# Advanced Method for Assignment of Absolute Configuration Utilizing an Induced CD and Computational Technique: Its Application to Natural Products Possessing a Secondary Alcohol

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A modified procedure for determining absolute configurations using an induced CD method and molecular mechanics calculations is disclosed. The practical usefulness of the present technique was demonstrated by its application to a few natural products.

Spectroscopic methods, especially using nuclear magnetic resonance (NMR) and circular dichroism (CD), for elucidation of absolute stereostructure have undergone great progress in recent years. Among them, the exciton-coupled CD (ECCD) method has been extensively applied to various organic molecules as a microscale method to establish their absolute configurations in a nonempirical manner.[1] Although its application has been limited to compounds having two or more functional groups, it has been extended to compounds with a single functional group.[2] In the course of our stereochemical studies of chiral monofunctional molecules by the ECCD method, we expected that axial chirality would be induced if a chiral alcohol was covalently attached to an achiral biaryl chromophore. On the basis of this idea, we developed a novel method to determine the absolute configuration of chiral alcohols by an induced exciton chirality of the binaphthyl CD auxiliary, 3-cyanocarbonyl-3′-methoxycarbonyl-2,2′-binaphthalene (**1**).[2e] Here we describe an advanced procedure of this method using a combination of an induced CD and conformational analysis, the usefulness of which was demonstrated by application to biologically active natural products.

In our preceding communication, [2e] we proposed a rule to determine the absolute configuration of a chiral secondary alcohol from the sign of exciton chirality of its binaphthyl ester and the relative bulkiness of the two substituents of the alcohol. In the communication, we also mentioned a close relationship between the sign of exciton chirality and the screw sense between the two longitudinal $^1B_b$ electric transition moments of 2-naphthoate groups in the most stable conformer of the binaphthyl derivative calculated by molecular mechanics: the esters showing positive exciton chirality had a clockwise (C) turn, whereas those with negative exciton chirality showed a counterclockwise (CC) turn.

In 2002, Kobayashi and co-workers used this relationship to determine the absolute configuration of serratezomine A,[3] whose secondary alcohol at C8 was converted to our binaphthyl ester **2**. The ester showed a negative exciton chirality:[4] a split CD curve having a negative Cotton effect at 256 nm and a positive one at 234 nm, indicating the screw sense of the two naphthyl groups to be a counterclockwise turn. As this result was in agreement with the more stable conformer predicted by calculations,[4] they concluded the absolute configuration at the C8 position to be *S*; this conclusion was also supported by the modified Mosher's method.[5]

Apparently, the relative bulkiness of the two substituents of a secondary alcohol is reflected in the calculation, and the predicted screw sense of the most stable conformer is expected to be the same as that predicted from the observed exciton chirality. Thus, without consideration of the relative bulkiness of the substituents, which we have discussed previously,[2e] the absolute configuration of a secondary alcohol can be determined as follows: (1) convert a secondary alcohol in question to the corresponding binaphthyl ester and measure the CD spectrum; (2) calculate the most stable conformer of the binaphthyl ester derived from either enantiomer of the secondary alcohol using CONFLEX;[6] (3) compare the sign of the exciton chirality and the predicted screw sense: for example, if the screw sense obtained from a calculation based on the *R*-isomer is clockwise and the observed sign of exciton chirality of the ester is positive, the absolute configuration of the alcohol can be assigned as *R*. However, since the observed CD spectrum is the sum of the contributions from all conformers in the solution, not only the energetically most stable conformer but also the global population ratio of stable conformers with clockwise and counterclockwise turns of the derivatives should be considered. In the above case, further molecular mechanics calculations for the 8*S*-isomer of **2** indicated that the conformers with a counterclockwise turn, that is, with the same screw sense as that of the most stable conformer, predominated (C/CC = 45/55). The absolute configuration at C8 could therefore be safely assigned as *S*.

The method was then applied to naturally occurring compounds in order to prove its usefulness for the assignment of absolute configuration. Yohimbine is an important indole alkaloid found in Yohimbe bark, *Pausinystalia yohimbe* (Rubiaceae).[7] The absolute configuration has already been determined by a single-crystal X-ray analysis of yohimbine hydrochloride (C17: *S*).[8] Treatment of yohimbine with reagent **1** gave the corresponding ester **3** (**1**, DMAP/$CH_3CN$, rt, 37% yield), the CD spectrum of which showed a bisignate CD curve ($\lambda_{ext}$ ($\Delta\epsilon$) nm ($CH_3CN$): 221.2 (−29.8), 230.0 (0), 236.2 (+30.2)), indicating a positive

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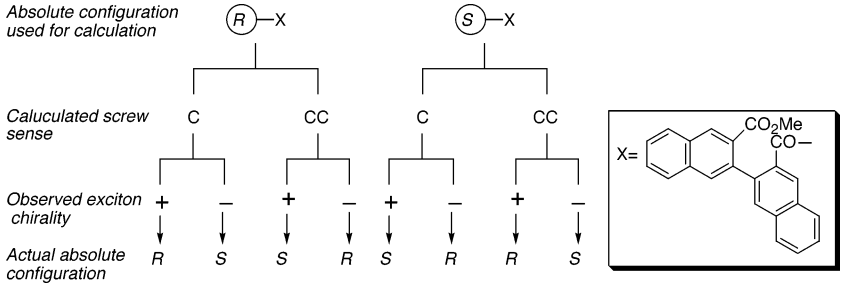


**Figure 1.**

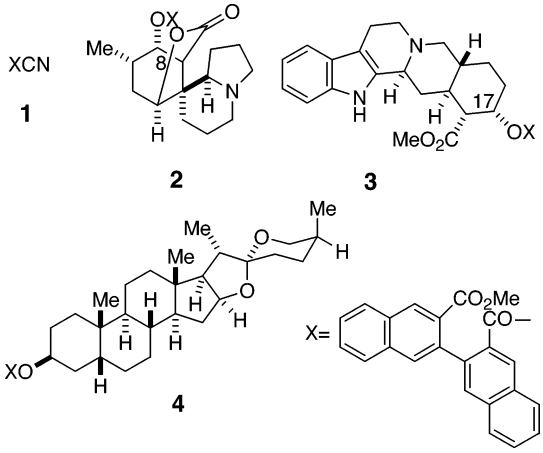


**Figure 2.**

exciton chirality. On the basis of the data from the molecular mechanics calculation of the 17*S*-derivative, it was found that the 17*S*-isomer preferentially exhibits a clockwise screw sense (C/CC = 56/44). The absolute configuration of yohimbine at C17 was thus *S*.

Next, sarsasapogenin, a steroid sapogenin isolated from *Smilax ornata* Hooker, fil. (Liliaceae), [9] was derived in the same way to afford the ester **4** in 31% yield. The absolute *S*-configuration at C3 of sarsasapogenin has been established by chemical correlations.[10] Similar to the two cases described above, the CD spectrum of the ester **4** showed a definite exciton split ($\lambda_{ext}$ ($\Delta\epsilon$) nm ($CH_3CN$): 223.2 (+13.0), 230.5 (0), 238.6 (−14.8)), indicating a negative exciton chirality. Calculations regarding the 3*S*-derivative indicated that it preferentially exhibited a counterclockwise turn (C/CC = 31/69). Thus, our method gave the same *S*-configuration at C3 in sarsasapogenin as previously reported. In summary, the central chirality of a secondary alcohol induced exciton-coupled CD arising from the interaction of the two chromophores on the binaphthyl auxiliary, which, coupled with conformational analysis of the derivatives, was used to determine the absolute configuration of the alcohol. The practical usefulness of the present method was demonstrated by application to diverse types of natural compounds. Further work is in progress to expand the scope of this methodology to other types of chiral molecules.

## Experimental Section

**General Experimental Procedures.** Unless otherwise noted, the following procedures were adopted. Nonaqueous reactions were carried out under argon in dried glassware. Anhydrous acetonitrile and tetrahydrofuran (THF) were freshly distilled under argon from $CaH_2$ and Na/benzophenone, respectively, prior to use. Infrared spectra (IR) were recorded on a Jasco IR-G spectrometer, and data are given in $cm^{-1}$ with the following relative intensities: s (strong 67−100%), m (medium 33−67%), or w (weak 0−33%). UV and CD spectra were recorded in a 1 cm cell on a Shimadzu UV-1600 spectrometer and a Jasco J-725S spectropolarimeter, respectively. Specific rotation, $[\alpha]_D$, was measured on a Horiba SEPA-300 polarimeter and reported in deg/dm at specified temperatures, and the concentration (*c*) is given in grams per 100 mL in the specified solvent. $^1H$ NMR spectra were recorded on a JEOL GX 500 (500 MHz) spectrometer using tetramethylsilane as an internal reference, and chemical shifts are given in $\delta$ values with coupling constants (*J*) in Hz. Mass spectra (MS) and high-resolution MS (HRMS) were recorded on a Hitachi M-80 machine, and $M^+$ and/or major peaks are indicated as *m*/*z* (intensity relative to base = 100%). Column chromatography was carried out with silica gel (Wacogel C-200). For thin-layer chromatography (TLC), Merck $GF_{254}$ precoated plates were used and spots were monitored under UV light (254 nm), then developed by spraying with 10% $H_2SO_4$ and heating the plate at 100 °C until coloration took place. Preparative TLC (PTLC) was performed with precoated silica gel plates, Merck 60 $F_{254}$ (1 mm thick).

**General Derivatization Procedure.** To a solution of a chiral alcohol (8−10 mg) and acyl cyanide **1** (1.2 mol equiv) in acetonitrile (1.0 mL) or acetonitrile/THF (1.0 mL, 1/1 (v/v)) was added 4-(dimethylamino)pyridine (DMAP) (3.0 mol equiv), and the whole was stirred at room temperature for the specified time. After removal of the solvent in vacuo, the crude product was purified by PTLC to give the binaphthyl ester.

**Yohimbine derivative (3):** pale yellow gum. $R_f$ (EtOAc) 0.38; $[\alpha]^{25}_D$ +17.7° (*c* 0.084, $CHCl_3$); UV ($CH_3CN$) $\lambda_{max}$ ($\epsilon$) 228.5 (77 200), 242.5 (77 600), 339.0 (3100) nm; CD ($CH_3CN$) $\lambda_{ext}$ ($\Delta\epsilon$) 221.2 (−29.8), 230.0 (0), 236.2 (+30.2) nm; IR (film) $\nu_{max}$ 2920 m, 1727 m, 1438 m, 1310 w, 1276 m, 1272 m, 1218 m, 1206 m, 1146 m, 1131 m, 1092 m, 1060 m, 747 m $cm^{-1}$; $^1H$ NMR (acetone-$d_6$, 500 MHz) $\delta$ 8.65 (0.4H, s), 8.64 (0.4H, s), 8.61 (0.6H, s), 8.57 (0.6H, s), 8.50−8.12 (2H, m), 8.03−7.89 (3H, m), 7.82−7.53 (6H, m), 7.33 (0.4H, d, *J* = 7.8 Hz), 7.31 (0.6H, d, *J* = 7.8 Hz), 7.24 (0.4H, d, *J* = 7.8 Hz), 7.20 (0.6H, d, *J* = 7.8 Hz), 6.99−6.87 (2H, m), 5.43 (1H, q, *J* = 2.5 Hz), 3.60 (1.2H, s), 3.55 (1.8H, s), 3.51 (1.8H, s), 3.43 (1.2H, s), 3.12−2.19 (5H, m), 1.79−0.77 (10.4H, m), 0.32 (0.6H, m); EIMS *m*/*z* 692 [$M^+$] (100), 691 (55), 357 (11), 356 (43), 336 (19), 335 (26), 334 (13), 312 (10), 311 (17), 297 (11), 296 (11), 295 (12), 281 (40), 280 (24), 253 (11), 252 (28), 239 (12), 169 (12); HRMS *m*/*z* 692.2889 (calcd for $C_{44}H_{40}N_2O_6$, 692.2886).

**Sarsasapogenin derivative (4):** colorless gum. $R_f$ (hexane/EtOAc, 3/1 (v/v)) 0.56. $[\alpha]^{23}_D$ −56.0° (*c* 0.0932, $CHCl_3$); UV ($CH_3CN$) $\lambda_{max}$ ($\epsilon$) 244.5 (68 700), 340.0 (2600) nm; CD ($CH_3CN$) $\lambda_{ext}$ ($\Delta\epsilon$) 208.9 (+12.9), 223.2 (+13.0), 230.5 (0), 238.6 (−14.8), 259.0 (−5.9) nm; IR ($CHCl_3$) $\nu_{max}$ 2995 w, 2920 m, 2860 m, 1720 m, 1621 w, 1441 m, 1366 w, 1339 w, 1315 w, 1277 s, 1220 m, 1202 m, 1200 m, 1168 w, 1148 w, 1131 m, 1095 w, 1060 m, 1047 w, 1013 w, 994 w, 979 m, 963 w, 907 m, 890 w, 844 w $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 8.63 (1H, s), 8.59 (0.43H, s), 8.56 (0.57H, s), 8.00 (1H, d, *J* = 8.3 Hz), 7.96 (1H, d, *J* = 8.3 Hz), 7.86 (1H, d, *J* = 8.3 Hz), 7.83 (0.57H, s), 7.83 (1H, d, *J* = 8.3 Hz), 7.77 (0.43H, s), 7.72 (0.57H, s), 7.69 (0.43H, s), 7.63−7.53 (4H, m), 5.13 (1H, brs), 4.36 (1H, q, *J* = 7.5 Hz), 3.93 (1H, dd, *J* = 11.0, 2.6 Hz), 3.64 (1.7H, s), 3.63 (1.3H, s), 3.28 (1H, brd, *J* = 11.0 Hz), 2.01 (1H, m), 1.94−0.75 (25H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.97 (1.3H, d, *J* = 6.8 Hz), 0.96 (1.7H, d, *J* = 6.8 Hz), 0.69 (1.3H, s), 0.67 (1.7H, s), 0.62 (1.3H, s),

0.62 (0.57H, m), 0.47 (1.7H, s), 0.41 (0.43H, m); EIMS *m*/*z* 754 [$M^+$] (27), 398 (11), 357 (60), 356 (100), 340 (12), 339 (40), 325 (24), 312 (20), 311 (28), 305 (10), 297 (19), 296 (21), 295 (27), 284 (16), 282 (14), 281 (62), 280 (37), 255 (31), 253 (11), 252 (28), 139 (60), 121 (10), 107 (13), 95 (12), 93 (15), 81 (14), 69 (14); HRMS *m*/*z* 754.4246 (calcd for $C_{50}H_{58}O_6$, 754.4233).

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