Evidence of Stereoelectronic Control in Osmium-Catalyzed Cis-Dihydroxylations of Sterically Unbiased 3,3-Diarylcyclopentenes

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Abstract: This study provides strong evidence for the stereoelectronic control of diastereoselectivity in the osmium tetraoxide-catalyzed cis-dihydroxylation of sterically unbiased 3-(4-X-phenyl)-3-phenylcyclopentenes **1** (X = NO_2, Br, Cl, OCH_3, $N(CH_3)_2$), producing diastereomeric *cis*-diols **2** in cis:trans ratios (diol relative to the substituted arene) varying from 70:30 to 36:64 as determined by ^1H NMR and ^{13}C NMR spectroscopy. The reactions were carried out at room temperature in an 8:1 acetone/water solvent system, utilizing trimethylamine *N*-oxide as the terminal oxidant. Structural assignments were made by 2D-NOE ^1H NMR spectroscopy, ^{13}C NMR spectroscopy, and X-ray crystallographic analysis. In all cases the addition occurred opposite the more electron-rich aromatic ring as predicted by Cieplak's theory for explaining stereoelectronic control. The observed ratios correspond to an overall energy difference of 1.1 kcal/mol. A Hammet plot of log (cis:trans) versus the σ_p parameter produced a linear relationship with a correlation coefficient of 0.97. An efficient synthesis of the diarylcyclopentenes is described. The diastereomeric diols, or derivatives thereof, were separable by preparatory thin-layer chromatography.

The effectiveness of asymmetric synthesis lies in the chemist's ability to control facial selectivity in organic reactions that can produce multiple isomers.[1] The selectivity in many organic transformations has been considered to be a result of steric interactions, but recent work studying the stereoelectronic control of stereoselective reactions has challenged this view.[2] The osmium tetraoxide-catalyzed cis-dihydroxylation of olefins, due to its importance as a synthetic method for the stereoselective preparation of *cis*-diols, has been the subject of intense scrutiny in an effort to understand and control diastereoselectivity in the oxidation of chiral alkenes. The stereoselective addition of osmium tetraoxide to several classes of synthetically interesting chiral substrates has recently appeared in the literature;[3] the substrates include allylic alcohols,[4] enoates,[4b] allylsilanes,[5] α,β-unsaturated esters,[6,7] and 1,1-disubstituted olefins containing an allylic, oxygen-bearing stereocenter.[8] The origin of the observed π-facial stereoselection of the dihydroxylation of chiral substrates is not well-understood and has been the object of a number of studies,[4a,7,8] several of which examine the role of stereoelectronic effects.[9] From a study of electrophilic cycloadditions involving acyclic allyl ethers, Houk et al. suggested that dihydroxylation opposite the best donor could be explained by a $\sigma-\pi$ electron donation stabilization of the transition state, though steric concerns would still dominate the selectivity.[9a] In a later study of the osmylation of allylic ethers, Vedejs et al. supported Houk's finding by concluding that steric interactions in the osmylation transition state were the primary cause of their observed selectivities.[9b] The free rotation of the aforestudied acyclic allylic ethers added an undesirable degree of complexity to the issue of sterics versus stereoelectronics in the osmium tetraoxide dihydroxylation of alkenes. Cieplak and Johnson avoided this complication by utilizing a cyclic substrate; they have published experimental evidence supporting a stereoelectronic effect in the osmylation reaction of 3-substituted methylenecyclohexanes.[9c] Recently, Vedejs and Dent have also taken advantage of the cyclohexyl framework in their study of the osmylation of 2-substituted 4-*tert*-butylmethylenecyclohexane derivatives.[9d] Their results showed no correlation between the electronic nature of the 2-substituent and the observed selectivity, which could be better explained by the interplay of steric factors, leading to the conclusion that steric considerations were much more important than stereoelectronic effects in controlling diastereoselectivity in the osmium-catalyzed dihydroxylation of these sterically biased alkenes. In the Cieplak and Johnson methylenecyclohexane study, although the conformational nature of the 6-membered ring contains a steric bias which predisposes the system toward axial attack, it was observed that as the remote equatorial 3-substituent was made a better electron donor the amount of equatorial attack increased. This result is consistent with the notion of stereoelectronic control as proposed by Cieplak.[10] The fact that Vedejs and Dent saw no such evidence for hyperconjugative effects in their study of a similar substrate could be a consequence of overwhelming 1,2-steric interactions between the original bond and the developing bond that do not exist in the Cieplak and Johnson 3-substituted methylenecyclohexane study. No study demonstrating stereoelectronic control in the osmylation of sterically unbiased alkenes has been reported.

We have been engaged in studying stereoelectronic effects to determine the degree of stereoselectivity in a variety of reactions involving sterically unbiased but electronically biased substrates. Recently we reported diastereoselectivity in the sodium borohydride reduction of sterically unbiased 2-(4-X-phenyl)-2-phenylcyclopentanones (X = NO_2, Br, Cl, OCH_3, OH, NH_2), producing diastereomeric cyclopentanols with stereoselectivities ranging from 79:21 to 30:70.[11] These ratios reflected a systematic trend of addition occurring opposite the best electron donor, a

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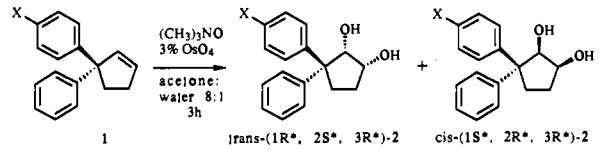
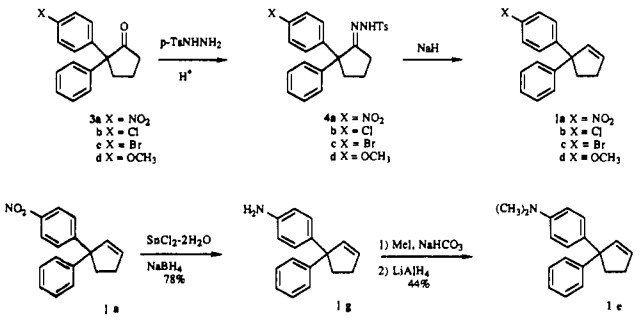


Figure 1. Dihydroxylation of 3,3-diarylcyclopentenes **1** X = (a) NO_2, (b) Cl, (c) Br, (d) OCH_3, (e) $N(CH_3)_2$.

Scheme I



result best explained by stereoelectronic rather than steric control of selectivity in the cyclopentanone reduction. In this paper we report the first example of osmium-catalyzed cis-dihydroxylations on the related sterically unbiased olefins, 3-(4-X-phenyl)-2-phenylcyclopentenes, a stereoselective reaction which also appears to be governed by stereoelectronic control (Figure 1).

Results

Synthesis of 3,3-Diarylcyclopentenes. The efficient synthesis of the four olefinic substrates **1a–d** proceeded via a Kwok elimination reaction[12,13] of the tosylhydrazones **4a–d** derived from the known 2,2-diarylcyclopentanones **3a–d**.[11] The synthesis of **1a** (X = NO_2) described here was quite analogous to the preparation of **1b** (X = Cl), **1c** (X = Br), and **1d** (X = OCH_3) (Scheme I). The toluenesulfonohydrazide conversion of 2-(4-nitrophenyl)-2-phenylcyclopentanone (**3a**) to its corresponding tosylhydrazone **4a** was accomplished in 60% yield without the need for further purification.[14] Sodium hydride-induced elimination of hydrazone **4a** to 3,3-diarylcyclopentene **1a** occured in 66% yield.[12] Selective reduction of the nitro functionality with sodium borohydride in the presence of tin dichloride proceeded in 78% yield to give amino-substituted alkene **1g**.[15] Exhaustive methylation of the amino group with methyl iodide followed by lithium aluminum hydride-induced loss of methane allowed for the generation of the (dimethylamino)phenyl substrate **1e**, which after preparative thin-layer chromatography gave pure **1e** as an orange oil in 44% yield.[16]

Asymmetric Osmium-Catalyzed Dihydroxylations. The five monosubstituted 3,3-diphenyl-substituted substrates were subjected to catalytic osmium tetraoxide cis-dihydroxylation in an 8:1 acetone/water solvent system at room temperature for approximately 3 h, with trimethylamine *N*-oxide acting as the terminal oxidant (Figure 1).[17,18] Thin-layer chromatography was used to follow the progress of the reaction, which was quenched with sodium bisulfite upon completion. The crude *cis*-diols were isolated by extraction into ethyl acetate. Exhaustive extraction of the aqueous portion with ethyl acetate was performed to prevent any diasteromeric enhancement due to incomplete product recovery. The combined organic portions were dried and concentrated to provide, in high yield, a diastereomeric mixture of diols. In each instance the ^1H and ^{13}C NMR spectra were recorded of the crude diols and the diasteromeric ratios taken from these spectra. The diastereomeric diols, or derivatives thereof, were purified by preparative thin-layer chromatography and fully characterized.

Table I. Ratios of Osmylation Products for Varying Para Substituents (X) of **2**

X	alcohol	σ_p	% trans	% cis	log (cis:trans)
NO_2	**2a**	0.778	30	70	0.368
Cl	**2b**	0.227	43	57	0.122
Br	**2c**	0.232	45	55	0.087
(H)	**2f**	0.0	(50	50)	0.0
OCH_3	**2d**	−0.268	57	43	−0.122
$N(CH_3)_2$	**2e**	−0.83	64	36	−0.301

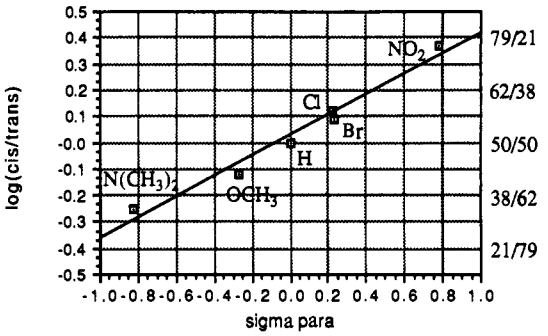


Figure 2. Graph of selectivity in formation of diastereomeric diols **2** vs σ_p value (correlation of 0.9 slope of 0.46).

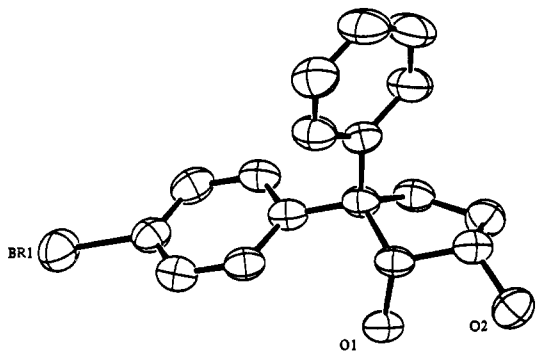


Figure 3. ORTEP plot of the major isomer of diol **2c** (X = Br) showing the 50% probability thermal ellipsoids.

The results of the dihydroxylations are summarized in Table I. The osmylations of these sterically unbiased olefins gave selectivities as high as 70:30 and an overall energy difference of 1.1 kcal/mol between addition opposite the (dimethylamino)phenyl ring in cyclopentene **1e** and addition opposite the unsubstituted phenyl ring in the nitrophenyl substrate **1a**. Assignments of stereochemistry were crucial and are discussed below. A graph (Figure 2) of the selectivities (expressed as log (cis:trans)) versus σ_p values for the substituents (NO_2, Cl, Br, H, OCH_3, $N(CH_3)_2$) can be linearly correlated with a coefficient of 0.97. The value for the nondiastereomeric diphenyl product, necessarily 50:50, has been added to the experimental data set.

Structure Determination. As in our earlier study of the stereochemistry of the cyclopentanone reduction, assignment of the stereochemistry of the diols was established by 2D ^1H NMR NOE (NOESY) studies[19] and ^{13}C NMR chemical shift correlations.[20]

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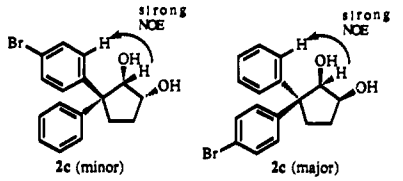

Figure 4. NOE results for bromo-substituted diol **2c**.

Confirmation of the stereochemical assignment through X-ray crystallographic analysis of the major isomer of the bromo-substituted diol was also accomplished (Figure 3). In all cases, with the exception of **2e** (X = OCH_3), the diastereomers could be separated via preparative thin-layer chromatography, and spectroscopic analysis was performed on the pure isomers. For the methoxy derivative **2e** it was necessary to convert the mixture of diols to the corresponding acetonides,[21] from which the diastereomers could then be separated by preparatory thin-layer chromatography. One isomer of the acetonide was back-correlated with the methoxy-substituted *cis*-diol **2e** by deprotection with BCl_3–$S(CH_3)_2$.[22]

The usefulness of the two-dimensional nuclear Overhauser experiment for structural determination was made possible by the sufficient resolution of the hydrogen resonances on the substituted and unsubstituted phenyl rings of the isomeric diols **2a**, **2c**, and **2d** (X = NO_2, Br, $N(CH_3)_2$) and the acetonide of the methoxy diol **2e**. The NOESY spectra were recorded for the major isomers of **2c** and **2d** (X = Br, $N(CH_3)_2$) and for the acetonide derived from the major methoxy diol **2d** (X = OCH_3), as well as recording spectra from the minor isomers of diols **2a** and **2c** (X = NO_2 and Br). The complementary results of the major and minor bromo-substituted diols **2c** were particularly supportive of our structural assignments. The major isomer exhibited a strong positive NOE effect between the tertiary hydrogen and the upfield hydrogens on the unsubstituted ring (Figure 4). The minor isomer clearly gave a positive NOE effect for the same tertiary hydrogen with the upfield hydrogens on the substituted phenyl ring. For each diol the result of the NOESY study was consistent with the assignment of stereochemistry given in Table I.

Supportive evidence for correct stereochemical assignments was found in the ^{13}C NMR spectra for the various diols. Since there is a hydroxyl group γ to the ipso carbons in the aromatic rings, a larger upfield shift of these carbons was expected when the ipso aromatic carbon was cis to the hydroxyl group.[20] The pattern of chemical shifts observed for each of the diol mixtures studied supported the assignments in Table I.

A final measure of the accuracy of our structural assignments was achieved through X-ray crystallographic analysis. A single-crystal X-ray diffraction study was performed on a colorless cubelike crystal of the major isomer of the bromo-substituted diol **2c** obtained from uninduced crystallization of the original oil upon standing at room temperature. The structure was solved using the TEXSAN program.[23] Details are given in the Experimental Section. From the ORTEP drawing for **2c** in Figure 3, the syn relationship between the hydroxyl groups and the substituted phenyl ring was clearly established.

In order to check for solvent or field effects, the osmium-catalyzed dihydroxylations of cyclopentenes **1** were repeated in *tert*-butyl alcohol, 8:1 *tert*-butyl alcohol/water, 3:1 THF/water, and 8:1 THF/water. Although the dielectric constants for these mixtures varied significantly, the diastereomeric ratios recorded in each case for the reactions in these various solvent systems were within experimental limits, the same as those obtained in the 8:1 acetone/water cases.

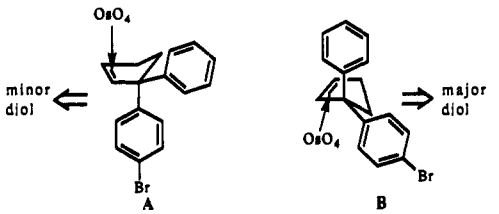

Figure 5. Postulated diastereomeric pathways for the dihydroxylation reaction.

Discussion

Our system has several advantages over those used previously to probe stereoelectronic control. The cyclopentyl framework eliminates much of the conformational ambiguity inherent in the freely rotating acyclic systems and much of the inherent steric bias of rigid cyclohexane systems where approach of the electrophile is not geometrically equivalent. Conformational flexibility of the 5-membered ring[24] allows for the geometric equivalence of the competing transition states. The transition state for the approach of osmium tetraoxide to a diarylcyclopentene can easily adopt a conformation in which the approaching osmium tetraoxide is antiperiplanar to a pseudoaxial phenyl group. The relative proximity of the electronically nonequivalent phenyl substituents, located adjacent to the center of reactivity, should induce greater stereoelectronic effects than the more distant 3-substituents in the Cieplak and Johnson methylenecyclohexane study, while the similarity in the size of the two aryl rings in our system avoids the question of facial bias due to the differing 1,2-steric interactions of the Vedejs and Dent methylenecyclohexane system. Our study also avoids the disputed question of whether C–H is a better donor than C–C since both bonds capable of electron donation/acceptance are carbon–carbon bonds.[10,25] An additional reason for investigating the osmylation of diarylcyclopentenes is the synthetically facile variation of the olefin's electronic nature which makes this conformationally flexible substituted 3,3-diarylcyclopentene uniquely suited to the study of stereoelectronic control.

We postulate two diastereomeric reaction pathways, A and B, for the approach of the osmium complex to the alkene (Figure 5). The minor product can be pictured to arise from addition of the osmium tetraoxide complex opposite the more electron-deficient aryl ring, while the major isomer is a result of attack opposite the best electron donor, which in the case of the bromo-substituted olefin is the unsubstituted aryl ring. In each case, the osmium reagent preferentially approaches the alkene and develops a geometry in the transition state antiperiplanar to the pseudoaxial phenyl and gauche to the syn pseudoaxial phenyl group. Although the X-ray structure of **2c** (major) has a hydroxyl group oriented antiperiplanar to a pseudoaxial phenyl group in much the same conformation we anticipate would be present for a transition-state structure, it remains difficult to establish the actual transition-state structure present in solution on the basis of a solid-state product structure. According to our scheme, however, the osmium reagent appears to be in a sterically similar environment along either pathway, and any stereoselectivity observed should be mainly due to electronic differences. This assertion is supported by the experimental data, which clearly show a linear correlation between electronic changes in one phenyl ring and selectivity in the osmylation reaction, a result difficult to explain by other arguments.

(20) Steric compression of the hydroxyl group with the ipso aromatic carbon leads to predictable chemical shifts in the ^{13}C NMR spectrum. See: Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; pp 404 ff.

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The insensitivity we observed for the stereoselectivity of the oxidation reaction with changing solvents is not consistent with strong solvent, π-stacking, or field effects controlling the stereochemical outcome of the reaction, but is not inconsistent with through-bond stereoelectronic control. Although the conformational mobility of the *gem*-diaryl groups could be argued to introduce a source of steric bias in the reactant 3,3-diarylcyclopentenes by inducing a substituent-dependent preference where one aryl ring adopts a sterically more demanding geometry in which the edge of the ring is turned parallel to the alkene and the second aryl group is turned perpendicular to the alkene,[26] it is difficult to rationalize why these conformational preferences would be linearly dependent on the electronic nature of the aryl substituent. We are currently building, however, a rigid analogue of our diarylcyclopentene system, which should result in the resolution of some of the questions concerning possible steric bias.

Conclusion. Evidence for stereoelectronic control in the asymmetric osmium-catalyzed cis-dihydroxylation of the sterically unbiased 3,3-diarylcyclopentenes has been provided. The selectivities can be satisfactorily explained by the Cieplak postulate of stereoelectronic control.[10] The levels of diastereoselectivity due to a variation in the electronic nature of the substrate are more pronounced than those observed in the earlier studies[9c,d] and correspond to an overall energy difference of 1.1 kcal/mol. This is the first study to clearly demonstrate that stereoelectronic control plays an important role in the osmium tetraoxide-induced dihydroxylations of olefins when competing steric factors are removed. Further studies of additional diastereoselectivities reactions and the possible role of phenyl ring conformations are currently under investigation.

Experimental Section

General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl. Dimethylformamide was distilled from calcium hydride. Other reaction and chromatographic solvents were purified and/or dried by standard methods.

^{1}H NMR (1D and 2D) and ^{13}C NMR spectra were recorded on a Varian XL-400 instrument. Data are reported as follows: chemical shifts (δ scale) in parts per million (ppm) relative to residual solvent peaks (multiplicity, coupling constants in hertz, number of hydrogens). For ^{1}H NMR spectra, the peak due to residual $CHCl_3$ is listed at 7.24 ppm and, for ^{13}C NMR spectra, the central peak of the $CDCl_3$ triplet is assigned a chemical shift of 77.0 ppm. Unless otherwise noted, multiplicities and compund ratios are deduced from the electronic integration by the XL-400. Infrared spectra were obtained on the Perkin-Elmer Model 681 spectrometer and were referenced to polystyrene (1601 cm^{-1}). Only characteristic and/or strong signals are reported. Low-resolution mass spectra reported as m/z (relative intensity) and high-resolution mass spectra (obtained by peak matching) were recorded on a Finnegan MAT-90 instrument. Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected.

2-(4-Nitrophenyl)-2-phenylcyclopentanone Tosylhydrazone (4a). General Hydrazone Synthesis. Three drops of concentrated hydrochloric acid were added to a solution of cyclopentanone **3a** (1.087 mmol, 0.306 g) and *p*-toluenesulfonohydrazide (1.305 mmol, 0.243 g) in 95% ethanol (8 mL). The solution was refluxed for 23 h and then cooled to −20 °C. After 24 h, crystals were collected via vacuum filtration. Removal of the solvent under vacuum resulted in a 37% yield of pure white crystalline hydrazone **4a**, which decomposed above 189 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.79 Hz, 2 H), 7.65 (d, J = 8.30 Hz, 2 H), 7.27–7.16 (m, 7 H), 7.10–7.03 (m, 2 H), 2.60 (m, 1 H), 2.42–2.34 (m, 6 H), 1.83 (m, 1 H), 1.72 (m, 1 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 167.29, 152.54, 146.61, 144.85, 142.82, 135.54, 129.92, 129.55, 128.73, 128.38, 128.21, 127.36, 123.14, 60.22, 39.89, 28.47, 21.68, 21.00; IR (KBr pellet) 3160, 2940, 1390, 1330, 1155, 689 cm^{-1}; MS (CI (NH_3) 150 eV) m/z 450 (M^+ + H, 100); HRMS (CI (NH_3) 150 eV) m/z (M^+ + H) calcd for $C_{24}H_{24}SN_3O_4$ 450.1488, obsd 450.1489.

2-(4-Bromophenyl)-2-phenylcyclopentanone Tosylhydrazone (4c). Following the general hydrazone synthesis with cyclopentanone **3c** (1.501 mmol, 0.279 g) gave a 79% yield of hydrazone **4c** as a pale yellow crystal, which decomposed above 188 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.06 Hz, 2 H), 7.58 (s, 1 H), 7.31–7.21 (m, 6 H), 7.12–7.08 (m, 2 H), 6.95 (d, J = 8.54 Hz, 2 H), 3.75–2.39 (m, 5 H), 2.37–2.34 (m, 2 H), 1.80–1.70 (m, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 168.03, 144.65, 143.91, 143.88, 135.62, 131.18, 130.42, 129.90, 128.44, 128.38, 128.31, 126.94, 120.61, 59.81, 39.79, 28.49, 21.74, 20.90; IR (KBr pellet) 3220, 2940, 1390, 1340, 1173 cm^{-1}; MS (CI (NH_3) 150 eV) m/z 485 [(M^+ + 2) + H, 100], 483 (M^+ + H, 95), 405 (6.8), 329 (17); HRMS (CI (NH_3) 150 eV) m/z (M^+ + H) calcd for $C_{24}H_{24}SBrN_2O_2$ 483.0742, obsd 483.0755.

2-(4-Chlorophenyl)-2-phenylcyclopentanone Tosylhydrazone (4b). Following the general hydrazone synthesis with cyclopentanone **3b** (0.886 mmol, 0.240 g) gave a 63% yield of hydrazone **4b** as a white crystal, which decomposed above 192 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.31 Hz, 2 H), 7.32–7.04 (m, 9 H), 7.02 (d, J = 8.54 Hz, 2 H), 2.52–2.40 (m, 5 H), 2.33 (m, 2 H), 1.79–1.72 (m, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 168.01, 144.64, 143.96, 143.29, 135.61, 132.40, 130.02, 129.88, 128.42, 128.36, 128.29, 128.20, 126.92, 59.72, 39.81, 28.42, 21.71, 20.87; IR (KBr pellet) 3210, 2980, 1383, 1337, 1168 cm^{-1}; MS (CI (NH_3) 150 eV) m/z 441 [(M^+ + 2) + H, 39], 439 (M^+ + H, 100), 283 (7.8); HRMS (CI (NH_3) 150 eV) m/z (M^+ + H) calcd for $C_{24}H_{24}SClN_2O_2$ 439.1247, obsd 439.1249.

2-(4-Methoxyphenyl)-2-phenylcyclopentanone Tosylhydrazone (4d). Following the general hydrazone synthesis with cyclopentanone **3d** (0.691 mmol, 0.184 g) gave a 59% yield of hydrazone **4d** as a pale yellow crystal, which decomposed above 195 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.25 Hz, 2 H), 7.28–7.19 (m, 5 H), 7.10–7.04 (m, 4 H), 6.75 (d, J = 8.79 Hz, 2 H), 3.81 (s, 3 H), 2.49–2.45 (m, 5 H), 2.35–2.31 (m, 2 H), 1.77–1.74 (m, 2 H); ^{13}C NMR (100 MHz, CD_2Cl_2) 168.80, 158.45, 144.91, 144.52, 136.16, 135.77, 129.88, 129.49, 128.40, 128.35, 128.20, 126.59, 113.53, 59.49, 55.48, 39.91, 28.44, 21.73, 20.85; IR (KBr pellet) 3185, 2940, 1395, 1334, 1346, 1170 cm^{-1}; MS (CI (NH_3) 150 eV) m/z 435 (M^+ + H, 100), 279 (9.9), 250 (28); HRMS (CI (NH_3) 150 eV) m/e (M^+ + H) calcd for $C_{25}H_{27}SN_2O_3$ 435.1742, obsd 435.1732.

3-(4-Nitrophenyl)-3-phenylcyclopentene (1a). General Olefination Procedure. A slurry of sodium hydride (0.712 mmol, 0.028 g) in dimethylformamide (2 mL) was added to a solution of hydrazone **4a** (0.356 mmol, 0.160 g) in dimethylformamide (5 mL). The mixture was stirred at 95 °C for 18 h, cooled to room temperature, and quenched with 5 drops of 1 N hydrochloric acid. The solution was extracted with diethyl ether. The organic portion was washed with saturated ammonium chloride, dried over magnesium sulfate, and concentrated. The crude product was purified by running it through a short silica plug with methylene chloride to give a 66% yield of **1a** as a brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.79 Hz, 2 H), 7.45–7.26 (m, 7 H), 6.23–6.21 (m, 1 H), 6.08–6.06 (m, 1 H), 2.72–2.55 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.69, 147.21, 146.07, 136.79, 131.99, 128.55, 127.97, 126.97, 126.45, 123.47, 61.83, 39.64, 32.19; IR (KBr pellet) 2930, 1590, 1510, 1340 cm^{-1}; MS (EI 70 eV) m/z (M^+, 100), 219 (31), 143 (44); HRMS (EI 70 eV) m/z (M^+) calcd for $C_{17}H_{15}NO_2$ 265.1102, obsd 265.1115.

3-(4-Bromophenyl)-3-phenylcyclopentene (1c). Following the general olefination procedure with hydrazone **4c** (0.309 mmol, 0.012 g) gave **1c** as a pale yellow oil in 89% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.54 Hz, 2 H), 7.29–7.16 (m, 5 H), 7.08 (d, J = 8.57 Hz, 2 H), 6.11 (m, 1 H), 5.93 (m, 1 H), 2.56–2.45 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.24, 148.06, 137.67, 131.29, 131.09, 129.05, 128.39, 127.11, 126.13, 119.82, 61.28, 39.86, 32.29; IR (film) 3050, 2930, 1595, 1487, 1073, 1005 cm^{-1}; MS (EI 70 eV) m/z 300 (M^+ + 2, 78), 298 (M^+, 81), 219 (100), 204 (38), 142 (39); HRMS (EI 70 eV) m/z (M^+) calcd for $C_{17}H_{15}Br$ 298.0357, obsd 298.0337.

3-(4-Chlorophenyl)-3-phenylcyclopentene (1b). Following the general olefination procedure with hydrazone **4b** (0.114 mmol, 0.050 g) gave **1b** as a pale yellow oil in quantitative yield: ^{1}H NMR (400 MHz, $CDCl_3$) 7.33–7.16 (m, 9 H), 6.16 (m, 1 H), 5.97 (m, 1 H), 2.59–2.49 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.25, 147.43, 137.61, 131.55, 130.96, 128.52, 128.25, 128.21, 127.00, 125.99, 61.10, 39.78, 32.15; IR (film) 3050, 2940, 1490, 1090, 1010, 1595 cm^{-1}; MS (EI 70 eV) m/z 256 (M^+ + 2, 28), 254 (M^+, 100), 219 (74), 177 (41), 143 (47); HRMS (EI 70 eV) m/z (M^+) calcd for $C_{17}H_{15}Cl$ 254.0862, obsd 254.0862.

3-(4-Methoxyphenyl)-3-phenylcyclopentene (1d). To a solution of hydrazone **4d** (1.880 mmol, 0.816 g) in diethyl ether (10 mL) at 0 °C was added methyllithium (1.4 M in diethyl ether, 5.40 mL, 7.520 mmol). The mixture was warmed to room temperature and stirred for 22 h. The reaction was quenched with water and extracted with diethyl ether. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give a quantitative yield of crude **1d** as a pale yellow oil, which was clean by ^{1}H NMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.11 (m, 7 H), 6.81 (d, J = 8.92 Hz, 2 H), 6.15 (m, 1 H), 5.91 (m, 1 H), 3.77 (s, 3 H), 2.54–2.46 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.58, 149.13, 141.03, 138.25, 130.26, 128.71, 128.08, 127.06,

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125.72, 113.45, 60.80, 55.19, 39.97, 32.19; IR (film) 3050, 2950, 1607, 1510, 1248, 1177 cm^{-1}; MS (EI 70 eV) m/z 250 (M$^+$, 100), 235 (11), 219 (19), 173 (40); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{18}H_{18}O$ 250.1358, obsd 250.1353.

3-(4-Aminophenyl)-3-phenylcyclopentene (1g). A solution of cyclopentene **1a** (1.146 mmol, 0.304 g) and tin(II) chloride dihydrate (5.729 mmol, 1.290 g) in absolute ethanol (4 mL) was heated to 60 °C. Sodium borohydride (0.573 mmol, 0.022 g) in absolute ethanol (2 mL) was added dropwise to the above solution. The reaction mixture was stirred for 30 min at 60 °C. After the reaction was cooled to 0 °C, cold water (2 mL) was added to the solution. Neutralization with 4 M NaOH was followed by extraction with diethyl ether and water. The combined organic portions were dried over magnesium sulfate and concentrated to give a 78% yield of clean **1g** as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5 H), 7.09 (d, J = 8.49 Hz, 2 H), 6.70 (d, J = 8.54 Hz, 2 H), 6.23 (m, 1 H), 5.99 (m, 1 H), 2.61–2.57 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.40, 144.09, 139.06, 138.43, 130.03, 128.06, 127.95, 127.09, 125.62, 115.01, 60.75, 39.96; 32.20; IR (film) 3430, 3365, 2940, 1615, 1510 cm^{pl}; MS (EI 70 eV) m/z 235 (M$^+$, 100), 220 (17), 158 (58); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{17}H_{17}N$ 235.1361, obsd 235.1371.

3-[4-(Trimethylammonio)phenyl]-3-phenylcyclopentenyl Iodide (1h). To a mixture of cyclopentene **1e** (0.637 mmol, 0.150 g) and sodium bicarbonate (1.912 mmol, 0.161 g) in methanol (9 mL) was added methyl iodide (3.183 mmol, 0.200 mL). After the reaction mixture was stirred at reflux for 24 h, another aliquot of methyl iodide (2.230 mmol, 0.140 mL) was added. Again the mixture was stirred at reflux for 24 h and a last aliquot of methyl iodide (2.230 mmol, 0.140 mL) was added. The reaction was allowed to continue for another 24 h at reflux to ensure completion. The mixture was concentrated, and the crude residue was taken up in methylene chloride. The extracted organic portion was washed with water, dried over magnesium sulfate, and concentrated to give a quantitative yield of the crude iodide salt **1h** as orange crystals, mp 138 °C (further purification was not necessary): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.77 (d, J = 9.08 Hz, 2 H), 7.45 (d, J = 9.03 Hz, 2 H0, 7.32–7.20 (m, 5 H), 6.18 (m, 1 H), 6.01 (m, 1 H), 3.90 (s, 9 H), 2.62–2.47 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.04, 147.08, 144.79, 136.63, 131.89, 129.21, 128.43, 126.86, 126.29, 119.59, 61.13, 57.77, 39.50; 32.01; IR (KBr pellet) 2910, 1450, 1090, 1020 cm^{-1}; MS (EI 70 eV) m/z 278 (M$^+$ − I, 2.3), 263 (100), 186 (67); HRMS (EI 70 eV) m/z (M$^+$ − I) calcd for $C_{20}H_{24}N$ 278.1908, obsd 278.1934.

3-[4-(Dimethylamino)phenyl]-3-phenylcyclopentene (1e). To a solution of lithium aluminum hydride (1.986 mmol, 0.075 g) in tetrahydrofuran (5 mL) was added solid iodide salt **1h** (0.397 mmol, 0.161 g) all at once. The solution was refluxed until evolution of methane had ceased then cooled to 0 °C. Cold 2.5 M NaOH was added very slowly with stirring, followed by extraction with methylene chloride and water. The organic portion was dried over magnesium sulfate and concentrated. The resulting product was purified via preparative SiO_2 TLC (2 developments, 9.5:0.5 petroleum ether/diethyl ether) to give the alkene **1e** as an orange oil in 44% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5 H), 7.15 (d, J = 8.35 Hz, 2 H), 6.74 (d, J = 8.54 Hz, 2 H), 6.23 (m, 1 H), 5.96 (m, 1 H), 2.99 (s, 6 H), 2.62–2.54 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.56, 148.70, 138.49, 136.89, 129.86, 128.02, 127.72, 127.12, 125.55, 112.45, 60.61, 40.70, 39.95, 32.21; IR (film) 2930, 1608, 1515, 1343 cm^{-1}; MS (EI 70 eV) m/z 263 (M$^+$, 100), 186 (66); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{19}H_{21}N$ 263.1674, obsd 263.1661.

3-(4-Nitrophenyl)-3-phenylcyclopentane-1,2-diol (2a). General Osmylation Procedure. To a mixture of cyclopentene **1a** (0.103 mmol, 0.029 g) and trimethylamine *N*-oxide dihydrate (0.206 mmol, 0.023 g) in 8:1 acetone/water (4.7 mL) was added 0.024 M OsO_4 (3%, 0.13 mL). The mixture was stirred at room temperature for 2.25 h, quenched with 10% $NaHSO_3$ (5 mL), and stirred for an additional 10 min. The crude diol was exhaustively extracted with ethyl acetate and 10% $NaHSO_3$. The organic portion was dried over magnesium sulfate and concentrated to give a quantitative yield of crude **2a** as an orange brown oil. The major:minor isomer ratio equals 70:30 by ^{1}H NMR in $CDCl_3$. The diastereomers were separated via preparative SiO_2 TLC (4 developments, 7:3 diethyl ether/petroleum ether): ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) major isomer (higher R_f) δ 8.10 (d, J = 8.95 Hz, 2 H), 7.50 (d, J = 8.93 Hz, 2 H), 7.35–7.15 (m, 5 H), 4.70 (d, J = 4.40 Hz, 1 H), 4.30 (m, 1 H), 2.75 (m, 1 H), 2.44 (m, 1 H), 2.25 (m, 1 H), 1.82 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer 152.68, 146.01, 144.56, 129.18, 128.83, 126.81, 126.68, 123.33, 78.29, 72.43, 58.42, 32.79, 30.48; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) minor isomer (lower R_f) δ 8.11 (d, J = 8.85 Hz, 2 H), 7.51 (d, J = 8.98 Hz, 2 H), 7.37–7.17 (m, 5 H), 4.64 (m, 1 H), 4.24 (m, 1 H), 2.87 (m, 1 H), 2.31 (m, 1 H), 2.20 (m, 1 H), 1.91 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) minor isomer 154.56, 146.13, 142.15, 128.77, 128.27, 127.81, 126.99, 123.67, 78.10, 72.56, 57.47, 32.86, 30.73; IR (film) 3420, 2950, 1595, 1510, 1345 cm^{-1}; MS (EI 70 eV) m/z 299 (M$^+$, 3.9), 281 (20), 225 (42), 178 (100), 165 (61); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{17}H_{17}NO_4$ 299.1158, obsd 299.1127.

3-[4-(*N*,*N*-Dimethylamino)phenyl]-3-phenylcyclopentane-1,2-diol (2e). Following the general osmylation procedure with cyclopentene **1e** (0.125 mmol, 0.031 g) gave a quantitative yield of crude **2e** as an orange brown oil. ^{1}H NMR in $CDCl_3$, and cut and weigh methods, showed a 61:39 ratio of diastereomers. The diastereomers were separated via preparative SiO_2 TLC (3 developments, 6:4 petroleum ether/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) major isomer (higher R_f) δ 7.41–7.16 (m, 7 H), 6.66 (d, J = 8.79 Hz, 2 H), 4.71 (m, 1 H), 4.35 (m, 1 H), 2.93 (s, 6 H), 2.76 (m, 1 H), 2.44–2.24 (m, 2 H), 1.82 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.59, 145.26, 133.46, 128.36, 127.77, 127.16, 125.90, 112.39, 78.11, 72.93, 57.30, 40.40, 32.64, 30.75; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) minor isomer (lower R_f) δ 7.40–7.15 (m, 7 H), 6.70 (d, J = 8.79 Hz, 2 H), 4.67 (m, 1 H), 4.30 (m, 1 H), 2.94 (s, 6 H), 2.79 (m, 1 H), 2.35–2.19 (m, 2 H), 1.88 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 148.83, 147.21, 131.27, 128.78, 128.20, 126.59, 125.74, 112.51, 77.95, 73.10, 56.74, 40.37, 33.11, 30.93; IR (film) 3400, 2910, 1600, 1510, 1340 cm^{-1}; MS (EI 70 eV) m/z 297 (M$^+$, 100), 236 (62), 210 (35); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{19}H_{23}NO_2$ 297.1728, obsd 297.1707.

3-(4-Bromophenyl)-3-phenylcyclopentane-1,2-diol (2c). Following the general osmylation procedure with cyclopentene **1c** (0.118 mmol, 0.035 g) gave a quantitative yield of crude diol **2c** as a colorless oil. ^{1}H NMR in C_6D_6 showed a 55:45 ratio of diastereomers. The diastereomers were separated and purified via preparative SiO_2 TLC (6 developments, 8:2 petroleum ether/ethyl acetate) to give the higher R_f material **2c** (major) as white crystals: mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) major isomer (higher R_f) δ 7.36 (d, J = 8.65 Hz, 2 H), 7.27–7.20 (m, 4 H), 7.19–7.11 (m, 3 H), 4.62 (m, 1 H), 4.25 (m, 1 H), 2.68 (m, 1 H), 2.32–2.16 (m, 2 H), 1.75 (m, 1 H); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) minor isomer (lower R_f) δ 7.39 (d, J = 8.98 Hz, 2 H), 7.32–7.27 (m, 4 H), 7.23–7.16 (m, 3 H), 4.63 (d, J = 4.58 Hz, 1 H), 4.27 (m, 1 H), 2.79 (m, 1 H), 2.46–2.20 (m, 2 H), 1.85 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer 145.65, 143.60, 131.40, 129.99, 128.57, 126.62, 126.37, 120.21, 78.08, 72.70, 57.61, 32.83, 30.69; ^{13}C NMR (100 MHz, $CDCl_3$) minor isomer 145.59, 143.54, 131.51, 128.62, 128.57, 128.08, 126.57, 120.40, 78.07, 72.75, 57.04, 32.82, 30.75; IR (KBr pellet) 3310, 2910, 1390, 1075 cm^{-1}; MS (EI 70 eV) m/z 334 (M$^+$ + 2, 7.3), 332 (M$^+$, 7.5), 260 (45), 258 (46), 179 (76), 178 (100), 165 (63); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{17}H_{17}BrO_2$ 332.0412, obsd 332.0421.

3-(4-Chlorophenyl)-3-phenylcyclopentane-1,2-diol (2b). Following the general osmylation procedure with cyclopentene **1b** (0.066 mmol, 0.017 g) gave a quantitative yield of crude diol **2b**. ^{1}H NMR in C_6D_6 showed a 57:43 ratio of diastereomers. The diastereomers were separated via preparative SiO_2 TLC (6 developments, 6:4 petroleum ether/diethyl ether) to give the higher R_f fraction **2b** (major isomer) as off-white crystals: mp 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) major isomer (higher R_f) δ 7.21–7.05 (m, 9 H), 4.58 (m, 1 H), 4.20 (m, 1 H), 2.64 (m, 1 H), 2.27–2.12 (m, 2 H), 1.71 (m, 1 H); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) minor isomer (lower R_f) δ 7.35–7.15 (m, 9 H), 4.61 (d, J = 4.64 Hz, 2 H), 4.23 (m, 1 H), 2.77 (m, 1 H), 2.27–2.17 (m, 2 H), 1.81 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer 145.76, 143.06, 132.05, 129.61, 128.56, 128.47, 126.63, 126.36, 78.12, 72.72, 57.56, 32.90, 30.71; ^{13}C NMR (100 MHz, $CDCl_3$) minor isomer 145.03, 143.67, 131.94, 128.61, 128.55, 128.18, 128.08, 126.36, 78.12, 72.75, 57.35, 32.87, 30.74; IR (KBr pellet) 3290, 2910, 1480, 1090, 1030 cm^{-1}; MS (EI 70 eV) m/z 290 (M$^+$ + 2, 2.8), 288 (M$^+$, 8.0), 270 (36), 216 (31), 214 (100), 203 (20), 179 (64); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{17}H_{17}ClO_2$ 288.0917, obsd 288.0914.

3-(4-Methoxyphenyl)-3-phenylcyclopentane-1,2-diol (2d). Following the general osmylation procedure with cyclopentene **1d** (0.200 mmol, 0.050 g) gave a quantitative yield of crude diol **2d** as a pale yellow oil (^{1}H NMR and ^{13}C NMR in $CDCl_3$ showed a 53:47 ratio of diastereomers): ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 7.45–7.20 (m, 7 H), 6.95 (d, J = 8.60 Hz, 0.94 H), 6.86 (d, J = 8.79 Hz, 1.06 H), 4.72 (m, 1 H), 4.36 (m, 1 H), 3.83 (s, 1.29 H), 3.83 (s, 1.71 H), 3.29 (m, 1 H), 2.43–2.31 (m, 2 H), 1.88 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.76, 157.62, 146.61, 144.85, 138.08, 136.34, 129.17, 128.42, 128.36, 127.91, 127.64, 126.59, 126.11, 126.00, 113.78, 113.71, 78.17, 78.04, 72.85, 72.79, 57.39, 57.17, 55.12, 33.08, 32.80, 30.77, 30.67; IR (film) 3420, 2940, 1600, 1247 cm^{-1}; MS (EI 70 eV) m/z 284 (M$^+$, 64), 223 (55), 210 (60), 197 (100); HRMS (EI 70 eV) m/z (M$^+$) calcd for $C_{18}H_{20}O_3$ 284.1413, obsd 284.1407.

Tetrahydro-4-(4-methoxyphenyl)-2,2-dimethyl-4-phenyl-4*H*-cyclopenta-1,3-dioxole (5d). A mixture of diol **2d** (0.781 mmol, 0.222 g), *p*-TsOH (0.008 mmol, 0.002 g) and 2,2-dimethoxypropane (6 mL) was stirred 8 h, diluted with diethyl ether, and extracted one time each with saturated sodium bicarbonate, water, and brine, respectively. The organic

portion was dried over magnesium sulfate and concentrated to give an 82% yield of the acetonide **5d**. The diastereomers were separated via preparative SiO_2 TLC (2 developments, methylene chloride) to give the higher R_f material **5d** (major isomer) as pale yellow crystals: mp 89-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer (higher R_f) δ 7.28-7.25 (m, 4 H), 7.19 (m, 1 H), 7.02 (d, J = 8.79 Hz, 2 H), 6.77 (d, J = 8.79 Hz, 2 H), 5.24 (d, J = 5.26 Hz, 1 H), 4.83 (t, J = 5.42 Hz, 1 H), 3.75 (s, 3 H), 2.66 (m, 1 H), 2.02 (m, 1 H), 1.73 (m, 1 H), 1.56 (m, 1 H), 1.35 (s, 3 H), 1.33 (s, 3 H); ^{1}H NMR (400 MHz, $CDCl_3$) minor isomer (lower R_f) δ 7.25-7.21 (m, 3 H), 7.17-7.14 (m, 2 H), 7.12-7.09 (m, 2 H), 6.80 (d, J = 8.81 Hz, 2 H), 5.23 (m, 1 H), 4.83 (m, 1 H), 3.76 (s, 3 H), 2.66 (m, 1 H), 2.01 (m, 1 H), 1.71 (m, 1 H), 1.53 (m, 1 H), 1.37 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer 157.55, 145.50, 137.94, 128.28, 128.10, 127.80, 125.73, 113.47, 109.31, 85.63, 80.61, 58.25, 55.14, 33.13, 30.61, 26.23, 24.01; ^{13}C NMR (100 MHz, $CDCl_3$) minor isomer 157.44, 146.27, 137.42, 129.15, 128.11, 127.30, 125.94, 113.20, 109.30, 85.52, 80.66, 58.28, 55.04, 33.49, 30.64, 26.27, 24.02; IR (KBr pellet) 2940, 1600, 1505, 1245, 1027 cm^{-1}; MS (EI 70 eV) m/z 324 (M^+, 21), 210 (100); HRMS (EI 70 eV) m/z (M^+) calcd for $C_{21}H_{24}O_3$ 324.1725, obsd 324.1722.

X-ray Structure Determination of 2c (Major Isomer). Single crystals of the major isomer of the bromo-substituted diol **2c** were grown by the uninduced crystallization of the initial oil upon standing for an extended period of time: monoclinic space group $P2_1/a$; a = 9.125 (5) Å, b = 12.793 (1) Å, c = 12.849 (2) Å, β = 103.866 (5)°, V = 1456.3 (8) Å^3, Z = 4, d(calcd) = 1.520 g cm^{-3}. For 1252 unique, observed ($>3\sigma(I)$) reflections and 181 parameters, the discrepancy indices are R = 0.033 and R_w = 0.045. The intensity data was obtained at 20 °C with a Rigaku AFC5R four circle autodiffractometer system using graphite monochromated Cu Kα radiation and a 12-kW rotating anode generator. The cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 25 centered reflections in the range $25 < 2\theta < 30$. Scans were made at a speed of 32 deg min^{-1} in omega. The weak reflections ($I < 10.0\ \sigma$) were rescanned (maximum of two rescans). The intensities of three standard reflections were measured after every 150 reflections and remained constant throughout the data collection; no decay correction was applied. The crystallographic calculations were performed using the TEXSAN program.[23] An emperical absorption correction, using the DIFABS program, was applied which resulted in transmission factors ranging from 0.91 to 1.00. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in calculated positions for the final full-matrix least-squares refinement cycles but were not refined.

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Supplementary Material Available: Tables of bond lengths, bond angles, and crystallographic, positional, and thermal parameters for **2c** (8 pages); tables of observed and calculated structure factors for **2c** (8 pages). Ordering information is given on any current masthead page.

Calicheamicins, a Novel Family of Antitumor Antibiotics. 4. Structure Elucidation of Calicheamicins β_1^{Br}, γ_1^{Br}, α_2^{I}, α_3^{I}, β_1^{I}, γ_1^{I}, and δ_1^{I}

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Abstract: The details of the structural assignment of the potent antitumor antibiotic, calicheamicin γ_1^{I} (**6**, $C_{55}H_{74}IN_3O_{21}S_4$), is reported. Methanolysis studies on **6** and *N*-acetylcalicheamicin γ_1^{I} (**8**, $C_{57}H_{76}IN_3O_{22}S_4$) permitted the structural assignment of the glycosidic chain. Details of the spectral analysis supporting the assignments of the 3-*O*-methyl-α-L-rhamnopyranoside (D-ring) and the methyl 2,4-dideoxy-3-*O*-methyl-4-(*N*-acetyl-*N*-ethylamino)-α-L-xylopyranoside (E-ring) is reported. The structure of calicheamicinone (**32**, $C_{18}H_{17}NO_5S_3$), containing a bicyclo[7.3.1]tridec-9-ene-2,6-diyne system and a methyl trisulfide, was elucidated by a series of chemical degradation studies, which included an unexpected free radical cycloaromatization reaction. The presence of 4,6-dideoxy-4-(hydroxyamino)-β-D-glucopyranoside (A-ring) and its N–O glycosidic linkage to the thio sugar (B-ring) was ascertained by X-ray crystallography of **24** ($C_{36}H_{40}INO_{13}S_2$), a degradation product of **6**. The chemical structures of calicheamicins β_1^{Br} (**1**), γ_1^{Br} (**2**), α_2^{I} (**3**), α_3^{I} (**4**), β_1^{I} (**5**), and δ_1^{I} (**7**) were assigned by correlating their ^{1}H and ^{13}C NMR data with that of calicheamicin γ_1^{I}. By tracking the biological activities of the degradation products, the enediyne system of calicheamicinone was shown to be essential for the DNA-damaging abilities of the calicheamicins. A mechanism whereby the enediyne could be triggered to cyclize via a 1,4-diyl, the putative DNA cleaving species, is proposed.

Microbial fermentation is a well-known source of compounds of diverse chemical structures and biological activities. Key to the discovery of new biologically active compounds from this rich source is a sensitive and specific assay. The biochemical induction assay (BIA) has been shown to be exquisitely sensitive to certain DNA-damaging antitumor agents although not all DNA-damaging agents respond to this test.[1] At the beginning of our search for novel antitumor agents, several major structural classes of fermentation-derived antitumor agents were known to be BIA positive. These were represented by the pluramycins,[2] mitomycins,[3]

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