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A simple circular dichroism method for the determination of the absolute configuration of allylic amines

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Abstract

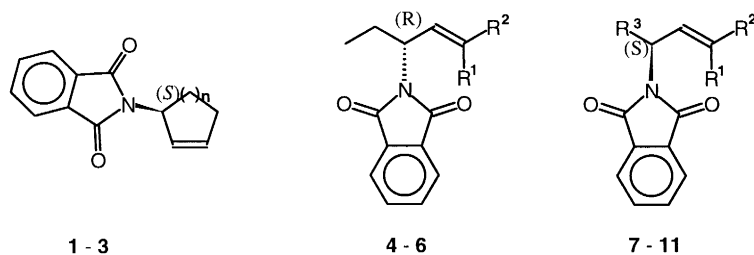
Absolute configurations of C(α)-chiral primary allylic amines can be determined from the CD spectra of their *N*-phthaloyl derivatives. This method is based on the exciton coupling of the allowed π – π^* transitions in the phthalimide and olefin chromophores: positive helicity of the N–C $_{\alpha}$ –C=C bond system results in a positive Cotton effect at ca. 220 nm, a negative Cotton effect is obtained for the negative helicity N–C $_{\alpha}$ –C=C bond chain. © 2000 Elsevier Science Ltd. All rights reserved.

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Chiral non-racemic *N*-protected allyl amines are becoming available by asymmetric synthesis.^{1–3} For example, *N*-phthaloyl allyl amines **1–3** have been synthesized by Trost and Bunt,^{1a} by catalytic asymmetric substitution of allylic acetates by phthalimide. Their absolute configurations were determined by transformation to known amines and by ¹H NMR shift correlation of diastereomeric *O*-methylmandelamides.⁴

In recent years we have developed a method for determining the absolute configuration (or conformation) of optically active chiral amines based on intramolecular exciton coupling of the phthalimide chromophore.⁵ Here we present a CD method for the determination of absolute configuration of *N*-phthaloyl allyl amines. This method is based on a non-empirical correlation of the sign of the long-wavelength exciton Cotton effect with the helicity of the bichromophoric electric dipole transition moment system.⁶ Both cyclic and acyclic allylic amines can be subjected to this determination.

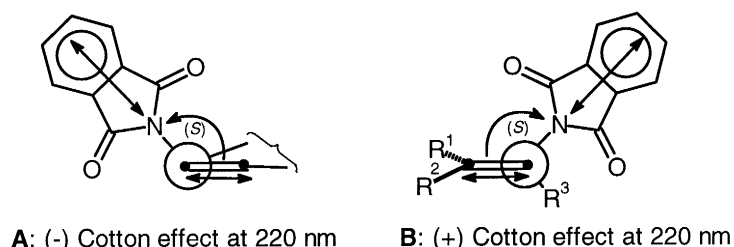
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The CD spectra of cyclic compounds **1–3** display a negative Cotton effect at ca. 220 nm, belonging to the π – π^* charge-transfer transition polarized along the C_2 axis of the phthalimide chromophore (Table 1).⁵ The sign of this Cotton effect correlates with M -helicity of the N – C_α – $C=C$ bond system in the S -configuration, as a result of coupling of the phthalimide 220 nm transition with the π – π^* transition of the alkene chromophore (Fig. 1A). The diminished magnitude of the Cotton effect of **3** apparently reflects increased conformational flexibility of the seven-membered ring.^{7,8}

Table 1
CD data

	R^1	R^2	R^3	n	Configuration	$\Delta\epsilon$ (ca. 220nm)
1	-	-	-	1	S	-21.0
2	-	-	-	2	S	-17.3
3	-	-	-	3	S	-7.5
4	H	H	-	-	R	-9.9
5	Me	H	-	-	R	-12.4
6	Me	Me	-	-	R	-10.5
7	H	H	Me	-	S	+2.4
8	Me	H	Me	-	S	+14.0
9	H	H	<i>i</i> -Pr	-	S	+6.2
10	Me	H	<i>i</i> -Bu	-	S	+20.0
11	Me	Me	<i>i</i> -Bu	-	S	+17.1



A: (-) Cotton effect at 220 nm

B: (+) Cotton effect at 220 nm

Fig. 1. CD correlation for cyclic (A) and acyclic (B) allylic phthalimides of (S) configuration (for (R) configuration the sign of the Cotton effect is reversed)

The acyclic N -phthaloyl allylic amines **4–11**⁹ display Cotton effects at ca. 220 nm whose sign likewise reflects the absolute configuration. The calculated minimum energy conformer of **7–11** is shown in Fig. 1B.^{7,10} The helicity of the N – C_α – $C=C$ bond system and hence the sign of the Cotton effect of **7–11** are reversed when compared to these of **1–3** of the same absolute configuration. Alkene substitution pattern in **4–11** exerts some effect on the magnitude, but not on the sign, of the 220 nm Cotton effect.

The simple electric dipole transition moment interaction scheme shown in Fig. 1 can be used to correlate the absolute configuration of any allylic amine with the sign of the Cotton effect.

A similar exciton CD method has been introduced by Harada and Nakanishi for the configuration determination of benzoates of allylic alcohols.¹¹

Acknowledgements

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7. Molecular modeling was initially performed with the MMX force field (PCMODEL, Serena Software, Bloomington, IN) and complemented by semiempirical calculations of heats of formation with AM1 (HyperChem, HyperCube Inc.).
8. For a similar trend in $[\alpha]_D$ values of analogous cyclic allylic benzoates, see: Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961.
9. Compounds **4–11** were prepared from (*R*)-2-amino-1-butanol (ee 80%) or the corresponding L-aminoacid precursors in the sequence of reactions involving reduction to α -aminoalcohols (Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517), followed by *N*-phthaloylation (Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 893), oxidation to α -phthalimidoaldehydes with TEMPO (Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051), and Wittig olefination at -78°C (Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487). The intermediate α -phthalimidoaldehydes showed little racemization (ee>90%), estimated by HPLC on a chiral column (DAICEL OD-H 250/4).
10. This conformation is additionally supported by the experimental $^3J_{\text{H,H}}$ in the range 6.6–9.8 Hz between the protons located at the chiral and the olefinic carbon atoms.
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