirical ZINDO/S-CI and TDDFT (PBE0/6-311+G(d,p) level) methods, are summarized in Table 2. ZINDO/S-CI predicts well the position and intensity of the observed bands I-III above 230 nm; however, a fourth intense band is found at 232 nm which has no experimental correspondence. TDDFT calculations, on the other hand, underestimate the intensity of band II. A switch of the functional to B3LYP or changes in the basis size and inclusion of diffuse functions did not appreciably affect the calculated intensities, and the vertical excitation energies shifted only modestly.

Interestingly, transition dipole directions and positions are calculated in a very similar way by both methods used (see structures in Table 2), which is relevant to the chiroptical analysis. In particular, transitions I and II are polarized almost parallel to the coumarin long axis (tilt angles are less than 5° for transition I). The center of transition dipole I is almost in the middle of the coumarin chromophore, slightly displaced toward the pyranone ring (see ESI† for details on the transition dipole position calculations). It may be concluded that in the case of the red-shifted transition I of 7-hydroxy coumarin, using the semi-empirical transition moment direction and naively placing the dipole in the center of the chromophore, would not introduce any sizeable error in coupled-oscillator calculations.

As for the styrene chromophore, a recent theoretical CASPT2 study afforded reliable transition dipole polarization for the K band.[31] This is in excellent agreement with our ZINDO/S-CI calculation, which also placed the center of K transition dipole very close to phenyl C-1 carbon (Table 2).

DeVoe coupled oscillator calculations. Fig. 5b and d show the comparison between experimental CD spectra for compounds (*R*)-**sty-5** and (*S*)-**sty-2**, and those calculated with the DeVoe method as a Boltzmann-weighted average at 300 K of DFT-computed structures (see Computational section for details on calculation parameters). The agreement between calculated and experimental CD is very good, which confirms the exciton chirality assignment above. The weaker CD amplitude (by about 30–35%) might be due to various factors, in particular, to other mechanisms of optical activity: first, the inherent CD of C-8 alkenyl dihydrofuroangelicins **2**–**6**, contributing to around 10–20% of the experimental 320 nm CD band of **sty-2**–**sty-6**; second, a coupling with some high energy transitions. However, it must be stressed that in general the agreement between experimental and DeVoe-calculated intensities is expected not to be perfect, especially for such extended π-chromophoric

Table 2 Experimental and calculated electronic transitions in the 240–330 nm region for 7-hydroxy coumarin and styrene chromophores[a]



7-Hydroxy coumarin

	Experimental[b]					ZINDO[c]			TDDFT[d]		
Trans.	λ_{max}	ν_{max}	$\Delta\nu_{max}$	D	f	λ_{max}	f	α	λ_{max}	f	α
I	323	31.0	3.0	14.0	0.20	315	0.38	+1	293	0.32	+2
II	292	34.2	4.0	8.5	0.14	290	0.19	+5	271	0.03	–6
III	254	39.3	nc	0.3	0.01	237[e]	0.03	–44	238	0.05	–63

Styrene

	Experimental[f]					ZINDO[c]		
Trans.	λ_{max}	ν_{max}	$\Delta\nu_{max}$	D	f	λ_{max}	f	β
K	250	40.0	4.0	30.0	0.56	243	0.65	+12

[a] λ_{max} wavelength maximum, nm; ν_{max} frequency maximum, 10^3 cm^{-1}; $\Delta\nu_{1/2}$ half-height width, 10^3 cm^{-1}; D dipolar strength, square Debye; f, oscillator strength; α and β, tilt angles between transition polarization and chromophore long axes (see structures). [b] From the UV spectrum of 7-hydroxy-4-methyl coumarin in acetonitrile. [c] ZINDO/S-CI calculations with 16 × 16 (7-hydroxy coumarin) and 8 × 8 (styrene) single CI. [d] TDDFT calculations with PBE0/6-311+G(d,p). [e] A further band calculated at 232 nm, $f = 0.49$, $\alpha = -61$. [f] From the UV spectrum of styrene in hexane.

systems at relatively short interchromophoric distances (around 7 Å between the effective point-dipole positions, and only 2.5 Å between the closest points).

The most important result from DeVoe calculations is that *all the six DFT minimum energy conformations for (S)*-**sty-2** give a positive CD couplet with comparable intensity; similarly, *all six (R)*-**sty-5** conformers give a negative CD couplet with comparable intensities. This is a final proof that the configurational assignment made on the basis of the straightforward exciton chirality approach is trustworthy. In conclusion, the theoretical findings above justify *the application of the current chemicall/exciton chirality methodology to new C-8 alkenyl dihydrofuroangelicin homologues without the need for extensive conformational analysis or quantitative CD calculations*, unless there is reason to suspect some conformational ambiguity.

Conclusion

The absolute configurations of the chiral dihydrofuroangelicins **2**–**6** bearing a variety of C-8 substituted double bonds have been assigned based on a new combined chemical/chiroptical protocol. The method consists of the conversion of C=C double bonds into a styrenoid chromophore through either (i) cross metathesis, (ii) Heck reaction, or (iii) a combined method of cross metathesis and Heck reaction. The styrenoid derivatives **sty-2**–**sty-6** are obtained in good yields and mild conditions with about 1 mg samples. They exhibit moderately intense and clear-cut CD couplets in the 230–350 nm region, arising from the exciton coupling between the coumarin chromophore (band I around 320 nm) and the introduced styrene chromophore (K band around 250 nm). A straightforward exciton analysis of the CD spectra leads to the assignment of the absolute configurations of the styrenoid derivatives, and therefore of the parent compounds.

In order to test the scope and limitation of the current exciton chirality approach, quantitative CD calculations on **sty-2** and **sty-5** (as model compounds) were performed with the DeVoe coupled-oscillator method. The necessary geometrical and spectroscopic parameters were extracted from: (a) a thorough confomational analysis in solution, with NMR and DFT molecular modeling; (b) semi-empirical and TDDFT electronic structure calculations of 7-hydroxy coumarin chromophore. Excellent agreement was seen between the calculated and experimental CD spectra.

Experimental

Materials and general procedures

Anhydrous dichloromethane and dimethylformamide were dried and distilled from CaH_2. Acetonitrile used for CD and UV-vis measurements was Optima grade. Unless otherwise noted, materials were obtained from a commercial supplier and were used without further purification. Grubbs' second generation ruthenium catalyst, tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]-ruthenium(IV) dichloride **9**, is commercially available from Strem Chemicals. All reactions were performed in pre-dried glassware under Ar. Purification was performed either by column chromatography using ICN silica gel (32–63 mesh) or by preparative TLC using silica gel plates, 60 F-254, 0.25 mm, E. Merck.

^{1}H NMR spectra were obtained on Bruker DMX 300 or 400 MHz spectrometers and are reported in parts per million (ppm) relative to TMS (δ), with coupling constants (J) in Hertz (Hz). 2D NMR spectra were obtained on a Varian INOVA 600 spectrometer. 2D ROESY spectra were recorded by the hypercomplex method, using cw irradiation (3 kHz rf field), with the following parameters: mixing time 200 ms, 8 scans, 196 time increments, 2048 data points zero-filled to 1K–4K. $^3J_{C,H}$ couplings were measured by means of pulsed field gradient HMBC spectra, recorded by varying J-refocusing time

τ between 0.04–0.15 s (10 ms interval), corresponding to $J = 1/2\tau = 3.3$–12.5 Hz. $^3J_{C,H}$ values were estimated with least-squares sinusoidal fit of the experimental cross-peaks intensities as a function of J.[32]

Low- and high-resolution FAB mass spectra were measured on a JEOL JMS-DX303 HF mass spectrometer using a glycerol matrix and Xe ionizing gas.

UV-vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer, and reported as λ_{max}/nm (ε_{max}/L mol^{-1} cm^{-1}). The CD spectra were recorded on a JASCO-810 spectrophotometer, using a 1 cm cell, and the following conditions: SBW 1 nm, 50 nm min^{-1}, response 1 s, and 16 scans. The CD spectra were measured in millidegrees and normalized into $\Delta\varepsilon_{max}$/L mol^{-1} cm^{-1}.

Enantiomeric separation conditions

Separations and collections of dihydrofurocoumarin enantiomers **2**–**6** were achieved using a HP 1050 HPLC system with UV detector, auto injector, using computer controlled Chemstation data processing software. Two chiral stationary phases, trade named Chirobiotic T and Chirobiotic TAG columns (250 × 4.6 mm i.d.), were obtained from Advanced Separation Technologies, Inc. (Astec, Whippany, NJ, USA). The chiral stationary phases were prepared by bonding the chiral selectors to a 5 μm spherical porous silica gel through a linkage chain.[8] Detection wavelengths were varied between 220 nm and 327 nm, which correspond to the two molecular absorption maxima of the dihydrofurocoumarins. Analytical separations were reported previously.[8] The preparative separation conditions used to isolate mg quantities of the pure enantiomers of compounds **2**–**6** are as follows. Racemates **3**–**5** were dissolved in neat ethanol to a concentration of 10 mg ml^{-1}. Up to 100 microliters of each sample were injected onto a Chirobiotic TAG column and eluted with heptane/ethanol, 90/10 (v/v). The individual enantiomers were collected manually and concentrated by evaporation at room temperature (21 °C). Racemates **2** and **6** were dissolved in neat methanol to a concentration of 5 mg ml^{-1}. Up to 20 μl of each sample were injected onto a Chirobiotic T column and eluted in the reversed mode with H_2O/methanol, 65/35 (v/v). Fractions of the individual enantiomers (from successive injections) were added together after manual collection. They were concentrated under vacuum at room temperature (21 °C). All mobile phases were premixed and degassed before use. The flow rate was 1.0 ml min^{-1}.

Styrenoid derivative of 2 (sty-2)

To a solution of **2** (first eluted enantiomer, 1.0 mg, 3.9 μmol) in dichloromethane (2.0 mL) was added Grubbs' second generation ruthenium catalyst **9** (760 μg, 890 nmol) and styrene (890 nL, 7.8 μmol) at room temperature, and the mixture was stirred at 40 °C for 5.5 h. The reaction mixture was concentrated *in vacuo* to give the crude products which were purified by preparative thin layer chromatography on silica gel (17% ethyl acetate in hexane) twice to afford the corresponding styryl derivative (750 μg, 60%) as a white solid: IR ($CHCl_3$, cm^{-1}) 1717, 1616, 1385, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.39 (d, 3H, J = 0.8 Hz), 3.29 (d, 1H, J = 16.0 Hz), 3.46 (d, 1H, J = 16.0 Hz), 6.09 (d, 1H, J = 0.8 Hz), 6.40 (d, 1H, J = 16.4 Hz), 6.67 (d, 1H, J = 16.0 Hz), 6.80 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 7.6 Hz), 7.31 (dd, 2H, J = 7.6, 7.6 Hz), 7.38 (d, 2H, J = 7.2 Hz), 7.43 (d, 1H, J = 8.8 Hz); HRFABMS calcd for $C_{21}H_{19}O_3$ $[M + H]^+$ 319.1334, found 319.1343.

Styrenoid derivative of 3 (sty-3)

To a solution of **3** (first eluted enantiomer, 2.3 mg, 9.0 μmol) in dichloromethane (2.0 mL) was added Grubbs' second generation ruthenium catalyst **9** (1.7 mg, 2.0 μmol) and styrene (2.1 μL, 18 μmol) at room temperature, and the mixture was stirred at 40 °C for 3.5 h. The reaction mixture was concentrated *in vacuo* to give the crude products which were purified by preparative thin layer chromatography on silica gel (25% ethyl acetate in hexane) to afford the corresponding styryl derivative (2.0 mg, 73%) as a white solid. The spectral data were in good agreement with those reported previously.

Styrenoid derivative of 4 (sty-4)

To a solution of **4** (first eluted enantiomer, 1.5 mg, 5.3 μmol) in dichloromethane (1.0 mL) was added Grubbs' second generation ruthenium catalyst **9** (1.0 mg, 1.2 μmol) and styrene (6.1 μL, 53 μmol) at room temperature, and the mixture was stirred at 40 °C for 2.0 h. The reaction mixture was concentrated *in vacuo* to give the crude products which were purified by preparative thin layer chromatography on silica gel (17% ethyl acetate in hexane) twice to afford the corresponding styryl derivative (1.5 mg, 61%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38–1.46 (m, 2H), 1.60–1.68 (m, 1H), 1.84–1.89 (m, 2H), 2.14–2.17 (m, 2H), 2.31–2.40 (m, 1H), 2.38 (d, 3H, J = 0.8 Hz), 3.77 (dd, 1H, J = 13.6, 7.6 Hz), 5.42 (dd, 1H, J = 8.0, 8.0 Hz), 6.09 (d, 1H, J = 1.2 Hz), 6.11 (ddd, 1H, J = 16.0, 7.2, 7.2 Hz), 6.29 (d, 1H, J = 16.0 Hz), 6.44 (dd, 1H, J = 16.0, 8.0 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 16.4 Hz), 7.15–7.19 (m, 1H), 7.25–7.38 (m, 7H), 7.41–7.44 (m, 3H).

Styrenoid derivative of 5 (sty-5)

To a solution of **5** (25.0 mg, 97.5 μmol, an entry of the best yield obtained was shown here during optimization of the reaction conditions using the racemic sample) in dimethylformamide (2.0 mL) was added iodobenzene (21.8 μL, 195 μmol), palladium(II) acetate (1.31 mg, 5.85 μmol), triphenylphosphine (3.07 mg, 11.7 μmol), and silver carbonate (53.8 mg, 195 μmol) at room temperature. After the reaction mixture was stirred for 2.5 h at 80 °C, H_2O was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude products, which were purified by column chromatography on silica gel (from 9% to 25% ethyl acetate in hexane) and then by preparative thin layer chromatography on silica gel (9% ethyl acetate in hexane) five times to afford the corresponding styryl derivative as its 2.7 : 1 mixture of **sty-5** and the minor isomer with an internal double bond (27 mg, 83%). These isomers were separated by HPLC using a YMC-Pack ODS-AM column (S-5 μm, 120 A, 25 cm × 10 mm) eluted with ethyl acetate/hexane (1 : 9) at 1 mL min^{-1}, while monitoring at 254, 280, and 318 nm. The retention times are 87 (major isomer **sty-5** as a white solid) and 82 (minor isomer with internal double bond) min: IR ($CHCl_3$, cm^{-1}) 1724, 1616, 1385, 1051; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.93 (d, 3H, J = 1.6 Hz), 2.40 (d, 3H, J = 1.2 Hz), 3.27 (d, 1H, J = 16.0 Hz), 3.48 (d, 1H, J = 16.0 Hz), 6.08 (d, 1H, J = 1.2 Hz), 6.68 (s, 1H), 6.80 (d, 1H, J = 11.6 Hz), 7.20–7.26 (m, 3H), 7.33 (dd, 2H, J = 7.4, 7.4 Hz), 7.44 (d, 1H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.2, 26.6, 38.5, 93.6, 106.6, 111.0, 113.2, 113.8, 123.9, 125.4, 126.4, 127.9, 128.9, 137.2, 139.1, 150.8, 152.9, 160.9, 162.4; HRFABMS calcd for $C_{22}H_{21}O_3$ $[M + H]^+$ 333.1490, found 333.1486.

Styrenoid derivative of 6 (sty-6)

To a solution of **6** (first eluted enantiomer, 2.2 mg, 8.6 μmol) in dichloromethane (2.0 mL) was added Grubbs' second generation ruthenium catalyst **9** (1.7 mg, 2.0 μmol) and styrene (2.0 μL, 17 μmol) at room temperature, and the mixture was stirred at 40 °C for 7.0 h. The reaction mixture was concentrated *in vacuo* to give the crude products which were roughly purified by column chromatography on silica gel (from 9% to 17% ethyl acetate in hexane) to afford the corresponding

exo-methylene derivative (2.5 mg, quant.) as a white solid. The obtained compound was used for the next Heck reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 2.39 (s, 3H), 3.19 (dd, 1H, J = 16.4, 8.0 Hz), 3.52 (dd, 1H, J = 16.0, 9.6 Hz), 4.96 (s, 1H), 5.11 (s, 1H), 5.35 (dd, 1H, J = 8.8, 8.8 Hz), 6.10 (s, 1H), 6.78 (d, 1H, J = 8.4 Hz), 7.41 (d, 1H, J = 8.4 Hz).

To a solution of the *exo*-methylene derivative obtained above (2.5 mg, 10 μmol) in dimethylformamide (1.0 mL) was added iodobenzene (2.3 μL, 21 μmol), palladium(II) acetate (0.14 mg, 620 nmol), triphenylphosphine (0.32 mg, 1.2 μmol), and silver carbonate (5.7 mg, 21 μmol) at room temperature. After the reaction mixture was stirred for 3.5 h at 80 °C, H_2O was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude products, which were purified by column chromatography on silica gel (25% ethyl acetate in hexane) twice to afford the corresponding styryl derivative as its 5 : 1 mixture of **sty-6** and the minor isomer with an internal double bond (1.8 mg, 66% in two steps). These isomers were separated by HPLC using a YMC-Pack ODS-AM column (S- 5 μm, 120 A, 25 cm × 10 mm) eluted with ethyl acetate/hexane (1 : 9) at 1 mL min^{-1}, while monitoring at 254, 280, and 319 nm. The retention time of the major isomer **sty-6** is 111 min: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (d, 3H, J = 1.0 Hz), 2.40 (s, 3H), 3.29 (dd, 1H, J = 16.4, 7.9 Hz), 3.60 (dd, 1H, J = 16.4, 9.9 Hz), 5.49 (dd, 1H, J = 9.5, 9.5 Hz), 6.11 (s, 1H), 6.65 (s, 1H), 6.81 (d, 1H, J = 8.5 Hz), 7.18–7.35 (m, 5H), 7.43 (d, 1H, J = 8.6 Hz); HRFABMS calcd for $C_{21}H_{19}O_3$ $[M + H]^+$ 319.1334, found 319.1326.

Computational section

Molecular modeling

All DFT calculations were run with Jaguar 4.2 (Schrödinger, Inc., Portland OR) with B3LYP functional, and 6-31G* or 6-31G** basis sets, either *in vacuo* or in $CHCl_3$ (GB/SA solvation model), with default parameters and convergence criteria. Initial *eq* and *ax* geometries for **sty-2** and **sty-5** were built starting from previously DFT optimized structures of **1**,[15] and pre-optimized with DFT at the B3LYP/6-31G* level. Angle $d_{8,10}$ was then scanned by 15° steps followed by geometry relaxation at the B3LYP/6-31G* level *in vacuo*. For each *eq* and *ax* conformer, three energy minima were isolated, which were finally optimized at the B3LYP/6-31G** level in $CHCl_3$. The resulting relative energies for all minima are reported in ESI† (Table ESI1); the two lowest energy conformers for each compound are showed in Fig. 2.

Electronic structure calculations

TDDFT calculations[33] were run with Gaussian 03 (Gaussian, Inc., Pittsburgh PA) with either B3LYP[34] or PBE0[35] functionals, and various basis sets (6-31G(d,p), 6-311G(d,p), 6-311+G(d,p), aug-cc-pVDZ), solving for up to 12 excited states, *in vacuo*; a selected result is showed in Table 1. ZINDO-S/CI calculations[36] were run with Hyperchem 7.1 (Hypercube, Inc., Canada) with default parameters and convergence criteria, including the highest 16 (8 for styrene) occupied and the lowest 16 (8 for styrene) virtual orbitals in the CI. Input structures for all calculations, having C_s symmetry, were optimized with DFT at the 6-31G** level *in vacuo*.

Coupled-oscillator calculations

DeVoe calculations were run with a Fortran program developed by Hug.[37] DFT-optimized structures (B3LYP/6-31G**) were used as input geometries; average CD spectra were calculated as Boltzmann-weighted at 300 K, using DFT energies. Spectroscopic parameters (transition frequency, dipole strength and half-height bandwidth) were extracted from the UV spectrum of 7-hydroxy-4-methyl coumarin in acetonitrile and styrene in hexane, and are summarized in Table 2. Transition moments directions were obtained with TDDFT and ZINDO-S/CI calculations for 7-hydroxy coumarin, and with ZINDO-S/CI calculations for styrene, and are shown in Table 2. Transition moment positions were estimated using the molecular orbitals resulting from ZINDO/S-CI and TDDFT methods (PBE0/6-311+G(d,p)), using the procedure described by Mason,[30] with both dipole-length (DL) and dipole-velocity (DV) formulations. In the latter case, average expectation values of the dipole-velocity elements for C–C and C–O bonds, $<\nabla_{C-C}>$ and $<\nabla_{C-O}>$, were taken from Inskeep *et al.*;[38] further details about the DL and DV calculations may be found in the ESI.† The results for the positions of transition I and II dipole moments of 7-hydroxy coumarin, using ZINDO/S-CI and TDDFT with PBE0/6-311G+(d,p) methods, are displayed in Table 2 as the center of the corresponding dipoles. Using TDDFT instead of ZINDO-derived parameters for the dipole positions and polarizations affected the DeVoe calculations to a very small extent. Moving the dipole positions within 0.5 Å from the calculated centers affected the calculated CD intensities without reverting the couplet sign for all structures.

Both coumarin transitions I and II were included in the DeVoe calculations; transition II did not dramatically affect the computed spectra in terms of intensity, but slightly improved their general appearance. The very small coumarin transition III did not affect the result at all. Only the styrene K band was considered in the final calculations, with the view that higher energy bands did couple with coumarin I–II to a much lesser extent. Higher energy coumarin bands were also neglected. It must be noted that, regardless of the presence of further bands at higher energies, the sign of at least the first Cotton effect allied to the coumarin transition I will be mainly dictated by the coupling with the styrene K band, therefore the couplet sign is safely predicted.

Quantitative NMR analysis

Experimental $^3J_{Me8,H9a}$ and $^3J_{Me8,H9b}$ values were compared with those estimated for the DFT calculated structures on the basis of the Karplus-type relation: $^3J_{C,H} = 3.6 \cos 2\varphi - \cos \varphi + 4.3$, where φ is one of the dihedrals $\varphi_{Me8-C8-C9-H9a}$ or $\varphi_{Me8-C8-C9-H9b}$. This equation had been purposely developed for $^3J_{Cexo\text{-}C(-O)\text{-}C-H}$ systems with a methyl or methylene carbon C_{exo} attached to a tetrahydrofuranyl ring.[24] In Table ESI2 of the ESI,† experimental values (estimated error +0.1 Hz) are compared with those evaluated on DFT-computed structures, both for the lowest energy eq_0 and ax_0 conformers as well as the Boltzmann's average at 300 K for all the minima.

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