

EtOAc/petroleum ether) of the crude product afforded 81 mg of isoxazolidine **14c** (75%) as an oil.  $^1\text{H NMR}$   $\delta$  0.95–1.60 (m, 9 H,  $-\text{COOCH}_2\text{CH}_3$ 's), 2.04–3.10 (m, 4 H, C-4 and C-6  $-\text{CH}_2$ 's), 3.70–4.50 (m, 8 H,  $-\text{COOCH}_2\text{CH}_3$ 's and  $-\text{NCH}_2\text{Ph}$ ), 4.58 (s, 2 H, C-3 and C-6a  $-\text{CH}$ 's), 5.94 (s, 2 H,  $-\text{OCH}_2\text{O}-$ ), 6.66–7.10 (m, 3 H, ArH), 7.17–7.50 (m, 5 H,  $-\text{C}_6\text{H}_5$ ). IR 3000, 2800, 1720, 1500, 1440, 1240, 1200, 1040, 800  $\text{cm}^{-1}$ .

Anal. Calcd for  $\text{C}_{29}\text{H}_{33}\text{NO}_5$ : C, 64.55; H, 6.16; N, 2.60. Found: C, 64.66; H, 5.93; N, 2.48.

**Registry No.** **11a**, 98525-96-3; **11b**, 98525-88-3; **11c**, 98525-89-4; **11d**, 98526-00-2; **11e**, 98526-01-3; **11f**, 98526-02-4; **12a**, 98525-97-4; **12b**, 98525-98-5; **12c**, 98525-99-6; **12d**, 98525-90-7; **12e**, 98539-82-3;

**12f**, 98525-91-8; **14a**, 98525-92-9; **14b**, 98526-05-7; **14c**, 98525-94-1; **15a**, 98526-03-5; **15b**, 98539-83-4; **15c**, 98526-04-6; **16**, 17605-06-0; **17**, 98525-68-9; **18**, 98525-69-0; **19**, 98525-70-3; **20**, 98525-71-4; **21**, 98525-72-5; **22**, 98525-73-6; **23**, 98525-74-7; **24**, 37935-47-0; **24** (X =  $\text{CH}_2\text{CH}_2\text{OH}$ ), 34626-51-2; **25**, 98525-84-9; **26**, 75958-95-1; **27**, 98525-85-0; **28**, 98525-75-8; **29**, 98525-76-9; **30**, 98525-77-0; **31**, 31608-22-7; **32**, 98525-81-6; **33**, 98525-82-7; **34**, 98525-83-8; **35**, 98525-78-1; **36**, 98525-79-2; **37**, 98525-80-5; **38**, 98525-86-1; **39**, 98525-87-2; **40**, 21339-47-9; **41**, 98539-81-2; **42**, 98525-95-2;  $\text{CH}_3\text{COCH}_2\text{COOEt}$ , 141-97-9;  $\text{C}_6\text{H}_5\text{C}(\text{CH}_2\text{Br})=\text{CH}_2$ , 3360-54-1;  $\text{C}_6\text{H}_5\text{C}\equiv\text{CCOOEt}$ , 2216-94-6;  $\text{Br}(\text{CH}_2)_4\text{OH}$ , 33036-62-3;  $\text{HC}\equiv\text{CCOOEt}$ , 623-47-2;  $\text{CH}_3\text{NHOH}\cdot\text{HCl}$ , 4229-44-1;  $\text{C}_6\text{H}_5\text{CH}_2\text{NHOH}$ , 495-18-1;  $\text{C}_6\text{H}_5\text{CH}_2\text{NHOH}\cdot\text{oxalate}$ , 98525-93-0.

## Structural Studies of 2-(*p*-Chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane

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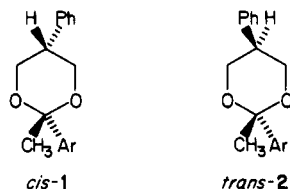
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The structure and conformation of *cis*- and *trans*-2-(*p*-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane have been established by a combination of NMR and X-ray analysis.

We recently required precise information regarding stereochemical preferences and interatomic distances for a number of 2,2,5-trisubstituted 1,3-dioxanes. The unusually large conformational strain that results from axial 2-alkyl groups and the diminished 1,3-diaxial nonbonded interactions from 5-axial substituents make this substitution pattern particularly interesting.<sup>1</sup> The absence of detailed stereochemical or structural studies for compounds of this type prompts a report of our results.

We have synthesized the isomeric 2-(*p*-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxanes **1** and **2** and elucidated



their structure by a combination of NMR spectroscopy and X-ray crystallography. These results have provided us with the needed structural parameters and have also contributed to our understanding of the structural and conformational preferences of this intriguing ring system.<sup>2</sup>

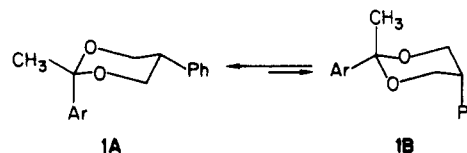
### Results and Discussion

Condensation of *p*-chloroacetophenone with 2-phenyl-1,3-propanediol (TSA,  $\text{CHCl}_3$ , Dean-Stark trap) results in formation of an isomeric mixture of 1,3-dioxanes (**1**, **2**). The reaction conditions used for their preparation often results in an equilibrium mixture; this was confirmed by equilibration studies on the isomeric mixture and pure major and minor components **1** and **2**. Dilute solutions of pure isomers in dry ether were equilibrated in the presence of Amberlyst ion exchange resin. After 48 h at

23.8 °C each isomer gave an identical 84:16 ratio of *cis*-*trans* isomers corresponding to a free energy difference of  $\Delta G^\circ_{297} = 1.05$  kcal/mol.

Fractional crystallization in 10% ether-hexane afforded pure samples of the isomeric 1,3-dioxanes.

The proton NMR of the major isomer (**1**) contains a nine-line triplet of triplets ( $J = 11.3, 4.8$  Hz) at 3.3 ppm which is assigned to the methine proton at C-5. The methylene protons at C-4(6) are resolved in this isomer and are found at 3.8 and 3.96 ppm. The high-field proton of the methylene group (3.8 ppm, dd) can be assigned the axial position with vicinal and geminal couplings of 11.3 and 11.4 Hz, respectively. The low-field proton (3.96 ppm) consists of a doublet of doublets ( $J = 11.4, 4.8$  Hz). With the reasonable assumption that this substitution pattern will not produce any unusual distortions resulting in nonchair conformations,<sup>3</sup> the NMR results for the major isomer are consistent with a 1,3-dioxane in which the 5-phenyl group occupies an equatorial position. Furthermore, on the basis of conformational equilibrium studies,<sup>4</sup> an axial 2-methyl group is expected to have greater steric strain than an axial 2-phenyl group. The NMR spectrum of the major isomer is entirely consistent with the *cis*-1,3-dioxane (**1**) that exists predominately in conformation **A**.



The proton NMR spectra of the minor isomer **2** is characterized by an apparent pentuplet (overlapping

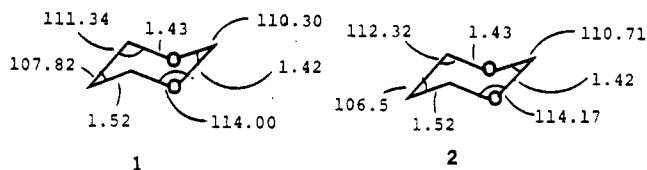
(1) (a) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444.

(b) Riddell, F. G.; Robinson, M. J. T. *Tetrahedron* **1967**, *23*, 3417.

(2) (a) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1. (b) Riddell, F. G. "The Conformational Analysis of Heterocyclic Compounds"; Academic Press: New York, 1980.

(3) Kellie, G. M.; Murry-Rust, P.; Riddell, F. G. *J. Chem. Soc., Perkin* **2**, **1972**, 2384.

(4) (a) Nader, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 3050. (b) Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 1971. The preferences (in kcal/mol) of the alkyl substituents for the equatorial (over the axial) position used in the calculation are 2-Me, 3.98; 2-Ph, 3.12; 5-Ph, 1.03.

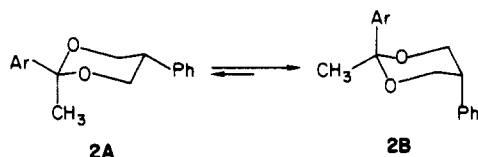


**Figure 1.** Bond angles and bond distances for the 1,3-dioxane rings of 1 and 2.

**Table I**

1,3-dioxane torsion angles	compounds		
	1	2	3
O <sub>3</sub> C <sub>2</sub> O <sub>1</sub> C <sub>6</sub>	56.2	53.7	63
O <sub>3</sub> C <sub>4</sub> C <sub>5</sub> C <sub>6</sub>	52.5	55.0	55
C <sub>2</sub> O <sub>3</sub> C <sub>4</sub> C <sub>5</sub>	56.2	59.4	59

triplet of triplets, 1 H) at high field (2.67 ppm), attributable to the benzylic proton at C-5. The two coupling constants are 3.5 and 3.9 Hz. At lower field (4.09 ppm, 4 H) is found a ddd,  $J = 3.5, 3.9,$  and 11.6 Hz. Decoupling the proton at 2.67 results in collapse of the low-field resonance to a doublet of doublets ( $J = 11.6$  Hz). Interestingly, this analysis is consistent with the diaxial-diaryl conformational isomer **B** of *trans*-1,3-dioxane 2.



This finding emphasizes that simple additivity of  $A$  values, which would predict that isomer **2A** is slightly favored (0.1–0.2 kcal/mol) over conformational isomer **2B**,<sup>4</sup> cannot be assumed.<sup>5–7</sup> Thus the NMR spectra permit assignment of the *cis* and *trans* diastereomers, but a more detailed analysis of the proton coupling constants suggests that the dominant conformational isomer of the *trans*-diaryl derivative has the 2,5-diaryl groups occupying axial positions.

### X-ray Analysis

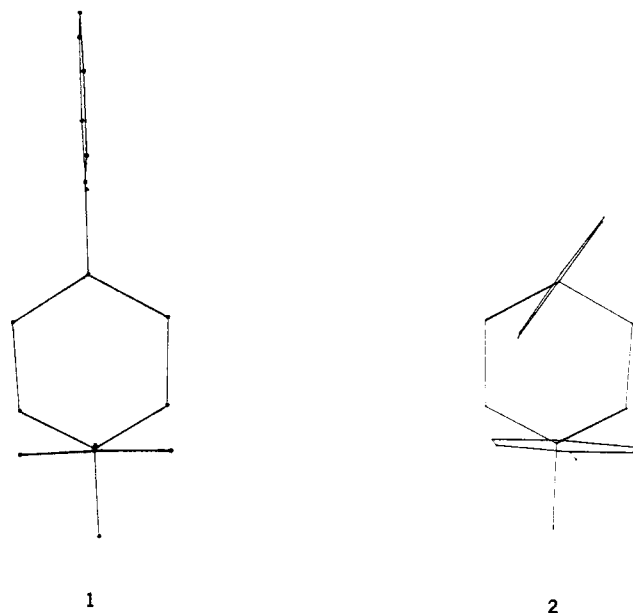
The X-ray crystal structures of 1 and 2 permits unambiguous assignment of both stereochemistry and conformation of the two diastereomers.<sup>8</sup> Bond distances and bond angles for the *cis* and *trans* isomers are given in Figure 1. In the *cis* isomer (1) the 1,3-dioxane ring exists

(5) Eliel, E. L.; Enanoza, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8072 and references cited therein.

(6) Bailey, W. F.; Connon, H.; Eliel, E. L.; Wiberg, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 2202.

(7) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

(8) (a) Crystal data for isomer 1: C<sub>17</sub>H<sub>17</sub>O<sub>2</sub>Cl, monoclinic, space group  $P2_1/c$ ,  $a = 14.758$  (3) Å,  $b = 7.761$  (3) Å,  $c = 14.396$  (3) Å,  $\beta = 112.43$  (2)°,  $V = 1524.2$  (5) Å<sup>3</sup>. Intensity measurements were made on a Syntex P2<sub>1</sub> diffractometer, Mo K $\alpha$  radiation,  $\lambda = 0.71073$  Å, graphite monochromator. Intensities of 3529 reflections with  $2\theta \leq 55^\circ$  was measured; of these 2130 had intensities  $I > 3\sigma(I)$ . The structure was solved by direct methods (MULTAN78) and refined by full matrix least-squares calculations to  $R = 0.043$ ,  $R_w = 0.053$  (anisotropic thermal parameters for carbon and oxygen, hydrogen atoms in calculated positions). (b) Crystal data for isomer 2: C<sub>17</sub>H<sub>17</sub>O<sub>2</sub>Cl, monoclinic, space group  $P2_1/n$ ,  $a = 8.164$  (3) Å,  $b = 10.433$  (4) Å,  $c = 17.56$  (1) Å,  $\beta = 91.35$  (4)°,  $V = 1499.5$  (8) Å<sup>3</sup>,  $Z = 4$ . Intensity measurements were made on a Syntex P2<sub>1</sub> diffractometer, Mo K $\alpha$  radiation,  $\lambda = 0.71073$  Å, graphite monochromator. Intensities of 3004 reflections with  $2\theta \leq 50.0^\circ$  was measured; of these 2034 had intensities  $I > 3\sigma(I)$ . The structure was solved by direct methods and refined in the same manner as 1. The final refinement converged to  $R = 0.045$ ,  $R_w = 0.059$  (anisotropic thermal parameters for carbon and oxygen, hydrogen atoms in calculated positions). Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances of both isomers are included as supplemental information.



**Figure 2.** Representation of 1 and 2 (top perspective) revealing the 2-aryl-5-phenyl orientation.

in a chair conformation with only slight differences in the ring torsion angles from the ideal (cyclohexane) value of 56° (Table I). The *trans* isomer 2 is also in a chair conformation with slight puckering in the C<sub>2</sub>O<sub>3</sub>C<sub>4</sub>C<sub>5</sub> region. For comparison, the torsion angles for 2-(*p*-chlorophenyl)-1,3-dioxane (3)<sup>9</sup> are also included. A general trend toward flattening the six-membered ring is noted upon introduction of the second (Axial) substituent at C-2.

Comparison of the C-2-aryl carbon bond with the C-5-phenyl carbon bond does not reveal any appreciable tilting of the axial substituent at these positions to alleviate 1,3-diaxial strain. The intersection of these two vectors (parallel in a perfect chair) is at 1.2° for the *cis* isomer and 2.1° for the *trans* isomer. Previous studies of substituted 1,3-dioxanes bearing non-hydrogen axial substituents at the 2 and 4 positions revealed a tilting of the 2-axial bond of up to 30°.<sup>10,11</sup> Assuming a correspondence between the solution phase and solid state, the X-ray results confirm that the dominant conformational isomer of *trans*-1,3-dioxane is **2B**.

The difference in free energy between **1A** and **2B**, the dominant conformer of the *cis* and *trans* isomers, is simply the difference in energy between the axial and equatorial positions for a 5-phenyl substituent. Our experimental number for this difference (1.05 kcal/mol) agrees quite well with earlier measurements (1.03 kcal/mol).<sup>1</sup> Assuming that the NMR of 2 can be interpreted in terms of a population ratio of at least 10:1 in favor of **2B**,<sup>12</sup> the free energy difference between these two conformers must be at least 1.3 kcal/mol.

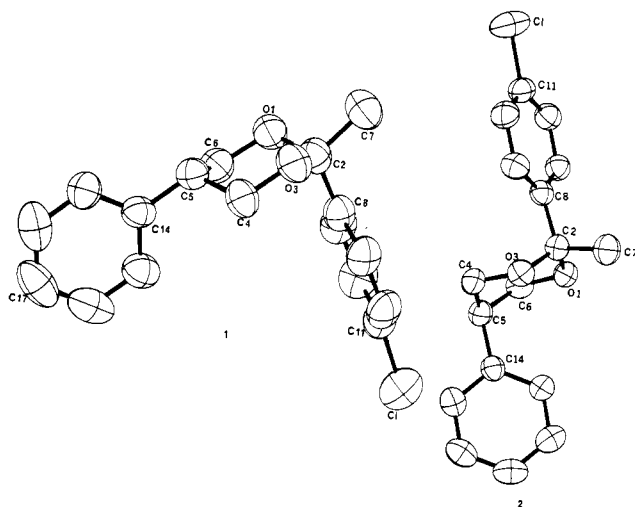
After taking into consideration the conformational energy differences for a 5-phenyl substituent in 1,3-dioxane, one computes the free energy difference between a geminally substituted axial phenyl-equatorial methyl and

(9) deKock, A. J. and Romers, C. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 313.

(10) Kellie, G. M., Murry-Rust, P., and Riddell, F. G., *J. Chem. Soc., Perkin Trans. 2* **1972**, 2384.

(11) Nader, F. W. *Tetrahedron Lett.* **1971**, 3259.

(12) The coupling constants for the *trans* isomer 2 ( $J_{4a,5a} = 3.9$  Hz,  $J_{4a,5a} = 3.5$  Hz) are normal for the 1,3-dioxane ring. A significant population of conformation **2B** would be expected to result in average coupling constants that deviate from the above values: Langer, E.; Lehner, H. *Monatsh Chem.* **1976**, *107*, 1.



**Figure 3.** An ORTEP drawing of *cis*-1 and *trans*-2 showing the atomic numbering schemes.

equatorial phenyl-axial methyl 2,2-disubstituted 1,3-dioxane to be  $>2.35$  kcal/mol in favor of the former. This result is in complete agreement with the value determined by Eliel and co-workers<sup>6,13</sup> of 2.55 kcal/mol. An explanation for nonadditivity of the *A* values, principally entropic in origin, is discussed in detail by these authors.

One of the more interesting features of these isomers is the disposition of the two phenyl groups. In the *cis* isomer (Figure 2), the planes of the two aryl groups are orthogonal. The 2-*p*-chlorophenyl plane lies on a tangent to C-2 of the hexagon (perpendicular conformation)<sup>14</sup> while the equatorial 5-phenyl plane bisects the C-4,5,6 bond angle (parallel conformation).<sup>14</sup>

The projection of *trans*-2 (Figure 2) graphically demonstrates the different steric requirements for axial substituents at C-2 and C-5 in 1,3-dioxane ring systems. These phenyl rotamers presumably result from minimization of the repulsions between the ortho hydrogens of the aryl group and the axial and equatorial hydrogens on carbons 4 and 6.<sup>6</sup>

A most interesting observation is found upon inspection of *trans*-2. The aryl group at C-2 is in a perpendicular conformation similar to that found in *cis*-1. The axial-5-phenyl group, however, is close to the bisected conformation and tilted  $31^\circ$  from the normal plane toward the oxygen at C-1. In this conformation the 4,6-equatorial-H/ortho-H repulsions in the perpendicular form<sup>14</sup> are avoided at the expense of axial ortho-H/oxygen-oxygen interactions.

Nonsymmetrical phenyl rotamers are frequently encountered in the solid state and have been considered to result from packing forces in the crystal.<sup>15</sup> However, if intramolecular origins are sought, one may consider the possibility of a weak attractive interaction between the oxygen lone pair and the ortho hydrogen of the phenyl group. Indeed the distance between the oxygen and hydrogen (2.39 Å) is well within the van der Waals radii (2.70 Å). A recent survey of neutron diffraction crystal structures has concluded that C-H...O interactions are more likely to be attractive than repulsive and can reasonably be described as hydrogen bonds.<sup>16</sup>

Although weak bonds between hydrogen attached to  $sp^2$  carbons and oxygen have been proposed in related systems,<sup>17</sup> the evidence for this interaction, particularly with an aryl group without electronegative substituents,<sup>18</sup> is less than compelling. Indeed, inspection of the unit cell of 2 reveals several nonbonded interactions between adjacent molecules and the C-5 phenyl substituent that may be responsible for the rotameric preference.<sup>19</sup> These observations, together with the failure to detect any significant differences in the IR or UV spectra of 1 or 2, prevents an unambiguous explanation for the nonsymmetrical phenyl rotamer in 2.

## Experimental Section

***cis*- and *trans*-2-(4'-Chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane (1, 2).** A mixture of 1,3-dihydroxypropane (3.1 g, 20 mmol), *p*-chloroacetophenone (2.83 g, 18 mmol), and *p*-toluenesulfonic acid (1 g) in toluene (300 mL) was refluxed for 24 h with a Dean-Stark trap attached for removal of water. While still hot the solution was poured onto 5 g of  $K_2CO_3$  and allowed to sit overnight. The clear solution was filtered and evaporated. Attempts to crystallize this mixture were unsuccessful. The crude mixture was passed through a silica gel column with 2:1 hexane-ether eluent. This was then crystallized in 10% ether in hexane. The first fraction was pure minor isomer later confirmed to be the *trans*-2. The second crop was pure major isomer, *cis*-1. Both isomers crystallized as clear colorless prisms suitable for X-ray analysis. The major isomer had significantly shorter retention times on both capillary and standard gas chromatography columns.

**Major isomer: 1, *cis*-2-(4'-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane,** mp  $80^\circ C$ : IR (KBr) 3092, 3060, 3022, 2985, 2965, 2940, 1595, 1490, 1250, 1180, 1138, 1089, 1042, 882, 870, 767, 702  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.44 (m, 5 H), 7.22 (m, 2 H), 7.00 (m, 2 H), 3.98 (A of  $A_2M_2X$ , 2 H,  $J = 11.4$ , 4.8 Hz), 3.80 ( $M_2$  of  $A_2M_2X$ , 2 H,  $J = 11.4$ , 11.3 Hz), 3.32 (X of  $A_2M_2X$ , 1 H), 1.57 (s, 3 H);  $^{13}C$  NMR ( $CDCl_3$ ) 139.64, 135.13, 133.07, 129.34, 128.87, 128.63, 127.73, 127.51, 100.30, 66.61, 41.19, 32.54; UV (cyclohexane) 278, 272, 264, 260, 256 nm. Anal. C, H.

**Minor isomer: 2, *trans*-2-(4'-chlorophenyl)-2-methyl-5-phenyl-1,3-dioxane,** mp  $131^\circ C$ : IR (KBr) 3100, 3060, 3020, 2980, 2940, 2880, 1600, 1490, 1380, 1240, 1180, 1120, 1090, 1015, 750, 700, 560  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.2-7.6 (m, 9 H), 4.13 ( $A_2$  of  $A_2B_2X$ , 2 H,  $J = 11.6$ , 3.9 Hz), 4.03 (B of  $A_2B_2X$ , 2 H,  $J = 11.6$ , 3.6 Hz), 2.67 (X of  $A_2B_2X$ , 1 H), 1.60 (s, 3 H);  $^{13}C$  NMR ( $CDCl_3$ ) 142.29, 140.64, 133.94, 129.02, 128.73, 128.38, 128.17, 126.99, 100.03, 65.56, 39.76, 29.75; UV (cyclohexane) 278, 274, 266, 260, 254 nm. Anal. C, H.

**Equilibration Studies.** Approximately 10 mg of pure isomer was dissolved in 10 mL of dry ether. One bead of Amberlyst ion-exchange resin was added, and gas chromatographic analysis of both solutions was begun. After 48 h at  $23.8^\circ C$  both solutions gave identical integrations of 84:16 in favor of the *cis* isomer (1). This corresponds to a free energy difference  $\Delta G^\circ_{297}$  of 1.05 kcal/mol.

**Low-Temperature NMR Studies.** 1% solutions of both pure isomers in  $CD_2Cl_2$  were subjected to low-temperature NMR analysis. In both cases the spectra did not change to  $-60^\circ C$ .

**Acknowledgment.** We wish to express our appreciation to Professor E.L. Eliel for very helpful suggestions in the interpretation of these results and for calling to our attention several important references relating to this work. We wish to thank the NIH and Hughes Aircraft for financial support of this work. We also wish to thank Professor Robert Doedens for assistance with the X-ray

(13) Eliel, E. L.; Bailey, W. F.; Wiberg, K. B.; Connon, H.; Nader, F. W. *Liebigs Ann. Chem.* **1976**, 2240.

(14) Allinger, N. L., and Tribble, M. T. *Tetrahedron Lett.* **1971**, 3259.

(15) Ermer, O. and Dunitz, J. D. *Helv. Chim. Acta* **1969**, *52*, 1861.

(16) Taylor, R.; Kennard, T. F. *J. Am. Chem. Soc.* **1982**, *104*, 5063.

(17) (a) Green, R. D. "Hydrogen Bonding by C-H Groups"; Wiley: New York, 1974; pp 109-118. (b) Stumpf, W. Z. *Elektrochem.* **1953**, *57*, 690.

(18) See, for example: Gorrie, T. M.; Haley, N. F. *J. Chem. Soc., Chem. Commun.* **1972**, 1081.

(19) Inspection of the unit cell reveals at least 10 nonbonded approaches of less than 3.0 Å to the 5-phenyl group.

analysis and Maureen Martin for help with the preparation of the ketals.

**Registry No.** 1, 98540-71-7; 2, 98540-72-8; 2-phenyl-1,3-dihydroxypropane, 1570-95-2; *p*-chloroacetophenone, 99-91-2.

**Supplementary Material Available:** Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances for *cis*-1,3-dioxane (1) and *trans*-1,3-dioxane (2) (8 pages). Ordering information is given on any current masthead page.

## Synthetic Opportunities Offered by Anti $\alpha$ -Methylene- $\beta$ -hydroxy- $\gamma$ -alkoxy Esters: Stereoselective Reactions at the Double Bond<sup>1</sup>

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Addition of *tert*-butyl  $\beta$ -(dimethylamino)propionate to (*S*)-*O*-[(benzyloxy)methyl]lactaldehyde and (*R*)-2,3-*O*-isopropylidene-glyceraldehyde gave, after *N*-methylation and elimination,  $\alpha$ -methylene- $\beta$ -hydroxy- $\gamma$ -alkoxy esters in fairly good yield (40–60%) and a high anti-syn ratio (7–12:1). These esters were easily lactonized, by acidic treatment, to the corresponding  $\alpha$ -methylene- $\beta$ -hydroxy- $\gamma$ -butyrolactones. The double bond of these compounds was submitted to various reactions (cuprate addition, reduction, dihydroxylation). The stereoselectivity of these reactions was studied and ranged from poor to good depending on the specific substrate and reaction used. Acyclic substrates proved to be more selective than the corresponding  $\gamma$ -lactones. The stereoconfiguration of the products was assigned by comparison to known compounds (blastmycinolactol-*a*, *epi*-*D*-hamamelose).

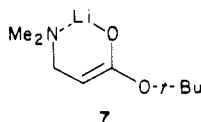
The aldol condensation is one of the most straightforward methods for generating C–C bonds in a stereoselective manner.<sup>2</sup> We recently reported that *tert*-butyl  $\beta$ -(dimethylamino)propionate (1), a synthetic equivalent of *tert*-butyl acrylate, readily reacts with  $\alpha$ -alkoxy aldehydes to give  $\alpha$ -methylene- $\beta$ -hydroxy- $\gamma$ -alkoxy esters 2 with anti-syn selectivity up to 24:1<sup>3</sup> (Chart I).

We wish to report here additional examples of this anti-selective reaction and the transformation of 2 to various  $\gamma$ -lactones using stereoselective reactions at the double bond.

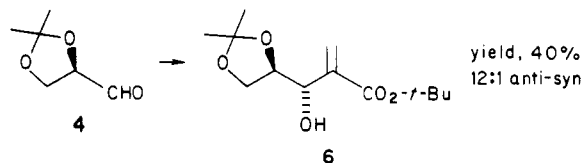
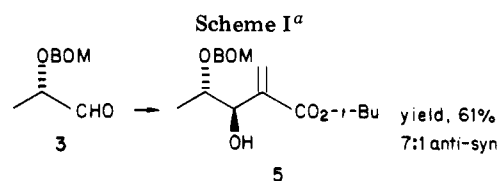
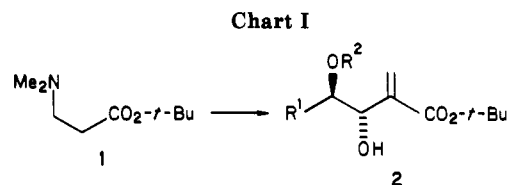
### Results and Discussion

Optically pure (*S*)-*O*-[(benzyloxy)methyl]lactaldehyde (3)<sup>3b</sup> and (*R*)-2,3-*O*-isopropylidene-glyceraldehyde (4)<sup>4</sup> were reacted, under previously described conditions,<sup>3b</sup> with *tert*-butyl  $\beta$ -(dimethylamino)propionate (1). The corresponding adducts were treated with K<sub>2</sub>CO<sub>3</sub> and MeI in methanol<sup>5</sup> to give  $\alpha$ -methylene- $\beta$ -hydroxy- $\gamma$ -alkoxy esters in fairly good yield (40–60%) and high anti-syn ratio (7–12:1) (Scheme I).

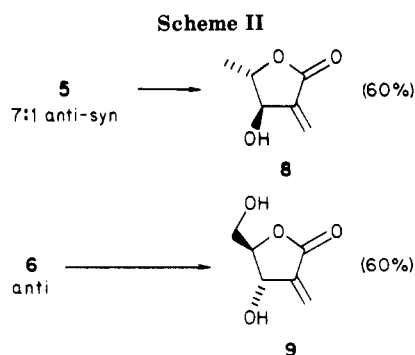
The condensation between 1 and lactaldehyde 3 was conducted in ethyl ether, after generating the enolate with LDA in ether at 0 °C in order to obtain the more stable and more anti-selective (*E*)-enolate 7.<sup>3b</sup> In the case of



glyceraldehyde 4, on the contrary, after generating the



<sup>a</sup> BOM = CH<sub>2</sub>OCH<sub>2</sub>Ph.



(1) We respectfully dedicate this work to the memory of Professor L. Canonica, untimely deceased in Aug, 1984. Part of this work has been preliminarily presented at the Fifth International Conference on Organic Synthesis, Freiburg, Aug 27–30, 1984, Abstract T24, p 108.

(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* 1982, 13, 1. Heathcock, C. H. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212.

(3) (a) Banfi, L.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun.* 1983, 1112. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* 1984, 3784.

(4) Baer, E. *Biochem. Prep.* 1952, 2, 31.

(5) Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* 1977, 22, 224.

enolate at 0 °C in ethyl ether, THF was added at –78 °C (THF–ether 5:1) in order to increase the reactivity toward the aldehyde. When the reaction was conducted in pure diethyl ether a slightly improved ratio was observed (13:1), accompanied by a much lower yield (15%). The one-pot *N*-methylation–elimination procedure used here (MeI–