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Atropisomerism about Aryl−C(sp^3) Bonds: Conformational Behavior of Substituted Phenylcyclohexanes in Solution

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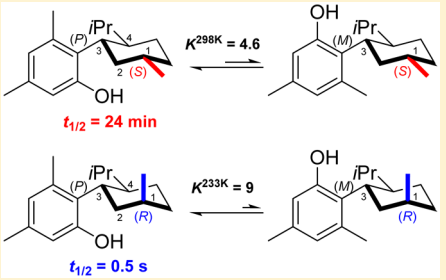
Supporting Information

ABSTRACT: A catalytic hydrogenation of cannabidiol derivatives known as phenylcyclohexenes was used to prepare epimeric (1*R*,1*S*) and/or rotameric (*M*,*P*) phenylcyclohexanes. The reaction is diastereoselective, in favor of the 1*S* epimer, when large groups are attached to the phenyl ring. For each epimer, variable-temperature NMR experiments, including EXSY spectroscopy and DFT calculations, were used to determine the activation energies of the conformational exchange arising from the restricted rotation about the aryl−C(sp^3) bond that led to two unequally populated rotamers. The conformational preference arises essentially from steric interactions between substituents vicinal to the pivot bond. The conformers of epimers (1*S*)-**2e,f** show high rotational barriers of up to 92 kJ mol^{-1}, unlike those of (1*R*)-**2e,f** and with much lower barriers of ∼72 kJ mol^{-1}. The height of the barriers not only depends on the substituents at the axis of chirality but also is influenced by the position of a methyl group on the monoterpene ring. The feature most favorable to high rotational barriers is when the methyl at C1 lies equatorially. This additional substituent effect, highlighted for the first time, seems fundamental to allowing atropisomerism in hindered ortho-substituted phenylcyclohexanes.



INTRODUCTION

Atropisomerism is associated principally with single bonds that join a pair of hindered planar groups, and the ortho-substituted biaryl atropisomers are of course by far the most well-known.[1] The resulting barrier to rotation is high enough to allow the isolation of conformational isomers. On the other hand, isolation of atropisomers originated from restricted rotation involving the tetrahedral carbon (about sp^2−sp^3 and sp^3−sp^3 C−C bonds) has been an attractive subject that has challenged chemists.[1−4] A review of high rotational barriers in fluorene and triptycene derivatives was first published by Ŏki.[2a] Separation and isolation of stable atropisomers have also been reported in hindered aryl carbinols.[3] Likewise, other atropisomers arising from the restricted rotation around aryl−C(sp^3) bonds have been isolated.[4] These compounds usually have bulky substituents on the aromatic ring at ortho positions, on the benzylic carbon, or on both. Apart from these rare examples, isolation of atropisomers from such bonds is generally not possible.

Moreover, Ŏki reported in 1990 that triptycene systems (with sp^3−sp^3 C−C bonds) can be used as probes for the detection of intramolecular weak yet attractive interactions as population ratios of the rotamers.[5] It can detect weak n → σ^* and n → π^* charge-transfer interactions as well as interactions involving a methyl group that could not be found in other systems. In the case of C(sp^2)−C(sp^3) single bonds, π−π interaction influencing the conformation of aromatic rings in isolable atropisomers of 2-arylindoline derivatives has also been demonstrated.[4a] Recently, we reported the stereoelectronic origins of the rotational control around aryl−C(sp^3) bonds through theoretical calculations in ortho-substituted phenylcyclohexene and epoxide derivatives of cannabidiol and linderatin.[6]

We now report studies of the conformational behavior in phenylcyclohexane derivatives obtained by catalytic hydrogenation of the corresponding phenylcyclohexenes displayed in Scheme 1.

Two major reasons motivated us. (1) Bioactive natural products having similar structures such as machaeridiols A and B[7a] and hydrogenated cannabidiol derivatives[7b] (Figure 1) attracted our attention because of the importance of axial chirality recognized in drug discovery.[8] (2) Molecular mechanics simulation of the rotation about C(sp^2)−C(sp^3) bonds at the MM2 level predicted atropisomerism in phenylcyclohexanes with partial or full methyl substitution around the pivot bond.[9]

RESULTS AND DISCUSSION

Synthesis of Phenylcyclohexane Diastereoisomers and Structure Determination by NMR. Eight phenylcyclohexanes **2a−h** carrying diverse ortho groups were

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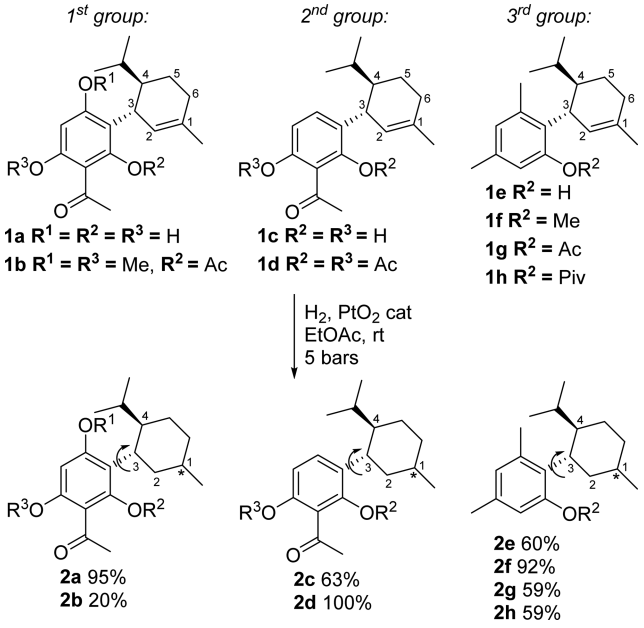
Scheme 1. Structures of the Synthesized Compounds (2a−h)



prepared (Scheme 1), with the aim of probing their potential for atropisomerism as previously done in phenylcyclohexenes **1a**, **1b**, and **1f−h** and their epoxide derivatives.[6] Therefore, these derivatives were classified into three categories according to the nature of the ortho substituents: (1) di-O-substituted compounds **2a,b** with hydroxyl or ether/ester groups, (2) mono-O-substituted substrates **2c,d** with a hydroxyl or ester group on one side and a smaller hydrogen atom on the other side, and (3) bulky methyl,O-substituted derivatives **2e−h** with hydroxyl, ether, or ester groups. In this work, we study both the diastereoselectivity of the hydrogenation reaction and the possible conformational exchange or atropisomerism in obtained phenylcyclohexanes **2a−h** by NMR experiments in solution. These compounds possess three stereogenic centers (C1, C3, and C4) with C1 generated, and a fourth element of chirality, i.e., the axis of chirality along the Car−C3 bond that can lead to conformers at room temperature,[10] as previously observed in their corresponding epoxide derivatives.[6] Consequently, the reaction could give complex mixtures of different diastereoisomers meaning two epimers 1*R* and 1*S* that can exist in turn as a mixture of two rotational diastereoisomers. In summary, four diastereoisomers, (1*R*,*M*), (1*R*,*P*), (1*S*,*M*), and (1*S*,*P*), could be obtained in variable ratios.

To assess the diastereoselectivity of the catalytic hydrogenation by reducing the number of diastereoisomers to two epimers (1*R* and 1*S*), phenylcyclohexene **1i** with a symmetrical aromatic moiety was selected (Scheme 2). Alkene **1i** was hydrogenated to yield a mixture of epimers (1*R*)-**2i** and (1*S*)-**2i** in a ratio of 10:90, while epoxidation of **1i** described in our previous study gives a single isomer.[11] Catalytic hydrogenation is therefore less diastereoselective than epoxidation.[6,11] However, hydrogenation occurs preferentially, as expected, on the less hindered face to give (1*S*)-**2i** as the major epimer.

This result shows that hydrogenation of **1a−h** with a nonsymmetrical phenyl group could also give minor epimers (1*R*)-**2a−h** as a mixture of two conformers, which makes the structural analysis of each diastereoisomer more difficult.

Compounds of the First Group. Hydrogenation of alkenes **1a,b** gave a mixture of two rotational diastereoisomers, (1*S*,*P*)-**2a,b** and (1*S*,*M*)-**2a,b** (Schemes 1 and 3). In this group, the reaction is totally diastereoselective, yielding epimers (1*S*)-**2a,b**. To demonstrate the interconversion between the two conformers, (1*S*)-**2b** isomers were analyzed by VT-2D EXSY spectroscopy (Figure 2). In the EXSY spectrum at 338 K, chemical exchange occurs between two signals assigned to the C3−H protons of conformers (1*S*,*P*)-**2b** and (1*S*,*M*)-**2b**. VT ^{1}H NMR experiments conducted on (1*S*)-**2b** conformers also confirm this conclusion by the coalescence of the two diastereomeric aromatic protons at 383 K in DMSO-d_6 (see spectra in the Supporting Information).

The structure of (1*S*,*P*)-**2b** and (1*S*,*M*)-**2b** obtained in a ratio of 40:60 in $CDCl_3$ could be identified with the aid of the chemical shift difference for C3−H protons in the ^{1}H NMR spectrum as previously observed in epoxide conformers.[6] As indicated in Scheme 3, the C3−H proton is observed at 3.18 ppm in minor rotamer (1*S*,*P*)-**2b** and at 2.57 ppm in major rotamer (1*S*,*M*)-**2b** in $CDCl_3$. This downfield shift, also observed in other solvents (see Table S1 of the Supporting Information), is caused by a deshielding effect of the oxygen lone-pair electrons of the ortho O substituent in front of C3−H. This means that important electronic interactions exist between C3−H and the ortho group in front, and the stronger interaction occurs with the OMe group in (1*S*,*P*)-**2b** with the most deshielded C3−H proton. The results of NOESY experiments conducted on (1*S*)-**2b** conformers in DMSO-d_6 are in agreement with these observations, and the significant correlations are specified in Scheme 3 (the full spectrum is shown in the Supporting Information).

For rotamers (1*S*,*P*)-**2a** and (1*S*,*M*)-**2a**, obtained in a ratio of 46:54 in CD_3OD, the C3−H chemical shifts are very close (2.98 and 3.07 ppm, respectively), which is not surprising in view of the similar nature of the substituents. Nonetheless, major rotamer (1*S*,*M*)-**2b** seems to have the most deshielded C3−H proton.

Moreover, (1*S*)-**2a** conformers were converted into (1*S*)-**2b** conformers in two steps (Scheme 3). As expected, the same ratio of 40:60 in $CDCl_3$ was found for conformers (1*S*,*P*)-**2b**

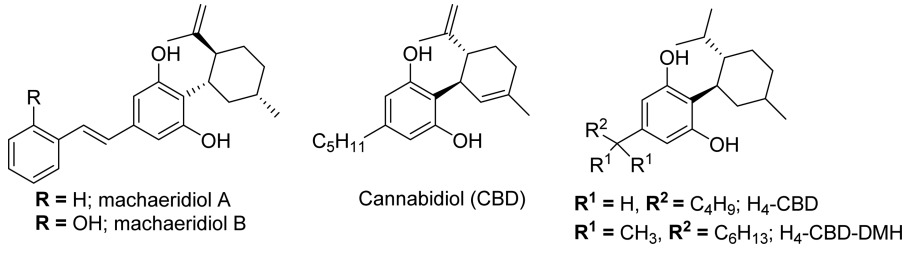


Figure 1. Structures of natural products and derivatives.

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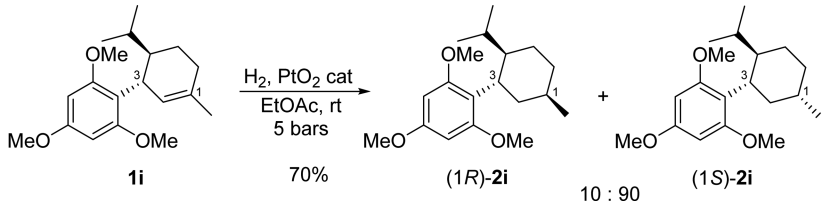
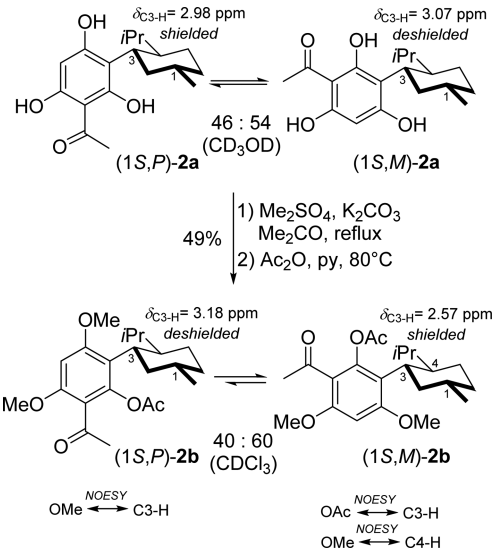
Scheme 2. Hydrogenation of 1i with a Symmetrically Substituted Aromatic Ring



Scheme 3. Conformational Analysis of (1*S*)-2a,b



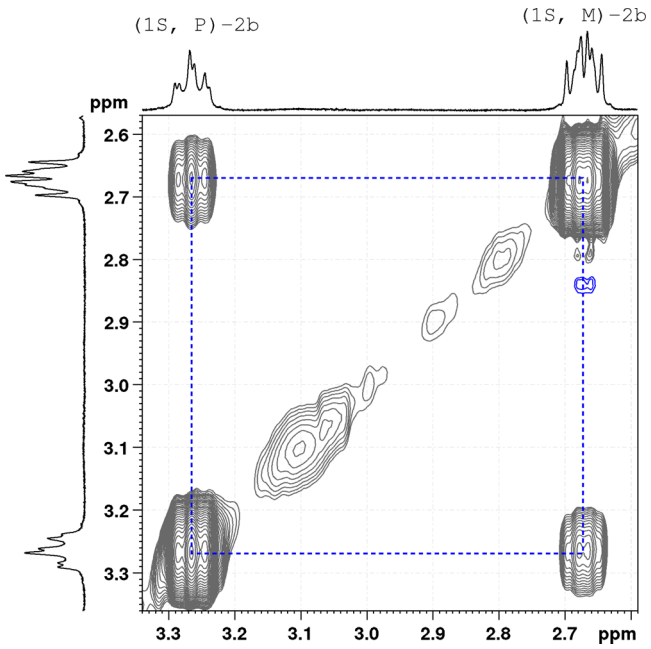
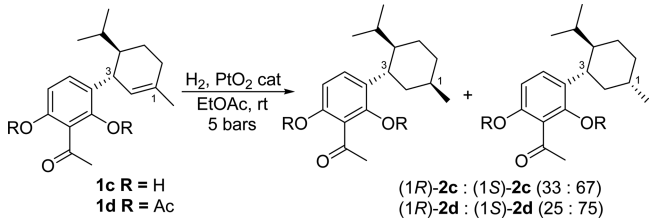


Figure 2. Expansion of the C3−H region of the 2D EXSY spectrum (500 MHz, mixing time of 0.2 s) of (1*S*)-**2b** in THF-d_8 at 338 K.

and (1*S*,*M*)-**2b**, which confirms the structure of these diastereoisomers.

Compounds of the Second Group. Hydrogenation of mono-O-substituted phenylcyclohexenes **1c,d** led to a mixture of two epimers (1*R*)-**2c,d** and (1*S*)-**2c,d** in ratios of 33:67 and 25:75, respectively (Schemes 1 and 4). The lack of correlation between the two signals corresponding to the C3−H protons in

Scheme 4. Synthesis of 2c and 2d Epimers



the NOESY/EXSY spectrum of **2d** at 293 K in DMSO-d_6 allowed us to identify unambiguously epimers (1*R*)-**2d** and (1*S*)-**2d** (Figure 3). In this family, the poor diastereoselectivity

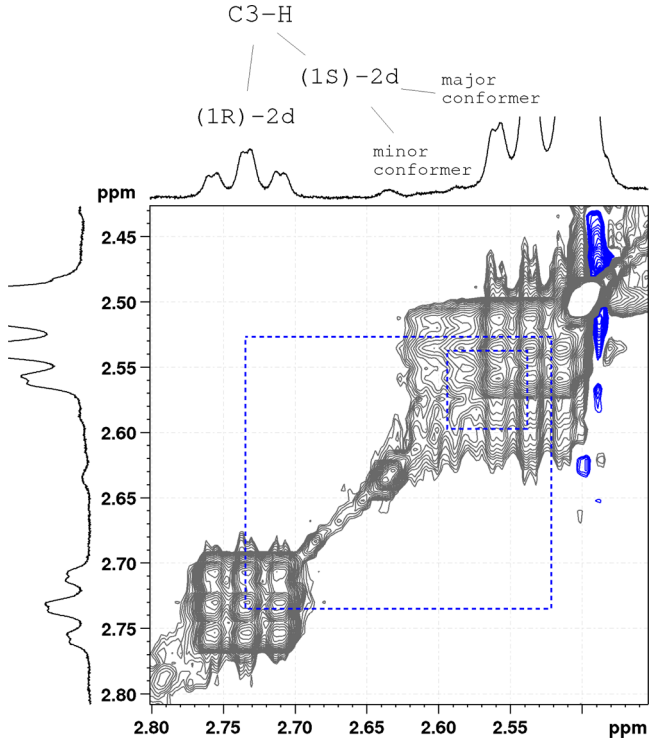


Figure 3. Expansion of the C3−H region of the 2D EXSY/NOESY spectrum (500 MHz, mixing time of 0.6 s) of **2d** in DMSO-d_6 at 293 K.

of hydrogenation can be explained by the fact that the phenyl ring is less substituted than in compounds **2a,b**. Furthermore, conformational analysis of this group is more difficult as much as conformers are not detectable in $CDCl_3$ at room temperature. Nevertheless, the EXSY spectrum displayed in Figure 3 also allowed us to highlight the presence of the very minor conformer of (1*S*)-**2d** (see also Figure S1 of the Supporting Information). These observations were verified by VT ^{1}H NMR investigations of **2d** (see spectra in the Supporting Information). The aromatic protons assigned to

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Scheme 5. Synthesis of 2e−h Diastereoisomers

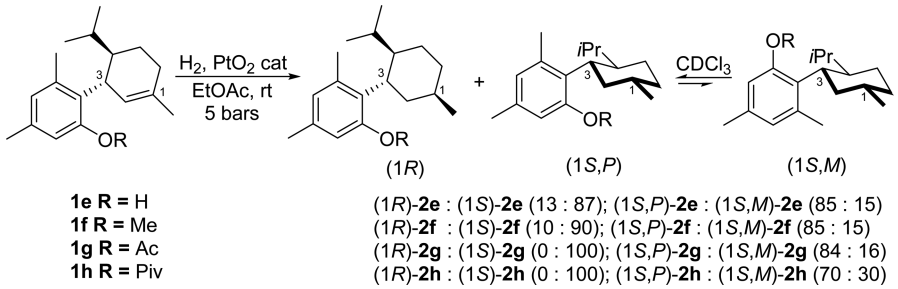
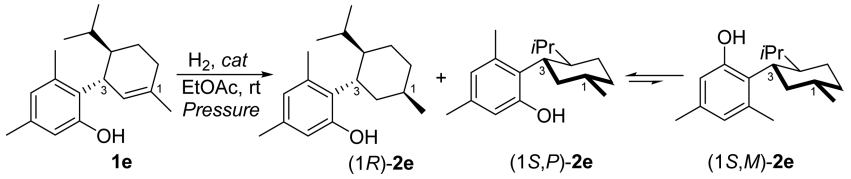


Table 1. Two Other Procedures of Catalytic Hydrogenation Applied to 1e



catalyst	pressure	yield in **2e** (%)	(1*R*)-**2e**:(1*S*)-**2e** epimeric ratio[a]	(1*S*,*P*)-**2e**:(1*S*,*M*)-**2e** conformational ratio[a]
PtO_2	atmospheric (∼1 bar)	38	30:70	87:13
Pd/C	5 bar	39	30:70	87:13

[a]Ratios measured from the ^{1}H NMR spectra in $CDCl_3$.

the very minor conformer of (1*S*)-**2d** were also detected at 293 K in DMSO-d_6 and at 213 K in THF-d_8.

Compounds of the Third Group. Hydrogenation of alkenes **1e−h** gave a mixture of three diastereoisomers in **2e,f** and a mixture of two rotational diastereoisomers in **2g,h** (Schemes 1 and 5). Indeed, compounds **2e** and **2f** exist as a mixture of epimers (1*R*)-**2e,f** and (1*S*)-**2e,f** in ratios of 13:87 and 10:90, respectively, and epimers (1*S*)-**2e,f** turn out to be a mixture of two conformers (1*S*,*P*)-**2e,f** and (1*S*,*M*)-**2e,f** in a ratio of 85:15 in $CDCl_3$ in both cases. Hydrogenation of **1e,f** is therefore not fully diastereoselective, unlike **1g,h** obtained as a mixture of two conformers (1*S*,*P*)-**2g,h** and (1*S*,*M*)-**2g,h** in ratios of 84:16 and 70:30 in $CDCl_3$, respectively. Consequently, the high diastereoselectivity of hydrogenation is significantly influenced by the presence of bulky substituents on the aromatic ring as observed in compounds (1*S*)-**2a,b**.

Moreover, the presence in **2e,f** at room temperature of both the minor epimer (1*R*) as a single compound and the major epimer (1*S*) as a mixture of two conformers is intriguing insofar as the restricted rotation about the aryl−C(sp^3) bond should occur in the same way for both epimers. A mixture of four diastereoisomers should therefore be obtained.

Separation of epimers (1*S*)-**2e** and (1*R*)-**2e** by chromatography (column and HPLC) was attempted to study their conformational process individually. For this reason, two other procedures of catalytic hydrogenation (variation of the pressure or change of catalyst) were employed to obtain a larger amount of minor epimer (1*R*)-**2e** (Table 1). For both procedures, epimeric ratios of ∼30:70 (1*R*:1*S*) were obtained but with poor yields. Unfortunately, three spots with two of them very close to each other appear on TLC corresponding to the 1*R* epimer and the two atropisomers of the 1*S* epimer, which made the isolation of each epimer difficult.[12] Nonetheless, efforts in separation by preparative TLC allowed us to collect an enriched fraction in epimer (1*R*)-**2e** with a ratio of 45:55 (1*R*:1*S*); its ^{1}H NMR spectrum is shown in Figure 4b.

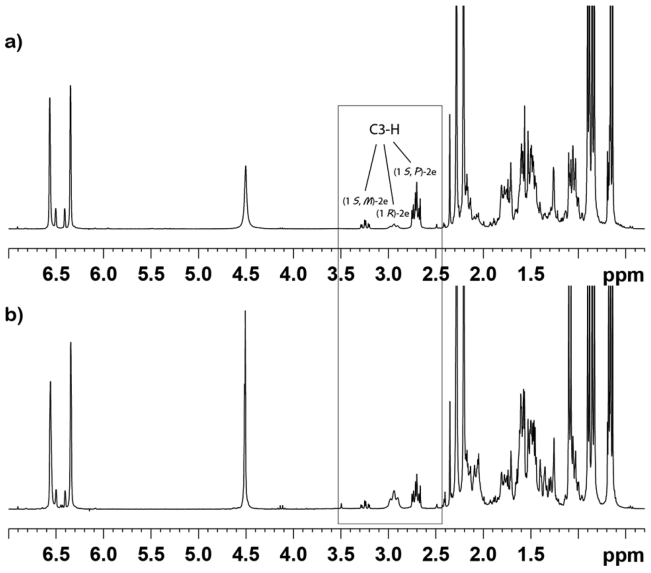


Figure 4. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of **2e** at rt (a) from PtO_2 catalytic hydrogenation at 5 bar [(1*R*)-**2e**:(1*S*)-**2e** dr of 13:87] and (b) from PtO_2 catalytic hydrogenation at 1 bar after preparative TLC separation [(1*R*)-**2e**:(1*S*)-**2e** dr of 45:55].

In the ^{1}H NMR spectra in $CDCl_3$ at room temperature (Figure 4), a very broad signal for the benzylic C3−H proton is assigned to epimer (1*R*)-**2e**, meaning that the rotation at the Car−C3 bond is restricted but not enough to observe conformers contrary to epimer (1*S*)-**2e**. These observations were demonstrated by VT NMR experiments (^{1}H 1D and 2D EXSY spectroscopy). The most significant results were obtained by exchange spectroscopy (Figure 5), which is better suited to the analysis of such complex mixtures than VT ^{1}H NMR spectroscopy (see spectra in the Supporting Information). Figure 5 shows that the two conformers of (1*R*)-**2e** do interconvert at room temperature in DMSO-d_6 and at a lower

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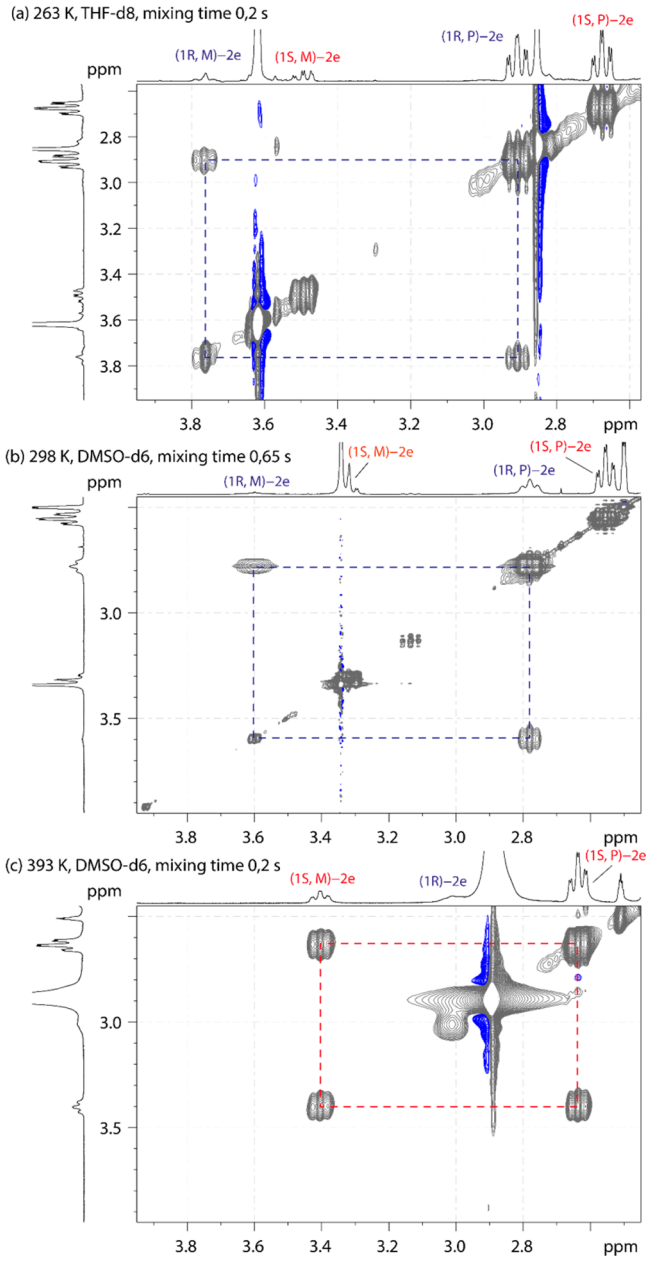

Figure 5. Expansion of the C3–H region of the VT 2D EXSY spectra of **2e** at 500 MHz.

temperature (263 K) in THF-d_8, while exchange occurs at only a much higher temperature (393 K) in (1*S*)-**2e** atropisomers.

To support these results, phenol **2e** as a mixture of three diastereoisomers was also converted into its methyl ether **2f**, acetate **2g**, and pivalate **2h** (Scheme 6). As expected, the obtained 1*R*:1*S* epimeric ratios of **2f–h** are similar to those of **2e**, and the conformational ratios in $CDCl_3$ of (1*S*,*P*)-**2f,g** and (1*S*,*M*)-**2f,g** come closer to those obtained from hydrogenation seen in Scheme 5.

The identity of atropisomers (1*S*,*P*)-**2e–h** and (1*S*,*M*)-**2e–h** was deduced by ^{1}H NMR spectroscopy from the shielding/deshielding effect of the oxygen lone-pair electrons of one ortho substituent on the C3–H proton chemical shift as done in conformers of (1*S*)-**2a,b**. In the ^{1}H NMR spectra in $CDCl_3$, the C3–H proton is observed at 2.73, 2.67, 2.73, and 2.72 ppm in major conformers (1*S*,*P*)-**2e–h** and at 3.28, 3.45, 2.83, and 2.88 ppm in minor conformers (1*S*,*M*)-**2e–h**, respectively (Figure 6). These observations are in agreement with the results of NOESY experiments conducted on conformers of (1*S*)-**2e** also displayed in Figure 6 (see the NOESY spectrum in full in the Supporting Information). It is also noteworthy that, in each case, the *P* conformer predominates. The rationale about the conformational preference is discussed below in Computational Studies.

Epimers (1*R*)-**2e,f** were obtained as single compounds in each case at room temperature in $CDCl_3$. VT NMR experiments were then conducted at low temperatures, and two rotamers (*P*:*M*) become evident in a ratio of 90:10 at 233 K for (1*R*)-**2e** and 95:5 at 273 K for (1*R*)-**2f** in THF-d_8, which is surprisingly diastereoselective (Figure 7). Here again, they could be identified by chemical shift variations of the C3–H proton in the ^{1}H NMR or 2D EXSY spectra.

The highlighted difference in the rotation rate about the Car–C3 bond between epimers (1*R*)-**2e,f** and (1*S*)-**2e,f** remains intriguing, and although quite distant from the chiral axis, the methyl at C1 plays evidently an important role. These epimers differ from each other only by the position of the methyl group at C1, which is at axial in the 1*R* epimer and lies equatorially in the 1*S* epimer.

Determination of Kinetic and Activation Parameters by VT NMR Experiments. EXSY spectra can also be employed to measure rate constants of interconversions in the range from ~0.05 to 20 s^{-1}.[13] We were thus able to obtain rate constants of the aryl–C(sp^3) bond rotation in ortho-substituted phenylcyclohexanes (1*S*)-**2b,e,f** and (1*R*)-**2e,f** at low temperatures for 1*R* epimers and at high temperatures for 1*S* epimers.[13b] Activation parameters were then determined at 298 K from the Eyring plots of the corresponding rates of interconversion obtained by EXSY spectroscopy (Table 2; see also Table S3 and details in the Supporting Information).

The highest bond rotation barriers (≥91 kJ mol^{-1}) were obtained for (1*S*)-**2e,f** atropisomers (Table 2, entries 2 and 4) bearing a bulkier ortho methyl group in contrast to (1*S*)-**2b** rotamers (Table 2, entry 1) with lower barriers (≈85 kJ mol^{-1}).

Furthermore, the difference in barriers to rotation between conformers of epimers (1*R*)-**2e,f** and (1*S*)-**2e,f** is confirmed, but the obtained large value of ~20 kJ mol^{-1} is very surprising. This huge difference in rotational barriers, due to only the position of the methyl at C1, may be attributed to the influence of the cyclohexane ring inversion on the interconversion around the indicated Car–C3 bond. The equatorial methyl in 1*S* epimer conformers has less freedom with respect to cyclohexane ring inversion unlike the axial methyl in 1*R* epimer conformers, which makes them less stable at this position and therefore more flexible to conformational change. The position of the methyl group at C1 is therefore effective in increasing or decreasing the rotational barriers in phenyl-cyclohexane conformers.

The $\Delta G_c^{\ddagger}$ values were also determined for (1*S*)-**2b,d,e,i** and (1*R*)-**2e** conformers by VT ^{1}H NMR experiments at coalescence temperatures from approximate equations[14] displayed in Table 3 (see also Table S2; spectra and details in the Supporting Information). Although this method gives crude estimates of the rate of the aryl–C(sp^3) bond rotation in these rotamers, we found that the values match with those obtained by EXSY spectroscopy for (1*S*)-**2b** and (1*R*)-**2e** conformers even if they are slightly higher in (1*S*)-**2b** conformers and lower in (1*R*)-**2e** conformers. For (1*S*)-**2e** conformers, the values obtained from VT ^{1}H NMR experi-

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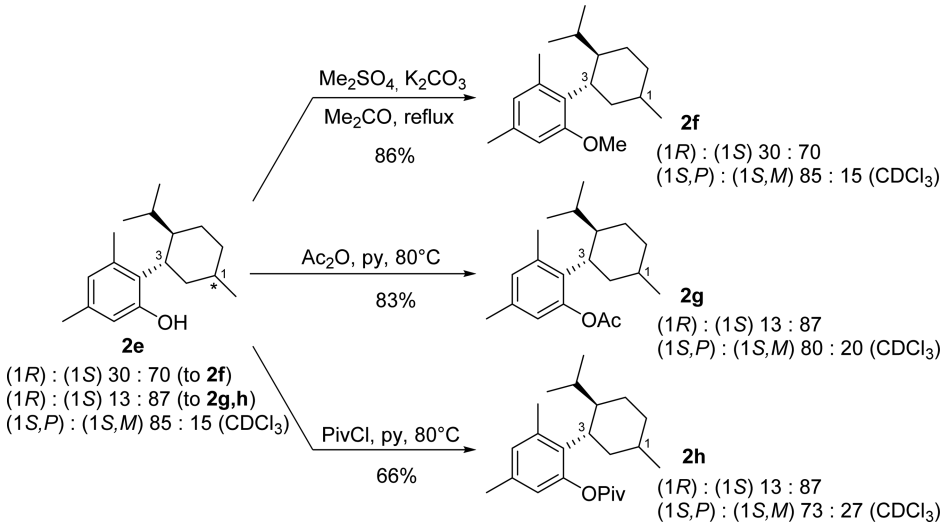
Scheme 6. Synthesis of 2f–h Diastereoisomers from 2e Diastereoisomers



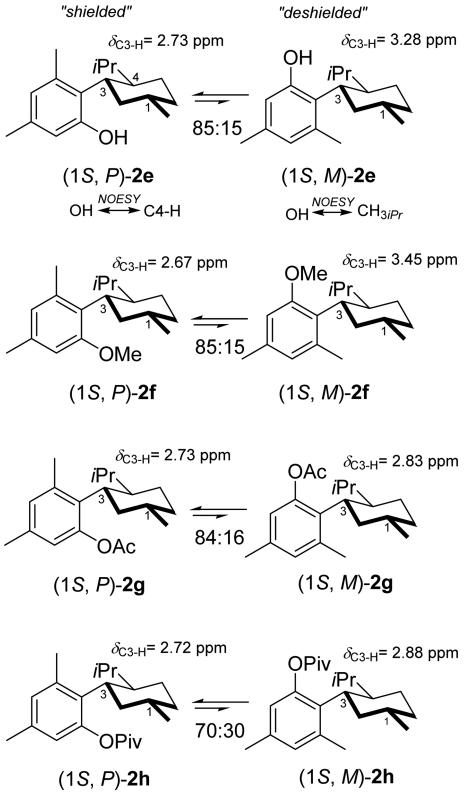


Figure 6. Conformational analysis based on the ^{1}H NMR spectra of (1*S*)-**2e–h** in $CDCl_3$ and on significant NOESY correlations in (1*S*)-**2e** in DMSO-d_6 at rt.

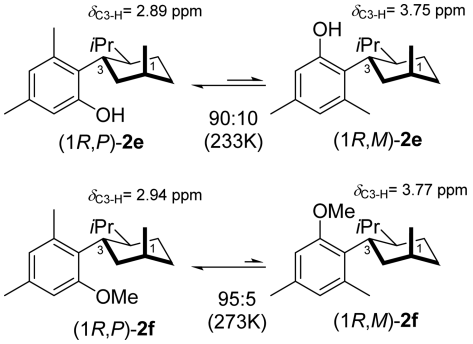


Figure 7. Conformational analysis based on the ^{1}H NMR and 2D EXSY spectra of (1*R*)-**2e,f** at low temperatures in THF-d_8.

Table 2. Activation Parameters of Phenylcyclohexane (1*S*)-2b,e,f and (1*R*)-2e,f Conformers at 298 K by VT 2D EXSY Spectroscopy

entry	compd	k (s^{-1}),[a,d] $k_{(P\rightarrow M)}$, $k_{(M\rightarrow P)}$	$\Delta G^{\ddagger}$ (kJ mol^{-1}),[b,d] $\Delta G^{\ddagger}_{(P\rightarrow M)}$, $\Delta G^{\ddagger}_{(M\rightarrow P)}$	$t_{1/2}$ (s),[c,d] $t_{1/2(P\rightarrow M)}$, $t_{1/2(M\rightarrow P)}$
1	(1*S*)-**2b**	0.009 ± 0.0005	84.6 ± 0.1	76 ± 4
		0.008 ± 0.0008	85.1 ± 0.3	90 ± 10
2	(1*S*)-**2e**	0.0005 ± 0.00002	91.9 ± 0.1	1434 ± 60
		0.002 ± 0.0002	88.5 ± 0.2	364 ± 30
3	(1*R*)-**2e**	1 ± 0.7	72.4 ± 1.1	0.5 ± 0.3
		11 ± 4	67.1 ± 0.8	0.06 ± 0.02
4	(1*S*)-**2f**	0.0007 ± 0.0001	91.1 ± 0.5	1038 ± 200
		0.003 ± 0.0004	87.7 ± 0.4	263 ± 40
5	(1*R*)-**2f**	0.7 ± 0.03	73.8 ± 0.1	0.9 ± 0.04
		8 ± 0.3	67.8 ± 0.1	0.09 ± 0.004

[a]Rate constants at 298 K. [b]Free energies of activation for bond rotation at 298 K. [c]Half-lives for interconversion at 298 K. [d]Error limits obtained from those reported for the slopes and intercepts in the Eyring plots.

ments are not reliable because only coalescing OH signal is not suitable. Indeed, proton exchanges could also occur with the water present in the deuterated solvent (DMSO-d_6) at high temperatures. To avoid this, another compound of the "third-family" (1*S*)-**2h** with two distinct Har signals for the two atropisomers and without the 1*R* epimer was chosen to follow up VT ^{1}H NMR studies. Remarkably, no coalescence of ^{1}H NMR signals was observed up to 423 K in (1*S*)-**2h** atropisomers, which means that the barriers to rotation at coalescence are higher than at 298 K in these rotamers. Accordingly, barriers to bond rotation seem to increase slightly with the temperature as also observed in (1*S*)-**2b** and (1*R*)-**2e** conformers and thus become temperature-dependent due to the sign of the entropy of activation. The discussion of the sign of $\Delta S^{\ddagger}$ is further developed in the next part with the computed values.

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J. Org. Chem. 2016, 81, 2372–2382

Table 3. Activation Parameters of Phenylcyclohexane (1*S*)-2b,d,e,i and (1*R*)-2e Conformers at Coalescence Determined by VT ^{1}H NMR Spectroscopy

entry	compd	coalescing signal	T_c (K)[a]	k_c (s^{-1}),[b] $k_{(P\rightarrow M)}$, $k_{(M\rightarrow P)}$	$\Delta G_c^{\ddagger}$ (kJ mol^{-1}),[c] $\Delta G^{\ddagger}_{(P\rightarrow M)}$, $\Delta G^{\ddagger}_{(M\rightarrow P)}$
1	(1*S*)-**2b**	Har	383	6	88.7
				9	87.5
2	(1*S*)-**2d**	Har	303	7	69.3
				81	63.1
3	(1*S*)-**2e**	OH	408	26	90.1
				145	84.2
4	(1*R*)-**2e**	OH	288	11	64.6
				101	59.5
5	(1*S*)-**2i**	Har	378	84	83.8

[a]Coalescence temperature (±5 K). [b]Rate constants at T_c. [c]Free energies of activation (±0.5−1.2 kJ mol^{-1}) for bond rotation at T_c.

With regard to the second group of compounds, lower barriers of around 69 and 63 kJ mol^{-1} were obtained for mono-O-substituted (1*S*)-**2d** conformers. Barriers decreased considerably over those of other di-ortho-substituted (1*S*)-phenylcyclohexanes [(1*S*)-**2b,e,i**], confirming the importance of the two ortho substituents.

Computational Studies. DFT computation[15] conducted on (1*S*)-**2b,e,f** and (1*R*)-**2e,f** also provided the thermodynamic and geometrical parameters of their conformers and transition states (Figure 8 and Table 4; see also Tables S4−S6 and details in the Supporting Information). Figure 8 shows the structures of the lowest-energy conformers and located transition states of epimers (1*S*)-**2e** and (1*R*)-**2e**, including their energetic barriers at 298 K. In (1*S*)-**2e** atropisomers, the computed values agree well with those determined by VT 2D EXSY experiments (Table 2, entry 2). In (1*R*)-**2e** conformers, the computed barriers, although slightly higher than those obtained experimentally, remain close to them (Table 2, entry 3). It is also noteworthy that there is a marked difference between the two TS structures [TS (1*S*)-**2e** and TS (1*R*)-**2e**] because of the position of the methyl group at C1, which should explain the large change in rotational barriers found experimentally. With regard to the cyclohexane moiety, a similar "boat" conformation characterizes the transition state structures in both epimers. However, a difference of almost 10° was calculated between the C6−C5−C4−C3 dihedral angles of TS (1*S*)-**2e** and TS (1*R*)-**2e** (45.28° vs 32.68° displayed in Table S5 of the Supporting Information). This difference could be assumed by the position of the methyl at C1, which directly influences the energetic cost of the cyclohexane ring inversion. Indeed, in TS (1*S*)-**2e**, the methyl at C1 and the substituted phenyl are axially on the same face of the cyclohexane ring and so interfere with each other, while only the phenyl is in the axial position in TS (1*R*)-**2e**. Therefore, the phenyl ring in TS (1*R*)-**2e** could easily rotate around the pivot bond unlike in TS (1*S*)-**2e**.

Table 4. Theoretical Thermodynamic Parameters of (1*S*)-2b,e,f and (1*R*)-2e,f Conformers at 298 K Calculated at the PCM/M06-2X/6-31G(d,p) Level of Theory

compd	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (kJ mol^{-1})
(1*S*)-**2b**$_{(M\rightarrow P)}$	81.3	−26.7	89.3
(1*S*)-**2e**$_{(P\rightarrow M)}$	85.5	−26.1	93.3
(1*R*)-**2e**$_{(P\rightarrow M)}$	74.9	−28.6	83.5
(1*S*)-**2f**$_{(P\rightarrow M)}$	87.2	−22.3	93.8
(1*R*)-**2f**$_{(P\rightarrow M)}$	79.1	−35.1	89.6

Table 4 reports the complete computed thermodynamic parameters of one conformer in (1*S*)-**2b,e,f** and (1*R*)-**2e,f**. As mentioned above, the theoretical barriers correlate reasonably with the experimental values. Table 4 shows also that $\Delta S^{\ddagger}$ values are small, in the range of −22.3 to −35.1 J mol^{-1} K^{-1}. Moreover, the negative sign of the entropies of activation, indicative of highly organized transition states, is in accordance with the experimental results (see Table S3 of the Supporting Information).[16] The influence of temperature on the rotational barriers is therefore confirmed in these substrates.

The identity of (1*S*)-**2b,e,f** and (1*R*)-**2e,f** conformers was also confirmed by computed ^{1}H NMR chemical shifts of C3−H (see Table S7 of the Supporting Information). To explain the conformational control in these compounds, the second-order

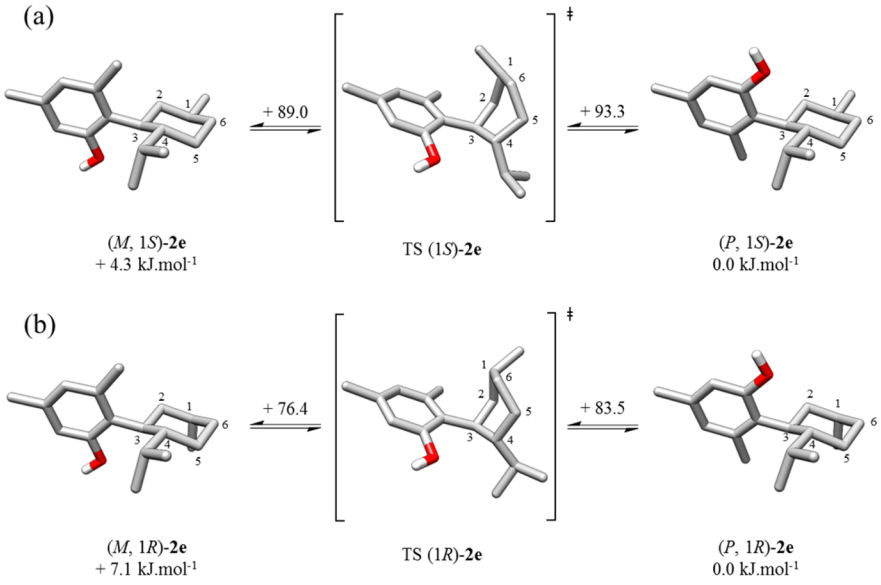

Figure 8. Structures and activated energies associated with the interconversion between (1*S*,*P*)-**2e** and (1*S*,*M*)-**2e** through TS (1*S*)-**2e** (a) and between (1*R*,*P*)-**2e** and (1*R*,*M*)-**2e** through TS (1*R*)-**2e** (b) at the PCM/M06-2X/6-31G(d,p) level of theory.

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perturbation energy $E(2)$ of donor−acceptor interactions in the NBO basis was calculated for each conformer of (1*S*)-**2b,e,f** and (1*R*)-**2e,f** at the IEFPCM/M06-2X/6-31G(d,p) level of theory (Table 5). Interestingly, the main electronic stabilization

Table 5. NBO Values of $E(2)$ (kilojoules per mole) and Relative Gibbs Free Energies (kilojoules per mole) for (1*S*)-2b,e,f and (1*R*)-2e,f Conformers at the IEFPCM/M06-2X/6-31G(d,p) Level of Theory

compd	$O_{lp} \rightarrow \sigma^*_{C2-H}$	$O_{lp} \rightarrow \sigma^*_{C4-H}$	$O_{lp} \rightarrow \sigma^*_{C3-H}$	total	ΔG_r°
(1*S*,*P*)-**2b**	3.6	ND[a]	6.6	10.2	0.88
(1*S*,*M*)-**2b**	2.1	4.6	2.9	9.6	
(1*S*,*P*)-**2e**	ND[a]	6.1		6.1	4.3
(1*S*,*M*)-**2e**			7.5	7.5	
(1*R*,*P*)-**2e**	ND[a]	5.9		5.9	7.1
(1*R*,*M*)-**2e**			8.2	8.2	
(1*S*,*P*)-**2f**	ND[a]	6.1		6.1	5.71
(1*S*,*M*)-**2f**			7.5	7.5	
(1*R*,*P*)-**2f**	ND[a]	5.1		5.1	7.00
(1*R*,*M*)-**2f**			8.1	8.1	

[a]Not determined (<2 kJ mol^{-1}).

by donor−acceptor charge-transfer interactions ($O_{lp} \rightarrow \sigma^*_{C3-H}$) is in favor of the minor conformers [(1*S*,*P*)-**2b**, (1*S*,*M*)-**2e,f**, and (1*R*,*M*)-**2e,f**] according to the NBO analysis. Despite a tentative lowering of the energetic threshold in the NBO basis (from 2 to 0.4 kJ mol^{-1}), the sum of the amounts of the charge transfer between the donor and acceptor is again in favor of the minor conformer in each case. It seems that the conformational equilibrium in these compounds is mainly driven by van der Waals interactions that counterbalance the favoring electronic interactions in the minor conformer. Today, quantifications of van der Waals interactions constitute a challenge in modern quantum chemistry. However, the NCI approach (NCI plot software) allows us to visualize these interactions (see Figure S2 of the Supporting Information).[17] Therefore, steric effects by van der Waals repulsion between the most bulky ortho group (acetyl or methyl) and the 2,4-diaxial C−H bonds could occur and destabilize these conformers despite the favoring electronic interactions. The conformational preference is thus mainly due to steric effects between substituents in close contact with each other on the two cycles. Likewise, these results could be extended to explain the stereoselectivity observed in the atropisomers of (1*S*)-**2g,h**. Notably, the best diastereoselectivity is attained in (1*R*)-**2e,f** conformers, followed by (1*S*)-**2e,f** atropisomers all bearing a hindered methyl group at the ortho position.

CONCLUSION

Some new cannabidiol and machaeridiol derivatives known as phenylcyclohexanes (**2a−i**) were synthesized by a catalytic hydrogenation as mixtures of two or three diastereoisomers. Spectroscopic NMR techniques were employed to analyze them and differentiate those originating from the prochiral center (C1) and those arising from the prochiral sp^2-sp^3 axis. The structures of each conformer in (1*S*)-**2a−i** and (1*R*)-**2e,f** were determined by means of ^{1}H NMR and/or 2D EXSY/NOESY spectra, and those for (1*S*)-**2b,e,f** and (1*R*)-**2e,f** were also confirmed by DFT computation, which also identified their transition structures. The NBO calculation was also applied to explain the conformational control in (1*S*)-**2b,e,f** and (1*R*)-**2e,f** conformers that is mainly due to steric interactions between the most hindered ortho group and two diaxial C−H bonds on the cyclohexane ring. Rotational barriers were determined by either VT 2D EXSY or VT ^{1}H NMR methods in (1*S*)-**2b,e,f** and (1*R*)-**2e,f** conformers, which were reasonably in line with the computed data. Comparison of both methods showed that barriers increase slightly with temperature. Mostly, we have demonstrated that atropisomerism is only reached with an equatorial methyl group at C1 and hindered ortho substituents in phenylcyclohexane (1*S*)-**2e−h** atropisomers, while an axial methyl decreases significantly the rotational barriers (of ∼20 kJ mol^{-1}) in the same ortho-substituted (1*R*)-**2e,f** rotamers. The computed transition state for the interconversion of the conformers in each epimer rationalizes this rotational energetic difference. The height of the barriers to rotation about the pivot bond in phenylcyclohexanes not only is ortho substituent-dependent but also is influenced by the axial versus equatorial positions of other substituents on the cyclohexane ring.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed under a N_2 atmosphere using oven-dried glassware unless otherwise noted. All organic solvents and reagents were commercially available and used without further purification unless indicated otherwise. Reactions were monitored by thin-layer chromatography (TLC) using silica gel 60-covered alumina plates F_{254}. TLC plates were viewed under UV light and stained using vanillin. Flash column chromatography was performed on silica gel (60A C.C 35−70 μm). Yields reported were for isolated, spectroscopically pure compounds that can exist as mixtures of diastereoisomers. ^{1}H NMR and ^{13}C NMR experiments were conducted on a 300 MHz instrument at ambient temperature unless otherwise noted. The residual solvent protons (^{1}H) or the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shifts in parts per million downfield from TMS (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. High- and low-mass spectra were recorded by electronic impact (EI) on a Mass Spectroscopy Quadripolar instrument (MSQ).

Compounds **1a−i** have been described in the literature.[6,11]

General Procedure for Catalytic Hydrogenation of 1a−i. **1a−i** and PtO_2 (10%) in ethyl acetate were placed under 5 bar of H_2 at rt. The reaction mixture was stirred for 24 h. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography to give **2a−i** as mixtures of diastereoisomers.

For compounds **2e,f** obtained as a mixture of three diastereoisomers [(1*R*)-**2e,f**, (1*S*,*P*)-**2e,f**, and (1*S*,*M*)-**2e,f**] and **2i** as a mixture of two epimers [(1*R*)-**2i** and (1*S*)-**2i**], analytical data were described only for major (1*S*) diastereoisomers.

*(P,M)-1-{2,4,6-Trihydroxy-3-[(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl]phenyl}ethanone (**2a**).* A mixture of two rotamers (335 mg, 95%) as an amorphous solid: dr 46:54 (1*S*,*P*:1*S*,*M*); R_f = 0.24 (CH_2Cl_2/EtOAc, 96:4); ^{1}H NMR (300 MHz, CD_3OD) δ 5.87 (s, 0.46H), 5.83 (s, 0.54H), 3.07 (dt, J = 3.2 Hz, 11.5 Hz, 0.54H), 2.98 (dt, J = 3.2 Hz, J = 11.7 Hz, 0.46H), 2.59 (s, 1.38H), 2.58 (s, 1.62H), 2.18 (m, 1H), 1.85−1.58 (m, 3H), 1.55−1.32 (m, 3H), 1.11−0.90 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.66 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 203.1 (C), 202.9 (C), 164.9 (C), 163.8 (C), 163.3 (C), 162.3 (C), 160.0 (C), 109.4 (C), 109.2 (C), 104.0 (C), 103.7 (C), 93.7 (CH), 93.1 (CH), 43.1 (CH), 42.8 (CH), 39.4 (CH_2), 39.0 (CH_2), 37.2 (CH), 36.7 (CH), 35.2 (CH_2), 33.3 (CH), 31.4 (CH_3), 31.3 (CH_3), 28.1 (CH), 28.06 (CH), 24.9 (CH_2), 21.5 (CH_3), 20.5 (CH_3), 14.7 (CH_3), 14.6 (CH_3); MS (EI) m/z (relative intensity, %) 306 (M^+, 32), 221 (46), 181 (100), 95 (40); HRMS (EI-TOF) m/z calcd for $C_{18}H_{26}O_4$ 306.1831, found

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306.1834. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.81; H, 8.75.

*(P,M)-2-Acetyl-6-[(1S,2R,5S)-2-isopropyl-5-methycyclohexyl]-3,5-dimethoxyphenyl Acetate (**2b**).* A mixture of two rotamers (17 mg, 20%) as a liquid: dr 40:60 (1*S*,*P*:1*S*,*M*); R_f = 0.21 (petroleum ether/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 0.4H), 6.34 (s, 0.6H), 3.86 (s, 1.2H), 3.853 (s, 1.8H), 3.85 (s, 3H), 3.18 (dt, *J* = 3.4 Hz, *J* = 11.6 Hz, 0.4H), 2.57 (ddd, *J* = 6.5 Hz, *J* = 8.8 Hz, *J* = 11.1 Hz, 0.6H), 2.47 (s, 1.2H), 2.46 (s, 1.8H), 2.25 (s, 1.8H), 2.23 (s, 1.2H), 2.04 (m, 0.6H), 1.85−1.62 (m, 2H), 1.61−1.51 (m, 2H), 1.50−1.30 (m, 2.4H), 1.21−0.89 (m, 2H), 0.88 (d, *J* = 6.0 Hz, 1.2H), 0.87 (d, *J* = 6.3 Hz, 1.8H), 0.81 (d, *J* = 7.0 Hz, 1.8H), 0.78 (d, *J* = 6.9 Hz, 1.2H), 0.64 (d, *J* = 6.9 Hz, 1.2H), 0.63 (d, *J* = 6.9 Hz, 1.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9 (C), 200.1 (C), 169.4 (C), 169.3 (C), 161.3 (C), 160.0 (C), 157.0 (C), 156.7 (C), 147.5 (C), 147.1 (C), 119.2 (C), 118.6 (C), 117.2 (C), 116.3 (C), 93.4 (CH), 92.6 (CH), 55.8 (CH_3), 55.7 (CH_3), 55.6 (CH_3), 55.3 (CH_3), 45.1 (CH), 43.6 (CH), 40.6 (CH_2), 40.0 (CH), 39.4 (CH_2), 37.3 (CH), 35.7 (CH_2), 35.2 (CH_2), 33.6 (CH), 33.5 (CH), 32.0 (CH_3), 31.5 (CH_3), 28.4 (CH), 28.1 (CH), 25.3 (CH_2), 25.0 (CH_2), 22.4 (CH_3), 21.62 (CH_3), 21.6 (CH_3), 21.4 (CH_3), 20.7 (CH_3), 15.7 (CH_3), 15.3 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 376 (M^+, 14), 334 (40), 249 (56), 209 (100); HRMS (EI-TOF) *m*/*z* calcd for $C_{22}H_{32}O_5$ 376.2250, found 376.2261. Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.19; H, 8.57. Found: C, 70.52; H, 8.81.

*(5SR)-1-{2,6-Dihydroxy-3-[(1S,2R)-2-isopropyl-5-methylcyclohexyl]phenyl}ethanone (**2c**).* A mixture of two epimers (63 mg, 63%) as a liquid: dr 67:33 (1*S*:1*R*); R_f = 0.36 (petroleum ether/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.4 (br s, 0.67H), 12.3 (br s, 0.33H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.53 (br s, 1H), 6.28 (d, *J* = 8.6 Hz, 0.67H), 6.27 (d, *J* = 8.3 Hz, 0.33H), 3.12 (m, 0.33H), 2.96 (dt, *J* = 3.1 Hz, *J* = 11.3 Hz, 0.67H), 2.745 (s, 2.01H), 2.74 (s, 0.99H), 2.00 (m, 0.33H), 1.86−1.67 (m, 2.01H), 1.65−1.11 (m, 5.32H), 1.08 (d, *J* = 7.2 Hz, 0.99H), 1.03−0.75 (m, 6.35H), 0.71−0.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9 (C), 161.0 (C), 160.7 (C), 156.9 (C), 134.7 (CH), 134.1 (CH), 125.8 (C), 109.8 (C), 106.5 (CH), 106.3 (CH), 47.2 (CH), 46.8 (CH), 44.5 (CH_2), 40.8 (CH_2), 34.0 (CH), 35.3 (CH_2), 33.6 (CH_3), 33.1 (CH), 31.9 (CH_2), 28.1 (CH), 27.8 (CH), 27.6 (CH), 24.6 (CH_2), 22.4 (CH_3), 21.6 (CH_3), 21.4 (CH_3), 18.8 (CH_2), 17.8 (CH_3), 15.8 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 290 (M^+, 43), 272 (12), 205 (59), 165 (100), 95 (25); HRMS (EI-TOF) *m*/*z* calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1888.

*(5SR)-2-Acetyl-4-[(1S,2R)-2-isopropyl-5-methylcyclohexyl]-1,3-phenylene Diacetate (**2d**).* A mixture of two epimers (22 mg, 100%) as a liquid: dr 75:25 (1*S*:1*R*); R_f = 0.26 (petroleum ether/EtOAc, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 0.75H), 7.04 (d, *J* = 8.6 Hz, 0.25H), 2.83 (dt, *J* = 5.2 Hz, *J* = 10.6 Hz, 0.25H), 2.57 (dt, *J* = 3.1 Hz, *J* = 11.5 Hz, 0.75H), 2.45 (s, 3H), 2.28 (s, 6H), 2.03 (m, 0.25H), 1.88−1.65 (m, 2.25H), 1.60 (m, 0.5H), 1.58−1.33 (m, 3.75H), 1.18−0.93 (m, 3H), 0.93−0.76 (m, 5.25H), 0.69−0.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3 (C), 169.0 (C), 168.8 (C), 168.6 (C), 145.1 (C), 145.0 (C), 136.9 (C), 129.4 (CH), 129.1 (CH), 127.7 (C), 120.6 (CH), 47.2 (CH), 47.0 (CH), 44.1 (CH_2), 41.0 (CH), 39.6 (CH), 35.0 (CH_2), 33.2 (CH), 31.9 (CH_2), 31.1 (CH_3), 27.7 (CH), 27.6 (CH), 27.5 (CH), 24.5 (CH_2), 22.3 (CH_3), 21.6 (CH_3), 21.1 (CH_3), 20.7 (CH_3), 18.5 (CH_2), 17.4 (CH_3), 15.6 (CH_3), 15.5 (CH_3), 14.1 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 374 (M^+, 3), 332 (38), 314 (2), 290 (100), 272 (20), 205 (34), 165 (61); HRMS (EI-TOF) *m*/*z* calcd for $C_{22}H_{30}O_5$ 374.2093, found 374.2105.

*(P,M)-2-[(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl]-3,5-dimethylphenol (**2e**).* A mixture of two atropisomers (362 mg, 60%) as a yellow liquid: dr 85:15 (1*S*,*P*/1*S*,*M*); R_f = 0.25 and 0.12 (petroleum ether/CH_2Cl_2, 90:10); HPLC (silica, hexane/CH_2Cl_2, 90:10) $t_{R(P)}$ = 17.3 min and $t_{R(M)}$ = 21.4 min, dr 80:20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 0.85H), 6.52 (s, 0.15H), 6.43 (s, 0.15H), 6.36 (s, 0.85H), 4.62 (br s, 1H), 3.28 (dt, *J* = 3.4 Hz, *J* = 11.9 Hz, 0.15H), 2.73 (dt, *J* = 4.5 Hz, *J* = 10.8 Hz, 0.85H), 2.38 (s, 0.45H), 2.31 (s, 2.55H), 2.23 (s, 3H), 2.17 (m, 0.85H), 1.88 (m, 0.15H), 1.85−1.67 (m, 2H), 1.67−1.33 (m, 4H), 1.15−0.93 (m, 2H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.68 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2 (C), 137.7 (C), 135.9 (C), 126.7 (C), 125.5 (CH), 124.1 (CH), 115.1 (CH), 113.9 (CH), 44.6 (CH), 44.5 (CH), 42.4 (CH), 40.3 (CH_2), 40.1 (CH_2), 39.2 (CH), 35.6 (CH_2), 35.5 (CH_2), 33.7 (CH), 28.3 (CH), 25.5 (CH_2), 25.4 (CH_2), 22.5 (CH_3), 21.8 (CH_3), 21.6 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 16.2 (CH_3), 15.5 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 260 (M^+, 55), 175 (80), 135 (100); HRMS (EI-TOF) *m*/*z* calcd for $C_{18}H_{28}O$ 260.2140, found 260.2142. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.68; H, 11.18.

*(P,M)-2-[(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl]-1-methoxy-3,5-dimethylbenzene (**2f**).* A mixture of two atropisomers (61 mg, 92%) as a liquid: dr 85:15 (1*S*,*P*/1*S*,*M*); R_f = 0.64 (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (s, 0.85H), 6.54 (s, 0.15H), 6.53 (s, 1H), 3.76 (s, 0.45H), 3.75 (s, 2.55H), 3.45 (dt, *J* = 3.4 Hz, *J* = 11.7 Hz, 0.15H), 2.67 (ddd, *J* = 5.5 Hz, *J* = 8.5 Hz, *J* = 10.8 Hz, 0.85H), 2.36 (s, 0.45H), 2.28 (s, 2.55H), 2.26 (s, 3H), 2.22 (m, 0.85H), 1.87 (m, 0.15H), 1.82−1.63 (m, 2H), 1.62−1.28 (m, 4H), 1.16−0.90 (m, 2H), 0.88 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 0.45H), 0.82 (d, *J* = 7.0 Hz, 2.55H), 0.64 (d, *J* = 6.8 Hz, 0.45H), 0.63 (d, *J* = 6.9 Hz, 2.55H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (C), 137.1 (C), 135.5 (C), 129.0 (C), 125.1 (CH), 124.0 (CH), 110.4 (CH), 109.7 (CH), 55.9 (CH_3), 55.0 (CH_3), 44.5 (CH), 44.1 (CH), 43.0 (CH), 40.3 (CH_2), 40.1 (CH_2), 38.3 (CH), 35.65 (CH_2), 35.6 (CH_2), 33.8 (CH), 33.7 (CH), 28.3 (CH), 25.6 (CH_2), 25.4 (CH_2), 22.6 (CH_3), 21.8 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 20.8 (CH_3), 16.2 (CH_3), 15.4 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 274 (M^+, 55), 189 (100), 149 (86), 136 (36), 119 (38); HRMS (EI-TOF) *m*/*z* calcd for $C_{19}H_{30}O$ 274.2297, found 274.2292. Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.61; H, 11.10.

*(P,M)-2-[(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl]-3,5-dimethylbenzene Acetate (**2g**).* A mixture of two atropisomers (49 mg, 59%) as a liquid: dr 84:16 (1*S*,*P*/1*S*,*M*); R_f = 0.28 (petroleum ether/CH_2Cl_2, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 0.84H), 6.80 (s, 0.16H), 6.66 (s, 1H), 2.83 (dt, *J* = 3.4 Hz, *J* = 11.8 Hz, 0.16H), 2.73 (dt, *J* = 3.4 Hz, *J* = 11.7 Hz, 0.84H), 2.40 (s, 0.48H), 2.32 (s, 2.52H), 2.31 (s, 0.48H), 2.30 (s, 2.52H), 2.26 (s, 3H), 1.93−1.69 (m, 3H), 1.68−1.56 (m, 1H), 1.55−1.18 (m, 3H), 1.16−0.89 (m, 2H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 6.8 Hz, 0.48H), 0.63 (d, *J* = 6.9 Hz, 2.52H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 149.0 (C), 137.8 (C), 135.7 (C), 131.7 (C), 130.9 (CH), 129.2 (CH), 122.1 (CH), 120.7 (CH), 45.2 (CH), 44.3 (CH), 42.4 (CH), 40.93 (CH), 40.9 (CH_2), 35.8 (CH_2), 35.4 (CH_2), 35.2 (CH_2), 33.9 (CH), 33.7 (CH), 28.0 (CH), 25.4 (CH_2), 25.3 (CH_2), 22.5 (CH_3), 22.4 (CH_3), 21.7 (CH_3), 21.6 (CH_3), 21.4 (CH_3), 20.73 (CH_3), 20.7 (CH_3), 16.0 (CH_3), 15.3 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 302 (M^+, 14), 260 (100), 175 (80), 135 (100); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{30}O_2$ 302.2246, found 302.2253. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.997. Found: C, 79.02; H, 10.17.

*(P,M)-2-[(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl]-3,5-dimethylbenzene Pivalate (**2h**).* A mixture of two atropisomers (112 mg, 59%) as a liquid: dr 70:30 (1*S*,*P*/1*S*,*M*); R_f = 0.28 (petroleum ether/CH_2Cl_2, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 0.7H), 6.77 (s, 0.3H), 6.60 (s, 0.3H), 6.51 (s, 0.7H), 2.88 (dt, *J* = 3.3 Hz, *J* = 11.7 Hz, 0.3H), 2.72 (dt, *J* = 3.4 Hz, *J* = 11.6 Hz, 0.7H), 2.38 (s, 0.9H), 2.32 (s, 2.1H), 2.25 (s, 3H), 1.91 (m, 1H), 1.84−1.535 (m, 3H), 1.53−1.28 (m, 12H), 1.14−0.89 (m, 2H), 0.88 (d, *J* = 6.2 Hz, 2.1H), 0.84 (d, *J* = 7.0 Hz, 0.9H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.66 (d, *J* = 6.8 Hz, 0.9H), 0.65 (d, *J* = 6.9 Hz, 2.1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 (C), 149.8 (C), 149.2 (C), 137.5 (C), 135.5 (C), 131.7 (C), 130.3 (CH), 128.6 (CH), 121.6 (CH), 120.5 (CH), 44.1 (CH), 42.1 (CH), 40.4 (CH), 40.1 (CH_2), 39.8 (CH_2), 35.3 (CH_2), 35.1 (CH_2), 33.6 (CH), 33.4 (CH), 29.5 (C), 29.2 (C), 27.7 (CH), 27.3 ($3CH_3$), 27.1 ($3CH_3$), 25.3 (CH_2), 25.0 (CH_2), 22.4 (CH_3), 22.2 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 20.7 (CH_3), 20.4 (CH_3), 15.8 (CH_3), 15.0 (CH_3); MS (EI) *m*/*z* (relative intensity, %) 344 (M^+, 47), 260 (100), 175 (72), 135 (100), 57 (51); HRMS (EI-TOF) *m*/*z* calcd for $C_{23}H_{36}O_2$ 344.2715, found 344.2719. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.40; H, 10.75.

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J. Org. Chem. 2016, 81, 2372−2382

*2-[(1S,2R,5S)-2-Isopropyl-5-methycyclohexyl]-1,3,5-trimethoxybenzene (**2i**).* Liquid (70 mg, 70%): R_f = 0.28 (petroleum ether/CH_2Cl_2, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, J = 2.4 Hz, 1H), 6.11 (d, J = 2.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.08 (dt, J = 3.7 Hz, J = 11.2 Hz, 1H), 2.02 (m, 1H), 1.83−1.28 (m, 6H), 1.11−0.89 (m, 2H), 0.87 (d, J = 6.2 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H), 0.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 158.5 (C), 158.4 (C), 114.4 (C), 91.1 (CH), 90.6 (CH), 55.7 (CH_3), 55.1 (CH_3), 54.9 (CH_3), 43.9 (CH), 40.1 (CH_2), 37.4 (CH), 35.4 (CH_2), 33.4 (CH), 28.4 (CH), 25.2 (CH_2), 22.4 (CH_3), 21.5 (CH_3), 15.6 (CH_3); MS (EI) m/z (relative intensity, %) 306 (M^+, 41), 221 (100), 181 (65); HRMS (EI-TOF) m/z calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2196. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.62; H, 9.96.

Two Other Procedures for Catalytic Hydrogenation of 1e. In procedure 1, **1e** (600 mg, 2.34 mmol) and PtO_2 (10%, 60 mg) in ethyl acetate (60 mL) were placed under an atmospheric pressure of H_2 at rt. The reaction mixture was stirred for 6 days. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 98:2) to give **2e** (230 mg, 38%) as a mixture of three diastereoisomers with ratios of epimers 1*S*/1*R* of 70:30 and atropisomers 1*S*,*P*/1*S*,*M* of 87:13 in $CDCl_3$. Preparative TLC (petroleum ether/EtOAc, 97:3) separation gave after two elutions a fraction enriched in the 1*R* epimer: ratios of epimers 1*S*:1*R* of 55:45 and atropisomers 1*S*,*P*:1*S*,*M* of 87:13 in $CDCl_3$.

In procedure 2, **1e** (100 mg, 0.55 mmol) and Pd/C (10%, 10 mg) in ethyl acetate (10 mL) were placed under 5 bar of H_2 at rt. The reaction mixture was stirred for 24 h. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2, 95:5) to give **2e** (39 mg, 39%) as a mixture of three diastereoisomers with ratios of epimers 1*S*:1*R* of 70:30 and atropisomers 1*S*,*P*:1*S*,*M* of 87:13 in $CDCl_3$.

Other Procedures for the Synthesis of 2b,f−h. *Synthesis of (1S)-**2b** from (1S)-**2a**.* A suspension of (1*S*)-**2a** (150 mg, 0.49 mmol) as a mixture of two rotamers 1*S*,*P*/1*S*,*M* (46:54 in CD_3OD), Me_2SO_4 (0.13 mL, 154 mg, 1.22 mmol), and anhydrous K_2CO_3 (135 mg, 0.98 mmol) in Me_2CO (5 mL) was stirred under reflux for 4 h. The reaction mixture was filtered and evaporated under reduced pressure to give a residue that was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 99:1) to yield the diether as a solid (158.3 mg, 97%). Ac_2O (2.25 mL) was then added to a solution of the diether (128 mg, 0.38 mmol) in pyridine (1.5 mL) at rt under a N_2 atmosphere, and the whole was stirred at 80 °C overnight. The reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 90:10) to yield (1*S*)-**2b** (71 mg, 49%) as a mixture of two rotamers 1*S*,*P*/1*S*,*M* (40:60 in $CDCl_3$).

*Synthesis of Ether **2f** from **2e**.* A suspension of **2e** (94 mg, 0.36 mmol) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 30:70 and atropisomers 1*S*,*P*/1*S*,*M* of 85:15 in $CDCl_3$, Me_2SO_4 (0.08 mL, 92 mg, 0.75 mmol), and anhydrous K_2CO_3 (143 mg, 0.90 mmol) in Me_2CO (5 mL) was stirred under reflux for 4 h. The reaction mixture was filtered and evaporated under reduced pressure to give a residue that was purified by silica gel column chromatography (petroleum ether) to yield **2f** (86 mg, 86%) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 30:70 and atropisomers 1*S*,*P*/1*S*,*M* of 85:15 in $CDCl_3$.

*Synthesis of Acetate **2g** from **2e**.* Ac_2O (1.5 mL) was added to a solution of **2e** (80 mg, 0.25 mmol) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 13:87 and atropisomers 1*S*,*P*/1*S*,*M* of 85:15 in $CDCl_3$ in pyridine (1 mL) at rt under a N_2 atmosphere, and the whole was stirred at 80 °C overnight. The reaction mixture was evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography to give acetate **2g** (63 mg, 83%) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 13:87 and atropisomers 1*S*,*P*/1*S*,*M* of 80:20 in $CDCl_3$.

*Synthesis of Pivalate **2h** from **2e**.* PivCl (1 mL) was added to a solution of **2e** (80 mg, 0.25 mmol) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 13:87 and atropisomers 1*S*,*P*/1*S*,*M* of 85:15 in $CDCl_3$ in pyridine (1 mL) at rt under a N_2 atmosphere, and the whole was stirred at 80 °C overnight. The reaction mixture was evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2, 90:10) to give pivalate **2h** (69 mg, 66%) as a mixture of three diastereoisomers with ratios of epimers 1*R*/1*S* of 13:87 and atropisomers 1*S*,*P*/1*S*,*M* of 73:27 in $CDCl_3$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02856.

^{1}H and ^{13}C NMR spectra of compounds **2a−i**, NOESY spectra of **1e** and **2b,e**, VT ^{1}H NMR spectra of **1e** and **2b,d,e,h,i**, VT 2D EXSY spectra of **2b,e,f**, Eyring plot data of **2b,e,f**, HPLC chromatogram of **2e**, and computational data of **2b,e,f** (PDF)

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Notes

The authors declare no competing financial interest.

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