Substrate Binding in the Asymmetric Dihydroxylation Reaction − Investigation of the Stereoselectivity in the Dihydroxylation of C_s-Symmetric Divinylcarbinol Derivatives

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Dedicated to K. Barry Sharpless on the occasion of his 60th birthday

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The mechanism of the asymmetric dihydroxylation (AD) reaction has been hotly disputed. We have studied the stereochemical outcome of the AD reaction on a series of C_s-symmetric divinylcarbinol derivatives in order to shed light on the binding mode of the substrate to the osmium tetroxide–ligand complex. The product distribution is dependent on the size of the allylic substituent, and on the type and class of ligand. It is postulated that the diastereospecificity of the reactions originates from attractive forces between the substrate and the ligand. These interactions are independent of the interactions responsible for the enantioselectivity in the AD reaction.

Introduction

The asymmetric dihydroxylation (AD) reaction is undoubtedly one of the most important processes in asymmetric synthesis.[1−4] Over the years, the AD reaction has been continuously refined by changes in solvent and cooxidant, the introduction of additives, as well as the development of new classes of ligands (Figure 1). Hence, monosubstituted to tetrasubstituted alkenes can successfully be transformed into chiral diols with high to excellent enantioselectivity.

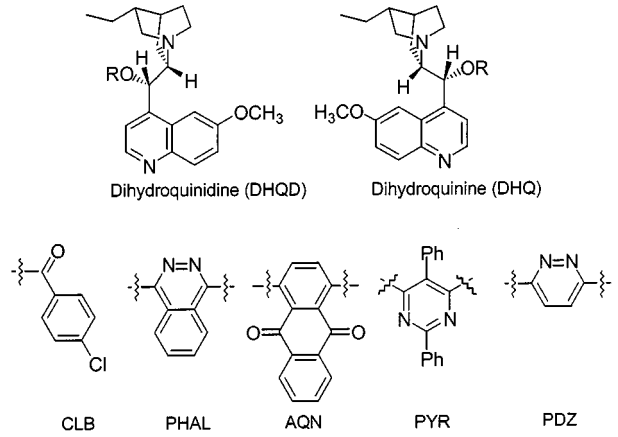

Figure 1. Typical *cinchona*-based ligands for osmium tetroxide mediated asymmetric dihydroxylation; the following abbreviations are used: DHQD (dihydroquinidine), DHQ (dihydroquinine), CLB (4-chlorobenzoate), PHAL (phthalazine), AQN (anthraquinone), PYR (2,5-diphenylpyrimidine) and PDZ (pyridazine)

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The mechanism of the AD reaction has been a subject of passionate debate for a number of years.[5−14] There are two main aspects in the controversy of the alkene addition in the AD process: the exact mechanism of the chiral amine-accelerated osmium tetroxide addition, and the origin of the enantioselectivity in the reaction. Two models have been proposed, one by Corey[7,11,14] [Figure 2 (left)] and one by Sharpless[8,9,12,13] [Figure 2 (right)]. Both proposals anticipate a strong link between the mode of alkene binding and the exact osmium tetroxide addition mechanism. Whether or not the mode of substrate binding is mandatory to the addition mechanism has been discussed remarkably little. Nevertheless, there have been a few reports suggesting that the strong link between the substrate binding and the addition mechanism has been exaggerated in the two opposing models,[15,16] and that the mode of alkene binding can be addressed separately from the detailed addition mechanism.

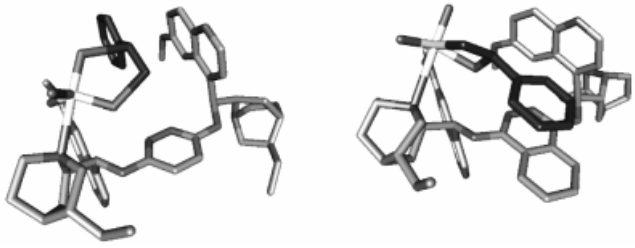

Figure 2. The transition state in the reaction between $(DHQD)_2$−PDZ·OsO_4 and styrene according to the Corey model (left); model of the osmaoxetane intermediate formed in the reaction between $(DHQD)_2$−PHAL·OsO_4 and styrene according to Sharpless (right)

Our aim is to study the mode of alkene binding in the AD reaction with divinylcarbinol derivatives **1**. The aromatic alkene substituent ensures good recognition of the substrate by the osmium tetroxide−ligand system, while the substituent at the prochiral center adjacent to the alkene

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moiety can probe the spatial properties in the binding cleft. The AD reactions of divinylcarbinol derivatives **1**, with changes in the size of the alkoxy substituent and variation in the type (DHQD or DHQ) and class (CLB, PHAL, AQN or PYR) of ligands (for structures and abbreviations see Figure 1), give rise to stereochemical information. This can be understood by a combination of Corey's mechanistic proposal and known models[17] for the diastereoselective dihydroxylation of allylic ether derivatives.

Stereochemical Features

Using divinylcarbinol derivatives **1**, a single experiment provides all relevant stereochemical information. The C_s-symmetric divinylcarbinol derivatives **1** can be divided into four quadrants as illustrated in Figure 3. Each quadrant represents an enantiotopic face that is a (*Re*) or a (*Si*) face, either *syn* or *anti* relative to the carbinol substituent. With a chiral (and nonracemic) ligand on osmium tetroxide, the reagent will be able to distinguish between the different stereotopic faces of the alkene, and four competing TS will result. The (*Re*)-*syn* TS, (*Re*)-*anti* TS, (*Si*)-*syn* TS and the (*Si*)-*anti* TS, will lead to the (1*R*,2*R*,3*S*), (1*R*,2*R*,3*R*), (1*S*,2*S*,3*R*) and the (1*S*,2*S*,3*S*) products, respectively. Since all transition states originate from the same substrate, the effect of kinetic resolution is avoided. The observed product distribution is invariant over time, and reflects only the relative rates of the different reactions and, hence, the relative energies of the transition states.

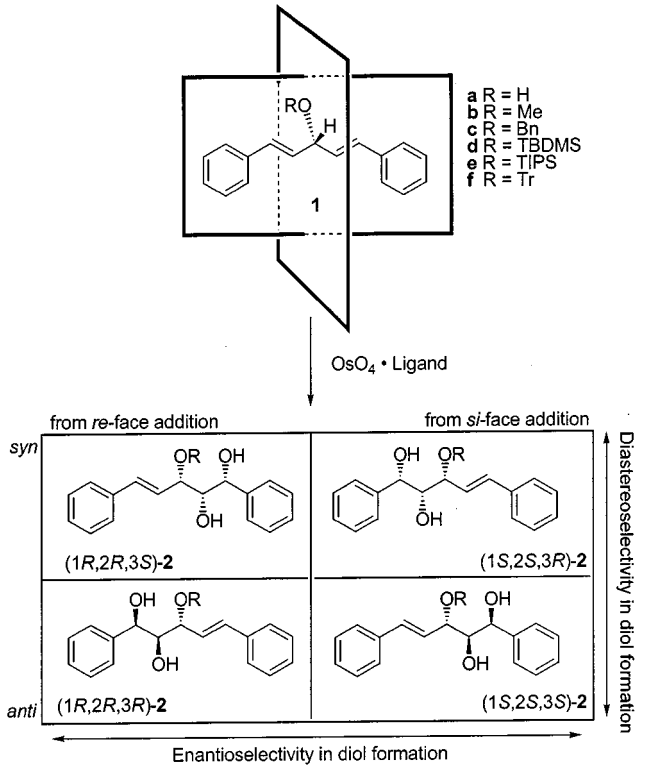


Figure 3. C_s-symmetric divinylcarbinol derivatives used in the study and the mono(dihydroxylated) products

The sensitivity of the transition state complex to the "external" chiral probe in the substrate is revealed as the total diastereomeric ratio between the *anti* and the *syn* isomers. The matched face *anti*/*syn* ratio can conveniently be defined as the *anti*-(*Re*)/*syn*-(*Re*) ratio for the DHQD-mediated reactions and the *anti*-(*Si*)/*syn*-(*Si*) ratio for the DHQ-mediated reactions. This is on the basis of the overall *anti* selectivity in osmium tetroxide mediated dihydroxylation of allylic alcohol derivatives and the well-established (*Re*)-face selectivity of the DHQD-based ligands and (*Si*)-face selectivity of the DHQ-based ligands. Mutatis mutandis, the mismatched ratio is defined as *anti*-(*Si*)/*syn*-(*Si*) for DHQD ligands and *anti*-(*Re*)/*syn*-(*Re*) for DHQ ligands. The match and mismatch face *anti*/*syn* selectivity may be seen as a direct measure of the sensitivity of the dihydroxylation for an external chiral centre when the substrate is bound in a preferred and nonpreferred manner, respectively. The total face selectivity [defined as the percentage excess of the (*Re*) isomers (*anti* and *syn*) for the DHQD-mediated reactions or the percentage excess of the (*Si*) isomers for the DHQ-mediated processes] is a measure of the effectiveness of the substrate binding; a high total face excess in the dihydroxylation shows effective binding and chiral recognition of the substrate.

Results

Synthesis of Divinylcarbinol Derivatives 1

The alcohol **1a** was prepared[18] by reduction of the corresponding ketone with $NaBH_4$. Standard methods[19,20] were mainly employed for the derivatization of alcohol **1a**. The alkyl ethers **1b**, **c** and **f**[21] and the triisopropylsilyl ether **1e**[22] were prepared by treatment of alcohol **1a** with an alkyl or silyl halide in the presence of silver oxide or nitrate. The silyl ether **1d** (R = TBDMS) was prepared from TBDMSCl with 4-dimethylaminopyridine (DMAP) as catalyst.[23]

Conformational Properties of 1

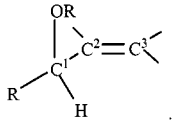
The conformation of the divinylcarbinol derivatives can be expected to influence the diastereoselectivity in the dihydroxylation reaction. Therefore, conformational studies of **1b** (R = Me) and **1f** (R = Tr) were undertaken, with the pseudosystematic Monte Carlo search routine in MacroModel[24] V5.0. The molecular mechanic calculations revealed differences in the minimum energy conformations for a divinylcarbinol derivative with a methyl (**1b**) or a trityl substituent (**1f**) (molecular models of the conformational minima are available in the Supporting Information). The dihedral angles and the corresponding energies of the different minima are compiled in Table 1. The lowest energy conformation of **1b** possesses both an eclipsed and a bisected arrangement of the double bonds and the allylic substituents. In the eclipsed conformation the allylic hydrogen atom eclipses the double bond, whereas in the bisected conformation the alkoxy group resides on the "inside" and faces the

double bond. A conformer with bisected conformations on both sides of the allylic substituent has nearly the same energy. In the highest energy minimum both double bonds were eclipsed with the allylic hydrogen atom. The most stable conformation of the trityl ether **1f** is with both double bonds in the bisected arrangement. In this conformation the large trityl moiety covers the *anti* face of one of the double bonds completely, while the *syn* face is readily accessible to the approaching reagent. The other double bond is rather open from both faces. ^{1}H NMR spectroscopic data supports the shielding by the trityl moiety on the double bonds, as the signals of the protons attached to the double bond appeared at higher field ($\Delta\delta \approx 0.4$) relative to the other derivatives. The conformations with one or two double bonds eclipsed were much higher in energy.

Table 1. Dihedral angles of the most important low-energy conformations calculated for divinylcarbinol derivatives **1b** and **1f** by the pseudosystematic Monte Carlo search routine in MacroModel V5.0

Substrate **1**	Rel. energy [kJ mol^{-1}]	Conf.[a]	Allylic dihedral angle[b][c]			
			O–C^1–C^2–C^3	H–C^1–C^2–C^3	O–C^1–C^2–C^3	H–C^1–C^2–C^3
1b (R = Me)	0.0	e/b	114.2°	–6.2°	15.2°	132.3°
	0.1	b/b	–43.4°	–162.9°	22.9°	139.8°
	1.6	e/e	117.4°	–2.8°	–109.3°	8.0°
1f (R = Tr)	0.0	b/b	–25.2°	143.2°	41.6°	162.9°
	1.0	e/b	–38.2°	–159.2°	–114.4°	4.2°
	2.6	e/e	137.8°	15.5°	–117.7°	1.4°

[a] e: eclipsed, b: bisected. – [b] The dihedral angle is defined as follows:



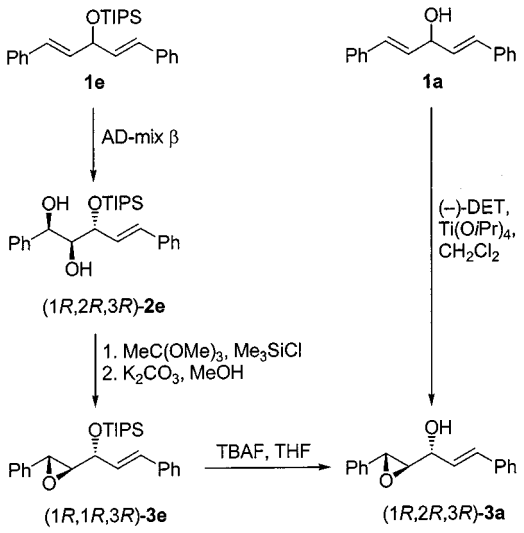
. – [c] Due to the C_s symmetry of the divinylcarbinol derivatives the two allylic dihedral angles are interchangeable.

Determination of the Absolute Configuration of the Dihydroxylation Products

The absolute configuration of the diols **2a**–**f** was predicted from the mnemonic device for the asymmetric dihydroxylation,[25] and the *anti*-diastereoselective osmylation of allylic alkoxy groups which has been reported.[17] Thus, the expected (1*R*,2*R*,3*R*)-isomer of diol **2e** was formed by (*Re*),-*anti*-selective dihydroxylation of **1e** using AD-mix β. The diol (1*R*,2*R*,3*R*)-**2e** was stereospecifically converted into the epoxide (1*R*,2*R*,3*R*)-**3e**[26] and subsequently deprotected to the epoxy alcohol (1*R*,2*R*,3*R*)-**3a** (Scheme 1). The identical epoxy alcohol [(1*R*,2*R*,3*R*)-**3a**] was prepared from **1a** (R = H) by the Sharpless asymmetric epoxidation employing D-(–)-diethyl tartrate (DET) as chiral ligand, which is in accordance with the mnemonic device for the asymmetric epoxidation.[1] The diols **2d** (R = TBDMS) and **2f** (R = Tr) were assigned after deprotection to the triols **2a** (R = H).

Dihydroxylation of the Divinylcarbinol Derivatives

The divinylcarbinol derivatives **1a**–**f** were dihydroxylated with potassium ferricyanide[27] as cooxidant and DHQD- and DHQ-derived ligands as well as quinuclidine. The stereoisomer distribution of the mono(dihydroxylated) products determined by HPLC and ^{1}H NMR is compiled in Table 2.



Scheme 1

The match and mismatch face *anti*/*syn* ratio as well as the total *anti*/*syn* ratio are compiled in Table 3. The enantiomeric excess for the *anti* and the *syn* isomers, in addition to the face excess, defined as the percentage excess of products formed by (*Re*)-dihydroxylation for the DHQD derivatives and (*Si*)-dihydroxylation for the DHQ derivatives, are also compiled in Table 3.

Dihydroxylation with Nonchiral Ligands – The Intrinsic Stereoselectivity of the Substrates

The catalytic dihydroxylation of divinylcarbinol derivatives using the achiral ligand quinuclidine was investigated to measure the inherent diastereoselectivity imposed by the substrate. The diastereoselectivity observed for **1a**–**f** was low (1:0.5 to 1:2.2), but comparable with the diastereoselectivity reported for similar substrates.[17] There was a preference for *anti* addition with small to moderate substituents (R = H, Me, Bn and TBDMS) and the degree of selectivity increased from methyl via benzyl to TBDMS. When the alkoxy substituent was larger, the stereoselectivity was lost (R = TIPS) or even reversed to *syn* (R = Tr).

Dihydroxylation with Chiral Ligands

Asymmetric dihydroxylation of divinylcarbinol derivatives **1a**–**f** was performed using chiral ligands of both the dihydroquinidine (DHQD) and dihydroquinine (DHQ) type. Four classes of ligands were investigated, one from the first generation monoalkaloid type (CLB), and three from the second generation bis(alkaloid) type (PHAL, AQN or PYR).

Total Diastereoselectivity

For the reactions mediated by the more complex chiral *cinchona* ligands the general trend is an increased total *anti*/*syn* selectivity relative to quinuclidine-mediated reactions. The different ligands increased the *anti* selectivity to a varying degree. With smaller allylic R groups the first generation monoalkaloid ligands gave superior *anti* selectivity com-

Table 2. Distribution of mono(dihydroxylated) products **2** by $K_3Fe(CN)_6$-catalysed osmylation of divinylcarbinol derivatives **1** in the presence of various ligands

Substrate **1**	Ligand	Product ratio (%) of **2** (1*R*,2*R*,3*R*)	(1*R*,2*R*,3*S*)	(1*S*,2*S*,3*S*)	(1*S*,2*S*,3*R*)
a	Quinuclidine	29	21	29	21
	DHQD−CLB	64	24	7	5
	$(DHQD)_2$−PHAL	63	33	2	1
	$(DHQ)_2$−PHAL	5	2	55	38
	$(DHQD)_2$−PYR	32	42	15	11
	$(DHQ)_2$−PYR	13	9	37	41
b	Quinuclidine	28	22	28	22
	DHQD−CLB	67	27	4	3
	DHQ−CLB	6	3	68	24
	$(DHQD)_2$−PHAL	66	33	1	0
	$(DHQ)_2$−PHAL	0	0	69	30
	$(DHQD)_2$−PYR	39	36	14	11
	$(DHQ)_2$−PYR	9	7	45	39
c	Quinuclidine	31	19	31	19
	DHQD−CLB	66	26	5	3
	$(DHQD)_2$−PHAL	67	30	2	0
	$(DHQD)_2$−PYR	42	26	19	13
d	Quinuclidine	34	16	34	16
	DHQD−CLB	76	19	3	2
	DHQ−CLB	6	1	70	22
	$(DHQD)_2$−PHAL	75	24	0	0
	$(DHQ)_2$−PHAL	8	0	46	46
	$(DHQD)_2$−AQN	65	27	6	2
	$(DHQ)_2$−AQN	16	2	56	26
	$(DHQD)_2$−PYR	49	16	23	12
	$(DHQ)_2$−PYR	14	12	59	15
e	Quinuclidine	25	25	25	25
	DHQD−CLB	73	22	2	3
	DHQ−CLB	4	4	67	24
	$(DHQD)_2$−PHAL	83	16	0	0
	$(DHQ)_2$−PHAL	4	1	61	34
	$(DHQD)_2$−PYR	41	19	22	19
	$(DHQ)_2$−PYR	20	17	47	17
f	Quinuclidine	17	33	17	33
	DHQD−CLB	47	40	4	9
	DHQ−CLB	5	11	56	28
	$(DHQD)_2$−PHAL	63	28	3	6
	$(DHQ)_2$−PHAL	2	5	73	20
	$(DHQD)_2$−PYR	27	30	14	30
	$(DHQ)_2$−PYR	17	27	27	30

pared with the more complex bis(alkaloid) ligands. The trityl derivative **1f** behaves uniquely, from *syn*-selective with quinuclidine, *anti*-selective with CLB or PHAL ligands, and *syn*-selective again with PYR ligands. For the other substrate−ligand combinations there were smaller differences in the diastereoselectivity imposed by the DHQD and the DHQ ligands. An exception to this trend is the significantly lower diastereoselectivity observed for the silyl ether derivatives **1d** and **1e** when $(DHQ)_2$−PHAL was used rather than the DHQD counterpart.

The match face *anti*/*syn* selectivity is a direct measure of the sensitivity of the dihydroxylation for an external chiral centre when the substrate is bound in a preferred manner. The *anti*/*syn* selectivity is usually low, and indicates that the substrate can effectively bind to the ligand−catalyst system both in the *anti* and the *syn* conformations. Once more, and contrary to what could be expected, the simple ligands (CLB) are generally more *anti*-selective than their more complex bis(alkaloid) PHAL counterparts. The difference in match face diastereoselectivity with CLB or PHAL ligands decreases with an increase in the size of the allylic substituent, however $(DHQ)_2$−PHAL yields markedly lower match face diastereoselectivity than the DHQD analogue for the larger substituents (R = TBDMS and TIPS). The PYR ligands show anomalous behaviour in this respect, with a higher diastereoselectivity for the DHQ than for the DHQD derivatives. For the trityl derivative, the DHQ ligands are more effective than the DHQD ligands, and $(DHQ)_2$−PHAL shows the highest selectivity.

The *anti*/*syn* selectivity for the mismatched face isomers reveals more substantial differences, especially for the larger allylic substituents (R = TBDMS and TIPS). The DHQ ligands are more efficient than the DHQD ligands, and the PHAL ligands are superior. In the exceptional trityl substrate both PHAL-class ligands are *syn*-selective.

Face Selectivity

The CLB ligands show only small changes in face selectivity, close to 85%, upon variation of the allylic substituent. The face selectivity is lower for the smallest R groups and increases with the bulk of R, but decreases again when R = Tr. As expected from the literature,[1−4] the DHQD derivat-

Table 3. *anti*/*syn* ratio and enantioselectivity in the mono(dihydroxylated) products **2** by $K_3Fe(CN)_6$-catalysed osmylation of divinylcarbinol derivatives **1** in the presence of various ligands

Substrate **1**	Ligand	*anti*/*syn* ratio			*ee* (%)		Face excess[c]
		Match face[a]	Mismatch face[a]	Total[b]	*anti*	*syn*	
a	Quinuclidine	–	–	1.4	–	–	–
	DHQD−CLB	2.7	1.5	2.5	80.1	67.2	76
	$(DHQD)_2$−PHAL	1.9	1.9	1.9	93.3	93.3	93
	$(DHQ)_2$−PHAL	1.4	2.6	1.5	82.7	90.0	86
	$(DHQD)_2$−PYR	0.8	1.4	0.9	34.9	58.3	47
	$(DHQ)_2$−PYR	0.9	1.5	1.0	47.4	64.9	56
b	Quinuclidine	–	–	1.3	–	–	–
	DHQD−CLB	2.5	1.3	2.4	89.8	81.5	87
	DHQ−CLB	2.9	2.0	2.8	83.9	77.8	82
	$(DHQD)_2$−PHAL	2.0	1.2	2.0	98.3	97.2	98
	$(DHQ)_2$−PHAL	2.3	1.2	2.3	98.9	98.5	99
	$(DHQD)_2$−PYR	1.1	1.3	1.1	48.0	54.5	51
	$(DHQ)_2$−PYR	1.2	1.4	1.2	65.8	69.2	67
c	Quinuclidine	–	–	1.7	–	–	–
	DHQD−CLB	2.5	1.8	2.4	85.7	80.8	84
	$(DHQD)_2$−PHAL	2.3	5.7	2.3	92.9	97.1	94
	$(DHQD)_2$−PYR	1.7	1.5	1.6	37.5	33.3	36
d	Quinuclidine	–	–	2.2	–	–	–
	DHQD−CLB	4.0	1.3	3.7	93.1	80.4	90
	DHQ−CLB	3.2	4.8	3.3	83.4	88.8	85
	$(DHQD)_2$−PHAL	3.1	0.6	3.1	99.5	97.3	99
	$(DHQ)_2$−PHAL	1.0	21.6	1.2	71.7	98.5	84
	$(DHQD)_2$−AQN	2.4	2.5	2.4	84.1	84.8	84
	$(DHQ)_2$−AQN	2.2	7.4	2.6	56.1	84.8	64
	$(DHQD)_2$−PYR	3.2	1.9	2.6	36.7	13.0	30
	$(DHQ)_2$−PYR	3.9	1.2	2.7	61.9	13.0	49
e	Quinuclidine	–	–	1.0	–	–	–
	DHQD−CLB	3.4	0.8	3.1	94.0	77.6	90
	DHQ−CLB	2.8	1.0	2.5	88.8	71.8	84
	$(DHQD)_2$−PHAL	5.1	1.0	5.0	99.0	94.8	98
	$(DHQ)_2$−PHAL	1.8	4.3	1.9	87.9	94.7	90
	$(DHQD)_2$−PYR	2.2	1.2	1.7	29.4	0	19
	$(DHQ)_2$−PYR	2.8	1.2	2.0	40.0	0	27
f	Quinuclidine	–	–	0.5	–	–	–
	DHQD−CLB	1.0	1.0	1.0	85.5	65.2	76
	DHQ−CLB	1.5	1.1	1.6	82.5	45.2	68
	$(DHQD)_2$−PHAL	2.2	0.4	1.9	91.9	62.8	82
	$(DHQ)_2$−PHAL	3.8	0.4	3.0	94.7	55.2	85
	$(DHQD)_2$−PYR	0.9	0.5	0.7	31.0	0	13
	$(DHQ)_2$−PYR	0.9	0.6	0.8	23.1	5.9	13

[a] Match face is (*Re*) for DHQD derivatives and (*Si*) for DHQ derivatives. Mismatch face is (*Si*) for DHQD derivatives and (*Re*) for DHQ derivatives. – [b] The total diastereoselectivity is defined as the ratio between the sum of the *anti* isomers and the sum of the *syn* isomers. – [c] Face excess is the % excess of the products formed by (*Re*) dihydroxylation for the DHQD-derivatives and the % excess of the products formed by (*Si*) dihydroxylation for the DHQ-derivatives.

ives are more effective in the induction of face selectivity than the DHQ derivatives. The PHAL-class ligands show superior face selectivity, close to 100% for R = Me, TBDMS, and TIPS. There are only small differences in face selectivity between the DHQD and DHQ derivatives of the same ligand class as long as the R group is small, but when the R group is large the DHQ derivatives lose face selectivity. The PYR ligands generally yield very poor face selectivity for divinylcarbinols, particularly when the allylic substituent is large.

Discussion

Conformational Properties of Divinylcarbinol 1 and the Stereochemical Bias for the Dihydroxylation Reaction

Numerous substrate-directed dihydroxylations have been reported in the literature,[17] and several groups have investigated the influence of allylic stereocenters with an alkoxy group on the diastereoselectivity of the reaction. The majority of dihydroxylations of chiral allylic ethers proceed with an *anti* relationship between the original alkoxy and the new hydroxy groups. Four different models have been proposed to explain the diastereoselectivity in the dihydroxylation process. Kishi[28] proposes a reactant-like transition-state structure, and the model relies on the importance of allylic 1,3-strain to rationalise the reactive conformation. The allylic hydrogen atom eclipses the double bond on the "inside" (Figure 4), and the osmium tetroxide reagent attacks on the face *anti* to the alkoxy group. In a simultaneous publication, Stork explains the diastereoselectivity in the dihydroxylation of α,β-unsaturated esters by an attack from the least hindered side of a conformation where the allylic hydroxy group eclipses the double bond.[29] Later Houk and Jäger refined the Stork model to a staggered transition-state conformation with the alkoxy group

"inside" due to secondary orbital interactions.[30−33] Vedejs has since questioned the importance of the hyperconjugative effects, and rather stressed the importance of the steric hindrance imposed by the approaching osmium tetroxide−ligand complex.[34−36] For (*E*)-alkenes Vedejs formulated two staggered conformations (Figure 4) where the allylic hydrogen atom (by far the smallest allylic substituent) faces the approaching reagent. One of these conformations will lead to *anti* addition while the other furnishes the *syn* product, and the distribution between the two conformations and, hence the diastereoselectivity of the addition, is governed by the relative size of the two other allylic substituents.

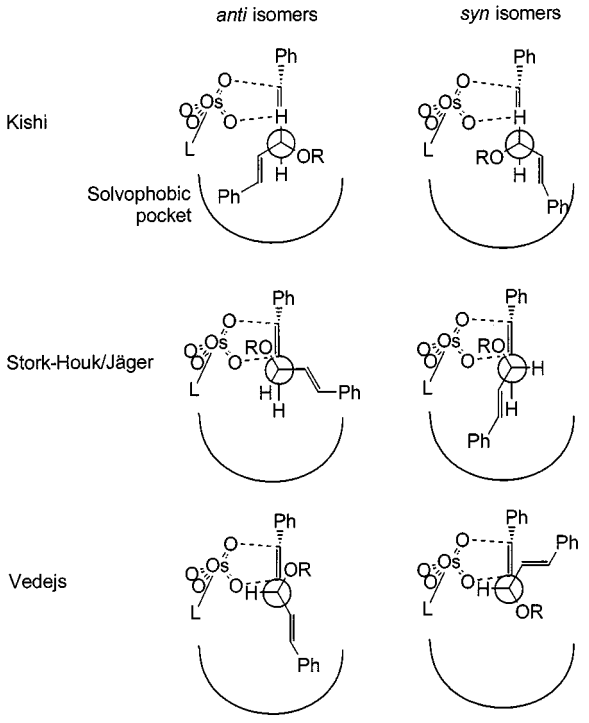


Figure 4. Proposed conformations in the osmium tetroxide mediated dihydroxylation of divinylcarbinol derivatives; the Kishi model (top), the Stork/Houk−Jäger model (center), and the Vedejs model (bottom)

For allylic ethers with small to medium-sized alkoxy groups *anti* isomers were expected from both Kishi- and Stork/Houk−Jäger-type conformations, albeit as the size of the alkoxy group increases the *anti* selectivity should increase for Kishi-type conformations and decrease for Stork/Houk−Jäger-type conformations. According to the Vedejs model, the *anti* selectivity should increase with an increase in the bulk of the alkoxy substituent until the relative size of the OR group and the styryl group becomes such that the conformational equilibrium shifts and favours the *syn*-producing conformation.

The results from the molecular modelling of **1b** and **1f** show that the ground state allylic conformations of the divinylcarbinol systems are either a Kishi (eclipsed) or a Stork/Houk−Jäger-type (bisected), and no conformations corresponding to the Vedejs model could be identified (Table 1). The divinylcarbinol derivatives are conformationally flexible, and the different minima are so close in energy that no model can be particularly favoured on the basis of the molecular modelling studies. The absence of Vedejs-type conformations in the modelling study is not unexpected, because in the Vedejs proposal the active conformations are imposed by the bulk of the approaching reagent. In the case of **1b** (R = Me), addition to both Kishi- and Stork/Houk−Jäger-types of conformation can be expected to give the *anti* isomers, but a Kishi-type conformation could be predicted to lead to lower *anti* selectivity than a Stork/Houk−Jäger-type conformation. In contrast to the methyl ether, the energy difference between the bisected/bisected and the eclipsed/bisected conformation increased to 1 kJmol^{-1} for the trityl derivative **1f**, with the doubly bisected conformation as the global minimum. For the doubly bisected conformation a weak *syn* selectivity should be expected. In the conformation with one double bond of Kishi- and one of Stork/Houk−Jäger-type (eclipsed/bisected), the bisected double bond is almost inaccessible and the eclipsed double bond is also sterically hindered, but any approaching reagent will favour *anti* addition. The doubly eclipsed conformation, which is highest in energy, will have a clear *anti* selectivity. On the basis of molecular modelling of **1f**, addition was expected to afford the *syn* isomers, albeit with low selectivity.

Dihydroxylations in the Presence of Quinuclidine

When the divinylcarbinol derivatives were subjected to dihydroxylation with the small and achiral ligand quinuclidine, the diastereoselectivity was generally low, with a weak *anti* selectivity. The *anti* selectivity increased with the increase in size of the alkoxy substituent until the selectivity started to decrease and even turn *syn*-selective for the sterically most demanding substituents. These results are completely in agreement with the Vedejs mechanistic proposal. However, the experimental results also agreed with the analysis of the conformational calculations, and thus indicate that the Kishi and the Stork/Houk−Jäger model should also be considered in the explanation of the diastereoselectivity in osmylation reactions.

Dihydroxylation in the Presence of Chiral Ligands

When the far more bulky chiral ligands were employed, the diastereoselectivity of the reaction changed very little. However, the reaction proceeded with variations in the face selectivity and the *anti*/*syn* ratio as a function of the alkoxy substituent and the ligand type and ligand class. For all ligand classes, except PYR, the face selectivity is far greater than the diastereoselectivity, and this shows that when a substrate is bound to the osmium tetroxide−ligand complex through the favoured face(s) of the alkene, binding modes corresponding to both the *anti* and the *syn* diastereoisomers can be accommodated. However, in the majority of cases the *anti* selectivity inherent in the substrate is aug-

mented by the presence of the chiral ligand. In the PYR class of ligands, the face selectivity of the process is low, and suggests that the substrate has difficulty in binding in a face preferred manner.

In order to achieve at least a qualitative interpretation of these results, we need to construct a model of the binding of the divinylcarbinol derivatives in the osmium tetroxide−*cinchona* alkaloid ligand complex. The two most prominent theories for the mechanism of the AD process differ in the mode of substrate binding. In the Corey mechanistic proposal,[37] the alkene substrate is bound between the two quinoline ring walls through favourable van der Waals interactions between the alkene and the binding cleft. On the other hand, Sharpless has suggested that the aromatic linker moiety in the bis(alkaloid) ligands (or the CLB group in the monoalkaloid ligands) provides a lipophilic "pocket" for an aryl group in the substrate.[8] The aryl group will locate itself in this pocket owing to attractive nonbonded interactions[8,27] and solvophobic interactions caused by the polar solvent.

One of the advantages with the Corey model is the heuristic value embodied in this simple transition-state model, and his proposal represents an attractive starting point for the construction of a qualitative model of the binding of the divinylcarbinol derivatives. Corey's approach proved particularly attractive as an IMOMM(BECKE3LYP:MM3) calculation on the TS in the reaction between styrene and the $(DHQD)_2$−PDZ−osmium tetroxide complex was published recently.[38] The styrene substrate in the calculated TS structure could easily be extended into a divinylcarbinol derivative. If the allylic conformations corresponding to the Kishi, Stork/Houk−Jäger and Vedejs diastereoselectivity models were superimposed on the ligand-bound divinylcarbinol structure, we obtain a set of schemes which qualitatively depict the substrate binding as shown in Figure 4. Although this model is only a coarse picture of the matched face situation, several interesting features emerge. We regard the Stork/Houk−Jäger model as the least likely scenario, particularly for the more bulky derivatives where the model requires the alkoxy substituent to approach the attacking osmium tetroxide with the induction of steric conflict. However, both the Kishi and, in particular, the Vedejs model appear acceptable. The divinylcarbinol binding model will have one of the styrene moieties bound in the Corey fashion and this gives rise to the enantioselectivity in the reaction, the other two allylic substituents (the second styryl group and the OR substituent) are placed in accordance with the proposed diastereoselectivity models. In order to explain many of the observed differences in the diastereoselectivity, attractive interactions between the allylic substituents in the divinylcarbinol substrate (the alkoxy group or the styryl group) and the chiral ligands are taken into consideration. These interactions are secondary and auxiliary to the interactions between the phenyl group and the quinoline ring, the latter interactions are responsible for the face selectivity in the Corey mechanistic proposal. A plausible site for such auxiliary interactions can be found by consideration of the Sharpless binding model.[8] Inspection of molecular models built on the Corey transition state show that the Sharpless lipophilic pocket should be able to accommodate the styryl moiety.

Topology of the Auxiliary Interaction Site

An interesting feature of the AD process is the superior enantioselectivity usually obtained with the DHQD ligands compared with their DHQ counterparts.[1−4,39] As a result, use of the DHQ ligands in the development of the reaction, especially in mechanistic studies of the AD process, has been limited. Molecular mechanics calculations and NMR studies performed by us and others[40] unequivocally show that the major topological difference between the DHQD and the DHQ bis(alkaloid) binding cleft is the orientation of the quinuclidine ethyl group. In the DHQD series, the ethyl substituent of the quinuclidine ring forms an integral part of the lipophilic pocket, whereas in the DHQ series the ethyl group is located away from the linker moiety and leaves a "hole" in the pocket. The size and topology of the pocket is also strongly dependent on the linker moiety. Generally, smaller aromatic linkers, for example, PDZ, reduce the lipophilicity of the lipophilic pocket compared with PHAL. Interestingly, $(DHQD)_2$−PHAL and $(DHQD)_2$−PDZ show similar behaviour in AD reactions with several substrates, while the $(DHQ)_2$−PDZ ligand is significantly less effective than its PHAL counterpart.[39] The failure of the $(DHQ)_2$−PDZ ligand could be explained as follows. In the $(DHQD)_2$−PDZ ligand, the effect of the quinuclidine ethyl group on the "inside" yields sufficient lipophilicity in the smaller PDZ linker to compete with the enantioselectivities of the ligand with the larger PHAL linker. However, in the $(DHQ)_2$−PDZ ligand, the quinuclidine ethyl group is on the "outside" and removes, to a large degree, the possibility for attractive nonbonding interactions with the substrate and yields a less effective ligand. $(DHQ)_2$−PHAL is also less effective than its DHQD counterpart, but the large linker increases the possibility of attractive nonbonded interactions, and therefore $(DHQ)_2$−PHAL usually performs better than the $(DHQ)_2$−PDZ ligand.[39] This hypothesis not only includes the auxiliary binding pocket, but also supports the proposal that the AD process may proceed through substrate binding in the Sharpless pocket. From the differences in the shape of the lipophilic pocket, it is predicted that the DHQ derivatives should yield a lower number of attractive nonbonded interactions with a substrate than in the corresponding DHQD pocket. On the other hand, the DHQ pocket should be better able to accommodate a substrate that is too large to fit into the tighter DHQD pocket.

The PHAL class of ligands may serve as an example of the interactions between the osmium tetroxide−ligand complex and the divinylcarbinol substrate. In $(DHQD)_2$−PHAL, the hydrophobic pocket is tight, enclosed by the phthalazine ring and the quinuclidine ethyl group, it can still manage to accommodate the styryl substituent easily, but anything bulkier is unlikely to be accommodated. This arrangement of the styryl group is possible in the Kishi conformation, but more likely in the Vedejs

anti conformation. Thus, the proposed extra stabilisation in the hydrophobic pocket reinforces the inherent *anti* diastereoselectivity of the substrate. The effect is not large for small alkoxy groups, but when the alkoxy group becomes very large the reinforcement of *anti* selectivity becomes significant; for example, for R = TIPS the *anti* selectivity for $(DHQD)_2$−PHAL is five times larger than for the quinuclidine-mediated process. As described above, the hydrophobic pocket in $(DHQ)_2$−PHAL is not as tight and, hence, yields less effective nonbonded stabilisation of the styryl group. When the alkoxy group becomes large, an increase in the *anti* diastereoselectivity of $(DHQ)_2$−PHAL-mediated reaction suddenly fails. An explanation for this interesting shift may be that the flexible DHQ pocket is capable of binding the large TBDMS group, and that the attractive nonbonded interaction between the TBDMS group and the DHQ pocket is slightly larger than the interaction with the styryl substituent. As the TBDMS-bound configuration yields the *syn* diastereoisomer, this effect can explain the unexpectedly large shift in selectivity when moving from $(DHQD)_2$−PHAL to $(DHQ)_2$−PHAL. For the even larger TIPS substituent a similar situation may occur, however, the process is still weakly *anti*-selective. The explanation for weak *anti* selectivity in this case may be that the TIPS group is on the verge of being too large to fit into the DHQ pocket, and shifts the Vedejs conformational "equilibrium" partially back to the *anti* situation.

The PYR series of ligands shows atypical behaviour. For R = H the PYR ligands are *syn*-selective, and become *anti*-selective as the alkoxy substituent increases. Once more, the explanation may be found by consideration of the lipophilic pocket. In the PYR ligands the spacer has a biphenyl structure where the phenyl ring partially fills the pocket and thus disables, to a large extent, the attractive nonbonded interactions with the styryl group. Thus, for the smallest alkoxy substituents, the Vedejs *syn* conformation is favoured because this conformation places the alkoxy group into the shallow pocket. This arrangement avoids steric conflicts between the alkoxy substituent and the phenyl group that comprises a part of the pocket, but little nonbonded stabilisation is obtained. When the alkoxy substituent becomes large the *syn* conformation becomes less favourable. The difficulties in forming stable *syn* or *anti* conformations for the PYR ligands is also reflected in the low face selectivities obtained. Once more the DHQ derivative has a more flexible pocket, and is more capable of accommodating the substrate than the DHQD analogue, this results in a higher *anti* selectivity as well as a higher face selectivity than the DHQD counterpart.

Conclusion

Important stereochemical features observed in the AD of divinylcarbinol derivatives can be understood with a substrate-binding model that is a combination of the Corey transition state proposal[7,11,14] and the Vedejs diastereoselectivity model.[34−36] The key element in our interpretation is the presence of a secondary attractive interaction between the substrate and the ligand complex, distinct from the attractive interactions responsible for the high *ee* in the AD process. If the Corey model is chosen as an explanation of the induction of face selectivity, the secondary attractive interaction must originate from an interaction between the substrate and a region in the ligand composed of the linker moiety (or the CLB group) and the adjacent parts of the "active"[26] quinuclidine system. Interestingly, this area is the same domain that is responsible for substrate binding in the Sharpless model.

This analysis does not rule out alternative explanations based on the Sharpless mechanistic proposal,[8,9,12,13] but the complexity of the Sharpless hypothesis makes it more difficult to build models, and hence alternative schemes have not been developed. It must be strongly emphasised that our interpretation is only qualitative, thus no detailed picture of the substrate binding can be offered. However, our results provide a basis for a quantitative analysis, for example, recently molecular mechanics calculations have been successfully applied to the AD reaction.[16] Another limitation of our model is that it is only suitable for interpretation of the match face diastereoselectivity. On the other hand, our results show the importance of stereochemical differences in the mismatch face system that could also be used to probe alternative binding modes in the osmium tetroxide−ligand complex.

Experimental Section

General: IR: Shimadzu IR-470 spectrophotometer. − NMR: Jeol JNM-EX 400 FT spectrometer (400 MHz or 100 MHz for ^1H and ^{13}C NMR, respectively). Chemical shifts are reported in ppm relative to residual proton in $CHCl_3$ (δ = 7.25) or the ^{13}C resonance of $CDCl_3$ (δ = 77.0, t). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; dd, double doublet; ddd double double doublet; dt, double triplet; m, multiplet. − HPLC: Waters 6000A apparatus equipped with a Chiralcel OD-H chiral column (46 cm, ID 0.46 cm) and a Waters 440 absorbance detector. − GLC: Varian 3300 equipped with a Supelco SPD-5 column (15 m, ID 0.25 mm) and flame ionization detector (FID). − GLC/MS: VG Tribrid mass spectrometer connected to a Hewlett Packard 5890 II gas chromatograph equipped with a Supelco SPB-5 column (20 m, ID 0.25 mm). The ionisation potential was 70 eV and the temperature in the ion source was 220 °C. − TLC: Aluminium sheets precoated with silica gel 60 F_{254} (Merck). − Preparative chromatography: Flash chromatography using 230−400 mesh silica gel. − Optical rotation: Perkin−Elmer 241 polarimeter. − Melting points: Büchi 535 apparatus; all values are corrected.

(1*E*,4*E*)-1,5-Diphenyl-1,4-pentadien-3-ol (1a):[18] To a cooled (0 °C) slurry of 1,5-diphenyl-1,4-pentadien-3-one (2.34 g, 10.0×10^{-3} mol) in methanol (20 mL), $NaBH_4$ (400 mg) was added in two portions. After 2 h, the resulting solution was poured into 1 M NaOH (100 mL), and the crystalline product was collected and recrystallized from heptane (50 mL) to give a white solid (2.03 g, 8.59×10^{-3} mol, 86%), m.p. 68.2−69.5 °C (ref.[18] 66−68 °C). − IR (KBr): $\tilde{\nu}$ = 3500−3200 cm^{-1} (O−H), 3020 (=C−H), 1495 (Ar). − ^1H NMR: δ = 1.89 (d, 1 H, J = 3.6 Hz, OH), 4.99 (broad t, 1 H, 3-H), 6.32 (dd, 2 H, J = 16.0, 6.2 Hz, 2- and 4-H), 6.67 (d, 2 H, J =

16.0 Hz, 1- and 5-H), 7.21−7.42 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 73.7, 126.6, 127.8, 128.6, 130.3, 130.9, 136.5. − MS; *m*/*z* (%) = 236 (5) [M$^+$], 234 (7) [M$^+$ − 2 H], 218 (100) [M$^+$ − H_2O], 115 (32), 202 (45).

(1*E*,4*E*)-3-Methoxy-1,5-diphenyl-1,4-pentadiene (1b):[21] To a solution of $AgNO_3$ (5.18 g, 30.49 × 10^{-3} mol) in water (7 mL), NaOH (1 M, 30 mL) was added dropwise until precipitation was just completed. The precipitated Ag_2O was isolated by filtration and washed with water. The alcohol **1a** (1.98 g, 8.38 × 10^{-3} mol), KOH (44.7 mg, 0.79 × 10^{-3} mol), the freshly prepared Ag_2O, and methyl iodide (15 mL) were stirred at room temp. under nitrogen for 28 h. The reaction mixture was diluted with EtOAc (70 mL), filtered, and concentrated. Flash chromatography (10% EtOAc/heptane) provided the methyl ether **1b** (1.72 g, 6.78 × 10^{-3} mol, 82%) as a pale yellow viscous solid. − IR: (KBr): $\tilde{\nu}$ = 3020 cm^{-1} (=C−H), 2820 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar), 1145 (C−O). − ^{1}H NMR: δ = 3.40 (s, 3 H, Me), 4.42 (t, 1 H, *J* = 7.0 Hz, 1-H), 6.21 (dd, 2 H, *J* = 15.8, 7.0 Hz, 2-H), 6.64 (d, 2 H, *J* = 15.8 Hz, 3-H), 7.24−7.42 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 56.1, 82.8, 126.6, 127.8, 128.7, 128.9, 132.0, 136.6. − MS; *m*/*z* (%) = 250 (2) [M$^+$], 218 (100) [M$^+$ − MeOH], 202 (20), 115 (13).

(1*E*,4*E*)-3-Benzyloxy-1,5-diphenyl-1,4-pentadiene (1c):[21] The alcohol **1a** (473 mg, 2.00 × 10^{-3} mol), KOH (7 mg, 0.12 × 10^{-3} mol), and Ag_2O, freshly prepared from $AgNO_3$ (850 mg, 5.00 × 10^{-3} mol), were stirred in DMF (2.5 mL). Benzyl bromide (357 mL, 3.00 × 10^{-3} mol) was added and the reaction mixture was stirred under dry nitrogen for 43 h. The solution was filtered, the filtrate was diluted with EtOAc, washed with H_2O (5 × 6 mL) and brine (2 × 6 mL), dried ($MgSO_4$) and concentrated. The benzyl ether **1c** (451 mg, 1.4 × 10^{-3} mol, 69%) was isolated by flash chromatography (10% EtOAc/heptane) as a light yellow oil which solidified during storage. − IR (neat): $\tilde{\nu}$ = 3020 cm^{-1} (=C−H), 2850 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: δ = 4.62 (s, 2 H, CH_2), 4.63 (t, 1 H, *J* = 7.0 Hz, 3-H), 6.28 (dd, 2 H, *J* = 7.0, 16.1 Hz, 2- and 4-H), 6.64 (d, 2 H, *J* = 16.1 Hz, 1- and 5-H), 7.23−7.45 (m, 15 H, aromatic H). − ^{13}C NMR: δ = 69.9, 80.4, 126.6, 127.6, 127.8, 128.5, 128.5, 128.7, 129.0, 132.0, 136.6, 138.5. − MS; *m*/*z* (%) = 326 (0.5) [M$^+$], 235 (4), 218 (100) [M$^+$ − BnOH], 91 (48) [Bn$^+$].

(1*E*,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-1,5-diphenyl-1,4-pentadiene (1d):[23] To a stirred solution of alcohol **1a** (47.9 mg, 0.2 × 10^{-3} mol) in CH_2Cl_2 (0.8 mL), triethylamine (27.5 mg, 0.27 × 10^{-3} mol), DMAP (0.98 mg, 0.008 × 10^{-3} mol), and *tert*-butylchlorodimethylsilane (44.2 mg, 0.29 × 10^{-3} mol) were added at 0 °C. The reaction mixture was allowed to warm to room temp. and stirred for 48 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aqueous NH_4Cl (2 × 5 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (3% EtOAc/heptane) provided the silyl ether **1d** (54.2 mg, 0.15 × 10^{-3} mol, 77%) as a colourless oil. − IR (neat): $\tilde{\nu}$ = 3020 cm^{-1} (=C−H), 2950 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: δ = 0.13 (s, 6 H, Me), 0.96 (s, 9 H, *t*Bu), 4.96 (t, 1 H, *J* = 5.9 Hz, 3-H), 6.23 (dd, 2 H, *J* = 15.8, 5.9 Hz, 2- and 4-H), 6.60 (d, 2 H, *J* = 15.8 Hz, 1- and 5-H), 7.20−7.40 (m, 10 H, aromatic H). − ^{13}C NMR: δ = -4.4, 18.6, 26.1, 74.4, 126.6, 127.6, 128.7, 129.3, 131.8, 137.1. − MS; *m*/*z* (%) = 350 (3) [M$^+$], 293 (21) [M$^+$ − *t*Bu], 218 (93) [M$^+$ − TBDMSOH], 75 (100) [Me_2SiOH^+], 91 (27).

(1*E*,4*E*)-1,5-Diphenyl-3-(triisopropylsilyloxy)-1,4-pentadiene (1e):[22] To a stirred solution of the alcohol **1a** (473 mg, 2.0 × 10^{-3} mol) and $AgNO_3$ (340 mg, 2.0 × 10^{-3} mol) in dry pyridine (5 mL), chlorotriisopropylsilane (425 mg, 2.0 × 10^{-3} mol) was added under nitrogen. The reaction mixture was stirred for 17 h at room temp. and filtered. Then the filtrate was diluted with EtOAc (ca. 20 mL), washed with water (2 × 10 mL), 10% (w/v) aqueous $CuSO_4$ (5 × 10 mL), water (1 × 10 mL), and brine (1 × 10 mL), and dried ($MgSO_4$). Purification by flash chromatography (5% EtOAc/heptane) gave the silyl ether **1e** (488 mg, 1.2 × 10^{-3} mol, 62%) as a white solid, m.p. 50.8−52.6 °C. − IR (KBr): $\tilde{\nu}$ = 3020 cm^{-1} (=C−H), 2950 (−C−H), 2850 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: δ = 1.05−1.15 (m, 21 H, *i*Pr), 5.04 (t, 1 H, *J* = 6.0 Hz, 3-H), 6.23 (dd, 2 H, *J* = 16.1, 6.0 Hz, 2- and 4-H), 6.62 (d, 2 H, *J* = 16.1 Hz, 1- and 5-H), 7.19−7.40 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 12.5, 18.2, 74.4, 126.6, 127.5, 128.6, 129.1, 132.2, 137.1. − MS; *m*/*z* (%) = 392 (6) [M$^+$], 349 (54) [M$^+$ − *i*Pr], 219 (100) [M$^+$ − TIPSO], 91 (47).

(1*E*,4*E*)-1,5-Diphenyl-3-trityloxy-1,4-pentadiene (1f): The alcohol **1a** (598 mg, 2.53 × 10^{-3} mol) and $AgNO_3$ (430 mg, 2.53 × 10^{-3} mol) were dissolved in dry pyridine (5 mL) under cooling. Trityl chloride (746 mg, 2.53 × 10^{-3} mol) in CH_2Cl_2 (2 mL) was added, and the reaction mixture was stirred under nitrogen for 144 h. The reaction mixture was diluted with EtOAc (40 mL), filtered and washed with water (2 × 10 mL), 10% aqueous $CuSO_4$ (4 × 10 mL), water (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), and brine (1 × 10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10% EtOAc/heptane) to give the trityl ether **1f** as a white solid (390 mg, 0.82 × 10^{-3} mol, 32%). − IR (KBr): $\tilde{\nu}$ = 3020 cm^{-1} (=C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: δ = 4.76 (t, 1 H, *J* = 6.6 Hz, 3-H), 5.96 (dd, 2 H, *J* = 16.1, 6.6 Hz, 2- and 4-H), 6.25 (d, 2 H, *J* = 16.1 Hz, 1- and 5-H), 7.14−7.28 (m, 19 H, aromatic H), 7.58 (m, 6 H, aromatic H). − ^{13}C NMR: δ = 76.0, 88.0, 126.5, 127.2, 127.3, 127.8, 127.8, 128.4, 129.0, 129.1, 130.5, 137.2, 144.9.

General Procedures

Dihydroxylation with Potassium Ferricyanide [$K_3Fe(CN)_6$] as Cooxidant:[27] Either an AD mix or a mixture of K_2CO_3 (83 mg, 0.6 × 10^{-3} mol), $K_3Fe(CN)_6$ (198 mg, 0.6 × 10^{-3} mol), $K_2OsO_2(OH)_4$ (0.4−1.1 mg, 0.5−1.5 mol-%), a ligand [PYR (2.2 mg, 1.2 mol-%), AQN (2.1 mg 1.2 mol-%), CLB (1.2 mg, 1.5 mol-%) or quinuclidine (10−40 mol-%)] and methanesulfonamide (19 mg, 0.2 × 10^{-3} mol) were dissolved in a mixture of *tert*-butyl alcohol/water (1:1, 2 mL). In cases where the diene showed low solubility, toluene (0.2 mL) was added. The diene (0.2 × 10^{-3} mol) was added in one portion and the reaction mixture was stirred vigorously at room temp. between 20 h and 20 d. The reaction was quenched with Na_2SO_3 (0.3 g) and the reaction mixture was stirred for 1 h before the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with KOH (2 M, 2 × 5 mL) to remove the sulfonamide, dried ($MgSO_4$) and concentrated. The crude product was then purified by flash chromatography.

(1*R,2*R**,3*S**,4*E*)-1,5-Diphenyl-4-pentene-1,2,3-triol [(1*R**,2*R**,3*S**)-2a] and (1*R**,2*R**,3*R**,4*E*)-1,5-Diphenyl-4-pentene-1,2,3-triol [(1*R**,2*R**,3*R**)-2a]:** The general procedure for dihydroxylation with $K_3Fe(CN)_6$ was followed. After flash chromatography (60% EtOAc/heptane), the product was collected as a diastereomeric mixture of triols. − IR (diastereomeric mixture, KBr): $\tilde{\nu}$ = 3450 cm^{-1} (OH), 3400−3200 (OH), 3020 (=C−H), 2900 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2a:** δ = 2.54 (broad s, OH), 3.71 (broad s, 1 H), 4.27 (broad s, 1 H), 4.86 (broad t), 6.25 (dd, *J* = 16.0, 7.0 Hz, 4-H), 6.62 (d, *J* = 16.0 Hz, 5-H), 7.23−7.47 (m, aromatic H); **(1*R**,2*R**,3*R**)-2a:** δ = 2.54 (broad s, 2 H, OH), 3.88 (t, 1 H, *J* =

4.4 Hz, 2-H), 4.33 (dd, 1 H, *J* = 7.0, 4.0 Hz, 3-H), 4.86 (d, 1 H, *J* = 4.4 Hz, 1-H), 6.33 (dd, 1 H, *J* = 16.1, 7.0 Hz, 4-H), 6.64 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.23−7.47 (m, aromatic H).

(1*R,2*R**,3*S**,4*E*)-3-Methoxy-1,5-diphenyl-4-pentene-1,2-diol [(1*R**, 2*R**,3*S**)-2b] and (1*R**,2*R**,3*R**,4*E*)-3-Methoxy-1,5-diphenyl-4-pentene-1,2-diol [(1*R**,2*R**,3*R**)-2b]:** The general procedure for dihydroxylation with $K_3Fe(CN)_6$ was followed. After flash chromatography (50% EtOAc/heptane), the product was collected as a diastereomeric mixture of diols. The *syn* and *anti* diastereomers could be separated by careful flash chromatography (40% EtOAc/heptane). − IR (diastereomeric mixture, neat): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3020 (=C−H), 2950 (−C−H), 2850 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2b:** δ = 2.85 (d, 1 H, *J* = 5.1 Hz, 2-OH), 3.13 (d, 1 H, *J* = 4.8 Hz, 1-OH), 3.35 (s, 3 H, Me), 3.77−3.69 (m, 2 H, 3-H and 2-H), 4.82 (dd, 1 H, *J* = 4.8, 4.4 Hz, 1-H), 6.16 (dd, 1 H, *J* = 16.1, 8.4 Hz, 4-H), 6.60 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.25−7.42 (m, 10 H, aromatic H); **(1*R**,2*R**,3*R**)-2b:** δ = 2.67 (d, 1 H, *J* = 5.5 Hz, 2-OH), 3.24 (d, 1 H, *J* = 3.3 Hz, 1-OH), 3.34 (s, 3 H, Me), 3.80 (dd, 1 H, *J* = 8.0, 4.0 Hz, 3-H), 3.86 (ddd, 1 H, *J* = 5.5, 4.4, 4.0 Hz, 2-H), 4.86 (t, 1 H, *J* = 4.4, 3.3 Hz, 1-H), 6.19 (dd, 1 H, *J* = 16.1, 8.0 Hz, 4-H), 6.58 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.25−7.42 (m, 10 H, aromatic H). − ^{13}C NMR: **(1*R**,2*R**,3*S**)-2b:** δ = 56.5, 74.1, 77.8, 82.8, 125.7, 126.7, 126.7, 127.9, 128.2, 128.5, 128.7, 135.2, 136.1, 141.2; **(1*R**,2*R**,3*R**)-2b:** δ = 56.9, 73.2, 77.0, 84.1, 125.1, 126.7, 126.8, 127.9, 128.3, 128.5, 128.8, 135.4, 136.1, 140.7. − Optical rotation: **(1*R*,2*R*,3*R*)-2b:** $[\alpha]_D^{22}$ = +63.8 (*c* = 10.0 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* 98%, *de* 98%); **(1*R*,2*R*,3*S*)-2b:** $[\alpha]_D^{22}$ = +31.4 (*c* = 4.55 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* >99%, *de* 98%).

(1*R,2*R**,3*S**,4*E*)-3-Benzyloxy-1,5-diphenyl-4-pentene-1,2-diol [(1*R**,2*R**,3*S**)-2c] and (1*R**,2*R**,3*R**,4*E*)-3-Benzyloxy-1,5-diphenyl-4-pentene-1,2-diol [(1*R**,2*R**,3*R**)-2c]:** The general procedure for dihydroxylation with $K_3Fe(CN)_6$ was applied. After flash chromatography (50% EtOAc/heptane) the product was collected as a diastereomeric mixture of diols. − IR (diastereomeric mixture, neat): $\tilde{\nu}$ = 3430 cm^{-1} (OH), 3020 (=C−H), 2870 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2c:** δ = 3.74 (dd, 1 H, *J* = 4.8, 4.4 Hz, 2-H), 4.00 (dd, 1 H, *J* = 8.3, 4.4 Hz, 3-H), 4.38 (d, 1 H, *J* = 11.5 Hz, CH*H*Ph), 4.68 (d, 1 H, *J* = 11.5 Hz, C*H*HPh), 4.78 (d, 1 H, *J* = 4.8 Hz, 1-H), 6.25 (dd, 1 H, *J* = 16.0, 8.3 Hz, 4-H), 6.60 (d, 1 H, *J* = 16.0 Hz, 5-H), 7.22−7.45 (m, aromatic H); **(1*R**,2*R**,3*R**)-2c:** δ = 3.91 (t, 1 H, *J* = 4.4 Hz, 2-H), 4.07 (dd, 1 H, *J* = 8.1, 4.4 Hz, 3-H), 4.40 (dd, 1 H, *J* = 11.5 Hz, CH*H*Ph), 4.66 (dd, 1 H, *J* = 11.5 Hz, C*H*HPh), 4.92 (d, 1 H, *J* = 4.4 Hz, 1-H), 6.26 (dd, 1 H, *J* = 16.1, 8.1 Hz, 4-H), 6.61 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.22−7.45 (m, aromatic H).

(1*R,2*R**,3*S**,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-1,5-diphenyl-4-pentene-1,2-diol [(1*R**,2*R**,3*S**)-2d] and (1*R**,2*R**,3*R**,4*E*)-3-(*tert*-Butyldimethylsilyloxy)-1,5-diphenyl-4-pentene-1,2-diol [(1*R**,2*R**, 3*R**)-2d]:** The general procedure for dihydroxylation with $K_3Fe(CN)_6$ was followed. Diols **2d** were isolated as a *syn* and *anti* mixture by flash chromatography (20% EtOAc/heptane). − IR (diastereomeric mixture, neat): $\tilde{\nu}$ = 3430 cm^{-1} (OH), 3050 (=C−H), 3020 (=C−H), 2950 (−C−H), 2870 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2d:** δ = 0.07 (s, 3 H, Me), 0.14 (s, Me), 0.96 (s, *t*Bu), 2.96 (d, 1 H, *J* = 6.2 Hz, 2-OH), 3.18 (d, 1 H, *J* = 4.8 Hz, 1-OH), 3.63 (ddd, 1 H, *J* = 6.2, 4.7, 4.4 Hz, 2-H), 4.30 (dd, 1 H, *J* = 8.2, 4.7 Hz, 3-H), 4.73 (dd, 1 H, *J* = 4.8, 4.4 Hz, 1-H), 6.25 (dd, 1 H, *J* = 16.1, 8.2 Hz, 4-H), 6.50 (d, 1 H, *J* = 16.1, 5-H), 7.25−7.40 (m, aromatic H); **(1*R**,2*R**,3*R**)-2d:** δ = 0.09 (s, 3 H, Me), 0.96 (s, *t*Bu), 0.14 (s, Me), 2.68 (d, 1 H, *J* = 6.2 Hz, 2-OH), 3.48 (d, 1 H, *J* = 2.8 Hz, 1-OH), 3.73 (1 H, dt, *J* = 6.2, 3.3 Hz, 2-H), 4.45−4.47 (dd, 1 H, *J* = 6.6, 3.3 Hz, 3-H), 4.97 (t, 1 H, *J* = 2.8 Hz, 1-H), 6.26 (dd, 1 H, PhC *J* = 16.1, 6.6 Hz, 4-H), 6.60 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.25−7.40 (m, aromatic H).

(1*R,2*R**,3*S**,4*E*)-1,5-Diphenyl-3-triisopropylsilyloxy-4-pentene-1,2-diol [(1*R**,2*R**,3*S**)-2e] and (1*R**,2*R**,3*R**,4*E*)-1,5-diphenyl-3-triisopropylsilyloxy-4-pentene-1,2-diol [(1*R**,2*R**,3*R**)-2e]:** The general procedure for dihydroxylation with $K_3Fe(CN)_6$ was followed. The *syn* and *anti* diastereomers of **2e** could be separated by careful flash chromatography (20% EtOAc/heptane). − IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (OH), 3050 (=C−H), 3020 (=C−H), 2950 (−C−H), 2870 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2e:** δ = 1.00−1.20 (m, 21 H, *i*Pr), 3.06 (broad s, 2 H, OH), 3.69 (dd, 1 H, *J* = 5.5, 3.3 Hz, 2-H), 4.50 (dd, 1 H, *J* = 8.4, 5.9 Hz, 3-H), 4.77 (d, 1 H, *J* = 3.3 Hz, 1-H), 6.27 (dd, 1 H, *J* = 16.1, 8.4 Hz, 4-H), 6.57 (d, 1 H, *J* = 16.1 Hz, 5-H), 3.36 (d, 1 H, *J* = 2.2 Hz, 1-OH), 7.25−7.40 (m, 10 H, aromatic H); **(1*R**,2*R**,3*R**)-2e:** δ = 0.99−1.08 (m, 21 H, *i*Pr), 2.71 (d, 1 H, *J* = 5.1 Hz, 2-OH), 3.81 (ddd, 1 H, *J* = 5.1, 4.8, 2.9 Hz, 2-H), 4.42 (dd, 1 H, *J* = 7.7, 2.9 Hz, 3-H), 4.87 (dd, 1 H, *J* = 4.8, 2.2 Hz, 1-H), 6.27 (dd, 1 H, *J* = 16.1, 7.7 Hz, 4-H), 6.50 (d, 1 H, *J* = 16.1 Hz, 5-H), 7.40−7.25 (m, 10 H, aromatic H). − ^{13}C NMR: **(1*R**,2*R**,3*S**)-2e:** δ = 12.6, 18.2, 72.7, 75.3, 78.5, 126.5, 127.7, 126.7, 128.1, 128.5, 128.8, 129.1, 133.0, 136.3, 141.8; **(1*R**,2*R**,3*R**)-2e:** δ = 12.4, 18.1, 73.2, 76.2, 78.6, 126.6, 126.8, 128.0, 128.1, 128.5, 128.8, 132.9, 136.4, 140.6. − Optical rotation: **(1*R*,2*R*,3*S*)-2e:** $[\alpha]_D^{33}$ = +57.9 (*c* = 6.25 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* 83%, *de* >99%); **(1*R*,2*R*,3*R*)-2e:** $[\alpha]_D^{33}$ = + 5.8 (*c* = 11.7 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* 99%, *de* 94%).

(1*R,2*R**,3*S**,4*E*)-1,5-Diphenyl-3-trityloxy-4-pentene-1,2-diol [(1*R**, 2*R**,3*S**)-2f] and (1*R**,2*R**,3*R**,4*E*)-1,5-Diphenyl-3-trityloxy-4-pentene-1,2-diol [(1*R**,2*R**,3*R**)-2f]**: The dihydroxylation was carried out as described in the general procedure for dihydroxylation with $K_3Fe(CN)_6$. The *syn* and *anti* diastereomers of **2f** could be separated by careful flash chromatography (30% EtOAc/heptane). − IR (diastereomeric mixture, KBr): $\tilde{\nu}$ = 3600−3200 cm^{-1} (OH), 3020 (=C−H), 2870 (−C−H), 1600 (Ar), 1495 (Ar). − ^{1}H NMR: **(1*R**,2*R**,3*S**)-2f:** δ = 2.73 (d, 1 H, *J* = 5.5 Hz, 1-OH), 2.83 (d, 1 H, *J* = 5.9, 2-OH), 3.64 (ddd, 1 H, *J* = 5.9, 5.5, 3.3 Hz, 2-H), 4.10 (dd, 1 H, *J* = 8.4, 5.5 Hz, 3-H), 4.81 (dd, 1 H, *J* = 5.1, 3.3 Hz, 1-H), 5.93 (d, 1 H, *J* = 16.1 Hz, 5-H), 6.18 (dd, 1 H, *J* = 16.1, 8.4 Hz, 4-H), 7.10−7.08 (m, 2 H, aromatic H), 7.16−7.30 (m, 17 H, aromatic H), 7.47−7.45 (m, 6 H, aromatic H); **(1*R**,2*R**,3*R**)-2f:** δ = 2.73 (d, 1 H, *J* = 3.3 Hz, 2-OH), 2.83 (d, *J* 1 H, = 1.8 Hz, 1-OH), 3.24 (dt, 1 H, *J* = 7.0, 3.3 Hz, 2-H), 3.94 (dd, 1 H, *J* = 8.5, 3.3 Hz, 3-H), 4.48 (dd, 1 H, *J* = 7.0, 1.8 Hz, 1-H), 5.95 (d, 1 H, *J* = 16.1 Hz, 4-H), 6.23 (dd, 1 H, *J* = 16.1, 8.5 Hz, 5-H), 7.05−7.03 (m, 2 H, aromatic H), 7.33−7.17 (m, 17 H, aromatic H), 7.44−7.42 (m, 6 H, aromatic H). − ^{13}C NMR: **(1*R**,2*R**,3*S**)-2f:** δ = 72.6, 76.9, 77.7, 87.8, 126.4, 126.5, 127.4, 127.6, 127.7, 127.8, 127.8, 128.0, 128.2, 128.4, 128.4, 129.1, 132.3, 136.6, 141.8, 144.3. − Optical rotation: **(1*S*,2*S*,3*R*)-2f:** $[\alpha]_D^{30}$ = −85.1 (*c* = 2.75 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* ≈56%, *de* >99%); **(1*S*,2*S*,3*S*)-2f:** $[\alpha]_D^{30}$ = +61.5 (*c* = 2.60 × 10^{-3} g ml^{-1}, CH_2Cl_2, *ee* 95%, *de* 98%).

(1*R*,2*R*,3*R*,5*E*)-1,5-Diphenyl-1,2-epoxy-5-penten-3-ol [(1*R*,2*R*,3*R*)-3a] from 1,5-Diphenyl-1,4-pentadien-3-ol (1a):[41] To a cooled (−20 °C) heterogeneous mixture of dry CH_2Cl_2 (3.5 mL) and powdered, activated molecular sieves (4 Å, 30 mg), D-(−)-diethyl tartrate (12.4 mg, 10.3 μL, 0.06 × 10^{-3} mol, 6 mol-%) and Ti(O*i*Pr)$_4$ (14.7 μL, 0.05 × 10^{-3} mol, 5 mol-%) were added. The reaction mixture was stirred at −20 °C, and anhydrous *tert*-butyl hydrogen peroxide

(278 μL, 1.5×10^{-3} mol, 5.39 M in isooctane) was added. The resulting mixture was stirred at −20 °C for 35 min before the addition of the alcohol **1a** (236 mg, 1×10^{-3} mol) in dry CH_2Cl_2 (tot. 1 mL). The reaction mixture was stirred at −20 °C for 42 h, and then allowed to heat to 0 °C. The mixture was slowly poured into a cooled (0 °C) solution of $FeSO_4$ (0.33 g, 1.2×10^{-3} mol) and tartaric acid (0.11 mg, 0.6×10^{-3} mol) in H_2O (1 mL). The mixture was stirred for 10 min before the phases were separated, and the aqueous phase was extracted with diethyl ether (2 × 2 mL). The combined organic phases were stirred vigorously with 30% (w/v) NaOH in saturated aqueous NaCl (0.1 mL) for 1 h. The mixture was diluted with water (0.5 mL), and the resulting emulsion was filtered before the two phases could be separated. The aqueous phase was extracted with CH_2Cl_2 (1 ×) and with diethyl ether (2 ×). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography (30% EtOAc/heptane) provided the epoxy alcohol (1*R*,2*R*,3*R*)-**3a** (163 mg, 63%) as a colourless oil. − IR (KBr): $\tilde{\nu}$ = 3500−3200 cm^{-1} (O−H), 3050 (C−H epoxide), 3020 (=C−H), 2950 (−C−H), 2850 (−C−H), 1650 (C=C), 1600 (Ar), 1580 (Ar), 1495 (Ar). − ^{1}H NMR: δ = 2.26 (broad d, 1 H, *J* = 6.2 Hz, OH), 3.26 (dd, 1 H, *J* = 3.0, 2.2 Hz, 4-H), 4.02 (d, 1 H, *J* = 2.2 Hz, 5-H), 4.62−4.65 (m, 1 H, 3-H), 6.25 (dd, 1 H, *J* = 16.0, 6.8 Hz, 2-H), 6.75 (d, 1 H, *J* = 16.0 Hz, 1-H), 7.26−7.42 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 54.9, 64.1, 70.2, 125.9, 126.2, 126.7, 128.2, 128.5, 128.6, 128.7, 133.2, 136.2, 136.6. − Optical rotation: $[\alpha]_D^{28}$ = +43.4 (*c* = 0.0089 g ml^{-1}, CH_2Cl_2, *ee* 99%, *de* 94%).

(1*R*,2*R*,3*R*,5*E*)-1,5-Diphenyl-3-triisopropylsilyloxy-1,2-epoxy-5-pentene [(1*R*,2*R*,3*R*)-3e] from the Corresponding Diol 2e:[26] Chlorotrimethylsilane (45 μL, 0.35×10^{-3} mol) and trimethyl orthoacetate (42 μL, 0.33×10^{-3} mol) were added to diol **2e** (*ee* 99%, *de* 94%) (107 mg, 0.25×10^{-3} mol) in CH_2Cl_2 (1.5 mL) at room temp. and the mixture was stirred for 15 h. After concentration, the crude acetoxy chloride was dissolved in methanol (2 mL), and K_2CO_3 (44 mg, 0.32×10^{-3} mol) was added, and the resulting suspension stirred at room temp. for 21 h. The mixture was poured into saturated aqueous NH_4Cl (1.5 mL) and extracted with CH_2Cl_2 (4 × 2 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (5% EtOAc/heptane) furnished the epoxide (1*R*,2*R*,3*R*)-**3e** (71.4 mg, 0.17×10^{-3} mol, 70%) as a colourless liquid. − ^{1}H NMR: δ = 1.00−1.18 (m, 21 H, *i*Pr), 3.10 (ddd, 1 H, *J* = 4.2, 1.9, 0.7 Hz, 2-H), 3.93 (d, 1 H, *J* = 1.9 Hz, 5-H), 4.51 (dd, 1 H, *J* = 6.5, 4.2 Hz, 3-H), 6.28 (ddd, 1 H, *J* = 16.0, 6.5, 0.7 Hz, 2-H), 6.67 (d, 1 H, *J* = 16.0 Hz, 1-H), 7.23−7.40 (m, 10 H, aromatic H). − ^{13}C NMR: δ = 12.4, 18.1, 56.4, 65.3, 72.8, 125.8, 126.7, 127.8, 128.2, 128.5, 128.7, 129.2, 131.4, 136.6, 137.3. − Optical rotation: $[\alpha]_D^{30}$ = −12.8 (*c* = 0.011 g ml^{-1}, CH_2Cl_2).

(1*R*,2*R*,3*R*,5*E*)-1,5-Diphenyl-1,2-epoxy-5-penten-3-ol [(1*R*,2*R*,3*R*)-3a] by Deprotection of (1*R*,2*R*,3*R*,5*E*)-1,5-Diphenyl-3-triisopropylsilyloxy-1,2-epoxy-5-pentene [(1*R*,2*R*,3*R*)-3e]:[42] To a cooled (0 °C) solution of triisopropylsilyloxy epoxide (1*R*,2*R*,3*R*)-**3e** (41 mg, 0.1×10^{-3} mol) in dry THF (1 mL), tetrabutylammonium fluoride (61 mg, 0.2×10^{-3} mol) was added. After 15 min, the reaction mixture was diluted with diethyl ether (4 mL), washed with HCl (0.1 M, 3 × 1 mL), saturated aqueous $NaHCO_3$ (1 × 1 mL), and brine (1 × 1 mL), and the mixture was dried ($MgSO_4$) and concentrated. Flash chromatography (30% Et_2O/pentane) provided the epoxy alcohol (1*R*,2*R*,3*R*)-**3a** (20 mg, 0.08×10^{-3} mol, 80%). The analytical data are in accordance with the data described above.

(5*E*)-1,5-Diphenyl-1,2-epoxy-5-penten-3-ols 3a by Deprotection of a Racemic Mixture of the Corresponding Triisopropylsilyl Ethers 3e: A racemic mixture of the triisopropylsilyloxy epoxides (diastereomeric mixture) **3e** (41 mg, 0.10×10^{-3} mol) was converted into the corresponding epoxy alcohols **3a** (15.7 mg, 0.063×10^{-3} mol, 63%) following the described procedure. − ^{1}H NMR: The data of (1*R**,2*R**,3*R**)-**3a** are in accordance with the data described above; **(1*R**,2*R**,3*S**)-3a:** δ = 2.26 (broad d, 1 H, *J* = 6.2 Hz, OH), 3.24 (dd, 1 H, *J* = 4.3, 2.1 Hz, 4-H), 3.97 (d, 1 H, *J* = 2.1 Hz, 5-H), 4.41 (m, 1 H, 3-H), 6.33 (dd, 1 H, *J* = 16.0, 6.2 Hz, 2-H), 6.75 (d, 1 H, *J* = 16.0 Hz, 1-H), 7.26−7.42 (m, 10 H, aromatic H).

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