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A CAVEAT ON THE SHARPLESS ASYMMETRIC DIHYDROXYLATION

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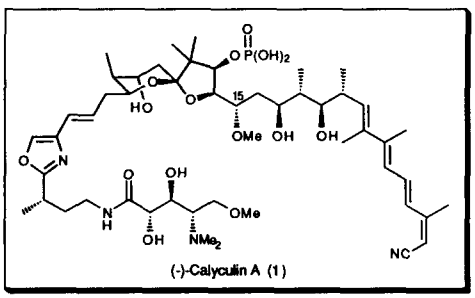
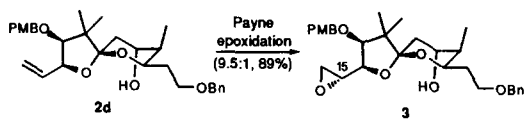
Abstract: Sharpless asymmetric dihydroxylation (AD) of the homochiral synthetic intermediates **2a-c** gave anomalous results: pairs of pseudoenantiomeric reagents, expected to generate complementary diastereomer ratios characteristic of double diastereoselection, instead generally furnished indistinguishable product mixtures. AD reactions of related monosubstituted olefins failed to pinpoint the structural features responsible for the unexpected behavior.

In connection with ongoing efforts directed toward the total synthesis of the calyculins (e.g., **1**), we recently investigated the stereoselective epoxidation of the homochiral spiroketal olefins **2a-e** (depicted in Table 1).[1] Considerable experimentation led to the discovery that Payne epoxidation of **2d** could deliver the requisite epimer **3** in good yield with 9.5:1 diastereoselectivity (Scheme 1).[1] Herein we call attention to the anomalous results obtained in related studies of the



Scheme 1

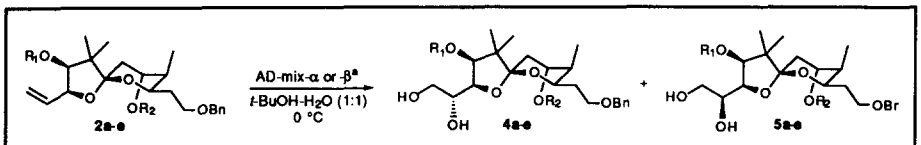


Sharpless asymmetric dihydroxylation[2] (AD) of **2**. In earlier double-diastereoselective AD reactions,[2] the mismatched Sharpless reagents sometimes failed to overcome the intrinsic diastereofacial bias of the substrates, but the product ratios obtained with pseudoenantiomeric reagents nonetheless were qualitatively appropriate for matched and mismatched reagent-substrate combinations. No precedents served to illuminate the remarkable behavior of calyculin substrates **2a-c**, which usually gave *identical* results in dihydroxylations with pseudoenantiomeric Sharpless ligands (Table 1).[3]

As shown in the Table,[4] we carried out AD reactions of **2a-c** with two pairs of ligands; each ligand contained two DHQ (for reagents designated as "AD-mix-α") or pseudoenantiomeric DHQD ("AD-mix-β") moieties linked to a phthalazine (PHAL) or diphenylpyrimidine (PYR) core. The latter spacer generally gives superior results with monosubstituted olefins, especially branched structures such as **2**.[2] The Sharpless mnemonic device for prediction of AD stereochemistry, first derived empirically and more recently substantiated and refined by molecular mechanics,[5] indicated that the α reagents should favor the desired relative configuration in **4**, whereas the β AD-mixes would maximize the formation of **5**. In the event, pseudoantipodal α and β AD-mixes afforded the same diastereomer ratios, within experimental error, for five of the six combinations of substrate and α-β reagent pairs. The lone exception involved dihydroxylation of **2c** with the PYR ligands;

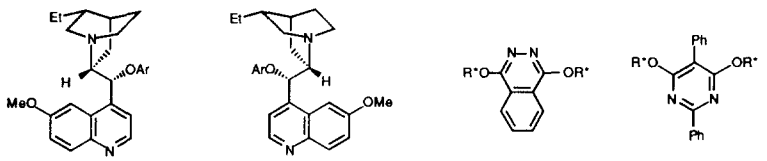
here we did observe typical double diastereoselection, with relative stereochemistries in accord with the Sharpless mnemonic. The AD reactions of **2d** and **2e** gave more complex product mixtures.

Table 1. AD reactions of calyculin intermediates **2a-e**.



Substrate	PHAL ligands			PYR ligands		
	α or β	Ratio **4**:**5**[b]	Yield (%)[c]	α or β	Ratio **4**:**5**[b]	Yield (%)[c]
2a $R_1 = R_2 = H$	α	1:3	75	α	1:3	78
	β	1:3	68	β	1:3	61
2b $R_1 = H$, R_2 = BPS	α	1:5	85	α	1:7	75
	β	1:5	80	β	1:8	83
2c R_1 = TBS, R_2 = BPS[d]	α	1:>20	87	α	3:2	80
	β	1:>20	83	β	1:8	73
	α[e]	1:>20	80			
2d R_1 = PMB, $R_2 = H$	α	4 products[f]	--			
2e R_1 = Ac, $R_2 = H$[d]	α	1:4	35[g]			

[a] $K_2OsO_2(OH)_4$ (4 mol%), ligand (10 mol%), $K_3Fe(CN)_6$ and K_2CO_3. [b] Determined by ^1H NMR and/or chromatographic separation. [c] Total yield of **4** and **5**. [d] *t*-BuOH-H_2O (2:1). [e] 20 mol% of ligand. [f] Partial cleavage of PMB group was observed. [g] Deacetylation and acetyl migration products were also obtained.

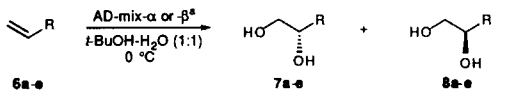


Because none of the previously reported double-diastereoselective AD reactions involved monosubstituted olefins,[2] we next studied several other homochiral examples (**6a-d**, Table 2)[4] which contained some of the basic structural features of the calyculin substrates and were readily available in our laboratory. The expected intrinsic diastereoselectivities were expressed by these olefins in the absence of chiral ligands. Thus, the predominant conversion of **6a** to **7a** presumably reflects hydrogen bonding of the oxidant with the homoallylic hydroxyl[2] in a chairlike arrangement; this diastereofacial preference was reversed upon silylation (**6b**→**8b**). The selective formation of erythro products **8c,d** from **6c** and **6d** follows the established pattern for chiral allylic ethers.[6] We also attempted to osmylate alcohol **6e**, a synthetic intermediate not directly related to **2a-c**, and unexpectedly obtained phenyl vinyl ketone rather than the desired triols.

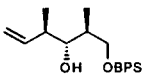
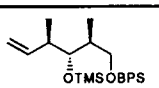
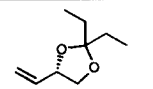
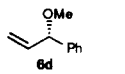
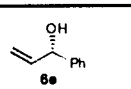
As before, each olefin was subjected to four AD reactions; the Sharpless mnemonic suggested that the α and β AD-mixes would favor the diastereomers **7** and **8**, respectively. Taking into account the intrinsic behavior of the substrates, the results obtained with **6a** and **6d** are characteristic of matched and mismatched combinations. Although the mismatched AD reagents proved unable to surmount the diastereofacial bias of **6c**, the isomer ratios did qualitatively reflect the predicted influences of the α and β ligand types, vis-à-vis the control. We observed unusual reactivity only for **6b**, as all four AD

reactions produced significantly higher proportions of **7b** than were found in the control experiment. The similar 3.2:1 and 1.6:1 mixtures of **7b** and **8b** generated with the α and β PHAL reagents may represent a less dramatic example of the phenomenon uncovered with **2a-c**: the matched β-PHAL AD-mix, which should favor **8b**, instead furnished a slight excess of **7b** (1.6:1), whereas the control gave a 1:6.6 **7b/8b** ratio. Moreover, with the PYR ligands, the matched β reagent was nonselective (1:1.2) but the mismatched AD-mix-α afforded excellent stereoinduction, with the configuration predicted by the mnemonic predominating (31.3:1).

Table 2. AD reactions of homochiral monosubstituted olefins **6a-e**.



6a-e **7a-e** **8a-e**

Substrate	PHAL ligands			PYR ligands		
	α or β	Ratio **7:8**[b]	Yield (%)[c]	α or β	Ratio **7:8**[b]	Yield (%)[c]
 **6a**	α	5.2 : 1[d]	86	α	25.9 : 1[d]	89
	β	1 : 1.5	82	β	1 : 1.2	80
	None[e]	3.5 : 1	88			
 **6b**	α	3.2 : 1[d]	74	α	31.3 : 1[d]	77
	β	1.6 : 1	71	β	1 : 1.2	82
	None[e]	1 : 6.6	80			
 **6c**	α	1 : 2.1[f]	68	α	1 : 1.6[f]	63
	β	1 : 5.3	71	β	1 : 4.5	75
	None[e]	1 : 2.8	70			
 **6d**	α	1.4 : 1[f]	87	α	1.2 : 1[f]	77
	β	1 : 5.0	81	β	1 : 5.3	82
	None[e]	1 : 1.9	81			
 **6e**	α	--		α	--	
	β	--	Trace[g]	β	--	Trace[g]
	None[e]	--				

[a] $K_2OsO_2(OH)_4$ (4 mol%), ligand (10 mol%), $K_3Fe(CN)_6$ and K_2CO_3. [b] Determined by ^1H NMR. [c] Total yield of **7** and **8**. [c] Configuration of the major diol was determined by ^{13}C NMR of 2,4-acetonide derivative. [e] $K_2OsO_2(OH)_4$ (4 mol%), $K_3Fe(CN)_6$ and K_2CO_3. [f] Configurations of diols were assigned via comparison with authentic samples. [g] Major product was phenyl vinyl ketone.

Our results do not provide a clear-cut explanation for the anomalous behavior of **2a-c** and **6b**. Homoallylic alcohols and ethers alone clearly do not dictate either normal or abnormal reactivity, and the studies outlined in Table 2 likewise indicate that neither monosubstituted olefins nor allylic ether moieties are inherently problematic. The calyculin data suggest that steric interactions may disfavor the normal AD transition states, causing both the matched and unmatched reagents to behave as bulky but effectively achiral species; however, the fully protected substrate **2c**, the only one to manifest any normal double diastereoselectivity, appears to be the most hindered of the three.[7]

The explication of our findings will probably entail molecular mechanics calculations, as recently described by Sharpless et al. for AD reactions of styrene derivatives.[5] We concur with their skeptical appraisal of space-filling models for analysis of these complex transformations. Indeed, as of this writing even the basic mechanism of asymmetric osmylation,

either a [2+2] or [3+2] cycloaddition, remains controversial.[8] We hope that these observations will stimulate further studies aimed at more clearly defining and rationalizing the scope and limitations of current AD methodology, perhaps leading in turn to the development of more effective reagents.

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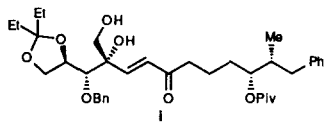
References and Notes

1. Smith, A. B. III; Iwashima, M. *Tetrahedron Lett.* **1994**, *35*, 6853. Also see: Smith, A. B. III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855. Smith, A. B. III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859. Smith, A. B. III; Salvatore, B. A. *Tetrahedron Lett.* **1994**, *35*, 1329. Our current synthetic intermediates embody the unnatural absolute stereochemistry (cf., **1** and **2-5**).

2. For a recent comprehensive review of asymmetric dihydroxylation, see: Kolb, H. C.; WanNievwenhze, M. S.; Sharpless, K. B. *Chem. Rev.*, in press.

3. Shortly before we submitted this manuscript, we became aware of a similar anomaly in the AD reactions of disubstituted olefin **I** with $(DHQD)_2$ PHAL and $(DHQ)_2$ PHAL: Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994** *116*, 10825.



I

4. All synthetic materials were purified by flash chromatography or preparative TLC on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.

5. Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470.

6. For leading references and discussion of related examples, see: Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698.

7. Interestingly, no qualitative anomalies are evident in the AD reactions of some carbohydrate-derived disubstituted olefins which resemble **2**: Brinacombe, J. S.; McDonald, G.; Abdur Rahman, A. *Carbohydr. Res.* **1990**, *205*, 422.

8. For critical discussion and relevant literature citations, see ref 5. See also: Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427.

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