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A General and Nonempirical Approach to the Determination of the Absolute Configuration of 1-Aryl-1,2-diols

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We describe herein a simple, general, and reliable nonempirical approach, based on the exciton coupling method, to assign the absolute configuration of the benzylic stereogenic center of 1-aryl-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 230−300 nm range, i.e., in the range corresponding to the long-axis ^1L_a transition of the biphenyl chromophore. From the sign of the CD couplet or Cotton effect at 260 nm it is possible to know the chirality defined by the aryl and biphenyl chromophore transitions and then to determine the absolute configuration of the benzylic carbon. By this approach, simple rules have been formulated which allow us to establish the absolute configuration of many classes of 1-aryl-1,2-diols.

Introduction

The development of reliable and practical methods for determining the absolute configuration (AC) of chiral molecules of both natural and synthetic origin is still a major task in modern organic chemistry. The classical X-ray diffraction and chemical correlation approaches are in fact very time-consuming and often not of general applicability.[1] In the past decades, circular dichroism (CD) spectroscopy emerged as a practical alternative for AC determination, being a faster technique and allowing analysis in solution of microscale quantities. In particular, CD spectroscopy has been extensively used for determining AC of chiral diols, a class of compounds of great importance in asymmetric catalysis[2,3] and natural product chemistry.[4] To this end several empirical and nonempirical approaches have been developed. Empirical approaches are mainly based on the in situ formation of complexes between diols and metal ions,[5] while nonempirical methods are based on the exciton chirality approach.[6] Exciton coupling arises from through-space interaction of two or more chromophores, which gives rise to Cotton effects in the CD spectrum correlated with their spatial arrangement and therefore with the overall molecular chirality. For this reason, to apply the exciton chirality model to chiral diols they are usually transformed in dichromophoric derivatives[7,8] such as the corresponding dibenzoates. The CD spectra of such compounds show in fact a typical couplet feature from the sign of which the AC of the diol can be nonempirically determined. This approach, however, requires a detailed conformational analysis of the substrate and therefore remain of difficult use for acyclic diols which are conformationally mobile. A practical expedient to overcome the problem of the flexibility of acyclic diols is their transformation in cyclic, conformationally defined derivatives. For example, 1,2-diarylethane-1,2-diols can be easily converted in their 2,2-dimethyl-1,3-dioxolanes,[9] where the two aryl chromophores are rigidly and chirally disposed

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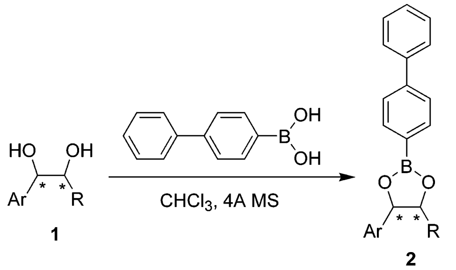
SCHEME 1



each other. These two chromophores can then give rise to exciton coupling and from the sign of the couplet(s) in the CD spectrum the AC 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. We recently presented two preliminary reports concerning new and complementary approaches which allow, respectively, AC determination of *threo* aliphatic diols[10] (i.e., diols devoid of chromophores) and 1-arylethane-1,2-diols (**1**),[11] i.e., diols having only one chromophoric group already present. In the latter approach, the diols were transformed into the corresponding 4-biphenylboronates (**2**) (Scheme 1), thus introducing a second chromophore and, at the same time, transforming them into cyclic and conformationally defined derivatives. In these derivatives the electric transition dipoles of the aryl chromophore belonging to the diol moiety and of the biphenyl chromophore are placed in a fixed and rigid relative disposition which depends only on the absolute configuration of the benzylic stereogenic center of the diol. These transitions can then give rise to exciton coupling, and then analysis of CD spectra unambiguously allows assignment of diols AC.[11] The choice of forming 4-biphenylboronates from the diols derived from two main reasons. First, biphenylboronates are prepared in very mild conditions, and due to sp^2 hybridation of the boron atom, no new stereogenic centers are formed in such derivatives.[12] In addition, biphenylboronates display a strong UV absorption at ca. 260 nm, which can be ascribed to the biphenyl long-axis ^1L_a transition.[13] Such a transition has a well-defined direction and lies in a wavelength range free from absorptions of most aryl chromophores, therefore constituting a particularly suitable spectroscopic probe for analysis of molecular chirality.[14]

In our previous study, this method was successfully applied to several *para*-substituted phenyl diols, while in this paper we describe the extension and generalization of this approach to the AC determination of most classes of chiral 1-aryl-1,2-diols, having different nature and substitution of the aryl moiety. These 1,2-diols plays an important role in chemistry: in fact many of them are bioactive natural products,[15] endogenous metabolites,[16] useful synthetic intermediates for the preparation of drugs,[17] and new materials.[18] A special goal of this investigation is to test if the chemical transformation of an open chain compound into a cyclic boronate is effective in simplifying the conformational analysis required in the exciton approach. Such an analysis is in fact an unavoidable feature of many methods of configurational assignment based on the interpretation of CD spectra, and very often this step is really plaguing the entire method, rendering it very heavy and practicable only by specialists. Moreover in this investigation we wanted to show that, once determined the main conformation of the boronate, the AC determination of the benzylic carbon could be achieved simply looking at the sign of the biphenyl CD band at 260 nm.

Results and Discussion

Synthesis. To generalize and validate our approach we analyzed the UV and CD spectra of biphenylboronates **2a**−**o**, prepared from the corresponding chiral diols **1a**−**o** (Chart 1). Diol **1a** was commercially available, while diols **1b**−**o** were prepared by asymmetric dihydroxylation[2] (AD) of the corresponding olefins. Enantiopure diols (−)-**1b**−**i** were prepared by AD of the corresponding vinylarenes in the presence of the (DHQD)$_2$PHAL chiral ligand. The 1,2-disubstituted *threo* diols (−)-**1j**,**k** were prepared by AD of (*E*)-methylcinnamate and (*E*)-anethole (1-(4′-methoxyphenyl)prop-1-ene), respectively, using the (DHQD)$_2$PHAL ligand. The *erythro* diol (−)-**1l** was prepared using the same ligand, but starting from (*Z*)-anethole, while *threo* (+)-**1m** comes from AD of the (*E*)-methyl-3-(2-thiophen)propenoate with (DHQ)$_2$PHAL.[19] Finally, the cyclic *erythro* diols (−)-**1n** and (+)-**1o** were prepared by AD of indene and 1,2-dihydronaphthalene, respectively,[20] using (DHQ)$_2$AQN ligand.[21] Diols (*R*)-(−)-**1a**,[22] (*R*)-(−)-**1b**,[22] (*R*)-(−)-**1c**,[23] (*R*)-(−)-**1f**,[24]

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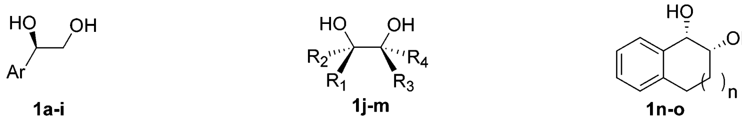
CHART 1



1a-i **1j-m** **1n-o**

A
- **1a** Ar = C_6H_5
- **1b** Ar = 4-$MeOC_6H_4$
- **1c** Ar = 4-$CF_3C_6H_4$
- **1d** Ar = 4-PhC_6H_4
- **1e** Ar = 3-BrC_6H_4
- **1f** Ar = 2-BrC_6H_4

B
- **1g** Ar = 2-Np
- **1h** Ar = 1-Np
- **1i** Ar = 9-Anthryl

C
- **1j** R_1= C_6H_5; R_4= CO_2Me; R_2= R_3= H
- **1k** R_1= 4-$MeOC_6H_4$; R_4= Me; R_2= R_3= H
- **1l** R_1= 4-$MeOC_6H_4$; R_3= Me; R_2= R_4= H
- **1m** R_2= 2-thienyl; R_3= CO_2Me; R_2= R_4= H

D
- **1n** n = 0
- **1o** n = 1

TABLE 1. Main UV and CD Features (THF) of Biphenylboronates 2a−o

compd	UV, λ ($\epsilon \times 10^3$)	CD, λ ($\Delta\epsilon$)
(*R*)-(−)-**2a**	265 (25.0)	263 (−3.2)
(*R*)-(−)-**2b**	264 (25.0)	262 (−4.5)
(*R*)-(−)-**2c**	263 (20.5)	259 (−1.0)
(*R*)-(−)-**2d**	260 (40.2)	244 (+5.4); 268 (−12.5)
(*R*)-(−)-**2e**	263 (29.9)	260 (−3.4)
(*R*)-(−)-**2f**	263 (21.2)	262 (−2.7)
(*R*)-(−)-**2g**	220 (sh 82.0); 226 (122.1); 266 (31.7)	225 (+2.3); 257 (−3.0)
(*R*)-(−)-**2h**	220 (sh 60.0); 225 (77.4); 264 (26.0), 282 (sh 19.0)	220 (−23.4); 257 (+0.5); 283 (−3.4)
(*R*)-(+)-**2i**	249 (sh 29.5); 257 (54.0)	250 (−3.6); 260 (+4.5)
(4*S*,5*R*)-(−)-**2j**	263 (41.0)	221 (+6.7); 258 (−3.7)
(4*R*,5*R*)-(−)-**2k**	265 (22.4)	260 (−3.4)
(4*R*,5*S*)-(−)-**2l**	263 (21.7)	262 (−2.5)
(4*R*,5*R*)-(+)-**2m**	245 (sh 16.0); 265 (22.2)	234 (−5.1); 260 (+5.6)
(4*S*,5*R*)-(−)-**2n**	265 (25.2); 272 (sh 22.1)	266 (+3.2); 272 (+4.3)
(4*S*,5*R*)-(−)-**2o**	263 (21.0)	271 (+0.9)

(*R*)-(−)-**1i**,[25](2*S*,3*R*)-(−)-**1j**,[26] (2*R*,3*R*)-(+)-**1m**,[27] (1*S*,2*R*)-(−)-**1n**,[28] and (1*S*,2*R*)-(+)-**1o**[29] were of known AC. The AC of diols (*R*)-(−)-**1d**,[30] (*R*)-(−)-**1g**,[30,31,20b] (*R*)-(−)-**1h**,[30] (*1R*,*2R*)-(−)-**1k**,[32] and (*1R*,*2S*)-(−)-**1l**[32] were attributed only on the basis of empirical correlations. Diol **1e**[33] was already described in optically active form, but its AC was not reported. Therefore, we tentatively assigned (*R*) AC to (−)-**1e** on the basis of the empirical Sharpless rule.[34] Such a rule is routinely used to get indications on the expected stereochemical outcome of the AD reaction, and even if its empirical predictions present some failures,[35] its results are satisfactorily reliable for simple olefins. All these diols were then reacted in $CHCl_3$ with 4-biphenylboronic acid, in the presence of 4 Å molecular sieves (Scheme 1). After filtration, evaporation of solvent, and chromatographic purification ($CHCl_3$), boronates **2a**−**o** were isolated in high yield (~70−90%) and their CD and UV spectra recorded in THF (Table 1).

Spectroscopic Analysis of 4-Biphenylboronates. In the boronic esters **2**, the biphenyl and the aryl chromophores are placed in a relative disposition which depends only on the absolute configuration of the C1 stereocenter, and exciton coupling[6] between the two chromophores can occur. If the Ar group absorbs in the same spectral region of the electrically allowed ^1L_a transition of the biphenyl chromophore, a degenerate exciton coupling[6e] occurs. Then a couplet feature will appear in the spectrum in correspondence to the 260 nm biphenyl absorption. Otherwise, when the two chromophores absorb in a different spectral region a nondegenerate exciton coupling will result. This type of coupling gives rise to two Cotton effects having opposite sign in correspondence to the absorptions of the chromophores involved[6e,7] (e.g., the biphenyl and the aryl ones). In the case of boronates **2**, however, the CD band in cor-

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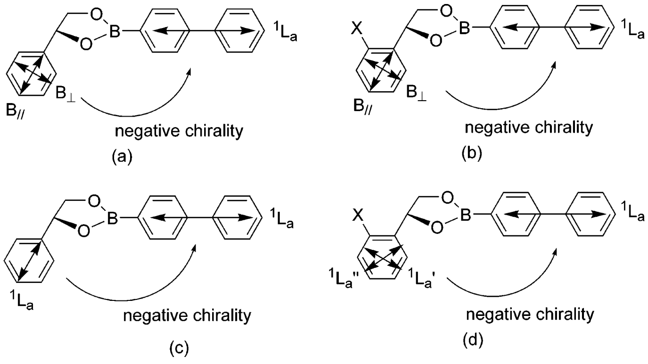

FIGURE 1. Most stable conformations and main transition dipoles of (R)-configured phenyl-substituted 4-biphenylboronates.

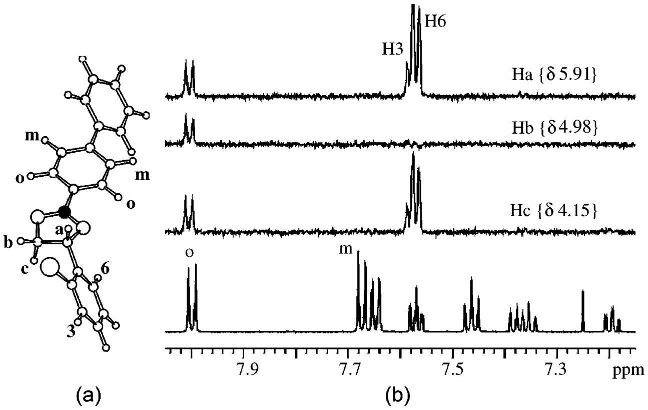

FIGURE 2. (a) Most stable conformations computed by Molecular Mechanics for **2f**. (b) NOE enhancements, all amplified by the same factor, observed in the aromatic region of **2f** irradiating the protons of the boroxolane ring. Lower trace: ^{1}H NMR (600 MHz) spectrum.

respondence to the aryl absorption (high-energy component) is often overlapped by other bands due to different optically active transitions (vide infra) and only the low-energy counterpart (around 260 nm) is detectable,[36] being in a region free from other absorptions. Then, depending on the type of aryl chromophore, the absolute configuration at C_1 can be safely and nonempirically determined from the sign of the couplet centered at 260 nm (degenerate coupling) or from the sign of the single monosignate Cotton effect at 260 nm (non degenerate coupling).

For sake of clarity, we can analyze and discuss separately the several classes of 1-aryl-1,2-diols studied, depending on the structure of their aryl moiety (see Chart 1). In fact, in depending on the aryl chromophore involved, different conformational situations and different transition moments must be taken into account.

Class A: Diols Having Phenyl-Substituted Chromophores. If we consider a phenyl- substituted diol **1** having (R) absolute configuration, the corresponding boronate (R)-**2** has the conformation depicted in Figure 1a.[37] The main transitions to be taken into account in the phenyl-substituted chromophores are the ^{1}B (180−210 nm), the ^1L_a (210−240 nm), and the ^1L_b transitions (240−280 nm). The amplitude of the Cotton effects due to the exciton coupling between two transition dipoles depends on their distance in space and energy, their intensity, and the dihedral angle defined by the dipoles. Therefore, the weakest ^1L_b transition reasonably gives rise to a very weak interaction with the biphenyl chromophore transition and its contribution can be ruled out, limiting our treatment to the more intense ^{1}B and ^1L_a transitions (Figure 1). In the phenyl-substituted chromophores, the strong electrically allowed ^{1}B transition[38] can be described by a couple of degenerate and orthogonal transition moments polarized in the benzene plane,[39] and it has been rigorously demonstrated that, for coupled oscillator calculations, such transitions can be described by any couple of orthogonal dipoles lying in the benzene ring.[40] Therefore, we can direct one of them (longitudinal transition moment, $B_{\parallel}$) along the C*-Ar bond direction and the second one perpendicular to it (transverse moment, $B_{\perp}$). In the 4-substituted phenyl boronates there is free rotation around the C*−Ar bond, and therefore, the transverse dipole of the ^{1}B transition assumes any possible orientation with respect to the biphenyl dipole. The coupling effect between these two dipole moments is then averaged to zero.[41] On the other hand, the longitudinal dipole moment $B_{\parallel}$ can give rise to a nondegenerate[6e] exciton coupling with the biphenyl one. These two dipoles define a negative chirality in (R)-**2**, and then a negative Cotton effect will be produced in correspondence to the biphenyl transition at 260 nm. A similar analysis can be performed for 3-substituted phenyl chromophores taking into account that a substituent in the 3 position does not sterically interfere with the rotation around the C*−Ar bond. Also in this case, therefore, the transverse dipole, assuming any possible orientation with respect to the biphenyl, does not gives rise to exciton coupling effects, while the longitudinal transition moment will define a negative chirality with the biphenyl one, giving rise to a negative Cotton effect at 260 nm. In the case of 2-substituted phenyl chromophores, the substituent in the *ortho* position it is bound to favor the ring to adopt a preferred conformation. To single out the effects of *ortho* substituents on the rotational equilibrium of the boronate aryl ring, we investigated further by ^{1}H NMR the preferred conformation in the 2-bromo derivative **2f**. We chose such compound because the large bromine substituent could constitute a good probe for understanding the steric influence of the *ortho*-substituents on the conformational equilibrium.

According to 2D and NOE experiments, the three protons of the boroxolane ring in **2f** were assigned as follows (Figure 2): the benzylic hydrogen (Ha) at δ 5.91, the methylenic hydrogen (Hb) vicinal to Ha and on the same side of the boroxolane ring at δ 4.98, and finally,

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[36] See, for instance: Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

[37] Such conformations can be derived either from molecular mechanics calculations (see ref 43) or by a simple visual inspection of molecular models.

[38] (a) Jaffe, H. H.; Orchin, M. *Theory and applications of UV spectroscopy*; Wiley: New York: 1962. (b) Michl, J.; Thulstrup, E. W. *Spectroscopy with polarized light*; VCH: New York: 1996.

[39] Sagiv, J. *Tetrahedron* **1977**, *33*, 2303.

[40] Shingu, K.; Imaio, S.; Kuritani, H.; Hagishita, S.; Kurijama, K. *J. Am. Chem. Soc.* **1983**, *105*, 6966.

[41] This kind of analysis has been employed, for instance, to interpret the optical activity of the ^{1}B transition of the naphthalene chromophore in (R,R)-(+)-2,2′-dimethyl-4-phenyl-5-(2-naphthyl)-1,3-dioxolane. See ref 9c.

the second methylenic hydrogen (Hc) at δ 4.12. The aromatic hydrogens in position 3 and 6 on the 2-bromophenyl moiety could be distinguished on the basis of the long-range coupling constants and assigned to the multiplets at δ 7.605 and 7.595, respectively. To investigate the preferred conformation adopted in solution by **2f**, NOE experiments[42] were carried out. The irradiation of Ha and Hc gave the main enhancement on H6 rather than on H3 and the *ortho* hydrogens (δ 8.02) of the biphenyl ring directly bonded to the boron atom. Whereas the irradiation of Hb only slightly enhances the hydrogens at δ 8.02. This suggests that the 2-bromophenyl moiety is well rotated from coplanarity with respect to the boroxolane ring, bearing the H6 below the ring, on the same side of Hc. On the contrary H3, giving only minor NOE enhancements, is set above the ring but quite far away from both Ha and Hb. Such tilted position also makes the Br pointing outward, thus relieving the phenyl from strong steric interactions with the atoms of the boroxolane ring.

A confirmation of such results could be achieved by combining the experimental NOEs with the interproton distances obtained by MMX calculations;[43] indeed, to a first approximation the NOE effects are dependent upon the 6th power of the reciprocal interproton distances.[44] The most stable conformation computed (Figure 2a) shows that the bromophenyl moiety forms a 93° dihedral angle with respect the boroxolane ring with H6 pointing inward the molecule and distant 3.7 Å from Ha, 3.17 Å from Hc, and 4.45 Å from Hb. In addition to that, the H3 is always set at a distance ≥5 Å from the boroxolane protons in agreement with the small NOEs observed. The ratios of independent NOEs and the relative interproton distances are in good agreement, confirming that the preferred conformation in solution is similar to the computed one. According to such analysis, in compounds having large *ortho*-substituents a predominant population of the conformer depicted in Figure 2a is expected. In such a conformation the large substituent is put far from the dioxaborolane ring, minimizing their steric interactions. In this conformer, the transverse dipole ($B_\perp$) allied to the ^1B transition has the orientation shown in Figure 1b, and in an (*R*)-configured boronate, it defines a negative chirality with the biphenyl long-axis transition, giving rise to a negative couplet feature in the CD spectrum. The directions of these two transition dipoles, however, define a small angle, and therefore, a couplet of small intensity is expected. The longitudinal transition moment ($B_\parallel$) of the phenyl chromophore behaves exactly as in the previous cases, defining again a negative chirality with the biphenyl transition and giving rise to an intense exciton coupling in the CD spectrum. For compounds having 2-substituents of small-to-medium size, we can instead assume a free rotation around the C*−Ar bond. Such compounds can then be considered exactly as the 3-substituted ones, where only the $^1B_\parallel$ transition dipole must be taken into account. Also in this case, such dipoles define, in an (*R*)-configured diol, a negative chirality with the biphenyl long-axis transition. In summary, also in *ortho*-substituted phenyl boronates both the ^1B transition dipoles define the same chirality with the biphenyl long-axis transition, giving rise to Cotton effects of the same sign. The coupling interactions given by the ^1L_a transition of the phenyl substituted chromophore with the biphenyl one are expected to be weaker than the previous one, being such transition much less intense than ^1B. Moreover, it can be demonstrated that such interactions do not change the sign of the Cotton effect at 260 nm. In fact, in 4-substituted phenyl chromophores the ^1L_a transition dipole is directed along the X−C(4) direction, parallel to the longitudinal ^1B transition, (Figure 1c), and therefore, it gives rise, with the biphenyl transition, to a couplet having the same sign. In the 3- and 2-substituted phenyl chromophores both the intensity and the polarization direction of the ^1L_a transition depends on the spectroscopic moment of the substituents.[9d,45,46] However, in 3-substituted derivatives and in the 2-substituted ones having small substituents, the free rotation around the C*−Ar bond makes such a transition dipole to generate a rotation cone whose axis is still directed along such bond. It results that the only component of such transition which remains is directed as the longitudinal ^1B transition, then giving rise to exciton coupling of the same sign. Finally, for (*R*)-configured 2-substituted phenyl chromophores having large substituents, we can again assume the preferred conformation in Figure 1d due to the restricted rotation around the C−Ar bond. The 2-substituted phenyl moiety can be considered as an analogue of a 2-substituted toluene chromophore. In such chromophores, the direction of the ^1L_a transition dipole is determined by the magnitude of the spectroscopic moment due to the substituent: if it is greater than that of the methyl group, therefore the dipole is approximately perpendicular to the position of the methyl ($^1L_a'$ in Figure 1d), otherwise the ^1L_a transition moment is directed orthogonally to the substituent position ($^1L_a''$ in Figure 1d). In both cases, the phenyl ^1L_a transition defines a negative chirality with the biphenyl ^1L_a transition. From this treatment we can conclude that *for any biphenylboronate, coming from phenyl substituted diols, a negative Cotton effect at 260 nm is related with an (R) AC of the benzyl chiral center, independently of the position and nature of the substituent.*

Clear experimental evidence of the exciton origin of the 260 nm Cotton effect and therefore of the soundness of the rule formulated above is given by the spectrum of the 4-biphenyl-substituted boronate (*R*)-**2d** (Figure 3), where a distinct negative couplet is observed between 300 and 230 nm. In fact, in (*R*)-**2d** an interaction between two ^1L_a equal biphenyl transitions is expected, giving rise to a degenerate[6e] exciton coupling and to a negative couplet in the CD spectrum, as experimentally observed. Such experimental evidence also demonstrates that the origin of the optically activity at 260 nm in the CD spectrum is really due to the exciton coupling mechanism. A further experimental confirmation of our analysis can be achieved by the inspection of CD spectra of boronates (*R*)-**2a**,**b**,**c**,**e**,**f** (Table 1), where a non degenerate[6e] exciton

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[42] Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199.

[43] Molecular mechanics calculations were performed using the MMX force field as implemented in PC Model 7.0, Serena Software, Bloomington, IN 47402-3076.

[44] (a) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers: New York, 1989. (b) Casarini, D.; Lunazzi, L.; Foresti, E.; Macciantelli, D. *J. Org. Chem.* **1994**, *59*, 4637. (c) Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759.

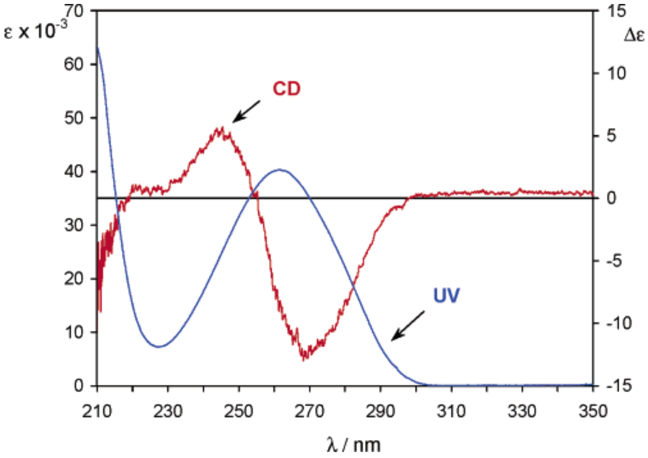

FIGURE 3. UV and CD spectra (THF) of compound (*R*)-**2d**.

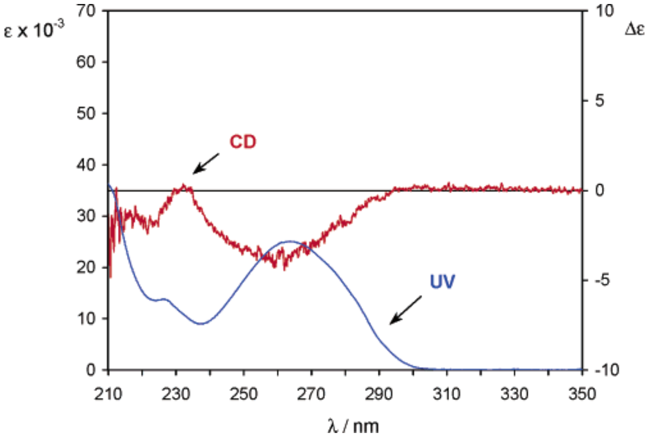

FIGURE 4. UV and CD spectra (THF) of compound (*R*)-**2b**.

coupling is expected. The CD spectra of both (*R*)-**2a** and (*R*)-**2b** (Figure 4) show a clear negative Cotton effect ($\Delta\epsilon \sim -3.2$ and -4.5, respectively) at ca. 260 nm, confirming our predictions[47] and a similar feature, with a negative Cotton effect at 263 nm, is displayed in the CD spectrum of (*R*)-**2c** ($\Delta\epsilon \sim -1.0$). The CD spectrum of the 3-bromo-substituted boronate (−)-**2e** presents a clear negative Cotton effect ($\Delta\epsilon \sim -3.4$) at 263 nm, as well as the 2-bromo-substituted boronate (*R*)-(−)-**2f**, which shows in the CD spectrum a weaker, but clearly visible negative band ($\Delta\epsilon \sim -2.7$) at 263 nm. The observed features of the CD spectrum of (−)-**2e** are then correlated to an (*R*) configuration of the parent diol, thus confirming the configurational assignment made on the basis of the AD Sharpless rule.

Class B: Diols Having Extended Aromatic Chromophores. In derivatives having extended aromatic chromophores such as the naphthyl-substituted boronates **2g**,**h** and the anthryl-substituted one **2i**, both the presence of several transitions in such chromophores and their spatial arrangement must be taken into account.

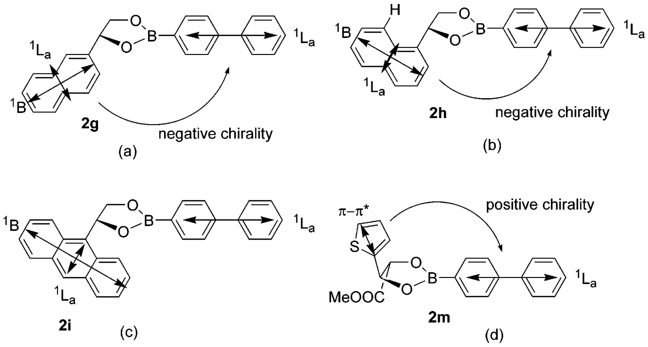

FIGURE 5. Most stable conformations and main transition dipoles of biphenylboronates (*R*)-**2g**, (*R*)-**2h** (*R*)-**2i**, and (4*R*,5*R*)-(+)-**2m**.

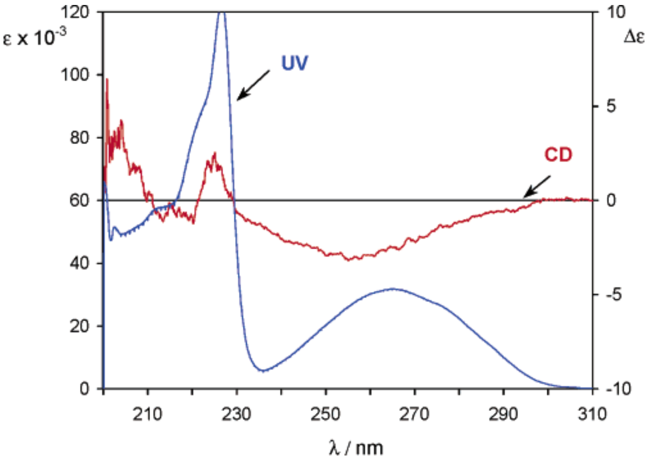

FIGURE 6. UV and CD spectra (THF) of compound (*R*)-**2g**.

In the case of the naphthalene chromophore, the most intense absorptions are due to the long-axis ^{1}B and short-axis ^{1}L$_a$ transitions at about 225 and 280 nm, respectively. In the 2-naphthyl-substituted boronate **2g** (Figure 5a) there is free rotation around the C*−Ar bond and therefore both the ^{1}L$_a$ and the ^{1}B dipole moments describe, upon rotation, a cone centered along the C*−Ar direction. Therefore, in an (*R*)-configured diol, such dipoles define a negative chirality with the biphenyl transition and a negative non degenerate couplet feature is to be expected in its CD spectrum. The observed UV spectrum of (*R*)-**2g** (Figure 6) shows a broad band centered at 265 nm due to the overlap of the ^{1}L$_a$ biphenyl transition at 260 nm and the ^{1}L$_a$ naphthalene transition at 280 nm. At shorter wavelengths a narrow peak due to the 225 nm ^{1}B naphthalene transition is visible. In the CD spectrum, the expected negative Cotton effect at 260 nm is clearly observable,[48] while the high energy (positive) counterpart at 225 nm is barely detectable. This fact can be explained considering that the very low dissymmetry factor *g* related to the 225 nm transition prevents any accurate CD measurement.[49] In addition, below 225 nm, overlapping[36] of different CD bands due to the biphenyl[9c,13] and the naphthalene chromophore[50] can occur, thus masking the expected above-mentioned band.

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[45] Platt, J. R. *J. Chem. Phys.* **1951**, *19*, 263.

[46] Collet, A.; Gottarelli, G. *J. Am. Chem. Soc.* **1981**, *103*, 204.

[47] It is important to point out that at around 260 nm the parent diol **1a** show a very weak Cotton effect (see: Fontana, L. P.; Smith, H. E. *J. Org. Chem*. **1987**, *52*, 3386); therefore, the Δϵ value observed for boronate **2a**, which is more than 10 times greater, is certainly the result of the exciton coupling between the aryl and the biphenyl moieties. This observation can be extended to all the diols studied.

[48] The presence of a single monosignate band at 260 nm clearly demonstrates that there is no exciton coupling between the biphenyl and the naphthalene ^{1}L$_a$ transitions.

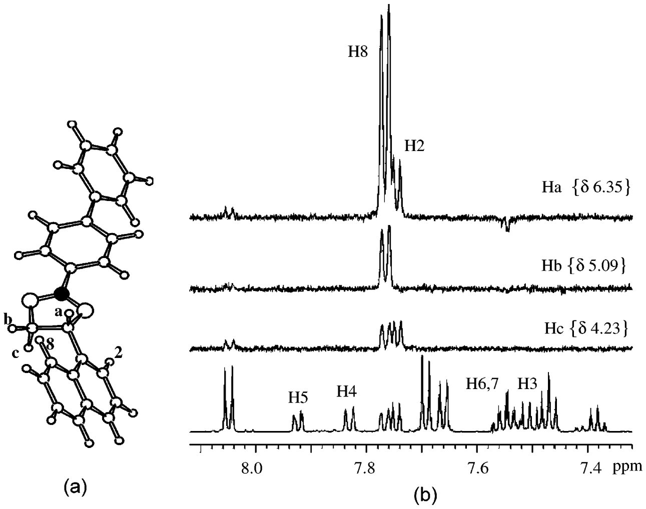

FIGURE 7. (a) Most stable conformations computed by Molecular Mechanics for **2h**. (b) NOE enhancements observed in the of the aromatic region of **2h** irradiating the protons of the boroxolane ring. Lower trace: reference ^{1}H NMR (600 MHz) spectrum.

In the 1-naphthyl-substituted boronate (*R*)-**2h**, the ^1L_a dipole transition is parallel to the C*−Ar bond, while the ^{1}B dipole is orthogonal to it. To perform a correct spectral analysis, the right location and direction of the ^{1}B dipole must be known, and therefore, an analysis of the preferred conformation adopted in solution is needed. Therefore, the approach previously adopted for **2f**, based on NMR analysis, was again used for the 1-naphthyl boronate **2h**. The protons of the boroxolane ring Ha, Hb, and Hc were assigned at 6.35, 5.09, and 4.23, respectively, whereas those of the naphthalene ring H2 and H8 were assigned to the multiplets at δ 7.74 and 7.77, respectively. The NOE traces reported in Figure 7 show that irradiation of Ha and Hb gave a major enhancement on H8 whereas the irradiation of Hc generates only a small enhancement on both H2 and H8. The most stable conformer obtained by MMX calculations[43] (Figure 7a) shows that also the naphthyl is nearly orthogonal to the boroxolane ring with both H2 and H8 pointing inward the molecule but on different sides of the boroxolane ring, wiz: H8 is set over the ring and far 2.20, 2.42, and 3.64 Å from Ha, Hb, and Hc, respectively, whereas H2, set under the ring, shows distances of 3.67, 4.54, and 3.32 Å from Ha, Hb, and Hc. Again the ratios between distances are in good agreement with the ratios of the observed NOEs, confirming the agreement between the conformation in solution and the calculated one. From this analysis emerges that the most stable conformation of (*R*)-**2h** is the one depicted in Figure 5b, where the biphenyl and the naphthyl moieties are on opposite sides and the *peri* hydrogen on the naphthalene moiety is directed toward the smallest substituent (the hydrogen) on the benzyl carbon atom. In this conformation the naphthyl ^1L_a transition dipole and the biphenyl one define a negative chirality and therefore, for (*R*) AC, a negative couplet feature is to be expected in the CD spectrum. In this conformation also the long-axis ^{1}B transition of the naphthalene nucleus define a negative chirality with the biphenyl transition, and therefore also the exciton coupling between these transition dipoles will afford a negative nondegenerate couplet in the CD spectrum. The experimental UV spectrum of (*R*)-**2h** (Figure 8) shows a broad absorption band centered at 270 nm ($\epsilon \sim 26\,000$), due to the overlap of the ^1L_a transition of the naphthyl chromophore ($\lambda_{max} \sim 280$ nm, $\epsilon \sim 7000$) and the biphenyl one at 260 nm. The UV spectrum shows also an intense absorption at 225 nm ($\epsilon \sim 77\,000$), followed by a shoulder at 220 nm, which can be ascribed to the ^{1}B naphthalene transition. In the CD spectrum between 240 and 300 nm are visible a negative band at 280 nm ($\Delta\epsilon \sim -3.4$) and a weak positive one ($\Delta\epsilon \sim +0.5$) at 257 nm, which can be considered as the branches of the expected nondegenerate negative couplet feature. The high energy band at 257 nm is reduced in intensity by the overlap with the strong negative Cotton effect at 220 nm ($\Delta\epsilon \sim -23.0$). The origin of this strong CD band can be reasonably found in the exciton interaction of the ^{1}B naphthalene transition dipole with the ^{1}B biphenyl one at 200−210 nm. Since the aim of this paper was to demonstrate that the inspection of the 260 nm Cotton effect is sufficient for reliable AC assignments, we did not face the problem of a complete assignment of the CD bands of the whole spectrum.

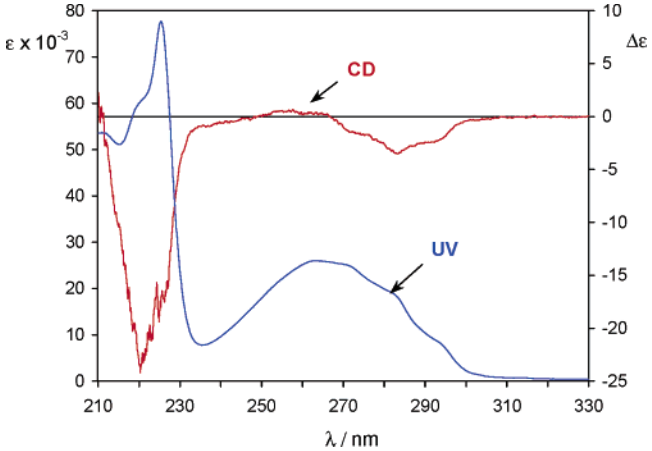

FIGURE 8. UV and CD spectra (THF) of compound (*R*)-**2h**.

The 9-anthryl-substituted boronate **2i** is an even more challenging case because the conformation of the anthryl chromophore must be carefully determined in order to foresee the interaction between its main allowed transitions and the ^1L_a biphenyl one. The strongest absorptions of the anthracene chromophore are due to the long-axis ^{1}B and short-axis ^{1}La transitions at 260 and 320−400 nm, respectively (Figure 5c). In boronate **2i** the anthryl moiety shall assume a spatial disposition which minimizes steric interactions between the 1 and 8 hydrogens and the dioxaborolane ring. From molecular mechanics calculations[43] the conformation depicted in Figure 9 for (*R*)-**2i** can be derived. In such conformation, the long-axis ^{1}B transition of anthracene and the ^1L_a biphenyl transition define a positive chirality. Since the two

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(49) 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 then a different g factor will result. At 260 nm g is 1.5×10^{-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. 5×10^{-6}, a value which makes very difficult any CD measurement.

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

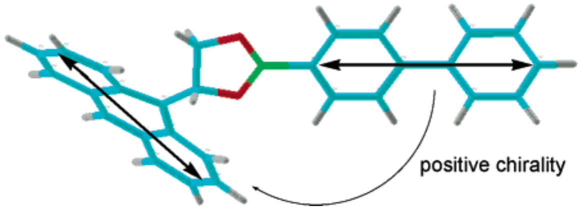

FIGURE 9. Most stable conformation and main transition dipoles of biphenylboronate (*R*)-**2i**.

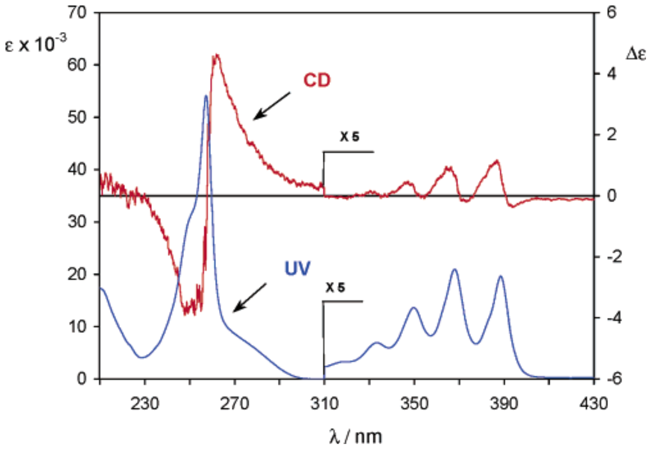

FIGURE 10. UV and CD spectra (THF) of compound (*R*)-**2i**.

transitions occur at similar energy, a quasidegenerate positive couplet feature is therefore to be expected at around 260 nm in the CD spectrum of (*R*)-**2i**.

The UV spectrum of (*R*)-**2i** (Figure 10) shows in the 400−310 nm range the following absorption bands: 387 nm ($\epsilon \sim 3800$), 367 nm ($\epsilon \sim 4200$), 350 nm ($\epsilon \sim 2600$), and 332 nm ($\epsilon \sim 1400$). Taking into account their position, intensity, and shape, they can be easily ascribed to the short-axis ^1L_a transition of the anthracene chromophore.[38a] At shorter wavelengths, a very strong band at 257 nm ($\epsilon \sim 54\,000$) followed by a shoulder at 249 nm are present. This spectral area, considering position, intensity, and shape of these bands, is clearly dominated by the long-axis polarized ^1B_b transition of the anthracene chromophore.[38a] In the CD spectrum, a positive couplet feature, centered at 255 nm, is clearly detectable. The latter spectral feature, which can be ascribed to the exciton coupling between the anthryl ^1B transition and the biphenyl ^1L_a one, perfectly agrees with our predictions, clearly establishing that the AC of (+)-**2i** is indeed (*R*). The long wavelength region of the CD spectrum presents a complex vibrational structure visible between 410 and 310 nm: the interpretation of such feature is well beyond the scope of the present paper.

Class C: Diols Having Phenyl-Substituted Chromophores and Two Chiral Centers. The above-described 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. In fact, according to our analysis, the presence of a nonchromophoric substituent in the 1 or 2 position on the diol does not affect the aryl/biphenyl coupling and therefore the assignment of the absolute configuration of the benzylic C_1 stereocenter. Moreover, if the *erythro*/*threo* relationship is known, for example by ^{1}H NMR analysis, with the present method it is possible to assign the configuration of both the stereocenters. In other words, these cases can be treated as the monoaryl-substituted derivatives. Therefore, for (*R*) AC of the benzylic stereogenic carbon, the ^1B and ^1L_a transitions of the aryl chromophore define a negative chirality with the biphenyl ^1L_a transition, and a negative couplet is expected in the CD spectrum, with a negative Cotton effect in correspondence of the biphenyl absorption at 260 nm. As examples of application to 1-aryl-2-alkylethane-1,2-diols, we shall discuss the cases of diols **1j**−**m**. Such diols are not only suitable examples and test molecules, but deserve also practical interest. In fact, (2*S*,3*R*)-**1j** is a synthetic precursor of Taxol side chain,[17a,26] while (1*R*,2*R*)-**1k** and (1*R*,2*S*)-**1l** are metabolites derived from the in vivo detoxification of (*E*)-anethole,[16a] an aromatic substance present in anise and other spices. In the CD spectra of their boronates (4*R*,5*S*)-**2j**, (4*R*,5*R*)-**2k**, and (4*R*,5*S*)-**2l**, having the same (*R*) absolute configuration at the benzylic carbon, a negative Cotton effect was clearly visible at ca. 260 nm as foreseen by our method.[51] Interestingly, the CD spectra of (4*R*,5*R*)-**2k** and (4*R*,5*S*)-**2l**, diastereoisomers having the same configuration at C_1, are almost super imposable, confirming that the CD spectral features are determined only by the absolute configuration of the benzylic stereocenter. An interesting example is afforded by the thiophene derivative (4*R*,5*R*)-**2m**.[52] In such compounds, the main spectral feature of the thiophene chromophore is the $\pi-\pi^*$ transition at 245 nm, polarized along the C_1-C_4 direction.[53] In a derivative (*R*)-configured at the benzylic carbon, the thiophene and the biphenyl chromophore will assume the relative disposition depicted in Figure 5d, defining a positive chirality. Such transitions are also near-in-frequency, and therefore, a quasidegenerate exciton coupling is expected, giving rise to a positive couplet in the CD spectrum. In the UV spectrum of (4*R*,5*R*)-**2m** (Figure 11) is present an intense ($\epsilon \sim 22\,000$) and large band at 265 nm, with a shoulder ($\epsilon \sim 16\,000$) at 245 nm. Such a band can be clearly ascribed to the overlap of the ^1L_a biphenyl and $\pi-\pi^*$ thiophene transitions. In the CD spectrum of such a compound a clear positive couplet feature is present in the 310−210 nm range as expected by our spectral analysis, providing a further support to the coupling oscillator nature of the CD in the 260 nm region and then to the correctness of our approach.

Class D: Benzocondensate Cyclic Diols Having Phenyl-Substituted Chromophores and Two Chiral Centers. The benzocondensate cyclic diols 1,2-dihydroxyindene **1n** and 1,2,3,4-tetrahydro-1,2-dihydroxynaphthalene **1o** deserve a detailed conformational analy-

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[51] Actually, (2*S*,3*R*)-**1j**, (1*R*,2*R*)-**1k**, and (1*R*,2*S*)-**1l**, have the same (*R*) AC at the benzylic carbon which is C_3 in **1j** and C_1 in **1k**, **l**. A formal inversion due to Cahn−Ingold−Prelog (CIP) rules instead occurs for C_2 in **1j** and C_2 in **1k**, which again have the same AC.

[52] It has to be noted that (2*R*,3*R*)-**1m** and (2*S*,3*R*)-**1j** have opposite AC at the C_3 benzylic carbon even if, due to Cahn−Ingold−Prelog (CIP) rules, they both must be (*R*) configured.

[53] Norden, B. *Chem. Scr.* **1975**, *7*, 226. Actually, two transitions having orthogonal polarization, along and perpendicular to the C_2 axis of the thiophene chromophore, can be found between 210 and 250 nm. Since the thiophene group in **2m** rotates almost freely, only the transition polarized along the C2−C5 direction (i.e., perpendicular to the C_2 axis) can give rise to exciton coupling.

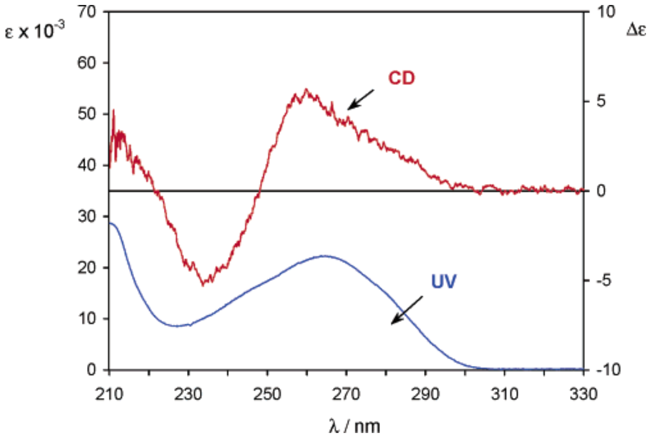

FIGURE 11. UV and CD spectra (THF) of compound (4*R*,5*R*)-**2m**.

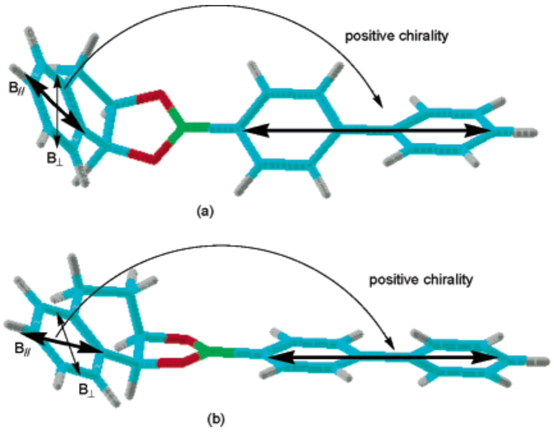

FIGURE 12. Most stable conformations and main transition dipoles of biphenylboronates (4*S*,5*R*)-**2n** (a) and (4*S*,5*R*)-**2o** (b).

sis. In such diols, the aryl chromophore is in fact analogous to a simple 1,2-dimethylbenzene, but the fusion of the rings blocks their conformation, making the aryl transitions assume a well-defined direction. From molecular mechanics calculations[43] we derived the more stable conformations of boronate (4*S*,5*R*)-**2n**, depicted in Figure 12a, where the longitudinal and transverse dipole moments allied to the ^{1}B aryl transition are reported. In such conformations, the longitudinal ^{1}B transition moment $B_{\parallel}$ and the ^1L_a biphenyl transition define a positive chirality, while the transverse dipole $B_{\perp}$ and the biphenyl one, being orthogonal one each other, do not give rise to exciton coupling. A positive Cotton effect is therefore expected in the CD spectrum at 260 nm. The UV absorption spectrum of (4*S*,5*R*)-**2n** (Figure 13) shows the intense biphenyl band at 265 nm ($\epsilon \sim 20\,500$) and a strong band below 210 nm. In the CD spectrum a positive Cotton effect at 260 nm ($\Delta\epsilon \sim 5.0$) is clearly visible, confirming the expected predictions. A similar treatment can be performed for boronate (4*S*,5*R*)-**2o**, whose most stable conformation, as derived from MMX calculations,[43] is depicted in Figure 12b. In such a conformation, the longitudinal ^{1}B dipole moment of the phenyl chromophore and the biphenyl ^1L_a transition are almost parallel, and therefore, their contribution to exciton coupling is negligible. The transverse ^{1}B phenyl transition moment and the biphenyl one define, on the other hand a positive chirality but, being almost orthogonal, they will provide a small contribution to optical activity. The UV absorption spectrum of (4*S*,5*R*)-**2o** shows spectral features very similar to **2n**, with the biphenyl band at 260 nm ($\epsilon \sim 21\,000$) and a strong band ($\epsilon \sim 50\,000$) at 205 nm. In the CD spectrum, the positive Cotton effect at 260 nm is, as expected, much weaker ($\Delta\epsilon \sim 0.8$) than in **2n** and not well resolved, but clearly confirming the expected positive chirality.

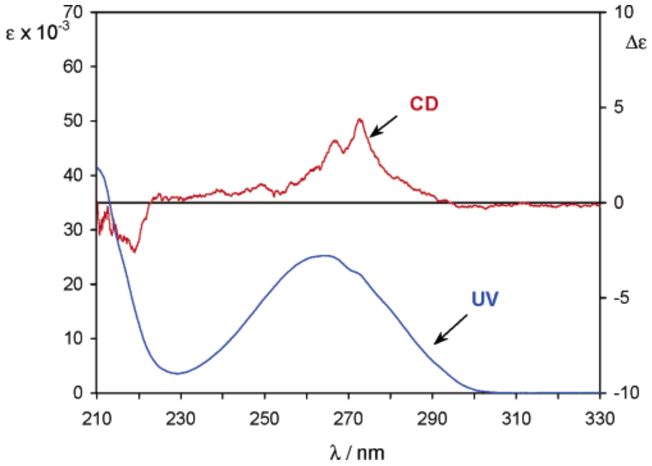

FIGURE 13. UV and CD spectra (THF) of compound (4*S*,5*R*)-**2n**.

Conclusions

We have described herein a simple, general, and reliable nonempirical approach based on the exciton coupling method to assign the absolute configuration of the benzylic stereogenic center of 1-aryl-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 230−300 nm range, i.e., in the range corresponding to the long-axis ^1L_a transition of the biphenyl chromophore. From the sign of the CD couplet or Cotton effect at 260 nm it is possible to know the chirality defined by the aryl and biphenyl chromophore transitions and then to determine the absolute configuration of the benzylic carbon. By this approach, the following simple set of rules has been formulated which allows to establish the absolute configuration of 1-aryl-1,2-diols. For phenyl-substituted diols with one or two chiral centers (Chart 1, class A and C), the presence of a negative couplet or a negative Cotton effect at ca. 260 nm in the CD spectrum corresponds to an (*R*) absolute configuration of the benzylic carbon. For diols bearing more complex and large aryl chromophores, such as the naphthyl and 9-anthryl ones (Chart 1, class B), a simple conformational analysis is needed in order to know the relative orientation of the main aryl transitions. The 2-naphthyl-substituted diols behave exactly as the phenyl substituted ones and therefore an (*R*) AC corresponds to a negative CD band at 260 nm, while for (*R*)-configured 1-naphthyl-substituted diols a negative CD couplet in that spectral range is observed. Due to a special steric situation the 9-anthryl chromophore assumes, in an (*R*)-configured derivative, a conformation in which its long-axis transition dipole defines a positive chirality with the biphenyl one. A positive CD couplet effect will therefore result. The ring fusion of *erythro* benzocondensate cyclic diols such as 1,2-dihydroxyindene and 1,2,3,4-tetrahydro-1,2-dihydroxynaphthalene (Chart 1, class D) determines a conformational arrangement of the boronates in which the aryl and biphenyl transitions define, for an (*R*)-configured benzylic carbon, a positive chirality, leading to a positive CD Cotton effect at 260 nm.

It is important to point out that in the boronate approach the conformational analysis is, in most cases, completely avoided, and for complex substrates, where simple molecular mechanics calculations are required, these are sufficient to achieve the preferential conformer. By simple inspection of the sign of the 260 nm band in the CD spectrum the AC of the diol benzylic stereocenter can be straightforwardly determined. From this point of view, the biphenyl boronate derivatization proves to be an ideal transformation. In fact, the boronic ester formation reduces the conformational analysis, while the ^1L_a biphenyl transition at 260 nm constitutes a suitable spectroscopic probe. As a consequence, the analysis of the CD data to arrive at the AC determination is made very simple. The approach described in this paper then constitutes a new and powerful tool available to the experimental organic chemist even without expertise in chirooptical techniques.

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Supporting Information Available: Full characterization and experimental procedures for compounds **1b**−**o** and **2a**−**o**. NOE data from ^{1}H NMR analysis for **2f**. Computational data for compounds (*R*)-**2i**, (*4S*,*5R*)-**2n**, and (*4S*,*5R*)-**2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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