

A New Approach in Exciton-Coupled Circular Dichroism (ECCD)—Insertion of an Auxiliary Stereogenic Center

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ABSTRACT There are cases in which exciton coupling between two chromophores does not occur because the two electric transition moments which should interact are coplanar. This is seen with cyclohexane-1,4-diols (both *ee* or *ea*) and a wide variety of 3-hydroxy carotenoids, 3-hydroxyretinoids, etc. A general approach to deal with such cases is to acylate one of the hydroxyl groups with a chiral allenic acid substituted with a suitable chromophore, e.g., CHROM-CH=C=CH-COOH. The allenic bond introduces a 90° twist at the italicized central carbon so that the allenic CHROM now couples with the second chromophore. This concept of introducing an auxiliary allenic center should be of general applicability in other similar cases. © 1995 Wiley-Liss, Inc.

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The through-space coupling of two or more chromophores in chiral substrates gives rise to exciton-coupled circular dichroism (ECCD), which is characterized by bisignate circular dichroism (CD) curves. The signs of these "split" Cotton effects (couplets) reflect the chirality between the electric transition moments of interacting chromophores (Fig. 1). Coupling also occurs when more than two identical or different chromophores are present; this gives rise to complex and characteristic CD curves. The exciton chirality method,^{1,2} based on the ECCD phenomenon, nonempirically establishes, on a microscale, absolute configurations or conformations in solution. Figure 1 shows the partial structure of a steroid 2,3-bis-*p*-substituted benzoate. Although the benzoate group can adopt various conformations, the most stable is the one depicted in which the ester bond is *s*-cis while the ester carbonyl and 3-H are eclipsed. This is supported by X-ray, MM2 calculations, and ECCD data; namely, all interpretations of the ECCD of benzoates and other acylates performed so far, including the extensive pyranose acylate library,³ have been based on this conformer and have proven this view to be correct.

Determination of the absolute configuration of the moiety shown in Figure 1 means determination of the absolute sense of chirality between the C(2)-O and C(3)-O bonds; this in turn is approximated by the chirality between the two longitudinal ¹L_a electric transition moments (μ) of the benzoate chromophore, which gives rise to the main absorption band. When the chirality constitutes a clockwise turn, viewed from C(3) to C(2) or from C(2) to C(3), it is defined as positive. Such through-space coupling of transition moments leads to a bisignate CD curve centered at the absorption maximum, with positive 1st, at longer wavelengths, and negative 2nd Cotton effects, respectively. Such a couplet is defined as a positive

couplet and vice versa. The distance between the peak and trough of a split CD curve is defined as the "amplitude" or *A* value and is expressed in $\Delta\epsilon$. There is no exception in the relationship between the signs of transition moment chiralities and those of bisignate CD curves, positive and negative chiralities always leading to positive and negative CD couplets, respectively. Some pertinent aspects of the practical significance of ECCD are listed below:

(i) The intensity of the *A* value usually is such that the amount of sample required for the exciton chirality method can be far less than that required for other CD measurements, i.e., several μg .

(ii) Any chromophore with large ϵ and known direction of the electric transition moment, μ , can be used.

(iii) The chromophore can be introduced by derivatization or could already be preexisting in the molecule, e.g., enone, diene, triene, etc.

(iv) In the case of cyclohexyl 1,2-bisbenzoates, the *A* value is maximal at a projection angle ca. 70°. There is no coupling when the projection angle is 0° or 180° (see also Fig. 3).

(v) When the two chromophores are identical, the *A* value is proportional to ϵ^2 and is inversely proportional to R^2 , where *R* is the interchromophoric distance.

(vi) When more than two identical chromophores are coupled, the *A* value is approximated by pair-wise addition of the interacting chromophores. For example, in the triad A/B/C,

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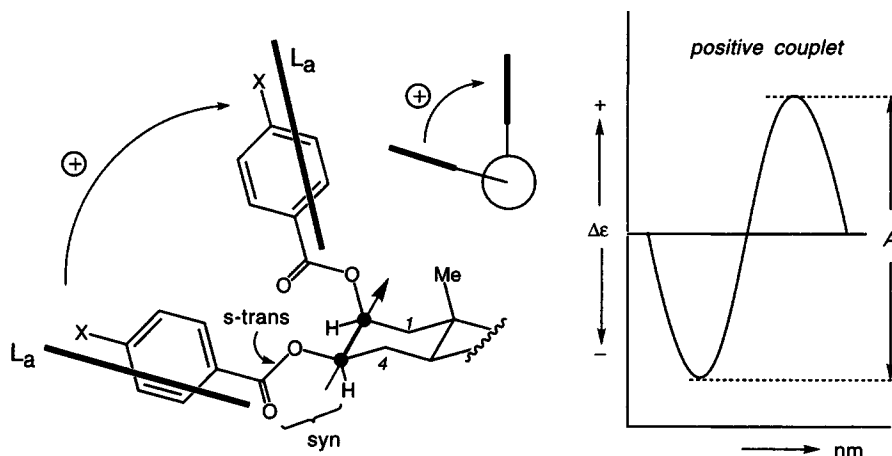


Fig. 1. The exciton chirality method nonempirically determines the absolute configurations of molecules in solution. A positive chirality between the electric transition dipoles gives a bisignate CD curve with a positive first Cotton effect. This is exemplified by the longitudinal 1L_a transition dipoles of *p*-substituted benzoates.

the A value is represented by the sum of respective A values of the component pairs A/B, B/C, and A/C (pair-wise additivity rule).

(vii) Chromophores with λ_{\max} as far apart as 100 nm can still couple.

(ix) The coupling of more than two different chromophores yields a complex CD curve extending over the range covered by these chromophores. The pair-wise additivity rule holds for such complex CD curves as well, therefore giving rise to characteristic fingerprint curves.³ For example, the *p*-bromobenzoate chromophore, 245 nm ϵ 19500 (in MeCN), and the *p*-methoxycinnamate chromophore, 306 nm ϵ 23400/227 nm, ϵ 12500 (in MeCN), esterified to the hydroxyl functions of hexopyranoses are intensely coupled and yield CD spectra which are characteristic of each substitution pattern in the range of 230–330 nm.³

Although the exciton chirality method is an extremely versatile microscale technique applicable to a wide variety of compounds, it cannot be applied to cases shown in Figure 2 because the amplitudes of the CD curves are extremely weak or nil (unpublished observations). The conditions for the absence or presence of coupling between two transition dipoles are illustrated in Figure 3.

In Figure 3I, if A, B, C, and D are all in the same plane, there is no coupling. This is exemplified in Figure 2 by the 3 β ,7 β -bisbenzoate of an A/B trans-steroid, 3 α ,7 α -bisbenzoates of an A/B cis-steroid, and the 2,4-bisbenzoate of glucose.

In Figure 3II, (a subset of I), if any three points, e.g., A, B, C, are collinear, D must form a plane with them and there is no coupling. Many 3-hydroxy-carotenoids and retinoids are known (Fig. 2), but despite the extensive CD studies performed by Noak,⁴ Liaen-Jensen,⁵ and others a nonempirical method to determine the configuration of the 3-hydroxy function is lacking.

In Figure 3III, the occurrence of exciton coupling requires A, B, C, and D to be noncoplanar. The 3-acylates of 3-hydroxyretinoids and 3-hydroxycarotenoids belong to category II and show only weak coupling (Fig. 2). The *p*-dimethylami-

nobenzoate chromophore (dmaBz), with its quite intense absorption, λ_{\max} (EtOH) 309 nm (ϵ 30400), is used widely in ECCD.² In the 3-*p*-dimethylaminobenzoate of (3R)-3-hydroxy- β -ionone, (3R)-IVc, it couples with the ionone chromophore, λ_{\max} (hexane) 280 nm (ϵ 8200) to give a negative split CD of low intensity (Fig. 4), UV (hexane) 300 nm (ϵ 33900); CD (hexane) 303 nm (–5.3), 273 nm (+3.0). This negative CD shows that the electric transition moments of the benzoate and the dienone constitute a negative chirality. However, this is an interesting case where we cannot assign the configuration at C-3 despite the negative couplet. There are several reasons for this: (i) as evidenced by the nuclear Overhauser effect (NOE) observed between both 7-H/8-H and the 1,1-*gem*-dimethyl and 5-methyl groups, the side-chain is fluctuating;⁶ then, depending on the side-chain conformation, its chirality with 3-benzoate becomes slightly positive or slightly negative; (ii) the cyclohexene conformation is also flexible; (iii) however, the overriding cause is the fact that the two chromophores are in a “para” position with respect to the cyclohexene ring (Fig. 2), and this makes this bichromophoric system fall closely into category II. The negative couplet in Figure 4 simply represents the overall chirality of a mixture of various conformers and cannot be used to assign the 3-hydroxy configuration. The amplitude is influenced by both the solvent and the nature of the 3-acylate. Attempts to assign configurations to 3-hydroxylated carotenoids by introducing appropriate chromophores, e.g., retinoates (Fig. 2), also failed because of weak or nil coupling (unpublished observations). A general approach to cope with such cases would be to incorporate an auxiliary chiral moiety that induces exciton coupling into the molecule. One such approach is to derivatize one of the hydroxyl groups with a chiral allenic acid substituted with a suitable chromophore, e.g., CHROM–CH=C=CH–COOH. The allenic bond introduces a 90° twist at the italicized central carbon so that the allenic CHROM now couples with the chromophore in the parent compound. In the case of 3-hydroxyretinoids or carotenoids, the chirality becomes clearly defined irrespective of side-chain and/or cyclohexenyl ring conformation. This concept of intro-

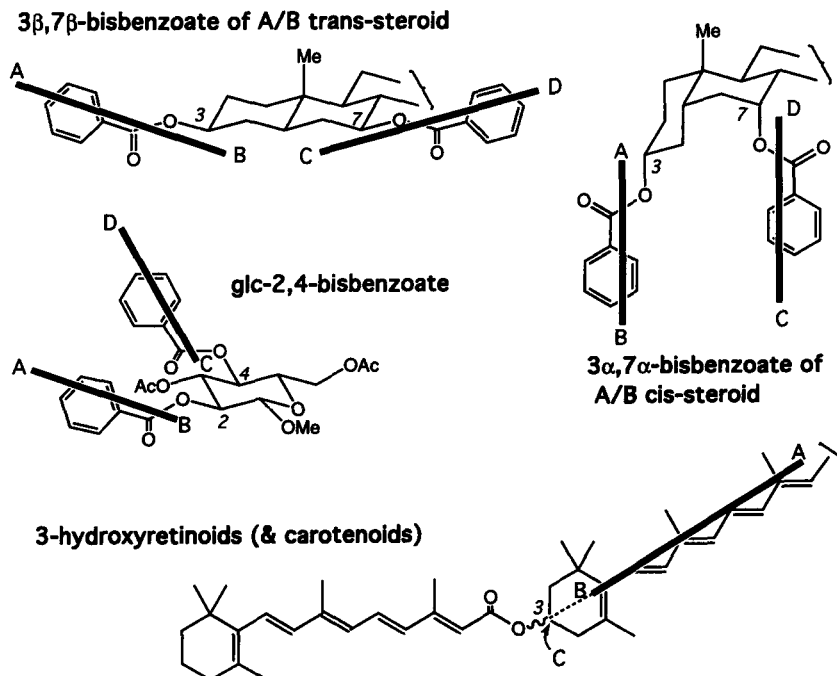


Fig. 2. Systems where the exciton chirality method cannot be applied because no characteristic exciton split CD curve is observed due to unfavorable alignment of the two chromophores.

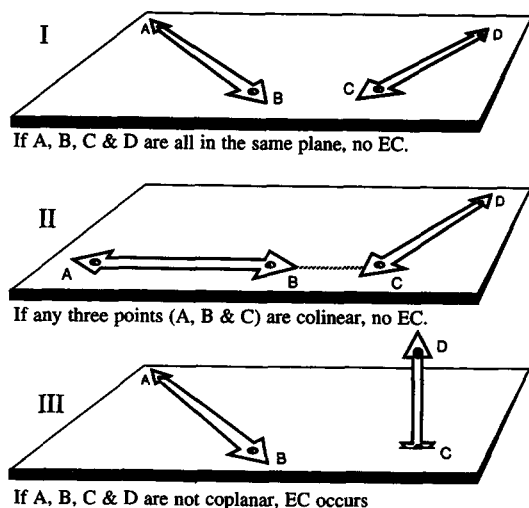


Fig. 3. The existence of ECCD can be determined from the relative positions of the four points (A, B, C, and D) that define the two transition dipoles.

ducing an auxiliary allenic center should have general applicability in other similar cases. The first such example is given in the following.

MATERIALS AND METHODS

General Experimental Procedures

Melting points are uncorrected. ^1H and ^{13}C -NMR spectra were recorded on a Varian (Walnut Creek, CA) VXR-400, 300 or 200 MHz spectrometers as noted. Electron impact (EI), chemical ionization (CI), and high resolution (HR)-EI

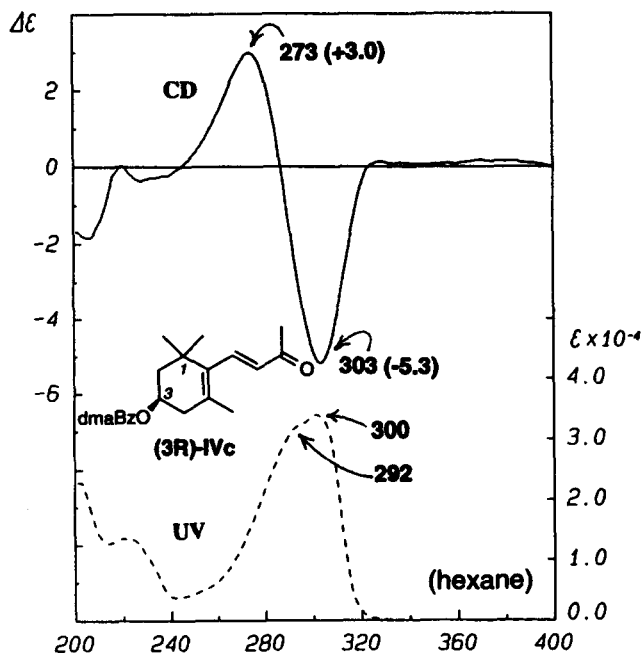
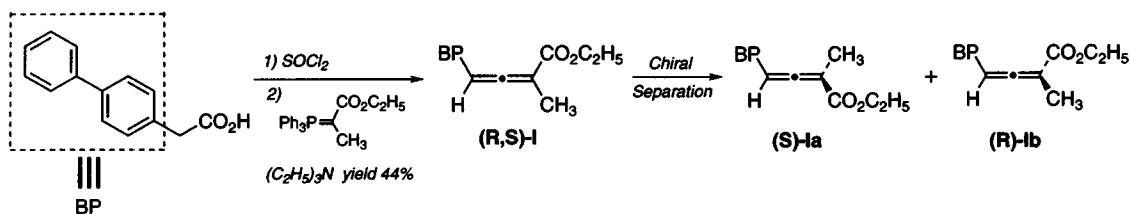


Fig. 4. CD spectrum of coupled (3R)-3-hydroxy- β -ionyl 4'-dimethylaminobenzoate [(3R)-IVc] (dmaBz = dimethylaminobenzoate).

mass spectra were measured on NERMAG (Paris, France) R1010 and JEOL (Tokyo, Japan) JMS-DX303 HF mass spectrometers, respectively. Ultraviolet-visible (UV/vis) and CD spectra were recorded in hexane or acetonitrile solution on a Perkin-Elmer (Norwalk, CT) Lambda 4B UV/vis spectrometer and a Jasco J-720 spectropolarimeter, respectively. Infra-



Scheme 1. Synthesis of biphenylallenic acid ethyl esters (S)-Ia and (R)-Ib.

red spectra were recorded (KBr and CCl_4) on a Perkin-Elmer 1600 FTIR spectrometer.

Synthesis of Biphenylallenic Acid (Scheme 1)

Ethyl 4-biphenyl-2-methylbuta-2,3-dienoate [(R,S)-I] 4-Biphenylacetic acid (212 mg, 1.00 mmol) was dissolved in thionyl chloride (10 ml) and refluxed for 3 h. The excess thionyl chloride was evaporated under reduced pressure. To a solution of acid chloride in CH_2Cl_2 (2 ml), a solution of triethylamine (280 ml, 2.0 mmol) and [1-carboethoxyethane]triphenyl-phosphorane (362 mg, 1.00 mmol) in CH_2Cl_2 (10 ml) was added and stirred overnight under argon atmosphere. The solvent was removed under reduced pressure and the solid residue was extracted with pentane. The pentane was evaporated and the crude product purified by flash chromatography (silica gel, CH_2Cl_2) to give the racemic biphenylallenic acid ethyl ester [(R,S)-I] (122 mg, 44%).

White powder, mp $94^\circ\text{--}97^\circ\text{C}$ (from pentane), 400 MHz $^1\text{H-NMR}$ (CDCl_3) δ 1.70 (t, 3H, $J = 7$ Hz, $\text{O-CH}_2\text{CH}_3$), 2.07 (d, 3H, $J = 3$ Hz, 2-CH_3), 4.27 (q, 2H, $J = 7$ Hz, O-CH_2), 6.56 (q, 1H, $J = 3$ Hz, 4-H), 7.3–7.7 (m, 9H). 75 MHz $^{13}\text{C-NMR}$ (CDCl_3): δ 14.2, 15.0, 61.0, 96.8, 99.4, 126.8, 127.3, 127.4, 127.6, 128.7, 131.5, 140.5, 140.5, 166.9, 212.5. IR (KBr) 3020, 3010, 2986, 1946, 1708, 1268, 1116 cm^{-1} . HR-EI calculated for $\text{C}_{19}\text{H}_{18}\text{O}_2$ 278.1307, found 278.1310.

Resolution of ethyl 4-biphenyl-2-methylbuta-2,3-dienoate [(R,S)-I] Resolution of the allenic enantiomers was achieved by chiral HPLC using a Chiralcel OD 250 mm \times 20 mm column. Baseline separation (Fig. 5) was possible for injections up to 10 μl at a concentration of 0.22 mg/ μl . Once a sufficient quantity of each enantiomer was isolated, the respective absolute stereochemistries could be determined by CD (see Fig. 6). The first fraction exhibited a positive CD corresponding to the S-allene, the second fraction gave a negative CD corresponding to the R-allene (see "Discussion").

UV (hexane) 276 nm (ϵ 28300), 210 (38800). CD (hexane) [(S)-Ia] 274 nm ($\Delta\epsilon$ +11.4), 226 nm ($\Delta\epsilon$ +6.9), 208 nm ($\Delta\epsilon$ +8.0); [(R)-Ib] 277 nm ($\Delta\epsilon$ -11.3), 226 nm ($\Delta\epsilon$ -6.7), 209 nm ($\Delta\epsilon$ -8.0).

4-Biphenyl-2-methylbuta-2,3-dienoic acid [(R,S)-II] (Scheme 2) A solution of racemic ethyl ester [(R,S)-I] (291 mg, 1.05 mmol) in 1,2-dimethoxyethane (DME, 10 ml) was treated with aqueous solution of potassium hydroxide (0.5 M, 10 ml). The solution was stirred at room temperature for 2 h, concentrated under reduced pressure, diluted with water (50 ml), and extracted with ether (50 ml) to remove any remaining ester. The aqueous phase was adjusted to pH \approx 1 with 1 M

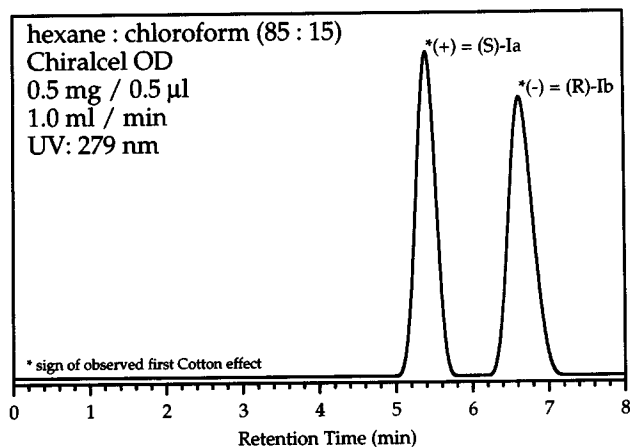


Fig. 5. Chiral separation of allene enantiomers [(S)-Ia, (R)-Ib] by HPLC.

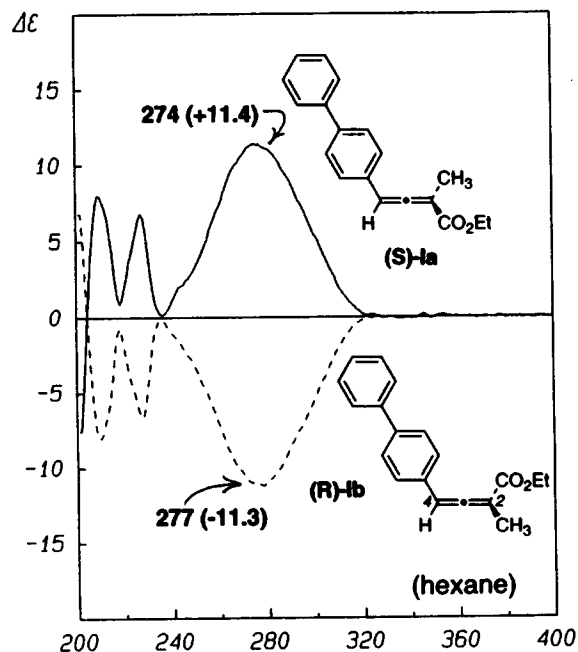
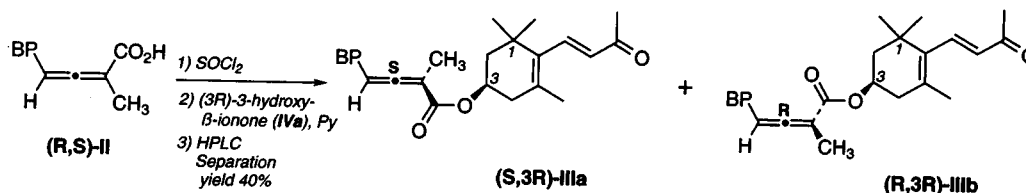


Fig. 6. CD spectra of the two enantiomeric biphenylallenic ethyl esters (S)-Ia and (R)-Ib.

HCl and extracted with CH_2Cl_2 (2×50 ml). The combined organic extracts were washed with brine (100 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 1%



Scheme 2. Formation of diastereomeric biphenylallenic (3R)-3-hydroxy- β -ionone esters [(S,3R)-IIIa and (R,3R)-IIIb].

acetic acid, 2% ethyl acetate/ CH_2Cl_2) to afford the racemic acid [(R,S)-II] (224 mg, 86%) as white powder.

White powder, mp $171^\circ\text{--}172^\circ\text{C}$ (from CH_2Cl_2), 400 MHz $^1\text{H-NMR}$ (acetone- d_6) δ 1.96 (d, 3H, $J = 3$ Hz, 2-Me), 6.69 (q, 1H, $J = 3$ Hz, 4-H), 7.35 (br. t, 1H, $J = 8$ Hz, ArH), 7.44 (4H, ArH), 7.65 (4H, ArH), 10.95 (br. s, 1H, CO_2H). IR (KBr) 2977, 2671, 2554, 1944, 1681, 1488, 1420, 1293, 1136 cm^{-1} . HR-EI calculated for $\text{C}_{17}\text{H}_{14}\text{O}_2$ 250.0993, found 250.0984. UV (CH_3CN) 279 nm (ϵ 31600), 211 (39600), 204 sh (36800). 75 MHz $^{13}\text{C-NMR}$ (acetone- d_6): δ 15.2, 97.1, 99.7, 127.5, 128.1, 128.3, 128.6, 129.7, 131.2 or 132.8, 141.1, 141.3, 167.9, 213.3.

(3R)-3-Hydroxy- β -ionyl 4'-biphenyl-2'-methylbuta-2',3'-dienoate [(S,3R)-IIIa and (R,3R)-IIIb] (Scheme 2) To a solution of acid [(R,S)-II] (12.4 mg, 0.050 mmol) in anhydrous CH_2Cl_2 , thionyl chloride (50 μl) was added slowly and stirred for 3 h at room temperature. The solvent and excess thionyl chloride was evaporated under reduced pressure. To a solution of acid chloride and (3R)-3-hydroxy- β -ionone [(3R)-IVa] (10.2 mg, 0.049 mmol) in CH_2Cl_2 (2 ml) was added pyridine (10 μl) at room temperature. The resulting mixture was refluxed for 2 h and organic solvents evaporated under reduced pressure. The products were purified by preparative TLC (silica gel, 5% ethyl acetate-hexane) to afford a diastereomeric mixture [(S,3R)-IIIa and (R,3R)-IIIb] (8.7 mg, 40%). Two diastereomers were purified by HPLC (Chiralcel OD, CHCl_3 ; hexane = 13:87).

Allenic β -ionone ester [(S,3R)-IIIa] 400 MHz $^1\text{H-NMR}$ (benzene- d_6) δ 0.83 (s, 3H, 1-Me), 0.92 (s, 3H, 1-Me), 1.38 (s, 3H, 5-Me), 1.49 (t, 1H, $J = 12$ Hz, 2-H β), 1.73 (br. d, 1H, $J = 12$ Hz, 2-H α), 1.86 (s, 3H, 9-Me), 2.02 (dd, 1H, $J = 10$ and 18 Hz, 4-H β), 2.09 (s, 3H, 2'-Me), 2.35 (dd, 1H, $J = 5$ and 18 Hz, 4-H α), 5.27 (m, 1H, 3-H), 5.99 (d, 1H, $J = 16$ Hz, 7-H), 6.35 (br. s, 1H, 4'-H), 7.02 (br. d, 1H, $J = 16$ Hz, 8-H), 7.22 (m, 5H, ArH), 7.43 (d, 4H, $J = 8$ Hz, ArH); IR (CCl_4) 2964, 2928, 1948, 1711, 1676, 1608, 1270, 1120 cm^{-1} ; HRMS (EI) calculated for $\text{C}_{30}\text{H}_{32}\text{O}_3$ 440.2351, found 440.2371.

UV (hexane) 276 nm (ϵ 36500).

CD (hexane) 281 nm ($\Delta\epsilon +16.0$), 227 nm ($\Delta\epsilon +7.6$), 217 nm ($\Delta\epsilon -2.7$), 210 nm ($\Delta\epsilon +2.2$).

Allenic β -ionone ester [(R,3R)-IIIb]

400 MHz $^1\text{H-NMR}$ (benzene- d_6) δ 0.89 (s, 3H, 1-Me), 0.94 (s, 3H, 1-Me), 1.34 (s, 3H, 5-Me), 1.50 (t, 1H, $J = 12$ Hz, 2-H β), 1.76 (br. d, 1H, $J = 12$ Hz, 2-H α), 1.86 (s, 3H, 9-Me), 1.98 (dd, 1H, $J = 10$ and 17 Hz, 4-H β), 2.09 (s, 3H, 2'-Me), 2.31 (dd, 1H, $J = 6$ and 17 Hz, 4-H α), 5.27 (m, 1H, 3-H), 5.97 (d, 1H, $J = 16$ Hz, 7-H), 6.35 (br. s, 1H, 4'-H),

7.01 (br. d, 1H, $J = 16$ Hz, 8-H), 7.22 (m, 5H, ArH), 7.44 (d, 4H, $J = 8$ Hz, ArH); IR (CCl_4) 2962, 2928, 1948, 1711, 1676, 1608, 1270, 1121 cm^{-1} . HRMS (EI) calculated for $\text{C}_{30}\text{H}_{32}\text{O}_3$ 440.2351, found 440.2374.

UV (hexane) 276 nm (ϵ 36500).

CD (hexane) 287 nm ($\Delta\epsilon -25.4$), 227 nm ($\Delta\epsilon -5.8$), 210 nm ($\Delta\epsilon -9.8$).

(3R)-3-Hydroxy- β -ionyl 4'-dimethylaminobenzoate [(3R)-IVc]

To a solution of (3R)-3-hydroxy- β -ionone [(3R)-IVa] (2.3 mg, 0.011 mmol) in 0.5 ml dry acetonitrile was added dimethylaminobenzoyltriazole⁷ (3.1 mg, 0.014 mmol) and distilled 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (2.2 mg, 0.014 mmol). The mixture was stirred at room temperature for 5 h, quenched by addition of 1 drop of water, concentrated, and purified by preparative TLC (silica gel, diethylether) to afford (3R)-3-hydroxy- β -ionyl 4'-dimethylaminobenzoate [(3R)-IVc] (3.0 mg, 81%). 400 MHz $^1\text{H-NMR}$ (CDCl_3) δ 1.21 (s, 3H, 1-Me), 1.15 (s, 3H, 1-Me), 1.73 (t, $J = 12$ Hz, 2-H β), 1.79 (s, 3H, 5-Me), 1.94 (br. d, 1H, $J = 12$ Hz, 2-H α), 2.28 (dd, 1H, $J = 9$ and 17 Hz, 4-H β), 2.32 (s, 3H, 9-Me), 2.6 (dd, 1H, $J = 6$ and 17 Hz, 4-H α), 3.05 (s, 6H, $\text{N}(\text{Me})_2$), 5.27 (m, 1H, 3-H), 6.15 (d, 1H, $J = 16$ Hz, 7-H), 6.65 (d, 2H, $J = 9$ Hz, ArH), 7.22 (d, 1H, $J = 16$ Hz, 8-H), 7.91 (d, 2H, $J = 9$ Hz, ArH). CI-MS (NH_3): 373 ($M + 18$).

UV (hexane) 300 nm (ϵ 33900), 292 sh (ϵ 31000), 221 (ϵ 13700).

CD (hexane) 303 nm (-5.3), 273 nm ($+3.0$).

RESULTS AND DISCUSSION

Preparation and Resolution of Biphenylallenic Acid Enantiomers

Racemic allenic acid ethyl ester [(R,S)-I] was prepared by the method reported by Lang and Hansen.⁸ 4-Biphenylacetic acid was converted to its acid chloride with SOCl_2 ; the acid chloride was reacted with the ylid ester⁹ to afford racemic biphenylallenic acid ethyl ester [(R,S)-I] (Scheme 1).

Assignment of Allene Absolute Configuration

The absolute configurational assignment of a chiral allene moiety remains a rather difficult task. So far, allene configuration has been determined mainly either by multistep stereospecific chemical transformations to or from a standard with previously known chirality¹⁰ or by theoretical methods.¹¹ Based on the chirality functions and semiempirical calculations of optical rotation, Runge and Kresze¹² assigned the absolute configurations of several aryl-substituted allene carboxylic ac-

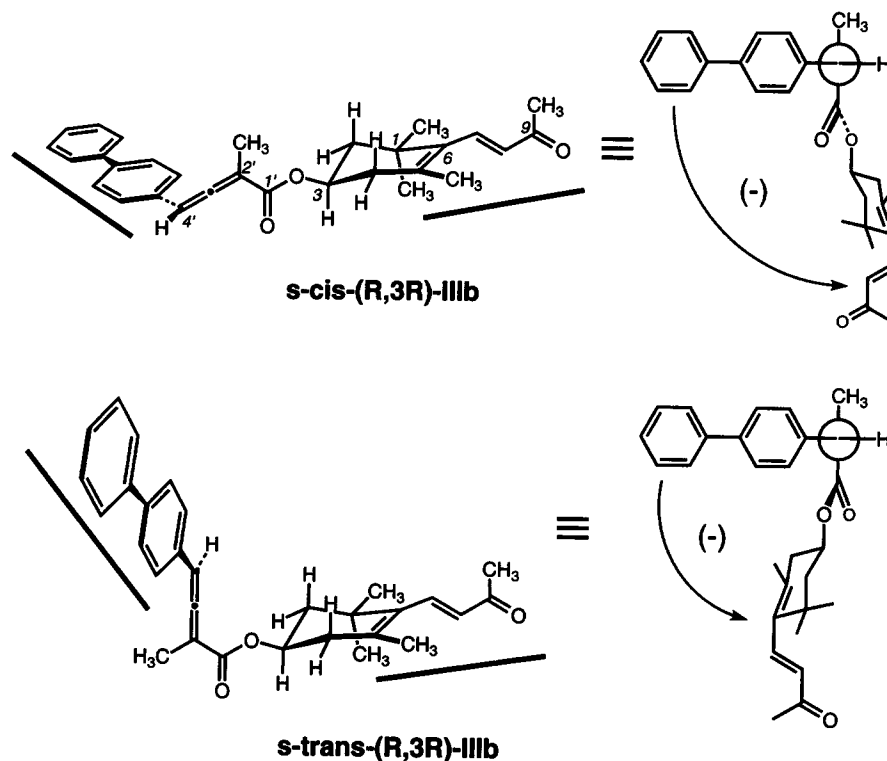


Fig. 7. Both the s-cis (top left and right) and s-trans (bottom left and right) conformations in the R-biphenyllallenic β -ionone ester [(R,3R)-IIIb] have the same chirality. Examination of the relationship between the two transition dipoles (—) reveals that both conformers exhibit negative CD couplets.

ids. Furthermore, a comparison of calculated and experimental UV and CD data for this type of chiral allene revealed a useful correlation between the sign of long axis B_{1u} aromatic Cotton effect and the absolute configuration; namely, all studied phenylallene carboxylic acids of S configuration consistently exhibit a positive CD band ca. 240–250 nm¹² and vice versa.

As expected, in biphenyllallenic ethyl esters **Ia** and **Ib** (Fig. 6) the longitudinal aromatic transition is shifted bathochromically in comparison to the long axis B_{1u} band of phenylallenic esters and appears as a UV band at 276 nm (ϵ 28300, hexane). The corresponding CD spectra of **Ia** and **Ib** in hexane exhibit a positive CD Cotton effect (274 nm, $\Delta\epsilon$ + 11.4) and negative Cotton effect (277 nm, $\Delta\epsilon$ - 11.3), respectively. In view of these experimental data and the above-mentioned correlation,¹¹ the biphenyllallenic ester **Ia** is of S configuration, while the ester **Ib** should be of R configuration.

S-cis and S-trans Isomerization

The asymmetry present in the allene chromophore provides a complication absent in symmetrical chromophores such as benzoate. The single bond between the ester carbonyl and the allene unit can exist in the s-cis or s-trans conformation. Studies have shown that the s-trans conformation is preferred in the crystalline state while the s-cis is only slightly preferred in solution.¹³ Clearly the s-cis and s-trans conformations will both exist in solution, so it is important to understand how this should affect the observed CD data.

When a chiral allene, R-biphenyllallenic acid [(R)-**Ib**] for example, is attached to a chiral alcohol, such as (3R)-3-hydroxy- β -ionone [(3R)-**IVa**], two conformers are possible (Fig. 7). Examination of the relationship between the two chromophore transition dipoles shows that the nature of the allene chromophore causes both s-cis and s-trans conformers to have negative chiralities between the two respective chromophores. Thus both the s-cis and s-trans conformers of the R-allene β -ionone [(R,3R)-IIIb] are predicted to give the same negative first Cotton effect.

It should be noted here that the S-biphenyllallenic β -ionone ester [(S,3R)-IIIa] (Scheme 2) also has two similar conformers with positive chiralities. Models show, however, that the dipole alignment in both of the S conformers suggests much weaker exciton coupling than either of the R conformers, leading to a smaller $\Delta\epsilon$.

Preparation and Purification of Coupled β -Ionone and Biphenyllallenic Acid

Hydrolysis of the allenic acid ethyl ester [(R,S)-**I**] (Scheme 1) was achieved with potassium hydroxide in water and DME. When methanol was used as cosolvent in the hydrolysis reaction, a methanol adduct to a center carbon atom of allene function was obtained. Moreover, when the chiral ethyl esters (S)-**Ia** or (R)-**Ib** were hydrolyzed, racemization of the chiral allene function was observed, presumably via an equilibrium between the allene and propyne functions.¹¹ Therefore, the racemic acid [(R,S)-**II**] was used for the next esterification

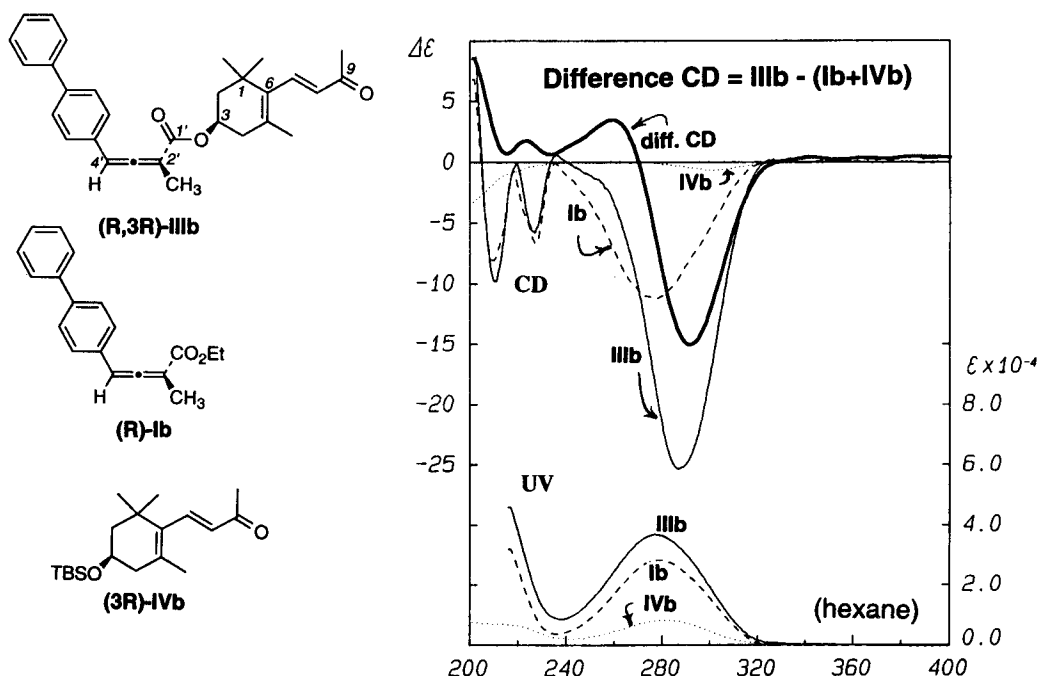


Fig. 8. Subtraction of the CD of (3R)-3-TBSO- β -ionone [(3R)-IVb] and biphenylallenic ethyl ester [(R)-Ib] from that of the (R)-biphenylallenic β -ionone ester [(R,3R)-IIIb] gives rise to a negative couplet. The difference CD represents the contribution of the coupling between the allenic and ionone chromophores.

(Scheme 2). This acid was transformed into the acyl chloride upon reaction with SOCl_2 and then converted into the ester by a reaction with the (3R)-3-hydroxy- β -ionone [(3R)-IVa] in the presence of pyridine in CH_2Cl_2 . These two diastereomeric (3R)-3-hydroxy- β -ionone esters [(S,3R)-IIIa and (R,3R)-IIIb] were separated by HPLC with a chiral column (Chiralcel OD). The stereochemistry of the allene portion of each diastereomer was assigned by comparison of the two characteristic CD bands between 200 nm and 230 nm with the corresponding bands of ethyl esters Ia and Ib.

Difference CD

In addition to the exciton-coupled CD (Fig. 8) of (R,3R)-IIIb, the β -ionone and biphenylallenic chromophores both exhibit independent CD spectra. To estimate the CD resulting from the interaction of these two chromophores, the contributions of individual components were subtracted from the overall CD. Thus the CD of β -ionone ester [(R,3R)-IIIb] was subtracted from the individual CD of R-biphenylallenic ethyl ester [(R)-Ib] and (3R)-3-TBSO- β -ionone [(3R)-IVb] to yield the difference CD shown in Figure 8. It shows a split CD with a large negative first Cotton effect and a weaker positive second Cotton effect arising from the exciton coupling between the biphenylallene and β -ionone chromophores. The sign is the same sign as predicted from models and represents the R configuration of the β -ionone alcohol. The asymmetrical shape of the difference CD is frequently observed in conventional ECCD as well and has been interpreted as being caused by the involvement of transitions other than the major transitions under consideration.

CONCLUSION

The use of allene as a chiral auxiliary induces clear-cut chirality leading to useful CD couplets in molecules where conventional usage of chromophores gives no couplets or to inconclusive interpretations of the couplets because the transition dipole chiralities are geometrically ambiguous. This concept of induced CD expands ECCD to molecules exemplified in Figure 2, where the exciton chirality method was not previously applicable. While the concept of the chiral auxiliary chromophore has been shown to work experimentally, the first chromophore to be used, the biphenylallene chromophore, presented many difficulties in its handling. Studies with other auxiliary chromophores are in progress.

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