Pergamon

Tetrahedron Vol. 51, No. 5, pp. 1345-1376, 1995

0040-4020/95 $9.50+0.00

0040-4020(94)01021-8

Selective Asymmetric Dihydroxylation of Polyenes

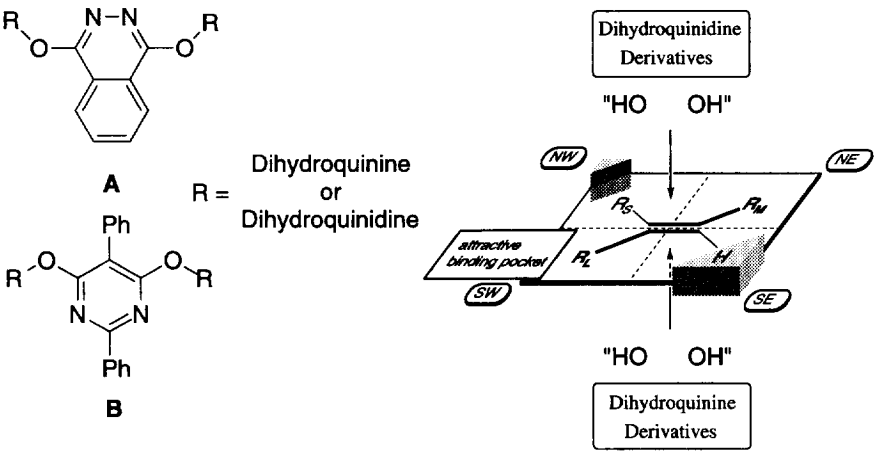
Heinrich Becker, Marcos A. Soler, and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037, USA

Abstract: The asymmetric dihydroxylation procedure (AD) is applied to a variety of polyenes. In many cases excellent regioselectivities are obtained. The observed selectivities are rationalized in terms of electronic and/or steric effects inherent to the substrate, superimposed on the substrate's favorable or unfavorable interactions with the binding pocket of the AD ligand. Surprisingly, for *medium* and *large* ring olefins with *trans*-double bonds outstanding enantioselectivities are realized using the pyrimidine ligands. A hexaol of D_3 symmetry is prepared from all *trans* cyclododecatriene.

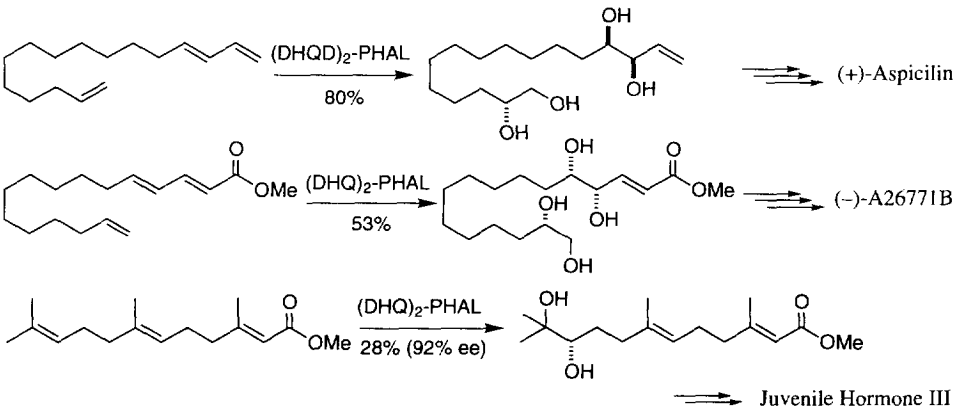
The asymmetric dihydroxylation (AD) of olefins has become a useful process in organic synthesis. Recent studies[1] have illustrated the wide range of possible substrates for this reaction. The phthalazine ligands **A**[2a] and the pyrimidine ligands **B**[2b] can be used in the oxidation of five of the six olefin-classes with high enantioselectivity and with a stereoselection predictable by the mnemonic device (Scheme 1).

Scheme 1:



The broad range of olefin-types which are good substrates for the asymmetric dihydroxylation leads naturally to the question of regio selectivity in the case of polyolefins. In the recent syntheses of the lichen macrolide (+)-aspicilin,[3] the macrolide antibiotic (−)-A26771B,[4] and juvenile hormone III[5] selective dihydroxylation of trienes plays a key role in the synthetic strategy. In all three cases, double bonds were oxidized with high regio- and stereoselectivity.

Scheme 2: Asymmetric dihydroxylation as a key step in natural product syntheses.

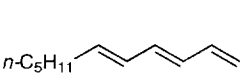
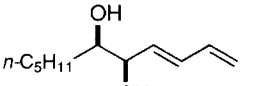
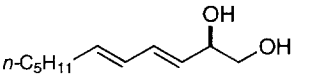
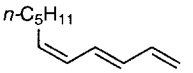
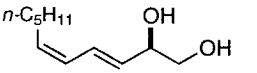
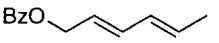
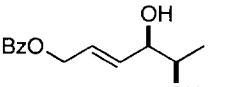
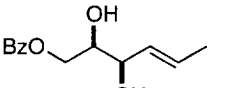
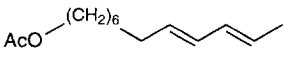
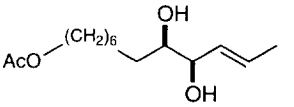
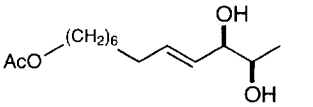
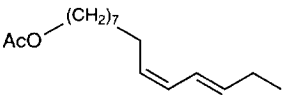
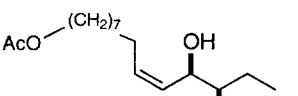
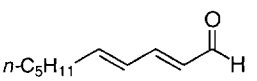
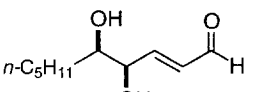


Several reports on the selective asymmetric dihydroxylation of polyenes have already appeared.[6,7] Both the electronic and steric properties of the individual double bonds seem to be important factors affecting regioselectivity. Recent kinetic studies with olefins containing isolated double bonds found much higher rate constants for the oxidation of *trans*-1,2-disubstituted and trisubstituted olefins than for *cis*-1,2-disubstituted and terminal olefins, when using the phthalazine ligands **A**.[8] However, due to the potential importance of asymmetric dihydroxylation of polyolefins in synthesis, we have undertaken a more thorough study of the factors affecting regioselectivities in these polyene oxidations. Presented here are results from the asymmetric dihydroxylation of dienes and trienes representing a variety of substitution patterns, including polyenes in acyclic systems as well as those in *normal*, *medium-sized*, and *large*[9] rings. Another key variable explored is the effect of conjugation, or the absence of it, on site selectivity in these polyene oxidations.

Acyclic Polyenes

In unfunctionalized, nonconjugated polyenes the substitution pattern and the steric environment of the double bonds are the key factors in determining the regioselectivity. In the mono-dihydroxylation of squalene (which contains only trisubstituted double bonds, all of which are very similar) there is only a modest preference for oxidation of the terminal double bond, but the resulting ee is excellent.[10] In nonconjugated polyolefins with variously substituted double bonds the degree of substitution and its pattern are usually the prime determinants of the reactivity hierarchy.

Table 1: Asymmetric dihydroxylation of various conjugated polyenes in the presence on $(DHQD)_2$-PHAL at 0°C.

Entry	Substrate	Diols	Σ Yield
1	 **1a**	 **1b** :  **1c** Ratio: 6 : 1	60%
2	 **2a**	 84%ee **2b**	48%
3	 **3a**	 >98%ee **3b**  **3c** Ratio: 14 : 1	91%
4	 **4a**	 95%ee **4b**  94%ee **4c** Ratio: 2 : 1	82%
5	 **5a**	 93%ee **5b**	82%
6	 **6a**	 94%ee **6b**	50%

For the trienes **1a** (Table 1, entry 1) and **2a** (Table 1, entry 2), no products resulting from oxidation of the internal double bond are observed. In **1a**, of the two "outside" double bonds the *trans*-disubstituted one is found to be the most reactive. In the corresponding *cis*-case **2a**, only oxidation of the terminal bond is

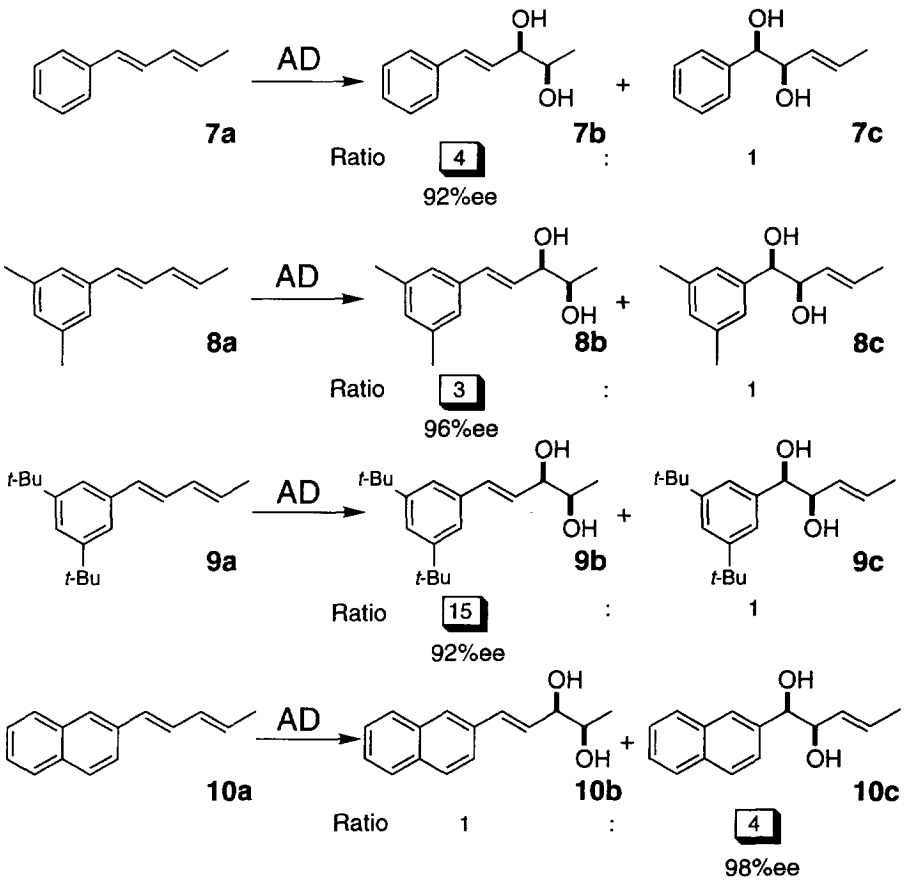
observed. Although *trans*-double bonds are usually much more reactive than *cis* disubstituted or monosubstituted double bonds, no reaction of the *trans*-double bond is observed in this case, where it would lead to disruption of conjugation. However, this simple rational may not be the entire story for triene **2a** since steric factors will tend to push the 3,4 and 5,6 olefinic links out of conjugation in any case. In fact, the kink in that part of the molecule would also be expected to disfavor its fit into the phthalazine ligand's binding pocket.[11] Dienes **4a** (Table 1, entry 4) and **5a** (Table 1, entry 5) provide additional evidence for the preference of the asymmetric dihydroxylation catalysts for trans-disubstituted double bonds.

Electron withdrawing oxygen-substituents like the benzoyloxy group in **3a** (Table 1, entry 3) have an important influence on the reactivity of the double bonds and can lead to high regioselectivities in the asymmetric dihydroxylation (see for example AD of geraniol derivatives in ref. 6b). If sterically accessible, the more electron rich double bond is the more reactive one. As the asymmetric dihydroxylation of **3a** shows, good differentiation is also possible with conjugated dienes. When a strong electron withdrawing functionality is directly *conjugated* with a polyene system it usually has a dramatic effect on the regioselectivity, directing attack (other things being equal) to the most distal double bond. Hence, dienal **6a** undergoes dihydroxylation only at the distal double bond (Table 1, entry 6).[12]

Olefins with conjugated aromatic substituents are of particular interest as substrates for the asymmetric dihydroxylation since very high ee's are usually obtained. The putative attractive interactions [11a,b] between the aromatic substituents on the olefin and those in the asymmetric dihydroxylation catalyst make these substrates particular interesting from a mechanistic point of view. It has recently been shown that one aromatic substituent on the double bond greatly enhances the rates relative to those for olefins bearing only aliphatic substituents. The size of the aromatic group seems to play an important role. In the case of the dihydroquinidine phthalazine ligand in *t*-BuOH, 2-vinylnaphthalene reacts almost five times faster than styrene and about thirty times faster than 1-decene.[11a] Molecular mechanics calculations[11b] and NMR experiments[11a] suggest, that stacking interactions between the phthalazine ring system and the aromatic substituent as well as attractive edge-to-face interactions between the aromatic substituent and a methoxyquinoline play an important role in the stabilization of the transition state[11d]. The more intense interaction with the larger 2-vinylnaphthalene leads to a faster reaction. Various substituents in the 3 and 5 position of styrene decrease or increase the observed rates and ee's depending on their size.[13] However, in the reaction of conjugated dienes with aromatic substituents, the situation is more complex.

In comparison to **7a**, the 3,5-dimethyl substituted **8a** shows a slightly greater preference for the double bond proximate to the aromatic ring, whereas di-*tert*-butyl substituted **9a** reveals a strong shift toward the site distal to the aromatic ring (Scheme 3). The general preference for attack at the outer double bond is not surprising given that oxidation at the internal site leads to greater disruption of conjugation. It has recently been shown, that methyl groups in the 3 and 5 position of styrene enhance reaction rates and ee's, whereas *tert*-butyl substituents in both positions reduce reactivity and enantioselectivity.[11d,13] The similarly substituted dienes **8a** and **9a** show, in comparison to the parent compound **7a**, a better (**8a**) or worse (**9a**) fit into the binding pocket.

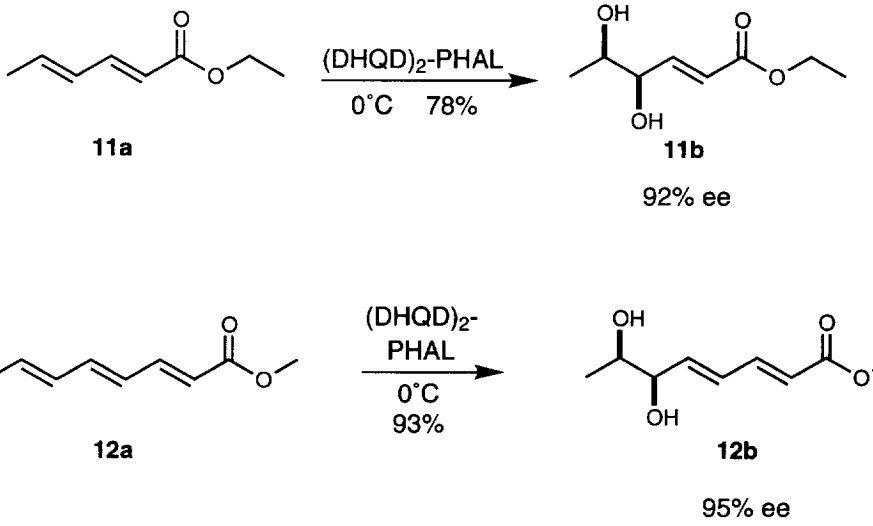
Scheme 3: Asymmetric dihydroxylation of conjugated aromatic dienes. The dihydroxylations were carried out at 0°C with dihydroquinidine phthalazine ($DHQD_2$-PHAL) as ligand. The ee was only determined for the major product.



In contrast, in the β-naphthyl substituted diene **10a** the internal double bond is oxidized predominantly, implying that the "disruption of conjugation" effect (*vide supra*) has somehow been overcome. This preference for dihydroxylation of the internal double bond may be due to favorable stacking interactions between the naphthyl group and the binding pocket of the phthalazine ligand. In the case of attack at the external double bond, strong binding interactions are not feasible. Apparently, a phenyl group does not provide enough binding interaction to overcome the normally observed preference for minimizing disruption of conjugation. A contribution to these differences from differences in the conjugation energy of the dienes **7a–10a** can not be ruled out, but calculation of the hydrogenation energies (AM1) of the internal double bond suggest, that the "disruption of conjugation" effect is similar in dienes **7a–10a**.

As shown earlier, with diene **11a** and triene **12a** (Scheme 4) only the double bond remote from the ester group is oxidized.[6a] There is, no doubt, a "disruption of conjugation" component to this regioselectivity, but the preference for attack distal to the electron withdrawing ester group is also a big factor.

Scheme 4: Asymmetric dihydroxylation of conjugated unsaturated esters.[6a]

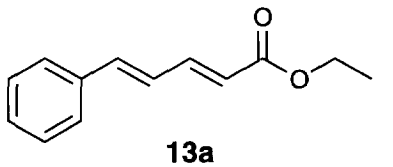


In polyenes, where the oxidation of any double bond would lead to disruption of conjugation, the selectivity of the asymmetric dihydroxylation should be forecast based on other applicable effects. For example, polyenes **13a** and **14a** (Scheme 5) react selectively at the double bond proximal to the aromatic group (binding pocket-effect) and distal to the ester group (electron withdrawing-effect).

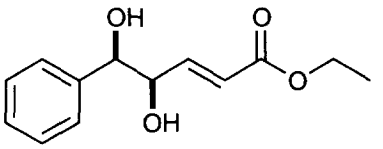
The ee's of **13b** and **14b** are exceptionally high (Scheme 5); only in the case of stilbene have ee's of this magnitude been observed.[2a] Even with the pyrimidine ligands, usually not the preferred ligands for *trans*-disubstituted olefins, high enantioselectivities are obtained. $(DHQD)_2$-PYR and $(DHQ)_2$-PYR show surprisingly different behavior with **13a**. With $(DHQ)_2$-PYR as ligand a much higher preference for oxidation of the double bond proximal to the phenyl group is found. Dihydroxylation of triene **14a** proceeds with similarly high enantioselection and even higher regioselection. Also in this case only minor oxidation of the double bonds distal to the aromatic group is observed.

Dihydroxylation of ketodienoic ester **15a** (a highly electron-deficient substrate) is successful using the buffered variation of the asymmetric dihydroxylation (Scheme 6).[14] Diols **15b** and **15c** are formed with low regioselectivity but good enantioselectivity using the phthalazine ligands. Surprisingly, the pyrimidine ligands and also quinuclidine show an ~6/1 selectivity for the double bond proximal to the keto group in **15a**.

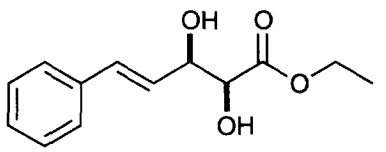
Scheme 5: Asymmetric dihydroxylation of polyenoic esters. The dihydroxylations were carried out with the indicated amount of ligand and an equal mol% of $K_2OsO_4 \cdot 2H_2O$. The ee's were determined only for the major products. With the phthalazine ligands, the amount of *ent*-**13b** or *ent*-**14b** produced is lower than 0.2%. The products shown are the enantiomers from those reactions with the DHQD-ligands.



13a

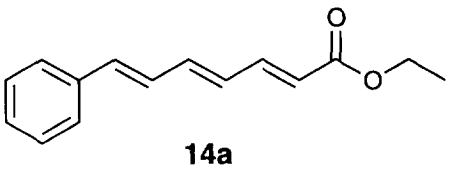


13b

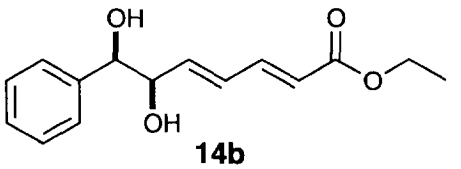


13c

Ligand	**13b** (ee)	**13c**	ΣYield
1% $(DHQD)_2$-PHAL	5 (99.5%+)	1	76% (11% starting material)
1% $(DH\ Q)_2$-PHAL	6.5 (99.5%+)	1	73% (10% starting material)
1% $(DHQD)_2$-PYR	6.5 (97%)	1	59% (28% starting material)
1% $(DHQ)_2$-PYR	16 (94%)	1	60% (24% starting material)
5% Quinuclidine	10	1	23% (42% starting material)



14a

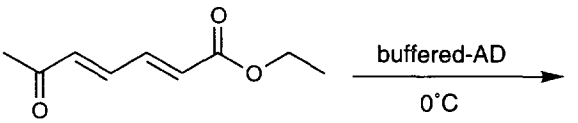


14b

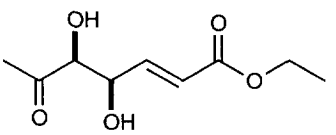
Ligand	ΣYield	
1% $(DHQD)_2$-PHAL	77% (ee=99.5%+)[a]	(22% starting material)
1% $(DHQ)_2$-PHAL	75% (ee=99.5%+)[a]	(20% starting material)
5% Quinuclidine	26%[a]	(55% starting material)

[a]: The diols contained about 5% of regioisomeric diols in the $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL cases and about 10% in the quinuclidine case.

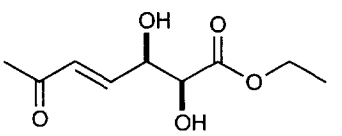
Scheme 6: Asymmetric dihydroxylation of ketodieneester **15a**. The products shown are the enantiomers from those reactions with the DHQD-ligands.



15a



15b

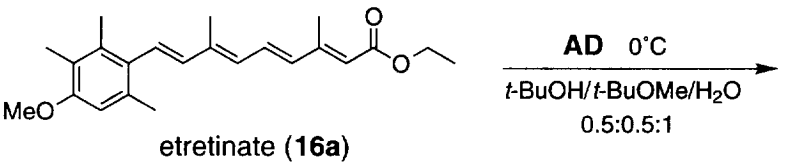


15c

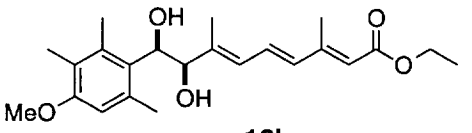
Ligands	**15b**	**15c**	Σ Yield
2% $(DHQD)_2$-PHAL	56 (97% ee)	44 (97% ee)	63% (30% starting material)
2% $(DHQ)_2$-PHAL	60 (97% ee)	40 (97% ee)	59% (25% starting material)
2.5% $(DHQD)_2$-PYR	83 (90% ee)	17 (89% ee)	60% (31% starting material)
2.5% $(DHQ)_2$-PYR	86 (91% ee)	14 (90% ee)	63% (28% starting material)
5% Quinuclidine	86	14	34% (56% starting material)

Etretinate (**16a**), an aromatic analog of retinoic acid used as a treatment for acne, is an interesting example of a complex, conjugated polyene where many different selectivity determining factors are involved (Scheme 7). Remarkably, dihydroxylation of the trisubstituted double bond next to the carboethoxy group is favored in this case. The double bond adjacent to the aromatic group, favored in the oxidation of **13a** and **14a**, reveals little reactivity in **16a** probably due to the high steric demand of the two *ortho*-methyl groups.

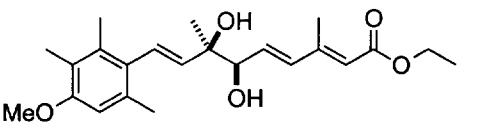
Scheme 7: Asymmetric dihydroxylation of etretinate (**16a**). Because of the low solubility of **16a**, *tert*-butyl methyl ether was used as cosolvent. To minimize the influence of over oxidation, the asymmetric dihydroxylation reactions were stopped at incomplete conversion. The products shown are the enantiomers from those reactions with the DHQD-ligands.



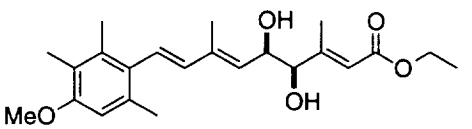
etretinate (**16a**)



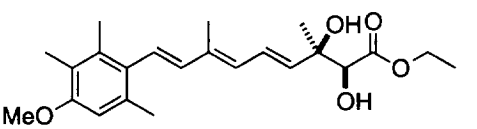
16b



16c



16d



16e

	Ratio [%]				
ligand	**16b**	**16c**	**16d**	**16e**	Yield
2%$(DHQD)_2$-PHAL	~2	7	19	72 (82%ee)	58% (2% tetrols, 30% **16a** recovered)
2% $(DHQ)_2$-PHAL	6	10	19	65 (82%ee)	43% (5% tetrols, 46% **16a** recovered)
5% Quinuclidine	8	34	49	9	19% (15% tetrols, 63% **16a** recovered)

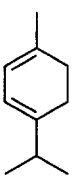
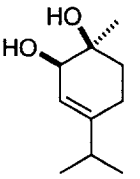
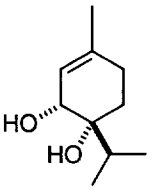
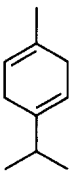
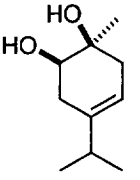
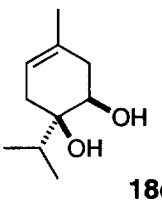
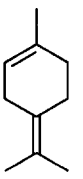
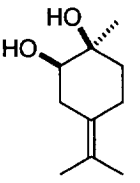
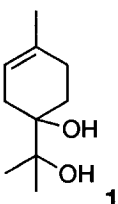
Small Cycles

Cyclic dienes **17a** and **18a** (Table 2, entry 1 and 2) show a surprisingly high differentiation between the methyl and the *iso*-propyl substituted double bonds. α-Terpinene **17a** (Table 2, entry 1) is dihydroxylated at the more accessible methyl substituted double bond with a preference of 8:1 and with an ee of 86% for the major product **17b**. The isomeric non-conjugated diene γ-terpinene **18a** (Table 2, entry 2) shows an even higher regioselectivity and enantioselectivity. In comparison, the asymmetric dihydroxylation of terpinolene **19a** (Table 2, entry 3) proceeds with only fair selectivity for the trisubstituted olefin.

Kinetic measurements reveal that simple acyclic trisubstituted double bonds usually react about ten times faster than tetrasubstituted analogs.[8] However, in this cyclic system (**19a**) the reaction rate of the tetrasubstituted double bond, while still substantially slower, is closer to that for its trisubstituted neighbor.

Applying our mnemonic device for rationalizing face selectivity (Scheme 1) to α-terpinene **17a** or γ-terpinene **18a**, the methyl or the *iso*-propyl group are pointing into the *southwest* quadrant. This is believed

Table 2: Asymmetric dihydroxylation of readily available monoterpenes in the presence of $(DHQD)_2$-PHAL.

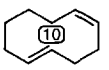
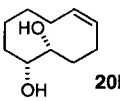
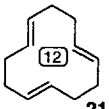
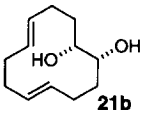
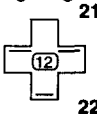
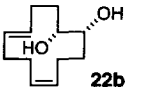
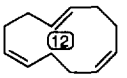
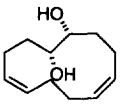
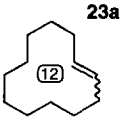
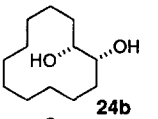
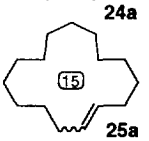
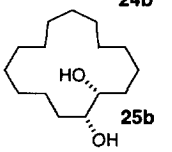
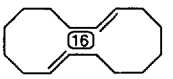
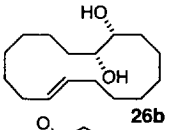
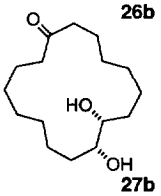
Entry	Substrate	Diols	Σ Yield
1	 **17a**	 **17b**  **17c**	78%
		86%ee Ratio: 8 : 1	
2	 **18a**	 **18b**  **18c**	84%
		96%ee Ratio: > 20 : 1	
3	 **19a**	 **19b**  **19c**	80%
		92%ee Ratio: 5 : 1	

to correspond to the region where an attractive interaction between substrate and ligand can take place. For example, this probably plays an important role in the asymmetric dihydroxylation of 1-phenyl-1-cyclohexene,[2,15] where the very high enantioselectivity of >99% with the $(DHQD)_2$-PHAL ligand is observed. The methyl groups in **17a** and **18a** are too small to have a good interaction with the binding pocket, but the results prove that they are better for this role than the *iso*-propyl substituents. Actually, the *iso*-propyl substituent in these systems probably acts more like a *t*-butyl substituent since steric interactions will force the methyls to lie above and below the plane of the cyclohexadiene rings in **17a** and **18a**. We have previously established that olefins with branched substituents (e. g. *t*-butyl), especially when that substituent must reside in the "southwest" binding pocket, usually give low ee's with the phthalazine ligands.

Medium and Large Rings

For cyclic polyenes in *normal-* and *medium* rings and with only *cis*-disubstituted double bonds, very poor enantioselectivity is usually observed.[16] As expected, *medium* and *large* ring polyenes with at least one

Table 3: Asymmetric dihydroxylation of *medium* and *large* ring olefins. The yields for reaction in the presence of $(DHQD)_2$-PYR are between 75% and 95%.[17,18]

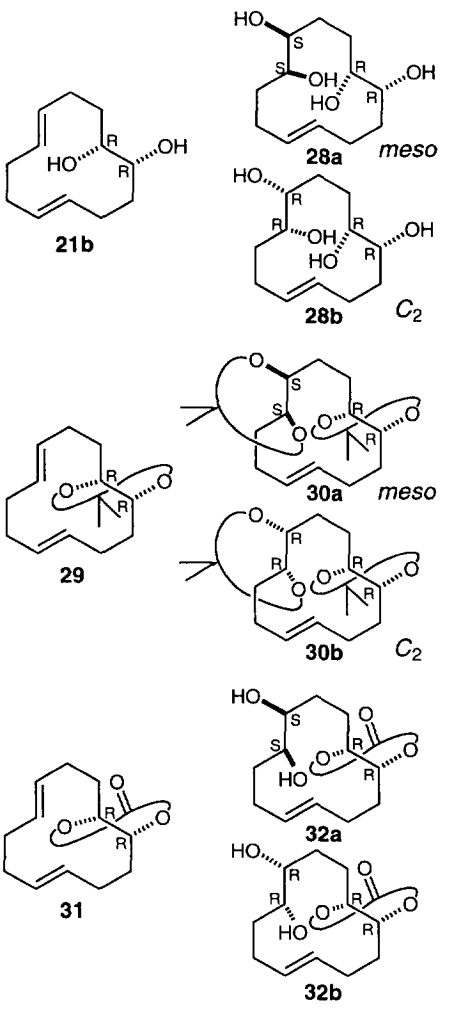
Entry	Substrate	Diol(s)	ee [%] $(DHQD)_2$-PYR	ee [%] $(DHQD)_2$-PHAL
1	 **20a**	 **20b**	**94**	51
2	 **21a**	 **21b**	**95**[a,c]	65
3	 **22a**	 **22b**	**88**[a,c]	69
4	 **23a**	 **23b**	**89**[c]	22
5	 **24a**	 **24b**	**97**[b]	60
6	 **25a**	 **25b**	**95**[b]	65
7	 **26a**	 **26b**	**92**[a]	50
8	 **27a**	 **27b**	**95**[b]	58

[a] In theses cases the reactions were stopped at low conversion.[21]
[b] See reference [19].
[c] See reference [20].

trans-double bond are much better substrates for the asymmetric dihydroxylation (Table 3).

Surprisingly, in all cases investigated, the pyrimidine ligands give far better enantioselectivity than the phthalazine ligands. Usually, only terminal olefins are satisfactorily oxidized in systems using pyrimidine ligands.[2b] However, especially in the 12-membered cycles *t,t,t*-1,5,9-cyclododecatriene (**21a**) (Table 3, entry 2) and cyclododecene (**24a**) (Table 3, entry 5) as well as in the 16-membered *t*-8-cyclohexadecenone (**27a**) (Table 3, entry 8) very high enantioselectivity is observed. In all cases with both *cis* and *trans* double bonds, only oxidation of the *trans* double bond is observed.[17] In three cases, (Table 3, entry 5, 6, and 8), *cis/trans*

Table 4: Influence of the ligand on the diastereofacial selectivity of the second dihydroxylation.[23]



	Ligand		
	Quinuclidine	$(DHQ)_2$-PYR	$(DHQD)_2$-PYR
	97	99.7	25
	..	..	..
	3	0.3	75
	94% de	99.4% de	50% de
ΣYield	61%	72%	65%
	89	99	11
	..	..	..
	11	1	89
	78% de	98% de	78% de
ΣYield	80%	85%	81%
	74	99	4.5
	..	..	..
	26	1	95.5
	48% de	98% de	91% de
ΣYield	87%	85%	80%

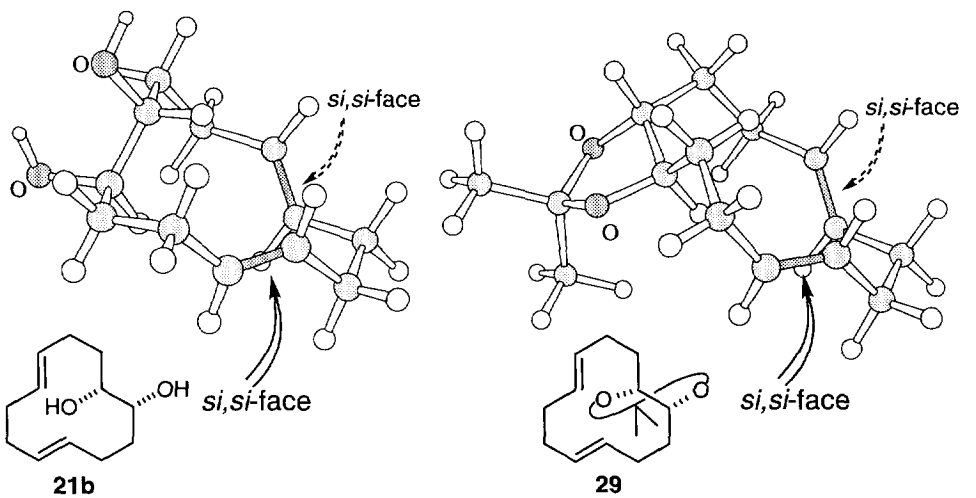
mixtures were used. Under 'standard' asymmetric dihydroxylation conditions, only in the 15-membered case (Table 3, entry 6) was diol from the dihydroxylation of the *cis* olefin observed.[18]

To minimize kinetic resolution of the product diols, the reaction of cyclic olefins with more than one *trans* double bond was performed at low conversion.[21] However, under the 'normal' asymmetric dihydroxylation conditions (see *Experimental Part: Typical procedure for the asymmetric dihydroxylation*), for *t,t,t*-cyclododecatriene **21a** and *c,t,t*-cyclododecatriene **22a**, higher enantiomeric excesses are observed.[22] Using the standard conditions, a 98–99% ee for diol **21b** (Table 3, entry 2) and 94% ee for diol **22b** (Table 3, entry 3) are realized. At even higher degrees of conversion, diol **21b** can be obtained enantiomerically pure, whereas with **22b**, a maximum of 95% ee is reached even at very high conversion.

In both cases, the second dihydroxylation step is slower than the first. In contrast to diol **21b**, the two remaining double bonds in **22b** are not equivalent. In **21b**, the minor *S,S*-enantiomer reacts faster in the presence of $(DHQD)_2$-PYR than the major *R,R*-enantiomer, which leads to improvement of the enantiomeric excess up to enantiomeric purity. In **22b** however, competing oxidation of the remaining *cis* and *trans* double bond lead to a "steady state" enantiomeric excess of about 95%.

The intrinsic diastereofacial preference of diol **21b** or the protected derivatives **29** and **31** can be shown by further diastereoselective dihydroxylation (Table 4). All reactions were performed with enantiopure (ee > 99.5%) starting materials. In all three cases, the *meso* compound is favored.[24] The intrinsic diastereofacial selectivity can be enhanced by $(DHQ)_2$-PYR (matched pair[25]) or reversed by $(DHQD)_2$-PYR (mismatched pair). Also in this application, pyrimidine ligands are the most effective.[26] The matched cases, leading to *meso* compounds, were carried out in the presence of 1% $(DHQ)_2$-PYR/1% $K_2OsO_4 \cdot 2H_2O$, the mismatched

Scheme 8: Lowest energy conformations of diol **21b** and acetonide **29** found by molecular mechanics calculation.[27]



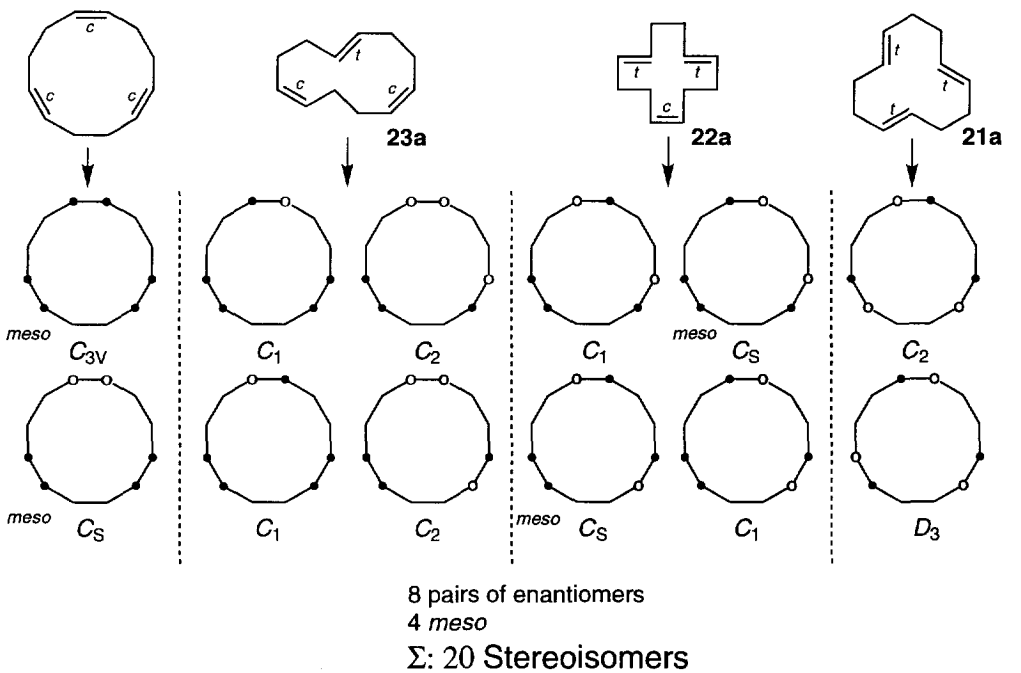
with 5% $(DHQD)_2$-PYR/5% $K_2OsO_4 \cdot 2H_2O$. Nevertheless, in the mismatched cases the reactions are, especially with diol **21b**, considerably slower.

The observed selectivities explain the kinetic resolution observed in the oxidation of *t,t,t*-cyclododecatriene **21a**. The major *R,R*-diol **21b** reacts slowly in the presence of $(DHQD)_2$-PYR, whereas the minor *S,S*-enantiomer *ent*-**21b** reacts faster, resulting in enhancement of the enantiomeric excess up to enantiomeric purity.

The direction of selectivity can be rationalized by molecular mechanics calculations.[27] The lowest energy structure for diol **21b** shows that the remaining two double bonds present their *si,si*-faces to the outside and their *re,re*-faces to the inside of the ring, suggesting that attack form the *re,re*-face is less favorable (Scheme 8). In the case of diol **21b**, the lowest energy conformation is 8.7 kJ/mol lower than the lowest energy conformation with a *re,re*-face of a double bond exposed to the outside. In acetonide **29**, the energy difference is considerably smaller (1.1 kJ/mol), which is consistant with the lower intrinsic diastereoselectivity.

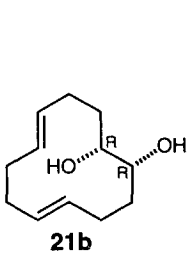
Nonselective dihydroxylation of all three double bonds in the four possible 1,5,9-cyclododecatrienes should lead to mixtures of hexaols. Of the 12 possible diastereomeric hexaols (8 pairs of enantiomers and 4 *meso* compounds)[28] only 2 diastereomers can be obtained from *t,t,t*-1,5,9-cyclododecatriene (**21a**) (Scheme 9).

Scheme 9: The 12 diastereomeric hexaols from the four possible 1,5,9-cyclododecatrienes.

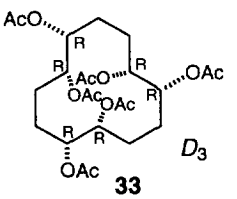


Starting from enantiomerically pure diol **21b** double dihydroxylation furnishes 2 diastereomeric hexaols.[29] After acetylation, using the result with quinuclidine as reference, one finds that the C_2 symmetric hexaacetate **34** is strongly favored over the D_3 symmetric product **33**.[31a] In the presence of $(DHQ)_2$-PYR only traces of the highly symmetric hexaacetate **33** are found, whereas $(DHQD)_2$-PYR furnishes a 1:2 mixture of **33** and **34** in 94% overall yield (Table 5).

Table 5: Bis-Dihydroxylation of dienediol **21b**.[30]

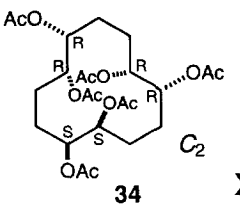


21b



D_3

33

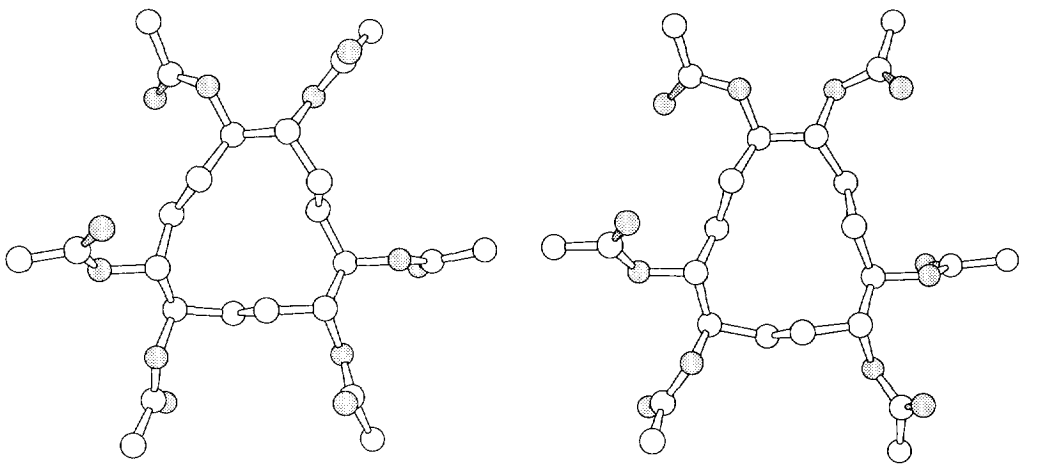


C_2

34

	Ligand		
	Quinuclidine	$(DHQ)_2$-PYR	$(DHQD)_2$-PYR
	2.5	0.4	36
	..	..	..
	97.5	99.6	64
	95% de	99.2% de	28% de
ΣYield	92%	93%	89%

Figure 1: Single crystal X-Ray structure of the D_3 symmetric hexaacetate **33** in the solid state. Molecules 3 and 4 (not shown) are similar to molecule 2 with some of the acetate groups slightly rotated.

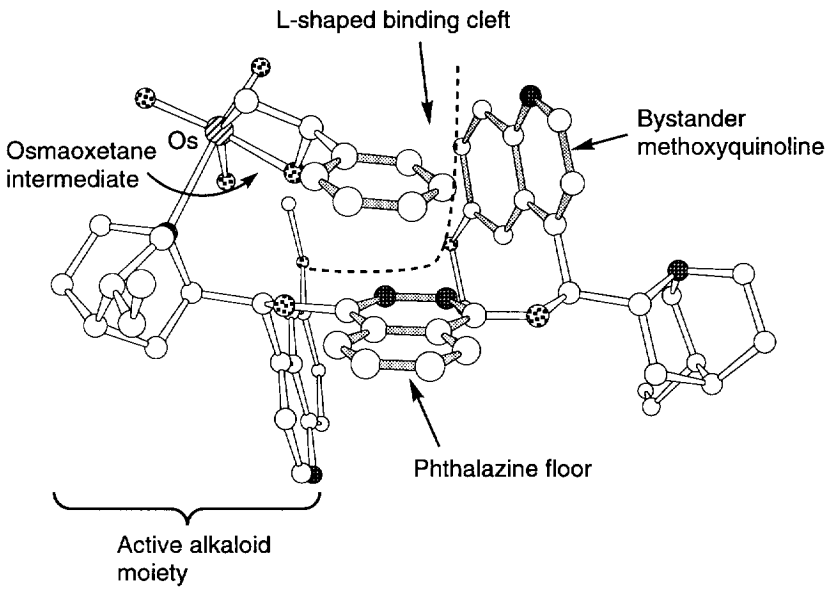


Molecule 1 Molecule 2

In the D_3 symmetric starting material **21a**, the high symmetry is maintained both in the solid state[31b] and in solution.[31c] However, an X-ray crystallographic structure of the D_3 symmetric hexaacetate **33** shows that this high symmetry is not maintained in the crystal lattice (Figure 1).[32] Of the 4 independent molecules in the unit cell only *molecule 1* approaches D_3 symmetry, whereas molecules 2, 3 and 4 adopt approximate C_2 symmetry.

For nearly all the *medium* and *large* ring cases examined here, the pyrimidine ligands give good to very good selectivity, whereas reactions with the phthalazine ligands, usually the favored ligands for *trans*-disubstituted double bonds, suffer from low selectivity and slow reactions. For the phthalazine ligands we have proposed a chiral L-shaped binding cleft consisting of a "floor" provided by the phthalazine ring system and an abutting, perpendicular "wall" provided by the methoxyquinoline moiety of the bystander alkaloid unit (Figure 2).[11]

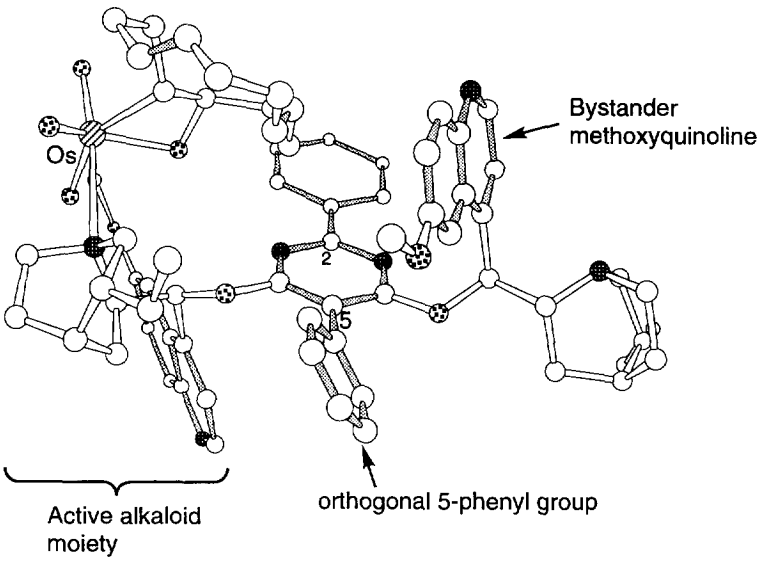
Figure 2: Structure of the proposed osmaoxetane intermediate derived from styrene and $(DHQD)_2$-PHAL.[11b] The hydrogen atoms are omitted for clarity.



The proposed mechanism enables very good transition state stabilization for most acyclic and "small ring" olefins, but also places limits on the size of certain substituents. Molecular mechanics calculations[27] for all the *medium* and *large* ring substrates in this study reveal that the ring stands *perpendicular* to the *trans* double bond(s), making the rings too large to fit well into the pocket of the phthalazine ligands in the ideal transition state geometry. The different topology of the pyrimidine ligands creates a more open binding cleft enabling the $(DHQD)_2$-PYR and $(DHQ)_2$-PYR ligands to offer a better fit for the *medium* and *large* ring

trans olefins which, unlike most olefins, present a rather peculiar three-dimensional shape. A three-dimensional representation of a possible osmaoxetane intermediate derived from *t,t,t*-cyclododecatriene and $(DHQD)_2$-PYR is shown in Figure 3.

Figure 3: Osmaoxetane from *t,t,t*-cyclododecatriene **21a** and $(DHQD)_2$-PYR calculated in manner similar to that used for the phthalazine analog[11b].



The more splayed arrangement of the two alkaloid units around the pyrimidine core (1,5-related, c.f. the 1,4-relationship in the phthalazine core) leads to a more open L-shaped binding cleft. Here the chiral pocket is not only provided by a polarized aromatic floor and the bystander methoxyquinoline but also receives a contribution from the 5-phenyl substituent on the pyrimidine-core. The twist of this phenyl group, found in an X-ray crystal structure of $(DHQ)_2$-PYR[33] and in molecular mechanics calculations[2b], seems to play an important role in the stabilization of the substrate in the binding pocket. In essence, this phenyl group appears to act as a "third boundary" further stabilizing the transition state for substrates which prefer to be in the pyrimidine binding pocket. Incidentally, the Corey–Noe "sandwich" mechanism[34] for the AD is impossible for these PYR ligands since the 2-phenyl substituent completely obstructs the binding pocket in their model. *Ab initio* calculations[35] show, as for the PHAL ligands,[11d] that for each alkaloid substituent the N=C–O–alkaloid dihedral angle must be near 0°. This forces both methoxyquinoline systems to be on opposite sides of the 2,5-diphenyl pyrimidine core, making a "sandwich" interaction between the substrate and the two methoxyquinolines impossible in the PYR ligand system.

CONCLUSION

This study reveals that the asymmetric dihydroxylation process (**AD**) can be highly selective when presented with a polyolefin target. We have tried to rationalize the various phenomena observed and a number of fundamental effects have been identified. However, one need only consider the results with etretinate (scheme 7) to realize that our predictive ability in these systems will often be poor. Taking all the factors discussed here and in earlier papers[6,7] into consideration, the major diol produced by AD of etretinate (**16a**) should have been **16c**. The reasons: 1) it is a trisubstituted acyclic olefin (the PHAL ligand's favorite type); 2) it is thrice removed from the deactivating carboethoxy group; and 3) the double bond most distant from the carboethoxy group bears an aromatic substituent which *cannot* fit well into the PHAL binding pocket. In the event (see table in scheme 7), diol **16c** is one of the minor products produced using the PHAL ligands. To make a stab at explaining this outcome, we can suggest that the *o,o*-disubstituted aryl group, forced to lie orthogonal to the conjugated tetraene system, also disables the binding pocket interactions necessary to facilitate attack on the central trisubstituted olefin (i.e., the route to diol **16c**). One could go further with such rationalizations, but for now there is no getting around the fact that the actual major diol product (**16e**) results from attack at one of the two sites we predicted to be least reactive.[37]

EXPERIMENTAL PART

For general experimental conditions see reference[11a].
The determination of the ee was performed by analytical HPLC using *Pirkle* 1-A Ionic spherical silica (25 cm × 4.6 mm I.D.) or *Chiralcel* OD-H, OB-H, OJ, OK, or OC (25 cm × 4.6 mm I.D.) columns respectively by analyzing the diols, dibenzoates, or MTPA[36]-esters. The UV-detector was set to 254 nm. GLC was performed on β-cyclodextrin, *J & W* CDX-B (30 m × 0.32 mm I.D.), or *J & W* DB-5 (30 m × 0.32 mm I.D.) columns.

Typical procedure for the asymmetric dihydroxylation reactions and work-up at 1 mmol scale in the presence of 1 mol% ligand and 1 mol% of $K_2OsO_4 \cdot 2H_2O$:
1 mol% ligand (8.0 mg in the phthalazine case, 8.9 mg in the pyrimidine case), $K_3Fe(CN)_6$ (990 mg, 3 mmol), K_2CO_3 (420 mg, 3 mmol), $CH_3SO_2NH_2$ (95 mg, 1 mmol), and $K_2OsO_4 \cdot 2H_2O$ (3.7 mg, 1.0 mol%) were dissolved in 1:1 *tert*-butyl alcohol/water (5 mL of each) at room temperature. It was cooled to 0°C and the diene or triene was added. The mixture was stirred at 0°C; for work-up $Na_2S_2O_5$ or Na_2SO_3 (1.5 g) was slowly added and the suspension was warmed to room temperature while stirring vigorously. If not mentioned otherwise, CH_2Cl_2 or ethyl acetate (~20 mL) was added, and the aqueous layer was further extracted with CH_2Cl_2 or ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was purified by *flash* chromatography on silica gel to obtain the ene diol. The absolute configuration of the diols (except **21b**, **22b**, **23b**, and **24b**)[20] was assigned by applying the *mnemonic device* (Scheme 1).

Polyenes **1a–6a**, **17a–19a**, **21a–25a**, and **27a** are commercially available. The conjugated aromatic dienes **7a–10a** were obtained by the *Wittig*-reaction of the corresponding benzylbromide with crotonaldehyde. Ester **13a** was obtained from the commercially available acid; triene **14a** was synthesized by the *Wittig–Horner* reaction of *trans*-triethyl-4-phosphono-2-butenoate and *trans*-cinnamaldehyde. Keto dieneester **15a** was prepared by the *Wittig*-reaction of *trans*-4-oxo-ethylcrotonate (prepared by SeO_2 oxidation of *trans*-ethylcrotonate) with 1-triphenylphosphoranylidene-2-propanone. *Etretinate* (**16a**) was a gift from Dr. Percy Manchand of *Hoffman-LaRoche*; compounds **20a** and **26a** were provided by Dr. Alois Fürstner (*Max-Planck-Institut für Kohlenforschung*/Mühlheim an der Ruhr).

(3*E*,5*R*,6*R*)-5,6-Dihydroxyundeca-1,3-diene (1b):
The AD-reaction was performed on triene **1a** (1 mmol) as described in the *typical procedure* (*vide supra*) using $(DHQD)_2$-PHAL as ligand. The diols **1b** and **1c** were obtained in 60% yield.
^1H NMR (400 MHz, $CDCl_3$) δ: 0.87 (m, 3H), 1.30 (m, 6H), 1.35 (m, 2H), 2.05 (s, 2H), 3.47 (m, 1H), 3.95 (t, J = 6.5 Hz, 1H), 5.15 (m, 1H), 5.25 (m, 1H), 5.68 (m, 1H), 6.33 (m, 2H). HRMS (FAB$^+$/NBA) calculated for $C_{11}H_{20}O_2$ (MNa^+), 207.1361; found, 207.1357.

(2*R*,3*E*,5*Z*)-Undeca-3,5-dien-1,2-diol (2b):
The AD-reaction was performed on triene **2a** (1 mmol) as described in the *typical procedure* (*vide supra*) using $(DHQD)_2$-PHAL as ligand. Diol **2b** was isolated with 48% yield. The ee was determined by HPLC analysis of the diol (*Chiralcel* OB-H, 5% *i*-PrOH/hexane, 0.5 ml/min).
$[\alpha]_D^{25}$ = +10.5 (c 0.71, $CHCl_3$); IR (neat) ν 3353 (br. s), 3004 (w), 2954 (s), 2926 (s), 2854 (s), 1460 (s), 1317 (w), 1069 (s), 1019 (m), 983 (m), 947 (m), 869 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 6.9 Hz, 3H), 1.30 (m, 4H), 1.37 (m, 2H), 2.17 (ddd, J = 14.6, 7.4, 1.4 Hz, 2H), 2.22 (s, 1H), 2.37 (s, 1H), 3.51 (dd, J = 11.2, 7.4 Hz, 1H), 3.66 (dd, J = 11.2, 3.5 Hz, 1H), 4.30 (m, 1H), 5.47 (dt, J = 10.8, 7.6 Hz, 1H), 5.61 (dd, J = 15.2, 6.4 Hz, 1H), 5.95 (dt, J = 11.2, 0.4 Hz, 1H), 6.60 (ddt, J = 15.3, 11.1, 7.0, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 27.8, 29.2, 31.4, 66.4, 73.1, 127.3, 127.8, 130.7, 133.9; UV λ_{max}=234 nm; HRMS (FAB$^+$/NBA) calculated for $C_{11}H_{20}O_2N$ (MNa^+), 207.1361; found, 207.1354.

(2*E*,4*R*,5*R*)-2,3-Dihydroxyhex-2-en-1-benzoate (3b):
The AD-reaction was performed on diene **3a** (1 mmol) as described in the *typical procedure* (*vide supra*) using $DHQD_2$-PHAL as ligand. The diols were obtained with 91% yield. The ee was determined by HPLC analysis of the diol (*Chiralcel* OB-H, 5% *i*-PrOH/hexane, 1 ml/min).
$[\alpha]_D^{25}$ = +2.2 (c 2.00, $CHCl_3$); IR (neat) ν 3402 (br. s), 2968 (s), 2933 (w), 2876 (s), 1702 (s), 1602 (m), 1443 (s), 1254 (s), 1111 (s), 969 (s), 713 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.16 (d, J = 6.4 Hz, 3H), 2.72 (s, 1H), 2.85 (s, 1H), 3.64 (t, J = 6.4 Hz, 1H), 3.90 (m, 1H), 4.81 (d, J = 5.6 Hz, 2H), 5.83 (dd, J = 15.6, 6.4 Hz, 1H), 5.97 (m, 1H), 7.42 (m, 2H), 7.52 (m, 1H), 8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 64.7, 70.6, 76.6, 126.9, 128.4, 129.7, 129.9, 133.1, 133.4, 166.4; HRMS (FAB$^+$/NBA) calculated for $C_{13}H_{16}O_4$ (MNa^+), 259.0946; found, 259.0937.

(8*R*,9*R*,10*E*)-8,9-Dihydroxydodec-10-en-1-yl-acetate (4b):
Diene **4a** (1mmol) was dihydroxylated according to the *typical procedure* with $(DHQD)_2$-PHAL as ligand. A mixture of diols **4b** and **4c** was obtained in 82% yield. The compounds were seperated by column chromatography. The ee of **4b** was determined by HPLC analysis of the bis-MTPA ester (*Chiralcel* OD-H, 1% *i*-PrOH/hexane, 1 ml/min).

$[\alpha]_D^{25}$ = +10.4 (c 1.63, $CHCl_3$); IR (neat) ν 3425 (br. s), 2926 (s), 2854 (s), 1737 (s), 1446 (m), 1382 (m), 1368 (m), 1239 (s), 1040 (s), 969 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.28 (m, 8H), 1.43 (m, 2H), 1.57 (m, 2H), 1.68 (dd, *J* = 6.4, 1.4 Hz, 3H), 2.00 (s, 3H), 2.55 (s, 2H), 3.37 (m, 1H), 3.79 (t, *J* = 6.9 Hz, 1H), 4.00 (t, *J* = 6.8 Hz, 2H), 5.43 (m, 1H), 5.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 21.0, 25.5, 25.8, 28.5, 29.1, 29.5, 32.8, 64.6, 74.6, 76.2, 129.5, 130.5, 171.3; HRMS (FAB$^+$/NBA) calculated for $C_{14}H_{26}O_4$ (MNa^+), 281.1729; found, 281.1720.

(8*E*,10*R*,11*R*)-10,11-Dihydroxydodec-8-en-1-yl-acetate (4c):

The ee was determined by HPLC analysis of the bis-MTPA ester (*Chiralcel* OD-H, 1% *i*-PrOH/hexane, 1 ml/min).

$[\alpha]_D^{25}$ = –6.2 (c 0.68, $CHCl_3$); IR (neat) ν 3431 (br. s), 2926 (s), 2855 (s), 1737 (s), 1453 (w), 1367 (m), 1239 (s), 1040 (s), 969 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (d, *J* = 6.4 Hz, 3H), 1.29–1.38 (m, 8H), 1.58–1.64 (m, 2H), 2.02 (s, 3H), 2.03 (m, 2H), 2.19 (s, 1H), 2.35 (s, 1H), 3.60 (m, 1H), 3.77 (t, *J* = 7.0 Hz, 1H), 4.03 (t, *J* = 6.8 Hz, 2H), 5.42 (ddt, *J* = 7.3, 2.9, 1.4 Hz, 1H), 5.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 21.0, 25.8, 28.5, 28.9, 28.9, 29.0, 32.2, 64.6, 70.9, 77.9, 129.1, 135.0; HRMS (FAB$^+$/NBA) calculated for $C_{14}H_{26}O_4$ (MNa^+), 281.1729; found, 281.1719.

(9*Z*,11*R*,12*R*)-11,12-Dihydroxytetradec-9-en-1-yl-acetate (5b):

The AD-reaction was performed with diene **5a** on 1 mmol scale as described in the *typical procedure* (*vide supra*) using $(DHQD)_2$-PHAL as ligand. Diol **5b** was isolated with 82% yield. The ee was determined by ^1H NMR analysis of the bis-MTPA ester.

$[\alpha]_D^{25}$ = +6.3 (c = 1.82, $CHCl_3$); IR (neat) ν 3402 (br. s), 3004 (w), 2933 (s), 2855 (s), 1730 (s), 1460 (m), 1367 (m), 1247 (s), 1118 (w), 1040 (s), 969 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, *J* = 7.4 Hz, 3H), 1.26–1.34 (m, 12H), 1.57 (m, 2H), 2.01 (s, 3H), 2.05 (m, 2H), 2.50 (s, 1H), 2.70 (s, 1H), 3.32 (m, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 4.16 (t, *J* = 8.4 Hz, 1H), 5.33 (m, 1H), 5.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.1, 21.0, 25.6, 25.8, 27.9, 28.5, 29.1, 29.1, 29.2, 29.4, 64.7, 70.8, 76.4, 128.6, 134.8, 171.4; HRMS (FAB$^+$/NBA) calculated for $C_{16}H_{30}O_4$ (MH^+), 287.2222; found, 287.2230.

(2*E*,4*R*,5*R*)-4,5-Dihydroxydec-2-enal (6b):

The AD-reaction was performed on aldehyde **6a** (1 mmol) as described in the *typical procedure* (*vide supra*) using 5mol% $(DHQD)_2$-PHAL as ligand. Diol **6b** was isolated with 50% yield. The ee was determined by HPLC analysis of the dibenzoates (*Chiralcel* OK, 0.25% *i*-PrOH/hexane, 0.5 ml/min).

$[\alpha]_D^{25}$ = +40.7 (c = 1.30, $CHCl_3$); IR (neat) ν 3402 (br. s), 2933 (s), 2861 (s), 1687 (s), 1460 (m), 1374 (m), 1118 (s), 1083 (s), 976 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87 (m, 3H), 1.30 (m, 6H), 1.52 (m, 2H), 2.56 (br. s, 1H), 3.08 (br. s, 1H), 3.58 (br. s, 1H), 4.24 (br. s, 1H), 6.37 (ddd, *J* = 15.7, 7.9, 1.6 Hz, 1H), 6.84 (dd, *J* = 15.7, 4.8 Hz, 1H), 9.56 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 25.3, 31.7, 33.2, 73.9, 74.0, 132.4, 156.0, 193.6; MS (FAB$^+$/NBA) calculated for $C_{10}H_{18}O_3$ (MH^+), 187.1334; found, 187.1339.

(2*R*,3*R*,4*E*)-5-Phenyl-2,3-dihydroxypent-4-ene (7b):

The AD-reaction was carried out on diene **7a** (0.2 mmol) as described in the *typical procedure* (*vide supra*) using $(DHQD)_2$-PHAL as ligand. The yield of **7b** and **7c** was 83%; the diols were seperated by *flash* chromatography. The ee was determined by HPLC analysis of the diol (*Chiralcel* OD-H, 5% *i*-PrOH/hexane, 1 ml/min).

$[\alpha]_D^{25}$ = −15.5 (c 0.34, $CHCl_3$); IR (neat) ν 3374 (br. s), 3025 (w), 2968 (m), 2919 (m), 1458 (w), 1453 (m), 1375 (m), 1260 (m), 1055 (s), 969 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 6.4 Hz, 3H), 2.34 (s, 2H), 3.74 (q, *J* = 6.4 Hz, 1H), 4.02 (t, *J* = 6.8 Hz, 1H), 6.18 (dd, *J* = 15.9, 7.0 Hz, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 7.26 (m, 1H), 7.32 (m, 2H), 7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 70.9, 77.8, 126.5, 128.0, 128.3, 128.6, 132.9; HRMS (FAB^+/NBA) calculated for $C_{11}H_{14}O_2$ (MNa^+), 201.0892; found, 201.0870.

(2*R*,3*R*,4*E*)-Phenyl-2,3-dihydroxyhex-4-enoate (7c):
$[\alpha]_D^{25}$ = +8.8 (c 0.57, $CHCl_3$); IR (neat) ν 3424 (br. s), 2918 (s), 1716 (s), 1446 (m), 1375 (w), 1275 (s), 1118 (s), 1068 (s), 1026 (m), 962 (m), 713 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.70 (dd, *J* = 6.5, 1.6 Hz, 3H), 2.52 (s, 1H), 2.91 (s, 1H), 3.84 (s, 1H), 4.11 (s, 1H), 4.31 (dd, *J* = 11.7, 6.4 Hz, 1H), 4.46 (dd, *J* = 11.7, 3.8 Hz, 1H), 5.56 (dd, *J* = 7.4, 1.6 Hz, 1H), 5.79 (dd, *J* = 6.5, 0.8 Hz, 1H), 7.43 (m, 2H), 7.54 (m, 1H), 8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.9, 65.9, 72.9, 73.2, 128.4, 129.3, 129.7, 129.7, 129.8, 130.4, 133.2, 166.9; HRMS (FAB^+/NBA) calculated for $C_{13}H_{16}O_4$ (MNa^+), 259.0946; found, 259.0934.

(2*R*,3*R*,4*E*)-5-(3',5'-Dimethyl)phenyl-2,3-dihydroxypent-4-ene (8b):
The AD-reaction of diene **8a** was performed on 1 mmol scale using $(DHQD)_2$-PHAL as ligand; the yield of the diols were 82%. Pure **8b** could be obtained by chromatography on a *Chromatotron* (hexane/ethyl acetate 4/1). The ee was determined by HPLC-analysis of the diol (*Chiralcel* OD-H, 5% *i*-PrOH/hexane, 0.8 ml/min).
$[\alpha]_D^{25}$ = +5.1 (c 0.919, $CHCl_3$); IR (KBr) ν 3340 (s), 3255 (s), 3022 (m), 2939 (m), 1312 (s), 1146 (s), 990 (m), 883 (m), 781 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.19 (d, *J* = 6.3 Hz, 3H), 2.29 (s, 6H), 2.93 (s, br., 2H), 3.69–3.74 (m, 1H), 3.98 (t, *J* = 7.0 Hz, 1H), 6.13 (dd, *J* = 15.9, 7.1 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.89 (s, 1H), 6.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.9, 21.2, 70.9, 77.8, 124.4, 127.9, 129.6, 132.9, 136.2, 138.0; HRMS (FAB^+/NBA) calculated for $C_{13}H_{18}O_2$ (MNa^+), 229.1205, found 229.1199.

(2*R*,3*R*,4*E*)-5-(3',5'-Di-*tert*-butyl)phenyl-2,3-dihydroxypent-4-ene (9b):
The AD-reaction of **9a** was carried out on 0.75 mmol scale with $(DHQD)_2$-PHAL as ligand; the diols **9b** and **9c** are obtained in 76% yield. Pure **9b** could be obtained by chromatography on a *Chromatotron* (hexane/ethyl acetate 4/1). The ee was determined by HPLC-analysis (*Chiralcel* OD-H, 1% *i*-PrOH/hexane, 0.5 ml/min, 254 nm).
mp 124°C; $[\alpha]_D^{25}$ = −4.7 (c 0.898, $CHCl_3$); IR (KBr) ν 3390 (s, br.), 2966 (s), 2905 (m), 2867 (m), 1596 (s), 1364 (s), 1057 (s), 1021 (s), 976 (s), 708 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.22 (d, *J* = 6.3 Hz, 3H), 1.31 (s, 18H), 2.23 (d, *J* = 3.8 Hz, 1H), 2.33 (d, *J* = 3.6 Hz, 1H), 3.73–3.78 (m, 1H), 3.99–4.03 (m, 1H), 6.15 (dd, *J* = 15.9, 7.2 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 7.22 (d, *J* = 1.6 Hz, 2H), 7.33 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.0, 31.4, 70.9, 78.0, 120.9, 122.4, 127.5, 134.1, 136.1, 151.1; HRMS (FAB^+/NBA) calculated for $C_{19}H_{30}O_2$ (MNa^+), 313.2144; found, 313.2155.

(1*R*,2*R*,3*E*)-1-Naphthyl-1,2-dihydroxypent-3-ene (10c):
The AD-reaction was performed with diene **10a** (0.3 mmol) analog described in the *typical procedure* (*vide supra*) using $(DHQD)_2$-PHAL as ligand. The Diols **10b** and **10c** were isolated with 71% yield. **10c** was purified by *flash* chromatography; the ee was determined by HPLC analysis of the diol (*Chiralcel* OD-H, 5% *i*-PrOH/hexane, 1 ml/min).
mp 83°C; $[\alpha]_D^{25}$ = −8.5 (c 0.90, $CHCl_3$); IR (KBr) ν 3502 (w), 3324 (br. s), 3053 (w), 3018 (w), 1438 (s), 1040 (s), 961 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.59 (dq, *J* = 6.5, 0.9 Hz, 3H), 2.55 (s, 1H), 3.03 (s,

1H), 4.23 (t, J = 6.6 Hz, 1H), 4.62 (d, J = 6.9 Hz, 1H), 5.42 (m, 1H), 5.60 (m, 1H), 7.37 (m, 3H), 7.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8, 76.8, 77.7, 124.8, 126.0, 126.0, 126.1, 126.2, 127.7, 128.0, 128.0, 129.1, 129.5, 133.1, 137.9; HRMS (FAB$^+$/NBA) calculated for $C_{15}H_{16}O_2$ (MNa^+), 251.1048; found, 251.1040.

(2*E*,4*R*,5*R*)-4,5-Dihydroxyhex-2-enoic acidethylester (11b): (see also *supplementary material* to ref. 6a)
The AD-reaction (2 mmol scale) of ethyl sorbate (**11a**) in the presence of $(DHQD)_2$-PHAL as ligand afforded diol **11b** in 78% yield. The ee was determined by HPLC analysis of the diol (*Chiralcel* OD, 8 % *i*-PrOH/hexane, 0.8 ml/min).
$[\alpha]_D^{24}$ = +64.0 (c = 1.10, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, J = 6.3 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.46 (br. s, 1H), 2.76 (br. s, 1H), 3.73 (quintet, J = 6.3 Hz, 1H), 4.07 (td. J = 5.6, 1.5 Hz, 1H), 4.21 (q. J = 7.1 Hz, 2H), 6.14 (dd, J = 15.3, 1.7 Hz, 1H), 6.92 (dd, J = 15.3, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.9, 60.6, 75.5, 122.2, 146.8, 166.6; HRMS (FAB$^+$/NBA) calculated for $C_8H_{14}O_4$ (MCs^+), 306.9946; found, 306.9952.

(2*E*,4*E*,6*R*,7*R*)-6,7-Dihydroxyocta-2,4-dienoic acidmethylester (12b): (see also *supplementary material* to ref. 6a)
The AD-reaction of **12a** was performed with $(DHQD)_2$-PHAL as ligand at 5 mmol scale; the yield of diol **12b** was 93%. The ee was determined by HPLC analysis of the diol (*Chiralcel* OD, 8 % *i*-PrOH/hexane, 0.8 ml/min).
mp 95°C; $[\alpha]_D^{24}$ = +73.9 (c = 1.02, EtOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6.4 Hz, 3H), 2.38 (br. s, 1H), 2.61 (br. s, 1H), 3.66–3.72 (m, 1H), 3.76 (s, 3H), 3.97–4.02 (m, 1H), 5.92 (d, J = 15.4 Hz, 1H), 6.10 (dd, J = 15.3, 6.2 Hz, 1H), 6.47 (dd, J = 15.3, 9.2 Hz, 1H), 7.28 (dd, J = 15.4, 11.1, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 51.6, 70.6, 76.6, 121.7, 129.7, 140.8, 143.6, 167.3; HRMS (FAB$^+$/NBA) calculated for $C_9H_{14}O_4$ (MH^+), 187.0970; found, 187.0976.

(2*E*,4*R*,5*R*)-4,5-Dihydroxy-5-phenylpent-2-enoic acidethylester (13b):
The AD-reaction of **13a** was carried out at 1 mmol scale; with use of $(DHQD)_2$-PHAL ligand the yield was 76% (for yields with other ligands, see table in Scheme 5). The ratio of **13b** and **14b** was determined by NMR and GC (DB-5, 80°C). Cleavage of the crude mixture with H_5IO_6 gave predominantly benzaldehyde. Pure **13b** was obtained by chromatography on a *Chromatotron* (1 mm plate, hexane/ethyl acetate 3/1). The ee was determined by HPLC (OD-H, 10 % *i*-PrOH/hexane, 0.5 ml/min). By addition of racemate, the detection limit could be determined to be 99.5%.
$[\alpha]_D^{23}$ = +57.6 (c = 0.898, $CHCl_3$); IR (neat) ν 3450 (br. s), 3033 (m), 2984 (m), 2903 (m), 1726 (s), 1454 (m), 1308 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 3.29 (s, br., 1H), 3.34 (s, br., 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.35 (s, br., 1H), 4.49 (d, J = 6.7 Hz, 1H), 6.05 (dd, J = 15.7, 1.8 Hz, 1H), 6.71 (dd, J = 15.7, 4.4 Hz, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 60.6, 75.3, 77.0, 122.2, 126.9, 128.4, 128.6, 139.8, 145.9, 166.5; MS (FAB$^+$/NBA) calculated for $C_{13}H_{16}O_4$ (MH^+), 237.1127; found, 237.1122.

(2*E*,4*E*,6*R*,7*R*)-6,7-Dihydroxy-7-phenylhept-2,4-dienoic acidethylester (14b):
The AD-reaction of **14a** was performed at 0.7 mmol scale; with use of $(DHQD)_2$-PHAL ligand the yield was 77% (for yields with other ligands, see table in Scheme 5). The purity of crude **14b** was ~95% by NMR. Cleavage of the crude product with H_5IO_6 gave predominantly benzaldehyde. Pure **14b** could be obtained by chromatography on a *chromatotron* (1 mm plate, hexane/ethyl acetate 2/1). The ee was determined by HPLC

(OJ, 20 % *i*-PrOH/Hexane, 0.5 ml/min). By addition of racemate, the detection limit was found to be 99.5%. $[\alpha]_D^{23}$ = +140.4 (c = 0.917, $CHCl_3$); IR (neat) ν 3420 (br. s), 3033 (w), 2984 (m), 2906 (m), 1711 (s), 1268 (s), 1140 (s), 1046 (s), 702 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.86 (s, br., 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.34 (t, *J* = 6.0 Hz, 1H), 4.50 (d, *J* = 6.8 Hz, 1H), 5.85 (d, *J* = 15.4 Hz, 1H), 5.90 (dd, *J* = 15.3, 5.3 Hz, 1H), 6.36 (dd, *J* = 15.4, 11.1 Hz, 1H), 7.17 (dd, *J* = 15.4, 11.1 Hz, 1H), 7.31–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 60.4, 76.0, 77.6, 121.8, 126.9, 128.3, 128.5, 129.2, 139.8, 139.8, 143.4, 167.0; MS (FAB^+/NBA) calculated for $C_{15}H_{18}O_4$ (MH^+), 263.1283; found, 263.1277.

(2*R*,3*R*,4*E*)-2,3-Dihydroxy-6-oxohepta-4-enoic acidethylester (15b):

The AD-reaction of **15a** was performed with 2 eq of $K_3Fe(CN)_6$ and 2 eq of K_2CO_3. Due to the low solubility of the starting material, *t*-BuOH/*t*-BuOMe/H_2O 0.5/0.5/1 was used as solvent. For workup, *no* $Na_2S_2O_5$ or Na_2SO_3 was added. In the case of $(DHQD)_2$-PHAL as ligand, a mixture of **15b** and **15c** was obtained in 63% yield; 30% starting material was recovered. For yields with other ligands see the table in Scheme 6. The mixture of diastereomeric diols was separated from the starting material by *flash*-chromatography on silica gel (hexane/ethyl acetate 1/1, then 1/2). The ratio of the diastereoisomers was determined by ^1H NMR and GC (DB-5, 5 min 60°C, then 5°/min). The compounds were separated by *flash*-chromatography (silica gel, hexane/ethyl acetate 1/2). The ee of the less polar **15b** was determined by HPLC analysis of the diol (OD-H, 10% *i*-PrOH/hexane, 0.5 ml/min).

$[\alpha]_D^{23}$ = +54.2 (c = 0.871, $CHCl_3$); IR (neat) ν 3450 (br. s), 2985 (m), 2908 (w), 1719 (s), 1705 (s), 1307 (s), 1185 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, *J* = 7.1 Hz, 3H), 2.30 (s, 3H), 2.57 (s, br., 1H), 3.22 (s, br., 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 2.6 Hz, 1H), 4.66 (t, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 16.0, 1.7 Hz, 1H), 6.84 (dd, *J* = 16.0, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 27.4, 62.5, 72.0, 72.9, 131.1, 144.5, 172.1, 198.4; MS (FAB^+/NBA) calculated for $C_9H_{14}O_5$ (MH^+), 203.0919; found, 203.0926.

(2*E*,4*R*,5*R*)-4,5-Dihydroxy-6-oxohepta-2-enoic acidethylester (15c):

The ee of the more polar **15c** was determined by HPLC analysis of the diol (OC, 20% *i*-PrOH/hexane, 0.5 ml/min).

$[\alpha]_D^{23}$ = +13.1 (c = 1.070, $CHCl_3$); IR (KBr) ν 3500 (br. s), 2992 (w), 1738 (s), 1696 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 3.9 (s, br, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 2.4 Hz, 1H), 4.73–4.75 (m, 1H), 6.12 (dd, *J* = 15.7, 1.8 Hz, 1H), 6.98 (dd, *J* = 15.7, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 26.0, 60.7, 71.3, 79.0, 122.2, 146.3, 166.4, 208.1; MS (FAB^+/NBA) calculated for $C_9H_{14}O_5$ (MH^+), 203.0919; found, 203.0927.

(2*R*,3*R*,4*E*,6*E*,8*E*)-2,3-Dihydroxy-9-(2',3',6'-trimethyl-4'-methoxyphenyl)-3,7-dimethyl-nonanoic acid ethylester (16e):

The AD-reaction was performed with etretinate (**16a**) (1.4 mmol) similar as described in the *typical procedure* (*vide supra*), but with 2 eq of $K_3Fe(CN)_6$ and 2 eq of K_2CO_3. Due to the low solubility of the starting material, *t*-BuOH/*t*-BuOMe/H_2O 0.5/0.5/1 was used as solvent; with $(DHQD)_2$-PHAL as ligand a mixture of diols was obtained in 58% yield. For yields with other ligands see table in Scheme 7. The ratio of the diols was determined by ^1H NMR. Pure **16e** could be obtained by chromatography on a *Chromatotron* (hexane/ethyl acetate 2/1). The ee was determined by ^{19}F NMR and HPLC-analysis of the 2-mono-MTPA-ester (*Chiralcel* OD-H, 5% *i*-PrOH/hexane, 0.5 ml/min).

mp 95°C; $[\alpha]_D^{25}$ = +31.0 (c 0.777, $CHCl_3$); IR (KBr) n 3320 (s, br.), 3004 (w), 2981 (m), 2929 (m), 2865 (m), 1690 (s), 1312 (m), 1269 (s), 1106 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 3H), 2.02 (d, *J* = 0.8 Hz, 3H), 2.13 (s, 3H), 2.21 (s, 3H), 2.26 (s, 3H), 2.94 (s, 1H), 3.08, (d, *J* = 5.9 Hz, 1H),

3.79 (s, 3H), 4.05 (d, J = 6.0 Hz, 1H), 4.23–3.34 (m, 2H), 5.83 (d, J = 15.2 Hz, 1H), 6.06 (d, J = 11.3 Hz, 1H), 6.17 (d, J = 16.3 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 6.58 (s, 1H), 6.76 (dd, J = 15.2, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.8, 12.7, 14.2, 17.4, 21.4, 24.5, 55.5, 62.3, 74.5, 76.8, 109.9, 122.6, 125.9, 127.0, 129.6, 130.1, 133.8, 135.2, 135.9, 136.1, 138.3, 172.7; HRMS (FAB$^+$/NBA) calculated for $C_{23}H_{32}O_5$ (MNa^+), 411.2147; found, 411.2158.

(1*S*,2*R*)-1,2-Dihydroxy-4-isopropyl-1-methylcyclohex-3-ene (17b):

The AD-reaction of α-terpinene (**17a**) in the presence of $(DHQD)_2$-PHAL was performed on 0.5 mmol scale; the diols were obtained in 78% yield. The ee was determined by HPLC analysis of the mono-MTPA ester (*Chiralcel* OD-H, 0.5% *i*-PrOH/hexane, 1 ml/min).

mp 43°C; $[\alpha]_D^{25}$ –42.2 (c 1.32, $CHCl_3$); IR (KBr) ν 3352 (br. s), 2954 (s), 2875 (s), 1460 (s), 1417 (s), 1303 (s), 1218 (m), 1146 (s), 1040 (s), 997 (s), 670 (s), 492 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (dd, J = 6.8, 2.9 Hz, 6H), 1.17 (s, 3H), 1.55 (m, 1H), 1.77 (m, 1H), 1.97 (m, 1H), 2.10 (m, 1H), 2.16 (m, 1H), 2.35 (s, 1H), 2.50 (m, 1H), 3.76 (s, 1H), 5.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 21.4, 24.3, 24.4, 32.3, 34.4, 70.1, 71.6, 119.5, 147.6; HRMS (FAB$^+$/NBA) calculated for $C_{10}H_{18}O_2$ (MNa^+), 193.1204; found, 193.1209.

(1*S*,2*R*)-1,2-Dihydroxy-4-isopropyl-1-methyl-4-cyclohexene (18b):

The AD-reaction of γ-terpinene (**18a**) in the presence of $(DHQD)_2$-PHAL was performed on 0.5 mmol scale; the diols were obtained in 84% yield. The ee was determined by HPLC analysis of the mono-MTPA ester (*Chiralcel* OD-H, 0.5% *i*-PrOH/hexane, 1 ml/min).

mp 71°C; $[\alpha]_D^{25}$ –7.9 (c 2.04, $CHCl_3$); IR (KBr) ν 3338 (br. s), 2961 (s), 2973 (s), 2897 (s), 1460 (s), 1424 (s), 1360 (s), 1189 (m), 1132 (s), 1061 (s), 890 (s), 734 (s), 670 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (dd, J = 6.8, 2.2 Hz, 6H), 1.19 (s, 3H), 2.13 (m, 5H), 2.23 (m, 1H), 2.28 (m, 1H), 3.62 (q, J = 5.7 Hz, 1H), 5.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 21.3, 24.6, 32.5, 34.3, 37.1, 71.0, 73.1, 115.9, 140.0; HRMS (FAB$^+$/NBA) calculated for $C_{10}H_{18}O_2$ (MNa^+), 193.1204; found, 193.1198.

(1*S*,2*R*)-1,2-Dihydroxy-4-isopropenyl-1-methylcyclohexane (19b):

The AD-reaction of terpinolene (**19a**) was done on 1 mmol scale with $(DHQD)_2$-PHAL as ligand; the diols were obtained in 80% yield. The ee was determined by HPLC analysis of the mono-MTPA ester (*Chiralcel* OD-H, 0.5% *i*-PrOH/hexane, 0.7 ml/min).

mp 66°C; $[\alpha]_D^{25}$ +32.0 (c 1.00, $CHCl_3$); IR (KBr) ν 3340 (br. s), 2960 (s), 1460 (s), 1420 (s), 1297 (s), 1208 (s), 1146 (s), 1040 (s), 996 (s), 670 (s), 492 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (d, J = 1.4 Hz, 3H), 1.34–1.42 (m, 1H), 1.66 (d, J = 5.2 Hz, 6H), 1.71 (m, 1H), 2.15 (t, J = 5.9 Hz, 3H), 2.25 (m, 2H), 2.47 (dd, J = 13.5, 4.1 Hz, 1H), 3.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1, 20.2, 25.4, 25.7, 34.2, 37.1, 71.3, 75.3, 127.1; HRMS (FAB$^+$/NBA) calculated for $C_{10}H_{18}O_2$ (MNa^+), 193.1204; found, 193.1210.

(1*R*,2*R*,5*Z*)-1,2-Dihydroxycyclodec-5-ene (20b):

The ee was determined by HPLC analysis of the bis-MTPA ester (*Pirkle* 1-A, 0.25% *i*-PrOH/hexane, 1 ml/min).

mp 119°C; $[\alpha]_D^{23}$ = +8.4 (c = 0.765, $CHCl_3$); IR (KBr) ν 3274 (br. s), 2996 (s), 2918 (s), 2847 (s), 1460 (s), 1346 (m), 1175 (s), 1040 (s), 705 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48–2.03 (m, 8H), 2.44 (m, 4H), 3.74 (m, 1H), 3.80 (m, 1H), 5.34 (m, 1H), 5.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4, 23.6, 24.6, 26.0, 30.5, 32.6, 69.2, 72.8, 129.3, 129.4; MS (FAB$^+$/NBA) calculated for $C_{10}H_{18}O_2$ (MNa^+), 193.1205; found, 193.1200.

(1*R*,2*R*,5*E*,9*E*)-1,2-Dihydroxycyclododeca-5,9-diene (21b):

For low conversion,[21] 0.3 eq $K_3Fe(CN)_6$, 0.3 eq K_2CO_3, and 0.5 eq $CH_3SO_2NH_2$ was used in *t*-BuOH/H_2O 3/1. With $(DHQD)_2$-PYR as ligand (6 mmol of olefin), 10% **21b** was isolated. The ee was determined by GLC analysis (CDX-B column, 150°C) or by HPLC-analysis of the dibenzoates (*Chiralcel* OD-H, 1% *i*-PrOH/hexane, 0.5 ml/min). To prove the absolute configuration, it was hydrogenated to **24b** (*vide infra*).[20]

mp 171°C; $[\alpha]_D^{23}$ = +137.9 (c = 1.213, MeOH); IR (KBr) ν 3295 (br. s), 3025 (w), 2973 (s), 2946 (s), 2847 (m), 1304 (m), 1138 (s), 1017 (s), 987 (s), 961 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 1.40–1.72 (m, 4H), 1.84–2.19 (m, 8H), 3.36–3.49 (m, 2H), 3.84 (br. s, 2H), 4.95–5.19 (m, 4H); ^{13}C NMR (DMSO-d_6, 62.5 MHz) δ 28.7, 31.3, 31.6, 66.5, 130.3, 131.3; MS (FAB$^+$/NBA) calculated for $C_{12}H_{20}O_2$ (MNa^+), 219.1361; found, 219.1365.

(1*R*,2*R*,5*E*,9*Z*)-1,2-Dihydroxycyclododeca-5,9-diene (22b):

Low conversion conditions were used as described for **21b** on 6 mmol scale. With $(DHQD)_2$-PYR as ligand, 13% **22b** was isolated. The ee was determined by GLC analysis (DB-5 column, 260°C) of the bis-MTPA ester. To prove the absolute configuration, it was hydrogenated to **24b** (*vide infra*).[20]

mp 171°C; $[\alpha]_D^{22}$ = +147.6 (c = 1.144, MeOH); IR (KBr) ν 3270 (br. s), 3083 (m), 2997 (s), 2854 (m), 1449 (m), 1409 (m), 1187 (m), 1028 (m), 1015 (m), 984 (s), 704 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 1.31–1.68 (m, 4H), 1.81–2.10 (m, 8H), 3.42–3.58 (m, 2H), 3.89 (br. s, 2H), 5.13–5.40 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.3, 28.8, 30.4, 30.8, 32.4, 43.2, 66.3, 67.2, 128.4, 129.3, 131.6, 131.8; MS (FAB$^+$/NBA) calculated for $C_{12}H_{20}O_2$ (MNa^+), 219.1361; found, 219.1365.

(1*R*,2*R*,5*Z*,9*Z*)-1,2-Dihydroxycyclododeca-5,9-diene (23b):

The AD-reaction of **23a** in the presence of $(DHQD)_2$-PYR was performed on 2 mmol scale; the diols were obtained in 91% yield. The ee was determined by GLC analysis (DB-5 column, 250°C) of the bis-MTPA ester. To prove the absolute configuration, it was hydrogenated to **24b** (*vide infra*).[20]

mp 173°C; $[\alpha]_D^{22}$ +84.4 (c = 0.883, MeOH); IR (KBr) 3259 (br. s), 3002 (s), 2954 (s), 2862 (m), 1461 (m), 1411(m), 1306 (m), 1038 (m), 1003 (m), 861 (m), 731 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.26–1.32 (m, 2H), 1.78–1.94 (m, 6H), 2.03–2.13 (m, 4H), 3.38–3.43 (m, 2H), 3.97 (d, *J* = 7.2 Hz, 2H), 5.26–5.33 (m, 2H), 5.43–5.49 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 22.8, 26.8, 31.5, 67.3, 129.2, 129.4; MS (FAB$^+$/NBA) calculated for $C_{12}H_{20}O_2$ (MNa^+), 219.1361; found, 219.1366.

(1*R*,2*R*)-1,2-Dihydroxycyclododecane (24b):

To **23b** (89% ee) (121 mg, 0.617 mmol) in 30 ml MeOH, 70 mg 10% Pd on activated carbon was added. It was hydrogenated at atmospheric pressure overnight at room temperature. It was filtered through *Celite* and the solvent was evaporated. Purification by *flash* chromatography (silica gel, hexane/ethyl acetate 1/1) gave 120 mg (0.599 mmol, 97%) of **24b** as a colorless solid. It was recrystallized from ethyl ether/pentane (0°C).

Diol **24b** was also obtained by AD reaction of olefin **24a** in 60% yield. The ee was determined by GLC analysis (DB-5 column,150°C, the 5°C/min) of the bis-MTPA ester.

mp 170°C; $[\alpha]_D^{22}$ = +28.6 (c = 1.004 $CHCl_3$); IR (KBr) ν 3325 (br. s), 2946 (s), 2861 (m), 1468 (m), 1447 (m), 1053 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.17–1.32 (m, 16H), 1.44–1.56 (m, 4H), 3.40 (br. s, 2H), 4.20 (br. s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.4, 22.5, 23.4, 23.7, 29.6, 70.0; MS (FAB$^+$/NBA) calculated for $C_{12}H_{24}O_2$ (MNa^+) 223.1674, found 223.1679.

(1*R*,2*R*)-1,2-Dihydroxycyclopentadecane (25b):
Olefin **25a** was dihydroxylated on 1 mmol scale as described in the *typical procedure*. With $(DHQD)_2$-PYR, diol **25b** was isolated in 60% yield. The ee was determined by HPLC analysis of the bis-MTPA ester (*Chiralcel* OD-H, 100% hexane, 1 ml/min).
mp 101°C; $[\alpha]_D^{22}$ = +6.5 (c = 1.075 $CHCl_3$); IR (KBr) ν 3317 (br. s), 2925 (s), 2847 (s), 1453 (s), 1346 (s), 1260 (w), 1154 (w), 1026 (s), 855 (m), 677 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31–1.60 (m, 26H), 1.90 (br. s, 2H), 3.73 (br. s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8, 26.4, 26.6, 26.7, 27.0, 32.1, 73.6, 73.7; MS (FAB$^+$/NBA) calculated for $C_{15}H_{30}O_2$ (MNa^+) 265.2144, found 265.2148.

(1*R*,2*R*,9*E*)-1,2-Dihydroxycyclohexadec-9-ene (26b):
Diene **26a** was dihydroxylated according to the *typical procedure* with $DHQD_2$-PYR as ligand on 4.5 mmol scale; as described for **21a**, low conversion conditions were used.[21] **26b** was obtained in 16% yield. The ee was determined by GLC analysis (DB-5 column, 250°C) of the bis-MTPA ester.
mp 72°C; $[\alpha]_D^{22}$ = +1.3 (c = 0.825, $CHCl_3$); IR (KBr) ν 3400 (br. s), 2929 (s), 2853 (m), 1461 (m), 1081 (m), 965 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15–1.60 (m, 18H), 1.95–2.12 (m, 6H), 2.32 (br. s, 2H), 3.47 (br. s, 2H), 5.30 (t, J = 3.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 26.9, 27.4, 28.5, 31.0, 32.1, 74.4, 131.1; MS (FAB$^+$/NBA) calculated for $C_{16}H_{30}O_2$ (MNa^+) 277.2144, found 277.2150.

(7*R*,8*R*)-7,8-Dihydroxycyclohexadecanone (27b):
The asymmetric dihydroxylation of **27a** was carried out as described in the *typical procedure* on 0.5 mmol scale. The ee was determined by HPLC analysis of the bis-MTPA ester (*Pirkle* 1-A, 1% *i*-PrOH/hexane, 1 ml/min).
mp 80°C; $[\alpha]_D^{22}$ = +9.9 (c = 0.755, $CHCl_3$); IR (KBr) ν 3295 (br. s), 2918 (s), 2854 (s), 2676 (w), 1702 (s), 1460 (s), 1346 (m), 1018 (s), 969 (m), 670 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25–1.56 (m, 22H), 2.34 (m, 3H), 2.44 (m, 3H), 3.44 (br. s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.1, 23.4, 27.2, 27.2, 27.4, 27.6, 27.6, 31.4, 32.0, 42.0, 42.2, 73.2, 73.7, 212.5; MS (FAB$^+$/NBA) calculated for $C_{16}H_{30}O_3$ (MNa^+) 293.2093, found 293.2101.

(1*R*,2*R*,5*R*,6*R*,9*E*)-1,2,5,6-Tetrahydroxycyclododec-9-ene (28b):
The asymmetric dihydroxylation of **21b** was carried out as described in the *typical procedure* on 0.5 mmol scale. Due to the high polarity of the tetrols **28a** and **28b**, the workup was changed.
After addition of $Na_2S_2O_5$, the aqueous phase was saturated with NaCl and extracted 5 times with a mixture of 50 ml $CHCl_3$ and 10 ml *i*-PrOH. The combined organic layers were dried by filtration through cotton. The mixture of tetrols was purified by *flash* chromatography (silica gel, hexane/*i*-PrOH 1/1) (65% yield with $(DHQD)_2$-PYR as ligand; see also Table 4). The ratio of the diastereomers **28a** and **28b** was obtained by converting to the diacetonides and GC-analysis as described below. Pure tetrol **28b** could be obtained by deprotection of diacetonide **30b** in MeOH/HCl, workup with aqueous $NaHCO_3$ and *flash* chromatography (hexane/*i*-PrOH 1/1). The assignment of the relative configuration is trivial due to the optical activity of **28b** and the lack of it for **28a** (*meso* compound).
mp 203°C; $[\alpha]_D^{23}$ = +17.0 (c = 1.008, DMSO); IR (KBr) ν 3259 (br. s), 2946 (s), 2926 (s), 2853 (m), 1412 (m), 1336 (m), 1128 (m), 1055 (s), 1033 (s), 985 (s), 851 (m), 673 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.22–1.32 (m, 4H), 1.42–1.47 (m, 2H), 1.60–1.69 (m, 2H), 1.93–2.03 (m, 2H), 2.04–2.09 (m, 2H), 3.28 (t, J = 5.5 Hz, 2H), 3.39 (br. s, 2H), 4.03 (d, J = 5.0 Hz, 2H), 4.20 (d, J = 5.4 Hz, 2H), 5.30 (t, J = 4.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.8, 28.1, 32.7, 69.8, 69.9, 131.6; MS (FAB$^+$/NBA) calculated for $C_{12}H_{22}O_4$ (MH^+), 231.1596 found, 231.1599.

(1*R*,2*R*,5*S*,6*S*,9*E*)-1,2,5,6-Tetrahydroxycyclododec-9-ene (28a):
Tetrol **28a** was obtained by asymmetric dihydroxylation of diol **21b** (following the procedure described for **28b**) in the presence of $(DHQ)_2$-PYR (4 mmol scale; yield 72%). After crystallization from *i*-PrOH/hexane, pure tetrol **28a** was obtained.
mp 151–155°C; $[\alpha]_D^{23} = 0.0$, $[\alpha]_{365}^{23} = 0.0$; IR (KBr) ν 3345 (br. s), 2989 (w), 2945 (m), 2930 (m), 2860 (w), 1442 (w), 1332 (m), 1299 (m), 1129 (m), 965 (m), 886 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 1.37–1.53 (m, 6H), 1.65–1.79 (m, 2H), 1.95–2.19 (m, 4H), 3.28–3.36 (m, 2H), 3.45–3.49 (m, 2H), 4.05 (br. s, 4H), 5.33 (t, J = 4.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 28.2, 28.7, 32.1, 68.5, 71.1, 131.6; MS (FAB^+/NBA) calculated for $C_{12}H_{22}O_4$ (MH^+), 231.1596 found, 231.1600.

(1*R*,2*R*,5*E*,9*E*)-1,2-Isopropylidenedioxycyclododeca-5,9-diene (29):
Diol **21b** (ee > 99.5%) (708 mg, 3.61 mmol) was dissolved in 50 ml of acetone, and 0.10 g of *p*-toluenesulfonic acid monohydrate was added. After stirring for 30 minutes at room temperature, the mixture was poured into 50 ml of saturated aqueous $NaHCO_3$ solution and extracted once with 300 ml of ethyl acetate and twice with 100 ml of ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by *flash* chromatography furnished 851 mg (3.60 mmol, quant.) of acetonide **29** as colorless oil.
$[\alpha]_D^{23} = +26.6$ (c = 0.977, $CHCl_3$); IR (neat) ν 3022 (m), 2983 (s), 2848 (s), 1438 (m), 1378 (s), 1243 (s), 1092 (s), 1009 (m), 974 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 6H), 1.57–1.68 (m, 4H), 2.04–2.24 (m, 8H), 4.03 (t, J = 2.3 Hz, 2H), 5.22–5.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0, 27.9, 30.8, 32.2, 77.7, 107.4, 131.5, 133.7; MS (FAB^+/NBA) calculated for $C_{15}H_{24}O_2$ (MH^+) 237.1855; found, 237.1858.

(1*R*,2*R*,5*S*,6*S*,9*E*)-1,2-5,6-Di(isopropylidenedioxy)cyclododec-9-ene (30a):
Pure acetonide **30a** was obtained from *meso*-tetrol **28a** as a colorless oil in 96% yield.
$[\alpha]_D^{23} = 0.0$, $[\alpha]_{365}^{23} = 0.0$; IR (neat) ν 2983 (s), 2932 (s), 2856 (m), 1443 (m), 1377 (m), 1239 (s), 1053 (s), 981 (m), 889 (m), 843 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.38 (s, 6H), 1.40 (s, 6H), 1.57–1.83 (m, 8H), 2.04–2.14 (m, 2H), 2.24–2.33 (m, 2H), 3.67–3.72 (m, 2H), 3.82–3.90 (m, 2H), 5.36 (t, J = 3.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 26.9, 27.5, 27.5, 30.4, 77.8, 79.6, 107.2, 132.3; MS (FAB^+/NBA) calculated for $C_{18}H_{30}O_4$ (MNa^+), 333.2042; found, 333.2046.

(1*R*,2*R*,5*R*,6*R*,9*E*)-1,2-5,6-Di(isopropylidenedioxy)cyclododec-9-ene (30b):
Compound **30b** was prepared from a mixture of tetrols **28b** and **28a** (75:25) analog as described for **29** in a yield of 96%. Recrystallization from pentane (–20°C) furnished 59% of pure **30b**. The assignment of the relative configuration is trivial due to the optical activity of diacetonide **30b** (cf. assignment of tetrols **28a/28b**).
mp 104°C; $[\alpha]_D^{23} = -3.1$, $[\alpha]_{365}^{23} = -20.5$, (c = 1.378, $CHCl_3$); IR (KBr) ν 2985 (s), 2931 (s), 2861 (s), 1370 (s), 1036 (s), 870 (s), 511 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.37 (s, 12H), 1.40–1.55 (m, 4H), 1.78–2.10 (m, 6H), 2.24–2.31 (m, 2H), 3.64–3.70 (m, 2H), 3.78–3.83 (m, 2H), 5.34 (t, J = 3.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 22.1, 28.2, 28.3, 32.3, 78.5, 80.2, 108.6, 133.1; MS (FAB^+/NBA) calculated for $C_{18}H_{30}O_4$ (MNa^+), 333.2042; found, 333.2042.

(1*R*,2*R*,5*E*,9*E*)-1,2-Carbonyldioxycyclododeca-5,9-diene (31):
Diol **21b** (463 mg, 2.36 mmol) was dissolved in 50 ml of dry toluene at 50°C under N_2. It was cooled to room temperature and 570 mg (3.54 mmol, 1.5 eq) of 1,1'-carbonyldiimidazole was added over a period of 10 hours. After stirring overnight the reaction mixture was poured into a mixture of 25 ml H_2O and 25 ml of

saturated aqueous NH_4Cl. The aqueous layer was 4 times extracted with 50 ml of ethyl acetate. The combined organic layers were washed with a mixture of 25 ml H_2O and 25 ml of saturated aqueous $NaHCO_3$. The aqueous phase was extracted 4 times with 50 ml of ethyl acetate and the combined organic layers were dried with $MgSO_4$. *Flash* chromatography (silica gel, hexane/ethyl acetate 4/1) furnished 404 mg (1.82 mmol, 77%) of carbonate **31** as colorless solid.

mp 111°C; $[\alpha]_D^{22} = -148.6$ (c = 0.738, $CHCl_3$); IR (KBr) ν 3029 (w), 2983 (m), 2930 (s), 2910 (s), 2854 (m), 1789 (s), 1432 (m), 1377 (m), 1166 (m), 1028 (m), 975 (m), 782 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.48–1.64 (m, 2H), 1.85–2.17 (m, 6H), 2.18–2.39 (m, 4H), 4.65 (t, J = 4.2 Hz, 2H), 5.21 (t, J = 3.1 Hz, 4H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.5, 32.7, 32.8, 80.7, 131.7, 133.2, 154.3; MS (FAB$^+$/NBA) calculated for $C_{13}H_{18}O_3$ (MNa^+), 245.1154 found, 245.1157.

(1*R*,2*R*,5*S*,6*S*,9*E*)-1,2-Carbonyldioxycyclododec-9-ene-5,6-diol (32a):

The asymmetric dihydroxylation of carbonate **31** was carried out as described in the *typical procedure* (*vide supra*). The product was purified by *flash* chromatography (silica gel, hexane/*i*-PrOH 2/1). The product ratio was determined by conversion to the diacetonides **30a/30b**. The mixture of carbonates was dissolved in 1 ml of MeOH, and 100 µl of trifluoroacetic acid was added. After refluxing for 60 min, the volatile components were removed *in vacuo*. The residue was dissolved in 1 ml of acetone and ~10 mg of *p*-toluenesulfonic acid was added. After 10 min standing at room temperature, the reaction mixture was purified by preparative TLC (hexane/ethyl acetate 4/1) and analyzed by GC (175°C, DB-5).

Pure carbonate **32a** was obtained by using $(DHQ)_2$-PYR ligand and isothermal crystallization from CH_2Cl_2/ethyl ether/pentane.

mp 141°C; $[\alpha]_D^{22} = -17.0$ (c = 1.004, MeOH); IR (KBr) ν 3484 (s), 3281 (br. s), 3007 (w), 2940 (m), 2866 (w), 2840 (w), 1812 (m), 1781 (s), 1179 (m), 1161 (m), 1025 (s), 1002 (m), 761 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.18–1.27 (m, 1H), 1.46–1.69 (m, 4H), 1.79–1.93 (m, 3H), 1.99–2.17 (m, 3H), 2.25–2.35 (m, 1H), 3.34–3.41 (m, 1H), 3.42–3.48 (m, 1H), 4.25 (d, J = 5.3 Hz, 1H), 4.27 (d, J = 6.2 Hz, 1H), 4.35–4.39 (m, 1H), 4.49–4.55 (m, 1H), 5.32–5.46 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.5, 26.8, 28.6, 28.8, 30.3, 31.9, 66.1, 70.8, 79.8, 82.0, 129.3, 133.0; MS (FAB$^+$/NBA) calculated for $C_{13}H_{20}O_5$ (MH^+), 257.1389 found, 257.1386.

(1*R*,2*R*,5*R*,6*R*,9*E*)-1,2-Carbonyldioxy-5,6-dihydroxy-9-cyclododecene (32b):

Pure carbonate **32b** (from diene **31**) was obtained by using $(DHQD)_2$-PYR ligand (1 mmol scale) and isothermal crystallization from CH_2Cl_2/ethyl ether/pentane.

mp 130°C; $[\alpha]_D^{22} = -41.5$ (c = 0.988, MeOH); IR (KBr) ν 3483 (s), 3330 (br. s), 2940 (s), 2867 (m), 1795 (s), 1438 (m), 1178 (s), 1167 (s), 1123 (m), 1001 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.30–1.46 (m, 1H), 1.49–1.68 (m, 5H), 1.86–2.03 (m, 3H), 2.13–2.30 (m, 3H), 3.21–3.29 (m, 1H), 3.37–3.51 (m, 1H), 4.39 (d, J = 4.2 Hz, 1H), 4.48 (d, J = 4.6 Hz, 1H), 4.43–4.51 (m, 1H), 4.65–4.70 (m, 1H), 5.26–5.35 (m, 1H), 5.46–5.54 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.3, 25.7, 26.7, 27.4, 30.2, 31.8, 70.1, 72.7, 79.8 (2C), 128.6, 134.8; MS (FAB$^+$/NBA) calculated for $C_{13}H_{20}O_5$ (MH^+), 257.1389 found, 257.1384.

(1*R*,2*R*,5*R*,6*R*,9*R*,10*R*)-1,2,5,6,9,10-Hexaacetoxycyclododecane (33):

The asymmetric dihydroxylation of **21b** (ee > 99.5%) was performed on a 1 mmol scale as described in the *General Procedure* (using $(DHQD)_2$-PYR), but 6 eq $K_3Fe(CN)_6$/6 eq K_2CO_3/3 eq $CH_3SO_2NH_2$ were used. After 3 days at 0°C the reaction was quenched with Na_2SO_3 and stirred for 2 h at room temperature. The solvent was removed *in vacuo*. The remaining water was removed aceotropically by adding 100 ml of $CHCl_3$ and evaporating under reduced pressure. 50 ml of warm (50°C) *i*-PrOH was added to the remaining

solid and the resulting slurry was filtered through *Celite*. The solid was extracted 2 times with 25 ml of 50°C *i*-PrOH and 3 times with 25 ml of 50°C MeOH. The solution was evaporated and dried under high vacuum. The residue was dissolved in 3 ml of dry CH_2Cl_2 and 1 ml of NEt_3, 1 ml of acetic anhydride, and 500 mg of 4-dimethyl-aminopyridine were added. After stirring 1 hour at room temperature the reaction mixture was poured into 50 ml of saturated aqueous $NaHCO_3$. It was extracted 3 times with 50 ml of CH_2Cl_2. The combined organic layers were dried by filtration through cotton. The ratio of the hexaacetates **33** and **34** were determined by GC analysis (200°C, DB-5) of the crude product. The hexaacetates were separated by *flash* chromatography (silica gel, hexane/ethyl acetate 1/1, and after elution of **33** hexane/ethyl acetate 1/2) and crystallized from ethyl ether/pentane. The relative configuration of **33** was confirmed by X-ray crystallography.

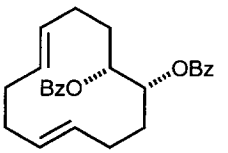
Crystals suitable for X-ray analysis were obtained by isothermal crystallization from ethyl ether/pentane.

R_F = 0.14 (hexane/ethyl acetate 1/1); mp 128°C; $[\alpha]_D^{22}$ = –23.7 (c = 1.036, $CHCl_3$); IR (KBr) ν 2952 (w), 1740 (s), 1373 (m), 1239 (s), 1047 (m), 975 (m), 853 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81 (br. s, 12H), 2.03 (s, 18H), 5.06 (br. s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 25.5, 73.0, 170.1; MS (FAB$^+$/NBA) calculated for $C_{24}H_{36}O_{12}$ (MNa^+), 539.2104 found, 539.2121.

(1*R*,2*R*,5*R*,6*R*,9*S*,10*S*)-1,2,5,6,9,10-Hexaacetoxycyclododecane (34):

R_F = 0.21 (hexane/ethyl acetate 1/1); mp 148°C; $[\alpha]_D^{22}$ = –4.4 (c = 0.915, $CHCl_3$); IR (KBr) ν 2960 (w), 1742 (s), 1374 (m), 1241 (s), 1028 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.55–1.93 (m, 12H), 2.00 (s, 6H), 2.01 (s, 6H), 2.03 (s, 6H), 4.97–5.04 (m, 2H), 5.12–5.17 (m, 2H), 5.28–5.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.7 (2C), 20.9, 22.9, 25.8, 26.4, 70.2, 70.4, 71.9, 170.0, 170.1, 170.2; MS (FAB$^+$/NBA) calculated for $C_{24}H_{36}O_{12}$ (MNa^+), 539.2104 found, 539.2113

(1*R*,2*R*)-1,2-Dibenzoyloxycyclododecane (35):



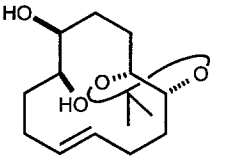
35

To 20 mg (0.100 mmol) of the (R,R)-dienediol **21b** (ee > 99.5%) in 2 ml of dry CH_2Cl_2 50 mg of DMAP (0.40 mmol) and 35 µl of freshly distilled benzoyl chloride (42 mg, 0.30 mmol) were added at room temperature. After stirring for 2 hours, the mixture was poured into 10 ml of 2 M aqueous HCl and extracted two times with 10 ml of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 ml) and dried by filtration through cotton. Flash chromatography (silica gel, hexane/ethyl acetate 10/1) furnished 36.5 mg (0.089 mmol, 89%) of dibenzoate **35** as colorless solid. **35** was recrystallized from ethyl ether/pentane.

The CD spectrum (MeOH) showed a minimum at 237 nm and a maximum at 222 nm.[20]

mp 92°C; $[\alpha]_D^{22}$ = –4.9 (c = 1.054, $CHCl_3$); IR (KBr) ν 2950 (s), 2935 (s), 2861 (s), 1717 (s), 1705 (s), 1283 (s), 1109 (s), 716 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.60 (m, 16H), 1.70–1.75 (m, 2H), 1.91–1.98 (m, 2H), 5.60 (t, *J* = 2.7 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 4H), 7.33–7.48 (m, 2H), 7.95 (dd, *J* = 8.3, 1.3 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 23.5, 24.3, 28.0, 72.9, 128.7, 130.1, 130.6, 133.3; UV (MeOH) λ_{max} = 226 nm; MS (FAB$^+$/NBA) calculated for $C_{26}H_{32}O_4$ (MH^+) 409.2379, found 409.2379.

(1*R*,2*R*,5*R*,6*R*,9*E*)-5,6-Dihydroxy-1,2-isopropylidenedioxy-9-cyclododecene (36):



36

The asymmetric dihydroxylation of **21b** was performed with 1% ligand/1% $K_2OsO_4 \cdot 2H_2O$ or 5% ligand/5% $K_2OsO_4 \cdot 2H_2O$. The ratio of the diastereomers was detected by conversion to the bis acetonides and GLC analysis (DB-5 column, 175°C).

$[\alpha]_D^{23}$ = –6.4 (c = 1.120, $CHCl_3$); IR (neat) ν 3420 (br. s), 2983 (m), 2935 (s), 2858 (m), 1441 (s), 1239 (s), 1090 (s), 922 (s), 733 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz)

δ 1.39 (s, 3H), 1.40 (s, 3H), 1.50–1.89 (m, 8H), 2.03–2.12 (m, 1H), 2.18–2.25 (m, 2H), 2.31–2.37 (m, 1H), 2.93 (br. s, 1H), 3.00 (br. s, 1H), 3.61 (br. s, 1H), 3.69–3.74 (m, 2H), 3.95 (q, J = 6.0 Hz, 1H), 5.31–5.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.2, 28.3, 28.5, 31.6, 33.0, 71.8, 78.3, 81.7, 108.3, 132.0, 132.8; MS (FAB$^+$/NBA) calculated for $C_{15}H_{26}O_4$ (MNa^+), 293.1729; found, 293.1734.

Acknowledgements: Financial support was provided by the *National Institutes of Health* (GM 28384). We also thank the *Fond der Chemischen Industrie* (postdoctoral fellowship to HB) and *Ministerio de Educación y Ciencia*, Spain, (postdoctoral fellowship to MAS). We are grateful to Dr. Ray K. Chadha and Dr. Russ Miller (Medical Foundation of Buffalo) for determining the X-ray crystal structure of **33**. We also thank Dr. Alois Fürstner (*Max-Planck-Institut für Kohlenforschung*/Mühlheim an der Ruhr) for providing the dienes **20a** and **26a** and Dr. Percy Manchand of *Hoffman-LaRoche* for the generous gift of etretinate (**16a**) used in these studies.

REFERENCES AND NOTES:

1 (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chemical Reviews*, in press; (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., VCH Publishers Inc.: New York, 1993; pp. 227–272.

2 (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. (b) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

3 Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1994**, *59*, 949.

4 Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789.

5 Crispino, G. A.; Sharpless, K. B. *Synthesis* **1993**, 777.

6 (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570; (b) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495.

7 (a) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485; (b) Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925; (c) Corey, E. J.; Noe, M. C.; Shieh, W.-C. *Tetrahedron Lett.* **1993**, *34*, 5995.

8 Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.

9 For the classification of cyclic molecules by ring size see: Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212.

10 Crispino, G. A.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273.

11 (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278; (b) Norrby, P.-O.; Kolb, H. C., Sharpless, K. B. *J. Am. Chem. Soc.*, **1994**, *116*, 8470; Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *Organometallics* **1994**, *13*, 344; (d) Becker, H.; Ho, P. T.; Kolb, H.C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 7315.

12 It should be noted that the aldehyde group is such a strong deactivator that no simple α,β-unsaturated aldehyde has yet been observed to react in the AD system (Sharpless, K. B. *et al.*, unpublished results).

13 Loren, S.; Sharpless, K. B. manuscript in preparation.

14 Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605.

15 King, S. B.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 5611.

16 Recently it was found that in certain special cases a surprisingly high level of enantioselectivity is realized: Wang, Z.-M .; Kiyomi, K.; Sharpless, K. B. *J. Org. Chem.*, in press.

17 With *c,c,t*-cyclododecatriene (Table 3, entry 4), no oxidation of the *cis*-double bonds is observed using either $(DHQD)_2$-PYR or quinuclidine. However, with $(DHQD)_2$-PHAL, about 2% of a product resulting from oxidation of a *cis*-double bond is found.

18 With the *cis/trans* olefin mixtures **24a** and **27a** the reaction was stopped after ca. 60% conversion and no product resulting from hydroxylation of the *cis* isomer was found.

19 Asymmetric dihydroxylation might be of general use for the preparation of pure *cis* disubstituted olefins from *cis/trans* mixtures by exploiting the faster reaction of the *trans* olefin to selectively remove it. *trans*-Disubstituted olefins generally react about 10 times faster than their *cis* diastereomers in the presence of the $(DHQD)_2$-PHAL ligand.[8] Furthermore, the rate difference between these *trans/cis* olefin pairs is even greater (ca. 20:1 in favor of the *trans* olefin) with the $(DHQD)_2$-PYR ligand, Andersson, P. G.; Sharpless, K. B., *unpublished results.*

20 The absolute configurations of the 12-membered ring diols **21b**, **22b**, and **23b** were determined by hydrogenation to the common diol **24b** followed by determination of the sign and magnitude of their optical rotations. The CD spectra for the dibenzoates of **21b**, **24b**, and **26b** are consistent with their configurational assignments (*Exiton Chirality Method*: Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257; Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy*, University Science Books: Mill Valley, 1983).

21 The reaction of *t,t,t*-cyclododecatriene **21a** (Table 3, entry 2) was stopped at 10% conversion, *c,t,t*-cyclododecatriene **22a** (Table 3, entry 3) at 13% conversion, and *t,t*-cyclohexadecadiene **26a** (Table 3, entry 7) at 16% conversion.

22 Asymmetric dihydroxylation in the presence of *p*-chlorobenzoyldihydroquinidine (DHQD-CLB, Aldrich) furnished diol of 70% ee from *c,t,t*-cyclododecatriene (**22a**) and 76% ee from *t,t,t*-cyclododecatriene (**21a**). These are two of the very few cases were the first generation CLB-ligand furnishes better results than the second generation PHAL and PYR ligands.

23 In all three cases, the ratio of diastereomers was determined by GC analysis of the diacetonides.

24 The assignment of the relative configuration is trivial due to the optical activity of the C_2 symmetric compounds and the lack of it for the *meso* compounds.

25 For the definitive review on double asymmetric synthesis see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

26 The phthalazine ligands furnished only very low diastereoselectivity. For the oxidation of diol **21b**, even quinuclidine gave the *meso* tetrol with better selectivity than $(DHQ)_2$-PHAL.

27 Molecular modeling studies were carried out with the MacroModel program using the modified MM2* force field (MacroModel V3.5X): Mohamadi, F; Richards, N. G. J.; Guida, W. C.; Liskamp, R;

Caufield, C; Chang, G; Hendrickson, T; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

28 Compared with the similar inositols (cyclohexanehexaols), the number of stereoisomers is higher due to the lower symmetry. The inositols have 8 possible diastereomers (7 *meso* forms and one pair of enantiomers): Anderson, L. in *The Carbohydrates*, Vol. IA, 2nd edition, pp. 521; Pigman, W.; Horton, D. (Ed.), Academic Press, New York, San Francisco, London, 1972; the original citation is: Bouveault, L. *Bull. Soc. Chim. Fr.* **1894**, *11* [3], 144.

29 Due to their insolubility, the hexaols are isolated and characterized as hexaacetates.

30 Note that the D_3 symmetric hexaol **33** can only be produced via the C_2 symmetric tetrol **28b**. Because of the known selectivity of the first oxidation step, it can be estimated that the second oxidation step proceeds with almost no selectivity using $(DHQD)_2$-PYR. This unexpected result is confirmed by asymmetric dihydroxylation of the C_2 symmetric diacetonide **30b** which shows almost no selectivity with either the pyrimidine or the phthalazine ligands.

31 (a) For a review on chiral organic molecules with high symmetry see: Nakazaki, M. in *Topics in Stereochemistry*, Vol. 15, **1984**, pp. 199; (b) Bogdanović, B.; Heimbach, P.; Kröner, M.; Wilke, G. *Justus Liebigs Ann. Chem.* **1969**, *727*, 143; (c) Anet, F. A. L.; Rawdah, T. N. *J. Am. Chem. Soc.* **1978**, *100*, 5003.

32 The ^1H NMR spectrum of **33** shows only 3 singlets, showing that the average conformation in solution is D_3 symmetric.

33 Chrispino, G. A.; Sharpless, K. B,. unpublished results.

34 (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579; (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861; (c) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427.

35 Becker, H.; Sharpless, K. B., unpublished results.

36 Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

37 Better prognosis of selectivity in these polyolefin oxidations (especially in complex cases like etretinate, **16a**) will require experience with many more substrates. Please contact us if you have questions or results to share.

E-mail: sharples@scripps.edu
FAX: +(619) 554 6406

(*Received in USA* 16 *September* 1994; *accepted* 14 *November* 1994)