Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 21, pp. 3555–3558, 1997
© 1997 Elsevier Science Ltd. All rights reserved.
Printed in Great Britain
0957-4166/97 $17.00 + 0.00

PII: S0957-4166(97)00515-6

The configurational assignment of the optically active 5-(1-hydroperoxyethyl)-3-ethoxycarbonyl-2-methylfuran and its alcohol by exciton-coupled circular dichroism (ECCD)

Waldemar Adam,[a] Hans-Ulrich Humpf,[b,*] Marion N. Korb[a] and Peter Schreier[b]
[a] Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany
[b] Institute of Food Chemistry, University of Würzburg, Am Hubland, D-97074 Würzburg, Germany

Abstract: The absolute configuration of the furan-derived hydroperoxide **1** and its alcohol **2**, readily available in optically active form by kinetic resolution of the racemic hydroperoxide with horseradish peroxidase (HRP), was determined by the exciton-coupled circular dichroism (ECCD) method on their 2-naphthoate derivatives **4**. © 1997 Elsevier Science Ltd

Recently we showed[1] that the optically active hydroperoxide (*S*)-(−)-**1** and the alcohol (*R*)-(+)-**2** are readily accessible by the enzymatic kinetic resolution of the racemic hydroperoxide **1** with horseradish peroxidase (HRP) on a preparative scale (Scheme 1). These optically active furan derivatives were independently reported in the Ti(O*i*Pr)$_4$-catalyzed enantioselective oxidation of allylic alcohols and sulfides.[2] Since the absolute configuration of these optically active compounds was unknown, we decided to employ the well established exciton-coupled circular dichroism (ECCD)[3] for this purpose. Recently, ECCD was applied successfully for the configurational assignment of optically active, functionalized compounds like α- and β-hydroxy carboxylic acids, homoallylic hydroperoxy alcohols and their corresponding diols, and acyclic hydroxy-substituted dienes.[4]

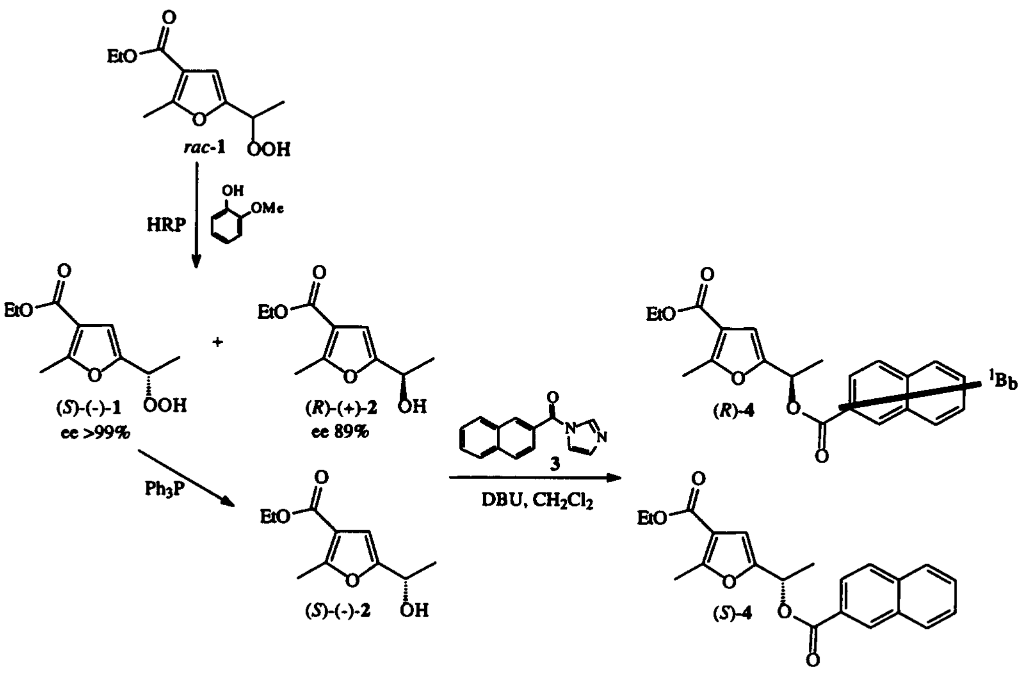
To apply the ECCD method on the hydroperoxide **1** and alcohol **2**, a second exciton-coupling chromophore with a large ε value and known direction of the transition dipole had to be introduced (Scheme 1).[3] This was achieved by reduction of the hydroperoxide (*S*)-(−)-**1** and subsequent acylation[5] of the alcohol **2** with 2-naphthoylimidazole **3** to the naphthoate derivative **4**.[6]

The CD and UV of **4** are shown in Figure 1a. In the chromophoric derivative (*S*)-**4**, the long-axis ^1B_b transition (Scheme 1) of the 2-naphthoate chromophore couples with the π–π* transition of the furan chromophore (ca. 225 nm) to give a positive split CD curve with extrema at 236 nm ($\Delta\varepsilon$=+21.1) and 212 nm ($\Delta\varepsilon$=−19.3) with an amplitude *A* of +40.4. This positive CD shows that the electric transition dipole of the 2-naphthoate and the furan[7] chromophores constitute positive chirality. The enantiomer (*R*)-**4** exhibits an opposite bisignate CD curve with a negative Cotton effect at 235 nm ($\Delta\varepsilon$=−21.0) and a positive one at 216 nm ($\Delta\varepsilon$=+5.3) with an amplitude *A*=−26.3. The underivatized alcohol **2** show only very weak Cotton effects around 216 nm which do not affect the exciton coupling CD spectra of the naphthoate derivatives **4**.

Since the ECCD method depends on the conformation of the molecule under examination, MM2 calculations (Macro Model 5.0) were conducted to assess the conformational preference of the naphthoate **4**, in an effort to reconcile the observed Cotton effects. These calculations have revealed the two planar conformations **A** and **B**, which give rise to Cotton effects of opposite signs. In these conformations the H-2 atom lies in the plane of the furan ring, in **A** it faces the H-1 atom and in **B** it points in the direction of the furan oxygen atom. An NOE experiment established conformation **A** as the preferred one for the naphthoate **4** with a 2% enhancement between the H-1 and H-2 atoms.

---

* Corresponding author.



Scheme 1. Synthesis of the optically active hydroperoxide (*S*)-(−)-1 and its alcohol (*R*)-(+)-2 and their derivatization to the naphthoates 4 (— transition dipole).

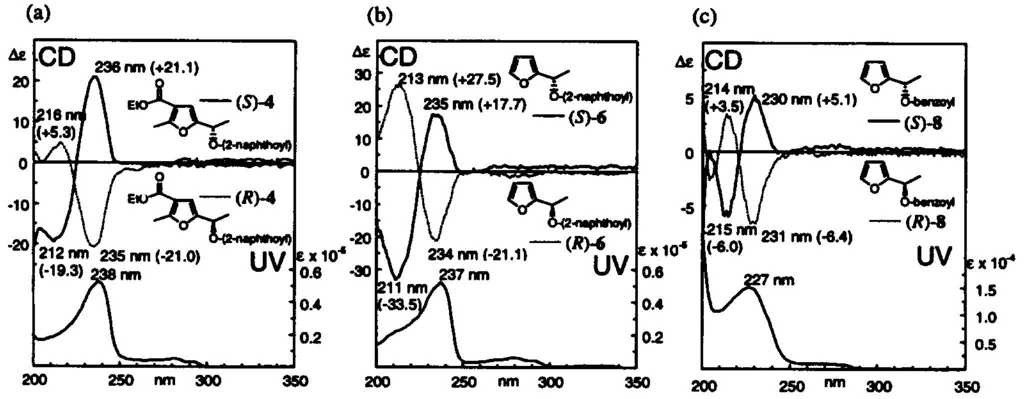
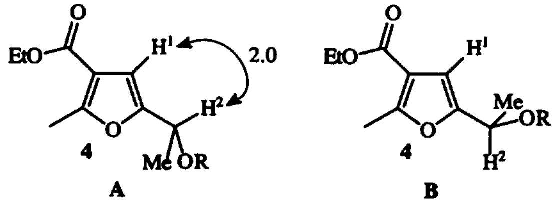


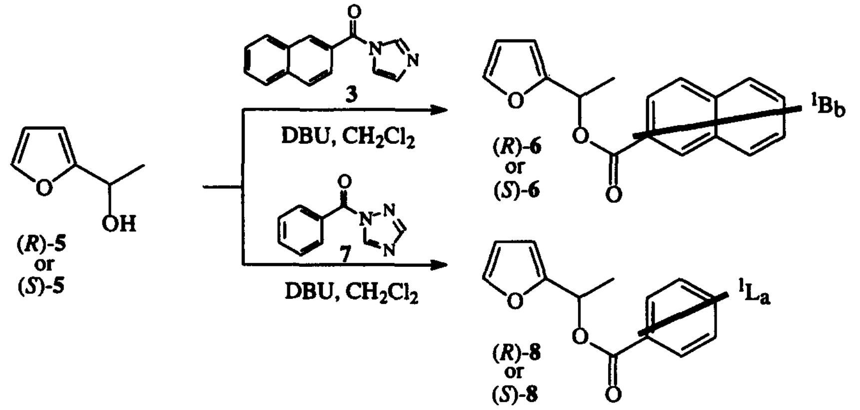
Figure 1. UV and CD spectra of the furan derivatives 4–6 in MeCN (1 cm cell).

The preference for conformer **A** also agrees with the literature data of furylcarbinols.[8] Thus, the hydroperoxide (−)-**1** possesses the *S* configuration and the alcohol (+)-**2** the *R* configuration.



To provide additional support for this configurational assignment, the commercially available enantiomers of 1-furylethanol (**5**) were derivatized[5] to the naphthoate **6** and the benzoate **8** (Scheme 2).

As shown in Figure 1b, the enantiomer (*S*)-**6** revealed a positive Cotton effect at 235 nm ($\Delta\varepsilon$=+17.7) and a negative effect at 211 nm ($\Delta\varepsilon$=−33.5) with *A*=+51.2, whereas the optical antipode (*R*)-**6** exhibited a mirror image CD at 234 nm ($\Delta\varepsilon$=−21.1) and 213 nm ($\Delta\varepsilon$=+27.5) with *A*=−48.6. The CD spectra of the benzoates **8** (Figure 1c) displayed the same shape as the corresponding enantiomers **6**, but with a smaller amplitude *A* [(*S*)-**8**: positive Cotton effect at 230 nm ($\Delta\varepsilon$=+5.1) and a negative effect at 215 nm ($\Delta\varepsilon$=−6.0) with *A*=+11.1; (*R*)-**8**: negative Cotton effect at 231 nm ($\Delta\varepsilon$=−6.4) and a positive effect at 214 nm ($\Delta\varepsilon$=+3.5) with *A*=−9.0]. These results match those obtained for the enantiomers **4** and, thus, confirm the configurational assignment.



Scheme 2. Derivatization of 1-furylethanol (**5**) to the naphthoate **6** and the benzoate **8** (— transition dipole).

The ECCD method has already been applied to 2-furylcarbinols, but only for the benzoate chromophore.[8] Since the UV absorption of the benzoate chromophore is relatively weak (ε=15,300), the resulting CD effects are also very small.[8] As shown here with the 2-naphthoate derivatives **6** and the benzoate derivatives **8** as model compounds, the 2-naphthoate chromophore (ε=54,000) yields the same but much stronger Cotton effects than the benzoate chromophore. These findings are in agreement with the fact that the direction of the dipole moments of the two chromophores are the same.[9] Since the CD spectra are often perturbed by other weak transitions in the 200–210 nm region, the sign of the first Cotton effect at around 236 or 230 nm is sufficient to deduce the absolute configuration of the optically active furans presently studied.

The above data clearly demonstrate that the absolute configuration of the optically active furane-derived hydroperoxide **1** and its alcohol **2** may be conveniently determined by the ECCD method after their derivatization to the naphthoate **4**. The presented microscale method should also be useful for other furyl alcohols and similar structural units.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (SFB 347 'Selektive Reaktionen Metallaktivierter Moleküle') and the Bayerische Forschungsstiftung (FORKAT) for generous financial support.

References

1. Adam, W.; Korb, M. N. *Tetrahedron: Asymmetry*, **1997**, *8*, 1131–1142.
2. (a) Scettri, A.; Bonadies, F.; Lattanzi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 629–632; (b) Lattanzi, A.; Bonadies, F.; Scettri, A. *Tetrahedron: Asymmetry*, **1997**, *8*, 2141–2151.
3. (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, NY. 1994.

4. (a) Gimple, O.; Schreier, P.; Humpf, H.-U. *Tetrahedron: Asymmetry* **1997**, *8*, 11–14; (b) Hoch, U.; Humpf, H.-U.; Schreier, P.; Saha-Möller, C. R.; Adam, A. *Chirality* **1997**, *9*, 69–74; (c) Schneider, C.; Schreier, P.; Humpf, H.-U. *Chirality* **1997**, in press.
5. ***Procedure for the derivatization of the alcohols 3 and 5.*** To a solution of the alcohol (100–200 μmol) in dry $\mathrm{CH_2Cl_2}$ (2 mL) were added 1.2 equiv. of 2-naphthoylimidazole (**3**) or benzoyltriazole (**7**) and 1.2 equiv. DBU. The reaction mixture was stirred at RT for 2 h, concentrated (20°C/20 Torr) and the product (yield 75–90%) purified by flash chromatography [silica gel, 1:1 petroleum ether (30–35°C):diethyl ether].
6. (*S*)-**4** and (*R*)-**4**: ^{1}H-NMR (200 MHz, $\mathrm{CDCl_3}$). δ=1.34 (t, *J*=7.1 Hz, 3 H, $\mathrm{CH_2C}H_3$), 1.74 (d, *J*=6.7 Hz, 3 H, $\mathrm{CHC}H_3$), 2.59 (s, 3 H, $\mathrm{CH_3}$), 4.29 (q, *J*=7.1 Hz, 2 H, $\mathrm{C}H_2\mathrm{CH_3}$), 6.21 (q, *J*=6.6 Hz, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 6.70 (s, 1 H, C=CH), 7.57 (m, 2 H, H arom.), 7.98 (m, 4 H, H arom.), 8.61 (s, 1 H, H arom.).
7. The π–π^* transition of the furan ring is polarized approximately perpendicularly to the C–C axis.
8. Gawronski, J.; Radocki, D. *J. Org. Chem.* **1990**, *55*, 1118–1120.
9. Dong, J.-G.; Akritopoulou-Zanze, I.; Guo, J.; Berova, N.; Nakanishi, K.; Harada, N. *Enantiomer*, **1997**, in press.

(Received in UK 14 August 1997; accepted 13 October 1997)