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Synthesis, Structural Analysis, and Chiral Investigations of Some Atropisomers with *EE*-Tetrahalogeno-1,3-butadiene Core

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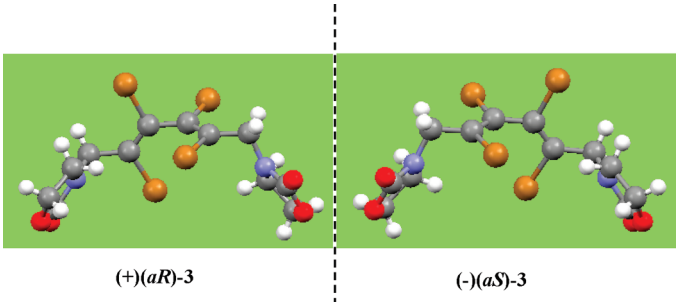

The atropenantiomers of stable 1,2,3,4-tetrahalo-1,3-butadiene derivatives (where halogeno stands for bromine or iodine) were separated with use of chiral HPLC. The barriers for the enantiomerization process were determined on-line by dynamic HPLC (DHPLC) or off-line by classical kinetic measurements. In the case of the tetrachloro compound, the barrier was too low for DHPLC and its value was obtained by dynamic NMR experiments. The obtained barriers for chloro, bromo, and iodo derivatives correlate with the van der Waals radii of the halogens. The absolute configuration of the isolated enantiomers of the tetraiodo and tetrabromo compounds was assigned by comparison of the experimental and conformations averaged calculated VCD spectra. The identification of a signature band of the absolute configuration of the butadiene core, the sign and location of which are independent from the different conformations and substituents, allowing the safe assignment of the absolute configuration of the enantiomers of chiral 1,3-butadienes, is also reported.

Introduction

Starting with the first resolution of the atropisomeric enantiomers of 6,6′-dinitro-2,2′-diphenic acid (Christie and Kenner in 1922)[1] the investigation of various compounds exhibiting atropenantiomers became an important target in organic chemistry.[2a−e]

Many axial chiral biphenyls [e.g., (*R*)-(+)-2,2′-bis-(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl (MeO-BIPHEP)],[3] binaphthyls [e.g., 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[4a] or 2,2′-dihydroxy-1,1′-dinaphthyl (BINOL)[4b]], naphthylisoquinoline alkaloids,[4c−e] and [2.2]cyclophanes with planar chirality [e.g., (*R*)-(−)-4,

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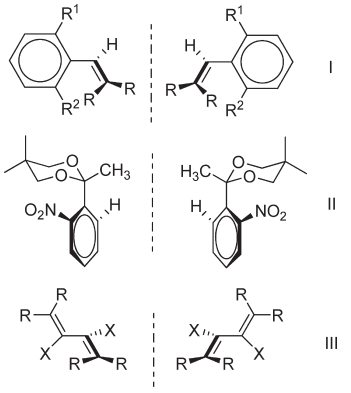
SCHEME 1



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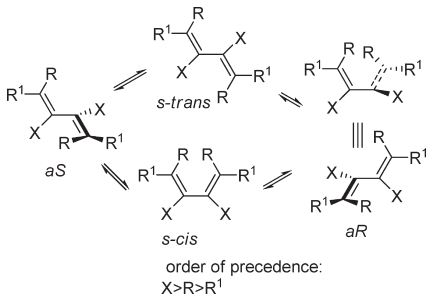


12-bis(diphenylphosphino)[2.2]paracyclophane (Phanephos)][5] are commercially available as chiral auxiliaries or are biologically active compounds. Besides these well-known atropenantiomeric compounds, atropisomerism and the axial chirality was evidenced for many other unexpected cases (e.g., vinylbenzenes I,[6] 2-aryl,2-methyl-1,3-dioxanes II,[7] 1,3-butadienes III;[8] Scheme 1).

The atropisomers of 1,3-butadienes are due to the hindered rotation around the central bond C^2-C^3. These compounds prefer the conformation with perpendicular arrangement of the double bonds, which ensure the longest distance between the large substituents at positions 2 and 3 (X, Scheme 2).

The racemization of the atropenantiomers (*aR* ⇆ *aS*) occurs by rotation around the C^2-C^3 bond, via either the *s-trans* isomer (*transoid*) or the *s-cis* structure (*cisoid*) of the 1,3-butadiene core.

The dynamic experiments and the molecular modeling indicate a considerably higher barrier of the inversion through the *cisoid* form,[9] thus the further discussion is focused on the interactions in the ground state (with perpendicular double bonds) and in the *transoid* isomer (with coplanar double bonds) which are mainly involved in the conformational equilibria of chiral 1,3-dienes.

SCHEME 3

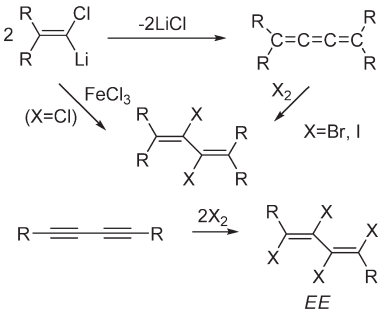
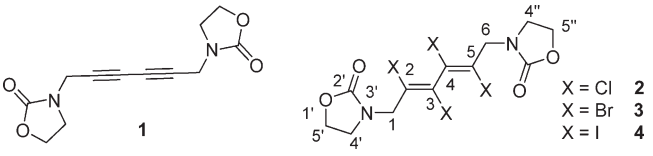


CHART 1



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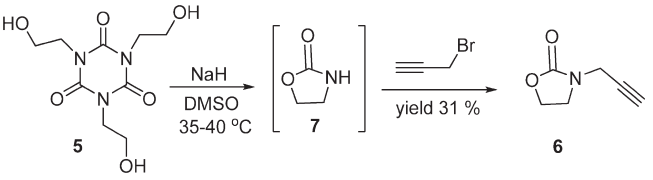

The values of the barriers of racemization are strongly correlated with X and R groups (named internal substituents). In several cases when these internal substituents are not very large (e.g., R, X = Cl, Cl; Cl, $CH_2C_6H_5$; Ph (CH_3), $COOC_nH_{2n+1}$; according to Scheme 2) the barriers could be estimated by dynamic NMR experiments.[8a−d,10] For few other compounds (e.g., R = X = Br, CH_3) the barriers could be determined using polarimetry measurements. In these cases a previous resolution of the racemates either by derivatization with CDAs (chiral derivatizing agent) or by chiral chromatography (triacetylcellulose as the chiral stationary phase) was required.[11a,b]

The majority of the compounds were obtained and were investigated in *EE* configuration, but for some cases, when the syntheses were not stereoselective and all isomers were obtained, the two other isomers (*EZ* and *ZZ*) were also separated and investigated. An increase of the rotation barrier in the series *ZZ* < *EZ* < *EE* was observed.[8d,10]

The R^1 groups (named external substituents) are not involved directly in the hindrance of the rotation around the C^2-C^3 bonds, but if they are large they increase the barrier of rotation by the *buttressing* effect.[8a,b,e,f] The sensitivity to the *buttressing* effect of the external substituents depends on the actual size of the buttressed substituents.[12a,b]

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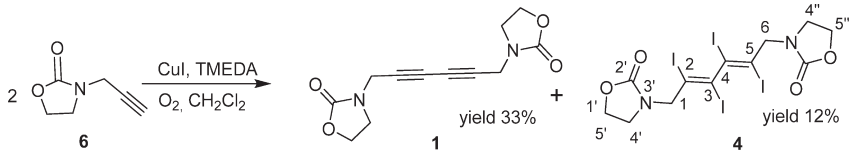
SCHEME 5



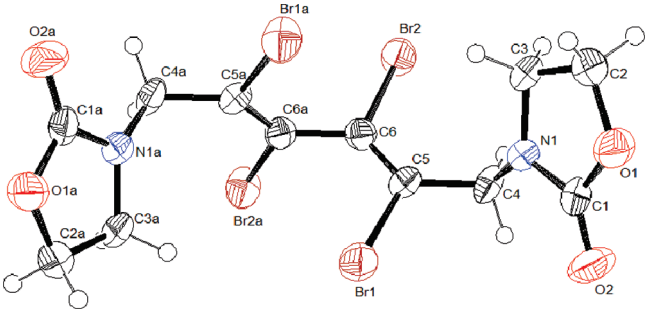
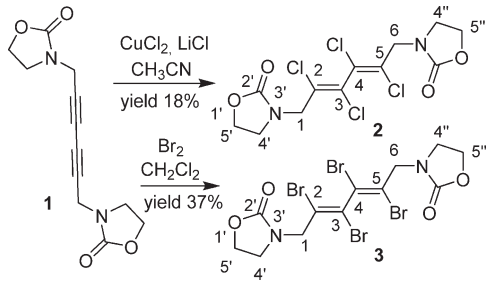


FIGURE 1. ORTEP diagram for compound **3**.

SCHEME 6



Chiral halogenodienes were obtained either by oxidative coupling reactions of vinyl derivatives or by halogen addition reactions to diynes or cumulenes (Scheme 3).[8a−d,f]

We considered it of interest to revisit and to develop the investigations in the field of chiral dienes with modern tools and to obtain starting from diyne **1** new chiral tetrahalo-2,4-hexadienes **2**−**4** (Chart 1), to determine their structure, to separate the enantiomers, to measure the barriers of racemization, and to determine the absolute configuration of the resolved enantiomers.

Results and Discussions

The strategy for the synthesis of target diyne **1** and then of the corresponding chiral tetrahalo-diene compounds **2**−**4** was based on obtaining *N*-propargyl-1,3-oxazolidine-2-one **6** by the reaction of the commercially available 1,3,5-tris(2′-hydroxyethyl)cyanuric acid **5** with propargyl bromide (Scheme 4). In the process the in situ transposition of **5** to the 1,3-oxazolidine-2-one **7** occurs. This transposition reaction was first achieved by Frazier et al. in vacuum pyrolysis.[13]

Diyne **1** was obtained by the Hay's coupling reaction (Scheme 5).[14] In the process, a part of the diyne **1** was transformed into the *EE*-tetraiodo-2,4-hexadiene **4** (Scheme 5; the **1**:**4** ratio ≈3).

TABLE 1. Values of Some Selected Bond Angles (the numbering corresponds to ORTEP diagrams; Figure [1] and Supporting Information)[a]

	bond angles (deg)		*d* [distances (Å)]	
compd	$X^1-C^5-C^6$; $X^{1a}-C^{5a}-C^{6a}$	$C^{6a}-C^6-X^2$; $C^6-C^{6a}-X^{2a}$	$X^2-H(C^3)$; $X^{2a}-H(C^{3a})$	$\Delta d = d(r_X + r_H)$[b]
2	117.86	113.39	2.691	−0.149
3	116.27	112.00	2.784	−0.156
4 (A)	118.01; 118.30	110.89; 112.72	2.782; 2.830	−0.288; −0.240
4 (B)	118.04; 119.18	110.49; 111.56	2.903; 2.836	−0.167; −0.234

[a] For **4** the crystal exhibits two type of molecules denoted with A and B (see Supporting Information). [b] r_X and r_H are the vdW radii of X and H: r_H = 1.09 Å; r_{Cl} = 1.75 Å; r_{Br} = 1.85 Å; r_I = 1.98 Å.[16]

Tetrachloro and tetrabromo 2,4-hexadienes **2** and **3** were synthesized as single *EE* isomers by direct halogenation of the corresponding diyne (**1**) using specific procedures (Scheme 6) reported for similar reactions on different substrates.[8b,e,15]

Solid State Structural Investigations of 2−4. The single crystal molecular structures for **2**−**4** (Figure 1 and the Supporting Information) were obtained by X-ray diffractometry, using suitable crystals obtained from double layered $CHCl_3$/hexane solutions. The crystals contain both enantiomers. The crystal of **4** due to the packing effects contains two different types of molecules (with slightly different interatomic distances and bond and torsion angles (Supporting Information). The molecular structures reveal the perpendicular orientation of the planes of the double bonds (torsion angles vary in the range 88.33−91.13°) and the ground state strain induced by the (1′,3′-oxazolidine-2′-one-3′-yl)methyl groups. This effect determines a diminishing (correlated with the increasing of the values of the van der Waals radii of the halogen atoms) of the bond angles $X^1-C^5-C^6$ ($X^{1a}-C^{5a}-C^{6a}$) and $C^{6a}-C^6-X^2$ ($C^6-C^{6a}-X^{2a}$) (Table 1). The values of the bond angles $X^1-C^5-C^6$ ($X^{1a}-C^{5a}-C^{6a}$) for **4** are somewhat higher than expected, probably due to intramolecular halogen−hydrogen interactions [$X^2-H(C^3)$; $X^{2a}-H(C^{3a})$] which can be appreciated by the amplitude of the differences between the sum of the van der Waals radii of hydrogen and halogen atoms and the corresponding measured distance in the X-ray structure (Table 1).

The lattice of **4** shows many supramolecular interactions (Supporting Information): halogen−halogen (d_{I-I} = 3.784

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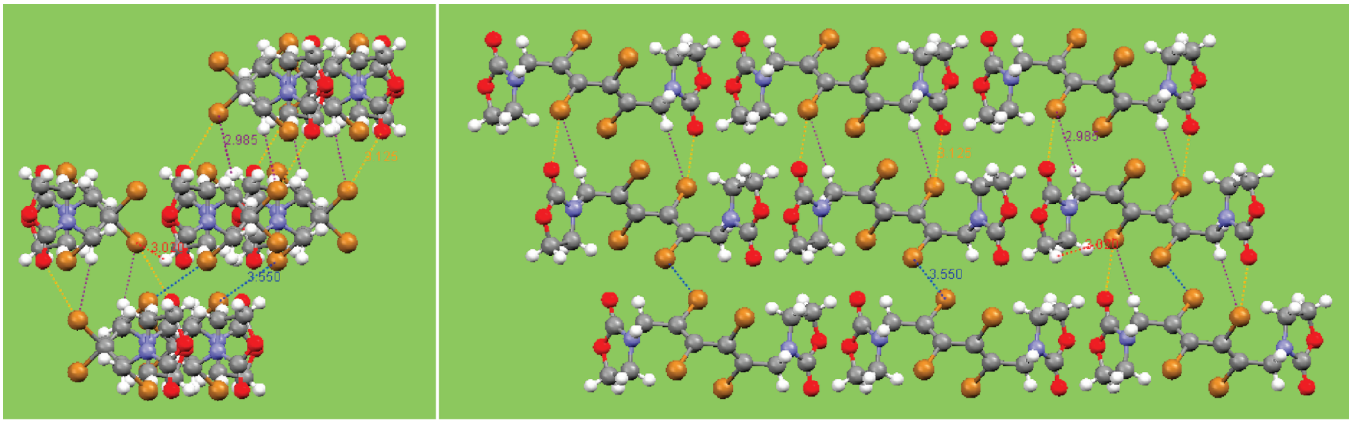

FIGURE 2. Views (A along the axis *a* and B along the axis *b*) of the lattice of **3** obtained with the Mercury program.

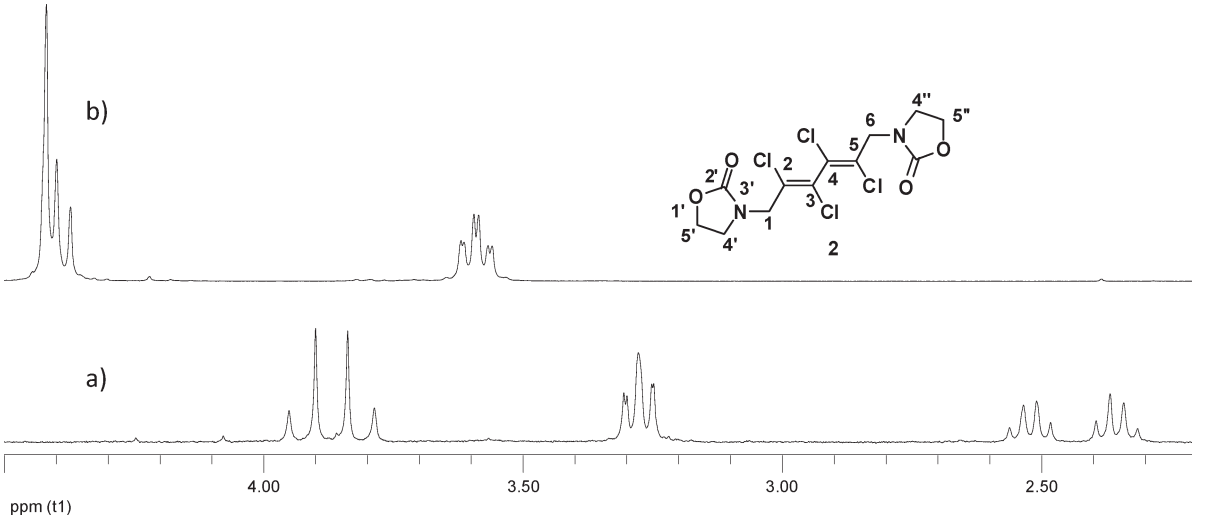

FIGURE 3. ^{1}H NMR (300 MHz) of compound **2** at room temperature in C_6D_6 (a) and $CDCl_3$ (b).

Å; type I interactions[17]), $C^{4(4a)}$–H---I (d_{H-I} = 3.101, 3.148 Å), $C^{2(2a),3(3a)}$–H---$O^{2(2a)}$=$C^{2(2a)}$ (d_{H-O} = 2.704 and 2.594 Å, respectively), and halogen bondings[18] (X bondings; X---$O^{2(2a)}$=$C^{2(2a)}$; d_{I-O} = 2.982, 3.069, 3.143, 3.154, 3.360 Å) which can also influence the values of the bonds angles (Table 1) in the X-ray molecular structure of this compound.

The inspection of the associations of the molecules in the lattices revealed for **2** and **3** layered structures (Figure 2 and the Supporting Information) in which the $C^{4(4a)}$–X bonds of different molecules exhibit antiparallel orientations generating favorable dipole–dipole interactions ($d_{C4(4a)-X}$ of neighboring molecules are 3.943 Å for X = Br and 3.743 Å for X = Cl, respectively). In addition halogen–halogen interactions (d_{Cl-Cl} = 3.454 Å; d_{Br-Br} = 3.550 Å; type I interactions[17]), $C^{4(4a)}$–H---X (d_{H-Br} = 2.985, 3.020 Å and d_{H-Cl} = 2.946 Å), $C^{2(2a),3(3a)}$–H--- $O^{2(2a)}$=$C^{2(2a)}$ interactions (d_{H-O}(**2**) = 2.652, 2.639 Å), and halogen bonding supramolecular interactions (X---$O^{2(2a)}$=$C^{2(2a)}$; d_{Cl-O} = 3.225 Å; and d_{Br-O} = 3.125 Å) were observed.[18,19]

This underlines the increase of the X bondings in the series Cl < Br < I suggested by the dramatic decrease of the X---O=C distances (d_{Cl-O} = 3.225 Å, d_{Br-O} = 3.125 Å, and d_{I-O} = 2.982) in a reversed relation with the values of the van der Waals radii of the halogens.

Structural Investigations in Solution of 2–4: Enantiomerization Barriers. Compounds **2**–**4** have large internal substituents and exhibit anancomeric structures (stable atropisomers at the NMR scale) and therefore their ^{1}H NMR spectra (C_6D_6) show at rt different signals for the protons of the prochiral centers (CH_2 groups) of the molecules (these protons are diastereotopic). As an example, the ^{1}H NMR spectrum of **2** (Figure 3) exhibits an AB system ($\delta_{1,6}$ = 3.92, $\delta'_{1,6}$ = 3.81 ppm; J = 15.4 Hz) for the protons of the CH_2 groups connected to the diene units and two overlapped doublets of doublets of doublets ($\delta_{5',5''}$ = 3.275 ppm, $\delta'_{5',5''}$ = 3.272 ppm; $J = J'$ = 8.1 Hz; $J'' \approx 0$ Hz) and two doublets of doublets of doublets ($\delta_{4',4''}$ = 2.51 ppm, $\delta'_{4',4''}$ = 2.35 ppm; J = 15.7 Hz, J' = 8.1 Hz; $J'' \approx 0$ Hz) for the protons at positions 5′(5″) and 4′(4″), respectively. The spectra of **2**–**4** run in $CDCl_3$ cannot differentiate the diastereotopic protons at positions 1 (6) and 5′ (5″) and these display unique signals (Figure 3 and the Supporting Information). Similar situations were recorded for some

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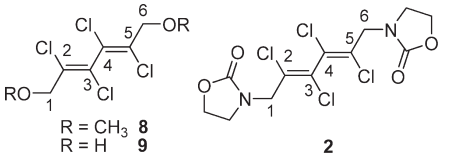
SCHEME 7



chiral N-substituted 1,3-oxazolidine-2-one derivatives bearing $-CH_2-R^*$ groups (R* is a chiral substituent).[20] These experiments reveal important ASIS (Aromatic Solvent Induced Shifts)[21] effects for the NMR spectra of **2**−**4**. To determine the barriers induced by the hindered rotation of the molecules around C^3-C^4 bonds we carried out variable-temperature NMR experiments by increasing the temperature. For compounds **3** and **4** the spectra run in C_6D_6 and DMSO-d_6 at higher temperatures (until 343 and 400 K, respectively) did not show significant modifications in comparison with the spectra recorded at rt, indicating that the barrier is too high to be determined by this method. Similar variable-temperature NMR experiments run with **2** using C_6D_6 as solvent gave relevant results. The coalescence of the signals was obtained at 333 K and the barrier (calculated from two sets of signals) was found to be $\Delta G^{\#} = 69.57 \pm 0.62$ kJ/mol, in excellent agreement with the data reported for other similar compounds.[8b,f]

The barrier for the 2,3,4,5-tetrachloro-1,6-dimethoxy-2,4-hexadiene **8** (Scheme 7: R = Me) was 70.3 kJ/mol by DNMR at 54 °C in decalin and the barrier for the diol analogue **9** (Scheme 7, R = H) was 68.8 kJ/mol by DNMR at 53 °C in toluene-d_8. The resulting mean value of the barriers obtained by DNMR in decalin, benzene, or toluene for three butadienes having in common the tetrachloro-diene core and differing by the substituent on the terminal methylene groups is 69.55 ± 0.95 kJ/mol. This value constitutes a good estimate of the barrier arising from the interaction in the tetrachloro core in the presence of substituted methyl groups. A buttressing effect was observed in the case of secondary or tertiary substituents in the place of the substituted methyl.[8f]

Compounds **2**−**4** were submitted to a screening on various chiral stationary phases. Chiralpak IC, a recently marketed column from Daicel composed of cellulose tris(3,5-dichlorophenylcarbamate) immobilized on silica, afforded baseline separation of the enantiomers of **3** and **4** at 25 °C. It is worth recalling that previous attempts of separation of compound **3** analogues by chromatography on chiral support lasted from the pioneering period of chiral chromatography on microcrystalline cellulose triacetate (MCTA). On MCTA no baseline separation was achieved and a recycling technique with peak shaving was used by Mannschreck's group in Germany to obtain enriched samples in one enantiomer.[11a,b] As known from DNMR experiments, compound **2** presents a too low barrier for a separation at room temperature and accordingly a single peak was observed. Cryogenic chromatography[22a,b] might be helpful in that case but no attempts were performed in that direction since the barrier was already available from NMR experiments.The enantiomers of the tetrabromo **3** and tetraiodo **4** derivatives were isolated under semipreparative conditions. In both cases the enantiomer with a (−) sign was eluted first on Chiralpak IC, using various mixtures of hexane−$CHCl_3$−EtOH.[23] The off-line first-order kinetic rate of racemization of the isolated enantiomers of **3** was determined in $CHCl_3$ at 40 °C yielding a barrier to enantiomerization ($\Delta G^{\ddagger} = 102.3 \pm 0.5$ kJ/mol) corresponding to a 101 min half-life. The rotation barrier is in the range of a possible observation of a plateau during chiral chromatography.[24a−d] Indeed when running chiral chromatography at 50 °C with the same mobile phase as for room temperature separation, a very clear plateau was observed allowing an estimation of the barrier by using Trapp and Schurig equation:[25] $\Delta G^{\ddagger} = 103.6$ kJ/mol at 50 °C in the mixture ethanol/chloroform/hexane 3/3/1 (corresponding to a 43 min half-life at 50 °C). The barriers of enantiomerization of two butadienes having in common with compound **3** the core of four bromides and differing by the so-called external group CH_2R' [R′ = OH, OMe, or oxazolidinone unit ($C_3H_4NO_2$) for **3**] have been reported in the literature.[11b] The barriers in acetone were 102.2 kJ/mol (recalculated at 53.5 °C) for R′ = OH and 104.5 kJ/mol (recalculated at 53.5 °C) for R′ = OMe. The barriers for **3** (this work) are 102.3 kJ/mol in $CHCl_3$ at 40 °C by off-line racemization and 103.6 kJ/mol by DHPLC at 50 °C in a mobile phase composed of EtOH/$CHCl_3$/hexane (3:3:1). Differences in barriers determined by DHPLC and off-line racemization have been observed and discussed already in terms of different rates of racemization on the chiral support and in the mobile phase in the DHPLC experiments. A serious issue is a possible temperature gradient in the column, which is difficult to evaluate.[26]

Noteworthy, the four determinations of the barriers under different solvent, temperature, and method afford a mean value of 103.15 ± 1.35 kJ/mol. Further discussion on possible entropy or solvent effect on such a small variation of the barriers is beyond the scope of this paper. The three external groups (CH_2OH, CH_2OMe, and $CH_2-C_3H_4NO_2$) all present a methylene group; in the transition state of the rotation, the bulky substituent is likely rotated away and thus the buttressing "if any" between the CH_2 and the bromines turns out to be very similar for the three compounds. Significant buttressing effects are expected if one or two of the methylene protons were substituted by a carbon.

The tetraiodo derivative **4** did not show a plateau, the off-line measured barrier of enantiomerization at 131 °C in

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(21) The use of C_6D_6, toluene-d_8, or pyridine-d_5 is a well-documented trick to enhance chemical shift difference for prochiral protons in (thio)amides, (thio)ureas, (thio)carbamates (such as in compounds **2**, **3**, and **4**), and dithiocarbamates. All these functional groups present a positive charge on the nitrogen and are very sensitive to ASIS. For other examples see: (a) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517–551. (b) Roussel, C.; Liden, A.; Chanon, M.; Metzger, J.; Sandstrom, J. *J. Am. Chem. Soc.* **1976**, *98*, 2847–2852. (c) Liden, A.; Roussel, C.; Liljefors, T; Chanon, M.; Carter, R. E.; Metzger, J.; Sandstrom, J. *J. Am. Chem. Soc.* **1976**, *98*, 2853–2860. (d) Grosu, I.; Plé, G.; Mager, S.; Martinez, R.; Mesaros, C.; Camacho, B. C. *Tetrahedron* **1997**, *53*, 6215–6232. (e) Mesaros, E.; Grosu, I.; Mager, S.; Plé, G.; Farcas, S. I. *Monatsh. Chem.* **1998**, *129*, 723–733.

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(23) The reported sign was found with a Jasco on-line polarimeter and corresponds to the summation of the optical rotation between 350 and 900 nm in the mobile phase: Roussel, C.; Vanthuyne, N.; Serradeil-Albalat, M.; Vallejos, J. C. *J. Chromatogr. A* **2003**, *995*, 79–85.

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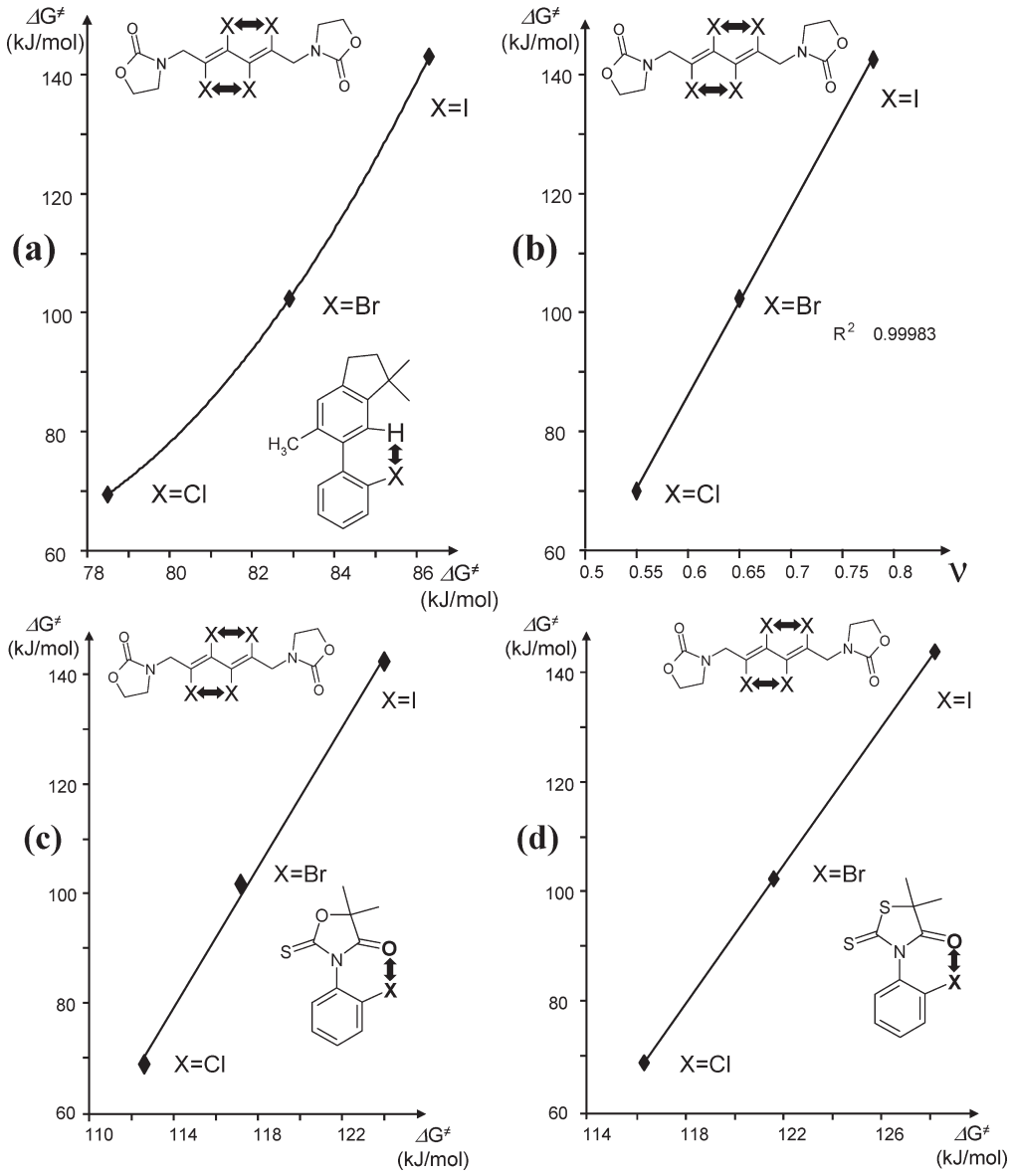

FIGURE 4. Correlations between barriers to rotation found in **2**, **3**, and **4** with barriers reported in the literature for the chloro, bromo, iodo halogen triad in different scaffolds (a, c, d). Correlation between barriers to rotation found in **2**, **3**, and **4** with υ parameters derived from van der Waals radii of the halogen series (b). The table of data and references used in these correlations are given in the Supporting Information.

chlorobenzene was 143 ± 1 kJ/mol corresponding to a 1.56 day half-life at 131 °C. This is the first experimental determination of the barrier of a tetraiodobutadiene derivative.

Having in hand the complete set of barriers for the halogen triad composed of chlorine, bromine, and iodine for the tetrahalogenobutadiene framework, these barriers shall be compared to barriers disclosed in the literature for the same triad in other frameworks. In the absence of specific interaction such as buttressing effect or conformational restriction, steric barriers extracted from different models should be linearly correlated, the slope of the correlation monitoring the sensitivity to the models. This statement is particularly true for spherical groups such as the halogens. Inspection of the literature reveals that very few complete sets of data are available for the chlorine, bromine, and iodine triad. The only available barriers for a complete set of dihalogen (Cl, Br, and I) on butadiene substituted by four benzyl groups were reported by Mannschreck and Coll.[8b] Unfortunately DNMR study did not allow the determination of the actual barriers to rotation. An estimated barrier was given for the dichloro derivative (ca. 88 kJ/mol, T_c = 140 °C), and lower limits for the barriers in dibromo and diodo compounds were guessed since coalescence in DNMR was not reached: > 92 kJ/mol at a higher temperature of 165 °C in decalin for dibromo compound and > 100 kJ/mol at a higher temperature of 195 °C in nitrobenzene for diiodo compound, respectively. Under these circumstances, references for the steric size of halogens under nonbuttressed conditions shall be taken outside the butadiene framework. The barriers in phenylindans carrying a halo and a methyl group in the ortho positions (Figure 4a) are available from a DNMR study.[27] In

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TABLE 2. Conformations and Energies of (*aS*)-3a−d and (*aS*)-4a−d

conformers	energies + ZPE (au)	ΔE^{ZPE} (kJ·mol^{-1})	Boltzmann population (%)
3a	−928.165204	0.00	32
3b	−928.1650985	0.28	28
3c	−928.1645934	1.60	17
3d	−928.1645149	1.81	15
4a	−920.3194935	0.00	33
4b	−920.3194672	0.07	32
4c	−920.3186295	2.27	13
4d	−920.3184769	2.67	11

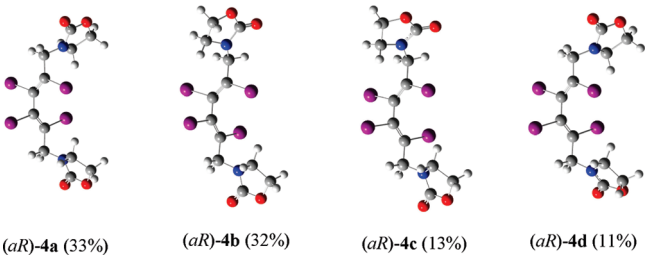

FIGURE 5. Most populated conformations for (*aR*)-**4**.

this model the barrier changes in the series chlorine, bromine, and iodine arise from the difference in interaction between a nonbuttressed halogen and a C_{ar}−H whereas all other contributions to the barrier are almost unvarying.

Plotting the barriers reported in the phenylindan model against those determined for **2**, **3**, and **4** reveals a significant curvature (Figure 4a) that could have been assigned to a buttressing effect in the congested butadienes.

However, as said before the barrier in the phenylindan model results from the interaction of a halogen presenting lone pairs of electrons with a C−H group. It is probably not a good model to account for the lone pair−lone pair interaction that occurs between halogens in close contact. A more realistic model that includes lone pair−lone pair interaction in a transition state to rotation is provided by the recent study of the barriers to rotation in axially chiral *N*-(*o*-halogenophenyl)-2-thioxo-oxazolidine-4-one and *N*-(*o*-halogenophenyl)-2-thioxo-thiazolidine-4-one (Figure 4, panels c and d).[28]

In these compounds, the nonbuttressed halogen situated in the ortho position on the phenyl group interacts in the transition state to rotation with a (thio)carbonyl group presenting a lone pair of electrons. The *v* steric parameters which are derived from van der Waals radii of the halogens extracted from symmetrical dihalogens provide another scale of halogen size that implicitly comprises the interaction of the lone pairs of electron in dihalogen equilibrium geometry.[29]

Panels c, d, and b of Figure 4 report the comparison of the barriers in the series **2**, **3**, and **4** with the corresponding barriers of *N*-heteroaryl atropisomers or the *v* steric parameters. In all these cases perfect linear correlations are observed between the data of tetrahalobutadienes and the reference compounds or the *v* steric parameters. The sensitivity

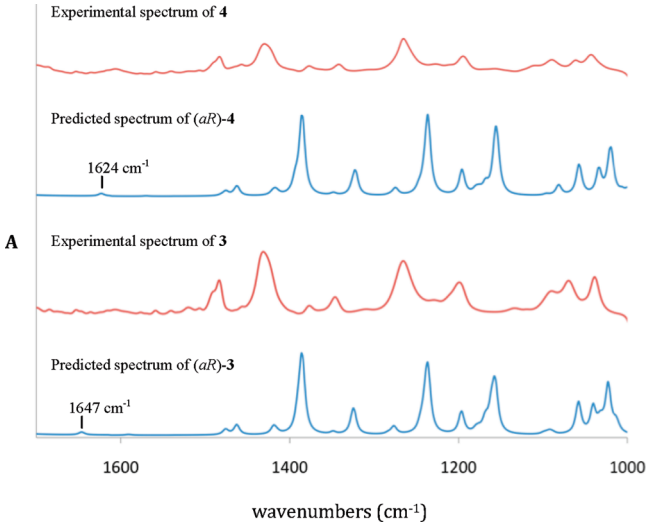

FIGURE 6. Comparison of the experimental IR spectra of **3** and **4** in CD_2Cl_2 solution (first and third traces) with the predicted IR spectrum (second and fourth traces) of the *aR* configuration of **3** and **4** obtained with the B3LYP/6-31+G(d,p) level. For predicted spectra, wavenumbers are scaled by the factor 0.96. The traces labeled "predicted" are the population-weighted spectra with populations given in Figure 5.

to the steric interactions in the butadiene framework is dramatically higher than that in the heteroaryl models as shown by the large value of the slope of the line. It turns out that no buttressing effect induced by the external substituent in **2**, **3**, and **4** can be detected or that the buttressing, if any, is linearly correlated with the size of the interacting groups.

Determination of the Absolute Configurations of 3 and 4 Enantiomers by VCD. The absolute configuration of (+)-**3**, (−)-**3**, (+)-**4**, and (−)-**4** was determined by means of vibrational circular dichroism (VCD) by comparing experimental spectra of both enantiomers with the calculated VCD spectra of the *aR* enantiomer.[30] The geometry optimizations, vibrational frequencies, IR absorption, and VCD intensities were calculated by using Density Functional Theory (DFT) with B3LYP functional and a 6-31+G(d,p) basis set for H, C, N, and O atoms. For I and Br atoms, we used the Stuttgart/Dresden effective core potential (ECP), respectively MWB46 and MWB28. IR absorption and VCD spectra were constructed from calculated dipole and rotational strengths assuming Lorentzian band shape with a half-width at half-maximum of 4 cm^{-1}. All calculations were performed with the Gaussian 03 package.[31,32] The conformational study of **4** showed that among the 20 conformations arising from the attached oxazolidine groups, only 4, (*aR*)-**4a**−**d**, have a Boltzmann population higher than 5% (Table 2 and Figure 5). Normal mode analysis confirmed that those conformations are minima on the potential energy surface since no

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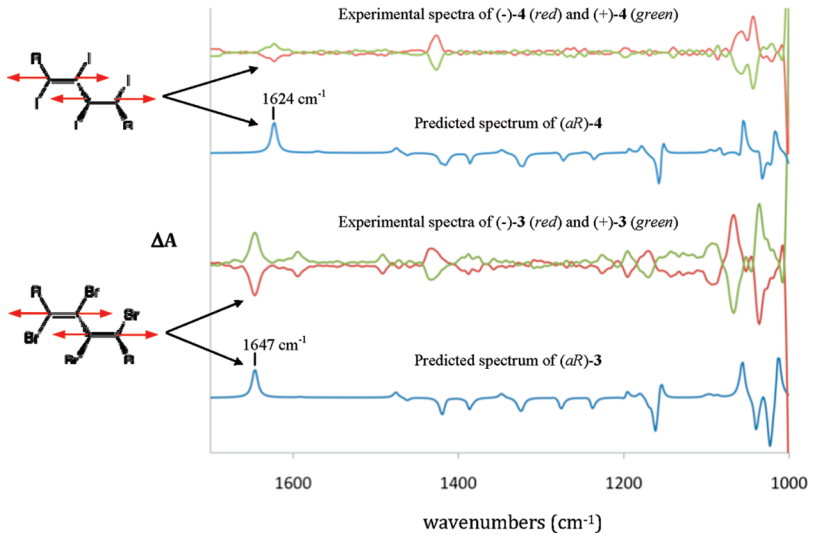

FIGURE 7. Comparison of the experimental VCD spectra of (−)-**3** (in red), (+)-**3** (in green), (−)-**4** (in red), and (+)-**4** (in green) in CD_2Cl_2 solution with predicted VCD spectrum of the *aR* configuration of **3** and **4** (in blue) obtained with the B3LYP/6-31+G(d,p) level. For predicted spectra, wavenumbers are scaled by the factor 0.96. The traces labeled "predicted" are the population-weighted spectra with populations given in Figure 5.

imaginary frequency was found. Similar results were obtained for **3** (Table 2).

As shown in Figures 6 and 7, the experimental IR absorption and VCD spectra of (+)-**3** and (+)-**4** (second eluted enantiomer on Chiralpak IC column) in CD_2Cl_2 solution are in good agreement with the predicted spectra of (*aR*)-**3** and (*aR*)-**4** which were obtained by weighting the spectrum of each conformer by its Boltzmann population. The shape and the relative intensities of the IR and VCD bands were well reproduced by the calculations. The calculated bands at 1647 cm^{-1} in **3** (experimental 1647 cm^{-1}) and 1624 cm^{-1} in **4** (experimental 1625 cm^{-1}) are particularly interesting. Both come from the symmetric stretching mode of the butadiene moiety (Figure 7) and are weakly affected by the attached groups.

The shift observed between these two bands is due to the drastic change of four iodine into four bromine atoms on the butadiene framework. For those bands, the IR absorptions are very weak and are not visible on the experimental spectra. On the other hand, the corresponding VCD bands are intense. The positive sign of those bands is an invariant in the calculated VCD spectra of each conformation of (*aR*)-**3** and (*aR*)-**4** (see Figure SI4 in Supporting Information). Further studies of that symmetric vibrational mode of a butadiene have shown that the positive sign of the corresponding VCD band can be safely associated to the (*aR*) absolute configuration, independently of the substituents of the butadiene. This work will be published elsewhere. The comparison in Figure 7 of the experimental and theoretical VCD spectra provides a high level of confidence for the assignment of the absolute configuration (*aR*) to (+)-**3** and (+)-**4**.

Conclusions

The structures of three new chiral sterically hindered tetrahalogenated dienes were investigated in the solid state by X-ray diffraction and in solution by NMR measurements. The enantiomers of the tetrabromo and tetraiodo dienes were separated by semipreparative chiral chromatography. The barrier for the rotation in the diene moiety was determined by off-line and by DHPLC for the tetrabromo compound ($\Delta G^{\#} \approx 103$ kJ/mol), by the racemization reaction at the boiling point of chlorobenzene coupled with chiral HPLC analysis of the process for the tetraiodo derivative ($\Delta G^{\#} = 143$ kJ/mol), and by DNMR experiments for the tetrachloro diene ($\Delta G^{\#} = 69.6$ kJ/mol). The absolute configurations of the enantiomers of the tetrabromo and tetraiodo derivatives were determined by VCD, and the presence of a specific VCD band, which facilitates the assignment of the configurations, was revealed.

Experimental Section

1,6-Bis(1′,3′-oxazolidine-2′-one-3′-yl)-2,3,4,5-tetrachlorohexane-2*E*,4*E*-diene 2. A solution of diacetylene **1** (80 mg, 0.32 mmol), $CuCl_2$ (174 mg, 1.29 mmol), and LiCl (22 mg, 0.512 mmol) in dry acetonitrile (7 mL) was refluxed overnight. Compound **2** was precipitated with acetone. Yield: 18% (22 mg), white crystals, mp 201 °C. Calcd for $C_{12}H_{12}Cl_4N_2O_4$: C, 36.95; H, 3.10; Cl, 36.36; N, 7.18. Found: C, 37.11; H, 3.02; Cl, 36.16; N, 7.31. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (m, 2H, 4′-H, 4″-H), 4.39 (m, 2H, 5′-H, 5″-H), 4.41 (s, 2H, 1-H, 6-H); ^{1}H NMR

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(300 MHz, C_6D_6) δ 2.35 (2H, dd, J = 15.7, 8.1 Hz, 4′-H, 4″-H), 2.51 (2H, dd, J = 15.7, 8.1 Hz, 4′-H′, 4″-H′), 3.27 (m, 4H, 5′-H, 5″-H), 3.81 (2H, d, J = 15.4 Hz, 1-H, 6-H), 3.92 (2H, d, J = 15.4 Hz, 1-H′, 6-H′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.88 (4′-C, 4″-C), 46.59 (1-C, 6-C), 61.92 (5′-C, 5″-C), 125.41 (2-C, 5-C), 131.49 (3-C, 4-C), 158.14 (2′-C, 2″-C). EI-MS m/z (%) 354 (7.5%, [M^+ − Cl]), 308 (23%), 264 (42%), 216 (65%), (literature data for similar cases 0.1% M^+, and 100% [M^+ − Cl][26]). Chiral HPLC: Chiralpak IC, 25 °C, ethanol/$CHCl_3$/hexane 3/3/1, 1 mL/min, one peak at 7.50 min, k = 1.42.

1,6-Bis(1′,3′-oxazolidine-2′-one-3′-yl)-2,3,4,5-tetrabromohexane-2*E*,4*E*-diene 3. To a solution of diacetylene **1** (125 mg, 0.5 mmol) in dichloromethane (50 mL) was added bromine (1 mmol, 160 mg dissolved in 1 mL of dichloromethane) dropwise. The mixture was stirred at room temperature overnight, and at the end the organic phase was washed with a solution of sodium sulfite and then with water. After drying over sodium sulfate, the solvent was removed and the crude product was purified by chromatography. R_f 0.35 (silica gel, toluene/acetone 4/1). Yield: 37% (106 mg), yellow solid, mp 215 °C dec. Calcd for $C_{12}H_{12}Br_4N_2O_4$: C, 25.38; H, 2.13; Br, 56.29; N, 4.93. Found: C, 25.49; H, 2.28; Br, 56.11; N, 4.77. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (m, 4H, 4′-H, 4″-H), 4.39 (m, 4H, 5′-H, 5″-H), 4.47 (s, 4H, 1-H, 6-H); ^{1}H NMR (300 MHz, C_6D_6) δ 2.41 (2H, dd, J = 15.4, 8.1 Hz, 4′-H, 4″-H), 2.60 (2H, dd, J = 15.4, 8.1 Hz, 4′-H′, 4″-H′), 3.31 (m, 4H, 5′-H, 5″-H), 3.88 (d, 2H, J = 15.4 Hz, 1-H, 6-H), 3.99 (d, 2H, J = 15.4 Hz, 1-H′, 6-H′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.82 (4′-C, 4″-C), 50.43 (1-C, 6-C), 61.97 (5′-C, 5″-C), 118.07 (2-C, 5-C), 122.53 (3-C, 4-C), 158.05 (2′-C, 2″-C). ESI-MS m/z 564.7 [M + H]$^+$, 586.7 [M + Na]$^+$. Chiral HPLC: Chiralpak IC, 25 °C, ethanol/$CHCl_3$/hexane 3/3/1, 1 mL/min, Rt_1 = 7.92 min (−), Rt_2 = 9.32 min (+), k_1 = 1.56, k_2 = 2.01, α = 1.29, and Rs = 2.88.

1,6-Bis(1′,3′-oxazolidine-2′-one-3′-yl)-2,3,4,5-tetraiodohexane-2*E*,4*E*-diene 4. CuI (6.07 g, 95.4 mmol) was added to a solution of *N*-propargyl-1,3-oxazolidine-2-one (0.2 g, 1.59 mmol) in dry dichloromethane (100 mL) containing dry TMEDA (7.37 g, 190.8 mmol). The reaction mixture was stirred for 1 h in dry air. The mixture was then diluted with dichloromethane (50 mL) transferred into a separating funnel, and washed with 2 M HCl (2 × 50 mL) and then several times with water until the aqueous layer remains colorless. The organic layer was then separated, dried over Na_2SO_4, and evaporated. The final product was then purified by column chromatography. R_f 0.21 (silica gel, toluene/acetone 4/1). Yield: 12% (72 mg), yellow solid, mp 190 °C dec. Calculated for $C_{12}H_{12}I_4N_2O_4$: C, 19.07; H, 1.60; I, 67.16; N, 3.71. Found: C, 18.89; H, 1.51; I, 66.97; N, 3.88. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (m, 4H, 4′-H, 4″-H), 4.36 (s, 4H, 1-H, 6-H), 4.40 (m, 4H, 5′-H, 5″-H). ^{1}H NMR (300 MHz, C_6D_6) δ 2.47 (dd, 2H, J = 15.6, 8.1 Hz, 4′-H, 4″-H), 2.69 (dd, 2H, J = 15.6, 8.1 Hz, 4′-H′, 4″-H′), 3.36 (m, 4H, 5′-H, 5″-H), 3.83 (d, 2H, J = 15.4 Hz, 1-H, 6-H), 3.93 (d, 2H, J = 15.4 Hz, 1-H′, 6-H′). ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.18 (4′-C, 4″-C), 59.19 (1-C, 6-C), 62.06 (5′-C, 5″-C), 102.64 (2-C, 5-C), 105.58 (3-C, 4-C), 158.01 (2′-C, 2″-C). ESI-MS m/z 756.7 [M + H]$^+$, 778.6 [M + Na]$^+$. Chiral HPLC: Chiralpak IC, 25 °C, ethanol/$CHCl_3$/hexane 3/3/1, 1 mL/min, Rt_1 = 8.20 min (−), Rt_2 = 9.63 min (+), k_1 = 1.65, k_2 = 2.11, α = 1.28, and Rs = 2.68.

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Supporting Information Available: Procedures and characterization of **1**, CIF files, ORTEP diagrams for **2** and **4**, views of the lattices for **2**−**4**, table of the parameters for the crystallographic determinations, DNMR experiment run with **2**, details of the chiral chromatography carried out with **3** and **4**, determination of the barriers of rotation for **2**−**4**, VCD spectra and the assignment of the absolute configuration of the enantiomers, and copies of ^{1}H and ^{13}C NMR spectra for **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.