



## 1-Naphthoic Acid: A New Type of Asymmetric Chromophore for Exciton-Coupled Circular Dichroism (ECCD)

Bianca Schreder, Zoltan Lukacs, Marko Schmitt, Peter Schreier and Hans-Ulrich Humpf<sup>\*</sup>

Lehrstuhl für Lebensmittelchemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

**Abstract:** 1-Naphthoic acid was used for the first time as a new type of asymmetric chromophore for exciton coupled circular dichroism (ECCD). The UV and CD spectra of 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester **1** derivatized with 1-naphthoic acid are presented and the CD data are compared with the corresponding 2-naphthoate and benzoate derivatives. 1-Naphthoic acid represents a new type of asymmetric ECCD chromophore which is useful for induced chirality.

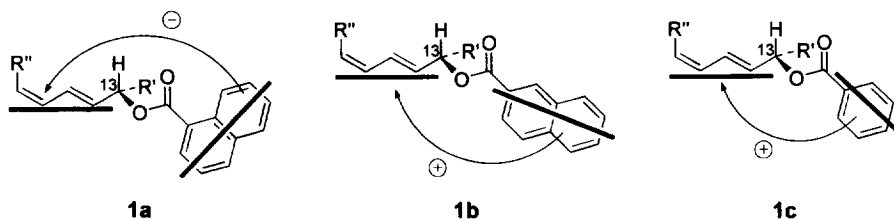
Copyright © 1996 Elsevier Science Ltd

The exciton-coupled circular dichroism (ECCD) is a microscale method to determine the absolute configuration and conformation of organic molecules and has been widely used in the field of natural products.<sup>1,2</sup> ECCD is based on the through space coupling of two or more chromophores in chiral substrates giving rise to a bisignate circular dichroism (CD) curve. The signs of these split Cotton effects (couplets) establish the absolute sense of twist of the electric transition moments in a nonempirical manner. If the chirality of the transition moments is clockwise, defined as positive, the CD shows a positive first and a negative second Cotton effect and vice versa.<sup>1,2</sup> Any chromophore with large  $\epsilon$  value and known direction of the electric transition moment  $\mu$  can be used. The chromophore can be introduced by O- or N-acylation or could already be preexisting in the molecule (e.g., enone, diene, etc.). Usually only symmetric chromophores e.g., p-substituted benzoates are used for ECCD. Recently other symmetric red shifted chromophores and porphyrine chromophores with intense absorption ( $\epsilon=350\ 000$ ) have been developed for new applications of ECCD.<sup>3,4</sup> In the following we describe the extension of ECCD to a new type of asymmetric chromophore like 1-naphthoic acid, which can be used for induced chirality.<sup>5</sup>

2-Naphthoic acid is a strong chromophore ( $\lambda_{\max}$  234 nm,  $\epsilon$  50 000, MeCN) and has already been used for ECCD.<sup>1,6</sup> The UV absorption is three times stronger than for the benzoate chromophore and the direction of the longitudinal  $^1B_u$  transition moment of the 2-naphthoate group is approximately parallel to the C-O bond (figure 1, **1b**). UV absorption of the 1-naphthoate chromophore is blue shifted and weaker compared to the 2-naphthoate group.<sup>7</sup> We selected 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester **1** as substrate to

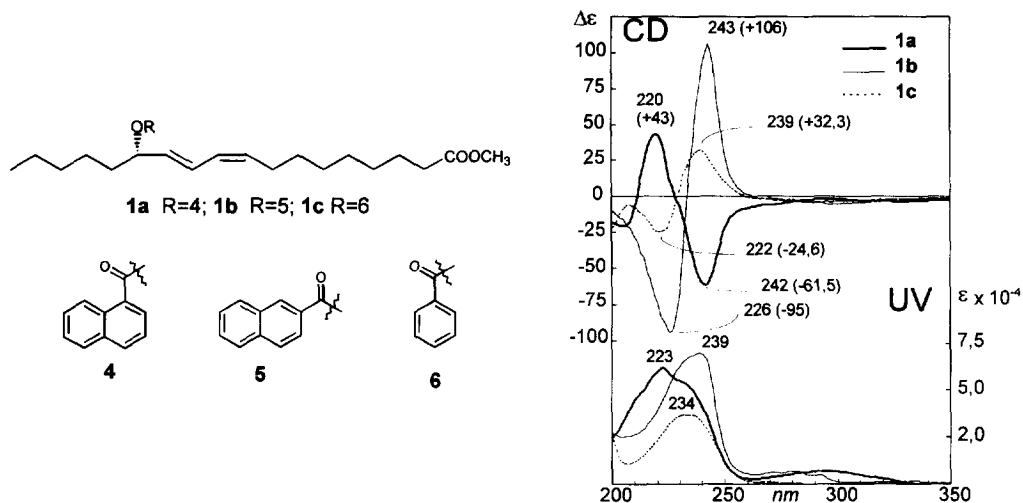
demonstrate the usefulness of 1-naphthoic acid as chromophore. Enantiomerically pure 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester **1** was obtained from linoleic acid by an enzymatic synthesis with soybean lipoxygenase according to the procedure of Hamberg<sup>8</sup>, followed by methylation of the free acid. The CD spectra of the 1-naphthoate derivative **1a** was compared with the corresponding 2-naphthoate **1b** and benzoate **1c** derivatives of 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester **1**. The chromophores were introduced by acylation of the substrate with chromophoric triazole amid as reagent.<sup>9</sup> A typical derivatization is as follows: The substrate was acylated by stirring with the chromophore triazole amide and a catalytic amount of DBU in MeCN at rt for 10h, yielding 90%; the product was purified by prep. TLC on silica gel.<sup>10</sup>

The UV and CD of the obtained derivatives<sup>12</sup> are depicted in figure 2. The CD of 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester (1-naphthoate) **1a** shows a negative split CD band with extrema at 220 nm ( $\Delta\epsilon$  +43) and 242 nm ( $\Delta\epsilon$  -61.5), amplitude  $A$  of -104.5, whereas the corresponding 2-naphthoate derivative **1b** shows an opposite CD curve, with a larger  $A$  value of +201 and Cotton effects at 226 nm ( $\Delta\epsilon$  -95) and 243 nm ( $\Delta\epsilon$  +106). The 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methylester benzoate **1c** shows also two split Cotton effects at 222 nm ( $\Delta\epsilon$  -24.6) and 239 nm ( $\Delta\epsilon$  +32.2), which are much weaker than those of the 2-naphthoate derivative **1b**. The signs of the Cotton effects are in agreement with those expected from the helicity between the 13(S)-C-O bond (and therefore the benzoate chromophore) and the diene chromophore of **1c**. It is already known that the  ${}^1B_u$  band of the 2-naphthoate is approximately parallel to the C-O bond, which means that we get similar CD curves with the same sign of Cotton effects for the 2-naphthoate and the benzoate derivatives. In **1b** the 2-naphthoate chromophore couples through space with the diene chromophore (MeCN,  $\lambda_{\max}$  234 nm ( $\epsilon$  25 000)) to give a positive split CD (figure 1, **1b**). This couplet shows that the electric transition moments of the 2-naphthoate and the diene constitute a positive chirality. From the negative couplet obtained for **1a** we can conclude that the direction of the  ${}^1B_u$  band of the 1-naphthoate chromophore is polarized parallel to the long axis of the 1-naphthoate chromophore (figure 1, **1a**). These results are in agreement with recently published data by Rosini *et al.*<sup>11</sup>



**Figure 1:** Conformational structure of **1a**, **1b** and **1c** and observed signs of the first Cotton effect (— transition dipoles).

The  ${}^1B_u$  band of the 1-naphthoate chromophore introduces approximately a  $90^\circ$  twist compared with the transition dipole of the 2-naphthoate, therefore the chirality between the 1-naphthoate and the diene structure of **1a** constitute a negative chirality and we obtain a negative CD couplet which is opposite to **1b**.



**Figure 2:** UV ( $\lambda_{\max}$  nm/ $\epsilon$ ) and CD ( $\lambda_{\text{ext}}$  nm/ $\Delta\epsilon$ ) spectra of derivatized 13(S)-hydroxy-9(Z),11(E)-octadecadienoic acid methyl ester **1a**, **1b**, **1c** in acetonitrile (MeCN).

There are many cases 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 (e.g. in 3-hydroxyretinoids<sup>5</sup>). A general approach to cope with such cases would be to introduce a chromophore, that induces exciton coupling into the molecule. Due to the twisted electric transition moment in the 1-naphthoate group, this new type of asymmetric chromophore can be used to induce chirality. The development of other asymmetric chromophores and applications of the 1-naphthoate chromophore are recently under investigation.

## ACKNOWLEDGEMENT

This work was supported by the *Fonds der Chemischen Industrie* and the *Universitätsbund Würzburg*. We thank G. Bringmann for using the CD spectrometer and K. Nakanishi and N. Berova for discussion.

## REFERENCES AND NOTES

1. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry*; University Science Books, Mill Valley, CA, 1983.
2. Nakanishi, K.; Berova, N. *The Exciton Chirality Method; in: Circular Dichroism Principles and Applications*; VCH Publishers: New York, 1994; pp 361-398.
3. Matile, S.; Berova, N.; Nakanishi, N.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc.* **1995**, *117*, 7021-7022.
4. Cai, G.; Bozhkova, N.; Odingo, J.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1993**, *115*, 7192-7198.
5. Person, R.V.; Monde, K.; Humpf, H.-U.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 128-135.
6. Dirsch, V.; Frederico, J.; Zhao, N.; Cai, G.; Chen, Y.; Vunnam, S.; Odingo, J.; Pu, H.; Nakanishi, K.; Berova, N.; Liotta, D.; Bielawski, A.; Hannun, Y. *Tetrahedron Lett.* **1995**, *36*, 4959-4962.
7. UV data of chromophores in MeCN: 1-naphthoate  $\lambda_{\max}$  221 nm,  $\epsilon$  42 000; 2-naphthoate  $\lambda_{\max}$  234 nm,  $\epsilon$  50 000; benzoate  $\lambda_{\max}$  229 nm,  $\epsilon$  15 300.
8. Enantiomerically pure **1** was synthesized according to: Hamberg, M. *Anal. Biochem.* **1971**, *43*, 515-526 and Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5329-5335.
9. Humpf, H.-U.; Zhao, N.; Berova, N.; Nakanishi, K.; Schreier, P. *J. Nat. Prod.* **1994**, *57*, 1761-1765.
10. Anal. TLC plates with concentrating zone (silica gel 60 F<sub>254</sub>, 0.25 mm, E. Merck), prewashed with methanol, were used. Solvent systems: diethylether / hexane (1:1) and (2:1).
11. Rosini, C.; Scamuzzi, S.; Focati, M.P.; Salvadori, P. *J. Org. Chem.* **1995**, *60*, 8289-8293.
12. **1a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) data:  $\delta$  2.16 (brq, J = 7.4 Hz, 2H, H8), 5.47 (dt, J = 7.4/11.0 Hz, 1H, H9), 5.61 (dd, J = 7.0/13.6, 1H, H13), 5.73 (dd, J = 7.0/15.0, 1H, H12), 5.98 (dd, J = 11.0/11.0 Hz, 1H, H10), 6.62 (dd, J = 11.0/15.0, 1H, H11), 7.55 (m, 2H, Ar), 7.88 (d, J = 8.8 Hz, 2H, Ar), 7.96 (d, J = 7.7 Hz, 1H, Ar), 8.07 (d, J = 8.8 Hz, 1H, Ar), 8.61 (s, 1H, Ar); HRMS *m/z* calcd 464.293, found 464.2926.  
**1b**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) data:  $\delta$  2.17 (brq, J = 7.4 Hz, 2H, H8), 5.47 (dt, J = 7.4/11.0 Hz, 1H, H9), 5.66 (dd, J = 7.0/13.6, 1H, H13), 5.74 (dd, J = 7.0/15.0, 1H, H12), 5.99 (dd, J = 11.0/11.0 Hz, 1H, H10), 6.66 (dd, J = 11.0/15.0, 1H, H11), 7.55 (m, 3H, Ar), 7.88 (d, J = 8.0 Hz, 1H, Ar), 8.01 (d, J = 8.0 Hz, 1H, Ar), 8.17 (d, J = 7.4 Hz, 1H, Ar), 8.89 (d, J = 8.8 Hz, 1H, Ar); HRMS *m/z* calcd 464.293, found 464.2926.  
**1c**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) data:  $\delta$  2.16 (brq, J = 7.4 Hz, 1H, H8), 5.46 (dt, J = 7.4/11.0 Hz, 1H, H9), 5.96 (dd, J = 11.0/11.0 Hz, 1H, H10), 6.59 (dd, J = 11.0/15.0, 1H, H11), 5.68 (dd, J = 7.0/15.0, 1H, H12), 5.54 (dd, J = 7.0/13.6, 1H, H13), 7.43 (dd, J=7.4Hz, 2H, Ar), 7.54 (dd, J=7.4 Hz, 1H, Ar), 8.05 (dd, J=7.4 Hz, 2H, Ar); HRMS *m/z* calcd 414.277, found 414.2771.

(Received in UK 5 March 1996; accepted 30 April 1996)