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Novel Development of Exciton-Coupled Circular Dichroism Based on Induced Axial Chirality

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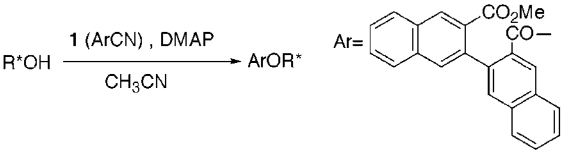
ABSTRACT



A simple method for determining the absolute configuration of chiral alcohols with a unique chromophoric reagent 1 based on induced exciton chirality has been developed. Practical usefulness of the present method was demonstrated by the determination of the absolute configuration of 17,18-dihydroxybergamottin.

Circular dichroism (CD) has been effective for stereochemical elucidation as a reliable tool as X-ray diffraction method. Exciton-coupled circular dichroism (ECCD), in particular, has been extensively applied to various organic molecules as a microscale method to determine their absolute configurations in a nonempirical manner.[1] Although its application to optically active alcohols has been limited to compounds having two or more hydroxy groups,[2] it has recently been extended to compounds having a single hydroxy group.[3] Ishiya and co-workers[3a] employed an achiral carboxylic acid with two chromophores, di(1-naphthyl)acetic acid, as a CD auxiliary, which can be used for determining the absolute configuration of chiral alcohols in combination with conformational analysis of the derivatives. Kurtán and co-workers[3b,c] introduced a complex formation of appropriately derivatized mono-alcohols with a dimeric zinc porphyrin host for induced CD-based determination of the absolute configuration.

In the course of stereochemical studies of optically active secondary alcohols by the ECCD method, we expected that axial chirality would be induced if a chiral alcohol is covalently attached to an achiral biaryl chromophore. On the basis of this idea, we lately introduced a new biaryl CD auxiliary, dinitrodiphenic acid. We found that the esters of various chiral alcohols showed simple Cotton effects at around 270 nm and the signs were correlated to the absolute configuration of the alcohols.[4] This fact indicated that the stereochemical information of the chiral alcohols was transmitted to the dinitrodiphenyl chromophore resulting in induction of axial chirality. Since the naphthalene chromophore has a strong longitudinal ^1B_b band (220 nm, ϵ = 107,300, EtOH), the binaphthyl group will exhibit intense split CD Cotton effects when axial chirality is induced in it. To realize this idea, we designed a new chromophoric

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[1] (a) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. (b) Nakanishi, K.; Berova, N. In *Circular Dichroism-Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers Inc.: New York, 1994; pp 361−398.

[2] Although there are several reports on determination of the absolute configuration of mono-functional compounds by an introduction of a single CD auxiliary, the substrates in these reports already have functional groups that enable the application of the CD exciton method. See, for example: Adam, W.; Luckacs, Z.; Viebach, K.; Humpf, H.-U.; Saha-Moller, C. R.; Schreier, P. *J. Org. Chem.* **2000**, *65*, 186−190.

[3] (a) Ishiya, F.; Ehara, H.; Yoshida, N.; Goto, H.; Monde, K.; Harada, N. 40th Symposium on the Chemistry of Natural Products, symposium papers, 1998; pp 85−90. (b) Kurtán, T.; Nesnas, N.; Li, Y.-Q.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2001**, *123*, 5962−5973. (c) Kurtán, T.; Nesnas, N.; Koehn, F. E.; Li, Y.-Q.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2001**, *123*, 5974−5982.

[4] (a) Hosoi, S.; Kamiya, M.; Ohta, T. *42nd Symposium on the Chemistry of Natural Products*, symposium papers, 2000; pp 571−576. (b) Hosoi, S.; Kamiya, M.; Kiuchi, F.; Ohta, T. *Tetrahedron Lett.* **2001**, *42*, 6315−6317.

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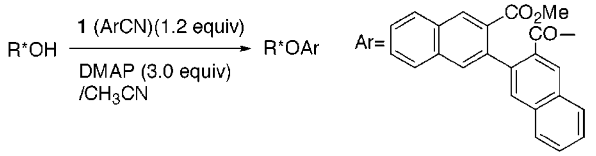
reagent, 3-cyanocarbonyl-3′-methoxycarbonyl-2,2′-binaphthalene **1**,[5] which can be easily introduced to alcohols and will exhibit a definite induced ECCD. Here, we disclose a new strategy to determine the absolute configuration of mono-alcohols using the ECCD method.

Condensation of *d*- and *l*-menthols with **1** gave the corresponding esters **2b** and **3b** in 84% and 80% yields, respectively.[6] The ^{1}H NMR spectra of **2b** and **3b** in $CDCl_3$ were entirely identical, indicating that **2b** and **3b** are enantiomeric to each other in the solution. The CD spectra of **2b** and **3b** in cyclohexane showed bisignate CD curves (**2b**: $A = +42.8$; **3b**: $A = -39.6$), which exhibited positive and negative exciton chirality, respectively (Figure 1).[8] These results showed that chiral information of the alcohols was definitely transmitted to the binaphthyl chromophore and induced axial chirality as expected.[9]

Scheme 1



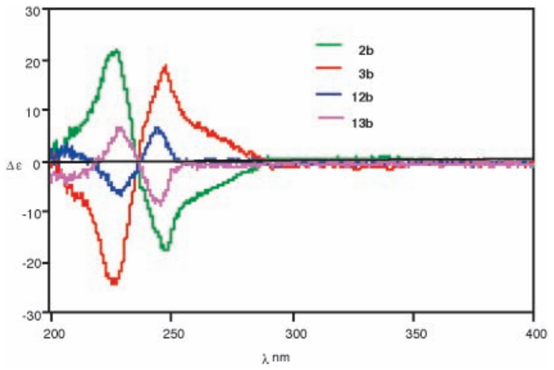


Figure 1. CD spectra of binaphthyl esters **2b**, **3b**, **12b**, and **13b**.

To confirm the generality of the observed phenomenon, CD spectra of various types of alcohols were examined. Alcohols were derived to the corresponding esters in 43−100% yields. In the case of sterically demanding alcohols (**12a**−**14a**), conversion yields were moderate. The UV and CD spectral data of their derivatives are summarized in Table 1. In all antipodal pairs, their CD spectra were symmetrical to the *x*-axis as in the case of menthol derivatives.[4] According to the analysis of the relationship between exciton chirality and absolute configuration, the alcohols employed in this study were found to be classified into two groups, A and B, which depend strongly upon the structure on the vicinal carbons. Group A constitutes compounds lacking any unsaturation or an oxygen atom on the vicinal carbons, whereas group B constitutes compounds possessing either an unsaturation or an oxygen atom at the vicinal position.

In group A, exciton chirality of (*R*)-alcohols was negative and that of (*S*)-alcohols was positive. On the contrary, the signs of exciton chirality were opposite in group B (Table 1). It is worthy to note that the CD spectra of dihydrocholesterol derivatives (**8b**, **9b**), which are different only at the configuration of the C3 position, exhibited opposite exciton chirality from each other.[10]

Next, molecular mechanics calculations were performed using CONFLEX-MM2[11] to assess the most stable conformation of the derivatives. The optimized conformers were enantiomeric in each antipodal pair. In the most stable conformers, calculated screw senses between the two longitudinal ^1B_b electric transition moments of 2-naphthoate groups were in good accordance with those expected from their exciton chiralities (Table 2). That is, in both groups (A and B), the esters (**3b**, **4b**, **10b**, **12b**) showing positive exciton chirality had a clockwise turn, whereas the turns of those (**2b**, **5b**, **11b**, **13b**) with negative exciton chirality were counterclockwise. Inspection of the molecular models of the most stable conformers revealed that, irrespective of the groups (A or B) and of notation of the absolute configuration of the carbinol carbon (*R* or *S*), the bulkier substituent occupied such a position as to avoid steric repulsion with the methyl ester group in all derivatives (Figure 2). This suggested that the transmission of the chirality occurred in a thermodynamically controlled fashion. Thus, taking a combination of the relative bulkiness[12] of the substituents on the carbinol carbon and the priority of these substituents

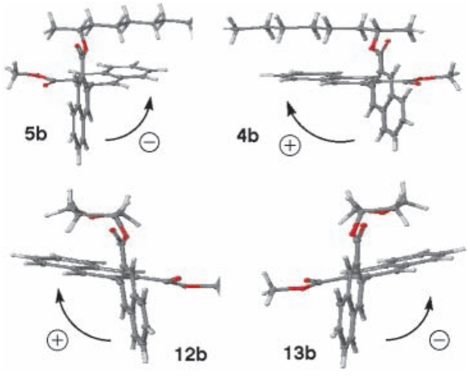


Figure 2. Optimized conformers by CONFLEX-MM2 and signs of chirality.

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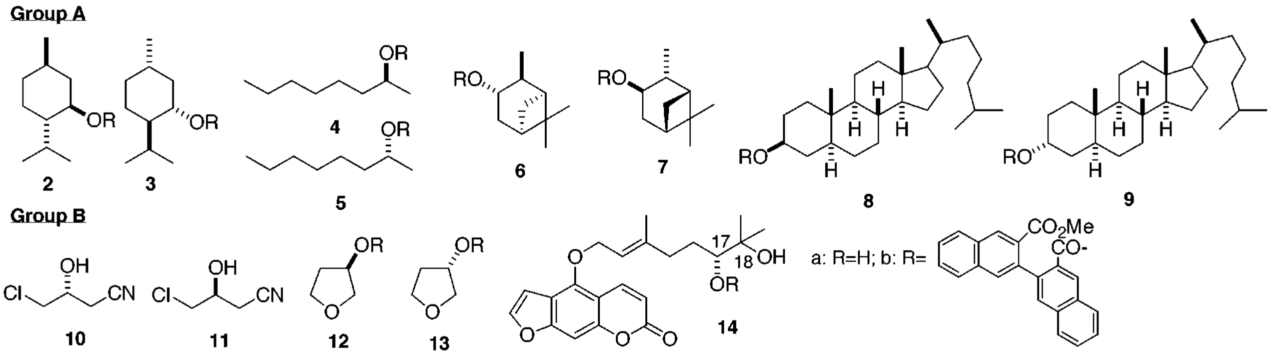
(5) The acyl cyanide **1** was stable in $CDCl_3$ at room temperature for at least 2 months. However, it is labile on silica gel, being easily hydrolyzed within 30 min.

(6) The acyl cyanide **1** was more reactive than 2,2′-binaphthalene-3,3′-dicarboxylic anhydride.[7] The yields of **2b** and **3b** with the anhydride under the same conditions were 22% and 18%, respectively. DMAP was the most efficient base in this acylation. The yields of **12b** in the presence of various bases were as follows (**1** (1.1 equiv), base (3.0 equiv), rt, in MeCN): pyridine (27%), Et_3N (71%), DBU (92%), DMAP (96%). Use of 1.2 equiv of reagent **1** afforded **12b** in 100% yield.

(7) Bacon, R. G. R.; Bankhead, R. *J. Chem. Soc.* **1963**, 839−845.

Table 1. UV and CD Data of the Binaphthyl Derivatives



group	product[a]	yield[b], %	UV λ_{max} (ϵ)[d], nm	CD λ_{ext} ($\Delta\epsilon$)[d], nm	exciton chirality	absolute config
A	**2b**	80	243.5(69700) 339.5(4500)	227.1(+22.4) 235.9(0) 248.1(−17.2)	−	*R*
	3b	84	243.5(75600) 339.5(4800)	226.5(−23.7) 236.0(0) 247.4(+19.1)	+	*S*
	4b	70	243.0(91200) 338.5(2700)	228.0(−23.0) 235.7(0) 244.8(+21.7)	+	*S*
	5b	82	243.0(97200) 339.0(3000)	228.2(+25.1) 235.6(0) 243.8(−23.1)	−	*R*
	6b	84	243.5(86300) 339.5(2100)	220.5(−2.5) 241.8(0) 245.5(+1.9)	+	*S*
	7b	100	243.5(81400) 339.5(2000)	221.1(+2.0) 240.6(0) 245.4(−1.7)	−	*R*
	8b	54	243.0(81600) 339.0(2400)	233.3(−6.1) 238.2(0) 247.0(+9.3)	+	*S*
	9b	43	244.5(69900) 339.0(3800)	232.9(+8.3) 242.2(0) 247.6(−2.8)	−	*R*
B	**10b**	100	245.0(81200) 339.0(2900)	231.3(−8.1) 237.2(0) 243.0(+8.4)	+	*R*
	11b	100	245.0(77800) 338.5(2800)	229.6(+8.0) 237.4(0) 242.7(−8.0)	−	*S*
	12b	100	244.0(81900) 340.0(2300)	228.8(−6.1) 236.9(0) 245.0(+6.6)	+	*R*
	13b	100	244.0(84700) 339.0(3800)	229.1(+7.0) 236.9(0) 245.4(−8.1)	−	*S*
	14b	45[c]	245.0(60500) 285.0(13000)	235.4(−5.6) 241.8(0) 246.7(+2.8)	+	*R*

[a] Unless otherwise noted, 3.0 equiv of base was added to a solution of alcohol and 1.2 equiv of the reagent **1** in MeCN, and the reaction was carried out at room temperature. [b] Isolated yield. [c] Recovery of starting material was 43%. [d] Measured in cyclohexane.

in the sequence rule[13] into account, the relationship between the sign of exciton chirality of the binaphthyl derivative and the absolute configuration of the original alcohol can be summarized as shown in Figure 3. When the sign of exciton chirality is positive and the orders of the substituents in bulkiness and in the sequence rule are the same, the configuration of the alcohol is assigned to be *S*, whereas when the sign is positive and the orders are opposite, the

Table 2. Relationship between Screw Sense and Exciton Chirality in the Binaphthyl Esters

group	compd	screw sense[a]	exciton chirality	absoliute config
A	**2b**	CC	−	*R*
	3b	C	+	*S*
	4b	C	+	*S*
	5b	CC	−	*R*
B	**10b**	C	+	*R*
	11b	CC	−	*S*
	12b	C	+	*R*
	13b	CC	−	*S*

[a] Based on most stable conformers calculated by CONFLEX-MM2. C: clockwise; CC: counterclockwise.

configuration is assigned to be *R*. In the case that the sign is negative, the relationship between the absolute configuration and the combination of the orders is the reverse.

On the basis of the above results, we now propose a new method to determine the absolute configuration of chiral mono-alcohols. A typical determination procedure is exemplified for **3a**: (i) Derivatize **3a** to the binaphthyl ester **3b** and determine the sign of exciton chirality (**3b**, negative). (ii) Compare the order of bulkiness and that of the priority of the substituents on the carbinol carbon (**3b**, the orders are the same). (iii) According to the above rule, the absolute configuration of the carbinol carbon in **3a** was determined to be *R*.

To prove the practical usefulness of the new CD method, we applied the method to determine the absolute configuration of 17,18-dihydroxybergamottin **14a**, isolated from grapefruit juice.[14] In the CD spectrum of its derivative **14b**, a split CD was observed, indicating a positive exciton chirality. Since the orders of the substituents were opposite, the absolute configuration was established as *R* according to the above rule.[15]

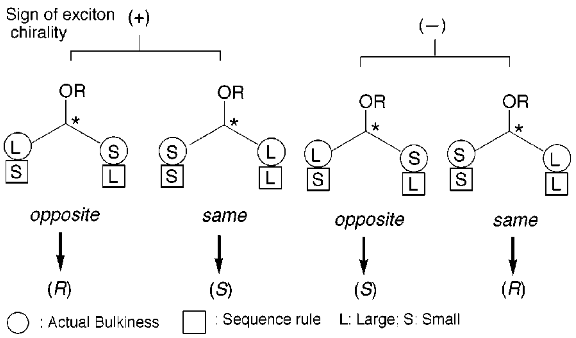


Figure 3. Proposed rule for determining absolute configuration of chiral alcohols.

In summary, we have developed a unique chromophore and a simple method for determining the absolute configuration of chiral alcohols based on induced exciton chirality. The structural feature of the α-positions of the carbinol carbon was found to be important to correlate the sign of the Cotton effect and the absolute stereochemistry of the alcohols. Practical usefulness of the present method was demonstrated by the determination of the absolute configuration of 17,18-dihydroxybergamottin. Further studies on the origin of the chiral transmission mentioned above and the scope and limitation of the present method are currently under way.

Acknowledgment. Dr. Fumiyuki Kiuchi (Kyoto University) is gratefully acknowledged for valuable discussions and suggestions.

Supporting Information Available: Preparation of **1**, typical derivatization procedure (with **12a**), and characterization of **1** and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The occurrence of exciton coupling of two or more chromophores requires noncoplanarity of electric transition moments of the chromophores (Person, R. V.; Monde, K.; Humpf, H.-U.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 128−135). The amplitude of *A* values of our binaphthyl chromophore is smaller than those of Harada's chromophore.[3a] The reason for this may be as follows: (i) There is only a small difference in the population of stable conformers with positive and negative Cotton effects. (ii) The angle between the two chromophores was not suitable for their effective interaction.

(9) For induced CD based on intermolecular association (hydrogen bonding) see: (a) Brittain, H. G. *Tech. Instrum. Anal. Chem.* **1994**, *14*, 307−341. (b) Mizutani, T.; Takagi, H.; Hara, O.; Horiguchi, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 1991−1994.

(10) These compounds were discriminated by complex formation with a dimeric zinc porphyrin host (see ref 3b). However, the CD spectra of di(1-naphthyl)acetic esters of epimeric sterols showed the same positive exciton Cotton effects, although there was a small difference between their amplitudes of *A* values (see ref 3a).

(11) Calculations were performed with CONFLEX-MM2 implemented in CAChe Ver. 4.1.1 for Apple Macintosh; Fujitsu Co. Ltd.: Chiba, Japan.

(12) Although Kurtán et al.[3b] estimated the bulkiness of substituents on the basis of so-called *A* values (Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; Weily: New York, 1994; pp 695−697), the whole van der Waals sphere of the substituents on the carbinyl carbon, in our cases, is considered to be the steric bulk in each side of the plane that is composed of the carbinyl C−H and C−O bonds. Thus, the order of the bulkiness is obvious in **2** −**7**. In **8** and **9**, the bulkier substituent consists of C4−C8 and C14−C16 of the steroid skeleton, whereas the less bulky side contains C-1, -2, -11 and -12. In **10** and **11**, a CN group is thought to be larger than a Cl atom, since a CN group is composed of two atoms, whereas Cl is a single atom. Similarly, CH_2CH_2 is thought to be bulkier than CH_2O in **12** and **13**. In **14**, the terpene chain with a furocoumarin moiety precedes the quaternary carbon substituent.

(13) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385−415.

(14) (a) Dreyer, D. L.; Huey, P. F. *Phytochemistry* **1973**, *12*, 3011−3013. (b) Tatum, J. H.; Berry, R. E. *Phytochemistry* **1979**, *18*, 500−502.

(15) The absolute configuration at the C17 position of **14a** was elucidated by the advanced Mosher's method;[16] see: Ohta, T.; Nagahashi, M.; Miyamoto, Y.; Hosoi, S.; Maruyama, T.; Kiuchi, F.; Yamazoe, Y. *41st Symposium on the Chemistry of Natural Products*, symposium papers, 1999; pp 439−444.

(16) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.