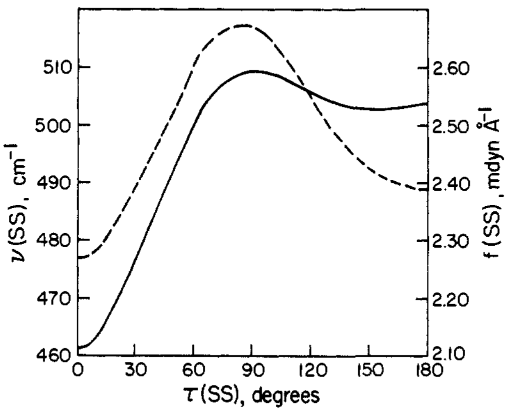

Figure 1. Variation of the S–S stretch force constant, f(SS) (---), and the S–S stretch frequency, ν(SS) (—), with the S–S dihedral angle, τ(SS), in dimethyl disulfide, as determined from ab initio and normal mode calculations.

and experimental[9] studies, asserting[9–11] that ν(SS) varies linearly with τ(SS) only in the range of 0–60°, being invariant in the range of 60–85° and expected to decrease in the 120–180° region. In contrast to Sugeta's normal mode calculation with a modified Urey–Bradley force field,[4] Kuptsov and Trofimov[12] showed that, even with an invariant f(SS)[4] (the S–S stretching force constant), a valence force field leads to a small variation in ν(SS) with τ(SS). In any case, there is general agreement[4,11] that in a CCSSCC moiety ν(SS) does depend on the τ(CS), the CC–SS dihedral angles.

Both the earlier CNDO/2[8] as well as more recent ab initio[13] calculations have shown that r(SS), the S–S bond length, varies with τ(SS), thus showing that f(SS) must also change. Of course, ν(SS) depends on the geometry as well as on f(SS), and therefore frequency estimates[8,11] based only on force constant trends cannot be completely reliable. The results of our ab initio and normal mode studies shed light on these issues.

Calculations were done with the 3-21G* basis set at the Hartree–Fock level. Analytical techniques were used to obtain force constants in cartesian coordinates, and these were then transformed to internal and symmetry coordinates. As usual,[14] force constants were scaled to match calculated with observed frequencies. Diagonal force constants were scaled according to internal coordinate types, six scaling factors being optimized to fit 15 observed frequencies.[15] Off-diagonal force constants were scaled with the geometric average of the diagonal scale factors.[14]

For each τ(SS), the geometric parameters were obtained from an ab initio geometry optimization. Ab initio force constants were calculated for the stationary energy conformers, viz., cis (τ = 0°), gauche (τ = 85.17°), and trans (τ = 180°). The f(SS) for other values of τ (30°, 60°, 120°, 150°) were obtained from the empirical formula relating f and r,[16] viz., $f = c/(r - d)^2$. First, the c and d parameters were obtained by optimizing the fit of the ab initio f and r to this relation. From this, the f at other values of r could be obtained from the ab initio optimized geometries. Since it is more convenient to have a correlation between f and τ, we obtained this by using a Fourier expansion, viz., $f = f_0 + {}^1/_2\sum_n f_n(1 - \cos n\tau)$. Having seven values, we used $n = 6$ for f(SS); for the other force constants we used the three ab initio values, and therefore $n = 2$. The scaled force constants were used to calculate frequencies and potential energy distributions, the unscaled force constants being used to calculate infrared and Raman intensities. Our vibrational assignments are consistent with those of Sugeta[4] for the gauche conformer; the average deviation between observed and calculated frequencies is 0.3%, and the observed relative band intensities are well predicted.

The results show that some of the force constants (such as f(CS)) do not change appreciably with τ(SS), while others do and are not a simple function of this dihedral angle. For example, Figure 1 shows the variation of f(SS) with τ(SS), indicating that it goes through a maximum near the gauche conformer. On the other hand, f(CSS) decreases monotonically in the 0–120° region and is then constant to 180°. The off-diagonal force constants all change significantly with τ(SS), in some cases changing sign.

The frequencies, as noted above, depend on the geometry as well as the force field. In Figure 1 we show the variation of ν(SS) with τ(SS). In the 0–85° range it follows the trend of f(SS), but in the region of 85–180° kinematic factors obviously counter the force constant trend, as previously recognized,[12] and ν(SS) decreases slightly (compared to a much larger decrease predicted from CNDO/2 calculations[8]). This variation is similar to that observed experimentally by Van Wart and Scheraga,[9] keeping in mind that in dimethyl disulfide there is no effect of τ(CS) on ν(SS). The changes in ν_s(CS) (symmetric stretch) and ν_a(CS) (antisymmetric stretch) with τ(SS) are relatively small ($\sim$10 and $\sim$15 cm^{-1}, respectively), but the changes in ν_a(CSS) and ν_s(CSS) ($\sim$100 and $\sim$50 cm^{-1}, respectively) are quite large, and while generally similar to previous results[4] are significantly different in detail.

Geometry optimization calculations on diethyl disulfide show a variation of r(SS) with τ(SS) similar to that in dimethyl disulfide, and therefore a similar variation in f(SS) is expected. We are also examining the effect of τ(CS) on the disulfide group frequencies. We believe that such ab initio methods offer a good possibility of elucidating the obviously complex dependence of disulfide vibrations on the internal rotation geometry of this group.

Acknowledgment. This research was supported by a grant from the Monsanto Company, St. Louis, MO.

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The Enzymatic Baeyer–Villiger Oxidation: Enantioselective Synthesis of Lactones from Mesomeric Cyclohexanones

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In a synthetic project directed toward the syntheses of the 3-acyltetramic acid antibiotics (e.g., tirandamycin[1]), we envisioned ketone **1** as a potential precursor.[2] The planned sequence involved the transformation of **1** into the ϵ-lactone **2** by using a peracid mediated Baeyer–Villiger oxidation. Because of the inherent mirror plane in **1**, chirality would not be established until after the oxygen atom had been inserted between the carbonyl group and one of the α-carbon atoms. If one could discriminate between the two enantiotopic carbon atoms flanking the carbonyl, then when the oxygen atom was inserted, a product which would be entirely one or highly enriched in one enantiomeric form would be produced. Insertion of the oxygen into the right-hand side of

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(1) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L. *J. Am. Chem. Soc.* **1973**, *85*, 4038.

(2) For the use of a similar intermediate and references to the pertinent synthetic work in the area, see: Boeckmann, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P.-E. *J. Am. Chem. Soc.* **1986**, *108*, 5549.

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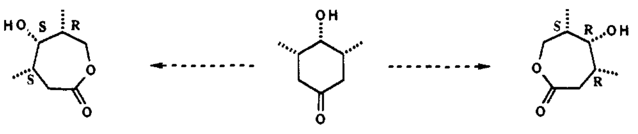
Scheme I



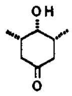
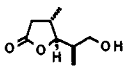
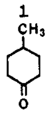
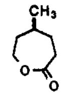
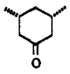
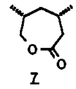
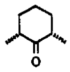
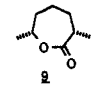
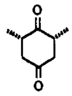
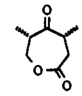
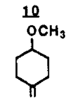
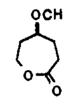
3S, 4S, 5R-**2** **1** 3R, 4R, 5S-**2**

carbonyl of cyclohexanone **1**, as depicted below, would produce lactone **2** possessing the 3S,4S,5R-configuration. On the other hand, if the oxygen were to be inserted into the left-hand side, the enantiomer would be obtained.

Contemplating how one might possibly control which of the carbons migrated during the Baeyer–Villiger oxidation an enzymatic process appeared to be a viable consideration because it is known that many enzymes are very efficient at discriminating between enantiomeric and mesomeric substrates.[3] It has also been demonstrated that nature makes use of the Baeyer–Villiger reaction in various biodegradation pathways.[4] Of the enzymes which have been found to effect the Baeyer–Villiger oxidation, the most promising and well studied appeared to be a bacterial flavoprotein monooxygenase known as cyclohexanone oxygenase (E.C.1.14.13.-) which was isolated from the bacteria *Acinetobacter* NCIB 9871.[5] Mechanistic studies by Schwab[6] and Walsh[7] have shown that the enzymatic Baeyer–Villiger reaction behaves like the nonbiochemical, peracid-mediated version, in that the oxygen atom is inserted into the more highly substituted position adjacent to the carbonyl carbon, there is retention of configuration at the migrating carbon center, and the carbonyl appears to function as an electrophile in the process. Trudgill had already established that cyclohexanone oxygenase catalyzes the conversion of a wide range of cyclic ketones into the corresponding lactones.[5] However, no characterization of the final products in terms of enantiomeric purity and absolute stereochemistry was reported.[8] We wish to describe the use of the enzymatic Baeyer–Villiger oxidation with the enzyme isolated from *Acinetobacter* NCIB 9871, cyclohexanone oxygenase, in the enantioselective preparation of lactones from a number of mesomeric cyclohexanones.

The bacteria were grown, and the enzyme was isolated and purified according to the procedure described by Walsh.[7] The ketones[9] were subjected to the enzymatic Baeyer–Villiger oxidation by adding them to a glycine-NaOH, pH 8.0, solution containing the purified enzyme and a catalytic amount of NADPH. The $NADP^+$/NADPH recycling technique was employed to circumvent the requirement of a stoichiometric amount of the relatively expensive NADPH.[10] This involved the addition of glucose-6-phosphate dehydrogenase to the buffer solution and then addition of a solution of glucose-6-phosphate during the course of the reaction. Upon complete consumption of the ketone substrate, the reaction was thoroughly extracted with ethyl acetate to afford, in most cases, the lactone products. In the case of ketone **1**, none of the expected seven-membered ring lactone **2** was isolated. Upon acidification of the solution and extraction, lactone **3** ($[\alpha]_D$ −25.98 (*c* 2.54, $CHCl_3$)) was the only product isolated. The ϵ-lactone had obviously undergone hydrolysis under the slightly basic reaction conditions. This hydrolysis was only observed to any significant degree for lactones **2** and **11**. The results from the substrates examined are shown in Table I.

Table I

substrate	product	$[\alpha]_D$	% yield	% ee
 **1**	 **3**	−25.98 (*c* 2.54, $CHCl_3$)	88	>98
 **4**	 **5**	−44.23 (*c* 1.56, $CHCl_3$)	80	>98
 **6**	 **7**	−12.69 (*c* 2.45, $CHCl_3$)	73	>98
 **8**	 **9**	−10.90 (*c* 1.56, $CHCl_3$)	27	>98
 **10**	 **11**	−14.38 (*c* 1.62, $CHCl_3$)	25[a]	>98
 **12**	 **13**	−12.01 (*c* 5.66, $CHCl_3$)	76	75

[a] The corresponding hydroxy acid was isolated as its methyl ester in 58% yield.

The enantiomeric purity of lactone **2** was checked by conversion of the alcohol to the (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester.[11] The enantiomeric purities of the other lactones were confirmed by first transforming them to the hydroxy esters by reaction with a catalytic amount of sodium methoxide in methanol followed by conversion to either the (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters. The enzyme derived products were then analyzed by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and compared with their racemic counterparts, obtained via the conventional peracid route. As seen in Table I, the enzyme was extremely effective at discriminating between the two sides of the carbonyl and delivered the lactone products in high enantiomeric purity.

Currently, only the absolute configurations for lactones **5**[12] and **7**[13] are known and are as represented in Table I. The configurational assignments for the other lactones are purely arbitrary. We are currently working on the establishment of these absolute configurations as well as attempting to extend this methodology to other cycloalkanones and polycycloalkanones. The results of these studies will be reported in due course.

Acknowledgment. We express our gratitude to Professor Chris Walsh and Jack Chen of Harvard University for their valuable assistance, Professor Phil Garner of Case Western Reserve University for aid in the measurement of some of the optical rotations, and a University of Akron Faculty Research Grant for support of this work.

Supplementary Material Available: Selected ^1H, ^{13}C, and ^{19}F spectra for the Mosher ester derivatives (15 pages). Ordering information is given on any current masthead page.

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(12) The assignment is based on the rotational comparison of the derived hydroxy ester with the compound obtained from *S*-(−)-β-citronellol via ozonolysis, oxidation, and esterification.

(13) This is based on comparison of the rotation of the derived hydroxy acid with the rotation of its enantiomer which was used in the total synthesis of monensin, see: Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. This data was kindly provided by Professor Yoshito Kishi of Harvard University.