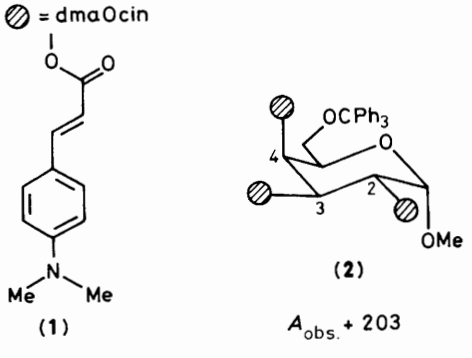
p-Dimethylaminocinnamate, a New Red-shifted Chromophore for Use in the Exciton Chirality Method. Its Application to Mitomycin C

Gregory L. Verdine and Koji Nakanishi*

Department of Chemistry, Columbia University, New York, New York 10027, U.S.A.

p-Dimethylaminocinnamate is useful as a new chromophore in applications of the exciton chirality method because of its strong absorption at the relatively long wavelength of 362 nm.

The exciton chirality method has been applied to a variety of compounds for the determination of absolute configuration.[1] When hydroxy or amino groups are involved as in glycols[2] ('dibenzoate method') or sugars,[3] they are usually converted into *p*-bromobenzoates, u.v. (EtOH) 244.5 nm, ε 19500, owing to ease of preparation, or to *p*-dimethylaminobenzoates (dmaOBz),[4] u.v. (EtOH) 311 nm, ε 30400, because of their strong absorption at long wavelengths. Chiral interaction of two or more such chromophores in spatial proximity, as in 1,2-dibenzoates, results in split c.d. curves with extrema of opposite signs, the difference in Δε between the two extrema being defined as *A* (amplitude) values. Since a linear relation exists between u.v. ε values and c.d. *A* values, a large value for ε is preferred.[1] Although the dmaOBz is satisfactory in most cases, it cannot be used when the substrate itself has a strong absorption around 310 nm with a transition moment of unknown direction because of the substrate–dmaOBz inter-



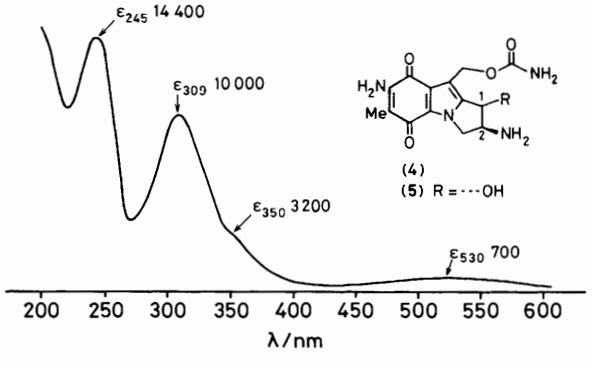


Figure 1. U.v. spectrum of mitosene (**5**) in MeCN.

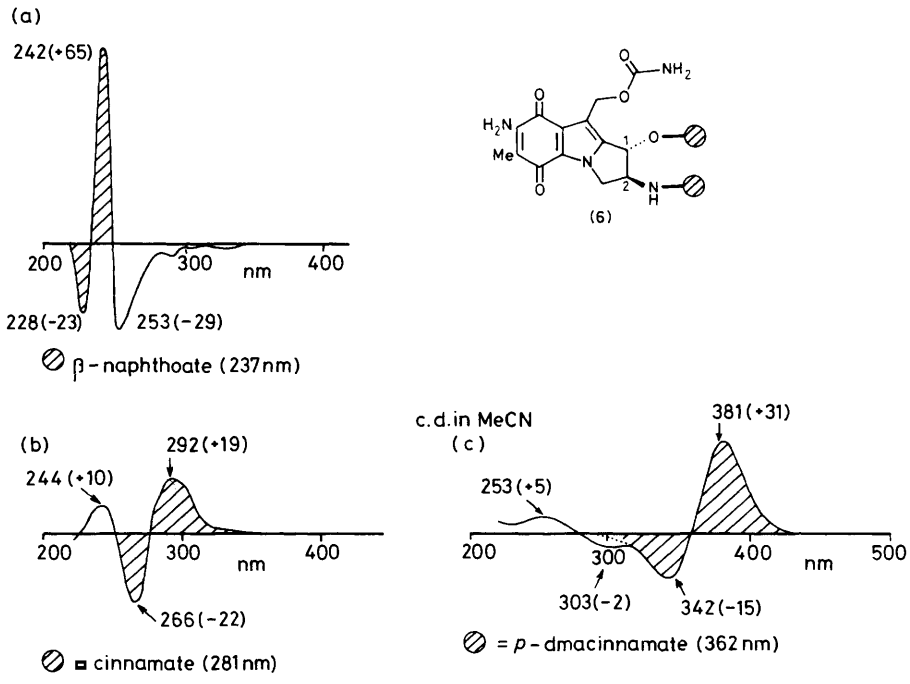


Figure 2. C.d. spectra of (**6**) in MeCN; (a) bis-naphoates; (b) bis-cinnamates, and (c) bis-dmacinnamates. The extrema, wavelengths (in nm), and intensities ($\Delta\varepsilon$) are shown on the curves.

action. As exemplified by mitosenes many biologically interesting molecules have strong absorptions in this region.

This communication reports the use of a new chromophore, *p*-dimethylaminocinnamate (dmaOcin) (**1**), which has an intense absorption band at 361 nm (ε 30 400 in MeCN),† can be readily prepared, and is fluorescent. The cinnamates are best prepared by treating the substrate with dmaOcin imidazole ester and NaH; if NaH destroys the substrate then the corresponding cinnamoyl chloride is used with pyridine–dimethylaminopyridine.

The imidazole ester is prepared by standard methods[5] from *p*-dimethylaminocinnamaic acid (suspended in tetrahydrofuran, THF) and carbonyldi-imidazole; the product is purified by flash chromatography using EtOAc as solvent, m.p. 166 °C (from EtOAc–MeOH). The imidazole ester has a yellow fluorescence on t.l.c. while the starting acid and all *O*- or *N*-dimethylaminocinnamates exhibit blue fluorescence, thus allowing easy monitoring. The cinnamoyl chloride is prepared from the acid and $SOCl_2$ and used without purification for acylations; the acid chloride can only be stored for a few days.

As in the case of *p*-bromobenzoates[3] and others,[6] the additivity relation also holds for the cinnamates. Thus the observed *A* value of 203 for tricinnamate (**2**)‡ with a positively split c.d. is in good agreement with the calculated *A* +181, the sum of the *A* values of the constituent dicinnamate units: 2,3-di-dmaOcin-4-acetoxy-6-trityl-α-methylgalactoside +88, 2,4-§ +33, and 3,4-§ +60 (all *A* values in MeCN).

An interesting application of this new chromophore is provided by mitomycin C, a clinically used antitumour agent, the absolute configuration of which was recently revised after an *X*-ray re-examination.[7] The alkylating capacity of (**3**) is unmasked by reductive or acidic activation to give strongly absorbing mitosenes of general structure (**4**) (Figure 1), in which the aziridine ring has opened with configurational retention at C-2 and nucleophilic attachment at C-1 with inversion or retention.[8] Authentic 1α-OH-2β-NH_2 mitosene (**5**), the *trans* configuration being determined from the 530 nm Cotton effect,[8] was converted into the 1,2-*O*,*N*-bis-dmaOcin derivative (**6**) (Figure 2; hatched circles denote the cinnamate chromophore). Mitosenes have strong absorptions at 245 and 309 nm and weak bands at 350 and 530 nm (Figure 1). The *O*,*N*-bis-β-naphthoate does exhibit a positively split c.d. centred around the naphthoate 237 nm u.v. maximum, Figure 2(a), but because of overlap or interaction of the strong mitosene (Figure 1) and naphthoate chromophores at 245 and 237 nm, respectively, the split c.d. sign may not be a correct represention of the chirality at C-1/C-2. The same applies to the 1,2-*O*,*N*-bis-cinnamate because of the overlap between the mitosene 309 nm and cinnamate 281 nm bands, Figure 2(b). However, this is not the case for the bis-dma-*O*,*N*-cinnamate derivative (dma = *N*,*N*-dimethylamino), Figure 2(c), since mitosenes lack strong absorption at 362 nm; the positively split c.d. *A* +46 at *ca.* 360 nm thus represents the chirality between 1,2-functions, and agrees with the revised absolute configuration of (**3**).

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† Methanol cannot be used as the solvent for c.d. measurements of benzoates because of ester exchange. Acetonitrile is the solvent of choice.

‡ *Preparation of tricinnamate* (**2**). 6-*O*-Trityl-α-methylgalactoside (21.8 mg) in 1.0 ml THF under Ar, 0 °C was treated with 6 mg (4 equiv.) 80% NaH–mineral oil, 0 °C for 30 min. The imidazole ester (13 mg, 4 equiv.) was added, the solution was left at room temperature for 20 min, treated with 10 mg NH_4Cl, and stirred for 20 min at room temp. The solvent was removed and the product was flash chromatographed and eluted with EtOAc–hexene 80 : 20; 45 mg or 95% yield.

§ 6-Trityl-α-methylgalactosides with acetoxy group at 3- or 2-position, respectively.

supply of mitosene (**5**), Dr. T. Takeda, Suntory Institute for Bioorganic Research, Osaka, for helpful discussions, and the National Institutes of Health for financial support.

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