in magnitude to shifts produced by other factors that may be present, such as conjugation and strain. In addition, there are always at least two carbonyl bands present, and a shift must be defined relative to some standard, whose selection may present difficulties. Solid-state vs solution IR spectra of such compounds often differ in the carbonyl region, but using those differences diagnostically is problematic because a variety of complications arise and the H-bonding patterns in solution can frequently only be guessed at.[6,7]

The most common H-bonding pattern for simple keto acids, acid pairing, involves an eight-membered dimeric ring structure, which permits strong coupling of the stretching vibrations for the two acid carbonyls. Because of the local centrosymmetry, the symmetric stretching mode produces no change in dipole moment and is IR-inactive but does create changes in polarizability and is Raman-active. The reverse is true for the unsymmetrical stretch, with an appreciable energy difference anticipated between the two coupled modes. Because no other observed pattern of hydrogen bonding in keto acids presents this combination of symmetry and strong vibrational coupling, we anticipated that the coordinated use of infrared and Raman spectroscopies might specify unambiguously the presence or absence of paired-carboxyl hydrogen bonding and thus serve as a screen for alternative H-bonding patterns.

We have tested this prediction with the eleven keto acids shown in Table I, whose single-crystal X-ray structures are also available.[3j,k,5,8a] The carbonyl vibrational modes for arrangements of low symmetry are active in both the IR and Raman spectra, at nearly identical frequencies. Only the carboxyl dimers exhibit IR and Raman bands at appreciably different frequencies, the average difference between the asymmetric and symmetric stretching modes being ca. 50 cm^{-1}.[9b]

This method appears ideal for efficient differentiation of solid-state carboxylic acids that are dimerically hydrogen-bonded from those with other H-bonding patterns.[11] It should be applicable not only to keto acids but to acids containing a variety of other additional H-bonding functions.

Acknowledgment. We thank Profs. R. Mendelsohn, E. Monse, and G. Spoog for helpful consultations and Prof. R. Sauers for a chemical sample.

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Stereoselective Osmylation of 1,1-Disubstituted Olefins: Effect of Allylic Substituents on Reaction Diastereoselectivity

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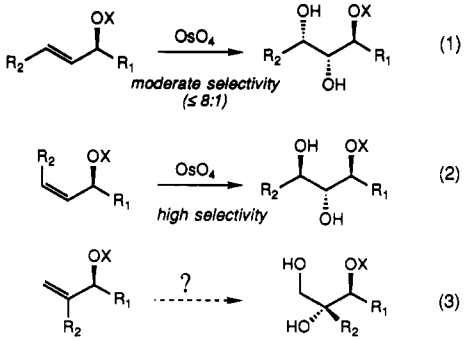
Summary: The osmylation of 1,1-disubstituted olefins possessing an allylic, oxygen-bearing stereocenter proceeds in a stereoregular fashion with high diastereoselectivity.

The reaction of osmium tetraoxide with 1,2-disubstituted olefins containing an allylic, oxygen-bearing stereocenter affords diols with a stereochemically predictable outcome (eqs 1-2).[1,2] A sufficient number of examples have now been studied to provide good precedent for projecting both the sense and degree of asymmetric induction in these reactions. On the other hand, documentation of the influence of structure on the stereoselective osmylation of 1,1-disubstituted allylic alcohol derivatives (eq 3) is limited to several cases which do not provide a sufficient body of information for confident extrapolation.

Scolastico has documented an example of a diastereoselective osmylation of an α,β-unsaturated ester which was found to afford one diastereomer (eq 4).[3] A highly stereoselective example was also described by Stork and Kahn for an *E* trisubstituted unsaturated ester as both the alcohol and the ethoxyethyl ether derivatives (eq 5).[4] In this study it was concluded that the electronic effect of the carbomethoxyl substituent in enhancing reaction diastereoselection was "considerable" based on the qualitative



(1) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3496 and 3947-3950; *Tetrahedron* **1984**, *40*, 2247-2255.

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(4) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951-3954.

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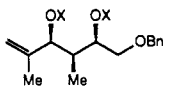
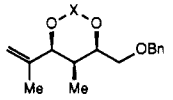
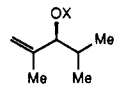
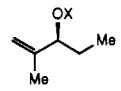
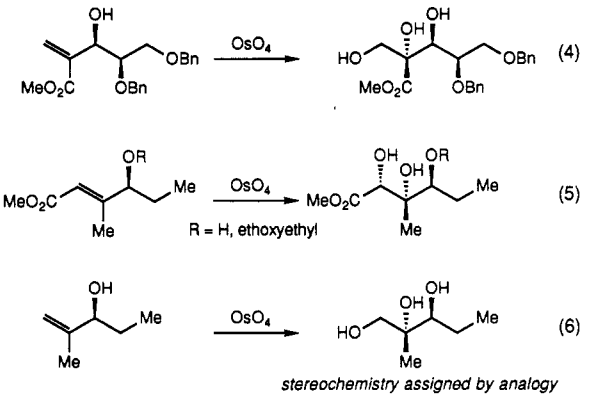
Table I. Diastereoselective Osmylation of 6 (eq 10)[a]

substrate	entry	X	7:8[b]
	A	H	35:1
	B	Ac	16:1
	C	Si(*t*-Bu)Me_2	6.2:1
	D	Si(*t*-Bu)$_2$	60:1
	E	CH(anisyl)	61:1
	F	CH_2Ph	17:1
	G	CH_2Ph	5.1:1

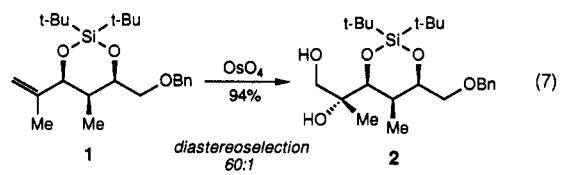
[a] All reactions were run with catalytic osmium tetraoxide (ref 7). Isolated yields of diols were >90% in all cases examined. [b] Ratios were determined by GLC of the tetrakis(trimethylsilyl) (entries A–E) or bis(trimethylsilyl) (entries F and G) derivatives.

observation that osmylation of the related isopropenylethyl carbinol (eq 6)[5] "showed considerably less stereoselectivity".

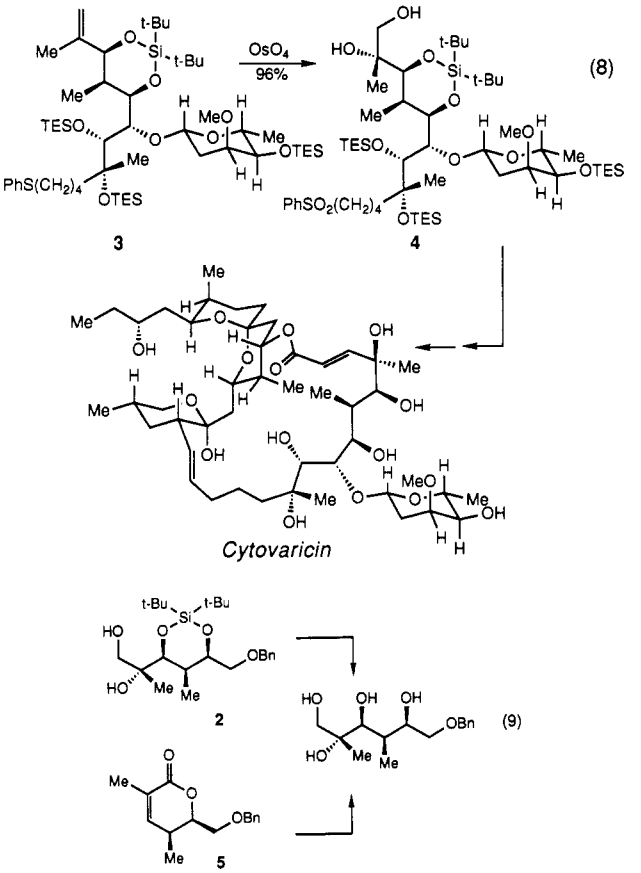


During the course of an investigation directed toward the total synthesis of cytovaricin,[6] we have had the occasion to examine the osmylation of a series of related, 1,1-disubstituted olefins (eq 3). In this paper, we disclose that such reactions proceed with a uniform sense of asymmetric induction, affording diols with high stereoselectivity. Some conclusions regarding the influence of structure on reaction diastereoselection have been drawn from this study.

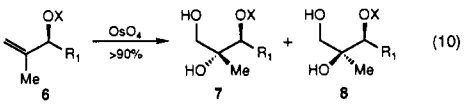
In one of the principal cases of interest, the osmylation of olefin 1, catalyzed by *N*-methylmorpholine *N*-oxide,[7] afforded the diol 2 in 94% isolated yield (eq 7). Careful



analysis of the unpurified product mixture revealed only trace quantities (<2%) of the diastereomeric reaction product. The closely analogous transformation of the more complex substrate 3 afforded the illustrated diol 4 in 96% yield as a single diastereomer (eq 8). The stereochemistry of 2 was determined by independent synthesis through the osmylation of the unsaturated lactone 5[8] and subsequent correlation of the two reaction products via the illustrated tetrol (eq 9), while the stereochemistry of 4 was secured by its subsequent conversion to cytovaricin.



Since the observed stereoselectivity of these osmylations was inferred to be substantially greater than that implied for the related allylic alcohol (eq 6), a study of the scope of this reaction was undertaken (eq 10, Table I). For entries A–E, proof of stereochemistry was achieved by correlation as previously described (eq 9). Stereochemical assignments for entries F and G were obtained by successive protection of the primary alcohol and conversion to the 2,3-diol acetonide, wherein the syn relationship between the methine ring hydrogen and the adjacent methyl group was established through the relevant NOE experiments.



Several features of the data set are noteworthy. All reactions proceed in a stereoregular fashion, affording diol 7 with moderate to high diastereoselectivity. There is a general correlation between the relative size difference between R_1 and OX and the ratio of 7 to 8 (entries F versus G and the series A–C), with the larger R_1 substituent affording the more diastereoselective reaction. Variation of the OX substituent (entries A–C) reveals that steric, rather

(5) In this study the determination of the stereochemistry on this substrate (eq 6) was not pursued.

(6) Evans, D. A.; Kaldor, S. W.; Jones, T. K. *J. Am. Chem. Soc.*, submitted for publication.

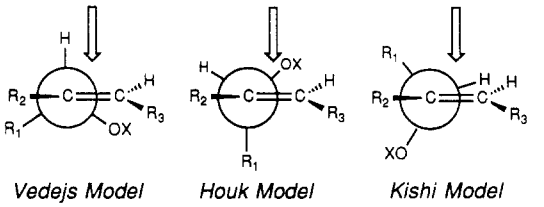
(7) This catalytic osmylation procedure was employed for all reactions in this study. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.

(8) The stereochemistry of the diol lactone derived from osmylation of 5 was unequivocally determined by NOE measurements.

than electronic effects are probably dominant with the smaller substituent affording the higher selectivity. Finally, the cyclic protected diols **6d** and **6e** are osmylated with exceptionally high diastereoselection (entries D–E). Nonetheless, a multiconformer analysis (MM2)[9] of **6d** reveals no apparent diastereofacial bias which might be imparted to the reaction by a particularly stable ground-state conformation.

The construction of a meaningful model for internal asymmetric induction in these osmylations is hampered at present by considerable mechanistic uncertainty. For example, it is as yet unclear whether these reactions proceed through a [3 + 2] cycloaddition pathway (O=Os=O + C=C)[10] directly to the diol osmate(VI) ester, or by the alternate [2 + 2] path (O=Os + C=C)[11] to an oxametallocyclobutane intermediate which rearranges to the osmate ester in a subsequent step.

In analyses of the stereochemical course of these reactions, it has been the working assumption that the product (diastereomer)-determining step involves competitive attack of the osmium(VIII) reagent on the two olefin diastereofaces in an irreversible transformation to the diol osmate ester. The Kishi empirical model[1] is based upon ground-state conformational effects and an implied stereoelectronic π-facial bias imposed for the allylic oxygen. Houk's model is essentially an extension of his "inside alkoxy" transition state for nitrile oxide cycloaddition reactions.[12] Finally, the transition structure proposed by Vedejs[13] emphasizes the steric effects imposed on the olefin and associated allylic substituents by the osmium reagent. Vedejs has recently concluded that hyperconjugative effects do not appear to be dominant control elements in these reactions. In fact, both the Vedejs and Houk models are consistent with the trends we have observed in the osmylation of 1,1-disubstituted olefins and, at the very least, serve as useful constructs for predicting the sense of induction for these reactions. On the other hand, we cannot explain the observed enhancement of diastereoselection on maximizing the size difference between the allylic substituents OX and R_1 with the Kishi model.[1] In spite of the predictive value of each of these models, there is still little kinetic evidence available to support the assumptions which form the basis of these mechanistic constructs. The basic assumption that the product-determining step in these osmylation reactions is the competitive attack of reagent on the olefin diastereofaces is not supported by any immutable evidence. If the diastereomer-determining step is not the competitive attack of reagent on the olefin diastereofaces, as is the case if either olefin–OsO_4 complexation or oxametallocyclobutane formation is reversible, a substantial revision of the rationale for asymmetric induction in these reactions would be required.



Vedejs Model *Houk Model* *Kishi Model*

Acknowledgment. Support has been provided by the National Institutes of Health and Merck. The NIH BRS Shared Instrumentation Program 1 S10 RR01748-01A1 is acknowledged for providing NMR facilities.

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