Synthesis, Stereochemistry, Carbon-13 Nuclear Magnetic Resonance, and Chiroptical Properties of Isomeric 1,2-Dihydroxy-3-phenylcyclohexanes

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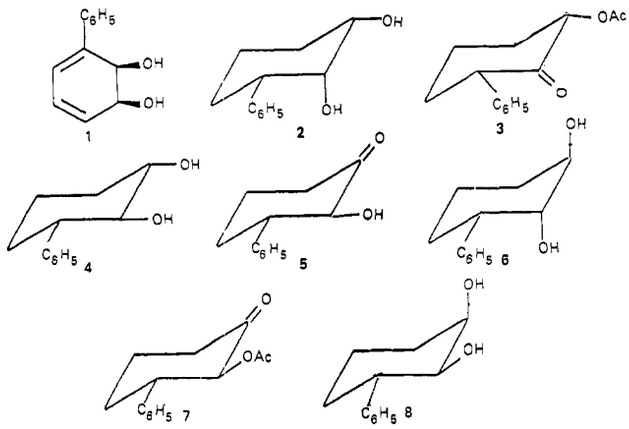
The isomeric 1,2-dihydroxy-3-phenylcyclohexanes have been prepared optically active. Two of the diols (**2** and **4**) were synthesized by chiral reduction (lithium aluminum hydride–*l*-darvon), and the others (**6** and **8**) were prepared from optically active (+)-(*R*)-3-phenylcyclohexene. The CD spectra of the diols were measured and the observed signs for the ^1L_a transition (~220 nm) were shown to agree with those predicted by the quadrant rule proposed by Verbit and Price. The ^1H NMR spectra of the diols were employed to assign relative stereochemistries and preferred conformations. The ^{13}C NMR spectra were recorded and the resonances were assigned using specifically deuterated derivatives, as well as by single frequency decoupling.

In order to determine the absolute stereochemistry of a metabolite,[1] **1**, obtained from microbial oxidation of biphenyl, it was necessary initially to establish the relative stereochemistry of the tetrahydro derivatives and finally the absolute stereochemistry of (+)-*cis,cis*-1,2-dihydroxy-3-phenylcyclohexane (**2**). Although the *trans,cis*- and *trans,trans*-



1,2-dihydroxy-3-phenylcyclohexanes have been reported,[2] their relative stereochemistries were incompletely elucidated, and neither the cis,trans nor the cis,cis isomers have been described. In an earlier study[3] we employed stereoselective syntheses to prepare and characterize the isomeric 1,2-dihydroxy-3-methylcyclohexanes. However, as the diols were now required in an optically active form, we elected to employ asymmetric synthesis, where chiral reduction[4] (*l*-darvon–lithium aluminum hydride) of an α-acetoxy ketone was potentially capable of yielding two optically active diastereomers.

In a preliminary experiment reduction of *cis*-2-acetoxy-6-phenylcyclohexanone (**3**), with lithium aluminum hydride yielded a mixture of diols (**2** and **4**, in an approximately 3:1 ratio). The configuration of the cis,cis diol was assigned from the synthesis employed in conjunction with the diol's ^1H NMR spectrum (see Table I). The chemical shifts of the protons, on the hydroxyl bearing carbon atoms, in the NMR spectrum of **4** were essentially identical at 220 MHz so that coupling constants could not be measured directly. In order to make the assignment and to obtain information on its preferred conformation, a deuterated sample of **4** was prepared by reducing **3** with lithium aluminum deuteride. The chemical shift of the proton on C-2 and $J_{2,3}$ (given in Table I) are consistent with the stereochemistry and conformation shown for **4**. When **3** was incompletely reduced with the 2:1 complex of *l*-darvon–lithium aluminum hydride, the resulting diols were optically active with optical yields[5] of 46% for **2** and 72% for **4**.

On hydrolysis, **3** was reported[6] to yield **5**, which potentially could be useful for preparing optically active **6**. However, the NMR spectrum of the keto alcohol obtained on alkaline hydrolysis of **3** shows a coupling constant ($J_{2,3}$ = 12 Hz) which suggests a trans diaxial orientation rather than the axial–equatorial relation required for a cis geometry. The alcohol was acetylated and the NMR spectrum of the keto acetate was again consistent with the trans geometry ($J_{2,3}$ = 14 Hz) as indicated in **7**. Reduction of **7** with lithium aluminum hydride yielded a mixture of two diols, separable by thick layer chromatography, whose stereochemistry was assigned from their NMR spectra as **4** and **8** (see Table I). Since **8** and **4** could only form from **7**, the keto acetate must have this constitution and configuration. When **7** is reduced with the *l*-darvon–lithium aluminum hydride complex the enantiomeric excess of **4** was less than 10%. Although further study of the reduction might have improved this asymmetric synthesis, an alternative approach was sought which could also be useful for preparing **8**.

Preliminary studies showed that oxidation of 3-phenylcyclohexene with osmium tetroxide produced **8** in good yield. Since methods exist for converting a cis to a trans diol,[7] optically active **8** could be used to prepare optically active **6** and **4**. Verbit and Price[8] have reported the resolution of *cis*-2-phenylcyclohexanol via its monophthalate, while Berti et al.[9] have described the conversion of the optically active alcohol to optically active 3-phenylcyclohexene. These procedures were combined to prepare optically active 3-phenylcyclohexene. Oxidation of (−)-(*S*)-3-phenylcyclohexene with osmium tetroxide yielded (+)-**8** in good yield; when partially resolved olefin was used in the oxidation, optically pure diol could be obtained after several recrystallizations. A sample of (+)-**6** was obtained from (−)-**8** by use of Newman's procedure[7] (see Scheme I), thus completing the preparation of the

Scheme I

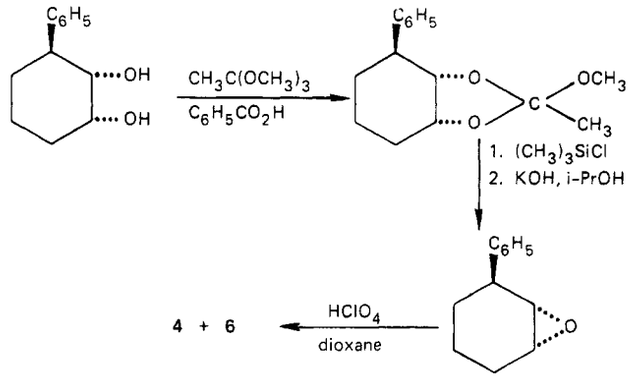


Table I. Proton Chemical Shifts and Coupling Constants of Isomeric 3-Phenyl-1,2-dihydroxycyclohexanes

	4 trans,trans	6 trans,cis	2 cis,cis	8 cis,trans
H-1		4.02	3.59	3.64
H-2	3.45	3.80	3.89	4.09
H-3	2.93	3.15	2.61	2.86
$J_{1,2}$		3 ± 1 Hz	~2 Hz	2.8 Hz
$J_{2,3}$	10.4	3 ± 1 Hz	~2 Hz	10.8 Hz

Table II. ^{13}C Chemical Shifts (ppm) Relative to Me_4Si

	4 trans,trans	6 trans,cis	8 cis,trans	2 cis,cis
C-1	74.8	69.8	69.0	72.4
C-2	79.2	74.1	75.6	73.8
C-3	50.2	42.4	45.5	47.1
C-4	32.9[a]	24.1	32.9	23.4[a]
C-5	23.7	19.8	19.6	23.6[a]
C-6	33.1[a]	27.5	30.8	28.4

[a] Assignments may be interchanged.

optically active isomeric diols.

The stereochemistries of **2** and **4** were assigned by oxidizing each of the compounds, by a two-step procedure, to 2-phenyladipic acid of established absolute stereochemistry.[10] Thus (+)-**2** yielded (+)-(*S*)-2-phenyladipic acid and (+)-**4** yielded (−)-(*R*)-2-phenyladipic acid. Since the relative stereochemistries of **2** and **4** are known (see section in NMR), it follows that (+)-**2** is (1*S*,2*R*,3*S*) and (+)-**4** is (1*R*,2*R*,3*R*). The absolute stereochemistries of **6** and **8** follow from their method of preparation: (+)-(*R*)-3-phenylcyclohexene yielded (−)-**8** (1*R*,2*S*,3*S*) on oxidation, which was converted to (+)-**6** (1*R*,2*R*,3*S*) by Newman's procedure.

The availability of optically active samples of these isomeric diols has permitted us to examine a suggestion by Verbit and Price[8] concerning the relation (quadrant rule) between the sign of the shorter wavelength (~220 nm) circular dichroism (CD) band and the compound's absolute stereochemistry. These authors had examined a limited number of 2-substituted phenylcyclohexanes and therefore it was desirable to study additional test compounds. In order to establish the conformations of the 3-phenyl-1,2-dihydroxycyclohexane isomers present and/or the possible presence of conformational equilibria we examined the ^1H and ^{13}C NMR spectra.

The results of the ^1H NMR spectra are summarized in Table I and the observed coupling constants suggest that the predominant conformer of compounds **2**, **4**, **6**, and **8** is that shown. In an analogous series of 3-methylcyclohexane-1,2-diols the ^1H NMR and the ^{13}C NMR spectra indicated[3] the presence of a conformational equilibrium for the trans,cis diol. The coupling constants $J_{1,2}$ and $J_{2,3}$ in the methyl series were 8.8 and 4.8 Hz, respectively, suggesting that in this isomer the conformation with equatorial hydroxyl groups and an axial methyl group was present in significant concentrations. The values for the trans,cis isomer **6** are $J_{1,2} = J_{2,3} = 3.0$–3.1 Hz, indicating that both hydroxyl groups are axial while the phenyl ring is equatorial in the preferred conformation. The phenyl group is equatorial in each preferred conformer, as a consequence of the large free-energy difference between an equatorial and axial phenyl.

In pursuing our interests[3] of assigning carbon-13 chemical shifts in stereochemical studies, we determined the carbon-13 spectra of the isomeric 3-phenyl-1,2-dihydroxycyclohexanes.

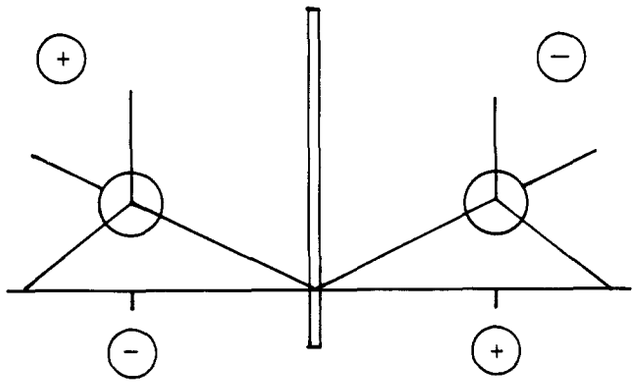


Figure 1.

The chemical shifts of C-1 and C-2 in **2** and **4** were assigned using deuterated compounds. Reduction of **3** with lithium aluminum deuteride yielded **2** and **4** with a deuterium atom on C-2 and a comparison of the ^{13}C NMR spectra of these samples with those of nondeuterated material easily established the identity of the C-2 resonance. The C-2 resonances in **6** and **8** were assigned by decoupling at a single frequency on a Varian XL-100 spectrometer. The frequency of the C-2 proton of **6** was established, in the ^1H NMR spectrum, in a decoupling experiment by irradiating the proton on C-3. Irradiating at the C-2 proton frequency (δ 4.02) decoupled C-2 in the ^{13}C NMR spectrum. The C-2 proton of **8** was assigned from an analysis of its coupling constants in the ^1H NMR and irradiating at this frequency (δ 4.09) identified the C-2 resonance in the ^{13}C NMR spectrum.

The chemical shift of C-3 in the ^{13}C NMR spectrum differed sufficiently from the other resonances present and consequently was easily assigned. The highest field resonance of those remaining was tentatively assigned to the C-5 carbon. In order to distinguish between C-4 and C-6 where possible and to verify the C-5 assignment Table III was prepared where differences in chemical shifts for pairs of compounds associated with changing an equatorial hydroxyl group for an axial hydroxyl were compared. Assignments were made to minimize differences between the two possible methods of calculation. The results show that this is possible, within 1.5 ppm, for carbons 4, 5, and 6. Although alternate assignments result in much greater differences, these assignments are tentative. While the ^1H NMR spectra were used to assign the stereochemistry of three of the four isomers, the ^{13}C NMR spectrum of **4** could be used in conjunction with the ^{13}C NMR spectra of the other isomers to assign the stereochemistry of **4**.

In examining the relationship between the sign of the chiroptical effect associated with substituted benzenes and their absolute stereochemistry several investigators[13] have recorded the CD spectra of natural products where the aromatic ring was substituted in a variety of ways. In some cases the conclusions from such studies are rather limited and controversial. In a theoretical treatment of the symmetry rules for the chiroptical properties of monosubstituted benzenes (and other chromophores), Schellman[14] argued that the sign of the CD band should be governed by a quadrant rule. The most reliable method of establishing a rule relating the sign of a CD band with absolute stereochemistry involves employing compounds with rigid geometries. The fact that monosubstituted benzene derivatives are not rigid helps one to understand why little progress has been made since the quadrant rule was first suggested.[8] Verbit and Price prepared several 1-substituted 2-phenylcyclohexanes and analyzed the sign of the CD curves associated with the short wavelength, ^1L_a transition, by means of a quadrant rule. The quadrants were formed from the intersection of the plane of the benzene ring and a cyclohexane ring plane perpendicular to it, as shown in Figure 1. The signs

Table III. Differences in ^{13}C Chemical Shifts Associated with Changing an Equatorial to Axial Hydroxyl Group

Position	Position at which change occurs	Orientation of constant hydroxyl group	Isomers being compared	Difference, ppm
C-1	C-2	Eq	t,t to c,c	−2.4
		Ax	c,t to t,c	0.8
C-2	C-1	Eq	t,t to c,t	−3.6
		Ax	c,c to t,c	0.3
C-3	C-1	Eq	t,t to c,t	−4.7
		Ax	c,c to t,c	−4.7
	C-2	Eq	t,t to c,c	−3.1
		Ax	c,t to t,c	−3.1
C-4	C-1	Eq	t,t to c,t	−0.2
		Ax	c,c to t,c	+0.7
	C-2	Eq	t,t to c,c	−9.5
		Ax	c,t to t,c	−8.8
C-5	C-1	Eq	t,t to c,t	−4.1
		Ax	c,c to t,c	−3.8
	C-2	Eq	t,t to c,c	−0.1
		Ax	c,t to t,c	0.2
C-6	C-1	Eq	t,t to c,t	−2.3
		Ax	c,c to t,c	−0.9
	C-2	Eq	t,t to c,c	−4.7
		Ax	c,t to t,c	−3.3

Table IV. Summary of CD Data for ^1L_a Transition

Compd	Absolute stereochemistry	θ	λ, nm	Predicted sign	Obsd sign
(+)-8	1*S*,2*R*,3*R*	+5200	215	+	+
(+)-2[a]	1*S*,2*R*,3*S*	+8700	211	+	+
(−)-4	1*S*,2*S*,3*S*	−4600	212	−	−
(+)-6	1*R*,2*R*,3*S*	+6500	215	+	+

[a] Optical purity of sample 40%, θ corrected for optical purity.

associated with the quadrants were assigned from the observed curves, and from symmetry considerations.

One serious limitation of the quadrant rule relates to the validity of analyzing a single rotamer (i.e., the phenyl ring can rotate about the carbon to carbon bond between rings) to determine its contribution to the sign of the CD band. Verbit and Price were able to interpret their data in a consistent fashion if they assumed that the plane of the benzene ring forms the vertical plane while the horizontal plane was chosen as perpendicular to the plane of the benzene ring passing through C-1 of cyclohexane. The presence of an axial substituent at C-2 in either the lower left or upper right quadrant made a levorotatory contribution to the CD band (at ~220 nm) while a substituent in the upper left or lower right quadrants made a dextrorotatory contribution.

We have determined the CD curves of each of the isomeric 1,2-dihydroxy-3-phenylcyclohexanes of known absolute stereochemistry, and have compared the signs predicted by this quadrant rule with those observed (see Table IV). In the case of the (+)-cis,trans isomer, **8**, the equatorial hydroxyl at C-2 makes a weak to moderate dextrorotatory contribution, as does the axial hydroxyl at C-1. The contribution of the latter is assumed to be weak, since its distance from the phenyl ring is greater than that of a substituent at C-2. A positive band was therefore predicted for this compound, in agreement with observations. The axial hydroxyl at C-2 in the (+)-cis,cis, **2**, isomer makes a relatively strong dextrorotatory contribution, while the contribution made by the equatorial hydroxyl at C-1 is very weak and of uncertain sign. In the (−)-trans,trans isomer, **4**, the equatorial hydroxyl at C-2 makes a weak to moderate levorotatory contribution and the equatorial hydroxyl at C-1 is again weak and of uncertain sign. Finally in the case of the (+)-trans,cis isomer, **6**, the axial hydroxyl at C-2 makes a dextrorotatory contribution while a weaker levorotatory contribution is assigned to the axial hydroxyl at C-1. Although the predicted and observed signs agree, the observed magnitude is significantly larger than that expected from summing contributions from each center. *Thus it is desirable to have additional results before attributing too much significance to quantitative aspects of the rule.*

The synthesis of optically active samples of **2**, **4**, **6**, and **8** and information as to their absolute stereochemistries has allowed us to examine systematically the relationship (quadrant rule) between the sign of the CD band for the ^1L_a transition with the compounds' absolute stereochemistries. The good agreement between predicted and observed signs has strengthened the experimental basis of the rule.

Experimental Section

The ^1H NMR spectra (in $CDCl_3$ solution) were determined on a Varian HR-220 MHz spectrometer operating at 220 MHz and at ambient probe temperature (20 ± 1 °C). The chemical shifts are measured downfield in parts per million from tetramethylsilane as an internal reference. The Fourier transform carbon-13 spectra were obtained on a Bruker WH-270 MHz spectrometer (operated at 67.9 MHz) with a Raytheon computer using the same solvent and reference. The single frequency decoupled carbon-13 spectra were obtained on a Varian XL-100 spectrometer (at 25 MHz) equipped with a Digilab Fourier transform accessory.

Synthesis of Racemic Compounds. *cis*-2-Acetoxy-6-phenylcyclohexanone (3). Compound **3** was prepared by mercuric acetate oxidation of 2-phenylcyclohexanone as described by Treibs and Weissenfels.[15]

Preliminary Reduction of 3. To a solution of 3.21 g of **3** in 125 mL of ether was added excess $LiAlH_4$ and the reaction allowed to stand overnight. The reaction mixture was worked up using 25% NaOH to yield 1.96 g (yield 74%) of a mixture, which was chromatographed on silica gel (60–80 mesh) with ethyl acetate–hexane to yield 1.254 g of the less polar **2** and 0.583 g of the more polar **4**. The diols were crystallized from benzene–hexane: **2**, mp 116–117 °C, and **4**, mp 116–118 °C. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found for **2**: C, 75.20; H, 8.57. Found for **4**: C, 74.70; H, 8.50.

Preparation of 6. To a solution of 968 mg of 3-phenylcyclohexene[16] in 4 mL of CH_2Cl_2 was added a solution of 1.34 g of *m*-chloroperbenzoic acid in 20 mL of CH_2Cl_2 at 0 °C and the mixture was allowed to stand overnight. The crude epoxide was hydrolyzed in 25 mL of THF containing 2 mL of 6% aqueous $HClO_4$ at room temperature overnight. The diol was isolated by preparative thick layer chromatography on silica gel (2 mm) using two developments with 30% ethyl

Table V. Chiral Reduction of 3 with $LiAlH_4$–*l*-Darvon Complex

Ketone:$LiAlH_4$:R*OH, molar ratios	Product	Yield, %	$[\alpha]^{25}D$[a]	c, g/100 mL	Opt yield, % (NMR)	Confign
	9	12	−4.17	1.15	8[b]	1*S*,2*R*,3*S*
1:1:1	**2**	49	+7.36	2.50	10[c]	1*S*,2*R*,3*S*
	4	23	+7.70	1.35	24[d]	1*R*,2*R*,3*R*
	9	20	+4.91	2.93	10[b]	1*R*,2*S*,3*R*
1:1.5:3	**2**	38	+33.8	2.16	46[c] [42][e]	1*S*,2*R*,3*S*
	4	21	+23.1	4.00	72[d] [77][e]	1*R*,2*R*,3*R*

[a] Solvent MeOH. [b] Based on calculated maximum rotation of $[\alpha]^{25}D$ +4.43°/0.09 optical purity = 49°. [c] Based on rotation of metabolite +72.7°. A similar value was obtained from $[\alpha]^{25}D$ +28.8/0.38 = 75.8°. [d] Based on calculated rotation +32°. [e] Values in brackets obtained from optical purity of 2-phenyladipic acid.

acetate–70% hexane to yield 206 mg of **6**, crystals from benzene–hexane, mp 103.5–104.5 °C. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found for **6**: C, 74.90; H, 8.45.

Preparation of 7. A sample of **3** was hydrolyzed with methanolic KOH as described by Treibs and Weissenfels.[15] The NMR spectrum of the product showed a doublet at δ 4.20 for the proton on the hydroxyl bearing carbon with $J_{2,3}$ = 12 Hz in agreement with that reported by Vedejs.[6] On acetylation with acetic anhydride/pyridine the product **7** showed absorption at δ 5.36 with $J_{2,3}$ = 14 Hz.

Preliminary Reduction of 7. A solution of **7** (170 mg) was treated with $LiAlH_4$ and worked up as above to yield the more polar **4** (54 mg) and less polar **8** (17 mg). The cis,trans diol **8** was crystallized from benzene–hexane, mp 106–107 °C. Anal. Found for **8**: C, 75.21; H, 8.55.

Synthesis and Oxidation of Optically Active Compounds. Asymmetric Reduction. Asymmetric reduction of **3** was conducted at 0 °C for 16 h using the lithium aluminum hydride–*l*-darvon complex prepared according to the procedure of Yamaguchi and Mosher.[17] The products were separated by thick layer chromatography (2 mm silica gel, 40% ethyl acetate–hexane) and sublimed. The results for 1 mmol of ketone are shown in Table V. The reduction of **7** was conducted in the same way to give (−)-**4** (28%), $[\alpha]^{25}D$ −1.7° (*c* 2.67, MeOH), optical yield 5%.

1-Acetoxy-2-hydroxy-3-phenylcyclohexane [**9**, 58 mg, $[\alpha]^{25}D$ +4.43° (*c* 4.15, methanol)] from several experiments was treated overnight with lithium aluminum hydride (40 mg) in ether (1 mL). Excess hydride was decomposed by the addition of a small amount of water, the aluminum hydroxide precipitate was dissolved in 2 N NaOH, and the mixture was extracted with ethyl acetate. Removal of solvent yielded 50 mg of colorless oil, which was purified by thick layer chromatography (silica gel 2 mm, 40% ethyl acetate–hexane) to give 36 mg of cis,cis diol as colorless crystals, $[\alpha]^{25}D$ −6.44° (*c* 1.8, MeOH), optical purity 9%.

Determination of Enantiomeric Excesses Using Eu(hfbc)$_3$. The sample was first treated with several drops of D_2O in $CHCl_3$ and the D_2O and $CHCl_3$ removed by azeotropic distillation with benzene. The sample was then dissolved in deuteriochloroform and small quantities (weighed) of tris(3-heptafluorobutyryl-*d*-camphorato)-europium(III) were added for optimum separation of the chemical shifts between enantiomers. When the signals due to the C-1 proton of each enantiomer were essentially or completely separated from each other, the areas under each peak were integrated. The averaged integration value was used to estimate the enantiomeric excesses present. The value (38% ee) observed for a sample of **2** agreed with the optical purity (40%) obtained if one assumed that the reduced metabolite from biphenyl were optically pure ($[\alpha]^{25}D$ 72.7°). **2**: $[\alpha]^{25}D$ +28.8° (*c* 4.75, MeOH); solvent, $CDCl_3$; concentration 0.2 mol/L; Eu/s 0.15; separation between peaks 0.23 ppm.

In an earlier report[4] the ee of a sample of **2** ($[\alpha]^{25}D$ +33.8°) was estimated as 64% using the chiral shift reagent. Since the diol had not been treated with D_2O, the presence of water resulted in a systematic error in estimating the enantiomeric excess of **2**.

Oxidation of (+)-*trans,trans*-1,2-Dihydroxy-3-phenylcyclohexane (4). To the solution of trans,trans diol [55 mg $[\alpha]^{25}D$ +23.1° (*c* 3.21, MeOH)] in 70% ethanol (2 mL) was added sodium periodate (75 mg) in the same solvent (6 mL) at room temperature and the solution stirred for 3 h. After dilution with water, the mixture was extracted with ethyl acetate and then washed with saturated sodium chloride solution. The solvent was removed in vacuo to leave 52 mg of colorless oil (2-phenyladipinaldehyde). This was dissolved in water (20 ml) and cooled to 0 °C. After addition of calcium carbonate (160 mg), 3.6 mL of bromine water was added while stirring. Stirring was continued for 3 h at 0 °C, then the mixture was made alkaline with saturated sodium bicarbonate solution and extracted with ether. The water layer was acidified with a few milliliters of concentrated hydrochloric acid, extracted into ethyl acetate which was washed with sodium chloride solution, and dried over sodium sulfate. Vacuum evaporation of solvent afforded 44 mg of 2-phenyladipic acid [$[\alpha]^{25}D$ −49° (*c* 2.2, EtOH), optical purity 77%]. Reported[10] for (−)-(*R*)-2-phenyladipic acid, $[\alpha]^{25}D$ −63.6°.

OsO_4 Oxidation of (−)-(*S*)-3-Phenylcyclohexene. To 130 mg of (−)-(*S*)-3-phenylcyclohexene[9] was added a solution of 250 mg of OsO_4 in 2.5 mL of pyridine. The solution was allowed to stand overnight in the refrigerator, poured into water containing sodium sulfite, and stirred overnight, and the product was purified by thick layer chromatography to yield 158 mg of **8**, $[\alpha]^{25}D$ +63.5° (*c* 1.02, methanol). The diol was purified by recrystallization twice from hexane containing small amounts of ethyl acetate to give colorless needles (70 mg, mp 90–91 °C), $[\alpha]^{25}D$ +80.9° (*c* 1.31, MeOH).

In addition to high optical purity of the starting material, and since the product melting point was not changed by repeated recrystallizations, these crystals were considered optically pure. Furthermore, the diol from (*R*)-(+) olefin showed an $[\alpha]D$ of equal but opposite sign.

A chiral shift reagent [Eu(hfbc)$_3$] experiment on this diol ($[\alpha]^{25}D$ −75°) showed no distinct signal splitting of the protons on C_1 and C_2, while the racemic diol over the same concentration range of diol and chiral shift reagent showed two sets of doublets.

Preparation of Optically Active 6. The cis,trans diol from (+)-(*R*)-3-phenylcyclohexene [80 mg, $[\alpha]^{25}D$ −81° (*c* 1.43, MeOH)] was heated at 100 °C for 2 h with trimethyl orthoacetate (200 mg) in the presence of a catalytic amount of benzoic acid according to the method of Newman.[7] Excess orthoacetate was removed under reduced pressure, and the residue was dissolved in 2 mL of methylene chloride and heated at 60 °C with trimethylsilyl chloride (0.12 mL) overnight. Excess trimethylsilyl chloride was removed in vacuo to leave a residue (109 mg), which was treated with 2 N KOH in 2-propanol at 60 °C for 2 h. After dilution with water, the reaction mixture was extracted with ether and washed with water, and the ether extracts were dried over sodium sulfate. Removal of the solvent yielded a colorless oil (67 mg), which was purified by thick layer chromatography to give 60 mg of (+)-(1*R*,2*S*,3*S*)-epoxide [$[\alpha]^{25}D$ +3.4° (*c* 2.65, benzene)] as a colorless oil. This epoxide was hydrated without further purification.

An 80% dioxane solution containing epoxide (53 mg) and 4 drops of 60% perchloric acid was allowed to stand overnight at room temperature. The reaction mixture was diluted with water, extracted with ether, and washed with saturated sodium bicarbonate solution and water. The solvent was evaporated in vacuo to leave 61 mg of colorless oil, which was submitted to thick layer chromatography (silica gel, 40% ethyl acetate–hexane).

The less polar band gave crude trans,cis diol [$[\alpha]^{25}D$ +66.7° (*c* 1.65 MeOH)], which was further purified by distillation (bath temperature 100–120 °C, 0.2 mm Hg) to give 27.2 mg of colorless oil [$[\alpha]^{25}D$ +72.1° (*c* 1.36, MeOH)].

From the more polar band the trans,trans diol [17 mg, $[\alpha]^{25}D$ −21.4° (*c* 0.85, MeOH)] was obtained as colorless crystals. This crude product was recrystallized from hexane–ethyl acetate mixture to give 7 mg of diol [mp 121–122 °C, $[\alpha]D$ −32° (*c* 0.35, MeOH)]. Further recrystallization did not change the melting point.

Acknowledgment. We wish to thank Dr. Ulrich Weiss for valuable discussions.

Registry No.—(±)-**2**, 61664-47-9; (+)-**2**, 57525-74-3; (±)-**3**, 61664-45-7; (±)-**4**, 61664-46-8; (−)-**4**, 61664-48-0; (+)-**4**, 57525-75-4; (±)-**6**, 61664-49-1; (+)-**6**, 61664-50-4; (−)-**6**, 61664-51-5; (±)-**7**, 61604-83-9; (±)-**8**, 61664-52-6; (+)-**8**, 61664-53-7; (+)-**9**, 61604-84-0; (−)-**9**, 61664-54-8; 3-phenylcyclohexene, 15232-96-9; *m*-chloroperbenzoic acid, 937-14-4; 2-phenyladipinaldehyde, 61604-85-1; (−)-(*R*)-2-phenyladipic acid, 61604-86-2; (−)-(*S*)-3-phenylcyclohexene, 61604-88-4; (+)-(*R*)-3-phenylcyclohexene, 17540-19-1; 8-methoxy-8-methyl-2-phenyl-7,9-dioxa[4.3.0]nonane, 61604-87-3.

References and Notes

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(12) The ^{13}C NMR spectrum of **8** obtained by irradiating at a single frequency corresponding to the chemical shift of the proton at C-1 (δ 4.09) was used to identify C-1. The ^{13}C NMR spectrum of **6** obtained by irradiating at a single frequency corresponding to the chemical shift of the proton at C-1 (δ 4.02) was used to identify C-1.
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Stereochemistry of Nucleophilic Addition Reactions. 2.[1] Kinetically Controlled Reaction of Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside with Hydrogen Cyanide. Important Role of Electrostatic Interaction

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The reaction of title compound **1** with hydrogen cyanide gave the 2-cyano-3-nitroglucopyranoside **5** and the 2-cyanohex-2-enopyranoside **6** in good yield. The data suggest that cyanide ion adds irreversibly from the equatorial side of **1** and that the intermediate of **6** is the 2-cyano-3-nitroallopyranoside **7**. The additions of hydrazoic acid and *p*-toluenesulfinic acid to **1** also gave the adducts with the gluco configuration. The stereochemistry of nucleophilic addition reactions to **1** and its α anomer **2** was discussed in terms of electrostatic interaction, stereoelectronic control, and steric hindrance.

Under the conditions of kinetic control axial attack of a nucleophile generally predominates in the nucleophilic addition reactions of conformationally rigid cyclohexene derivatives.[2] This is attributed to stereoelectronic control;[3] almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state leads to a product with the newly attached substituent in an axial orientation on a chair form rather than the alternative quasi-axial on a boat conformation. Exceptions to this are reported by Abramovitch and co-workers in the reactions of diethyl malonate to 4-*tert*-butyl-1-cyanocyclohexene[4] and 4-*tert*-butylcyclohexene-1-carboxylate,[5] in which preferred equatorial attack of the bulky diethyl malonate was attributed to large diaxial nonbonded interactions in the transition state for axial addition. On the other hand, regardless of the bulkiness various kinds of nucleophiles added from the equatorial side of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**1**);[6-8] these results do not appear to be explained by steric hindrance only. From the facts that some reactions of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-*erythro*-hex-2-enopyranoside (**2**) (the α anomer of **1**) gave the thermodynamically less stable α-D-mannopyranoside[7,9] we cannot immediately conclude that the corresponding reactions of **1**, which gave the more stable β-D-glucopyranoside, are also controlled kinetically, because the β-D-mannopyranoside should be much less stable than the α-D-mannopyranoside due to Δ^2 effect[10] and easily epimerize to the stable β-D-glucopyranoside. In fact, predominance of axial attack was found in the reactions of **1** with *o*-aminobenzoic acid[11] and hydrogen cyanide,[12] where the less stable β-mannopyranoside were isolated in 56 and 15% yield, respectively. On the contrary, we have shown that the reaction of phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside with hydrazoic acid in THF–deuterium oxide exclusively gave the adduct with the gluco configuration, of which about 50% were deuterated at C-3, indicating that it is controlled kinetically, at least partially.[8]

In addition, methyl 4,6-*O*-benzylidene-2-deoxy-2-nitro-β-D-glucopyranoside (**3**) and the corresponding 3-nitro sugar were obtained in 14 and 70% yield, respectively, in the reaction of **1** with nitrous acid,[13] where a dinitro intermediate should be involved, at least, in the formation of the 2-nitro sugar **3**. If nitrite ion added to the C-2 position from the equatorial side, the dinitro intermediate has the allo and/or gluco structure. The former should give predominantly 2-nitrohex-2-enopyranoside since the nitro group at C-3 is in a trans-diaxial relationship with H-2; however, the latter seems to lack such a high degree of selectivity. The yield of the 2-nitro sugar **3**, therefore, should be affected by stereochemistry