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The Kinetics and Thermodynamics of Bicyclic Ketal Formation: An Application to the Synthesis of the Zaragozic Acids.§

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Abstract: The kinetics and thermodynamics of ketalization of tetrahydroxyketones are examined in the synthesis of the ketal core of zaragozic acid Bx3.

In this paper, we describe the results of our study of the kinetics and thermodynamics of the formation of ketals from polyhydroxyketones and the use of these cyclizations in the synthesis of the 2,8-dioxabicyclo[3.2.1]octane core of the zaragozic acids. Bicyclic ketals are present in a wide variety of important natural products. When designing syntheses of bicyclic ketals, it has become routine for chemists to disconnect the ketal moiety retrosynthetically to afford the corresponding ketone-diol. The structural and stereochemical features of the resulting acyclic structure can then be considered in this simplified context. Then, often late in the synthesis, the alcohols and ketone are simultaneously liberated and the ketal is expected to form spontaneously. This strategy has been highly effective in a large number of syntheses. However, it does not take advantage of the potential for the ketalization process to control stereochemistry about the emerging bicyclic ring structure and indeed the shape of the bicycle itself. In the case of the bicyclization of a ketone-diol, there is only one possible ketal isomer that may form. For ketone-polyols, there are multiple options for bicyclization. If it were possible to predict (either based on kinetics or thermodynamics) that the bicyclization should favor the formation of only one of the possible isomers, then the bicyclization of polyhydroxyketones could be used to access rapidly structures of high complexity and structural diversity for use in the synthesis of ketal-containing synthetic targets.

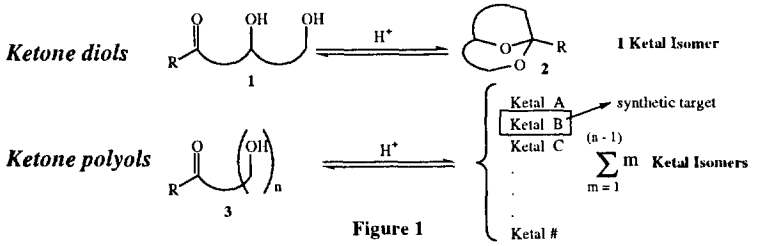
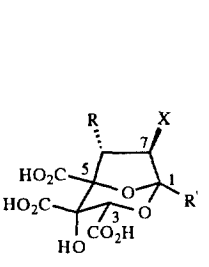


Figure 1

§Dedicated with affection and gratitude to Professor Samuel J. Danishefsky, a great mentor and scholar.

The zaragozic acids, also known as the squalestatins, are fungal metabolites possessing a novel, highly oxygenated, bicyclic ketal core (Figure 2).[1] They are potent inhibitors of the enzyme squalene synthase (IC_{50} =12 nM), and have demonstrated potent antifungal activity.[2] The unusual, 2,8-dioxabicyclo[3.2.1]octane core structure and biological activity of the zaragozic acids have stimulated interest among synthetic chemists, resulting in total syntheses of zaragozic acids A[3] and C.[4]



Zaragozic Acids

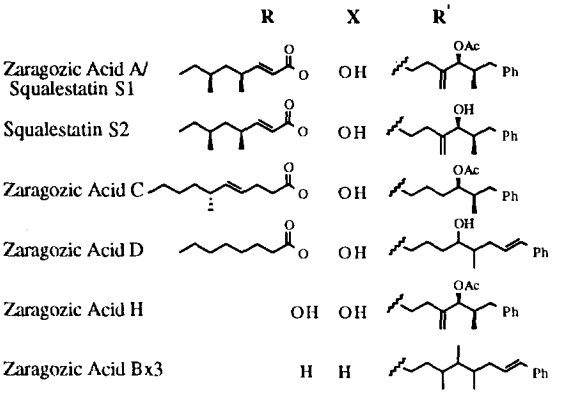


Figure 2

Results and Discussion

Our retrosynthetic analysis of the zaragozic acids (Figure 3) called for the introduction of the carboxylic acid at C-3, and oxidation of alcohols at carbons 4 and 5 late in the synthesis, thus affording intermediate ketal **5**. Disconnection of **5** at the ketal moiety leads to tetrahydroxyketone **6**. If it were possible to control the ketalization to furnish a single ketal isomer, such as **5**, from **6**, then introduction of the C-3 carboxylate would afford directly, the carbon framework of the zaragozic acids. However upon cyclization of tetrahydroxyketone **6**, six distinct bicyclic ketals are possible. To understand the multiple pathways of this ketalization, we initiated computational and experimental model studies.

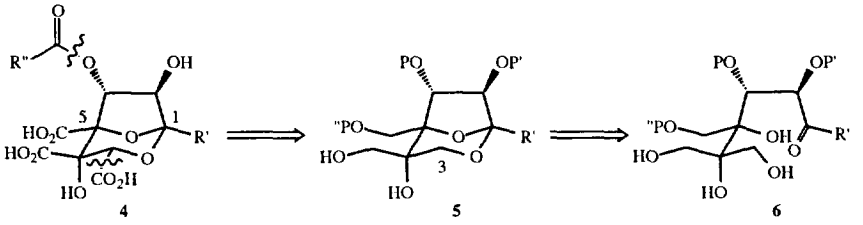


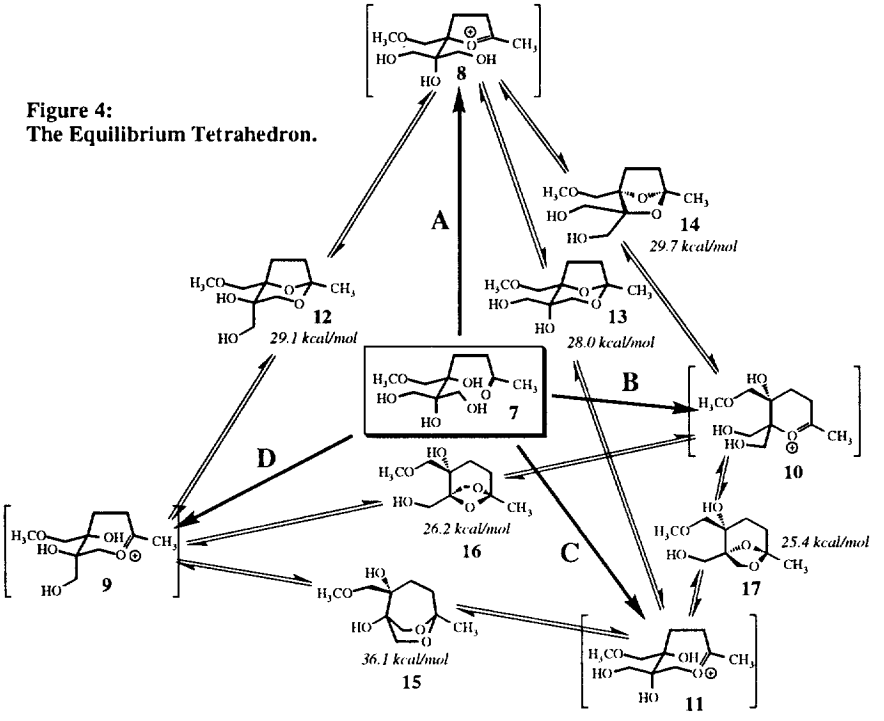
Figure 3

The complex equilibria connecting model tetrahydroxyketone **7** and its corresponding ketals are shown in Figure 4. Tetrahydroxyketone **7** is placed at the center of the equilibrium tetrahedron. The four possible monocyclic oxonium ions formed by cyclization of **7** form the vertices of the tetrahedron. In the center of each edge are the six possible ketals.

To evaluate the thermodynamics of the ketalization process, we calculated the energies of each of these ketals. Interestingly, ketals **12** and **13** possessing the 2,8-dioxabicyclo[3.2.1]octane skeleton found in the

zaragozic acids are not the lowest energy isomers. Instead the lowest energy isomer is **17**, a 7,8-dioxabicyclo[3.2.1]octane.[5] Ketal **17** is lower in energy by over 3 kcal/mol relative to **12** and **13**. The 7,8-dioxabicyclo[3.2.2]nonane isomer **15** and the 1,7-dioxabicyclo[2.2.1]heptane isomer **14** are predicted to be sufficiently high in energy that isolation of these materials from a cyclization experiment seemed unlikely. However, from a purely thermodynamic standpoint, it appeared that cyclization of ketotetraol **7** would not lead to the desired 2,8-dioxabicyclo[3.2.1]octane structure.

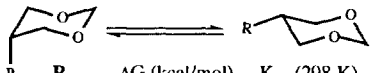
Figure 4:
The Equilibrium Tetrahedron.



We next examined the kinetics of ketalization. If the ketone were liberated to initiate the ketalization process, formation of the hemiketal would rapidly follow. Under acid catalysis, loss of water would generate oxonium intermediates **8** through **11** following arrows A through D. We expected that pathway A, leading to the 5-membered oxonium ion **8**, would be the fastest of the four, since pathways B, C, and D lead to the formation of 6- or 7-membered oxonium ions. Addition of one of the three free hydroxyl groups to the oxonium ion of **8**, followed by loss of proton would the lead to formation of the ketal. The kinetics of these reactions can best be analyzed in the context of Baldwin's rules for ring closure.[6] Ketals **12** and **13**, with the desired 2,8-dioxabicyclo[3.2.1]octane ring system, would be formed from **8** via allowed 6-*endo*-trig processes, whereas ketal **14** would be formed through a disallowed 5-*endo*-trig closure. Thus, although their formation is disfavored thermodynamically relative to other isomers, ketals **12** and **13** were expected to be the kinetic products of the ketalization process. We expected that the equilibrium between **12** and **13** would be facile since they are interconverted via retro 6-*endo*-trig followed by 6-*endo*-trig processes. Experimentally determined ΔG values for substituents in the 5 position of 1,3-dioxanes (Table)[7] and our own computational

results suggested that pseudoequatorial isomer **13** would be the favored component in this equilibrium. Based on this analysis we could predict that *the desired 2,8-dioxabicyclo[3.2.1]octane framework (ketals 12 and 13) required for the synthesis of the zaragozic acids would be the major products* of the ketalization after short reaction times.

Table 1. Conformational Free Energies in 5-Substituted-1,3-Dioxanes



R	-ΔG (kcal/mol)	K_{eq} (298 K)
$-CH_3$	0.8	3.86
$-CH_2CH_3$	0.7	3.26
$-CH(CH_3)_2$	1.0	5.42
$-C(CH_3)_3$	1.4	10.65

To evaluate experimentally the equilibrium of bicyclization, we synthesized tetrahydroxy ketal **19** and examined its acid-catalyzed transketalization to afford bicyclic ketals (Figure 5). We prepared **19** from alkene **18** by dihydroxylation using OsO_4.[8] Treatment of tetrahydroxy ketal **19** with 0.1 equiv trifluoroacetic acid in chloroform lead to the rapid formation of two new ketal products in a ratio of 3:2. Based on our previously described analysis of the ketalization process, we believed these ketals to be 2,8-dioxabicyclo[3.2.1]octanes **20** and **21**. The 2:3 ratio of the two ketal products did not change over the one hour course of the reaction, nor were any other ketals detected under these conditions, even after prolonged exposure. Thus, it is likely that the 2:3 ratio represents a thermodynamic equilibrium rather than a kinetic ratio. The two ketal products **20** and **21** could be easily separated by silica gel chromatography and each could be converted to a similar 2:3 mixture of the two isomers. Our calculated energies for analogs **12** and **13** (Figure 4) strongly suggested that the major component was the pseudoequatorial isomer **21**. Ketal **21** may also be favored due to its ability to engage the proton of the tertiary alcohol in a transannular hydrogen bond with the ketal oxygen atoms.[9] To

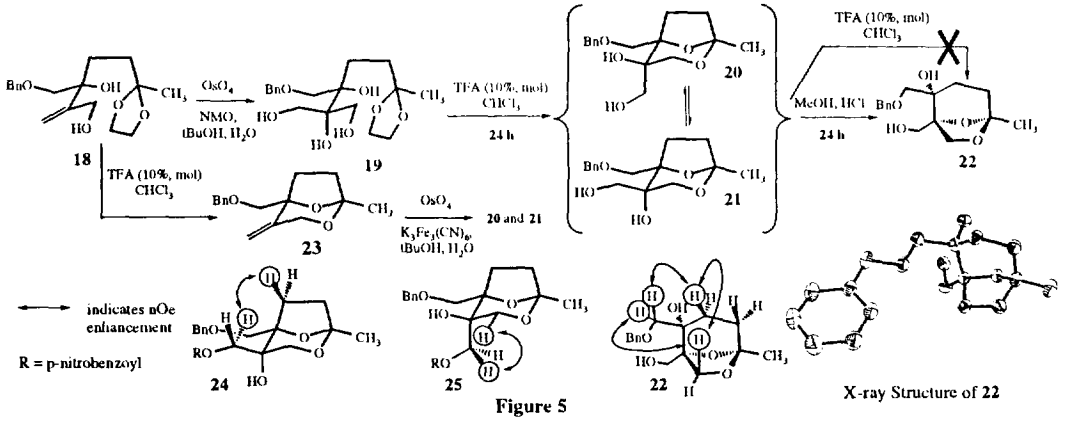


Figure 5

confirm the assignment of the 2,8-dioxabicyclo[3.2.1]octane, we synthesized ketals **20** and **21** via a structurally secure route. Dihydroxylation (OsO_4, $K_3Fe_3(CN)_6$, *t*-BuOH/H_2O) of the *exo*-methylene moiety of ketal **23**, obtained as the unique product of the acid-catalyzed transketalization of **18**, afforded ketals **20** and **21** in a 3:7 ratio. We presumed that the major isomer was again **21**, the result of dihydroxylation from the *exo*-face of the bicyclic ring system in **23**. We confirmed these assignments by the observation of diagnostic nOe enhancements in the NOESY spectra of *p*-nitrobenzoate derivatives **25** and **24** of **20** and **21**.

In the ^1H NMR spectra of both **20** and **21** taken in $CDCl_3$, the proton of the primary hydroxyl groups are strongly coupled to the protons of the adjacent methylene groups. Intramolecular hydrogen bonding is the likely source of this slow exchange. We investigated the transketalization reaction in a hydroxylic solvent that would disrupt intramolecular hydrogen bonding. Treatment of ketal **19** with HCl in methanol resulted in exceptionally rapid transketalization to afford ketals **20** and **21**. Within several minutes, a third product began appearing. After 24 hours, the new product was the major ketal containing component in the reaction mixture. Examination of the NOESY spectrum for this ketal revealed strong enhancements (see Figure 5) that were either weak or absent in either **20** or **21**. Single crystal X-ray analysis revealed that the new ketal isomer possessed a 7,8-dioxabicyclo[3.2.1]octane ring system and was the structural analog of the predicted lowest energy isomer **17** (Figure 4). The relatively slow rate at which isomer **22** is formed relative to **20** and **21** can be rationalized using kinetic arguments (*vide supra*).

We looked again to the equilibration of the bicyclic ketal as a means of achieving stereocontrol during the introduction of the final carbon atom and stereocenter of the core of the zaragozic acids. Since both **20** and **21** (Figure 5) were available via equilibration and easily separated by silica gel chromatography, either of these compounds could serve as viable synthetic intermediates. In contrast to **21**, ketal **20** presents an attractive option for introduction of the C-3 substituent. In **20**, the carbon destined to be C-3 (zaragozic acid numbering) in the final structure is stored as the pseudoaxial hydroxymethyl group. Chelation controlled addition of nucleophiles to aldehyde **26** (prepared by oxidation of **20**)[10] would occur from the *Re* face of the aldehyde, away from the bulk of the bicyclic system. Computational analysis of vinyl anion adduct **28** and its rearranged isomer **30** suggested that the acid-catalyzed equilibration of **27** and **29** would favor the desired isomer.

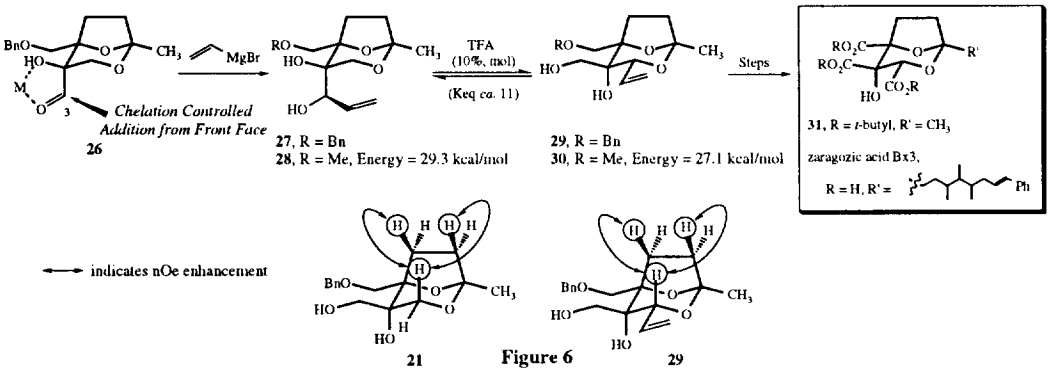


Figure 6

We prepared aldehyde **26** by oxidation of diol **20** (Figure 6).[11] We then treated this aldehyde *in situ* with excess vinylmagnesium bromide to furnish a single allylic alcohol formulated as **27**. The final equilibration of the ketal to establish the complete carbon framework of the zaragozic acids was examined

next. In analogy to the acid-catalyzed interconversion of **20** and **21**, we treated ketal **27** with 0.1 equiv TFA in dichloromethane and observed a rapid (20 h) and virtually complete (K_{eq} = *ca.* 11) conversion of **27** to **29**. Strong nOe enhancements between the allylic proton and the *endo* protons of the two-carbon bridge confirmed the stereochemistry at C-3 and the integrity of the ketal.[12] We have not observed any other ketals in this equilibration. Ketal **29** contains the complete carbon framework for the ketal core of the zaragozic acids. We have carried out the oxidation sequence to convert **29** into tricarboxylate **31**, the core ketal of zaragozic acid Bx3.[10]

Conclusion

Polyhydroxylated ketones are, under the correct circumstances, highly useful synthetic intermediates. By controlling the kinetics of ketalization, ketal isomers other than those lowest in energy may be isolated and used in synthesis. The bicyclic ketal is the core of the zaragozic acids and the reversibility of ketalization is at the center of our synthetic strategy. We have demonstrated that by taking advantage of this reversibility, the stereochemistry and functionality of the zaragozic acid ketal can be fashioned with ease. This strategy is generally applicable to the more oxidized members of this class of natural products. Indeed, computational analysis of structures possessing oxidation on carbons 6 and 7 (Figure 3, Column 3) shows that the desired ketal isomer is lowest in energy. We are currently applying this strategy to the synthesis of zaragozic acid C.

Experimental Section

General Procedures. Air- and moisture-sensitive liquids and solutions were transferred by oven-dried syringes or stainless steel cannula. Air-sensitive, non-aqueous reactions were performed using flame-dried glassware under (typically) a dynamic atmosphere of argon. Organic solutions were concentrated by rotary evaporation below 40 °C under reduced pressure (water aspirator). All reagents unless otherwise indicated, were commercially obtained. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl prior to use. Dichloromethane and triethylamine were distilled from calcium hydride prior to use. Dimethyl sulfoxide was dried with 3 Å molecular sieves, then distilled from calcium hydride and stored over 4 Å molecular sieves. Purification by forced-flow chromatography on Bodman ICN Silitech, 60 Å, 250-400 mesh, 32-63 D silica gel as described by Still[13] was employed. Thin-layer chromatography (TLC) was performed on Analtech 0.25 mm silica gel GHLF. The analytical plates were eluted as indicated and visualized by either iodine on solid support silica or by an ethanolic vanillin dip.

NMR spectra were recorded on a Bruker ARX-400 spectrometer operating at 400 MHz and 100 MHz for ^1H and ^{13}C, respectively, or on a Bruker AM-360 operating at 360 MHz and 90 MHz for ^1H and ^{13}C. Spectra are referenced internally relative to solvent. Data for ^1H are reported as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet), integration, coupling constant (Hz), and assignment (when indicated, numbered protons refer to Zaragozic Acid C numbering.[14] IR spectra were recorded on Nicolet 510p FT-IR spectrometer using NaCl plates or solution cells and are reported in cm^{-1}. High and low resolution mass spectra were obtained from the UCLA Mass Spectral Facility. X-ray data was collected by Dr. Saeed Khan at the James D. McCullough X-Ray Crystallography Laboratory, Department of Chemistry and Biochemistry, UCLA (*vide infra*).

Molecular Modeling. Energy calculations were performed with the CAChe Worksystem (Version 3.7) on a Power PC/MAC 7100. The parameters used in all calculations can be found in the MM2 force field from the CAChe program. The sampling conformers were minimized based on the molecular mechanics calculations of the MM2 force field. The optimization was done with the Conjugate Gradient algorithm for no more than 300 updates, or until convergence to 0.001 kcal/mole was reached.

2-(3-benzyloxymethyl-3,4,5-trihydroxyl-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane (19). To a solution of 2-(3-benzyloxymethyl-3-hydroxyl-4-hydroxymethylpent-4-enyl)-2-methyl-1,3-dioxolane (**18**) (200.0 mg, 0.62 mmol) in t-BuOH/H_2O 1:1 (total of 2.0 mL) were added N-methylmorpholine-N-oxide (242 mg of 60 wt % aqueous solution, 1.24 mmol, 2.0 equiv) and osmium tetroxide (0.12 ml of 0.25 M stock solution in toluene, 0.03 mmol, 0.05 equiv). The mixture was stirred at room temperature for 9 h. At that time the reaction mixture was partitioned between EtOAc and 0.75 M copper sulfate solution. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over anhydrous sodium sulfate, and filtered, and concentrated under reduced pressure. The resulting residue was chromatographed (EtOAc to 2% MeOH in EtOAc). Fractions containing **19** were concentrated under reduced pressure to afford **19** as a brown oil (222 mg, 100%). TLC R_f = 0.08 (2:3 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.26-7.37 (m, 5H, H_{arom}), 4.55 (d, 1H, *J*= 11.7 Hz, -OC*H*$_2$Ph), 4.48 (d, 1H, *J*= 11.7 Hz, -OC*H*$_2$Ph), 3.87-3.94 (m, 6H, -OC*H*$_2$C*H*$_2$O-, tertiary OH (2H)), 3.69-3.78 (m, 4H, -C*H*$_2$OH, -C*H*$_2$OH), 3.55 (d, 1H, *J*= 9.70 Hz, -C*H*$_2$OBn), 3.39 (d, 1H, *J*= 9.68 Hz, -C*H*$_2$OBn), 1.71-1.79 (m, 4H, -C*H*$_2$C*H*$_2$-), 1.30 (s, 3H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.0, 128.6, 128.2, 128.0, 110.0, 76.8, 76.0, 73.8, 71.3, 64.6 (2 lines), 63.8, 63.6, 32.0, 26.3, 23.9; IR (thin film) ν 3385 (br), 2916, 2885, 1653, 1456, 1390, 1190, 1070, 1061, 973, 847, 717, 669.

4R*-5-benzyloxymethyl-4-hydroxyl-4-hydroxymethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octane (20) and 4S*-5-benzyloxymethyl-4-hydroxyl-4-hydroxymethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octane (21). To a solution of 2-(3-benzyloxymethyl-3,4,5-trihydroxyl-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane (**19**) (46.0 mg, 0.13 mmole) in chloroform (0.5 mL) was added 13.0 µl trifluoroacetic acid stock solution (1.0 M in chloroform) (0.013 mmole, 0.1 equiv). The mixture was stirred at room temperature for 24 h. At that time, the volatile components were removed azeotropically with benzene and the residue was chromatographed over silica gel (30% EtOAc in hexanes to 50% EtOAc in hexanes). Fractions containing **20** and **21** were concentrated under reduced pressure to afford **20** (10.8 mg, 28.8%) and **21** (16.2 mg, 43.2%) in an overall yield of 72%. **21**: TLC R_f = 0.40 (2:3 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.25-7.37 (m, 5H, H_{arom}), 4.59 (d, 1H, *J*= 11.8 Hz, -OC*H*$_2$Ph), 4.50 (d, 1H, *J*= 11.8 Hz, -OC*H*$_2$Ph), 3.87 (d, 1H, *J*= 9.55 Hz, H_{3eq}), 3.78 (d, 1H, *J*= 12.2 Hz, -C*H*$_2$OBn), 3.75 (s, 1H, tertiary O*H*), 3.63 (d, 1H, *J*= 12.2 Hz, -C*H*$_2$OBn), 3.61(m, 1H, -C*H*$_2$OH), 3.43 (d, 1H, *J*= 9.60 Hz, H_{3ax}), 3.41 (m, 1H, -C*H*$_2$OH), 2.70 (t, 1H, *J*= 5.6 Hz, -CH$_2$O*H*), 1.89-2.12 (m, 4H, -C*H*$_2$C*H*$_2$-), 1.51 (s, 3H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.2, 128.6, 128.0, 127.9, 106.7, 86.0, 74.0, 71.7, 71.5, 67.7, 63.6, 33.4, 29.5, 23.7; IR (thin film) ν 3457 (br), 2988, 2940, 2874, 1475, 1454, 1389, 1325, 1273, 1103, 1069, 1041, 916, 868, 733; HRMS (CI) calc'd for $C_{16}H_{22}O_5$, 294.1467, calc'd for $C_{16}H_{23}O_5$ $(M+H)^+$, 295.1546; found 295.1542 $(M+H)^+$. **20:** TLC R_f = 0.46 (2:3 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.34-7.39 (m, 5H, H_{arom}), 4.68 (d, 1H, *J*= 11.8 Hz, -OC*H*$_2$ Ph), 4.54 (d, 1H, *J*= 11.8 Hz, -OC*H*$_2$ Ph), 4.12 (dd, 1H, *J*= 11.6, 4.08 Hz, -C*H*$_2$OH), 3.73 (d, 1H, *J*= 11.6 Hz, H_{3eq}), 3.69 (s, 2H, -C*H*$_2$OBn), 3.65 (dd, *J*= 11.5, 1H, 9.69 Hz, -CH$_2$O*H*), 3.58 (d, 1H,

J= 11.6 Hz, H_{3ax}), 3.49 (s, 1H, tertiary O*H*), 3.16 (dd, 1H, *J*= 4.10, 9.25 Hz, -CH_2OH), 2.43-2.51 (m, 1H, -CH_2CH_2-), 2.06-2.14 (m, 1H, -CH_2CH_2-), 1.88-1.96 (m, 1H, -CH_2CH_2-), 1.59-1.68 (m, 1H, -CH_2CH_2-), 1.48 (s, 1H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.6, 128.7, 128.3, 128.1, 106.8, 84.9, 74.4, 72.8, 69.0, 67.2, 64.2, 34.1, 30.4, 23.4; IR (thin film) ν 3480 (br), 2941, 2890, 1456, 1390, 1327, 1196, 1151, 1080, 908, 735, 650; HRMS (EI) calc'd for $C_{16}H_{22}O_5$, 294.1467; calc'd for $C_{16}H_{23}O_5$, $(M+H)^+$ 295.1546, found 295.1545 .

4R*-5-benzyloxymethyl-4-hydroxyl-4-hydroxymethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octane (20) and 4S*-5-benzyloxymethyl-4-hydroxyl-4-hydroxymethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octane (21). 5-benzyloxymethyl-4-methylene-1-methyl-2,8-dioxabicyclo[3.2.1]octane (**23**) (614.6 mg, 2.36 mmole) was dissolved in a mixture of *t* -butanol (15 ml)[15] and H_2O (15 ml). Potassium ferricyanide (2.1 g, 6.8 mmole, 2.8 equiv), K_2CO_3 (1.2 g, 8.7 mmole, 3.7 equiv) and DABCO (67 mg, 0.60 mmole, 0.25 equiv) were then added and the suspension was stirred until a homogeneous yellow solution resulted. To this solution was added osmium tetroxide (0.1 ml, 0.25 M stock solution in toluene, 0.025 mmole, 0.01 equiv) and the resulting red-brown solution was stirred for 12 h. The reaction mixture was then treated with Na_2SO_3 (0.81 g, 6.4 mmole) and stirred for 3 h. The tan slurry was then transferred to a separatory funnel containing 100 ml Et_2O and 10 ml 0.75 M $CuSO_4$. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 ml). The pooled organic phases were washed with brine (50 ml) and then dried over Na_2SO_4 and filtered. The solution was concentrated *in vacuo* and the resulting oil was chromatographed on silica gel (gradient elution: 3:2 hexane/ethyl acetate ---> 2:3 hexane/ethyl acetate). Two products, **20** (236 mg, 33%) and **21** (467 mg, 67%) were obtained in an overall yield of 100%. See above for analytical data.

Equilibration of 20 and 21. To a solution of **21** (467 mg, 1.58 mmole) in 8.0 ml CH_2Cl_2 was added 0.16 ml TFA (1.0 M stock solution in CH_2Cl_2, 0.16 mmole, 0.1 equiv) and the mixture became slightly more yellow immediately but did not become more intensely colored as it was stirred at room temperature for 24 hours. The contents were concentrated under reduced pressure to a smaller volume and the concentrated solution was chromatographed on silica gel (gradient elution: 3:2 hexane/ethyl acetate---> 2:3 hexane/ethyl acetate) to afford **20** (160 mg, 34%) and **21** (308 mg, 66%) of clear, colorless oils. See above for analytical data.

5-benzyloxymethyl-4-methylene-1-methyl-2,8-dioxabicyclo[3.2.1]octane (23). To a solution of 2-(3-benzyloxymethyl-3-hydroxyl-4-hydroxymethylpent-4-enyl)-2-methyl-1,3-dioxolane (**18**) (1.03 g, 3.02 mmole) in dichloromethane (15 mL) was added 0.19 ml TFA stock solution (1.0 M in CH_2Cl_2, 0.1 equiv) dropwise over two minutes. The reaction mixture stirred for 36 h. The reaction mixture was then concentrated under reduced pressure to a volume of *ca.* 2-3 ml and eluted through a short silica pad. The resulting colorless solution was concentrated *in vacuo* to afford an oil. Purification by flash chromatography on silica gel (3:1 hexane/ethyl acetate) provided 780.5 mg of **19** (93%) as a clear, colorless oil: TLC R_f = 0.58 (7:3 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.26-7.34 (m, 5H, H_{arom}), 4.87 (s, 1H, -C=CH_2), 4.80 (s, 1H, -C=CH_2), 4.61 (d, 2H, *J*= 1.70 Hz, -OCH_2Ph), 4.42 (m, 1H, H_{3eq}), 4.17 (d, 1H, H_{3ax}, *J*= 13.5 Hz), 3.80 (d, 1H, *J*= 9.99 Hz, -CH_2OBn), 3.69 (d, 1H, *J*= 9.99 Hz, -CH_2OBn), 2.1-2.25 (m, 2H, -CH_2CH_2-), 1.94-2.06 (m, 1H, -CH_2CH_2-), 1.83-1.92 (m, 1H, -CH_2CH_2-), 1.51 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7, 138.0, 128.4, 127.9, 127.7, 106.3, 105.8, 84.0, 73.7, 71.6, 65.3,

34.6, 32.4, 24.2; IR (thin film) ν 2990, 2953, 2863, 1454, 1387, 1321, 1229, 1207, 1175, 1154, 1098, 868, 739; HRMS (EI) calc'd for $C_{16}H_{20}O_3$, 260.1412, calc'd for $C_{16}H_{21}O_3$, 261.1491 $(M+H)^+$, found 261.1487.

4-benzyloxy-4-hydroxy-5-hydroxymethy-7,8dioxabicyclo[3.2.1]octane (22). To a solution of 2-(3-benzyloxymethyl-3,4,5-trihydroxyl-4-hydroxymethylpentyl)-2-methyl-1,3-dioxolane (**19**) (31.7 mg, 0.089 mmole) in methanol (0.4 ml) was added 2% aqueous HCl/MeOH (0.4 ml). The initially brown mixture immediately turned golden yellow. The mixture was stirred at room temperature for 24 h. At that time, the mixture was partitioned between EtOAc (30 ml) and 10% aqueous $NaHCO_3$ (2.0 ml). The aqueous phase was extracted with EtOAc (3 x 30 ml) followed by washing with brine (3.0 ml). The combined organic phases were then dried over Na_2SO_4, filtered and concentrated to afford a slightly yellow oil. The residue was chromatographed over silica gel (30% EtOAc in hexanes to 50% EtOAc in hexanes) to afford **22** (12.7 mg, 49.0%). **22** TLC R_f = 0.44 (2:3 hexane/EtOAc); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.27-7.36 (m, 5H, H_{arom}), 4.60 (d, 1H, *J*= 11.9 Hz, -OC*H*$_2$ Ph), 4.53 (d, 1H, *J*= 11.9 Hz, -OC*H*$_2$ Ph), 4.03 (d, 1H, *J*= 8.0 Hz, H_{endo}), 3.85 (dd, 1H, *J*= 12.2, 5.82 Hz, -C*H*$_2$OH), 3.75 (dd, 1H, *J*= 12.2, 7.36 Hz, -C*H*$_2$OH), 3.57 (d, 1H, *J*= 8.0 Hz, H_{exo}), 3.54 (s, 1H, tertiary O*H*), 3.49 (d, 1H, *J*= 10.2 Hz, -C*H*$_2$OBn), 3.44 (d, 1H, *J*= 10.2 Hz, -C*H*$_2$OBn), 3.33 (dd, 1H, *J*= 5.94, 7.16 Hz, -CH$_2$O*H*), 1.90-1.96 (m, 2H, -C*H*$_2$C*H*$_2$-), 1.89-1.91 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.47-1.52 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.48 (s, 1H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8, 128.6, 128.0, 127.8, 108.6, 85.4, 74.1, 73.8, 71.9, 69.1, 62.8, 32.5, 28.3, 23.9; IR ($CHCl_3$) ν 3430 (br), 2939, 2893, 1454, 1386, 1358, 1258, 1207, 1047, 939, 925, 896, 858, 769, 737; HRMS (EI) calc'd for $C_{16}H_{22}O_5$, 294.1467, calc'd for $C_{16}H_{23}O_5$, 295.1546 $(M+H)^+$ found 295.1541. Analysis calc'd for $C_{16}H_{22}O_5$: C 65.27%, H 7.48 %; found C 65.04%, H 7.54%. After concentration, the material was recrystallized from diethyl ether (m.p. 125-6°). Crystal structure details: $C_{16}H_{22}O_5$, FW = 294.35, monoclinic, $P2_1/c$, *a* = 10.388(6), *b* = 7.486(6), *c* = 18.98(1) Å, β = 92.25(5)°, V = 1475 Å^3, Z = 4, D_x = 1.326 g/cm^{-3}, monochromatized radiation λ(K_α) = 1.5418 Å, μ = 0.77 mm^{-1}, F(000) = 632, T = 100 K. Data collected on a Rigaku AFC5R diffractometer to a θ limit of 60° with 1560 observed, at $I > 3\sigma(I)$, reflections out of 2305 measured. Structure solved by direct methods (SHELX86, G.M. Sheldrick, *Acta Crystallogr.*, **1990**, A46, 467-473) and refined using full-matrix least-squares on *F* using 191 parameters. All non-hydrogen atoms refined with anisotropic thermal displacements. Final agreement statistics are: R = 0.060, R_w = 0.079. Coordinates for **22** have been deposited.

4S*-5-benzyloxymethyl-4-hydroxyl-4-(1R*-1-hydroxylprop-2-enyl)-1-methyl-2,8-dioxabicyclo[3.2.1]octane (27). To a cooled (-78 °C) solution of oxalyl chloride (0.14 ml, 1.57 mmole, 2.0 equiv) in THF[16] (3 mL) was added, dropwise, dimethyl sulfoxide (0.22 ml, 3.13 mmole, 4.0 equiv). Evolution of gas occurred and quickly subsided. After 1 h, **20** (232 mg, 0.79 mmole) in THF (*ca.* 2 mL) was added by syringe. Within a few minutes, the reaction mixture became turbid. The mixture was stirred at -78 °C for 1 h and then freshly distilled triethylamine (0.65 ml, 4.68 mmole, 6.0 equiv) was added dropwise. The flask was allowed to warm to room temperature over 30 min. The mixture was then cooled to -78 °C and vinyl magnesium bromide (3.9 ml, 1.0 M in THF, 3.9 mmole, 5.0 equiv) was added dropwise. After 10 h, the pale yellow solution was warmed to -50 °C for 5 hours and to room temperature overnight. Excess vinylmagnesium bromide was quenched by pouring the reaction mixture into a vigorously stirred mixture of Et_2O (70 ml) and Na/K tartrate solution (5 ml, saturated in water). The phases were separated and the aqueous phase extracted with Et_2O (3 x 50 ml). The combined organic phases were washed with brine,

dried over Na_2SO_4, filtered and concentrated to a yellow oil. Chromatography on silica gel (4:1 hexane/ethyl acetate) afforded **27** (175 mg, 70%): TLC R_f = 0.23 (4:1 hexane/ethyl acetate); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.31-7.38 (m, 5H, H_{arom}), 6.06 (m, 1H, -*H*C=CH_2), 5.33 (d, 1H, *J*= 17.2 Hz, -HC=C*H*H_{trans}) 5.24 (d, 1H, *J*= 10.4 Hz, -HC=C*H*H_{cis}), 4.72 (m, 1H, -*H*COH), 4.69 (d, 1H, *J*= 12.0 Hz, -OC*H*$_2$Ph), 4.54 (d, 1H, *J*= 12.0 Hz, -OC*H*$_2$Ph), 3.84 (d, 1H, *J*= 11.9 Hz, H_{3eq}), 3.80 (d, 1H, *J*= 3.5 Hz, -HCO*H*), 3.74 (s, 2H, -C*H*$_2$OBn), 3.61 (s, 1H, tertiary O*H*), 3.51 (d, 1H, *J*= 11.9 Hz, H_{3ax}), 2.43 (m, 1H, -C*H*$_2$C*H*$_2$-), 2.04-2.15 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.88-1.98 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.58-1.68 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.48 (s, 1H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.8, 136.2, 128.6, 128.2, 128.1, 117.3, 106.7, 85.7, 74.3, 72.9, 72.6, 70.3, 65.9, 34.2, 30.8, 23.3; IR (thin film) ν 3462, 2990, 2939, 2883, 1454, 1389, 1219, 1198, 1155, 1076, 1028, 920, 868, 735; HRMS (EI) calc'd for $C_{18}H_{24}O_5$, 320.1624, calc'd for $C_{18}H_{25}O_5$ (M+ H)$^+$ 321.1703; found 321.1702. Analysis calc'd for $C_{18}H_{24}O_5$: C, 67.48%; H 7.55%. Found: C 67.56%; H 7.72%.

3R*, 4S*-5-benzyloxymethyl-3-ethenyl-4-hydroxyl-4-hydroxymethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octane (29). To a solution of **27** (182.2 mg, 0.569 mmole) in CH_2Cl_2 (3 ml) was added TFA (60 μL, 1.0 M stock solution in CH_2Cl_2, 0.06 mmole, 0.1 equiv). The solution was stirred at room temperature for 24 h. The reaction mixture was then concentrated under reduced pressure and chromatographed on silica gel (gradient elution: 85:15 hexane/ethyl acetate---> 4:1 hexane/ethyl acetate) to afford **29** (145.0 mg, 79%) as a slightly pale yellow oil: TLC R_f = 0.11 (85:15 hexane/ethyl acetate); ^{1}H-NMR ($CDCl_3$, 400 MHz) ppm δ 7.30-7.36 (m, 5H, H_{arom}), 5.96 (m, 1H, -*H*C=CH_2), 5.35 (m, 1H, -HC=C*H*$_2$), 5.32 (m, 1H, -HC=C*H*$_2$), 4.61 (d, 1H, *J*= 11.6 Hz, -OC*H*$_2$Ph), 4.53 (d, 1H, *J*= 11.6 Hz, -OC*H*$_2$Ph), 4.17 (d, 1H, *J*= 7.72 Hz, H_{3ax}), 4.00 (d, 1H, *J*= 9.23, -C*H*$_2$OBn), 3.57 (m, 2H, -C*H*$_2$OH), 3.41 (d, 1H, *J*= 9.23, -C*H*$_2$OBn), 3.35 (s, 1H, tertiary O*H*), 2.76 (m, 1H, -CH$_2$O*H*), 2.29-2.34 (m, 1H, -C*H*$_2$C*H*$_2$-), 2.12-2.18 (m, 1H, -C*H*$_2$C*H*$_2$-), 1.94-2.03 (m, 2H, -C*H*$_2$C*H*$_2$-), 1.52 (s, -C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9, 133.5, 128.6, 128.2, 128.1, 120.6, 106.6, 86.4, 76.4, 74.1, 71.9, 71.7, 62.5, 34.1, 29.7, 23.8; IR (thin film) ν 3476, 2878, 1564, 1454, 1387, 1317, 1219, 1094, 1024, 910, 731; HRMS (EI) calc'd for $C_{18}H_{24}O_5$, 320.1624, calc'd for $C_{18}H_{25}O_5$, 321.1703; found 321.1696 (M+H)$^+$.

NOESY Spectra. Prior to NOESY experiments, all samples were degassed by five, freeze/pump-thaw cycles. Standard phase-sensitive NOESY sequences were performed on a Bruker ARX 500 MHz spectrometer using XWINNMR.™ States-TPPI phase cycling was employed with a mixing time of 750 msec.

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