Acyclic Stereocontrol Induced by Allylic Alkoxy Groups. Synthetic Applications of Stereoselective Dihydroxylation in Natural Product Synthesis†

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Received February 15, 1995 (Revised Manuscript Received May 1, 1995)

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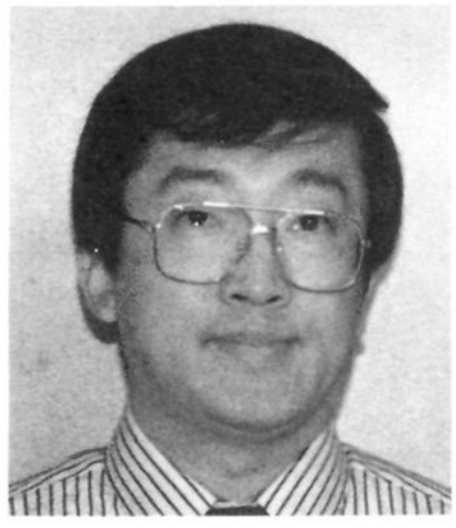
I. Introduction

Stereochemical control presents a formidable challenge to synthetic chemists in the design and development of synthetic methodology. In the past two decades impressive advances have been made in the design of reactions which allow high levels of stereoselectivity not only with cyclic compounds, but also with conformationally flexible acyclic substrates. The stereocontrolled introduction of new stereogenic centers is commonly based on π-facially selective addition to a prochiral double bond. Such processes can be achieved by taking advantage of a facial bias imposed by preexisting stereochemical elements of substrates, powerful "reagent-controlled" synthetic protocols, or both.[1] For example, very highly stereoselective additions of nucleophiles to aldehydes and ketones are routinely available, and have, in fact, represented one of the most powerful tools for the stereoselective construction of carbon–carbon bonds. Not surprisingly, stereoselective elaboration of carbon–carbon double bonds has met with limited success. Synthetically useful levels of stereoselection, on the other hand, have been attained in the presence of a polar group, especially an oxygen substituent, at the allylic position. Subtle conformational (steric or stereoelectronic) constraints imposed by an alkoxy group or its attractive interaction with incoming reagents influence the stereochemical outcome of the process. Thus, a stereogenic allylic alkoxy site can be exploited to exert a unique stereodirecting effect on adjacent prochiral sp^2 sites. In addition, the ready availability of optically pure allylic alcohols by enantioselective reduction of the corresponding ketones lends itself to practical asymmetric synthesis.[2,3]

Jin K. Cha received a B.S. degree in chemistry from Seoul National University in 1975. In 1981, he received his D.Phil. degree from University of Oxford, England under the direction of Professor Jack E. Baldwin. The first two years of graduate study were spent at Massachusetts Institute of Technology. After a two-year period of postdoctoral training under Professor Yoshito Kishi at Harvard University, he joined the faculty at Vanderbilt University in 1983. In Fall 1991 he moved to the University of Alabama where he is currently Associate Professor of Chemistry. His research interests include the development and applications of new methods and strategies for natural product synthesis.



No-Soo Kim was born in Seoul, Korea, in 1957. He obtained a B.S. degree in industrial chemistry from Hanyang University, and a M.S. degree in organic chemistry from Korea Advanced Institute of Science. In 1992, he received his Ph.D. in organic chemistry under the direction of Professor James D. White at Oregon State University. His Ph.D. dissertation involved synthetic studies toward trichothecene. After a postdoctoral study at the University of Alabama with Professor J. K. Cha, he joined Youngdong Institute of Technology as an Assistant Professor in Spring 1994. His research interests include the synthesis of biologically active compounds.

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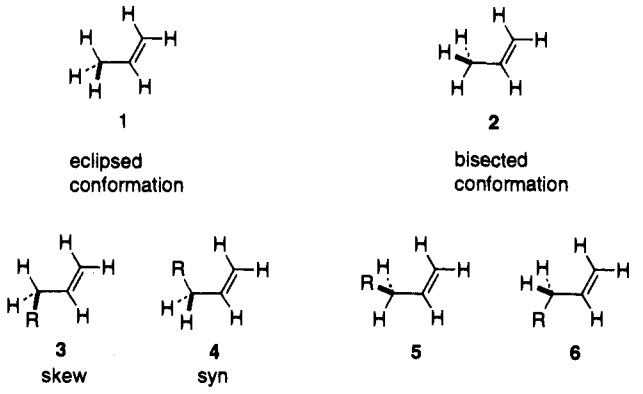
0009-2665/95/0795-1761$15.50/0 © 1995 American Chemical Society

This article is primarily focused on *acyclic* stereocontrol achieved by an allylic alkoxy group, with particular emphasis on stereoselective dihydroxylation and its applications to stereoselective syntheses of bioactive natural products. In light of a recent, comprehensive review on heteroatom-directed stereoselective reactions (e.g., directed cyclopropanation, epoxidation, hydrogenation and carbometalation),[4] this review is confined to 1,2-diastereoselection based on the conformational discrimination induced by an allylic alkoxy moiety without its prior coordination to an incoming catalyst or reagent. Those reactions where secondary allylic alcohols or ethers undergo cleavage during stereoselective transformations are also excluded.[5]

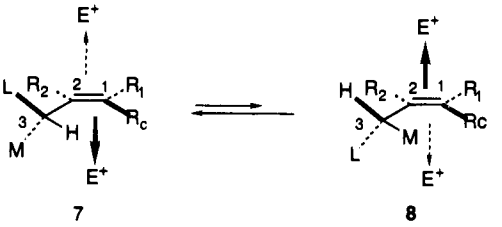
II. General Considerations

Information on the relative energies of the preferred conformations between the allylic stereocenter and the prochiral olefin functionality is crucial to mechanistic understanding. On the basis of the microwave spectroscopic analysis of propene, the minimum energy conformation is thought to have a hydrogen atom eclipsing the double bond (rotamer **1**), which is favored over the bisected rotamer **2**. In 3-substituted propenes, there are two possible eclipsed conformations (skew **3** and syn **4**), both of which are energetically favored over the bisected conformers **5** and **6**. The relative energies of the syn and skew conformations are very similar, with the difference estimated to be 0.1−0.4 kcal/mol.[6] With the exception of compounds such as 3-fluoropropene, 3-methoxypropene, and 3-cyanopropene, the skew conformation is slightly more stable than the syn.

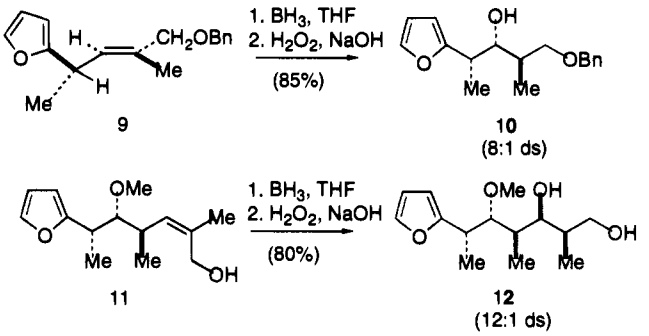


In addition to the allylic stereocenter, the presence of substituents on the olefin plays an important role in determining the overall conformational preferences. These effects can be rationalized in terms of the allylic strain concept which was first advanced by Johnson in 1968.[7,8] For example, the *Z* substituent at C-1 of the olefinic substrates is expected to greatly affect the relative stabilities of the various possible conformations due to allylic 1,3-strain. Specifically, the energy difference between the eclipsed and bisected conformations would decrease, and the relative energies of the syn and skew conformers would be affected. Similar considerations are applicable to 2-substituted olefins, although the effect of allylic 1,2-strain is often smaller than that of allylic 1,3-strain.

These conformational considerations of the ground states have been extrapolated to the analysis of the transition state structures to rationalize the observed stereochemical outcome of electrophilic addition to a C=C double bond adjacent to a stereogenic center. In most cases, conformer **7** (H eclipsing) would be anticipated to be more stable than conformer **8**. Approach of the electrophile from the less hindered face (opposite to the largest group, *L*) would result in the typically observed stereochemical outcomes.



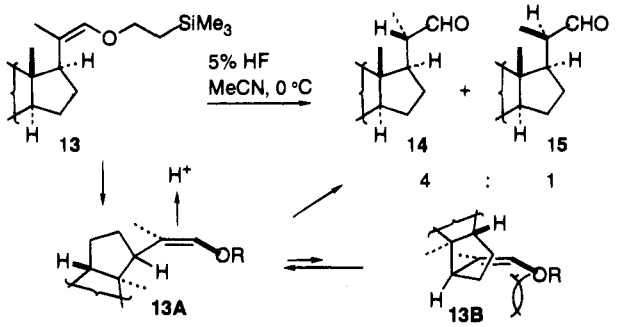
The paradigm of this diastereofacial discrimination can be found in Kishi's landmark synthesis of monensin.[9a] Hydroboration of olefins **9** and **11** took place with 8:1 and 12:1 diastereoselectivities, respectively. This result can be directly ascribed to $A^{(1,3)}$-strain.[10,11] Along these lines, it has been found that electrophilic attack at (*Z*)-alkenes often proceeds with higher diastereoselectivities than that at (*E*)-alkenes. The presence of a bulky *Z*-substituent is expected to greatly favor the population of conformer **7** over conformer **8**. This additional conformational restraint would be translated into higher selectivities for *Z*-olefins.



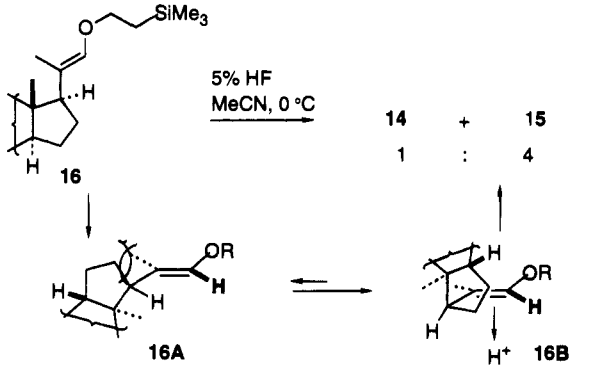
In studies with allylsilanes, however, Fleming noted that the opposite sense of diastereoselection may predominate where R_c is hydrogen and *M* is relatively small (i.e., methyl).[12] Here, allylic 1,2-strain is thought to play an important role in determining the relative stabilities of conformers **7** and **8** and, consequently, the stereochemical outcome.

The intricate interplay between $A^{(1,3)}$-strain and $A^{(1,2)}$-strain can be seen in the stereochemistry of enol protonation reported by Zbiral: treatment of the *Z*-enol ether **13** with HF gave primarily the aldehyde **14** with the natural steroid configuration at C-20, whereas protonation of the corresponding *E*-enol ether **16** proceeded with the opposite stereochemical outcome.[12b,13] The preferred conformation of the *Z*-enol ether **13** is conformer **13A** (which corresponds to the generalized conformation **7**), which is expected to be more stable than **13B** due to severe allylic 1,3-

strain. On the other hand, the *E*-enol ether **16** can



adopt either conformation **16A** or **16B**, because the olefin substituent *cis* to the stereogenic center is hydrogen (vide supra). In this case, it is reasonable that conformer **16B** (which corresponds to the generalized conformation **8**) would be favored, since allylic 1,2-strain is minimized. Protonation from the less hindered α-face of the transition state arising from **16B** would then afford aldehyde **15**.



It should be noted that the underlying assumption of such conformational analysis is that the geometry of the transition structure is closely related to that of the ground state. This inference is well justifiable in the cases of exothermic reactions such as protonation and alkylation of enols or enolates. In fact, Evans has put forth a similar explanation in connection with an interesting bisalkylation of succinamide enolates, as well as for enolate alkylations.[14a]

When electronically different substituents are present at the allylic stereogenic center, an interesting and complicated question as to the conformational preference arises. An alkoxy or other polar substituent would exert both steric and stereoelectronic effects. For example, in the conformation **7** when M = OR, or the related staggered conformation resulting from partial rotation (~30°) of the allylic bond, the low-lying σ^*_{CO} orbital overlaps with the alkene π orbital, and the electron density of the π bond gets diminished.[15] Thus, it has been argued that **7** would be the less reactive conformation toward electrophilic attack with respect to other conformers such as **8** (M = OR). In conformer **8**, overlap of the σ^*_{CO} and π orbitals is minimized. The population of the ground-state conformations may well be delicately balanced between **7** and **8**, as the difference in energy between them is generally small. It is interesting to note that allylic ethers are known to exhibit conformational preference for **8**, whereas **7** is suggested to be the preferred conformation of allylic benzoates.[6,16]

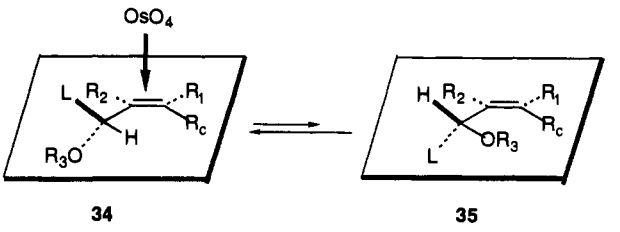
Recently several stereoselective and useful transformations of allylic alcohols and derivatives have been documented and have resulted in many experimental and theoretical studies.[17] In the succeeding sections representative examples of diastereoselective and synthetically useful transformations of allylic alcohol systems are described, together with the sense and degree of diastereoselection. In addition, synthetic applications in the stereocontrolled syntheses of bioactive natural products are enumerated.

III. Dihydroxylations

A. Introduction

In 1983 Kishi reported that osmium tetroxide dihydroxylations of allylic alcohols and ethers take place with synthetically useful levels of diastereoselectivity. The relative stereochemistry between the resident alkoxyl group and the newly introduced adjacent hydroxyl group of the major product is *erythro* (*anti*). Some representative examples are shown in Table 1.[18,19]

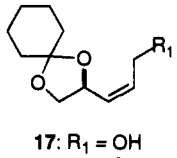
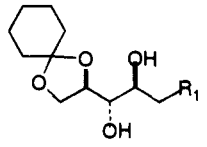
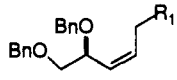
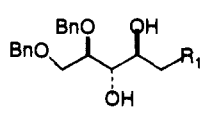
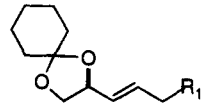
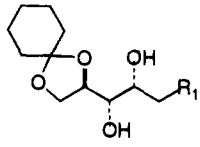
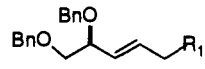
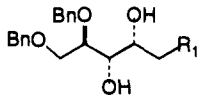
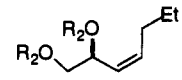
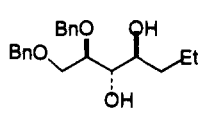
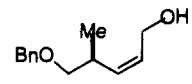
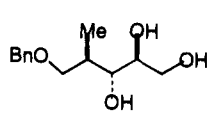
In these and other related examples, several general trends were found. The extent of stereoselectivity observed for *Z*-olefins was higher than that for the corresponding *E*-olefins (see entries 1 and 2 vs 3 and 4). With the exception of the acyl derivatives, the type of the protecting group on the allylic hydroxyl functionality did not significantly affect diastereoselectivity. For the cases of acyl compounds, however, diastereoselectivity was found to diminish considerably or completely (see entry 5). The presence of an allylic alkoxy stereocenter seems to be essential for preparatively useful levels of stereoselectivity. For comparison, poor selectivity was obtained for osmylation of the allylic methyl derivative (entry 6). The stoichiometric osmylation procedure provided slightly higher stereoselectivity than the catalytic procedure. In order to further enhance the selectivity, Kishi subsequently developed a slight modification of the stoichiometric procedure by employing a low reaction temperature (−78 °C) and a diamine ligand.[21,22] Addition of an amine, which is known to accelerate the rate of osmylation of olefins, allows the dihydroxylation to proceed with a reasonable rate at a low temperature. On the basis of these observations, along with the stereochemical outcome of osmylation of cyclic allylic alcohols (e.g., 2-cyclohexen-1-ol), Kishi proposed a reactant-like transition structure model, as depicted in the H-eclipsed conformer **34**.



34 **35**

As summarized in Table 2, the empirical rule advanced by Kishi seems to be applicable to *E*-α,β-

Table 1. Representative Examples of Stereoselective OsO_4 Dihydroxylation of Allylic Alcohols and Related Systems[18,19]

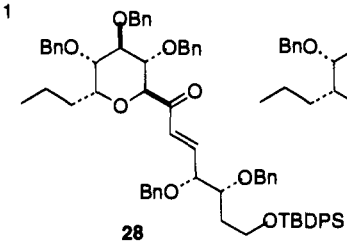
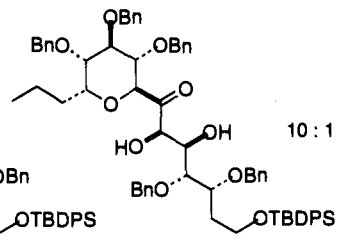
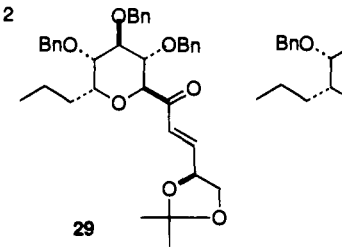
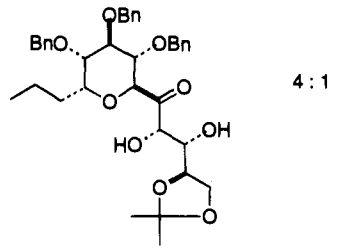
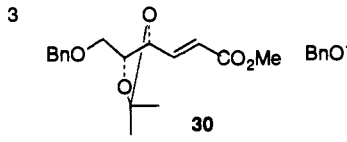
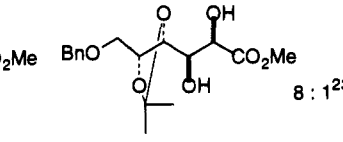
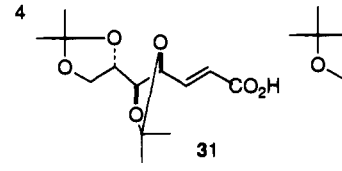
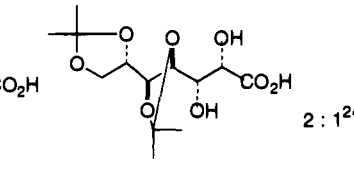
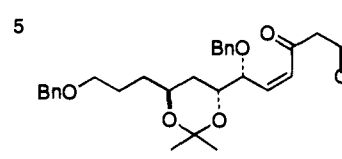
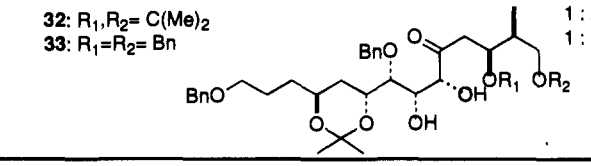
Entry	Substrate	Major Product	Stereoselectivity
1			
	17: R_1 = OH **18**: R_1 = Et		6 : 1 8 : 1
2			
	19: R_1 = OH **20**: R_1 = Et		7 : 1 8 : 1
3			
	21: R_1 = OH **22**: R_1 = Et		3 : 1 4 : 1
4			
	23: R_1 = OH **24**: R_1 = Et		3 : 1 6 : 1
5			
	25: R_2 = Ac **26**: R_2 = $COC_6H_4NO_2$-*p*		2 : 1 1 : 1
6			
	27		1 : 1

Osmylation was carried out under catalytic conditions[20] employing OsO_4 (0.05 equiv) and NMO (2.0 equiv) in acetone-water (8:1) at rt.

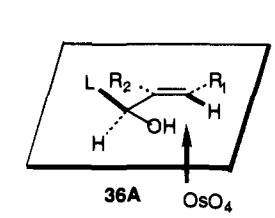
unsaturated carbonyl compounds as well (entries 1–4).[18] However, caution is appropriate for *Z*-α,β-unsaturated carbonyl substrates, since osmylation of such systems (entry 5) has been found to breach Kishi's stereochemical formulation.

At the same time, Stork reported similar results for the osmylations of α,β-unsaturated esters (Table 3).[25] It is important to note that, in marked contrast to *E*-esters **36**–**38**, osmylation of *Z*-ester **39** gave the *syn*, not *anti*, stereochemistry. These results were rationalized by invoking two different transition state models for *E*- and *Z*-esters (**36A** and **39A**, respectively). The transition structure **36A** is closely related to the generalized conformer **8**. To account for the "opposite" stereochemistry of the *Z*-α,β-unsaturated carbonyl compound **39**, Stork proposed the conformation **39A** having an "outside" alkoxy

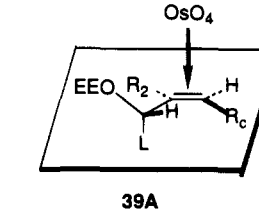
Table 2. Some OsO_4 Dihydroxylation Examples of γ-Alkoxy-α,β-unsaturated Carbonyl Systems[18]

Entry	Substrate	Major Product	Stereoselectivity
1			10 : 1
	28		
2			4 : 1
	29		
3			8 : 1[23]
	30		
4			2 : 1[24]
	31		
5			(anti:syn)
	32: R_1,R_2 = $C(Me)_2$ **33**: R_1=R_2= Bn		1 : 2 1 : 4

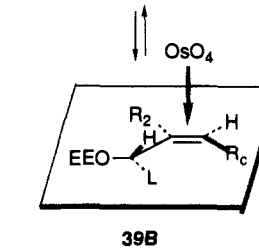
group, whereas Kishi invoked the participation of **39B** by analogy to the dipolar model of Cram's rule.[26]



36A



39A



39B

Table 3. Stereoselective OsO_4 Dihydroxylations of γ-Alkoxy-α,β-unsaturated Esters[25]

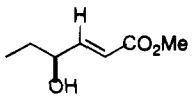
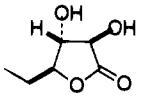
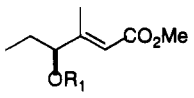
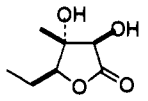
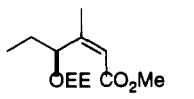
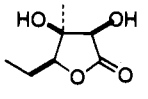
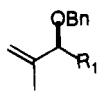
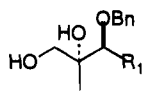
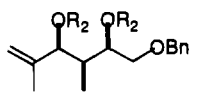
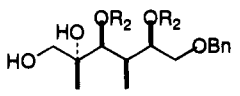
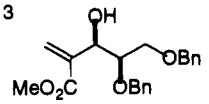
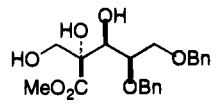
Entry	Substrate	Major Product	Stereoselectivity
1	 **36**		1 : 0
2	 **37**: R_1 = H **38**: R_1 = CH(OEt)Me (EE)		1 : 0 1 : 0
3	 **39**		0 : 1

Table 4. Stereoselective OsO_4 Dihydroxylations of 1,1-Disubstituted Olefins[27]

Entry	Substrate	Major Product	Stereoselectivity
1	 **40**: R_1 = Et **41**: R_1 = *i*-Pr		5 : 1 17 : 1
2	 **42**: R_2 = H **43**: R_2 = Ac **44**: R_2 = TBS		35 : 1 16 : 1 6 : 1
3	 **45**		1 : 0[28]

Subsequently, Evans found that osmylation of 1,1-disubstituted olefins also proceeds with exceptionally high stereoselectivity (Table 4).[27] There appears to be a general correlation between the diastereoselectivity and the relative size difference between R_1 and the alkoxy moiety (entry 1).

B. Recent Examples

Since Kishi and Stork independently made initial reports on the diastereoselective osmylation of allylic alcohols and related systems, there have appeared a large number of analogous examples.[29] The increasing importance of carbohydrates and related polyhydroxy compounds as useful tools in elucidating or controlling complex biological processes and as synthetic targets has undoubtedly stimulated considerable interest in stereoselective dihydroxylation. Recent literature examples are compiled in Tables 5–15, according to the olefin substitution patterns. In nearly all cases, with the single exception of *Z*-α,β-unsaturated carbonyl compounds, a useful predictive tool can be found in Kishi's empirical formulation that the major product of osmylation has the newly introduced, adjacent hydroxy group *anti* to the resident alkoxy (or hydroxy) stereocenter. The stereoselectivity is given in the ratio of *anti* to *syn*.[19] Unless noted otherwise, dihydroxylation was carried out under catalytic conditions employing *N*-methylmorpholine *N*-oxide (or trimethylamine *N*-oxide) as cooxidant at room temperature.[20] Mention should be made that trioxo Os(VIII) glycolate is most likely involved in osmylations under homogeneous catalytic NMO conditions.[20c] Recent examples, where double stereodifferentiation is examined, are discussed in a separate section (Tables 14 and 15).

1. Monosubstituted Olefins (Table 5)

Dihydroxylation of monosubstituted olefins has been shown to proceed with moderate to excellent stereoselectivity ranging from 50% to 100% ds.

2. 1,2-Disubstituted Nonconjugated Olefins (Tables 6–8)

(1) Comparison of E- and Z-1,2-Disubstituted Olefins (Table 6). Most of the literature reports on dihydroxylation of allylic alcohols and ethers examine 1,2-disubstituted olefins. Recall that the stereoselectivity for *Z*-1,2-disubstituted olefins was higher than that for the corresponding *E*-olefins where an allylic alcohol or ether is present at the sole stereocenter in the molecule (see Table 1).[18]

Comparisons of structurally more complex *E*- and *Z*-pairs are shown in Table 6. Not surprisingly, the same trend is no longer observed for the allylic systems containing multiple stereocenters where there exists another competing or overriding steric element (entry 9 vs entry 10). Striking are entries 5 and 12, which illustrate the effects of a homoallylic substituent on the stereochemical outcome. These interesting results can be rationalized by the application of Kishi's empirical model (**46** ≡ **34**). As pointed out by Danishefsky for entry 12,[15d] it is conceivable that the bulky benzoate group (vis-à-vis the smaller hydroxyl group) partially shields attack from the

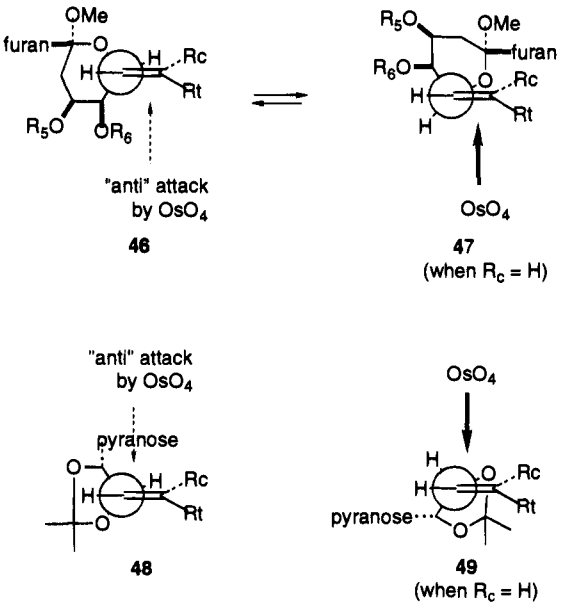
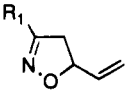
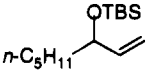
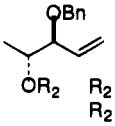
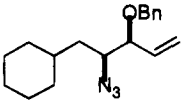
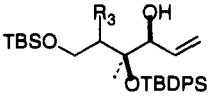
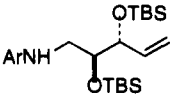
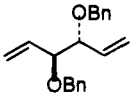
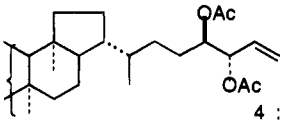
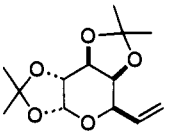
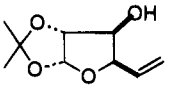
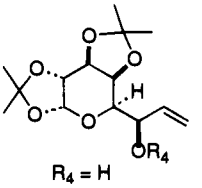
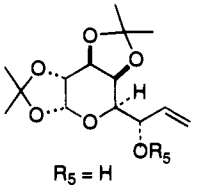
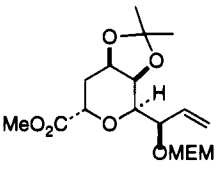
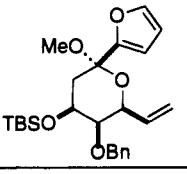


Table 5. Dihydroxylation of Monosubstituted Olefins[a]

Entry	Substrate	Selectivity (Yield)	Ref
1			
	R_1 = Me	4 : 1 (80%)	30
	R_1 = Ph	3 : 1 (74%)	
	R_1 = CO_2Et	3 : 1 (83%)	
2	R_1 = Me	3 : 1 (38%)	31
	R_1 = CH_2OBn	3 : 1 (60%)	
	R_1 = CO_2Et	3 : 1 (38%)	
3		5 : 1	32
4			
	R_2 = Bn	10 : 1 (90%)	33a
	R_2 = TBS	12 : 1 (85%)	33b
5		9 : 1 (88%)	34
6			
	R_3 = β-OAc	19 : 1 (82%)[b]	35
	R_3 = α-OBz	1 : 0 (78%)[b]	
7		1 : 0 (98%)	36
8		6 : 1	37
9		4 : 1 (90%)	38
10		3 : 1 (94%)	39
11		3 : 1 (71%)	39
12			
	R_4 = H	1 : 0 (79%)	47
	R_4 = Bn	5 : 1 (92%)	40
13			
	R_5 = H	3 : 1 (75%)	41
	R_5 = Bn	4 : 1 (96%)	
14		6 : 1 (90%)	42
15		1 : 0 (94%)	43[c]

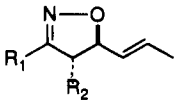
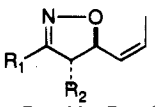
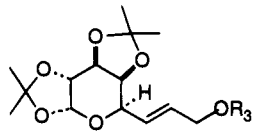
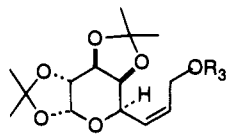
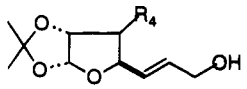
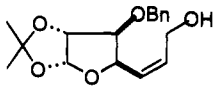
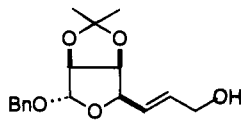
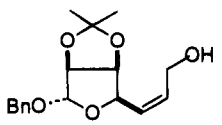
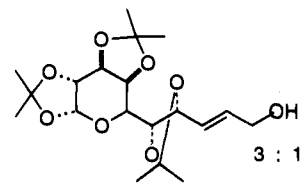
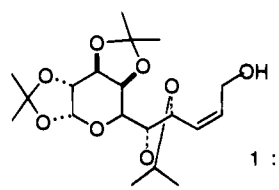
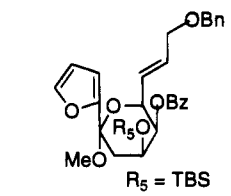
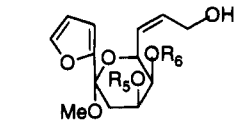
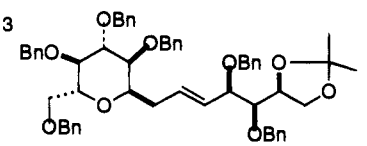
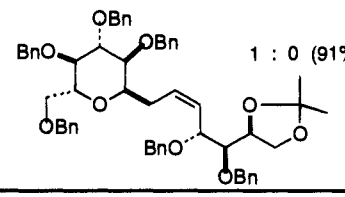
a. Unless noted otherwise, dihydroxylation was carried out under catalytic conditions (ref. 20) using *N*-methylmorpholine *N*-oxide or trimethylamine *N*-oxide as a co-oxidant.
b. Dihydroxylation took place with concomitant TBDPS migration to the terminal hydroxyl group and partial acetate migration. No benzoate migration was found.
c. Osmylation was carried out under stoichiometric conditions in pyridine at -25 °C.

otherwise preferred "*anti*" (from the allylic oxygen) face of the eclipsed conformer **46**.[83] For the corresponding *E*-isomer (entry 11), such steric hindrance to OsO_4 attack could be avoided if the olefin adopts the alternate conformation **47** (≡ *O*-eclipsed conformer **35**), which should also provide the "*erythro*" isomer. The potential importance of the *O*-eclipsed conformer has been noted earlier for related *E*-alkenes (when R_c = H) in section II. Of course, the *O*-eclipsed conformer would be unlikely for *Z*-alkenes on steric grounds. The identical consideration would account for complete lack of selectivity in entry 10 (conformer **48**), in comparison with entry 9 (conformer **49**). The noticeable difference in diastereoselectivity between β- and α-benzyloxy groups in entry 5 might also be attributed to steric crowding in the "*anti*" face of the *H*-eclipsed conformer by the α-benzyloxy group.

(2) Z-1,2-Disubstituted Olefins (Table 7). The conspicuous difference in stereoselectivity of the galactose and glucose configurations in entries 8 and 10 is in accord with the above-mentioned rationalization. Entry 11, an exception to Kishi's empirical rule, could be rationalized in terms of the *H*-eclipsed conformer as well. In contrast, an exceptionally high selectivity was obtained for a related *E*-compound (Table 8, entry 20).

Where allylic stereocenters are present at both ends of the C=C double bond, their effects are

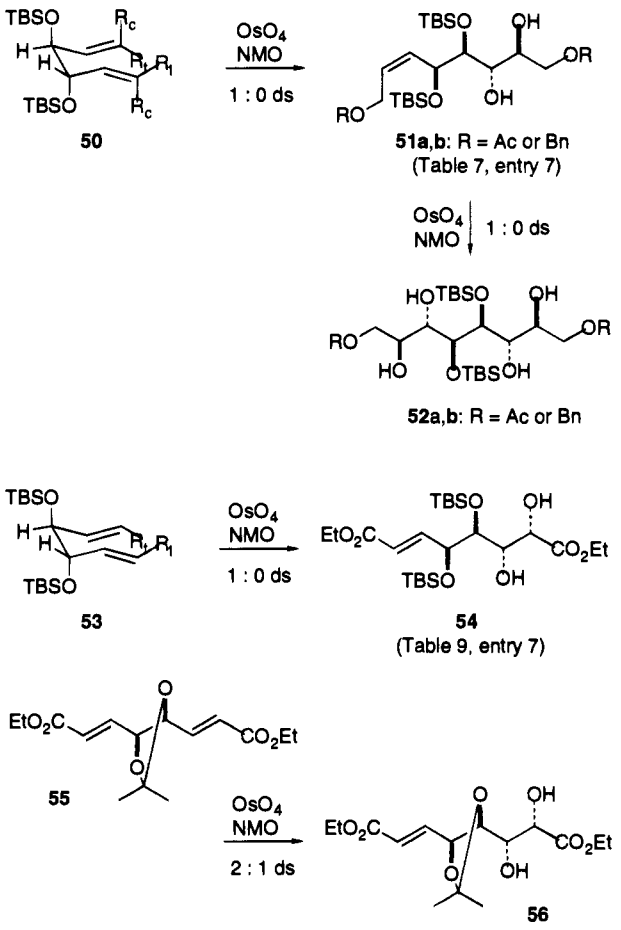
Table 6. Dihydroxylation of 1,2-Disubstituted Olefins–Comparison between *E*- and *Z*-Olefins

Entry	Substrate	Selectivity (Yield)	Ref
1			
	R_1 = Me, R_2 = H or Me	3 : 1 (70%)	30
	R_1 = H, R_2 = H	4 : 1 (65%)	31
2			
	R_1 = Me, R_2 = H	6 : 1 (80%)	30
	R_1 = Me, R_2 = Me	12 : 1 (70%)	
	R_1 = H, R_2 = H	7 : 1 (34%)	31
3			
	R_3 = H	7 : 1 (57%)	40
	R_3 = Bn	3 : 1 (92%)	
4			
	R_3 = H	7 : 1 (67%)	40
5			
	R_4 = β-OBn	5 : 1 (79%)	39
	R_4 = α-OBn	1 : 1 (70%)	
6			
		7 : 1 (82%)	39
7			
		7 : 1 (92%)	39
8			
		6 : 1 (75%)	39
9			
		3 : 1 (74%)	44
10			
		1 : 1 (77%)	44
11			
	R_5 = TBS	15 : 1	15d[a]
12			
	R_5 = TBS, R_6 = H	15 : 1	15d[a]
	R_5 = TBS, R_6 = Bz	2 : 1	
13			
		12 : 1 (88%)	45[b]
14			
		1 : 0 (91%)	45[b]

[a,b]Osmylation was carried out under stoichiometric conditions in 4:1 THF-pyr (*a*) at -20 °C or (*b*) -35 °C.

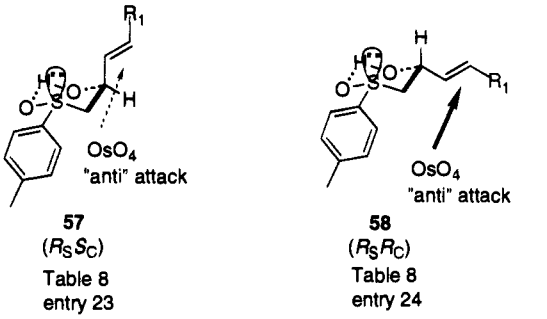
additive. As observed for entry 1, poor selectivity arises when the two allylic stereocenters exert opposite π-facial preference. Use of a tertiary amine, which is known to accelerate the rate of osmylation, allows the reaction to proceed at a reasonable rate at a lower temperature and with enhanced selectivity (entry 3). Exceptionally high stereoselectivity was obtained for bis-allylic compounds (entry 7) and related C_2-symmetric derivatives (e.g., Table 8, entry 27, and Table 9, entries 5 and 7). Saito and Moriwake provided an attractive explanation for excellent levels of π-face differentiation on the basis of the staggered conformer **50**, in which the two bulky substituents, –OTBS, are placed *anti* to each other.[52,84] In **50**, one of each of the π-faces is clearly shielded in the resulting topography. The finding that dihydroxylation of acetonide **55** afforded a 2:1 mixture of **56** and its isomer (compared to ~1:0 selectivity for **53**) was cited to support the pivotal role of conformer **50**. Interestingly, subsequent osmylation of **51a,b** was also highly selective to give **52a,b** as single isomers. On the basis of extensive NMR studies Marshall and Gung recently reported that the bis-OTBS allylic compounds have a more profound preference for the *O*-eclipsed form than the monoallylic counterparts, although the conformation of both compounds is not rigid.[85] In any event, the use of bis-allylic compounds such as **50** and **53** holds

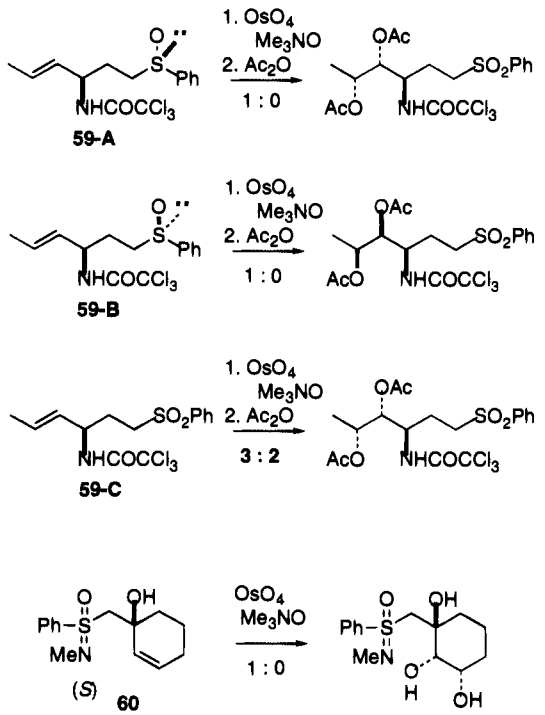
considerable synthetic potential in "two-directional chain" stereoselective syntheses.[70a,b]



(3) E-1,2-Disubstituted Olefins (Table 8). Dihydroxylations of these olefins were found to proceed with moderate to excellent selectivities as well. Again, better selectivity was obtained for a galactose derivative than the glucose counterpart (entries 3 and 5), as was the case for *Z*-olefins (Table 7, entries 8 and 10). The additive effect of two allylic stereocenters is apparent in entries 11 and 12. In the "mismatched" situation where the two stereocenters exert opposite directing influences, the superior directing influence of an alkoxyl or hydroxyl group with respect to an acyloxy substituent was utilized (entry 14).

In entries 23 and 24, stereoselectivity was significantly enhanced when a long unbranched chain (i.e., R_1 = *n*-pentyl) is attached to the double bond for the (R_S,R_C) diastereomer, compared to (R_S,S_C). Solladié rationalized this observation in terms of the conformations **57** and **58** for the (R_S,S_C) and (R_S,R_C) isomers, respectively.[67] He argued that, in the former conformer, the preferred "*anti*" attack by OsO_4 encounters repulsion by the axial sulfur lone pair. Osmylation of the corresponding methoxy derivatives (entries 25 and 26), as well as β-hydroxysulfones, was shown to result in low diastereoselectivity of 2:1.[86] The directing effect by the chirality of remote sulfoxides has previously been reported by Hauser.[87] Catalytic osmylation of the diastereomeric sulfoxides **59A** and **59B** and subsequent acetylation furnished the diastereomeric diacetate sulfones as the sole products in each case. The intrinsic "*anti*" diastereofacial selectivity imposed by the allylic amide group was determined to be 3:2 by catalytic dihydroxylation of sulfone **59C**. Johnson also reported very highly stereoselective dihydroxylation of the cyclic allylic β-hydroxysulfoximine **60**, where osmylation was believed to be directed by the neighboring sulfoximine, as well as the complementary "*anti*" effect of the allylic hydroxyl group.[88] However, extension of sulfoximine-directed osmylation to the preparation of enantiomerically pure acyclic diol ketones was less successful.

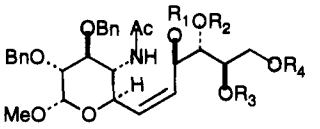
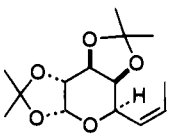
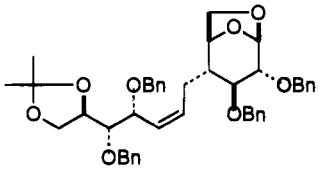
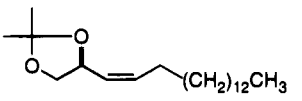
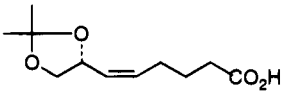
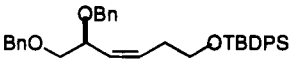
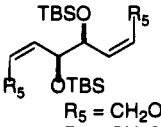
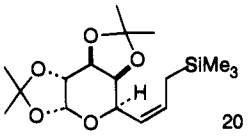
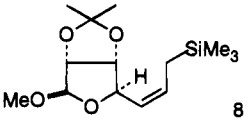
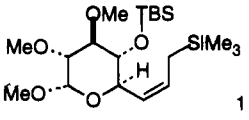
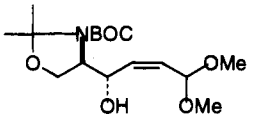




3. 1,2-Disubstituted Olefins Bearing a Conjugated Carbonyl Group (Tables 9–11)

(1) E-β-Monosubstituted α,β-Unsaturated Carbonyl Compounds (Table 9). No special comment is necessary for entries 1–13. For *E*-1,2-disubstituted alkenes, the presence of a conjugated carbonyl group seems to have no significant influence on diastereoselectivity (e.g., Table 9, entry 1, vs Table 6, entry 1; Table 9, entry 9, vs Table 8, entry 3; Table 9, entry 10, vs Table 8, entry 8). On the other hand, the

Table 7. Dihydroxylation of *Z*-1,2-Disubstituted Olefins

Entry	Substrate	Selectivity (Yield)	Ref
1		$R_1,R_2 = R_3,R_4 = C(CH_2)_5$ ~1 : 1	46
2		1 : 0 (78%)	47
3		OsO_4, NMO, DABCO, 5 °C 3 : 1 (71%) OsO_4, pyr, -35 °C 6 : 1 (71%) OsO_4, achiral diamine, -80 °C 18 : 1 (70%)	48[a,b]
4		1 : 0 (89%)	49
5		9 : 1 (69%)	50
6		5 : 1 (100%)	51
7		$R_5 = CH_2OAc$ 1 : 0 (79%) $R_5 = CH_2OBn$ 1 : 0 (72%)	52
8		20 : 1 (80%)	53
9		8 : 1 (93%)	53
10		1 : 3 (84%)	53
11		1 : 3 (57%)	54

a. Osmylation under catalytic conditions did not proceed in the absence of DABCO.
b. *N,N'*-Bis(mesitylmethyl)-1,2-diaminoethane was used as the achiral amine ligand.

apparent, albeit modest, preference for the *syn* diol product in entry 15 is surprising and difficult to explain. A rare reversal of the stereochemical outcome under stoichiometric and catalytic osmylation conditions was also reported (entry 14).

(2) Z-β-Monosubstituted α,β-Unsaturated Carbonyl Compounds (Table 10), and Comparison of E- and Z-β-Monosubstituted α,β-Unsaturated Esters (Table 11). A limited number of examples available in the literature indicate that dihydroxylation of *Z*-β-substituted α,β-unsaturated carbonyl compounds results in the irregular stereochemical outcome, as was previously noted by Kishi (vide supra). The complete reversal in facial selectivity for Table 11, entry 2, from those of Table 11, entry 1, and Table 6, entry 12, is most striking.

To probe the origin of these intriguing stereochemical outcomes, Danishefsky determined the solid-state conformation of entry 2 (Table 11) by X-ray crystallography. The measured dihedral angle of the C=C double bond and the allylic C–O of 162° corresponds to the antiperiplanar conformer implied in structure **61**.[15d] In this antiperiplanar conformation, the attenuation of electron density due to overlap between the π-system of the double bond and σ^*_{C-O} is avoided. When the electron-withdrawing ester functionality is present, this stereoelectronic effect might become important in osmylation. Mindful of the limitations associated with relying on ground-state conformations to account for the stereochemical outcome, Danishefsky nevertheless pointed out that the less hindered, β-attack on conformer **61** would nicely accommodate the observed facial stereoselection. Interestingly, the solid-state conformation of the corresponding *E*-isomer (Table 11, entry 1) is synplanar with the pertinent dihedral angle of −6.5°. It should be noted that the synplanar conformer **62** (see also **47**) corresponds to the *O*-eclipsed conformation **35**. The observed "*anti*" stereochemistry can be rationalized by the less hindered, α-attack on the synplanar conformer **62**. The preference of the synplanar conformation of type **35** over the

Table 8. Dihydroxylation of *E*-1,2-Disubstituted Olefins

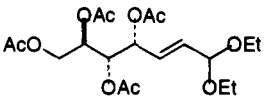
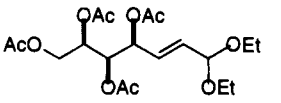
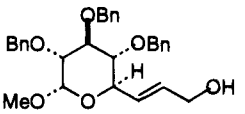
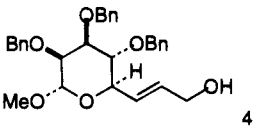
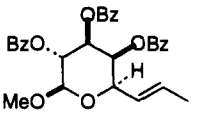
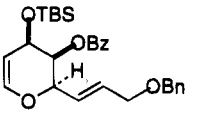
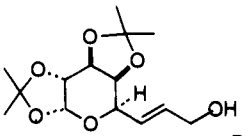
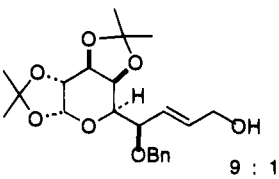
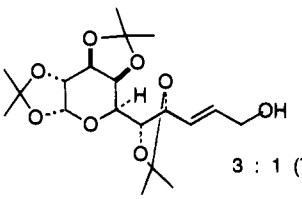
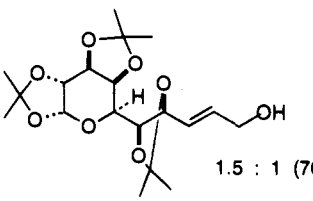
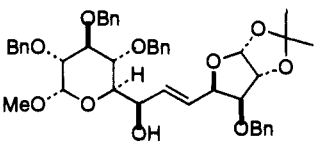
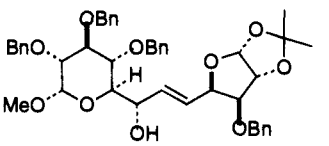
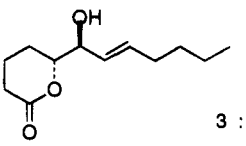
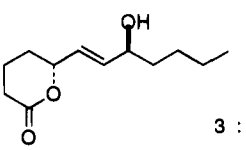
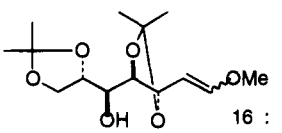
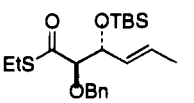
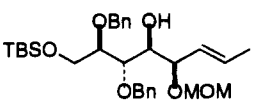
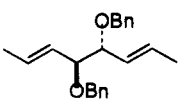
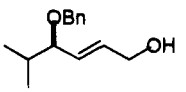
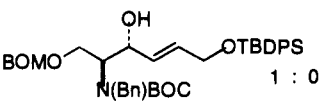
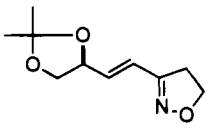
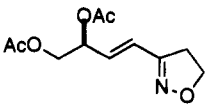
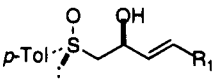
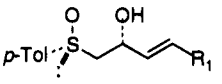
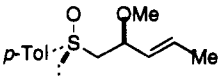
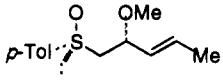
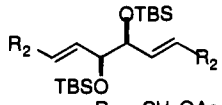
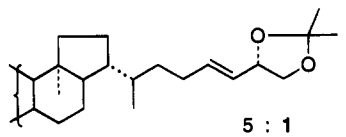
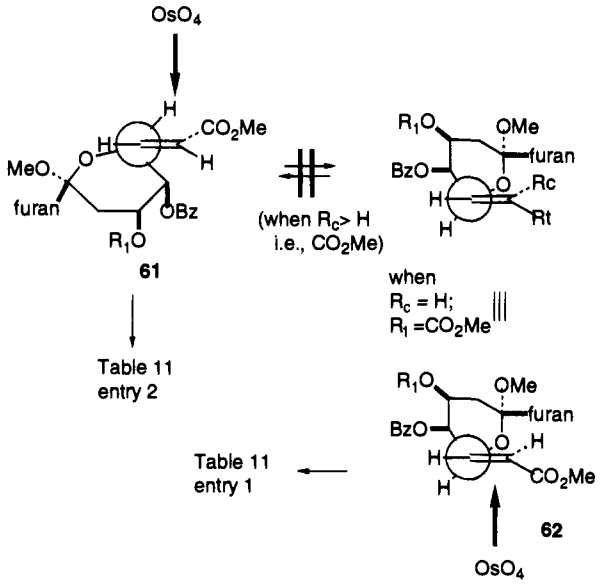
Entry	Substrate	Selectivity (Yield)	Ref	Entry	Substrate	Selectivity (Yield)	Ref
1		6 : 1 (94%)	55	2		5 : 1 (82%)	55
3		3 : 1 (76%)	56	4		4 : 1 (64%)	56
5		1 : 0 (89%)	15b	6		8 : 1	57[a]
7		7 : 1	56	8		9 : 1 (83%)	40a
9		3 : 1 (74%)	58	10		1.5 : 1 (76%)	58
11		6 : 1 (79%)	59	12		2 : 1 (70%)	59[b]
13		3 : 1 (79%)	60	14		3 : 1 (75%)	60[c]
15		16 : 1	61[d]	16		3 : 1 (75%)	62
17		3 : 1 (99%)	63	18		7 : 1 (43%)	37
19		12 : 1 (53%)	64	20		1 : 0	65

Table 8 (Continued)

Entry	Substrate	Selectivity (Yield)	Ref	Entry	Substrate	Selectivity (Yield)	Ref
21		3 : 1 (85%)	66	22		3 : 1 (83%)	66
23		R_1 = Me 4 : 1 (74%) R_1 = Ph 3 : 1 (90%) R_1 = n-C_5H_{11} 5 : 1 (75%)	67	24		R_1 = Me 4 : 1 (70%) R_1 = Ph 3 : 1 (90%) R_1 = n-C_5H_{11} 19 : 1 (74%)	67
25		2 : 1	67	26		2 : 1	67
27		R_2 = CH_2OAc 1 : **0** (87%)	52	28		5 : 1	68

a. Both double bonds underwent stereoselective dihydroxylation in accord with Kishi's formulation.
b. The major product has the α,α-diol configuration, i.e. *anti* to the alkoxyl group.
c. The stereochemistry of the major product has the α,α-diol, i.e. *anti* to the free hydroxyl group.
d. Osmylation was carried out under stoichiometric conditions in the presence of $(i\text{-PrNHCH}_2)_2$ in CH_2Cl_2 at -78 °C.

H-eclipsed conformation of type **34** (see also **46**) in the cases of *E*-α,β-unsaturated carbonyl compounds could be attributed to stereoelectronic effects discussed above.



4. 1,1-Disubstituted Olefins (Table 12)

In all of the dihydroxylation reactions of 1,1-disubstituted olefins which are shown in Table 12 (and in Table 4), an exceptionally high degree of diastereoselection is apparent, and could be a direct consequence of additional conformational constraints imposed by $A^{(1,2)}$-strain. The substituent *S* (see conformer **63**) at the double bond can be an alkyl or an ester group. In retrospect, the finding that 1,1-disubstituted olefins undergo osmylation with the highest diastereoselectivity is not surprising. The preference for the synplanar conformer **64** over the *H*-eclipsed conformer **63** would be anticipated in consideration of $A^{(1,2)}$-strain. The presence of potential $A^{(1,2)}$-strain should also impede the interconversions between various conformers. Consequently, π-facial discrimination is expected to develop more fully, and result in an overall enhanced selectivity. Inasmuch as the product of entry 6 is **65**, it formally represents the opposite sense of the Kishi formulation. It is tempting to speculate that this complete reversal of diastereoselectivity is due to overriding

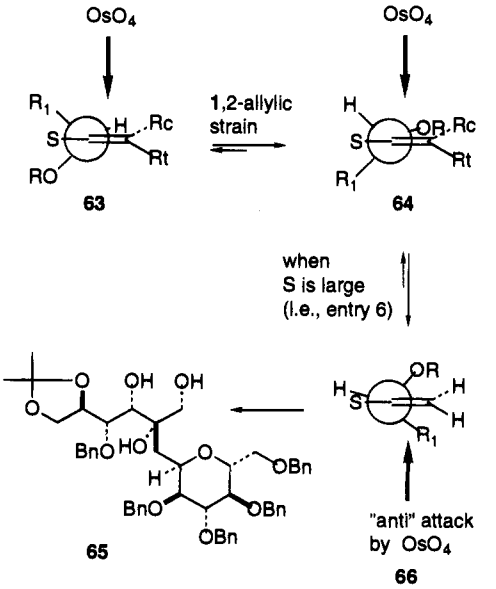
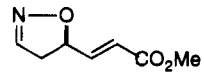
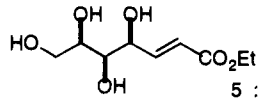
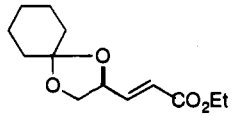
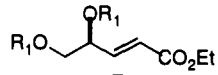
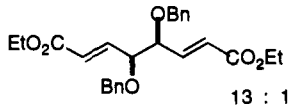
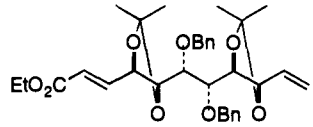
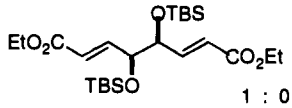
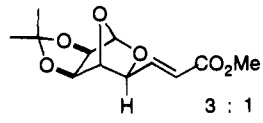
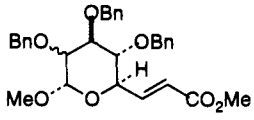
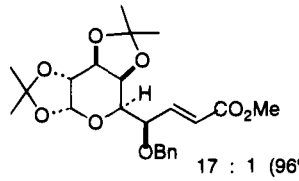
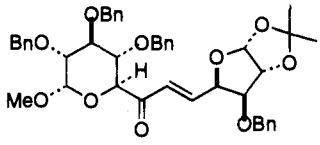
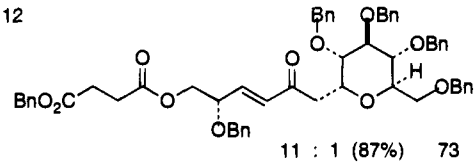
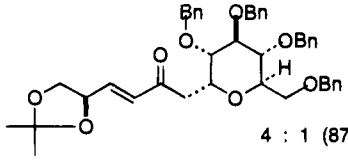
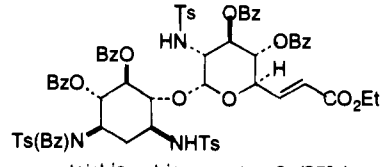
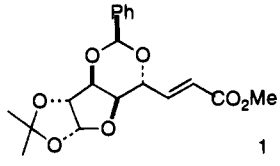


Table 9. Dihydroxylation of *E*-α,β-Unsaturated Carbonyl Compounds

Entry	Substrate	Selectivity (Yield)	Ref
1		5 : 1 (43%)	31
2		5 : 1 (82%)	24b
3		catalytic 2 : 1 (91%) stoichiometric[a] 12 : 1 (87%)	69
4		R_1 = TBS 6 : 1 (98%) R_1 = MPM 5 : 1 (75%) R_1 = MOM 3 : 1 (73%) R_1 = Ac 4 : 1 (79%) R_1 = Me 7 : 1 (64%)	69
5		13 : 1 (71%)	70
6		7 : 1 (88%)	70[b]
7		1 : 0	52
8		3 : 1 (75%)	71
9		α-OBn 9 : 1 (91%) β-OBn 6 : 1 (99%)	72
10		17 : 1 (96%)	40a
11		2 : 1 (57%)	59
12		11 : 1 (87%)	73
13		4 : 1 (87%)	73
14		stoichiometric 1 : 3 (85%) cat OsO_4, *t*-BOOH 6 : 1 (55%)	74
15		1 : 2 (94%)	72

a. Osmylation was carried out under stoichiometric conditions in the presence of TMEDA at -78 °C.
b. Both double bonds underwent stereoselective dihydroxylation in accord with Kishi's formulation.

constraints imposed by $A^{(1,2)}$-strain. Especially when R_c = H and *S* is very large, the favored conformation could be conformer **66**; the ensuing *"anti"* (to the allylic oxygen) attack would provide the observed stereochemical outcome. Further studies of correlating the bulkiness of the double-bond substituent, *S*, with stereoselectivity should provide interesting results.

5. Trisubstituted Olefins (Table 13)

Although only limited data have been reported for trisubstituted olefins, it is likely that the exceptionally high stereoselectivity obtained for osmylation of 1,1-disubstituted olefins would be observed for *E*-1,1,2-trisubstituted olefins as well. Indeed, the *E*-1,1,2-trisubstituted olefins have been found to undergo highly selective dihydroxylation (entry 1; see also

Table 10. Dihydroxylation of *Z*-α,β-Unsaturated Compounds

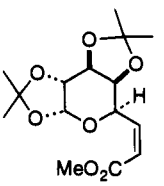
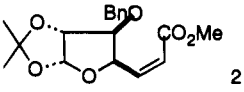
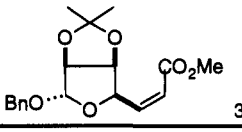
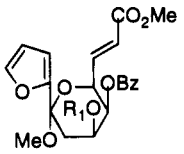
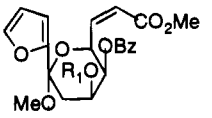
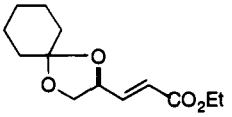
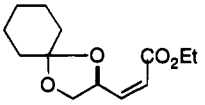
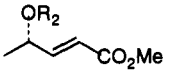
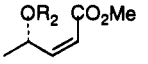
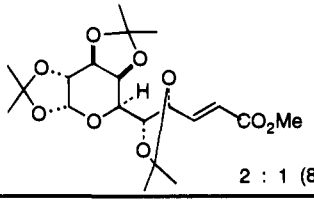
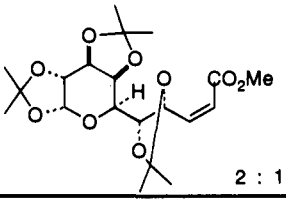
Entry	Substrate	Selectivity (Yield)	Ref
1		1 : 4 (84%)	40b
2		2 : 3 (94%)	39
3		3 : 2 (98%)	39

Table 11. Dihydroxylation of α,β-Unsaturated Esters–Comparison between *E*- and *Z*-Olefins

Entry	Substrate	Selectivity (Yield)	Ref
1		R_1 = TBS 25 : 1	15d[a]
2		R_1 = TBS 0 : 1 (92%)	15d[a]
3		catalytic 2 : 1 (91%) 3 : 1 (73%) stoichiometric[a] 12 : 1 (87%)	69 75 69
4		catalytic 1 : 1 (96%)	69 75
5		R_2 = Bn 3 : 1 (70%) R_2 = BOM 2 : 1 (76%) R_2 = H 7 : 1 (70%)	28b[b]
6		R_2 = Bn 1 : 1 (85%) R_2 = BOM 1 : 1 (85%)	28b
7		2 : 1 (83%)	58b
8		2 : 1	58b

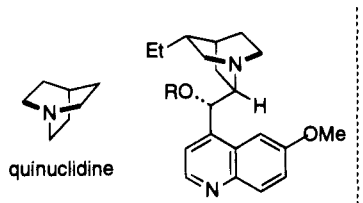
a. Osmylation was carried out under stoichiometric conditions in the presence of TMEDA at -78 °C.
b. When R_2 = H, the product was isolated as the lactone.

Table 3, entry 2). On the other hand, the stereochemical outcome for the corresponding *Z*-trisubstituted olefins is difficult to predict (Table 13, entries 2–6).

C. Double Stereodifferentiation

With the recent landmark discovery of a practical asymmetric dihydroxylation by Sharpless,[89-91] an interesting question arises whether or not the intrinsic diastereofacial selectivity of allylic alcohols and derivatives can be raised or overridden by the use of a chiral ligand in "matched" and "mismatched" pairing. Results of such double differentiation are listed in Tables 14 and 15.

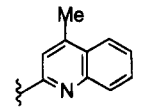
When the intrinsic diastereoselectivity of an allylic ether in osmylation was matched with the enantiofacial selectivity of a chiral catalyst, DHQ–OAc (**68**) or DHQ–CLB (**70**), the expected enhancement of selectivity was found (Table 14, entries 1–4). Recently Cozzi and Hirama independently examined the matching and mismatching of the substrate-directed diastereoselectivity with chiral ligands including the C_2-symmetric bispyrrolidines **79** and **80**, in addition to DHQD–OAc (**67**), DHQD–CLB (**69**), and **70** (entries 5–14).[69,75] The inherent "*anti*" selectivity noted previously was improved 4-fold by the influence of an achiral amine in a low-temperature stoichiometric osmylation (entries 7 and 8). Use of a chiral amine gave rise to further enhancement of approximately 45–50:1, when the ligand and substrate were matched (entries 10 and 13). In the mismatched cases, however, only poor (≤2:1) syn selectivity was observed (entries 12 and 14).



dihydroquinidine (DHQD) when R = H

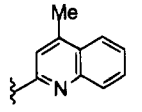
dihydroquinine (DHQ) when R = H

67: R = Ac (DHQD-OAc)
69: R = COC_6H_4-*p*-Cl (DHQD-CLB)
71: R =



(DHQD-MEQ)

68: R = Ac (DHQ-OAc)
70: R = COC_6H_4-*p*-Cl (DHQ-CLB)
72: R =

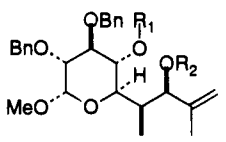
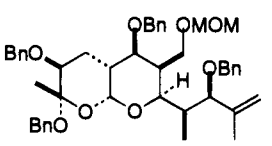
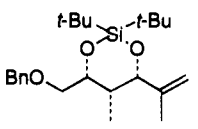
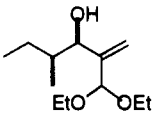
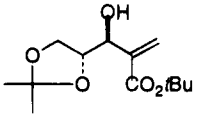
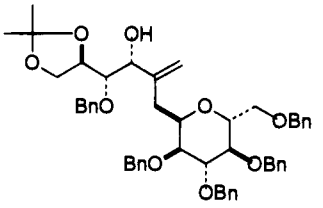


(DHQ-MEQ)

The effect of hydroxy protecting groups was next examined (entries 15–26). It is particularly noteworthy that the acetate (entries 21–23) and the methyl ether (entries 24–26) proved to be very amenable to asymmetric dihydroxylation. When an acyl protecting group is utilized, the intrinsic "*anti*" selectivity can evidently be overridden by a judiciously chosen chiral ligand (see also Table 15, entries 15–18). On the other hand, the poor substrate-controlled diastereofacial selectivity of the *Z*-α,β-unsaturated ester was scarcely changed in asymmetric dihydroxylation (Table 14, entries 27–33).

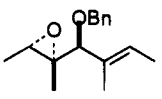
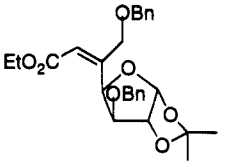
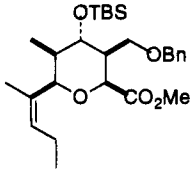
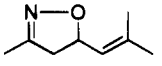
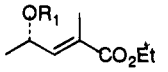
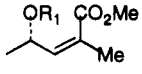
Striking improvements including the refinement of chiral ligands and the experimentally important transition from stoichiometric to *catalytic* asymmetric dihydroxylation have been made by Sharpless and co-workers.[89-90] In particular, the use of 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, $(DHQD)_2$–PHAL (**73**) or 1,4-bis(9-*O*-dihydroquininyl)phthalazine,

Table 12. Dihydroxylation of 1,1-Disubstituted Olefins

Entry	Substrate	Selectivity (Yield)	Ref
1		R_1 = Ac; R_2 = Bn 1 : 0 (85%) R_1 = Bz; R_2 = H 1 : 0 (85%)	76a
2		1 : 0 (63%)	76b
3		60 : 1 (94%)	77
4		10 : 1	78
5		1 : 0 (100%)	28a
6		0 : 1	79[a]

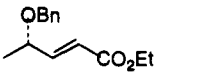
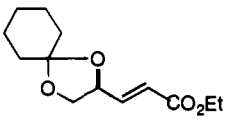
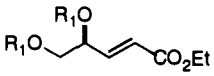
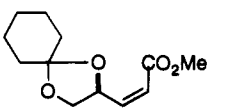
a. Osmylation was carried out under stoichiometric conditions in 2:1 pyr-THF at -78 °C.

Table 13. Dihydroxylation of Trisubstituted Olefins

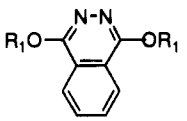
Entry	Substrate	Selectivity (Yield)	Ref
1		15 : 1 (89%)	80
2		2 : 1	81
3		2 : 3	82
4		8 : 1 (70%)	30
5		R_1 = Bn 3 : 1 (85%) R_1 = BOM 2 : 1 (94%) R_1 = H 1 : 1.2 (95%)[a]	28b
6		R_1 = Bn 2 : 1 (91%)	28b

a. The osmylation product was isolated as the γ-lactone.

Table 14. Double Stereodifferentiation in Asymmetric Dihydroxylation of Chiral Olefins

Entry	Substrate	Ligand	Conditions	Anti/Syn Selectivity Yield	Ref
					
1		TMEDA	stoich. -78 °C	3 : 1 (70%)	28b
2		quinuclidine	stoich. -20 °C	4 : 1 (51%)	75
3		DHQ-OAc (**68**)	stoich. -20 °C	7 : 1 (50%)	
4		DHQ-CLB (**70**)	stoich. -20 °C	11 : 1 (88%)	
					
5		none	cat. rt	2 : 1 (91%)	69
6		none	cat. rt	3 : 1 (73%)	75
7		quinuclidine	stoich. -20 °C	10 : 1 (40%)	75
8		TMEDA	stoich. -78 °C	12 : 1 (87%)	69
9		DHQD-OAc (**67**)	stoich. -20 °C	20 : 1 (80%)	75
10		DHQD-CLB (**69**)	stoich. -20 °C	45 : 1 (80%)	
11		DHQD-CLB (**69**)	cat. rt	2 : 1 (75%)	
12		DHQ-CLB (**70**)	stoich. -20 °C	1 : 1.2 (44%)	
13		*RR*-**79**	stoich. -78 °C	50 : 1 (96%)	69
14		*SS*-**80**	stoich. -78 °C	1 : 2 (95%)	
					
15	R_1 = TBS	none	cat. rt	6 : 1 (98%)	69
16		*RR*-**79**	stoich. -78 °C	9 : 1 (97%)	
17		*SS*-**80**	stoich. -78 °C	1 : 3 (96%)	
18	R_1 = MPM	none	cat. rt	5 : 1 (75%)	69
19		*RR*-**79**	stoich. -78 °C	20 : 1 (94%)	
20		*SS*-**80**	stoich. -78 °C	1 : 3 (91%)	
21	R_1 = Ac	none	cat. rt	4 : 1 (79%)	69
22		*RR*-**79**	stoich. -78 °C	23 : 1 (97%)	
23		*SS*-**80**	stoich. -78 °C	1 : 17 (93%)	
24	R_1 = Me	none	cat. rt	7 : 1 (64%)	69
25		*RR*-**79**	stoich. -78 °C	50 : 1 (73%)	
26		*SS*-**80**	stoich. -78 °C	1 : 15 (72%)	
					
27		none	cat. rt	1 : 1 (66%)	75
28		quinuclidine	stoich. -20 °C	1 : 1 (43%)	
29		DHQD-OAc (**67**)	stoich. -20 °C	1 : 1.5 (100%)	
30		DHQD-CLB (**69**)	stoich. -20 °C	1 : 1.2 (84%)	
31		DHQ-CLB (**70**)	stoich. -20 °C	2.5 : 1 (91%)	
32		*RR*-**79**	stoich. -78 °C	2 : 1 (98%)	69
33		*SS*-**80**	stoich. -78 °C	1 : 1 (94%)	

$(DHQ)_2$–PHAL (**74**) as the chiral catalyst has given excellent stereoselectivity under catalytic conditions.

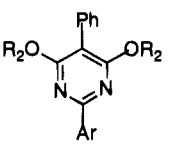


phthalazine (PHAL)

73: R_1 = DHQD $(DHQD)_2$-PHAL

74: R_1 = DHQ $(DHQ)_2$-PHAL

In addition, these catalytic asymmetric dihydroxylations are easy to perform, especially since a mixture of all the osmylation ingredients is now commercially available as AD-mix-β (containing **73**) and AD-mix-α (containing **74**). Results of catalytic and stoichiometric asymmetric dihydroxylations are summarized in Table 15. In entries **1**–9, Sharpless assessed several different ligands in matched and mismatched asymmetric dihydroxylations. Excellent "*anti*" selectivity was obtained by the phthalazine ligand $(DHQD)_2$–PHAL (**73**) for the matched case (entry 4). In the mismatched examples, the pyrimidine derivative $(DHQ)_2$–$PYR(OMe)_3$ (**78**) gave a synthetically useful, although less spectacular, level of diastereoselectivity (entry 9).



diphenylpyrimidine (PYR): Ar = Ph
$PYR(OMe)_3$: Ar = 3,4,5-trimethoxyphenyl

75: R_2 = DHQD $(DHQD)_2$-PYR

76: R_2 = DHQ $(DHQ)_2$-PYR

77: R_2 = DHQD $(DHQD)_2$-$PYR(OMe)_3$

78: R_2 = DHQ $(DHQ)_2$-$PYR(OMe)_3$

Table 15. Additional Examples of Double Stereodifferentiation

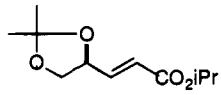
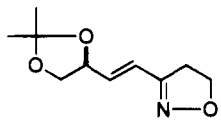
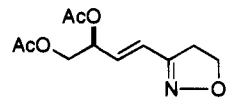
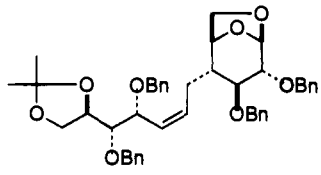
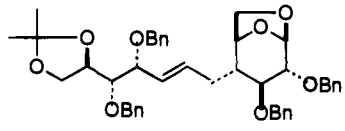
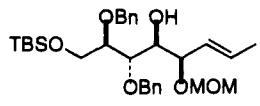
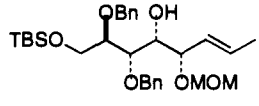
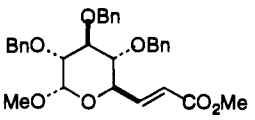
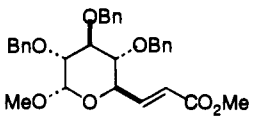
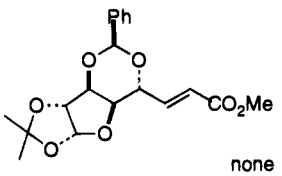
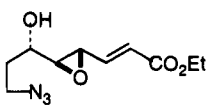
Entry	Substrate	Ligand	Conditions	Anti/Syn Selectivity (Yield)	Ref
					
1		quinuclidine	cat. rt	3 : 1 (85%)	92
2		DHQD-CLB (**69**)	"	10 : 1 (87%)	
3		DHQ-CLB (**70**)	"	1 : 1 (85%)	
4		$(DHQD)_2$-PHAL (**73**)	"	39 : 1 (84%)	
5		$(DHQD)_2$-PYR (**75**)	"	7 : 1 (90%)	
6		$(DHQD)_2$-PYR$(OMe)_3$ (**77**)	"	12 : 1 (89%)	
7		$(DHQ)_2$-PHAL (**74**)	"	1 : 1.3 (52%)	
8		$(DHQ)_2$-PYR (**76**)	"	1 : 4 (86%)	
9		$(DHQ)_2$-PYR$(OMe)_3$ (**78**)	"	1 : 7 (90%)	
					
10		none	cat. rt	3 : 1 (85%)	66
11		DHQD-MEQ (**71**)	cat. rt	8 : 1 (52%)	
12		DHQD-MEQ (**71**)	stoich. rt	4 : 1 (48%)	
13		$(DHQD)_2$-PHAL (**73**)	cat. rt	24 : 1 (53%)	
14		$(DHQ)_2$-PHAL (**74**)	cat. rt	1 : 8 (62%)	
					
15		none	cat. rt	3 : 1 (83%)	66
16		DHQ-MEQ (**72**)	cat. rt	1.1 : 1 (66%)	
17		$(DHQD)_2$-PHAL (**73**)	cat. rt	49 : 1 (82%)	
18		$(DHQ)_2$-PHAL (**74**)	cat. rt	1 : 19 (85%)	
					
20		DABCO	cat. 5 °C	3 : 1 (71%)	48
21		pyridine	stoich. -35 °C	6 : 1 (60%)	
22		(*R,R'*) diamine **81**	stoich. -80 °C	58 : 1 (84%)	
23		(*S,S'*) diamine **82**	stoich. -50 °C	5 : 1 (5% conversion)	
					
24		(*R,R'*) diamine **81**	stoich. -80 °C	18 : 1 (63%)	48
					
25		none	cat. rt	3 : 1 (99%)	63
26		$(DHQ)_2$-PHAL (**74**)	cat. 0 °C	7 : 1 (50%)	
27		$(DHQD)_2$-PHAL (**73**)	cat. 0 °C	1 : 1	
					
28		none	cat. rt	4 : 1 (93%)	63
29		$(DHQD)_2$-PHAL (**73**)	cat. 0 °C	*a*	

Table 15 (Continued)

Entry	Substrate	Ligand	Conditions	Anti/Syn Selectivity (Yield)	Ref
					
30		none	cat. rt	9 : 1 (91%)	72,93
31		DHQ-CLB (**70**)	cat. 0 °C	21 : 1 (87%)	
32		DHQD-CLB (**69**)	cat. 0 °C	1.3 : 1 (87%)	
					
33		none	cat. rt	7 : 1 (99%)	72,93
34		DHQ-CLB (**70**)	cat. 0 °C	16 : 1 (87%)	
35		DHQD-CLB (**69**)	cat. 0 °C	3 : 1 (87%)	
					
36		none	cat. rt	1 : 2 (94%)	72,93
37		DHQD-CLB (**69**)	cat. 0 °C	1 : 5 (87%)	
38		DHQ-CLB (**70**)	cat. 0 °C	1 : 1.6 (87%)	
					
39		none	cat. rt	2 : 1	94
40		$(DHQD)_2$-PHAL (**73**)	cat. rt	20 : 1	
41		$(DHQ)_2$-PHAL (**74**)	cat. rt	1 : 10	

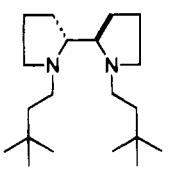
a. The osmylation reaction with AD-mix-β containing **73** was less than 10% completed even after 7 days.

Wade investigated a similar set of experiments and reported good levels of matched and mismatched diastereoselectivity (entries 10–14).[66] Larger quantities of the osmium reagent and the ligand were necessary than in the typical Sharpless catalytic procedure, presumably due to chelation of the dihydroisoxazole nitrogen with the osmate(VI) ester and the resulting low rate of catalyst turnover. As noted above for Table 14, entries 21–23, the acetate protecting group furnished the highest level of selectivity (entries 13 and 14 vs 17 and 18).

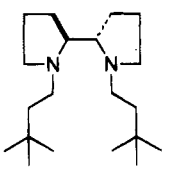
In other recent examples reported by Marshall, asymmetric dihydroxylation has met with limited success (entries 25–29).[63] In entry 29, it is conceivable that incorporation of the substrate into the active site of the AD-mix reagent is impeded on steric grounds. In addition, an allylic oxygen substituent appears to retard the rate of asymmetric dihydroxylation.[95]

Brimacombe examined the asymmetric dihydroxylation of the carbohydrate-derived α,β-unsaturated esters (entries 30–38). In matched examples (entries 31 and 34), the diastereoselectivity was enhanced. On the other hand, in each mismatched example (entries 32 and 35), the chiral ligand had little impact on the inherent diastereofacial preference of the allylic substrate. Table 15, entry 36 (≡ Table 9, entry 15) shows a modest preference for the *syn* diol product, and thus represents one of a very few exceptions to the Kishi empirical rule.

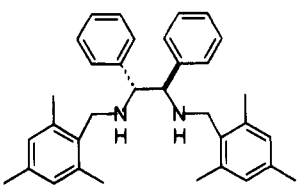
In synthetic studies of 1,4-linked *C*-disaccharides, Kishi reported that the intrinsic diastereoselectivity of 6:1 for the dihydroxylation could be raised to 58:1 by the method of Corey[91e] employing *N,N'*-bis(mesitylmethyl)-(*R,R'*)-1,2-diphenyl-1,2-diaminoethane (**81**)



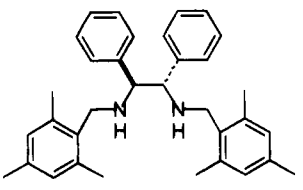
R,R-**79**



S,S-**80**



R,R-diamine (**81**)



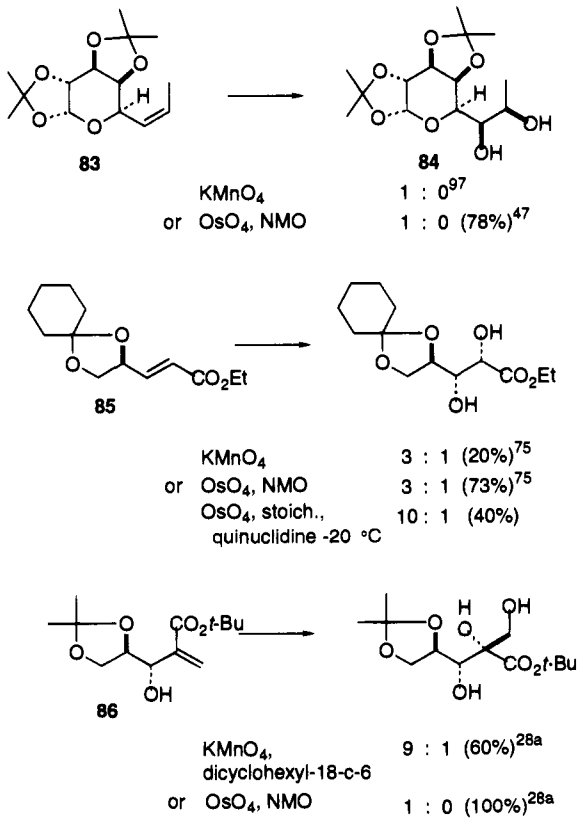
S,S-diamine (**82**)

(stoichiometric OsO_4, CH_2Cl_2, −80 °C, 1 day; entries 20−23).[22] In the mismatched example, the *S,S'*-antipode **82** failed to override the substrate-directed diastereofacial preference; the overall selectivity was 5:1 in the extremely sluggish osmylation process (less than 5% conversion at −50 °C after 1 week). Interestingly, when achiral *N,N'*-bis(mesitylmethyl)-1,2-diphenyl-1,2-diaminoethane was used as the ligand, synthetically useful 18:1 selectivity was obtained under otherwise identical conditions.

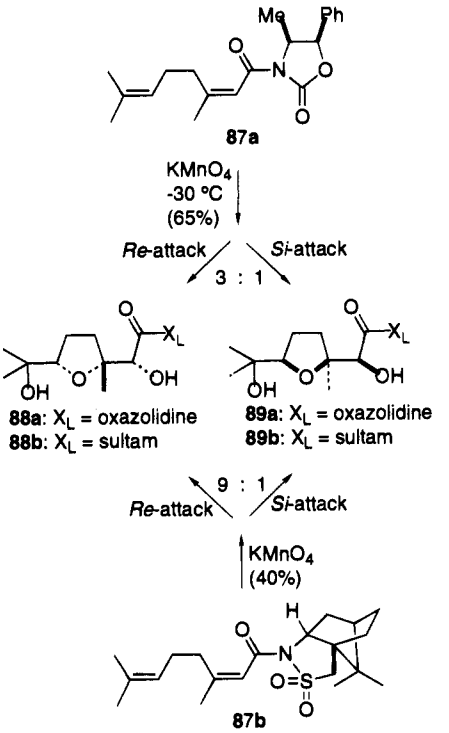
During our synthetic studies of castanospermine and 6,7-diepicastanospermine, we examined the asymmetric dihydroxylation of a γ,δ-epoxy-α,β-unsaturated ester (entries 39−41).[94] Whereas the intrinsic "*anti*" diastereoselectivity induced by the epoxy group was 2:1, this epoxide was amenable to the directive influence of the chiral ligand in both matched and mismatched cases.

D. Permanganate Dihydroxylation

It is pertinent to mention that dihydroxylation by $KMnO_4$ of allylic ethers also exhibits the "*anti*" selectivity in a manner similar to osmylation, although the yield is often inferior.[96] For example, in 1970 Szarek reported that treatment of olefin **83** with aqueous potassium permanganate gave diol **84** as the sole product.[97] As shown in Table 7, entry 2, exclusive "*anti*" selectivity was obtained for catalytic osmylation.[47] There have appeared two additional comparison studies: both $KMnO_4$ and OsO_4 dihydroxylations of olefin **85** (Table 11, entry 3) gave the *anti* diol in 3:1 selectivities. Similar results were obtained for olefin **86** (from Table 12, entry 5).



Thus, comparable diastereofacial selectivity has been observed for the $KMnO_4$ and OsO_4 oxidations of these allylic systems. However, these reagents have the opposite electronic preference: given similar steric environments, electron-withdrawing substituents in the olefin appear to accelerate the permanganate oxidations, whereas the same substituents retard the reaction of olefins with osmium tetroxide.[98] This electronic preference by permanganate is well illustrated by an elegant synthetic application developed by Walba in the permanganate-induced oxidative cyclization of 1,5-dienes.[99−101] Oxidation of enantiomerically pure dienoate **87a** (4'*S*,5'*R*) afforded the tetrahydrofuran diols **88a** and **89a** in a 3:1 ratio and 65% yield. The major product **88a** arose from attack of permanganate on the *re* face (bottom face) of the conjugated double bond. The diastereofacial selectivity was raised to a 9:1 ratio by use of Oppolzer's sultam **87b**.

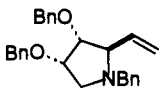
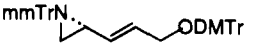
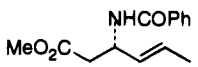
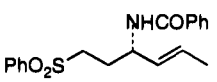
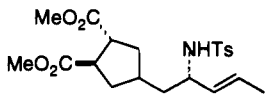
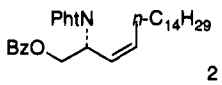
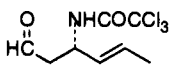
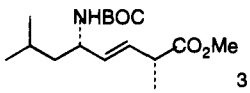
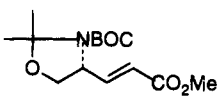
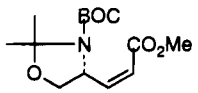
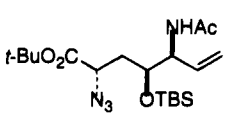
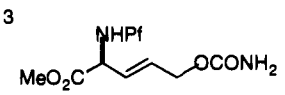
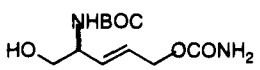
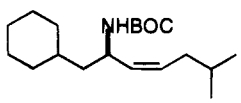
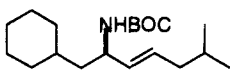
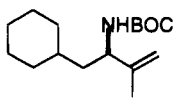


We have taken advantage of the opposite electronic preference by osmium tetroxide in our synthetic studies of α-pyrone polyene mycotoxins, which are described in detail in a later section. The similarity in the stereochemical outcome for the permanganate and osmylation reactions of allylic ethers should be taken into account in mechanistic analysis.

E. Stereocontrol by Allylic Amino Substituents

In marked contrast to the large number of investigations concerning π-facial diastereoselection by allylic alkoxy groups, the effect of allylic nitrogen substituents has received scant attention. Dihydroxylations of secondary allylic amines, amides, and carbamates are summarized in Table 16. Notwithstanding two exceptions (entries 1 and 10), osmylation of allylic amino derivatives generally proceeds with poor to moderate diastereofacial selectivity. In entries 2 and 13, secondary or tertiary amines exhibit modest "*syn*" selectivity, but the opposite facial selectivity was found in entry 1. Mechanistic analy-

Table 16. Dihydroxylation of Allylic Amines, Amides, and Carbamates

Entry	Substrate	Selectivity (Yield) (anti/syn)	Ref
1		1 : 0 (71%)	102[a]
2		OsO_4, NMO 1 : 1 OsO_4, DHQD-CLB (**69**) 1 : 4 (86%)	103
3		1.6 : 1 (91%)	104
4		1.5 : 1 (94%)	87
5		4 : 1	105
6		2 : 1 (90%)	106
7		1.5 : 1	104
8		3 : 1 (73%)	107
9		1 : 1	108
10		1 : 0 (50%)	108
11		7 : 1 (77%)	109
13		$KMnO_4$, -25 °C 1 : 2 (75%) OsO_4, NMO 1 : 1 (90%) OsO_4, DHQ-MEQ (**72**) 1 : 2 (90%) OsO_4, DHQD-MEQ (**71**) 3 : 1 (90%)	111[c]
12		1 : 2.5 (97%)	110[b]
14		OsO_4, NMO, THF-H_2O 1 : 1 OsO_4, NMO, *i*-PrOH 1 : 5 stoich. OsO_4 1 : 10	112
15		OsO_4, NMO, *i*-PrOH 1 : 2 OsO_4, a DHQD ligand 1 : 6 OsO_4, a DHQ ligand 3 : 1	112
16		OsO_4, NMO, *i*-PrOH 1 : 2[d]	112

mmTr = monomethoxytrityl; Pf = 9-phenylfluoren-9-yl

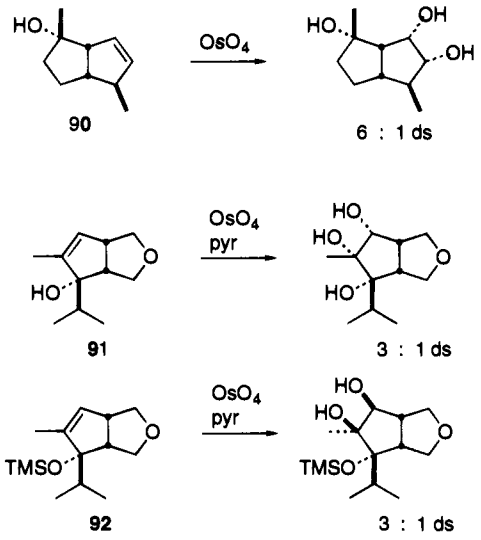
a. The osmylation products include the anti diol (61%) and the corresponding *N*-oxide (10%).
b. Dihydroxylation was achieved by buffered $KMnO_4$ oxidation, and the product was isolated as an inseparable mixture of two γ-lactols (derived from concomitant oxidation of the primary alcohol.
c. The diol products were isolated as the corresponding γ-lactones, following treatment with triethylamine.
d. The stereochemical assignment is tentative.

sis is complicated by the known complexation of tertiary amines with osmium tetroxide. Thus, a parallel analogy of π-facial diastereoselection by allylic alcohols and ethers to the corresponding amines would be inoperative.

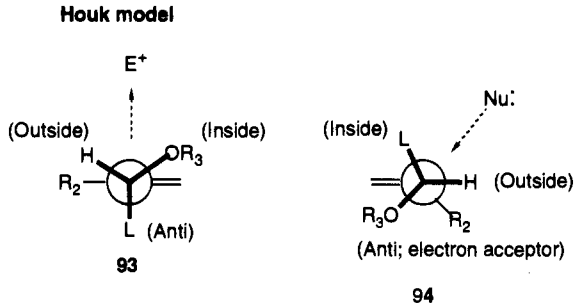
Dihydroxylations of allylic amides and carbamates also proceed in a stereoirregular manner: preferences for either *anti* products (entries 3–11) or *syn* products (entries 12–16) were observed. It is interesting to note that poor selectivity was obtained even for a 1,1-disubstituted olefin (entry 16), whose analogous allylic ether systems (cf. Tables 4 and 12) afford exceptionally high selectivity. In entry 14, scientists at Abbott Laboratories were able to improve the selectivity by changing the solvent from the standard THF–water mixture to 2-propanol. Stoichiometric osmylation was also found to raise syn selectivities, which was attributed to the deleterious intervention of osmium glycolate species under catalytic conditions.[89d,112] Sharpless asymmetric dihydroxylation of the corresponding *E*-olefin was also examined (entry 15); use of a quinidine-derived ligand gave the *threo* to *erythro* diastereomers in a 6:1 ratio, whereas the *erythro* isomer was the major product (3:1) when a quinine-derived ligand was used. It is interesting to note that this result is not in accord with the Sharpless enantioselectivity mnemonic.[113] On the other hand, the double stereodifferentiation results shown in entries 2 and 13 (involving allylic amines) are predicted by the Sharpless mnemonic. Further systematic studies are necessary to adequately assess the directive effect by allylic nitrogen substituents.

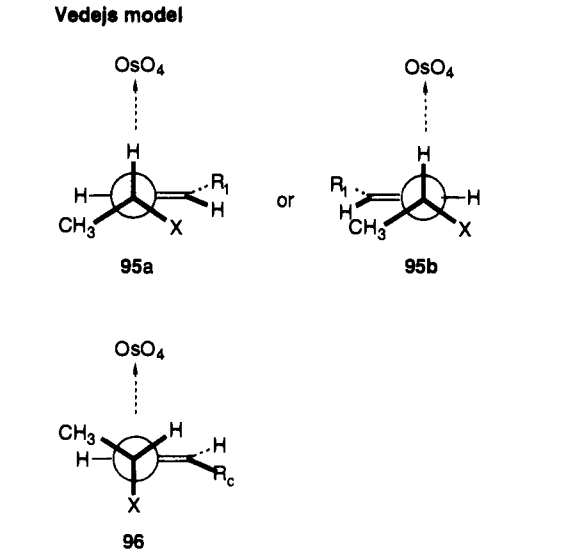
F. Mechanistic Considerations

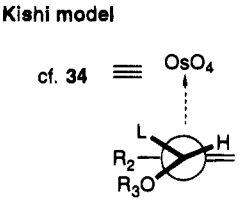
In the over 100 examples listed in Tables 1−15, the uniform "*anti*" diastereofacial selectivity can be seen for osmylation of allylic alcohols and ethers, with the exclusion of *Z*-α,β-unsaturated carbonyl compounds. Since the mechanism of *cis*-dihydroxylation by OsO_4 is not well understood,[90,114] construction of an exact working model to account for the observed "*anti*" diastereoselectivity is fraught with uncertainties. Nonetheless, several working models of considerable predictive value have been advanced. Implicit in these working hypotheses is the basic premise that the product-determining step is the *irreversible*, competitive attack by osmium tetroxide at the olefin π-faces, presumably via [3 + 2] cycloaddition or oxametallocyclobutane formation. In addition, a substrate-directed reaction involving chelation of OsO_4 with an allylic hydroxyl group is deemed to be unlikely. Despite the two examples **90** and **91** (cf. **92**) where such chelation was implicated,[115,116] no compelling kinetic evidence has appeared thus far.



On the basis of theoretical studies of nitrile oxide cycloadditions to allylic ethers, Houk extended the "inside alkoxy" transition state model **93** to osmylation, which could be regarded as a refinement of the picture **35**.[117,118] The computational prediction that, unlike the ground-state conformation, the preferred transition state has a staggered geometry is the cornerstone of Houk's model: it can be generalized as **93** and **94** for electrophilic and nucleophilic additions to olefins, respectively. It should be noted that the structure **94** is closely related to the Felkin−Anh model. As stated in the previous section, both conformations **93** and **94** are also anticipated to be favored on minimization of torsional strain and stereoelectronic grounds. In the case of nitrile oxide cycloadditions, Houk argued that alkyl substituents at the stereocenter prefer the sterically least encumbered "*anti*" conformation, while an allylic ether group prefers the "inside" conformation due to secondary orbital interactions: the alkoxy preference for inside vis-à-vis outside orientation was rationalized in terms of minimized repulsion between the allylic oxygen and the nitrile oxygen.







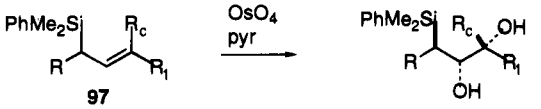
Recently, Vedejs questioned the dominant controlling role of the hyperconjugative effects.[119] In osmylation studies of 3-penten-2-yl derivatives containing bulky donor (X = $PhMe_2Si$) and bulky acceptor (RSO_2, along with *t*-$BuMe_2SiO$) substituents at the allylic position, all of the *Z*-alkenes showed the "*anti*" selectivity, irrespective of a σ-donor or σ-acceptor substituent. For *E*-alkenes, the "*anti*" preference was found for compounds bearing an allylic oxygen substituent, whereas those with a third-row element exhibited the opposite diastereofacial selectivity. These interesting results, which are summarized in Table 17, prompted Vedejs to stress the importance of steric effects exerted on the substrates by the osmium reagent and associated ligand(s). For *E*-alkenes, steric requirements of osmium ligands are dominant, and conformations **95a** or **95b** are prevalent with the allylic hydrogen near osmium. The choice between **95a** and **95b** is governed by the relative size of an allylic substituent (with respect to methyl). For *Z*-alkenes, on the other hand, the sterically dominant interactions are proposed to lie between the R_c substituent (i.e., methyl) and the allylic substituent. As indicated in **96**, the "inside" allylic hydrogen orientation is clearly favored on steric grounds. Ligand interactions are reduced by

Table 17. Dihydroxylation of $CH_3CH{=}CHCH(X)CH_3$[119a]

Entry	Isomer	X	Selectivity (anti:syn)	Entry	Isomer	X	Selectivity (anti:syn)
1	*Z*	$PhMe_2Si$	3.6 : 1	2	*E*	$PhMe_2Si$	1 : 1.9
3	*Z*	$PhSO_2$	4.0 : 1	4	*E*	$PhSO_2$	1 : 3.6
5	*Z*	$MeSO_2$	4.9 : 1	6	*E*	$MeSO_2$	1 : 4.6
7	*Z*	PhS	5.3 : 1	8	*E*	PhS	1 : 2.0
9	*Z*	*t*-$BuMe_2SiO$	1.6 : 1	10	*E*	*t*-$BuMe_2SiO$	1.6 : 1
11	*Z*	CH_3CO_2	2.3 : 1	12	*E*	CH_3CO_2	1.6 : 1

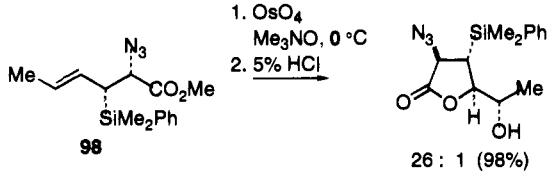
distorting the osmium reagent toward the unsubstituted olefin side.

Attention should be drawn to recent results reported by Fleming and Panek that osmylation (catalytic conditions) of both (*E*)- and (*Z*)-crotylsilanes **97** and **98** proceeds with moderate to good levels of *anti* selectivity.[139a,b] This stereochemical outcome is at



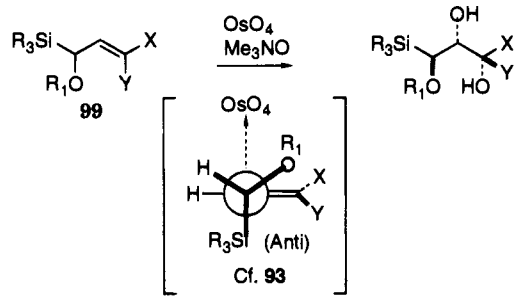
97

a: R = *i*-Pr, R_1 = Me, R_c = H 2 : 1
b: R = Ph, R_1 = Me, R_c = H 12 : 1
c: R = *i*-Pr, R_1 = H, R_c = Me 6 : 1
d: R = Ph, R_1 = H, R_c = Me 5 : 1



98

26 : 1 (98%)



99

Cf. **93**

a: R_1 = H, R_3Si = $SiMe_3$, X = Me, Y = H 27 : 1 (60%)
b: R_1 = H, R_3Si = Si*t*-$BuMe_2$, X = Me, Y = H 120 : 1 (62%)
c: R_1 = H, R_3Si = Si*t*-$BuMe_2$, X = H, Y = Me 4.7 : 1 (45%)
d: R_1 = R_3Si = Si*t*-$BuMe_2$, X = Me, Y = H 10 : 1 (92%)
e: R_1 = Ac, R_3Si = $SiMe_3$, X = Me, Y = H 4.5 : 1 (63%)
f: R_1 = Ac, R_3Si = Si*t*-$BuMe_2$, X = Me, Y = H 7.0 : 1 (61%)
g: R_1 = Ac, R_3Si = Si*t*-$BuMe_2$, X = H, Y = Me 1.4 : 1 (94%)

variance with a slight *syn* preference reported by Vedejs for osmylation of (*E*)-3-penten-2-yl compounds bearing a third row element at the allylic stereocenter (vide supra). Discrepancy can be attributed to the relative stabilities of conformers **95a** and **95b** with respect to the size of the alkyl substituent. For larger alkyl compounds, conformation **7** (where *L* = $SiMe_2$-Ph, *M* = R) is favored over conformation **8** on steric grounds, and the major product arises from addition of osmium reagent *anti* to the silyl group.[12] Panek also reported highly diastereoselective dihydroxylation of the corresponding allylic alkoxy silanes **99** to predominantly afford *anti* products.[139c] Highest *anti* stereoselection was obtained for the allylic alcohols (R_1 = H). As the trialkylsilyl group becomes larger, the *anti* selectivity increases. The (*Z*)-crotylsilanes gave considerably lower selectivities than the corresponding *E*-isomers. The *anti*-stereochemistry observed in osmylation of the alkoxy silanes **99** was rationalized in terms of the transition state model, where the trialkylsilane being the largest and best σ-donor group adopts an orientation antiperiplanar to the p orbitals of the C=C bond and the OR_1 group occupies the "inside" position.

As noted in the previous section, Kishi model **34** is reactant-like, and closely resembles the known ground-state conformation of allylic ethers. Also delineated was a tantalizingly close correlation between the X-ray crystallographic ground-state conformations of several structurally complex alkenes and the stereochemical outcome of their osmylations.[15d] In addition to the two examples **61** and **62** (discussed in detail in section II.B), Danishefsky also provided the X-ray crystal structure of an *E*-1,2-disubstituted olefin (Table 8, entry 5), whose solid ground-state conformation has the allylic hydrogen in eclipse with the double bond.[15b,c] More recently Brimacombe undertook four additional X-ray structure determinations: the two mono-substituted olefins (Table 5, entries 12 and 13, where R_4 = R_5 = H) and a *Z*-α,β-unsaturated ester (Table 11, entry 8). All assume an eclipsed conformation having the smallest group, the allylic hydrogen, eclipsing the double bond.[120,121] On the other hand, the *E*-α,β-unsaturated ester (Table 9, entry 10) has been shown to possess a synplanar conformation, which coincides with the X-ray structure of ester **62**.[120a]

Notwithstanding the implicit theoretical limitations, these ground-state conformations in the solid state provide satisfactory explanations for the observed diastereofacial selectivities for all cases—excellent selectivity for Table 8, entry 5 (especially with respect to the analogous glucose configuration, i.e., Table 8, entry 3), and strikingly different stereoselectivities of Table 5, entries 12 vs 13, along with Table 9, entry 10, vs Table 11, entry 7. For Table 5, entry 13, for example, the approach of OsO_4 from the preferred direction "*anti*" to the allylic oxygen (Kishi model) suffers from nonbonded interactions with the 3,4-*O*-isopropylidene group, and, consequently, results in lower selectivity. On the other hand, rela-

Table 18. Dihydroxylation of Cyclic Allylic Ethers

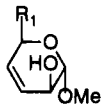
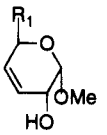
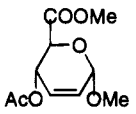
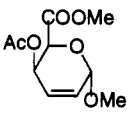
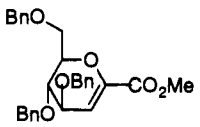
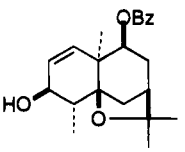
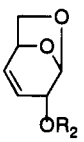
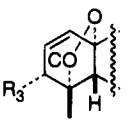
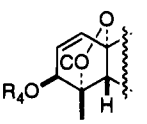
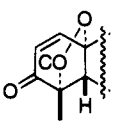
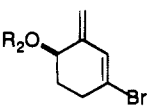
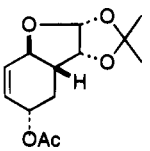
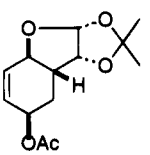
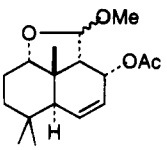
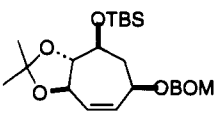
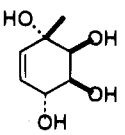
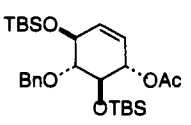
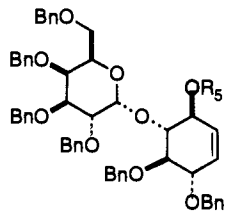
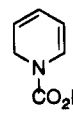
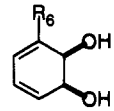
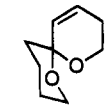
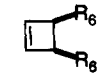
Entry	Substrate	Selectivity (Yield) (anti/syn)	Ref
1		R_1 = H, CH_2OH, CH_3 6 : 1 ~27 : 1	122
2		R_1 = H, CH_2OH, CH_3 3 : 1 ~10 : 1	122
3		1 : 0	123
4		1 : 0	123[a]
5		1 : 0 (92%)	124
6		1 : 0 (66%)	125[b]
7	 R_2 = COAr' R_2 = COt-Bu R_2 = COAc R_2 = H R_2 = Bn R_2 = TBDPS	1 : 6 1 : 12 1 : 4 1 : 3.5 1 : 2 1 : 1 2 : 1	126
8	 R_3 = H R_3 = OH R_3 = OAc	1 : 0 (92%) 1 : 0 (84%) 1 : 0 (83%)	127
9	 R_4 = H R_4 = Ac	1 : 0 (90%) 6 : 1 (82%)	127[c]
10		1 : 1.1 (77%)	127
11	 R_2 = Ac R_2 = t-BuC(O)	5 : 1 (87%) 3 : 1 (91%)	128[d]
12		1 : 0 (53%)	129[e]
13		1 : 0	129[e]
14		3 : 1	130
15		20 : 1 (97%)	131
16		1 : 0 (55%)	132
17		10 : 1 (60%)	133[f]

Table 18 (Continued)

Entry	Substrate	Selectivity / Yield (anti/syn)	Ref
18			
	R_5 = H	2 : 1 (91%)	134[g]
	R_5 = Ac	6 : 1	
20		1 : 0 (85%)	136[h]
21			
	R_6 = H	2.5 : 1 (64%)	137
	R_6 = Me	2.0 : 1 (57%)[i]	
	R_6 = Cl	1.2 : 1 (88%)	
	R_6 = Br	1.1 : 1 (84%)	
19		1 : 0 (78%)	135
22			
	R_6 =OMs	1 : 8 (80%)	138
	R_6 = OCO_2Me	1 : 3 (84%)	
	R_6 = Cl	1 : 1.5 (94%)	
	R_6 = OBn	1.3 : 1 (76%)	

a. The major product was the β,β-diol, i.e., anti to the C-1 alkoxy and syn to the C-4 acetate.
b. Dihydroxylation was carried out under stoichiometric conditions in pyridine.
c. The major product was the α,α-diol, i.e., anti to -OR_4.
d. When R_2 = Ac, some acyl transfer to the primary alcohol took place.
e. Osmylation product took place anti to the acetate.
f. The major product was the α,α-diol, i.e., anti to -OTBS.
g. In both cases, the major product was the α,α-diol, i.e., anti to -OR_5 and syn to -OBn.
h. The tetrol was obtained as a sole product.
i. There were additional products resulting from dihydroxylation at the trisubstituted double bond.

tively unimpeded access to the double bond is available for such "*anti*" attack by OsO_4 in Table 5, entry 12.

In the Kishi model lies the basic assumption that osmylation takes place preferentially on the olefin face opposite to the allylic oxygen. Although the effect is not always large, there appear few exceptions.[18] This "*anti*" preference has been further corroborated by recent examples of dihydroxylations of conformationally rigid, cyclic compounds (Table 18).

Of special interest are those examples where dihydroxylation proceeds from the sterically more congested face of the molecule. This contrasteric "*anti*" approach is illustrated in entries 6, 7, and 9. In the gibberellin compounds (entries 8–10), the α-face of the A-ring has been demonstrated to be the more sterically hindered one.[127] Entry 7 indicates that the alkoxy group (in particular, −OTBDPS) can negate steric hindrance more effectively than the acyloxy group. It is also apparent that an increase in the steric bulk of the acyl protecting group does not result in an increased kinetic preference for *anti* attack (see also entry 11). The presence of the 1α,2α-diol product in entry 10 is unexpected. In entry 18, the larger directive effect by −OAc than by −OH is surprising, especially against the effect of the allylic −OBn group. While excellent diastereoselectivity was observed for bis-dihydroxylation of a diene (entry 20), the dienes in entry 21 showed surprisingly poor selectivities. The interesting results of entry 22 were rationalized in terms of the nonplanar cyclobutene. In addition, the effect of solvents on facial stereoselectivity was also reported.[138]

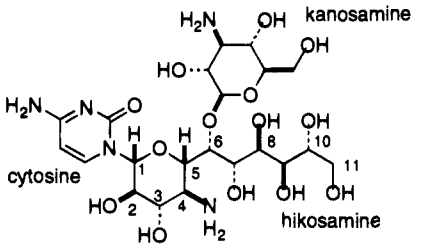
When all these data are taken together, some useful *empirical*, albeit oversimplified, correlations emerge, which allow for reliable stereochemical predictions even for osmylations of structurally complex substrates by carefully examining the local environment of the preferred conformation imposed by an allylic oxygen substituent. For nonconjugated, monosubstituted, and *Z*- or *E*-1,2-disubstituted olefins bearing an allylic oxygen substituent, the "*anti*" attack on the *H*-eclipsed conformer **34** originally advanced by Kishi is consistent with the general trends of diastereoselection reported in the literature. For 1,1-disubstituted or *E*-1,1,2-trisubstituted olefins, 1,2-allylic strain would result in a different preferred conformation, the "inside-alkoxy" conformer **36A**. This model accounts for the considerable enhancement of diastereoselectivity observed by Evans, when the size difference between the allylic substituent OX (or OH) and L is maximized.[27] The stereochemistry of osmylation of *E*- and *Z*-α,β-unsaturated carbonyl compounds can best be accommodated by Danishefsky's analysis based on stereoelectronic considerations, as well as solid-state conformations established by X-ray structure determinations.[140] Thus, synplanar and antiperiplanar conformers **62** and **61** are proposed for *E*- and *Z*-substrates, respectively. In view of the apparent stereochemical vagaries in the osmylation of *Z*-α,β-unsaturated carbonyl compounds, circumspection is required in predicting the stereochemical outcome, but *syn* diols might well be the major isomers.

G. Synthetic Applications

1. (−)-Hikizimycin

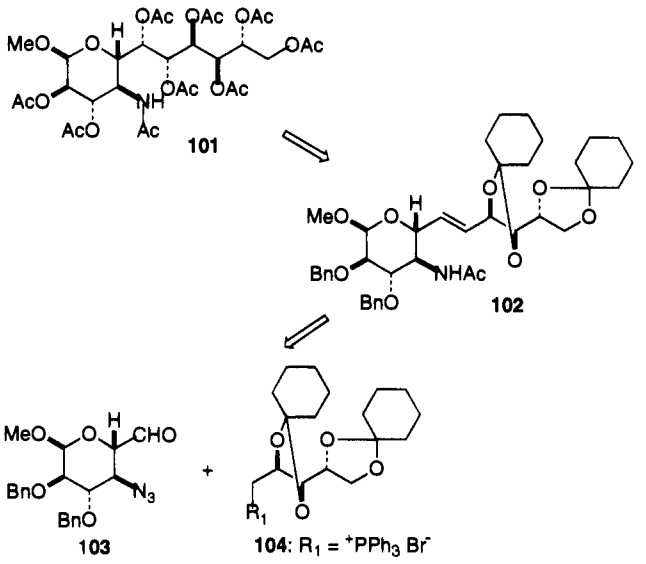
One of the early applications of stereocontrolled dihydroxylations in natural product synthesis was

reported by Secrist in a synthesis of a protected derivative **101** of hikosamine, the 4-aminoundecose portion of hikizimycin (**100**).[46] Hikizimycin (**100**)

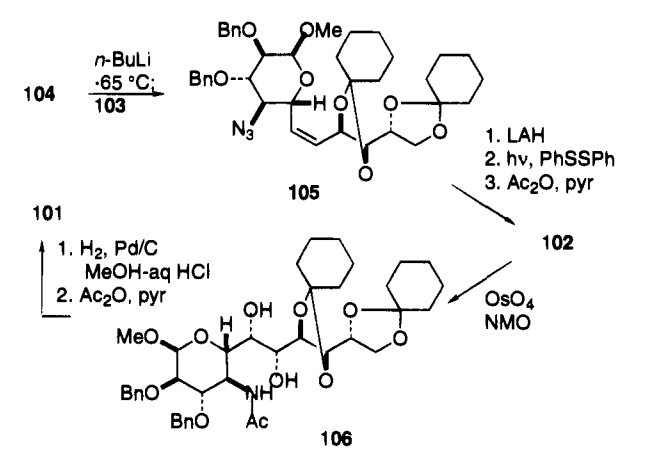


hikizimycin (anthelmycin)
(100)

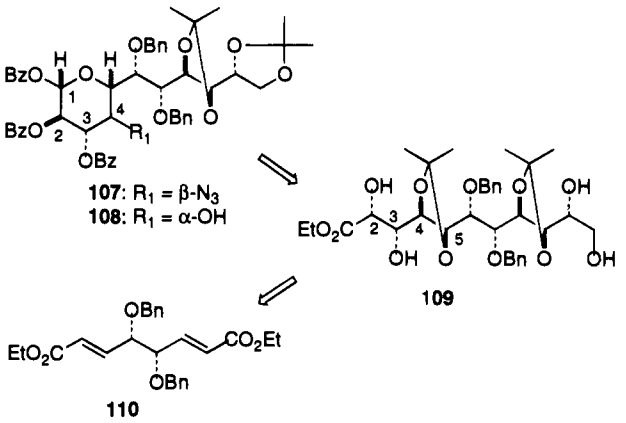
(also named anthelmycin), isolated from *Streptomyces longissimus* and *Streptomyces A-5*, is a powerful anthelmintic agent.[141] A key step involved the formation of the C-6–C-7 double bond by the Wittig olefination of aldehyde **103** with the carbohydrate phosphonium salt **104**. Dihydroxylation of the *E*-olefin **102** should proceed with excellent stereoselectivity, inasmuch as the two allylic stereocenters reinforce each other's directive effect.



Generation of the ylide from **104** (1 equiv of *n*-BuLi, 2:1 THF–HMPA, −65 °C), followed by addition of aldehyde **103**, gave exclusively *Z*-olefin **105** in 50% yield. Subsequent azido reduction ($LiAlH_4$), followed by isomerization (*hν*, PhSSPh, cyclohexane), gave a 3:2 mixture of the *Z*- and *E*- olefins. Chromatographic separation and *N*-acetylation afforded pure **102**. Subsequent osmylation under catalytic conditions produced diol **106** as a sole isomer in 78% yield. Global deprotection of the benzyl and cyclohexylidene groups was then accomplished by hydrogenation in acidic methanol. Finally, peracetylation furnished methyl peracetyl-α-hikosaminide (**101**) in 47% overall yield.[142]

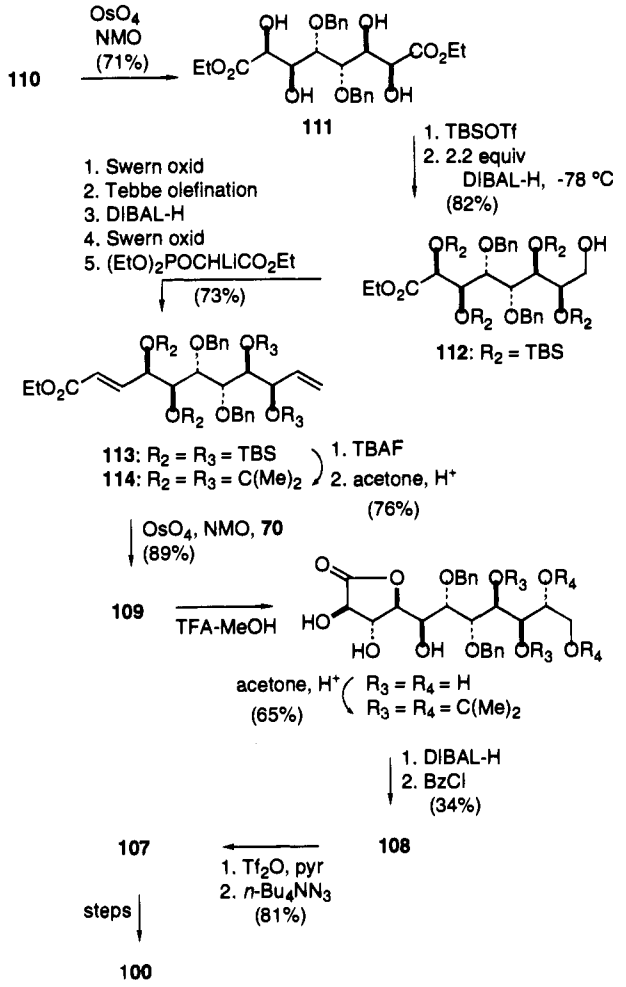


Recently, Schreiber described a two-directional chain synthetic strategy, in which the nascent chain is simultaneously homologated at both termini, in



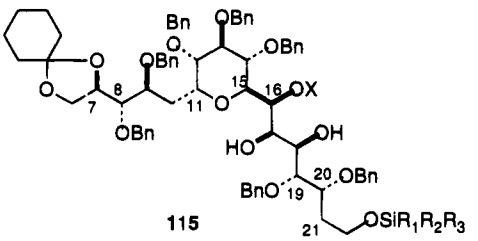
an elegant synthesis of (−)-hikizimycin (**100**), as wel l as a suitably protected hikosamine derivative **107**.[70] The key feature lies in replacement of the C-4 amino group with a hydroxyl group with inversion of configuration and recognition of the C_2-symmetry element present in the resulting C-2–C-11 fragment **109**. The latter in turn was prepared from bis-allyl ester **110** by a two-directional synthesis employing two sets of olefination-osmylation steps.

Bis-osmylation of the starting material **110**, which was prepared in two steps from L-(+)-diethyl tartrate, afforded tetrol **111** with high selectivity (see Table 9, entry 5). After conversion of **111** to a tetrasilyl ether, terminus differentiation of the C_2-symmetric chain was achieved by regioselective DIBAL–H (2.3 equiv) reduction at −78 °C to give monoalcohol **112**. The undecose chain of hikosamine was then constructed sequentially in both directions to produce ester **113**. Unfortunately, the inherent *anti* selectivity in bis-osmylation of **113** was shown to be marginal. However, after the TBS protecting groups were replaced by acetonides, Sharpless asymmetric dihydroxylation of the resulting bis-acetonide **114** in the presence of DHQ–CLB (**70**)[89,90] provided tetrol **109** in good overall diastereoselectivity. Acid-catalyzed γ-lactonization, followed by selective ketalizations, DIBAL–H reduction and selective benzoylations, then gave monoalcohol **108**. With the C4 hydroxyl group differentiated, the requisite nitrogen substituent was introduced to provide azide **107**. Finally, a total synthesis of (−)-hikizimycin (**100**) was accomplished by subsequent introduction of the cytosyl group, followed by glycosidation employing the sulfoxide activation method of Kahne.[143]



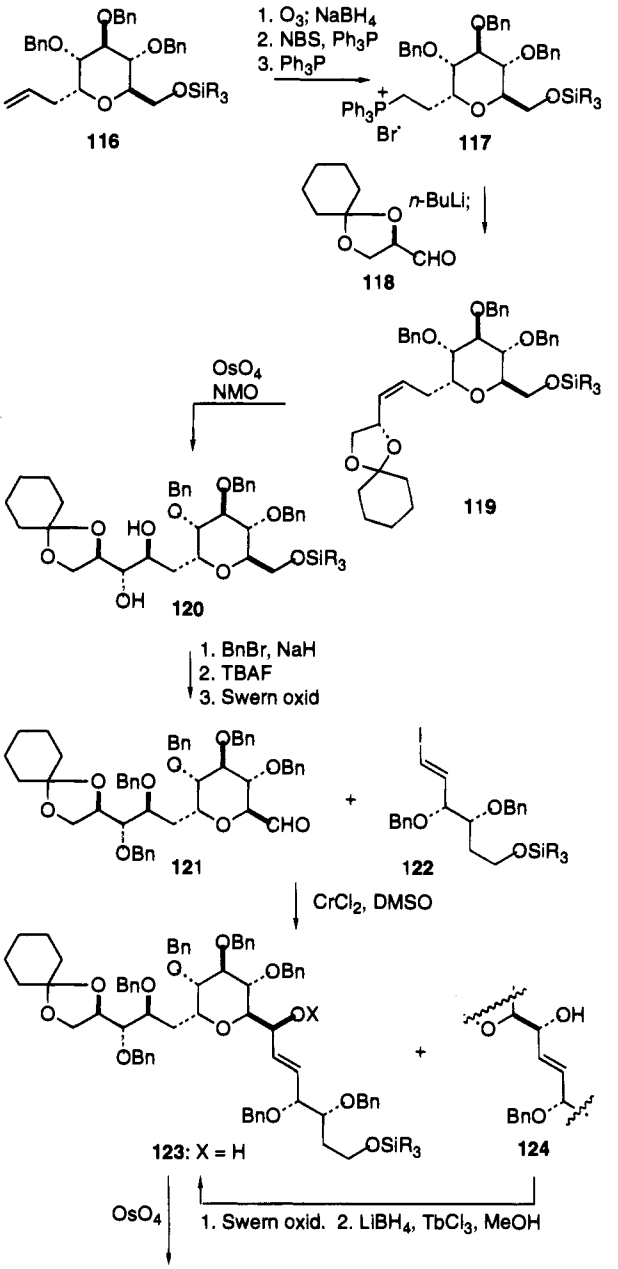
2. Palytoxin

The olefination–dihydroxylation sequence was also employed by Kishi in his synthesis of palytoxin.[144,145] For example, the C-7–C-22 segment **115** bearing a



challenging stereochemical array was prepared from the *C*-glycoside **116**, derived from tri-*O*-benzyl-1,6-anhydro-D-glucose.[146] Olefin **116** was first converted into the phosphonium salt **117** in three steps, and subsequent Wittig olefination with *O*-cyclohexylidene-D-glyceraldehyde (**118**) afforded the *Z*-olefin **119** in high yield. Osmylation then gave the desired *anti* diol **120** in 10:1 selectivity.

Next the right-hand side chain was introduced by the chromium(II)-mediated addition of *E*-iodoolefin **122** to aldehyde **121**.[147] Under carefully controlled reaction conditions, a 2:5 mixture of adducts **123** and **124** was obtained in greater than 80% yield. The undesired alcohol **124** was then recycled by the oxidation–reduction sequence. Interestingly, in the



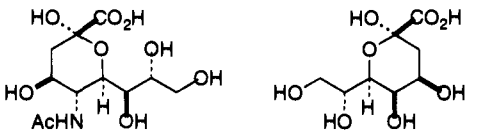
123	115 (β,β-diol)	+	125 (α,α-diol)
a: X = H	1	:	3
b: X = Ac	4	:	1
c: X = $COCF_3$	5	:	1
d: X = COC_6H_5	10	:	1

latter Luche reduction[148] there exists a bell-shape correlation between the stereoselectivity and the size of a lanthanide.[149] The highest (8:1) selectivity was obtained with $TbCl_3$; $TbCl_3 > EuCl_3 \approx HoCl_3 > CeCl_3 \approx ErCl_3 > LaCl_3$.

Finally, catalytic osmylation of alcohol **123a** yielded a 1:3 mixture of **115a** and **125a**. Since the major product **125a** had the undesired stereochemistry at the C-17 and C-18 positions, the free hydroxyl group of alcohol **123a** was acylated so as to minimize its directive effect. Indeed, dihydroxylations of all acyl derivatives **123b–d** gave rise to the desired diols **115b–d** in good selectivities. The best diastereofacial selection was achieved with the benzoate **123d** in over 80% yield.

3. N-Acetylneuraminic Acid

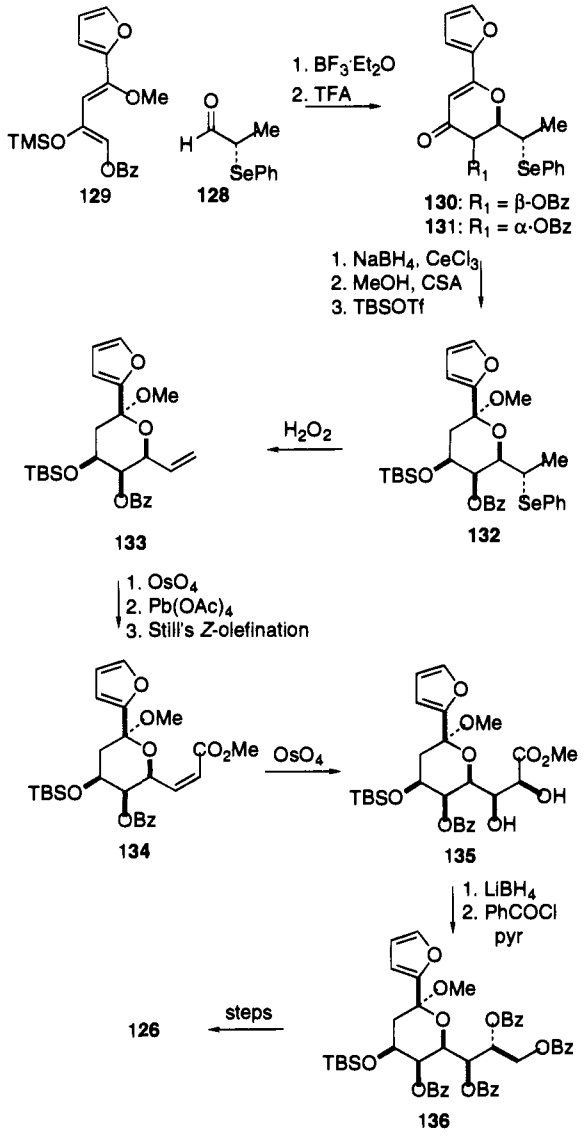
Recently, elucidation of the biological functions of neuraminic or sialic acids has been an active area of research. Danishefsky reported stereoselective syntheses of *N*-acetylneuraminic acid (Neu5Ac, **126**) and 3-deoxy-D-manno-2-octulosonic acid (KDO, **127**) in enantiomerically pure form.[43] In each compound the



N-acetylneuraminic acid
126

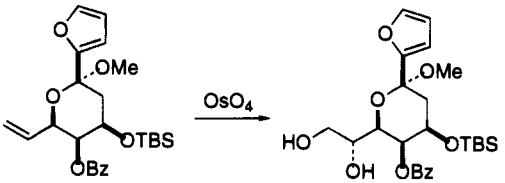
KDO
127

stereocontrolled construction of the side chain was accomplished by osmylation with excellent selectivity. The starting material was found in the *S*-selenoaldehyde **128**.[150] Cyclocondensation with diene **129** in the presence of $BF_3{\cdot}Et_2O$ at −78 °C afforded a 5:1 mixture of *cis*- and *trans*-dihydropyrans (**130** and **131**) in 76% yield. Luche reduction of **130**, followed by addition of methanol through the action of CSA and subsequent TBS protection, gave rise to TBS ether **132**. Oxidative elimination of the phenylseleno



function then afforded olefin **133** in 81% overall yield from **130**. In order to introduce the requisite diol functionality in the correct configuration, the olefin **133** was converted (67%) to the *Z*-enoate **134** by employing Still's procedure.[151] As described in Table 11, entry 2, osmylation proceeded to furnish diol **135** with high syn selectivity in 90% yield. Reduction of the ester function and perbenzoylation then gave the tetrabenzoate **136** (80%). Subsequent manipulations of the functional groups including the conversion of the furan ring to the carboxylic acid, a benzoyl migration triggered by TBS deprotection, and the installation of the C-5 amino group as an azide, afforded Neu5Ac (**126**).

Osmium tetroxide hydroxylation of *ent*-**133** proceeded smoothly to furnish the diol **137** as a single isomer (cf. Table 5, entry 15), which was then successfully converted to the natural enantiomer of KDO (**127**).



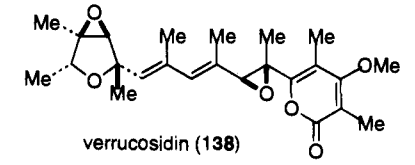
ent-**133**

137

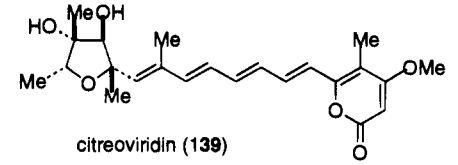
4. α-Pyrone Polyene Mycotoxins

Conspicuously missing in the synthetic applications is osmylation of 1,3-dienes,[152] which offers considerable utility in one-step synthesis of polyhydroxylated compounds containing up to four additional contiguous stereocenters. Some years ago we initiated synthetic programs which built upon the regio- and stereoselective osmylation of 1,3-dienes. As target compounds we chose a group of α-pyrone polyene mycotoxins, most of which have been shown to function as potent inhibitors of mitochondrial F_1,F_0-ATPase activity. They have found use in biochemical studies of oxidative phosphorylation. These polyketide-derived fungal toxins include verrucosidin (**138**), citreoviridin (**139**), citreoviral (**140**) (**138**–**140**, Chart 1), aurovertins A–E (**141**), citreoviridinol

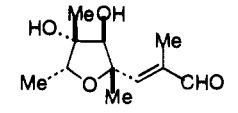
Chart 1



verrucosidin (**138**)

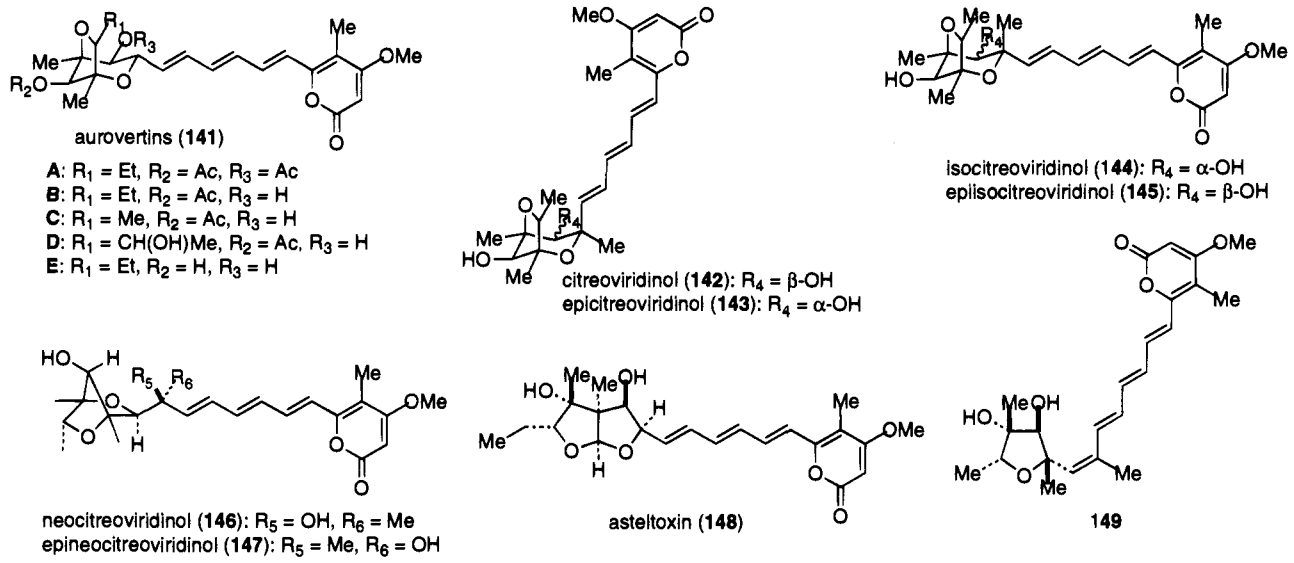


citreoviridin (**139**)



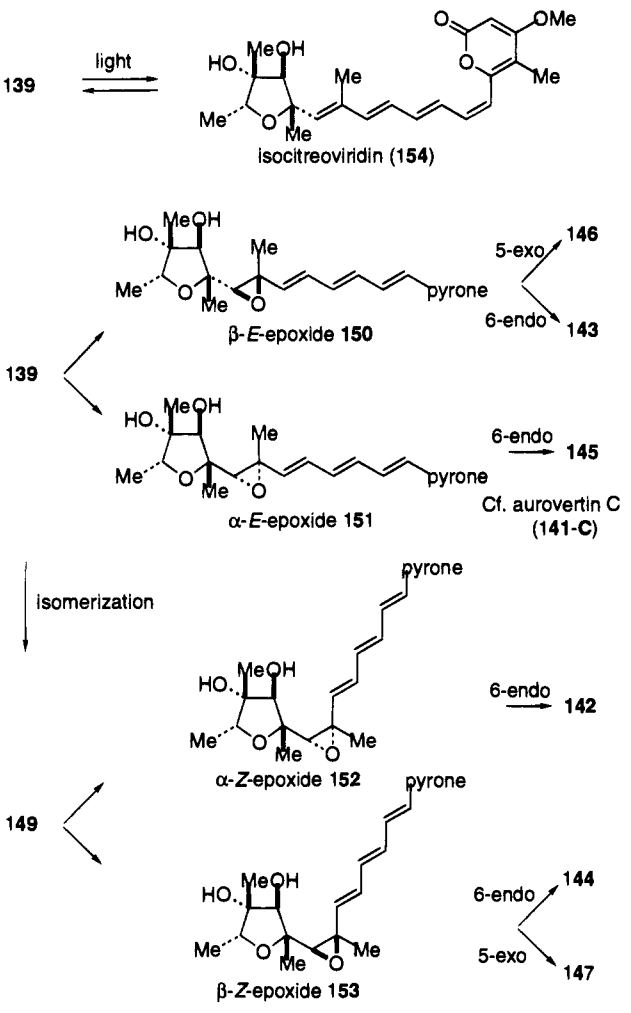
citreoviral (**140**)

Chart 2



(**142**), epicitreoviridinol (**143**), isocitreoviridinol (**144**), epiisocitreoviridinol (**145**), neocitreoviridinol (**146**), epineocitreoviridinol (**147**), and asteltoxin (**148**)[153-155] (**141**–**149**, Chart 2).

Inspection of these structures shows the close structural relationship between citreoviridin (**139**) and the metabolites **141**–**147**. Citreoviridin (**139**) undergoes light-induced isomerization to afford isocitreoviridin (**154**), which no longer shows any inhibitory activity of membrane-bound F_1-ATPase.[156] On the other hand, the putative biosynthetic intermediate **149** (Chart 2), the *Z*-isomer of citreoviridin, has not been isolated as yet. In any event, it is hardly surprising that all of the previous synthetic studies of this family of interesting mycotoxins have been directed at citreoviridin (**139**) and/or citreoviral (**140**) as the common advanced precursors to compounds **141-147**.[157-160]



Citreoviridin (**139**) is formed from a C-18 polyketide and five C_1 units derived from methionine. On the basis of elegant ^{18}O isotope incorporation studies, Vleggaar has further shown that a monooxygenaseis involved in the formation of the tetrahydrofuran subunit of **139**, and proposed a biosynthetic pathway involving the bisepoxide **155**.[154,161-163] As attractive as Vleggaar's original biosynthetic postulate is, the epoxide function present in the tetrahydrofuran moiety **158** of verrucosidin (**138**) cannot be easily accommodated. Although **138** and **139** were isolated from different microorganisms, their closely related structural similarity suggests a common biosynthetic pathway in the formation of the tetrahydrofuran moieties. Thus, we proposed a slight modification of Vleggaar's hypothesis, and invoked the intermediacy of the 2,5-dihydrofuran **159**, which in turn would be derived from rearrangement of the vinyl epoxide **160** (or **161**)[164] (Scheme 1).

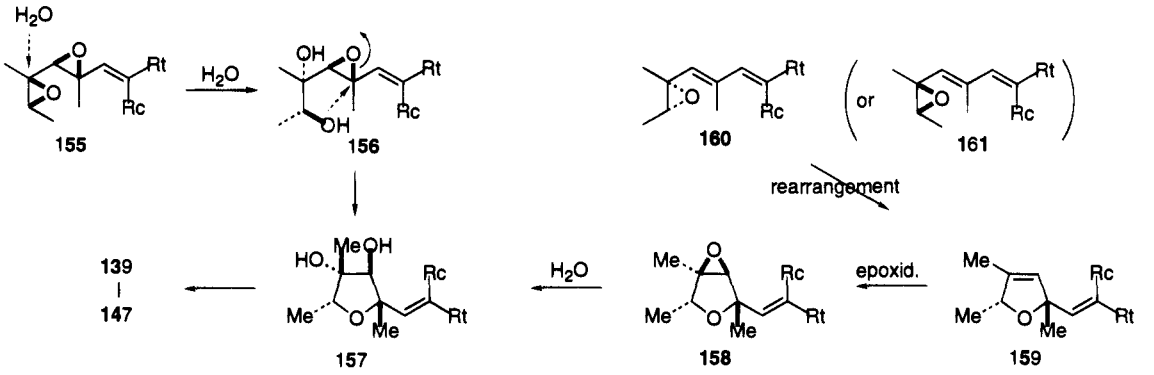
Consequently, we felt that a unified synthetic strategy for preparing these mycotoxins (**138**–**147**) could be evolved from the tetrahydrofuran subunit **158** of verrucosidin (**138**). An acid-catalyzed ring opening of the epoxide function would give rise to diol **157**. Subsequent introduction of an epoxide functionality into the side chain would lead to the remaining metabolites **141**–**147**. Hence we chose verrucosidin (**138**) as our first synthetic target.

In our synthetic planning, we decided at the outset to eschew our postulated biosynthetic precursor **159** as the key synthetic intermediate. We were concerned that the epoxidation step would probably suffer from poor stereoselectivity. Indeed, Klein[165] and Marshall[166] have reported that *m*-CPBA or

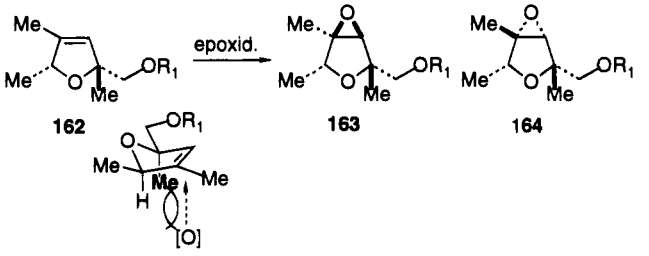
Scheme 1

(a) Vleggaar's biosynthetic postulate for **139**.

(b) Our modification of Vleggaar's biosynthetic postulate.

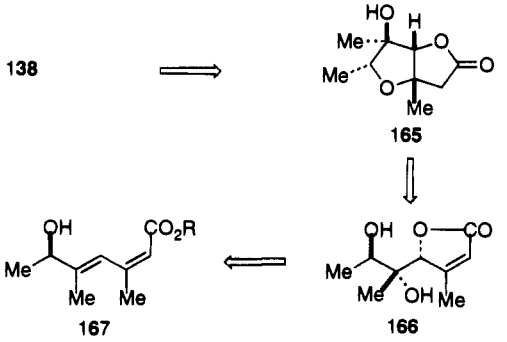


transition metal-catalyzed epoxidation of **162a–f** results in primarily the undesired diastereomer.



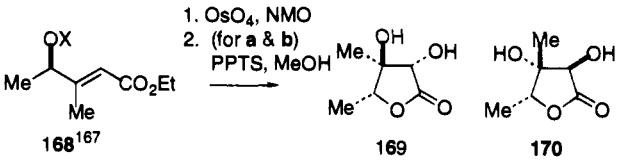
a: R_1 = H	*m*-CPBA, CH_2Cl_2, rt	1	:	20
	t-BuOOH, $(acac)_2MoO_2$ PhH, reflux	1	:	20
b: R_1 = Ac	*m*-CPBA, CH_2Cl_2, rt	1	:	2
a: R_1 = H	*m*-CPBA, CH_2Cl_2,0 °C	1	:	9
c: R_1 = TBS	" "	1	:	3.8
d: R_1 = DPS	" "	1	:	1.9
e: R_1 = TIPS	" "	1	:	1.9
f: R_1 = MMTr	" "	1	:	1.6

It occurred to us that an ideal precursor to verrucosidin (**138**) could be found in the bicyclic lactone **165**, where all four contiguous stereocenters are imbedded in the correct relative configuration. The bicyclic lactone should be readily available from internal Michael reaction of butenolide **166**, which in turn would be prepared regio- and stereoselectively by osmylation of the ϵ-hydroxy-*Z*,*E*-diene ester **167**.



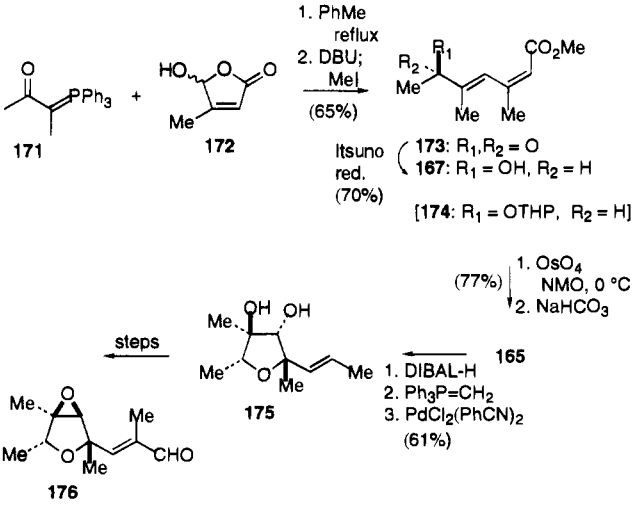
Regioselective osmylation was expected to take place at the distal C=C bond from the ester functionality. In addition, dihydroxylation should be accompanied by the butenolide formation, which would allow further elaboration in a stereocontrolled fashion. Finally, excellent diastereofacial selectivity was anticipated, as osmylation of *E*-1,1,2-trisubstituted olefins proceeds in a stereoregular fashion (see section III.B).

In a preliminary study, diastereocontrol in dihydroxylation (catalytic conditions) was first examined with *E*-α,β-unsaturated esters **168a–c**.[167] The diastereoselectivity was 10:1 for one tetrahydropyranyl diastereomer, and 8:1 for the other. In both cases, the resulting diols were converted smoothly by PPTS (in MeOH) to give lactone **169** as the major product. Interestingly, osmylation of the free alcohol **168c** gave a single lactone, which was identical to the major product **169**. As noted in section II.B., our results are in accord with Evans' observation that diastereoselectivity is enhanced by maximizing the size difference between the allylic substituent OX and the methyl group.[27]



a: X = THP	10	:	1
b: X = THP'	8	:	1
c: X = H	1	:	0

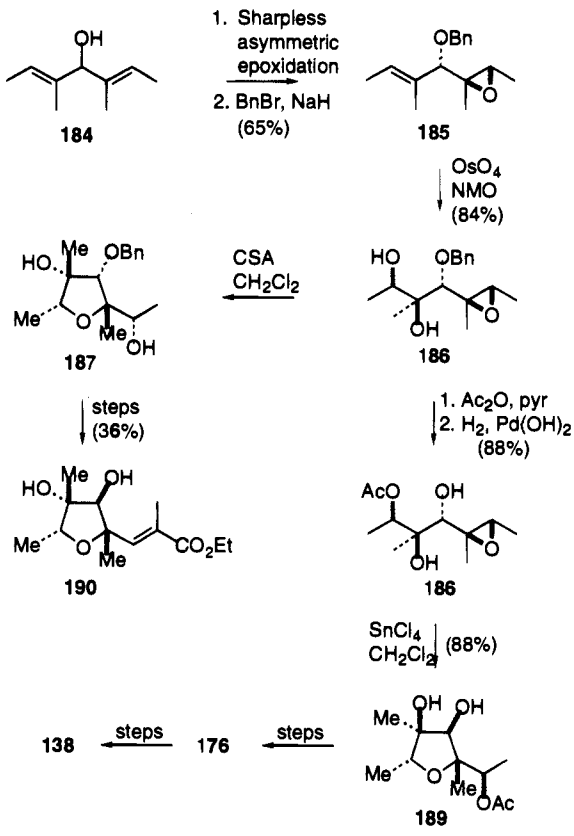
The dihydroxylation substrate **167** was readily prepared in enantiomerically pure form by the Wittig condensation of hydroxybutenolide **172** and ketophosphorane **171**, followed by methylation and Itsuno



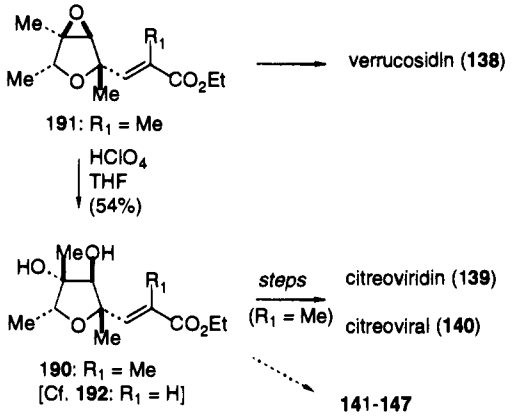
BH_3 reduction of the prochiral dienone **173** in the presence of (*S*)-diphenylvalinol.[168] The pivotal OsO_4 dihydroxylation gave the desired butenolide **166** as a single isomer, which was then converted (77% overall) to the lactone **165** after treatment with $NaHCO_3$. As was the case with **168a-c**, the (diastereomeric) THP ethers **174** gave lower selectivity in osmylation: one diastereomer gave a 5:1 diastereofacial selectivity, while a 2:1 ratio was found for the other. The lactone **165** was then converted by a standard method to give aldehyde **176**.

After several attempts to couple aldehyde **176** with a pyrone segment were unsuccessful, we decided to adopt the elegant coupling protocol utilized by Takano and co-workers[169] in their first synthesis of verrucosidin (vide infra). Enantiomerically pure ketone **177** was prepared from 6-ethyl-4-methoxy-3,5-dimethyl-α-pyrone (**178**). Aldol condensation of pyrone **177** and aldehyde **176**, followed by dehydration to give dienone **180**, and subsequent desilylation furnished α-hydroxy ketone **181**. Both LAH or $NaBH_4$–$CeCl_3$ reduction of **181** suffered from poor stereoselectivity, affording inseparable 1:2 and 3:2 mixtures of **182** and **183**, respectively. Ultimately, stereoselective (7:1) reduction was achieved by use of an acyloxyborohydride derived from $NaBH_4$ and *d*-tartaric acid in the presence of a lanthanide.[170,171] As noted previously by Kishi in his synthetic studies of palytoxin,[149] we also found that the stereoselectivity in reduction is affected by varying the effective ion radius of a lanthanide: $SmCl_3$ (7:1) > $PrCl_3$ (5:1) > $CeCl_3$ (3:1). Finally, treatment of the 7:1 mixture of diols **182** and **183** with Martin's sulfurane[172] stereospecifically afforded verrucosidin (**138**) and its C-7 epimer in the identical ratio.[173]

Prior to the completion of our own synthetic studies, Takano and co-workers reported a first total synthesis of verrucosidin, as well as of citreoviridin.[169] As summarized below, their syntheses started from divinylcarbinol **184**. Sharpless asymmetric epoxidation, followed by benzylation and stereoselective (>15:1) dihydroxylation (Table 13, entry 1) of the resulting allylic ether **185**, afforded diol **186**. Upon treatment with CSA, **186** underwent exo-cyclization to afford tetrahydrofuran **187** in 84% yield, whereas the corresponding acetate **188** was treated with $SnCl_4$ to produce **189**. Tetrahydrofuran **187** was then converted to diol **190**, which represents a formal synthesis of citreoviral and citreoviridin.[158] On the other hand, tetrahydrofuran **189** was successfully converted via the aldehyde **176** to verrucosidin (**138**).

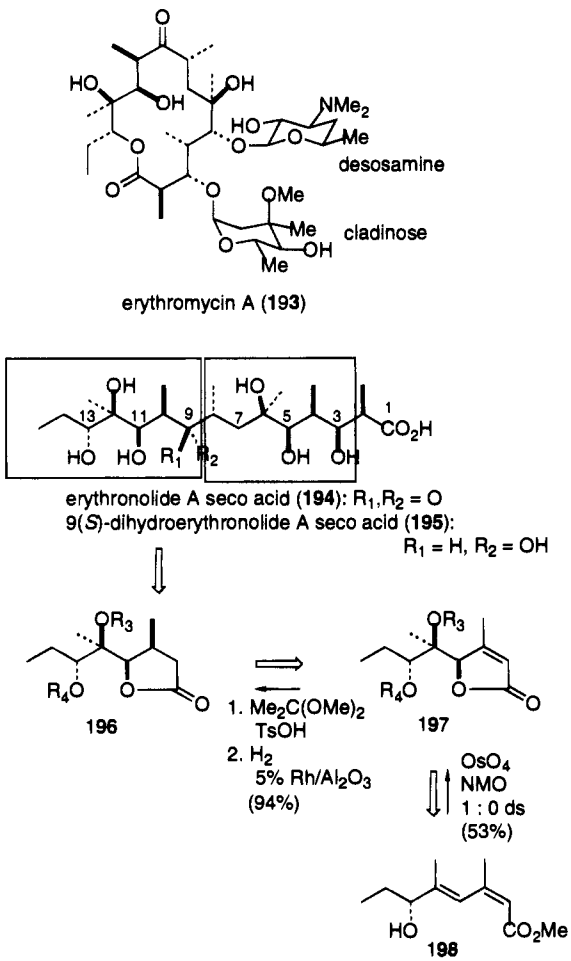


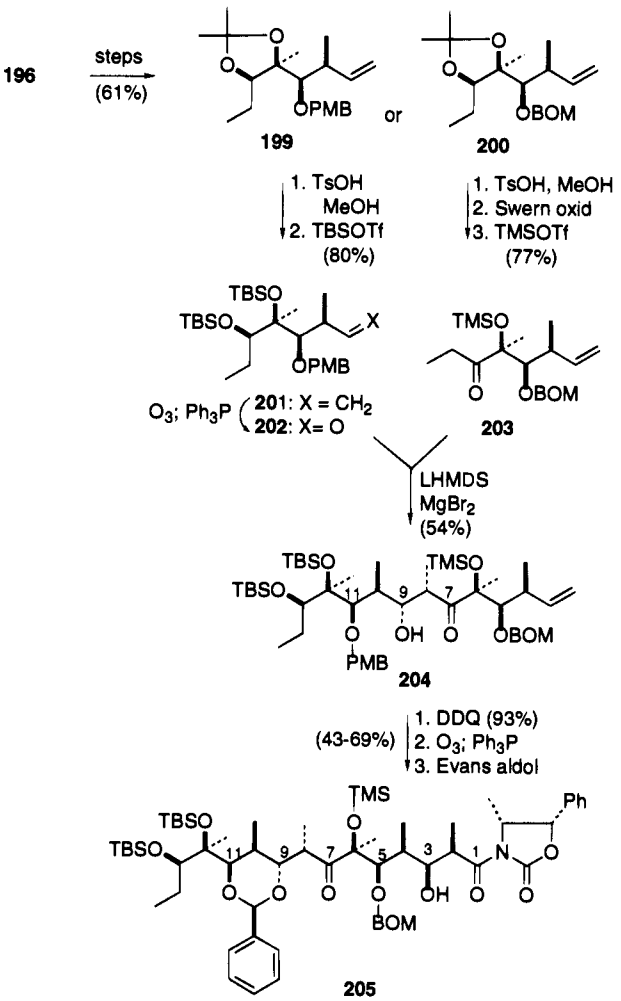
In following up our biosynthetic hypothesis, treatment of epoxide **191** (cf. **176**) with aqueous $HClO_4$ in THF stereoselectively gave the diol **190**, which was then converted to citreoviridin (**139**) and citreoviral (**140**).[164,174] In summary, we have developed a unified synthetic strategy for the citreoviridin family of the mycotoxins **138**–**147**, which centers around the regio- and stereoselective dihydroxylation of the ε-hydroxy-*Z*,*E*-diene ester **167**.



The osmylation-based "butenolide-template" tactic, which we developed for a total synthesis of verrucosidin (**138**), should also be useful in the synthesis of other polyoxygenated natural products.[175] In particular, analogous stereoselective dihydroxylation of an ϵ-hydroxy-*Z*,*E*-diene ester would offer an efficient solution to the considerable synthetic challenges posed by the presence of the two tertiary stereocenters in the aglycon of erythromycin A (**193**).[176-179] In our retrosynthetic analysis for the seco acids **194** and **195** of erythronolide A and 9(*S*)-dihydroerythronolide A, respectively, we also recognized the possibility of utilizing the common synthetic intermediate **196**. Enantiomerically pure lactone **196** should be readily available by stereoselective osmylation of diene **198**, followed by catalytic hydrogenation. Indeed, osmylation of the hydroxy diene ester **198**, a homolog of our starting material **167** for verrucosidin (**138**), gave butenolide **197** as a single isomer. The fourth contiguous stereocenter in **196** was then introduced stereoselectively by catalytic hydrogenation of the butenolide **197**. Not surprisingly, initial conversion of the polar hydroxy groups to the acetonide [R_3, R_4 = $C(CH_3)_2$] was necessary to achieve highly stereoselective (>15:1) hydrogenation to afford acetonide **196** in multigram scale.[180]

The key common intermediate **196** was then converted to the two compounds **202** and **203**. Aldol condensation of these segments in the presence of $MgBr_2$ afforded the aldol product **204** in 10:1 diastereoselectivity. Subsequent standard transformations afforded the acetal **205**, the fully assembled backbone of 9(*S*)-erythronolide A.[181]

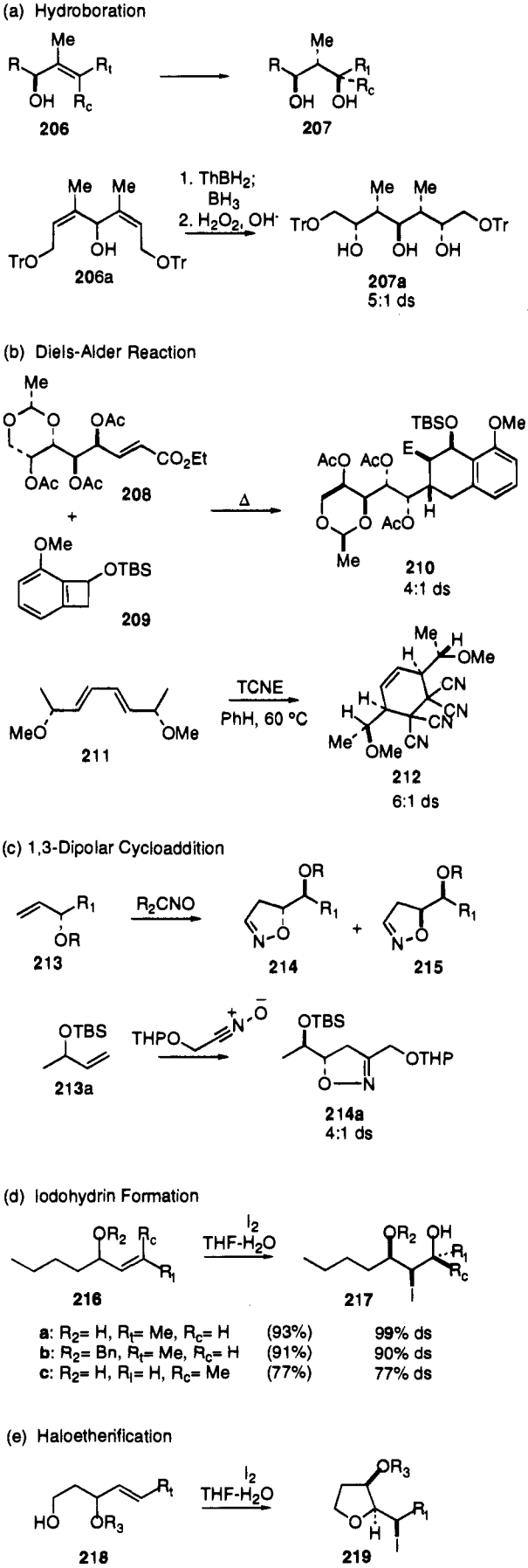




IV. Stereochemical Control in Other Transformations

Acyclic stereocontrol by an allylic alkoxy substituent has also been achieved in other types of transformations. For example, they include (a) hydroboration of allylic alcohols **206** to afford 1,3-diols **207**;[182,183] (b) Diels–Alder reactions where an allylic oxygen substituent was placed either in a dienophile (e.g., **208**) or a diene (e.g., **211**) partner;[184,185] (c) nitrile oxide or nitrone cycloadditions to allylic alcohols and ethers **213**;[186-189] (d) iodohydrin formation

from (*Z*)- or (*E*)-allylic alcohols **216**, which has been shown to take place with high regio- and stereoselectivity to produce **217**;[190] and (e) a large number of diastereoselective intramolecular reactions (halolactonization, haloetherification, amidohalogenation, etc.) of allylic alcohols and ethers **218** to give **219**.[191-193]



In conclusion, numerous acyclic allylic alcohols and related systems have been shown to undergo a wide variety of transformations with synthetically useful levels of stereochemical control. Future work will certainly result in many new methods for stereoselectively functionalizing the allylic alcohol systems in an efficient synthesis of bioactive natural products.

V. Acknowledgments

One of us (J.K.C.) is greatly indebted to his group members, past and present, whose hard work and dedication helped to crystallize ideas. We thank the National Institutes of Health for generous financial support (GM35956) and a research career development award (GM00575). We also thank Drs. Drury Caine, Elli Hand, and Steve Woski of this department for their critical reading and helpful suggestions.

VI. References

(1) For an excellent review on stereochemical control by acyclic "reagent-controlled" and "substrate-controlled" approaches, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1-30.

(2) See, inter alia: (a) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129-3131. (b) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867-869. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (d) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539-1546. (e) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856-5858.

(3) For recent reviews on enantioselective reduction, see: (a) Haubenstock, H. *Top. Stereochem.* **1983**, *14*, 231-300. (b) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553-1561. (c) Singh, V. K. *Synthesis* **1992**, 605-617. (d) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16-24. (e) Noyori, R. *Chemtech* **1992**, *22*, 360-367. (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784. (g) Dhar, R. K. *Aldrichimica Acta* **1994**, *27*, 43-51.

(4) For an excellent review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

(5) See, inter alia: (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 503-572. (b) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864-4872 and references cited therein.

(6) (a) Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167-203. See also: (b) Smith, Z.; Carballo, N.; Wilson, E. B.; Marstokk, K.-M.; Møllendal, H. *J. Am. Chem. Soc.* **1985**, *107*, 1951-1957. (c) Wiberg, K. B.; Schreiber, S. L. *J. Org. Chem.* **1988**, *53*, 783-785 and references cited therein. (d) For simple carbonyl compounds such as propanal and 2-butanone, the syn rotamer is shown to be the lowest energy conformation.

(7) Johnson, F. *Chem. Rev.* **1968**, *68*, 375-413.

(8) There have appeared many synthetic studies based on conformational preference of acyclic allylic systems. For general reviews in this area, see: (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860. (b) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1-72.

(9) (a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259-260. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888.

(10) For related examples of stereoselective hydroboration reactions, see: (a) Matsumoto, T.; Hosoda, Y.; Mori, K.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3156-3160. (b) Heathcock, C. H.; Jarvi, E. T.; Rosen, T. *Tetrahedron Lett.* **1984**, *25*, 243-246. Compare: (c) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577-4580.

(11) Houk proposed a refinement of Kishi's model: Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257-2274.

(12) (a) Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3363-3369 and nine preceding papers. (b) Fleming, I.; Lewis, J. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3257-3266 and footnote 28. Compare: (c) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643-1645.

(13) Zbiral, E.; Schonauer, K. *Tetrahedron Lett.* **1983**, *24*, 573-576.

(14) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 96–100. See also: (b) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435–1437. (c) Tomioka, K.; Yasuda, K.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 3247–3250. (d) Shirai, F.; Gu, J.-H.; Nakai, T. *Chem. Lett.* **1990**, 1931–1934.

(15) (a) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723–6724. (b) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274–1280. (c) Danishefsky, S. J.; DeNinno, M. P.; Schulte, G. *J. Org. Chem.* **1987**, *52*, 3171–3173. (d) DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925–3929. (e) Lessard, J.; Saunders, J. K.; Phan Viet, M. T. *Tetahedron Lett.* **1982**, *23*, 2059–2062. (f) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647–3650. Compare: This spatial arrangement is closely related to the Felkin-Anh model for nucleophilic addition to a carbonyl group: Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162.

(16) Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775–3776.

(17) In 1957 Henbest reported the first example of the stereodirecting effect by an allylic hydroxyl group in the epoxidation of 2-cyclohexen-1-ol. The observed stereochemical outcome can best be rationalized by hydrogen bonding between the hydroxyl group and the peracid. Subsequently the stereochemistry of the epoxidation of acyclic allylic alcohols was examined in detail by several groups. Progress in this area culminated in the discovery of Sharpless asymmetric epoxidation: Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Ley, S. V., Ed.; Pergamon: New York, 1991; Vol. 7, pp 389–432.

(18) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943–3946. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947–3950. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255.

(19) For clarity, diastereoselectivity is given in integers throughout this review. Moreover, unless specified by authors, selectivity greater than 20:1 is shown as 1:0.

(20) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. (b) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450. (c) We thank Professor K. Barry Sharpless for bringing this aspect to our attention.

(21) Compare: Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213–6215; *Tetrahedron Lett.* **1990**, *31*, 1741–1742.

(22) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468–481.

(23) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373–1378.

(24) (a) Kochetkov, N. K.; Dmitriev, B. A. Tetrahedron **1965**, *21*, 803–815. (b) Dmitriev, B. A.; Chernyak, A. Y.; Kochetkov, N. K. *Zh. Obshch. Khim.* **1971**, *41*, 2754–2760.

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

(26) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112–127.

(27) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698–1700.

(28) (a) Bernardi, A.; Beretta, M. G.; Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1985**, *50*, 4442–4447. (b) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 491–502.

(29) For recent reviews, see: (a) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1988**, *179*, 21–30. (b) Nakajima, M.; Tomioka, K.; Koga, K. *J. Synth. Org. Jpn.* **1989**, *47*, 878–888.

(30) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217–1225.

(31) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569–5575.

(32) Shimizu, M.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* **1987**, 689–690.

(33) (a) Hatakeyama, S.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1986**, *27*, 4485–4488. (b) Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791–5794.

(34) Atsuumi, S.; Nakano, M.; Koike, Y.; Tanaka, S.; Funabashi, H.; Hashimoto, J.; Morisha, H. *Chem. Pharm. Bull. Jpn.* **1990**, *38*, 3460–3462.

(35) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457–1464.

(36) Smith, D. B.; Wang, Z.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793–4808.

(37) Küfner, U.; Schmidt, R. R. *Liebigs Ann. Chem.* **1986**,1610–1620.

(38) Neunlist, S.; Rohmer, M. *J. Chem. Soc., Chem. Commun.* **1988**, 830–832.

(39) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *150*, 35–51.

(40) (a) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *158*, 81–89. (b) Brimacombe, J. S.; Hanna, R.; Bennett, F. *Carbohydr. Res.* **1985**, *135*, c17–c21.

(41) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1988**, *174*, 37–45.

(42) Tadanier, J.; Lee, C.-M.; Whittern, D.; Wideburg, N. *Carbohydr. Res.* **1990**, *201*, 185–207.

(43) Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929–3940.

(44) (a) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 823–828. (b) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2421–2426.

(45) Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88–96.

(46) Secrist, J. A., III; Barnes, K. D. *J. Org. Chem.* **1980**, *45*, 4526–4528.

(47) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S.; Bennett, F.; Taylor, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 815–821.

(48) (a) Babirad, S. A.; Wang, Y.; Kishi, Y. *J. Org. Chem.* **1987**, *52*, 1370–1372. (b) ref 22.

(49) Kumar, V.; Dev, S. *Tetrahedron* **1987**, *43*, 5933–5948.

(50) Wu, W.-L.; Wu, Y.-L. *J. Chem. Res. (Synop.)* **1990**, 112–113.

(51) Kang, S. H.; Kim, W. J. *Synlett* **1991**, 520–521.

(52) (a) Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424–5426. (b) Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T.; Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292–6302.

(53) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819.

(54) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772–3787.

(55) Prenner, R. H.; Binder, W. H.; Schmidt, W. *Liebigs Ann. Chem.* **1994**, 73–78.

(56) (a) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1987**, *168*, c5–c7. (b) Barnes, J. C.; Brimacombe, J. S.; Kabir, A. K. M. S.; Weakley, T. J. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3391–3397.

(57) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1989**, *111*, 2193–2204.

(58) (a) Brimacombe, J. S.; Kabir, A. K. M. S.; Taylor, I. D. *Carbohydr. Res.* **1985**, *140*, c9–c12. (b) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *152*, 335–338.

(59) (a) Jarosz, S. *Carbohydr. Res.* **1988**, *183*, 209–215. (b) Jarosz, S. *Carbohydr. Res.* **1992**, *224*, 73–81.

(60) Jefford, C. W.; Moulin, M.-C. *Helv. Chim. Acta* **1991**, *74*, 336–342.

(61) Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541–7544.

(62) Mukaiyama, T.; Anan, H.; Shiina, I.; Kobayashi, S. *Bull. Soc. Chim. Fr.* **1993**, 388–391.

(63) Marshall, J. A.; Seletsky, B. M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413–3420.

(64) Ichikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 907–908.

(65) Golebiowski, A: Jurczak, J. *Synlett* **1993**, 241–245.

(66) Wade, P. A.; Cole, D. T.; D'Ambrosio, S. G. *Tetrahedron Lett.* **1994**, *35*, 53–56.

(67) (a) Solladié, G.; Fréchou, C.; Hutt, J.; Demailly, G. *Bull. Chim. Soc. Fr.* **1987**, 827–836. (b) Solladié, G.; Fréchou, C.; Demailly, G. *Tetrahedron Lett.* **1986**, *27*, 2867–2870.

(68) Bisseret, P.; Rohmer, M. *J. Org. Chem.* **1989**, *54*, 2958–2964.

(69) Oishi, T.; Iida, K.-i.; Hirama, M. *Tetrahedron Lett.* **1993**, *34*, 3573–3576.

(70) (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9657–9659; **1992**, *114*, 2524–2536. (b) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563–566.

(71) Neff, D.-P.; Chen, Y.; Vogel, P. *Helv. Chim. Acta* **1991**, *74*, 508–516.

(72) Barnes, J. C.; Brimacombe, J. S.; McDonald, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1483–1489.

(73) (a) Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 642–643. (b) Lay, L.; Nicotra, F.; Pangrazio, C.; Panza, L.; Russo, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 333–338.

(74) Martin, O. R.; Szarek, W. A. *Carbohydr. Res.* **1984**, *130*, 195–219.

(75) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1988**, *44*, 6897–6902.

(76) (a) Mootoo, D. R.; Fraser-Reid, B. *J. Org. Chem.* **1987**, *52*, 4511–4517. (b) Mootoo, D. R.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 739–746.

(77) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

(78) Tabuchi, H.; Ichihara, A. *Tetrahedron Lett.* **1992**, *33*, 4933–4936.

(79) O'Leary, D. J.; Kishi, Y. *J. Org. Chem.* **1993**, *58*, 304–306.

(80) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201–5203.

(81) Gurjar, M. K.; Das, S. K.; Saha, U. K. *Tetrahedron Lett.* **1994**, *35*, 2241–2244.

(82) Burke, S. D.; Schoenen, F. J.; Nair, M. S. *Tetrahedron Lett.* **1987**, *28*, 4143–4146.

(83) It is interesting to speculate that additional erosion of selectivity would occur for the C-5 (benzoate) epimer compared to entry 12, since the equatorial substituent should more effectively shield the "*anti*" face. In fact, analogous examples can be found in Table 7, entries 8 and 10.

(84) Double Michael additions of these compounds also take place with excellent stereoselectivity: Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535.

(85) Gung, B. W.; Melnick, J. P.; Wolf, M. A.; Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 5609–5613.
(86) However, the reason for the enhanced selectivity with an increasing size for R_1 in entries 23 and 24 is not entirely clear.
(87) (a) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458–2459. (b) Hauser invoked the complexation between the oxygen of the sulfoxide and OsO_4 to account for the stereochemistry.
(88) (a) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459–2461. (b) Johnson, C. R. *Pure Appl. Chem.* **1987**, *59*, 969–974.
(89) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588. (c) McKee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.* **1991**, *70*, 47–53. (d) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125. (e) Jacobsen, E. N.; Markó, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737–739. (f) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (g) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265.
(90) For excellent and comprehensive reviews on catalytic asymmetric dihydroxylations, see: (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 2483–2547. (c) We thank Professor Sharpless for providing us with preprints of both manuscripts.
(91) For other asymmetric dihydroxylations, see: (a) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131–134. (b) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951–3954. (c) Reference 21. (d) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834–5835. (e) Corey, E. J.; Jardin, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243–9244.
(92) Morikawa, K.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5575–5578.
(93) (a) Brimacombe, J. S.; McDonald, G. *Carbohydr. Res.* **1989**, *194*, c4–c7. (b) Brimacombe, J. S.; McDonald, G.; Rahman, M. A. *Carbohydr. Res.* **1990**, *205*, 422–427.
(94) (a) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096–7099. (b) Kim, N.-S.; Kang, C. H.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3489–3492.
(95) Compare: (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571. (b) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1994**, *59*, 949–951.
(96) For a general review of permanganate oxidations in organic synthesis, see: (a) Fatiadi, A. J. *Synthesis* **1987**, 85–127. Compare: (b) Bhushan, V.; Rathore, R.; Chandrasekaran, S. *Synthesis* **1984**, 431–433.
(97) Howarth, G. B.; Szarek, W. A.; Jones, J. K. N. *J. Chem. Soc. (C)* **1970**, 2218–2224.
(98) Compare: House, H. O. In *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 275–278 and references cited therein.
(99) (a) Walba, D. M.; Przybyla, C. A.; Walker, C. B., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 5624–5625 and references cited therein. (b) Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4396–4397.
(100) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E.-M. *J. Chem. Soc., Chem. Commun.* **1979**, 918–920.
(101) Klein, E.; Rojahn, W. *Tetrahedron* **1965**, *21*, 2353–2358.
(102) Bernotas, R. C. *Tetrahedron Lett.* **1990**, *31*, 469–472.
(103) Moran, E. J.; Tellew, J. E.; Zhao, Z.; Armstrong, R. W. *J. Org. Chem.* **1993**, *58*, 7848–7859.
(104) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227–228. (b) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236–2240. (c) Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041–5044.
(105) (a) Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 1592–1602. (b) Dyong, I.; Friege, H.; Luftmann, H.; Merten, H. *Chem. Ber.* **1981**, *114*, 2669–2680.
(106) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961–5968.
(107) Rehders, F.; Hoppe, D. *Synthesis* **1992** 865–870.
(108) Koskinen, A. M. P.; Chen, J. *Tetrahedron Lett.* **1991**, *32*, 6977–6980.
(109) Glänzer, B. I.; Györgydeák, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 343–369.
(110) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979–2984.
(111) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990–6995.
(112) Krysan, D. J.; Rockway, T. W.; Haight, A. R. *Tetrahedron: Asymmetry* **1994**, *5*, 625–632.
(113) These stereochemical outcomes of Sharpless asymmetric dihydroxylations are unexpected, especially because (*E*)-1,2-disubstituted olefins are generally amenable to Sharpless asymmetric dihydroxylations using $(DHQD)_2$–PHAL or $(DHQ)_2$–PHAL as the chiral ligand.
(114) Schröder, M. *Chem. Rev.* **1980**, *80*, 187–213.
(115) (a) Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399–3402. (b) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217–1226.
(116) Alternatively, steric arguments could be made to rationalize these interesting results.
(117) (a) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754–2755. (b) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438–2440. (c) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117.
(118) In separate computational studies, Hehre advanced an electrostatic model for several electrophilic additions to allylic double bonds: (a) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7396–7398. (b) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R. Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650–663. (c) Chao, T.-M.; Baker, J.; Hehre, W. J.; Kahn, S. D. *Pure Appl. Chem.* **1991**, *63*, 283–288.
(119) (a) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094–1096. Compare: (b) Vedejs, E.; Dent, W. H., III. *J. Am. Chem. Soc.* **1989**, *111*, 6861–6862. (c) Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437–5446.
(120) (a) Barnes, J. C.; Brimacombe, J. S.; Irvine, D. J. *Carbohydr. Res.* **1990**, *200*, 77–89. (b) Barnes, J. C.; Brimacombe, J. S. *Carbohydr. Res.* **1991**, *216*, 11–20.
(121) Compare: Gung, B. W.; Karipides, A.; Wolf, M. A. *Tetrahedron Lett.* **1992**, *33*, 713–716.
(122) Compare: Zamojski, A.; Banaszek, A.; Grynkiewicz, G. *Adv. Carbohydr. Chem.* **1982**, *40*, 1–129.
(123) (a) Schmidt, R. R.; Angerbauer, R. *Carbohydr. Res.* **1981**, *89*, 159–162. Compare: (b) Forrest, A. K.; Schmidt, R. R.; Huttner, G.; Jibril, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1981–1987. (c) Schmidt, R. R.; Schiebe, R. *Liebigs Ann. Chem.* **1980**, 1307–1320.
(124) Crich, D.; Lim, L. B. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2209–2214.
(125) Huffman, J. W.; Raveendranath, P. C. *J. Org. Chem.* **1986**, *51*, 2148–2150: *Tetrahedron* **1987**, *43*, 5557–5565.
(126) Matsumoto, K.; Ebata, T.; Koseki, K.; Kawakami, H. *Heterocycles* **1991**, *32*, 2225–2239.
(127) Willis, C. L. *Tetrahedron Lett.* **1990**, *31*, 6437–6440.
(128) Paquette, L. A.; Thompson, R. C. *J. Org. Chem.* **1993**, *58*, 4952–4962.
(129) Tadano, K.-i.; Fukabori, C.; Miyazaki, M.; Kimura, H.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2189–2196.
(130) (a) Colombo, M. I.; Somoza, C.; Zinczuk, J.; Bacigaluppo, J. A.; Rúveda, E. A. *Tetrahedron Lett.* **1990**, *31*, 39–42. (b) Colombo, M. I.; Zinczuk, J.; Bacigaluppo, J. A.; Somoza, C.; Rúveda, E. A. *J. Org. Chem.* **1990**, *55*, 5631–5639.
(131) Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414–9418.
(132) Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1991**, *32*, 1671–1674.
(133) Arjona, O.; Candilejo, A.; de Dios, A.; de la Pradilla, R. F.; Plumet, J. *J. Org. Chem.* **1992**, *57*, 6097–6099.
(134) Mereyala, H. B.; Guntha, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 841–844.
(135) (a) Brimble, M. A.; Nairn, M. R.; Wu, Y. *Tetrahedron Lett.* **1991**, *32*, 4049–4050. (b) Brimble, M. A.; Nairn, M. R. *Aust. J. Chem.* **1993**, *46*, 195–201.
(136) Backenstrass, F.; Streith, J.; Tschamber, T. *Tetrahedron Lett.* **1990**, *31*, 2139–2142.
(137) Carless, H. A.; Busia, K.; Dove, Y.; Malik, S. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2505–2506.
(138) Burdisso, M.; Gandolfi, R.; Rastelli, A. *Tetrahedron Lett.* **1991**, *32*, 2659–2662.
(139) (a) Fleming, I.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 157–159. (b) Panek, J. S.; Zhang, J. *J. Org. Chem.* **1993**, *58*, 294–296. (c) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873–4878.
(140) (a) Attention should be drawn to a recent elegant study by Halterman on osmylation of sterically unbiased 3,3-diarylcyclopentenes. Evidence for stereoelectronic control has been presented: Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 980–985. (b) However, the similarity in the stereochemical outcome for the permanganate and osmylation reactions leaves an open question as to the importance of the hyperconjugative effects in the $KMnO_4$ oxidations of α,β-unsaturated compounds.
(141) (a) Hamill, R. L.; Hoehn, M. M. *J. Antiobiot., Ser. A.* **1964**, *17*, 100–103. (b) Uchida, K.; Ichikawa, T.; Shimauchi, Y.; Ishikura, T.; Ozaki, A. *J. Antibiot.* **1971**, *24*, 259–262.
(142) Danishefsky also reported an imaginative synthesis of methyl peracetyl-α-hikosaminide (**101**) by a Lewis acid-catalyzed cyclocondensation reaction: ref 57.
(143) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882.

(144) For the full structure determination and numbering system of palytoxin, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M. *J. Am. Chem. Soc.* **1982**, *104*, 7369–7371 and references cited therein.

(145) (a) Kishi, Y.; Christ, W. J.; Taniguchi, M. In *Natural Products and Biological Activities–a Naito Foundation Symposium*; Imura, H., Goto, T., Murachi, T., Nakajima, T., Eds.; University of Tokyo Press: Japan, 1986; pp 87–98. (b) Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.-i.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7525–7530; 7530–7533. (c) Suh, E. M.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11205–11026.

(146) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

(147) (a) Jin, H.; Uenishi, J.; Chirst, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050. (c) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. (d) Aldehyde **121** was prone to undergo elimination to furnish the corresponding α,β-unsaturated aldehyde, even with an organocuprate reagent.

(148) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(149) Kishi, Y. Personal communication.

(150) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417–419.

(151) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

(152) Compare: Recently there appeared hydroxylations of conjugated dienes: (a) Park, C. Y.; Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* 1991, *32*, 1003–1006. (b) Narkunan, K.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1705–1706. (c) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571.

(153) For isolation, see: **138**: (a) Burka, L. T.; Ganguli, M.; Wilson, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 544–545. **139**: (b) Hirata, Y.; Sakabe, N.; Goto, T. *Tetrahedron* **1977**, *33*, 3077–3081. (c) Franck, B.; Gehrken, H.-P. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 461–462. **140**: (d) Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 4771–4774. **141**: (e) Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, 874–876. (f) Norrestam, B. R. *Acta Crystallgr., Sect. A* **1978**, *A34*, s79. (g) Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Chem. Commun.* **1979**, 1041–1042. **142–144**: (h) Niwa, M.; Endo, T.; Ogiso, S.; Furukawa, H.; Yamamura, S. *Chem. Lett.* **1981**, 1285–1288. (i) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S.; Terada, Y.; Niwa, M.; Kawai, K.; Furukawa, H. *Tetrahedron Lett.* **1985**, *26*, 3243–3246. **145**: (j) Nishiyama, S.; Shizuri, Y.; Toshima, H.; Ozaki, M.; Yamamura, S.; Kawai, K.; Kawai, N.; Furukawa, H. *Chem. Lett.* **1987**, 515–518. **146,147**: (k) Nishiyama, S.; Shizuri, Y.; Yamamura, S.; Terada, Y.; Kawai, K.; Furukawa, H. *Tetrahedron Lett.* **1985**, *26*, 6239–6242. **148**: (l) Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441–442.

(154) For biosynthetic studies, see: (a) Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239–256 and references cited therein. (b) Reference 153c.

(155) For a recent review on related pyrones, see: Moreno-Mañas, M.; Pleixats, R. *Adv. Heterocycl. Chem.* **1992**, *53*, 1–84.

(156) Sayood, S. F.; Suh, H.; Wilcox, C. S.; Schuster, S. M. *Arch. Biochem. Biophys.* **1989**, *270*, 714–721.

(157) Citreoviral (**140**) is probably a catabolic product of citreoviridin (**139**).

(158) For syntheses of citreoviridin (**139**), see: (a) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067–5079. (b) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470–481. (c) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231–234.

(159) For syntheses of citreoviral (**140**), see: (a) Shizuri, Y.; Nishiyama, S.; Shigemori, H.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1985**, 292–293. (b) Bowden, M. C.; Patel, P.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4793–4796. (c) Begley, M. J.; Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1951–1958. (d) Williams, D. R.; White, F. H. *Tetrahedron Lett.* **1986**, *27*, 2195–2198. (e) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485–6488. (f) Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375–378.

(160) For syntheses of other metabolites, see: **141B**: (a) Nishiyama, S.; Toshima, H.; Kanai, H.; Yamamura, S. *Tetrahedron* **1988**, *44*, 6315–6324. **142** and **146**: (b) Nishiyama, S.; Toshima, H.; Yamamura, S. *Chem. Lett.* **1986**, *11*, 1973–1976. **145**: (c) ref 153j. **148**: (d) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186–4188; *Tetrahedron Lett.* **1986**, *27*, 2575–2578. (e) Tadano, K.-i.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron* **1990**, *46*, 2353–2366. (f) Mulzer, J.; Mohr, J.-T. *J. Org. Chem.* **1994**, *59*, 1160–1165. (g) Nishiyama, S.; Kanai, H.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1322–1327.

(161) Subsequently Pattenden extended Vleggaar's postulate to the 2,6-dioxabicyclo[3.2.1] system of aurovertins (**141**), where a cascade of cyclizations of a triepoxide was considered: Forbes, J. E.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1959–1966.

(162) An epoxide-mediated rearrangement involving a triepoxide was previously advanced by Vleggaar to account for the formation of the 2,8-dioxabicyclo[3.3.0]octane moiety of asteltoxin (**148**), a structurally unique member of this citreoviridin family: (a) de Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1985**, 1633–1635. (b) Recently we have successfully accomplished a formal synthesis of **148** in parallel to Vleggaar's biosynthetic postulate: Raman, J. V.; Lee, H. K.; Vleggaar, R.; Cha, J. K. *Tetrahedron Lett.* **1995**, *36*, 3095–3098.

(163) In this connection, the coisolation of citreodiol, along with **139**, **140**, and **142**, from *Penicillium citreoviride*, might be significant.[153d] It should be added that citreomontanin, a C18-polyene α-pyrone, was also isolated from *Penicillium* sp., but failed to be incorporated into **139**: Rebuffat, S.; Davoust, D.; Molho, L.; Molho, D. *Phytochemistry* **1980**, *19*, 427–431. Synthesis: (a) Patel, P.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4789–4792. (b) Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1941–1945. (c) Venkataraman, H.; Cha, J. K. *Tetrahedron Lett.* **1987**, *28*, 2455–2458.

(164) Whang, K.; Venkataraman, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7174–7177.

(165) Klein, L. L. *Tetrahedron Lett.* **1986**, *27*, 4545–4548.

(166) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180–7184.

(167) (a) Cooke, R. J. Ph.D. Dissertation, Vanderbilt University, 1989. (b) (*R*)-Antipodes are shown for uniformity, although **168a–c** were prepared in the *S*-configuration starting from readily available ethyl (*S*)-(−)-lactate. (c) The *anti* stereochemistry of **169** was firmly established by its independent synthesis from D-glucose diacetonide.

(168) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555–557.

(169) Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201–5203.

(170) (a) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317–384. (b) Adams, C. *Synth. Commun.* **1984**, *14*, 955–959.

(171) (a) Whang, K. Ph.D. Dissertation, Vanderbilt University, 1991. (b) The choice of the hydride reagents was based on the assumption that the lanthanide would form a 6-membered chelate with the pyrone oxygen. Subsequent internal hydride transfer by an acylborohydride would result in the *anti* diol.

(172) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604–4611.

(173) (a) Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985–8987. (b) Cha, J. K.; Cooke, R. J. *Tetrahedron Lett.* **1987**, *28*, 5473–5476.

(174) Williams and Wilcox groups independently reported two previous total syntheses of citreoviridin (ref 158). Wilcox introduced two alkyl groups at the anomeric carbon of a pentose in his synthesis of the tetrahydrofuran subunit, while Williams utilized iodoetherification of β-alkoxy-γ,δ-olefinic benzyl ethers. Stereocontrol by an allylic ether of the latter type has been another fertile area of research.

(175) Stork has developed a stereocontrolled synthesis of polypropionate-derived chains by iterative use of butenolides: (a) Stork, G.; Rychnovsky, S. D. *Pure Appl. Chem.* **1986**, *58*, 767–772. (b) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565–1567.

(176) For recent reviews on synthetic studies of macrolide antibiotics, see: (a) Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 4. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (c) Boeckman, R. K., Jr.; Goldstein, S. W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7, pp 1–139. (d) Hoffmann, R. W.; Stürmer, R. In *Antibiotics and Antiviral Compounds*; Krohn, K., Kirst, H. A., Maag, H., Eds.; VCH: New York, 1993; pp 103–110.

(177) Woodward R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213; 3213–3215; 3215–3217.

(178) (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131–7134. (b) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauvé, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818–2820. (c) Nakata, M.; Arai, M.; Tomooka, K.; Ohsawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618–2635. (d) Reference 178b. (e) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7–9. (f) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2223–2226. (g) Sviridov, A. F.; Borodkin, V. S.; Ermolenko, M. S.; Yashunsky,

D. V.; Kochetkov, N. K. *Tetrahedron* **1991**, *47*, 2317–2336. (h) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247–6256. (i) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463–7466. (j) Stûrmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 101–103. (k) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843–1846. (l) Reference 82.

(179) (a) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620–4622. (b) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. K. *Tetrahedron Lett.* **1987**, 28, 3835–3838 and 3839–3842. (c) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910–923. (d) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568–1571. (e) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636–1648.

(180) (a) Kim, Y. G.; Whang, K.; Cooke, R. J.; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 3275–3278. (b) Kim, Y. G. Ph.D. Dissertation, Vanderbilt University, 1991. (c) Oh, J.; Cha, J. K. Unpublished results.

(181) The remaining task involves the removal of the superfluous C7-keto functionality and the straightforward functional group management to complete a concise synthsis of the seco acid **195** of (9*S*)-erythronolide A.

(182) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489. Compare: (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467 and footnote 32 cited therein. (c) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1988**, *29*, 2077–2080.

(183) Compare: Directed, rhodium(I)- or iridium(I)-catalyzed hydroboration reactions have also been reported: (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917–6918. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 2280–2282. (c) Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett.* **1989**, *30*, 395–398. (d) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179–1191.

(184) (a) Franck, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *J. Am. Chem. Soc.* **1982**, *104*, 1106–1107. (b) Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187–3190. (c) Franck, R. W. In *Cycloaddition Reactions in Carbohydrate Chemistry;* Giuliano, R. M., Ed.; ACS Symposium Series 494; American Chemical Society: Washington, DC, 1992; pp 24–32.

(185) (a) Grée, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carrié, R. *Tetrahedron Lett.* **1984**, *25*, 3697–3700. See also (b) Hamada, T.; Sato, H.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1989**, *30*, 6405–6408.

(186) In general, the syn isomer **215** is slightly favored for allylic alcohols and, to a greater extent, the *anti* isomer **214** for allylic ethers. Stereoselective nitrile oxide cycloaddition reactions have been reviewed: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Gazz. Chim. Ital.* **1989**, *119*, 253–269. (b) Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261–327.

(187) (a) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788–5789. (b) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1984**, *49*, 2762–2772. (c) Curran, D. P.; Choi, S.-M.; Gothe, S. A.; Lin, F.-t. *J. Org. Chem.* **1990**, *55*, 3710–3712 and references cited therein.

(188) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686–1688.

(189) An interesting comparison was made between osmylation and nitrile oxide cycloaddition of the identical allylic ether substrate (Table 5, entries 1 and 2). Both reactions were found to proceed with the same level (4:1) of diastereoselectivity: ref 31.

(190) (a) Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, *40*, 2297–2302. (b) Reference 77. Compare: (c) Midland, M. M.; Halterman, R. L. *J. Org. Chem.* **1981**, *46*, 1227–1229.

(191) In constructing a working model to account for the observed stereochemical course in these reactions, the reversible nature of the initial attack by an electrophile should be taken into account. The overall diastereoselectivity is determined by the relative energies of the various transition structures involved in the rate-determining step, when the diastereomeric bridged intermediates are in rapid equilibrium with each other.

(192) For an excellent review of earlier work, see: Partlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 411–454.

(193) (a) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825. (b) Tamaru, Y.; Hojo, M.; Kawamura, S.-i.; Sawada, S.; Yoshida, Z.-i. *J. Org. Chem.* **1987**, *52*, 4062–4072. (c) Freeman, F.; Robarge, K. D. *J. Org. Chem.* **1989**, *54*, 346–359. (d) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III. *J. Org. Chem.* **1987**, *52*, 4191–4202. (e) Williams, D. R.; Osterhout, M. H.; McGill, J. M. *Tetrahedron Lett.* **1989**, *30*, 1327–1330. (f) Kim, Y. G.; Cha,J. K. *Tetrahedron Lett.* **1988**, *29*, 2011–2014. (g) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204–2210. (h) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240–245. (i) Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 7455–7456, and references cited in these articles.

CR941109Q