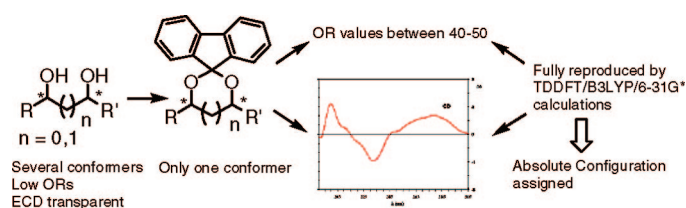


## A Chemical/Computational Approach to the Determination of Absolute Configuration of Flexible and Transparent Molecules: Aliphatic Diols As a Case Study

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By reacting flexible and optically transparent in UV–vis molecules such as 1,2-, *syn*- and *anti*-1,3-diols, 1,3-sulfanylalcohols of known absolute configuration (AC) with fluorenone dimethyl acetal, the corresponding ketals are obtained. They are conformationally well-defined (only one conformer in most cases) compounds exhibiting medium-high optical rotation (OR) values, which are independent of the solvent, and electronic circular dichroism (ECD) spectra, which show several (up to five) Cotton effects in the 350–200 nm range due to valence shell  $\pi \rightarrow \pi^*$  transitions. These features allow simulation of the chiroptical properties of these compounds at the TDDFT/B3LYP/6-31G\* level of theory to obtain, using the known ACs of these compounds, a satisfactory reproduction of the OR values (sign and order of magnitude; quantitatively, the predicted values are twice the experimental ones), and a more than satisfactory reproduction of the ECD spectra (sign, intensity, and position of the lowest-energy four Cotton effects) for all the compounds studied. Therefore, this approach can be used to assign the AC of such flexible molecules, in particular, *syn*-1,3-diols, which are important substrates in organic synthesis and for which nonempirical methods of AC assignment have not been devised so far. Furthermore, since the fluorene chromophore leads to the presence of several Cotton effects from, say, 350 to 200 nm, their correct simulation of sign, intensity, and position is a guarantee of the correct assignment of AC: in this way, ECD spectroscopy gains the same advantages of VCD spectroscopy, that is, the need of reproducing many ECD bands and then a solid guarantee of a correct AC assignment.

### Introduction

The quantum-mechanical calculation of the chiroptical properties<sup>1</sup> (optical rotation (OR))<sup>2</sup> electronic circular dichroism (ECD),<sup>3</sup> and vibrational circular dichroism (VCD)<sup>4</sup> spectra can allow a safe determination of the molecular absolute configuration, as demonstrated in very recent years by several papers where chiroptical data of molecules having known absolute configuration (AC) have been correctly predicted,<sup>3,4</sup> while, even more recently, the absolute configuration of unknown molecules has been assigned, in particular, by the concerted<sup>5</sup> use of these

techniques. However, in spite of these significant progresses, some problems still remain: in particular, the treatment of the electronic chiroptical properties of all those compounds showing small  $[\alpha]_D$  and/or weak ECD signals, such as aliphatic alcohols,

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diols, ethers, amines, and so on. In fact, such compounds are species without typical UV–vis chromophores and, in addition, present a large conformational flexibility so that many conformers showing different (even opposite) OR values and/or ECD spectra are simultaneously present, leading to a weighted average value which is small. For instance, for (2*R*,3*R*)-butanediol, Polavarapu has recently<sup>6</sup> pointed out that at least 10 conformers are appreciably populated at room temperature and, as a matter of fact, it shows a low OR,  $[\alpha]_D -17$  (*c* 1, chloroform). It is immediately clear that a case of this type presents many formidable obstacles: a really accurate determination of the conformers' population is necessary, the calculation must be repeated 10 times, and, considering the chemical nature of the

compound, a very large basis set is absolutely required. The overall process is therefore quite long and arduous, without any guarantee of obtaining the correct answer owing to the large number of variables. It is to be noted that such an approach can become even impracticable for larger molecules. Therefore, in such cases, alternative methods are required to avoid all these difficulties. From this point of view, it seems obvious to think to some simple transformation of the original flexible compound in order to remove (or at least reduce) its conformational mobility. A further advantage of this simple derivatization could be that the reduction of the conformational freedom could be carried out introducing, at the same time, a chromophoric group.

So a derivative possessing more intense (and so more easily measurable and possibly interpretable) chiroptical properties might be obtained, where the newly derivatizing group introduced would help in reducing the number of conformers and work as a probe of the absolute stereochemistry of the starting compound. We have been using this kind of reasoning for some years<sup>7</sup> when we first tackled the problem of the assignment of the absolute configuration of optically active 1,2-diaryl-1,2-ethanediols via the analysis of the ECD spectra of their suitable derivatives. The approach was later extended to 1-arylethane-1,2-diols and subsequently to aliphatic (transparent) 1,*n*-diols: here their transformation into biphenyl ketals guarantees a strong reduction of the number of the conformers, and the biphenyl chromophore, with strong ECD signals easily correlated to the AC of the original 1,2-diol, acts as a probe of the overall molecular chirality. Interestingly, Stephens and co-workers have recently employed<sup>8</sup> the method of reducing the conformational flexibility to make the analysis of the VCD spectra of (–)-borneol easier. Therefore, we decided to verify further the approach indicated above using a group of known diols and sulfanylalcohol **1j** (Chart 1) as benchmark molecules, molecules that play an important role in asymmetric catalysis<sup>9,10</sup> and natural product chemistry<sup>11,12</sup> and exhibit high conformational flexibility, low OR values, and weak ECD spectra.

They will be transformed in the corresponding cyclic ketals **2** (Chart 2) using the commercially available ketone 9-fluorenone **3**. In this way, on passing from the acyclic compounds **1** to the cyclic ones **2**, the conformational freedom will certainly be reduced.

Furthermore, the introduction of the biphenyl chromophore of **2** with electronically allowed transitions at 260 and 210 nm should guarantee the existence of Cotton effects in the near-UV region which, in turn, should contribute at increasing the value of  $[\alpha]_D$  of **2** with respect to the corresponding values of compounds **1**. In our opinion, these facts should allow a reliable

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CHART 1

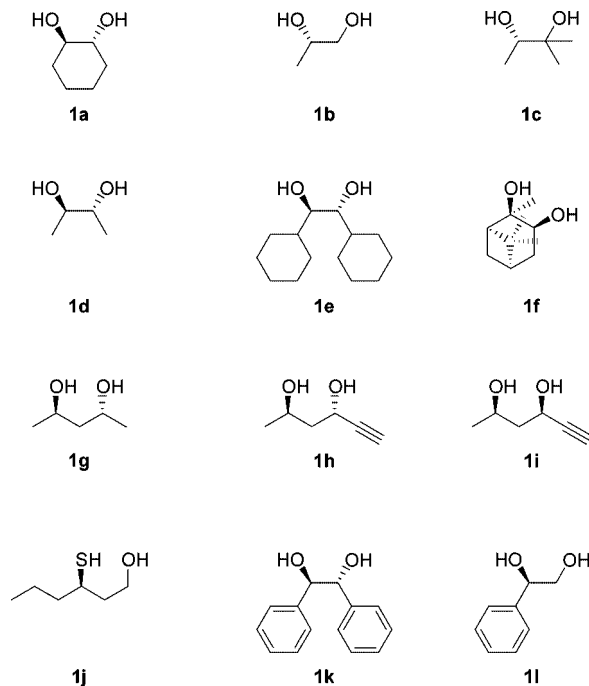
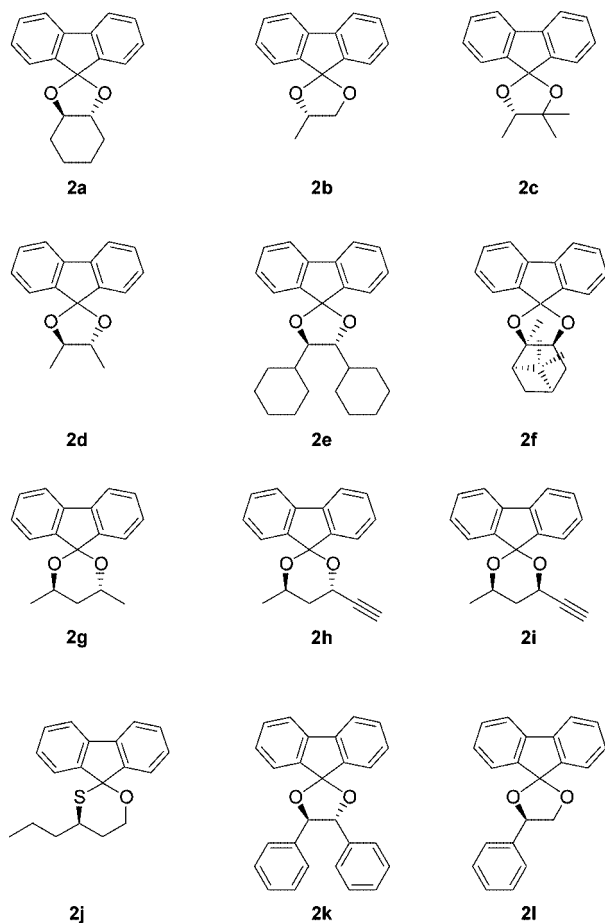
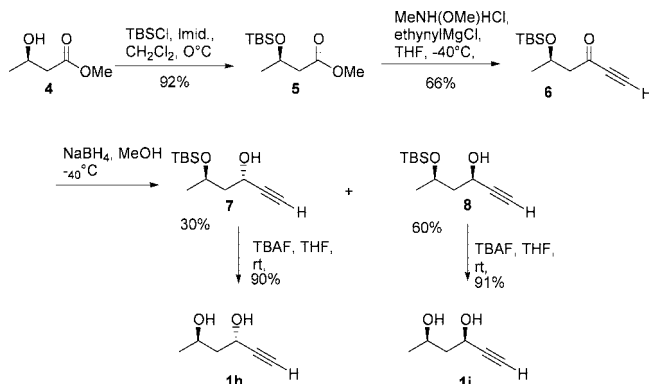


CHART 2



simulation of  $[\alpha]_D$  by computational methods and then a safe AC assignment. In addition, compounds **2**, owing to the presence of the biphenyl group, should show intense Cotton effects in the UV-vis region, in contrast to compounds **1** and, for this

SCHEME 1



reason, the correct simulation of the ECD bands could constitute an independent tool by which the AC of compounds **2** (and therefore of compounds **1**) can be reliably assigned.

## Results and Discussion

**Synthesis.** Compounds **1** are representative of several classes of diols: 1,2-aliphatic diols (**1a–f**), 1,3-*anti*- and *syn*-aliphatic diols (**1g**, **1h**, and **1i**, respectively), 1,2-aromatic diols (**1k** and **1l**). In addition, there is the sulfur-containing compound **1j**. All these substrates will be used to verify the applicability of our ideas to systems having different structures. Compounds **1a**, **1b**, **1d**, **1e**, **1f**, **1g**, and **1l** are commercially available, **1c** has been prepared by addition of methylmagnesium bromide to ethyl lactate,<sup>13</sup> **1k** has been prepared by asymmetric dihydroxylation of the corresponding olefin.<sup>9</sup> Diols **1h** and **1i** have been prepared starting from the commercially available ester **4**, protected as its silyl ether **5**.<sup>14</sup> On adding excess ethynylmagnesium chloride to a mixture of Me(MeO)NH·HCl and methyl ester **5**, complete conversion to ketone **6** has been observed, without the formation of the Weinreb amide intermediate.<sup>15</sup> Then ketone **6** was reduced with NaBH<sub>4</sub> in methanol to a mixture of compounds **7** and **8**, monoprotected *anti*- and *syn*-1,3-diols, respectively, which were separated by column chromatography. Deprotection of the silyl group with TBAF gave diols **1h** and **1i** in high yield (90 and 91%, respectively)<sup>16</sup> (Scheme 1).

The sulfanylalcohol **1j** has been prepared, in optically active form, by the reported procedure.<sup>17</sup>

Ketals **2** have been prepared by reaction of diols with the corresponding dimethylacetal **9** of 9-fluorenone **3**, as reported below (Scheme 2). Compounds **2** (Chart 2) have been characterized by NMR and mass spectrometry.

**Chiroptical Properties.** Table 1 collects the experimental rotatory powers of compounds **2** compared to those of the corresponding compounds **1**. In several cases, on passing from **1** to **2**, we have a remarkable increase of the OR, in the cases of **a**, **d**, **g**, and **h**, this passage guarantees a variation of the  $[\alpha]_D$  of about +80 units, while in the cases of **c**, **e**, and **f**, the increase is even larger (an order of magnitude). This fact is really

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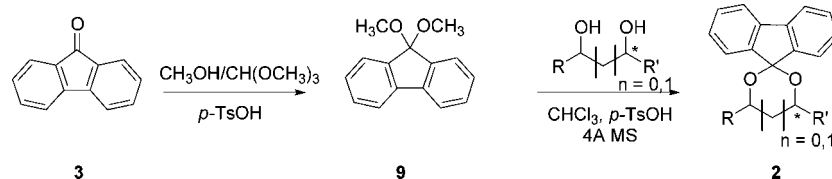
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## SCHEME 2

TABLE 1.  $[\alpha]_D$  Values of the Compounds 1a–l and of the Corresponding Derivatives 2a–l

diol 1	$[\alpha]_D^a$ (c (g/100 mL), solvent)	ketal 2	$[\alpha]_D^a$ (c (g/100 mL), solvent)
<b>1a</b>	−29 (c 0.78, CHCl <sub>3</sub> ) −30 (c 0.81, MeOH)	<b>2a</b>	+51 (c 0.6, CHCl <sub>3</sub> ) +50 (c 0.78, hexane) +54 (c 0.74, MeOH)
<b>1b</b>	+23 (c 1, CHCl <sub>3</sub> )	<b>2b</b>	−9 (c 0.61, CHCl <sub>3</sub> )
<b>1c</b>	+4 (c 1.02, CHCl <sub>3</sub> )	<b>2c</b>	−50 (c 1.25, CHCl <sub>3</sub> )
<b>1d</b>	−17 (c 1, CHCl <sub>3</sub> ) −5 (c 1, MeOH)	<b>2d</b>	+52 (c 1, CHCl <sub>3</sub> ) +58 (c 1, hexane)
<b>1e</b>	−1 (c 0.78, CHCl <sub>3</sub> )	<b>2e</b>	+61 (c 2.08, CHCl <sub>3</sub> )
<b>1f</b>	−2 (c 1.2, CHCl <sub>3</sub> )	<b>2f</b>	−35 (c 1, CHCl <sub>3</sub> ) −38 (c 1, hexane)
<b>1g</b>	−36 (c 1, CHCl <sub>3</sub> )	<b>2g</b>	+41 (c 1, CHCl <sub>3</sub> )
<b>1h</b>	−32 (c 0.8, CHCl <sub>3</sub> )	<b>2h</b>	+41 (c 1, CHCl <sub>3</sub> )
<b>1i</b>	+6 (c 1, CHCl <sub>3</sub> )	<b>2i</b>	−4 (c 0.95, CHCl <sub>3</sub> )
<b>1j</b>	−8 (c 0.8, CHCl <sub>3</sub> ) <sup>b</sup>	<b>2j</b>	+216 (c 1, CHCl <sub>3</sub> )
<b>1k</b>	+73 (c 0.57, CHCl <sub>3</sub> ) +71 (c 0.61, CH <sub>3</sub> CN) +84 (c 1, EtOH)	<b>2k</b>	+247 (c 0.63, CHCl <sub>3</sub> )
<b>1l</b>	−64 (c 0.82, CHCl <sub>3</sub> ) −38 (c 3, EtOH)	<b>2l</b>	+63 (c 1.04, CHCl <sub>3</sub> )

<sup>a</sup> deg [dm g/cm<sup>3</sup>]<sup>−1</sup>. <sup>b</sup> Pickenhagen, M.; Bronner-Schindler, H. *Helv. Chim. Acta*, **1984**, *67*, 947–952.

noteworthy because in the case of **1c**, **1e**, and **1f** a direct calculation of such a low value of OR on these flexible molecules (they exist as a mixture of several conformers, vide infra) cannot lead to a reliable result as basis of a safe configurational assignment.

By contrast,  $[\alpha]_D$  values of the order of 50–60 deg [dm g/cm<sup>3</sup>]<sup>−1</sup> constitute a figure which can be reasonably reproduced by the present calculations, especially considering that the number of conformers of compounds **2** is much smaller than for compounds **1**. It is particularly interesting to note a very strong increase of OR on passing from **1j** to **2j**: from −8 to 216! We cannot provide a reasonable explanation for this observation, yet. In fact, in the case of other 1,3-diols (**1g**, **1h**), we do not have a relevant change in the absolute value of OR, while here on passing from **1j** to **2j**, the OR value becomes 25 times larger. Only in the cases of **2b** and **2i** we do not observe an increase of OR. However, it is interesting to note that even when the  $[\alpha]_D$  value remains small (cf. **1b** and **2b**: from +23 to −9) we have a variation of 32 units, in absolute value. Another important observation is that the  $[\alpha]_D$  values of compounds **2** are independent of the solvent: the OR of **2a** does not change on passing from hexane to chloroform to methanol, that is, over three very different solvents (see Table 1). Therefore, we can compare the experimental results obtained in a solvent with predicted figures obtained in the gas phase; this means that we can avoid the use of solvation models,<sup>18</sup> saving a great amount of computational effort. The absorption and ECD spectra of **2a** (acetonitrile), as representative example of compounds **2**, are reported in Figure 1.

The absorption and ECD spectra of compounds **2b–2l**, which are entirely similar to that reported in Figure 1, are reported in the Figures 1–8 of Supporting Information. In the UV spectrum of **2a**, several different regions of absorption can be easily pointed out: a broadband with absorption maximum at about 280 nm ( $\epsilon \sim 10\,000$ ), a couple of bands at 240 nm ( $\epsilon \sim 30\,000$ ) and 230 nm ( $\epsilon \sim 30\,000$ ), and a last broadband centered at 205 nm ( $\epsilon \sim 30\,000$ ). Taking into account that the only chromophore

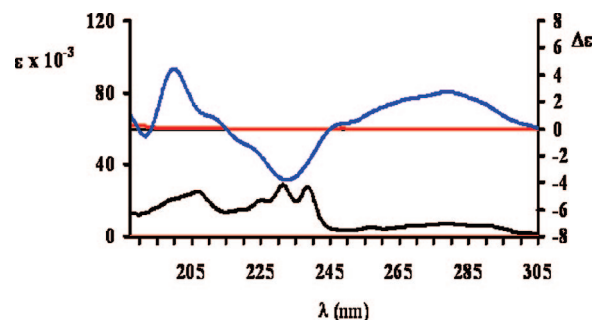


FIGURE 1. Absorption (black line) and ECD spectrum (blue line) of **2a** in acetonitrile.

present in **2a** is the fluorene group, it is reasonable to assign the observed bands to  $\pi-\pi^*$  transitions localized on such a chromophore and then polarized in the fluorene plane along the C<sub>2</sub> axis or perpendicular to it, as suggested by Sagiv and co-workers.<sup>19</sup> In the ECD spectrum, it is possible to observe Cotton effects centered at 280 nm ( $\Delta\epsilon +3$ ), 235 nm ( $\Delta\epsilon -4$ ), 205 nm ( $\Delta\epsilon +4$ ), a weak, negative CD band followed by the onset of a fifth, positive CD band. Clearly these bands are related to the  $\pi-\pi^*$  transitions discussed above. The presence of these Cotton effects in the ECD spectra is of paramount importance. From a completely ECD transparent compound, where it is possible to measure with the commercial instruments, only a tail showing very low ECD intensity (Figure 9 of Supporting Information) and which is useless for a reliable configurational assignment, the diol  $\rightarrow$  ketal transformation allows one to obtain a simple derivative which shows a spectrum with many intense Cotton effects having differing signs. In this way, if the computational procedure is able to simulate the correct sequence of Cotton effects (sign, position, intensity), we shall have a reliable configurational assignment based on the simulation of several Cotton effects. In other words, we have introduced to electronic chiroptical spectroscopy the main advantage of vibrational CD

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TABLE 2.  $[\alpha]_D$  Values and Number of Conformers of the Compounds **1a–l** and of the Corresponding Derivatives **2a–l**

diol	$[\alpha]_D$	No. of conformers <sup>a</sup>	ketal	$[\alpha]_D$	No. of conformers <sup>a</sup>	predicted $[\alpha]_D$	
						<b>6–31G*</b>	<b>6–31++G**</b>
<b>1a</b>	–29	4	<b>2a</b>	+51	1	+107	+126
<b>1b</b>	+23	21	<b>2b</b>	–9	2	–52	–59
<b>1c</b>	+4	10	<b>2c</b>	–50	1	–107	–73
<b>1d</b>	–17	10	<b>2d</b>	+52	1	+122	+134
<b>1e</b>	–2	32	<b>2e</b>	+61	3	+141	
<b>1f</b>	–2	3	<b>2f</b>	–35	1	–76	
<b>1g</b>	–36	22	<b>2g</b>	+41	1	+68	+50
<b>1h</b>	–32	12	<b>2h</b>	+41	2	+76	
<b>1i</b>	+6	6	<b>2i</b>	–4	1	–4	–7
<b>1j</b>	–8	22	<b>2j</b>	+216	1	+402	408
<b>1k</b>	+73	6	<b>2k</b>	+247	1	+632	
<b>1l</b>	–64	12	<b>2l</b>	+63	1	+355	+286

<sup>a</sup> Number of conformers obtained by molecular mechanics calculations, retaining the structures within 4 kcal/mol above the most stable one.

spectroscopy,<sup>4c,k,20</sup> that is, the presence of several Cotton effects and the need to reproduce all of them as a guarantee of a safe configurational assignment. A last observation, for each compound **2**,  $[\alpha]_D$  and the lowest-energy Cotton effect have the same sign, and this band provides the largest contribution to the OR at 589 nm. This suggests that the calculation of the chiroptical properties of **2** could be carried out<sup>21</sup> at a relatively low level of theory (e.g., TDDFT/B3LYP/6-31G\*) without reducing the reliability of the results but reducing the computational effort. This is an important point. In fact, one might argue that on passing from **1b** to **2b**, for instance, there is a significant increase of the molecular complexity (from 42 to 120 electrons) with a consequent increase of the computational effort. However, as will be shown later, the large reduction in the number of conformers and the use of the above-mentioned low level of theory provide an easy and reliable simulation of the chiroptical properties with a reduced computational effort (when compared to that required to treat compounds **1**).

#### Computational Analysis of the Chiroptical Properties.

Following the procedure described in the Computational Details, the first step of the computational analysis of the chiroptical properties of compounds **2** is the determination of number and structure of the conformers of compounds **2**. The results of such an analysis are collected in Table 2.

An important comparison concerns the reduction of the conformational flexibility of the compounds **1** by transforming them in the derivatives **2**. For each of the compounds **1**, a simple molecular mechanics analysis (Spartan02,<sup>22</sup> MMFF94s force field, retaining only the structures having a total energy of 4 kcal/mol or less with respect to that of the most stable one) provides a very large number of conformers: for example, 21 conformers for **1b**, 32 for **1e**, 22 for **1g**, and 12 for **1h**. (Polavarapu established<sup>6</sup> that for **1d** at least 10 conformers are

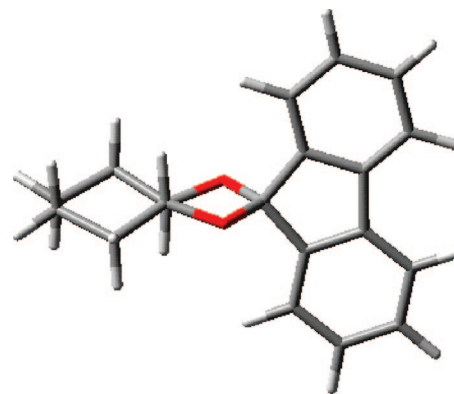


FIGURE 2. Structure (DFT/B3LYP/6-31G\*) of **2a**.

appreciably populated at room temperature.) Compounds **1** having a fewer number of conformers are **1a** (4) and **1f** (3). Compound **1j** and its derivative **2j** present some difficulties due to the presence of the *n*-propyl tail linked to the stereogenic center. In order to simplify the treatment, we substituted the *n*-propyl group with a methyl group. Although this substitution might affect the predicted OR value, it should not affect the simulated ECD spectrum, taking into account that the observed ECD bands are due to electronic transitions localized on the fluorene chromophore. However, in this case, we found two different conformers with populations of 97 and 3%, respectively. So, the calculations on this compound were carried out for the most stable conformer only. In summary, it is important to note that, on passing to **2**, we found that these derivatives possess only one conformer with the sole exceptions of **2b** (2), **2e** (3), and **2h** (2). Gratifyingly, the derivatization of **1** to **2** exerts the effect we expected: a very strong reduction of the number of conformers.

The structure of **2a** is reported in Figure 2, as representative example, while Tables 1–17 of Supporting Information report the geometries of the compounds **2a–l** as obtained at the DFT/B3LYP/6-31G\*<sup>23</sup> level of theory.

OR values have then been calculated, for compounds **2**, at the TDDFT/B3LYP/6-31G\* level of theory, and the results are reported in Table 2.

We call attention to five points. (1) The calculations reproduce the experimental OR values in sign and order of magnitude for all compounds **2**. This means that the present method constitutes a simple technique by which it is possible to carry out a safe configurational assignment even in the particularly difficult cases of compounds having a large number of conformers and very

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**TABLE 3. Conformer Population, TDDFT/B3LYP/6-31G\* Calculated OR Value for Each Conformer, and the Boltzmann Average Compared with the Experimental Rotatory Power for 2e**

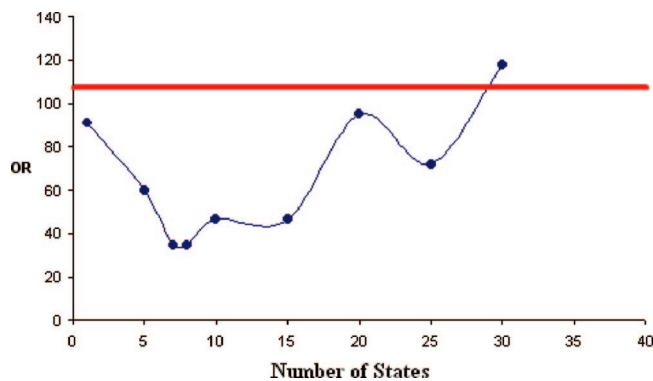
conformer	energy difference (kcal/mol)	population (%)	calcd $[\alpha]_D$	Boltzmann average	exptl $[\alpha]_D$
1	0	74	+131	+141	+61
2	0.95	15	+167		
3	1.12	11	+145		

low ORs. The examples of **1c**, **1e**, and **1f** are particularly representative because one cannot imagine arriving at a safe configurational assignment with an approach where calculation of the OR of the diol is directly attempted.

In summary, only by coupling the computational analysis with some simple organic chemistry logic can we arrive at a fully reliable configurational assignment. In the case of **2e** with three different conformers, the energies and populations of each are given in Table 3. This table indicates that all the conformers are dextrorotatory, with similar values of OR, so the average rotation is clearly positive, in satisfactory agreement with experiment.

(2) In the case of **2i**, the experimental OR value ( $-4$ ) is exactly reproduced by our TDDFT/B3LYP/6-31G\* calculation.

This almost perfect experiment/theory agreement is fortuitous. Using the larger (6-31++G\*\*) basis set, we obtain  $-7$ , that is, a number which simulates the experimental value in sign and order of magnitude. The observation that by increasing the quality of the calculation for **2i** we still obtain a negative OR value of the correct order of magnitude indicates that we can reproduce correctly even low OR values, even if the TDDFT/B3LYP/6-31G\* result was fortuitous. Thus we can assign the AC of *syn*-1,3-diols, which are substrates for which no reliable methods of configurational assignment based on analysis of chiroptical properties are yet reported<sup>24a</sup> and only the empirical method of the dimolybdenum tetracetate has been used to date.<sup>24b,c</sup> This result is fully confirmed by the ECD calculations (vide infra). (3) The case of **2j** deserves more comment. Here, in fact, we contracted the *n*-propyl tail to a simple methyl group. It is interesting to note that this approximation does not much affect the final result of the calculation. In fact, here too, we predict an OR value twice the experimental, as in all the other cases. (4) We have also attempted a calculation of  $[\alpha]_D$  using the method of the sum-over-states (SOS),<sup>1</sup> following an approach recently introduced by Wiberg and co-workers.<sup>25</sup> In Figure 3, the OR value of **2a**, calculated as sum over the first 35 states, is reported together with the value corresponding to that from the linear response theory prediction.



**FIGURE 3.** Optical rotation of **2a**, calculated with the method of sum-over-states, at the TDDFT/B3LYP/6-31G\* level, as a function of the number of states. The horizontal line corresponds to the figure obtained with linear response theory at the same level of theory.

It may be seen that, even if this number of states does not suffice to achieve convergence with the linear response theory predictions, the sum-over-states prediction oscillates around the limit value. This is because here, as we noticed above,  $[\alpha]_D$  and the lowest-energy Cotton effect have the same sign, and this band provides the largest contribution to the OR at 589 nm. In fact, an SOS calculation employing only the first excited state gives an OR value which is correct in sign and order of magnitude, and the inclusion of other states simply modifies the numerical value from +91 (only the lowest-energy state) to +107 (linear response theory). (Wiberg and co-workers say that all the states coming from the excitation of valence electrons have to be included in the sum.)<sup>25</sup>

This behavior can be found for other compounds **2** (**2d**, **2k**, **2l** in Figures 19–21 of Supporting Information). For example, the predicted ORD curve (between 589 and 405 nm) of **2a** is monosignate and positive ( $\lambda$  589 nm, +107;  $\lambda$  577 nm, +114;  $\lambda$  546 nm, +132;  $\lambda$  435 nm, +274;  $\lambda$  405 nm, +364). Furthermore, the predicted ORD curve, taking into account only the rotational strength of the lowest-energy Cotton effect, is essentially the same ( $\lambda$  589 nm, +91;  $\lambda$  577 nm, +96;  $\lambda$  546 nm, +112;  $\lambda$  435 nm, 228;  $\lambda$  405 nm, 300) as that obtained above by means of the linear response theory. This shows clearly that the OR values in the long wavelength region, where no electronic transitions appear, are dominated by the lowest-energy Cotton effect, that is, the same behavior found<sup>26</sup> by Polavarapu in the case of (*R*)-3-chloro-1-butyne, (*R*)-3-methylcyclohexanone, and (*R*)-3-methylcyclopentanone (5). From a quantitative point of view, the agreement between experimental and predicted values cannot be considered as perfect. In fact, the predicted  $[\alpha]_D$  values are larger than the experimental ones: they are 2–3 times larger for **2a** and **2c–k** and much larger (6 times) for **2b** and for **2l**. The use of a larger basis set (6-31++G\*\*) does not improve the results much, with the exceptions of **2c**, **2g**, and **2l**, where the predicted  $[\alpha]_D$  value of **2l** is significantly reduced (from +355 to +286) toward better agreement with the experiment. Since it is now generally recognized that the TDDFT/B3LYP method tends to overestimate the OR figures (sometimes of a factor of 2),<sup>5f,26,27</sup> the behavior of **2a** and **2c–k** can be explained on this basis. Obviously, the larger difference observed in the

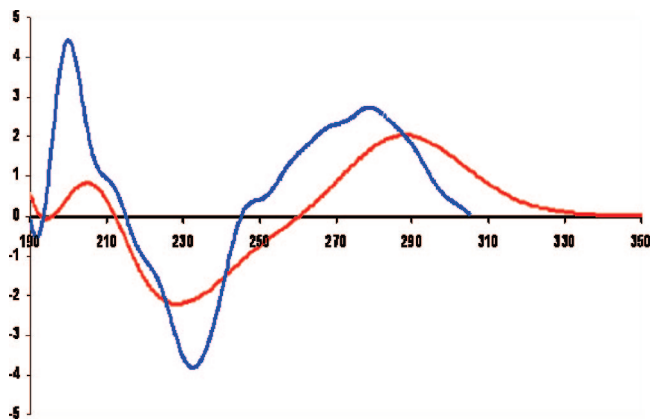
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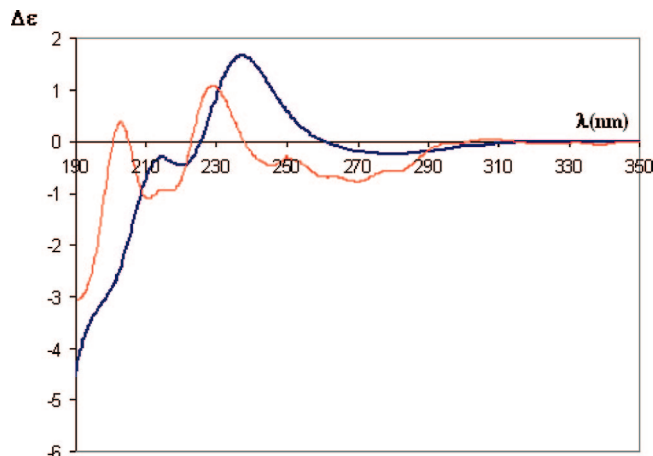
**FIGURE 4.** Comparison of the experimental (acetonitrile, blue line) and predicted (TDDFT/B3LYP/6-31G\*, velocity formalism, red line) ECD spectra of **2a**.

cases of **2b** and **2l** deserves more attention: (i) In the case of **2b**, we have an equilibrium between two conformers (equatorial methyl group, 86% and axial methyl group 14%), and the OR values of the two conformers are  $-62$  and  $+7$ , respectively. An average value of  $-52$  results. This figure depends on two different parameters, that is, relative populations and values of rotation of the two conformers. There are at least two sources of error to be checked. (ii) In the case of **2l**, we have evaluated the role of the rotation of the benzene ring linked to the dioxolane ring, following a known procedure<sup>28</sup> by which, in cases of this type, the optical rotation can be obtained by the following equation:

$$[\alpha]_D = \frac{\int_0^{360} \text{OR}(\theta) \cdot e^{-\frac{E(\theta)}{RT}} d\theta}{\int_0^{360} e^{-\frac{E(\theta)}{RT}} d\theta} \quad (1)$$

where  $E(\theta)$  is the function which gives the variation of the free energy of the molecule varying the dihedral angle  $\theta$ , which describes the rotation of the benzene ring around the  $\text{C}_{\text{ar}}-\text{C}^*$  bond, and  $\text{OR}(\theta)$  is the function linking the OR to the same angle  $\theta$ .

$E(\theta)$  and  $\text{OR}(\theta)$  have been calculated at the DFT/B3LYP/6-31G\* and TDDFT/B3LYP/6-31G\* levels of theory, respectively, varying  $\theta$  with a step of  $20^\circ$ . The corresponding curves are reported in Figure 18 of the Supporting Information. They have been interpolated by two eighth-order polynomial functions, so obtaining  $E(\theta)$  and  $\text{OR}(\theta)$ . The Boltzmann averaged  $[\alpha]_D$  value was calculated at 298 K using the equation above, obtaining a value of  $+278$ , which is still an overestimation of the experimental one ( $+63$ ) but represents a significant improvement with respect to the value obtained with the single conformer ( $+355$ ). Combining reasonably the effect of the basis set and the effect of the rotation of the benzene ring, which both lead to a reduction of the calculated OR, one could arrive at a better agreement with the experiment. It is noteworthy that assuming free rotation around the above  $\text{Ph}-\text{C}^*$  bond provides an OR value of  $+71$ , in excellent agreement with the experiment. ECD spectra of the compounds **2** have been calculated, as well. Details of these calculations are reported in the Computational Details; the comparison between calculated and experimental spectra of **2a** is given in Figure 4, while comparison between



**FIGURE 5.** Comparison of the experimental (acetonitrile, red line) and predicted (TDDFT/B3LYP/6-31G\*, velocity formalism, blue line) ECD spectra of **2i**.

the experimental and predicted spectra of **2b–l** is collected in the Figures 10–17 of the Supporting Information.

Examination of Figure 4 immediately reveals that the present calculations are able to reproduce correctly a sequence of at least four different Cotton effects in sign, position, and intensity of the bands: this constitutes clear evidence that the absolute configuration employed in the calculations is the right one; that is, the absolute configuration has been safely assigned. This is a consequence of the type of treatment for compounds **1**. The transformation **1**  $\rightarrow$  **2** guarantees the origin of a series of intense and differently signed Cotton effects the theoretical reproduction of all of which guarantees, in turn, the reliability of the configurational assignment. In Figure 5, the comparison between the experimental and simulated ECD spectra of the *syn*-1,3-diol ketal **2i** is reported.

In this case, as well, we note that the four Cotton effects observed in the experimental spectrum are reproduced by the calculations in sign, intensity, and position (the theoretical ECD bands are red-shifted, 10–15 nm, with respect to the experimental ones), thereby strongly indicating that the (*R,R*) AC employed in the calculations corresponds to the real one. Consequently, the computational analysis of the chiroptical properties of the fluorenone ketals of *syn*-1,3-diols can constitute a safe method for assigning the AC of these important substrates.

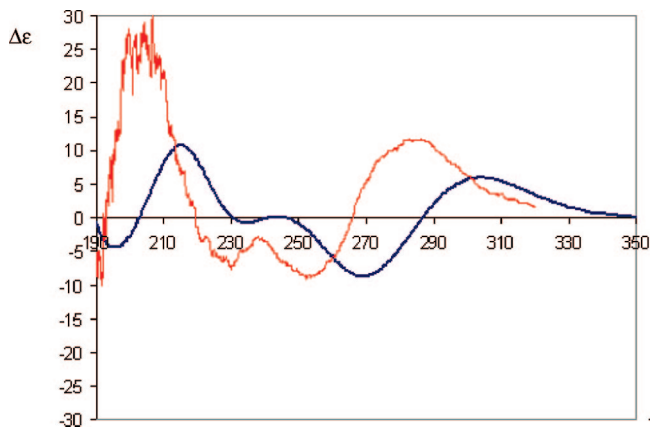
An examination of Figures 10–17 of the Supporting Information reveals that the result above is valid for all the ketals examined, and therefore, the method herein proposed is general for aliphatic 1,*n*-diols. It is also important to comment on the case of the derivative **2j**. We already indicated (*vide supra*) our attempts to further simplify the computational step by contracting an *n*-propyl tail linked to a stereocenter down to a simple methyl group, and this approximation did not affect the OR calculation in a significant way. Thus the experimental value was reproduced in sign and order of magnitude, with the predicted value being twice the experimental one, as compared to the other examples. Looking at Figure 6, we can see immediately that all of the Cotton effects present in the experimental spectrum are quite well simulated in sign, intensity, and position, again confirming that the approximation above could have general validity.

## Conclusions

The main results of this work show clearly that computational analysis of the chiroptical properties of flexible and transparent

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**FIGURE 6.** Comparison of the experimental (acetonitrile, red line) and predicted (TDDFT/B3LYP/6-31G\*, velocity formalism, blue line) ECD spectra of **2j**.

molecules can be made simpler by blocking conformational flexibility and introducing a near UV-active chromophore. Flexible systems, in principle, represent a problem requiring an enormous computational effort because the calculation must be repeated for each conformer and each single calculation must be carried out at a high level of theory taking into account that the Cotton effects are located in the far-UV region. In this way, we have a smaller number of conformers (hopefully only one) and, dealing with low-lying Cotton effects, a lower level of theory can be used.

Furthermore, if the selected chromophore leads to several Cotton effects in the near UV region (e.g., from 350 to 200 nm), the correct simulation of sign, intensity, and position is a guarantee of the correct assignment of AC. In this way, ECD spectroscopy gains the same advantages as VCD spectroscopy, that is, the need for reproducing many CD bands as a solid guarantee of a correct AC assignment.

Consequently, ECD spectroscopy can be used even alone without a concerted use of the three chiroptical spectroscopies. Other important conclusions of the present work include the following: (i) with the fluorenone ketal method, we can safely assign the AC of *syn*-1,3-diols, which are very difficult cases for chiroptical spectroscopy; (ii) the method is also successful in the case of sulfanylalcohols, important substrates in the field of natural flavors; (iii) the present method could be extended also to amino alcohols and diamines which are important compounds to the field of synthetic intermediates in medicinal chemistry, chiral ligands, and catalysts in asymmetric synthesis. Work is now in progress on (iii).

## Experimental Section

**Computational Details.** The calculations of this investigation have been carried out following the protocol described below. The structures to be used as starting geometries in the QM optimizations have been created by means of a conformational analysis with the SPARTAN02<sup>22</sup> software, using the methods of molecular mechanics (MMFF94s force field) and retaining only the structures differing by 2 kcal/mol in energy or less. All the resulting geometries have been fully optimized at the DFT/B3LYP/6-31G\*<sup>23</sup> level in the gas phase. All conformers are real minima; no imaginary vibrational frequencies have been found. In all cases, the free energy values at  $T = 298$  K have been employed to calculate the population of each conformer, using the Boltzmann statistics. The calculations of the optical rotatory power have been carried out at TDDFT/B3LYP/6-31G\* or 6-31++G\*\* levels in the gas phase. The

theoretical values of optical rotation (to be compared with the experimental ones) have been obtained as weighted averages on the Boltzmann populations calculated in the gas phase. Rotational strength calculations have been carried out at the TDDFT/B3LYP/6-31G\* level in the gas phase both in velocity and in length formalism for the first 30 states. The simulated ECD spectra have been obtained using overlapping Gaussian functions with a width  $s = 0.15$  eV, according to ref 21e. All the QM calculations have been carried out using the Gaussian03 package.

**Preparation.** All reactions were performed in flame-dried glassware under nitrogen, unless noted. Chloroform was refluxed over  $P_2O_5$  and distilled under nitrogen atmosphere before its use. THF was refluxed over sodium/benzophenone and distilled under nitrogen atmosphere before use. Chromatography separations were carried out on suitable dimension columns using silica gel 60 (70–230 mesh). Analytical thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (0.2 mm). NMR spectra were recorded in  $CDCl_3$  on a 300 or 500 MHz NMR spectrometer using TMS as the internal standard and are reported in part per million (ppm) relative to TMS (0), with coupling constants ( $J$ ) in hertz. Optical rotatory powers at 589 nm have been measured with a digital polarimeter, using standard cuvettes ( $l = 0.1$  and 1 dm). Gas chromatographic analyses and mass spectra (EI) were carried out on GC/MS chromatograph equipped with a mass selective detector and a capillary column (30 m  $\times$  0.25 mm, 5% phenyl methyl siloxane as stationary phase) using helium as carrier gas. Absorption and ECD spectra were recorded by a J-600 spectropolarimeter. Melting points were measured with a Scientific SMP3 machine and are uncorrected. Unless otherwise noted, commercially available diols, **1a**, **1b**, **1d**, **1e**, **1f**, **1g**, and **1n** were used without further purification. Compound **1c** was prepared by addition of MeMgBr to ethyl lactate,<sup>13</sup> **1j** was prepared as reported.<sup>17</sup> Compounds **1h** and **1i** have been prepared as follows:

(–)-(**R**)-Methyl-3-(*tert*-butyldimethylsilyloxy)butyrate (**5**): To a cooled (0 °C) solution of the alcohol **4** (0.5 g, 2.1 mmol) in  $CH_2Cl_2$  (6 mL) were added imidazole (0.432 g, 6.35 mmol) and TBSCl (0.477 g, 3.17 mmol). The mixture was stirred at room temperature for 23 h, then hydrolyzed with a saturated aqueous solution of  $NH_4Cl$  and diluted with  $CH_2Cl_2$ . The aqueous layer was extracted with  $CH_2Cl_2$ . The combined organic layers were washed with brine and dried over  $Na_2SO_4$ . The concentrate was purified by column chromatography on silica gel (petroleum ether/EtOAc 9:1) to provide **5** (0.453 g, 92%) as a colorless oil:  $[\alpha]_D^{25} = -32$  ( $c$  1.3,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.20 (d,  $J = 6.0$  Hz, 3H), 2.39 (dd,  $J = 14.0$  Hz, 5.0 Hz, 1H), 2.49 (dd,  $J = 14.0$  Hz, 8.0 Hz, 1H), 3.68 (s, 3H), 4.29 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) –5.1, –4.5, 17.9, 23.9, 25.7, 44.7, 51.4, 65.8, 172.1; IR ( $cm^{-1}$ ) 2956, 2930, 2896, 2858, 1741. Anal. Calcd for  $C_{11}H_{24}O_3Si$ : C, 56.85; H, 10.41. Found: C, 56.91; H, 10.24.

(–)-(**R**)-5-(*tert*-Butyldimethylsilyloxy)hex-1-yn-3-one (**6**): To a slurry of ester **5** (0.864 g, 3.72 mmol) and Me(MeO)NH $\cdot$ HCl (0.473 g, 4.85 mmol) in THF (30 mL) at –40 °C under argon atmosphere was added the solution of ethynylmagnesium chloride (0.5 M in THF, 46.50 mL, 23.25 mmol) over 2 h. After 4 h at this temperature, the reaction mixture was warmed to 25 °C, stirred overnight, and then quenched with a saturated aqueous solution of  $NH_4Cl$ . The aqueous layer was extracted with  $Et_2O$ . The combined organic layers were washed with brine and dried over  $Na_2SO_4$ . The concentrate was purified by column chromatography on silica gel (petroleum ether/EtOAc 97:3) to provide **6** (0.555 g, 66%) as a colorless oil:  $[\alpha]_D^{25} = -21$  ( $c$  1,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.21 (d,  $J = 6.0$  Hz, 3H), 2.62 (dd,  $J = 15.0$  Hz, 5.0 Hz, 1H), 2.80 (dd,  $J = 15.0$  Hz, 7.0 Hz, 1H), 3.24 (s, 1H), 4.43 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) –5.0, –4.4, 17.9, 23.9, 25.8, 55.1, 65.2, 78.6, 81.9, 185.65; IR ( $cm^{-1}$ ) 3302, 3257, 2957, 2930, 2896, 2858, 2360, 2342, 2094, 1686; MS (EI)  $m/z$  225 ( $M^+ - 1$ , 1), 169 (100), 125



(73), 83 (100), 75 (49). Anal. Calcd for  $C_{12}H_{22}O_2Si$ : C, 63.66; H, 9.80. Found: C, 63.91; H, 9.74.

(-)-(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-hex-1-yn-3-ol (**7**): To a stirred solution of ketone **6** (0.486 g, 2.15 mmol) in methanol (20 mL) was added  $NaBH_4$  (0.163 g, 4.3 mmol) at  $-40^\circ C$ . Then the solution was stirred at that temperature for 24 h. To this solution was added a solution of saturated aqueous solution of  $NH_4Cl$ . The organic phase was separated, dried over  $Na_2SO_4$ , and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 9:1) to give the title compound **7** (0.147 g) as clear oil (30% yield):  $[\alpha]_D = -56$  (c 1,  $CHCl_3$ );  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  (ppm) 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.21 (d,  $J = 6.0$  Hz, 3H), 2.62 (dd,  $J = 15.0$  Hz, 5.0 Hz, 1H), 2.80 (dd,  $J = 15.0$  Hz, 7.0 Hz, 1H), 3.24 (s, 1H), 4.43 (m, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm)  $-4.8$ ,  $-4.2$ , 17.9, 23.4, 25.8, 44.8, 60.1, 67.0, 72.5, 84.9; IR ( $cm^{-1}$ ) 3420, 3312, 2957, 2929, 2896, 2857, 2360, 2342; MS (EI)  $m/z$  227 ( $M^+ - 1$ , 1), 119 (100), 75 (75). Anal. Calcd for  $C_{12}H_{24}O_2Si$ : C, 63.10; H, 10.59. Found: C, 63.21; H, 10.70.

(-)-(3*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-hex-1-yn-3-ol (**8**): Further elution provided **8** (0.294 g) as clear oil (60%):  $[\alpha]_D = -42$  (c 1,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 0.10 (s, 6H), 0.91 (s, 9H), 1.22 (d,  $J = 6.0$  Hz, 3H), 1.82 (m, 1H), 1.93 (m, 1H), 2.47 (s, 1H), 2.84 (br s, 1H), 4.09 (m, 1H), 4.55 (m, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  (ppm)  $-4.9$ ,  $-4.0$ , 17.9, 24.2, 25.7, 46.6, 61.3, 67.7, 72.8, 84.7; IR ( $cm^{-1}$ ) 3420, 3312, 2957, 2929, 2896, 2857, 2360, 2342; MS (EI)  $m/z$  227 ( $M^+ - 1$ , 1), 119 (100), 75 (77). Anal. Calcd for  $C_{12}H_{24}O_2Si$ : C, 63.10; H, 10.59. Found: C, 63.23; H, 10.67.

(-)-(2*R*,4*S*)-Hex-5-yne-2,4-diol (**1h**): To a stirred solution of **7** (99 mg, 0.43 mmol) in THF (0.66 mL) was added tetrabutylammonium fluoride (1 M solution in THF, 0.66 mL). Then the solution was stirred at room temperature for 1 h. THF was evaporated, and the crude mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc 2:1) without extractive workup to give the title compound **1h** as a colorless oil (44 mg, 90%):  $[\alpha]_D = -33$  (c 0.8,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.27 (d,  $J = 6.0$  Hz, 3H), 1.86 (m, 2H), 2.12 (br s, 1H), 2.51 (s, 1H), 3.20 (bs, 1H), 4.40 (m, 1H), 4.68 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) 23.7, 43.9, 60.6, 65.7, 73.2, 84.4; IR ( $cm^{-1}$ ) 3344, 3294, 2967, 2923. Anal. Calcd for  $C_6H_{10}O_2$ : C, 63.14; H, 8.83. Found: C, 63.10; H, 8.70.

(+)-(2*R*,4*R*)-Hex-5-yne-2,4-diol (**1i**): Same procedure of compound **7** was followed on compound **8** to afford **1i** as a clear oil in 91% of yield:  $[\alpha]_D = +6$  (c 1,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.22 (d,  $J = 6.0$  Hz, 3H), 1.84 (m, 2H), 2.49 (s, 1H), 3.32 (br s, 1H), 4.00 (br s, 1H), 4.07 (m, 1H), 4.61 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) 23.7, 45.4, 61.7, 67.4, 73.1, 84.4; IR ( $cm^{-1}$ ) 3344, 3294, 2967, 2923. Anal. Calcd for  $C_6H_{10}O_2$ : C, 63.14; H, 8.83. Found: C, 63.09; H, 8.82.

9,9-Dimethoxyfluorene (**9**): To a solution of 9-fluorenone **9** (1.0 g, 5.55 mmol) in methanol (12 mL) were added trimethyl orthoformate (1.21 mL, 11.1 mmol) and traces of *p*-toluenesulfonic acid, and the solution was stirred at room temperature for 16 h.

Then, the reaction mixture was diluted with diethyl ether and treated with an aqueous 1 M solution of NaOH. The separated organic phases were washed with brine, dried over  $Na_2SO_4$ , and concentrated. The crude product was purified by crystallization from methanol (72%): mp =  $82-84^\circ C$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 3.40 (s, 6H), 7.34 (t,  $J = 7.5$  Hz, 2H), 7.42 (t,  $J = 7.5$  Hz, 2H), 7.58 (d,  $J = 7.5$  Hz, 2H), 7.64 (d,  $J = 7.5$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) 50.6, 119.1, 123.5, 126.8, 128.9, 138.9, 140.5; MS (EI)  $m/z$  226 ( $M^+$ , 9), 195 (100), 180 (39) 152 (18). Anal. Calcd for  $C_{15}H_{14}O_2$ : C, 79.62; H, 6.24. Found: C, 79.69; H, 6.18.

**General Procedure for the Preparation of Ketals 2a–1:** To a solution of 113 mg (0.5 mmol) of dimethylacetal **9** in chloroform (6.5 mL) were added diol **1** (0.5 mmol), activated molecular sieves (4 Å), and traces of *p*-toluenesulfonic acid, and the reaction mixture was stirred at room temperature for 16 h. Filtration and evaporation of solvent at reduced pressure gave the crude product, which was purified by chromatography column on silica gel (petroleum ether/dichloromethane 6:4) and/or crystallization from methanol.

(+)-(3*aR*,7*aR*)-3*a*,4,5,6,7,7*a*-Hexahydrospiro[1,3-benzodioxole-2,9'-fluorene] (**2a**): Yield 52%; mp =  $122-126^\circ C$ ;  $[\alpha]_D = +51$  (c 0.6,  $CHCl_3$ ), +50 (c 0.78, hexane), +54 (c 0.74,  $CH_3OH$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  (ppm) 1.37 (m, 2H), 1.58 (m, 2H), 1.85 (m, 2H), 2.21 (d,  $J = 11.5$  Hz, 2H), 3.73 (d,  $J = 9.0$  Hz, 2H), 7.18 (t,  $J = 6.7$ , 2H), 7.26 (t,  $J = 7.2$ , 2H), 7.40 (d,  $J = 6.5$  Hz, 2H), 7.45 (d,  $J = 7.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  (ppm) 22.9, 28.4, 80.7, 118.8, 123.0, 127.3, 129.1, 138.7, 143.8; MS (EI)  $m/z$  278 ( $M^+$ , 61), 180 (100), 165 (41), 152 (48). Anal. Calcd for  $C_{19}H_{18}O_2$ : C, 81.99; H, 6.52. Found: C, 81.90; H, 6.48.

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**Supporting Information Available:** Spectroscopic and analytical data for ketals **2b–1**. Absorption and ECD spectra of **2b–1** in acetonitrile. Absorption and ECD spectra of diol **1d** in acetonitrile. Comparison of the experimental (acetonitrile, red line) and predicted (TDDFT/B3LYP/6-31G\*, velocity formalism, blue line) ECD spectra of **2b–1**. Relative energies (kcal/mol) and optical rotation at the sodium D line (deg [ $dm\ g/cm^3$ ] $^{-1}$ ) of ketal **2l** with respect to the rotation of the Ph group around the Ph–C\* bond. All quantities have been obtained at the B3LYP/6-31G\* level, performing a relaxed scan of the Ph rotation with a  $20^\circ$  step in the angle. Optical rotation at the sodium D line of ketals **2d**, **2k**, and **2l** calculated with the method of sum-over-states. DFT/B3LYP/6-31G\* optimized geometries of all the conformers of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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