

# Determination of the Absolute Configuration of 1-Arylethane-1,2-diols by a Nonempirical Analysis of the CD Spectra of Their 4-Biphenylboronates

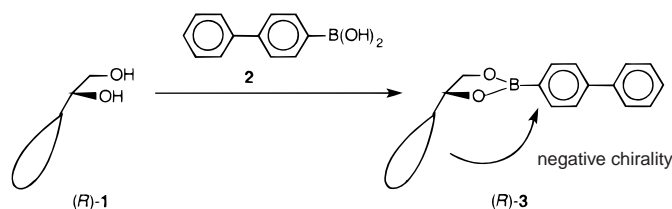
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## ABSTRACT



1-Arylethane-1,2-diols **1**, reacting with 4-biphenylboronic acid **2**, form the conformationally defined boronates **3** where the aryl and biphenyl chromophores assume a fixed and known relative disposition. These chromophores thus define an exciton coupled system, whose chirality (revealed by the sign of the biphenyl CD band at 260 nm) allows an unambiguous assignment of the absolute configuration of the stereogenic center. This approach provides the hitherto unreported absolute configuration of diols **1c–f**.

Chiral acyclic 1,2-diols play a prominent role in organic chemistry. In fact, they are important synthetic intermediates<sup>1</sup> and auxiliaries in stereoselective processes,<sup>2</sup> and the 1,2-diol moiety is present in many natural products.<sup>3</sup> Their role has been further strengthened by the discovery of the asymmetric dihydroxylation (AD) process<sup>1</sup> that allows one to obtain chiral 1,2-diols in very high ee's and, on the basis of an empirical rule,<sup>4</sup> with a somewhat predictable stereochemistry. These routinely used empirical predictions however present some failures<sup>5</sup> and a method for a safe

configurational assignment is still needed. Several research efforts have been devoted to developing general, simple, and reliable methods of assigning the absolute configuration to acyclic 1,2-diols. To this end some empirical and non-empirical approaches based on the use of CD spectroscopy have been developed but, despite their increasing number, they still present some limitations. In fact, the CD analysis of complexes formed in situ by 1,2-diols and metal ions,<sup>6</sup> being a totally empirical approach, does not allow an immediate and completely reliable correlation between CD spectrum and configuration. On the other hand, nonempirical approaches based on the exciton analysis<sup>7</sup> of dichromophoric derivatives<sup>8</sup> require a conformational determination that, in the case of acyclic compounds, may constitute a difficult

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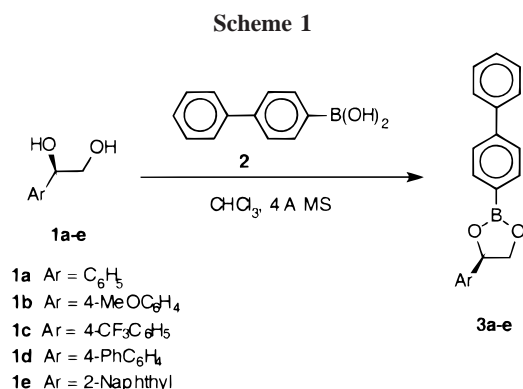
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task.<sup>8,9</sup> The problem of the conformational flexibility of acyclic 1,2-diols has been successfully overcome, at least in the case of 1,2-diarylethane-1,2-diols, by converting them into conformationally defined derivatives such as their 2,2'-dimethyl-1,3-dioxolanes.<sup>10</sup> Here the two aryl chromophores, being rigidly and chirally disposed to each other, give rise to exciton coupling, and from the sign of the couplet(s) in the CD spectrum the absolute configuration of the starting 1,2-diol can be nonempirically determined. This method however does not have general validity, requiring the presence of two chromophores on the stereogenic centers of the diol. It cannot be applied, for instance, to 1-arylethane-1,2-diols (**1**) where only one chromophoric group is present. The aim of this paper is to show how this approach can be easily modified, extending its applicability to monoaryl-substituted diols **1**.

In the case of monoaryl diols **1**, it is necessary to introduce a second chromophore and, at the same time, to transform them into conformationally defined derivatives (e.g., by forming a cycle). In these derivatives the electronic transition dipoles of the two chromophores must be placed in a fixed and rigid relative disposition which depends only on the absolute configuration of the stereogenic centers of the diol. This task can be achieved by reacting **1** with a suitable derivatizing agent which bears a chromophore with electronic transitions of known polarization and which can give rise to cyclic, rigid derivatives. Accordingly, 4-biphenylboronic acid (**2**) (Scheme 1) is an ideal derivatizing agent. In fact it can



be easily prepared.<sup>11</sup> It forms cyclic boronates with 1,2-diols in mild conditions,<sup>12</sup> and it bears a chromophore, such as

(7) Treatments of exciton coupling and its application in organic stereochemistry: (a) Mason, S. F. *Quart. Rev.* **1962**, *17*, 20. (b) Mason, S. F. Theory II. In *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Sneath, G., Ed.; Heyden and Son: London, U.K., 1967; Chapter 4, p 71. (c) Gottarelli, G.; Mason, S. F.; Torre, G. *J. Chem. Soc. B* **1971**, 1349. (d) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (e) Mason, S. F. *Molecular Optical Activity and the Chiral Discriminations*; Cambridge University Press: Cambridge, 1982. (f) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

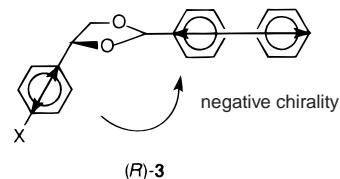
(8) Nakanishi, K.; Berova, N. In *Circular Dichroism: Principles and Applications*; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCH Publishers Inc.: New York, 1994; pp 361–398.

(9) Harada, N.; Saito, A.; Ono, H.; Murai, S.; Li, H.-Y.; Gawronski, J.; Gawronska, K.; Sugioka, T.; Uda, H. *Enantiomer* **1996**, *1*, 119. Hartl, M.; Humpf, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1549.

the biphenyl one, having<sup>13</sup> a well-defined electrically allowed transition at 260 nm, polarized along the biphenyl long axis. The use of such a chromophore presents the further advantage that the above absorption band is located in a wavelength range free from interference due to absorptions of most aryl chromophores. Moreover, since the boron atom is sp<sup>2</sup> hybridized, new stereogenic centers are not formed in the boronate preparation.<sup>14</sup>

In the boronic esters **3**, the biphenyl and the aryl chromophores are placed in a relative disposition which depends only on the absolute configuration of the C<sub>1</sub> stereocenter, and exciton coupling<sup>7</sup> between the two chromophores can occur. If the Ar group absorbs in the same spectral region of the electrically allowed transition of the biphenyl chromophore, a degenerate exciton coupling<sup>7e</sup> occurs. Then a couplet feature corresponding to the 260 nm biphenyl absorption will appear in the spectrum. Otherwise, when the two chromophores absorb in different spectral regions, a nondegenerate exciton coupling will result. This type of coupling gives rise to two Cotton effects having opposite sign which correspond to the absorptions of the chromophores involved<sup>7e,8</sup> (e.g., the biphenyl and the aryl ones). In the case of boronates **3** however, the CD band that corresponds to the aryl absorption (high-energy component) can be overlapped by other bands due to different optically active transitions (vide infra) and only the low-energy counterpart (around 260 nm) is visible,<sup>15</sup> being in a region free from other absorptions. Then, depending on the type of aryl chromophore, the absolute configuration at C<sub>1</sub> can be safely and nonempirically determined from the sign of the couplet (degenerate coupling) or from the sign of the single monosignate Cotton effect at 260 nm (nondegenerate coupling).

If we consider diol **1** having an (*R*) absolute configuration, the corresponding boronate (*R*)-**3** has the conformation depicted in Figure 1. If the aryl group is a *p*-substituted

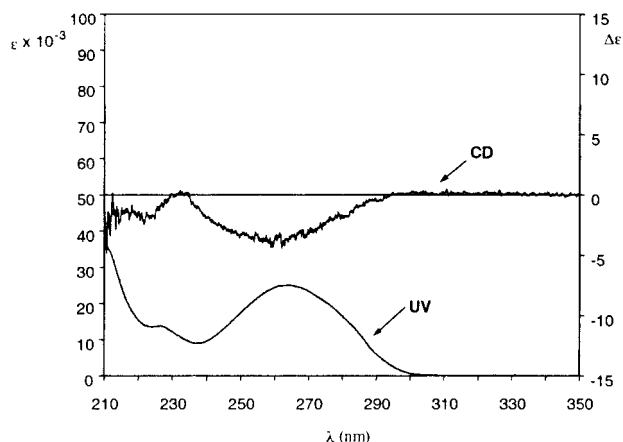


**Figure 1.** In 4-biphenylboronate **3** derived from 1-arylethane-1,2-diol and with an (*R*) configuration, the aryl and biphenyl chromophores define a negative chirality.

benzene or a 2-naphthyl ring, we can predict the sign of the above-mentioned Cotton effect as follows. The substituted benzene chromophore possesses a strongly allowed transition (<sup>1</sup>A<sub>1g</sub> → <sup>1</sup>E<sub>1u</sub> in the parent benzene chromophore) which can be described<sup>16</sup> by a pair of degenerate transition moments polarized in the benzene plane (the first oriented along the C\*–Ar direction, the second orthogonal to it). Taking into account that there is free rotation about the C\*–Ar bond, the transverse dipole of the <sup>1</sup>A<sub>1g</sub> → <sup>1</sup>E<sub>1u</sub> transition assumes

any possible orientation with respect to the biphenyl dipole, so that the coupling effect is averaged to zero.<sup>17</sup> Therefore, only the nondegenerate<sup>7e</sup> exciton coupling between the biphenyl transition and the C\*–Ar dipole will remain. These two dipoles define a negative chirality in (*R*)-**3**, and a negative Cotton effect will be produced that corresponds to the biphenyl transition at 260 nm. A similar analysis, leading to the same prediction, can be performed for the case of the 2-naphthyl group.

To prove the validity of the above considerations, diols (*R*)-(-)-**1a,b**, of known absolute configuration,<sup>18</sup> were reacted with 4-biphenylboronic acid (**2**), in CHCl<sub>3</sub>, in the presence of 4Å molecular sieves (Scheme 1). After filtration, evaporation of solvent and chromatographic purification (CHCl<sub>3</sub>), boronates (*R*)-(-)-**3a,b** were isolated in high yield (≈ 90%) and their CD spectra (THF) recorded. The CD spectra of both (*R*)-(-)-**3a** and (*R*)-(-)-**3b** (Figure 2) showed



**Figure 2.** Absorption (UV) and circular dichroism (CD) spectra of (*R*)-(-)-**3b** in THF in the 210–350 nm range.

a clear negative Cotton effect ( $\Delta\epsilon$  ca.  $-3.0$  and  $-5.0$ , respectively) at 260 nm, confirming our expectations.<sup>19</sup>

Once the reliability of our approach was verified, we applied this method to the determination of the absolute

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(11) Diorazio, L. J.; Widdowson, D. A.; Clough, J. M. *Tetrahedron* **1992**, *48*, 8073. Suenaga, H.; Mikami, M.; Yamamoto, H.; Harada, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1733. Boronic acid **2** is also commercially available from Lancaster, U.K.

(12) Kobayashi, Y.; Mizojiri, R.; Ikeda, E. *J. Org. Chem.* **1996**, *61*, 5391.

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(14) On the contrary, the derivatization of the diols by simple formation of cyclic acetals with aromatic aldehydes leads to the introduction of a new chiral center and then to the formation of a couple of diastereoisomers.

(15) See, for instance: Harada, N.; Iwabachi, J.; Yokota, Y.; Uda, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

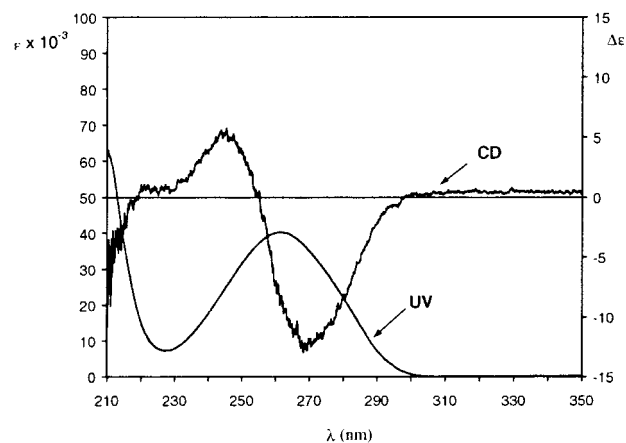
(16) Sagiv, J. *Tetrahedron* **1977**, *33*, 2303.

(17) This kind of analysis has been employed, for instance, to interpret the optical activity of the <sup>1</sup>B transition of the naphthalene chromophore in (*R,R*)-(+)-2,2'-dimethyl-4-phenyl-5-(2-naphthyl)-1,3-dioxolane. See ref 10b.

(18) Ferraboschi, P.; Grisenti, P.; Manzocchi, A.; Santaniello, E. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2469.

configuration of some unknown 1-aryl-substituted diols such as (-)-**1c–e**. To the best of our knowledge, diols **1c–e** have already been described in optically active form; the absolute configuration of **1c** has not been reported,<sup>20</sup> while the (*R*) configuration has been attributed to diols (-)-**1d**<sup>21</sup> and (-)-**1e**<sup>22</sup> on the basis of empirical correlations. Enantiopure diols (-)-**1c–e** were prepared by AD<sup>1</sup> of the corresponding alkenes in the presence of the (DHQD)<sub>2</sub>PHAL ligand which, according to the Sharpless empirical rule,<sup>4</sup> should afford diols having the (*R*) absolute configuration. From these diols the boronates (-)-**3c–e** were then prepared and their CD spectra recorded.

In the spectrum of (-)-**3d** a distinct negative couplet was observed (Figure 3) between 300 and 230 nm. The presence



**Figure 3.** Absorption (UV) and circular dichroism (CD) spectra of (*R*)-(-)-**3d** in THF in the 210–350 nm range.

of such a couplet clearly demonstrates that the (degenerate)<sup>7e</sup> exciton coupling mechanism is operative. The CD spectrum of (-)-**3c** showed a feature similar to that of (*R*)-(-)-**3a,b**, with a negative Cotton effect at 260 nm, due to a nondegenerate<sup>7e</sup> exciton coupling. The case of (-)-**3e** deserves some additional comments: the observed UV spectrum shows absorptions due to the biphenyl (260 nm) and naphthalene (225 nm) chromophores. In the CD spectrum the expected negative Cotton effect at 260 nm is clearly observable, while the high-energy (positive) counterpart at 225 nm is barely detectable. This fact can be explained by considering that the very low dissymmetry factor *g* related to the 220 nm transition prevents any accurate CD measure-

(19) It is important to point out that at around 260 nm the parent diols **1** show a very weak Cotton effect ( $\Delta\epsilon \sim 0.1$ , see Supporting Information for spectrum of **1e**, and Fontana, L. P.; Smith, H. E. *J. Org. Chem.* **1987**, *52*, 3386 for spectrum of **1a**); therefore the  $\Delta\epsilon$  values observed for boronates **3**, which are more than 10 times greater, are certainly the result of the exciton coupling between the aryl and the biphenyl moieties.

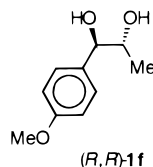
(20) Nelson, D. W.; Gypser, A.; Ho, P. T.; Kolb, H. C.; Kondo, T.; Kwong, H.-L.; McGrath, D. V.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840.

(21) Miao, G.; Rossiter, B. E. *J. Org. Chem.* **1995**, *60*, 8424.

(22) Howe, R.; Moore, R. H.; Rao, B. S. *J. Med. Chem.* **1973**, *16*, 1020. Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.

ment.<sup>23</sup> In addition, below 220 nm, overlapping<sup>15</sup> of different CD bands due to the biphenyl<sup>10c,13</sup> and the naphthalene chromophore<sup>24</sup> can occur, thus masking the expected above-mentioned band. According to our previous remarks, the observed features of the CD spectra of (–)-**3c–e** are then correlated to the (*R*) configuration of the parent diol, thus confirming the configurational assignment made on the basis of the AD Sharpless rule.

This approach to the determination of the absolute configuration can also be applied to any *erythro* or *threo* 1-aryl-1,2-diol substituted in the 1- and/or 2-position with alkyl groups or other nonchromophoric moieties. As an example of application to 1-aryl-2-alkyl-1,2-diols, we discuss the following case. The diol **1f** is a metabolite derived from the in vivo detoxification of (*E*)-anethole (1-(4'-methoxyphenyl)-prop-1-ene), an aromatic substance present in anise and other spices,<sup>25</sup> and its absolute configuration has been determined only *empirically* by correlation of the CD spectra of its camphanyl ester.<sup>26</sup>



By AD of (*E*)-anethole with (DHQD)<sub>2</sub>PHAL as ligand, we prepared the *threo* diol (–)-**1f**, which was then trans-

(23) In fact the 260 nm and the 220 nm transitions carry the same rotational strength (in absolute value) but they show different dipolar strength and a different *g* factor will result. At 260 nm *g* is  $1.5 \times 10^{-5}$  (which is already a low limit for accurate CD measurements) while at 220 nm, owing to a strong increase of the related dipolar strength, *g* is ca.  $5 \times 10^{-6}$ , a value which makes very difficult any CD measurement.

(24) Salvadori, P.; Piccolo, O.; Bertucci, C.; Menicagli, R.; Lardicci, L. *J. Am. Chem. Soc.* **1980**, *102*, 6859.

(25) Marshall, A. D.; Caldwell, J. *Food Chem. Toxicol.* **1992**, *30*, 467.

formed in the corresponding boronate (–)-**3f**. In the CD spectra of (–)-**3f** a negative Cotton effect was clearly visible at ca. 260 nm and the (*R*) configuration was *nonempirically* assigned to the benzyl carbon atom. This case clearly shows that the presence of a nonchromophoric substituent in the 1- or 2-position does not affect the aryl/biphenyl coupling and therefore the assignment of the absolute configuration of the C<sub>1</sub> stereocenter. Thus, if the *erythro/threo* relationship is known, with the present method it is possible to assign the configuration of both the stereocenters.<sup>27</sup>

In conclusion, we have described herein a simple and reliable nonempirical approach to the assignment of the absolute configuration of 1-arylethane-1,2-diols. According to this method, it is only necessary to prepare the 4-biphenylboronic esters of the diols and to record their CD spectra in the 230–320 nm range. If a negative couplet or a negative Cotton effect is observed at ca. 260 nm, then the (*R*) absolute configuration has to be assigned to the aryl-substituted stereogenic center of the diol. Work is now in progress to carry out the boronate formation on a microgram scale and to extend this approach to *o*- and *m*-phenyl-substituted 1,2-diols.

**Acknowledgment.** Financial support from Università della Basilicata (Potenza) and Murst (Roma) is gratefully acknowledged.

**Supporting Information Available:** Full experimental and analytical data for compounds **1b–f**, **2**, and **3a–f**. CD and UV spectra for compounds **1e**, **3a**, **3c**, **3e**, and **3f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(26) Ishida, T.; Bounds, S. V. J.; Caldwell, J.; Drake, A. F.; Takeshita, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3113.

(27) It has to be pointed out that the relative stereochemistry of the diol stereocenters can be often easily established via <sup>1</sup>H NMR analysis.