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Kinetic Resolution of Mono- and Bicyclic Diels-Alder Adducts *via* Sharpless Asymmetric Dihydroxylation

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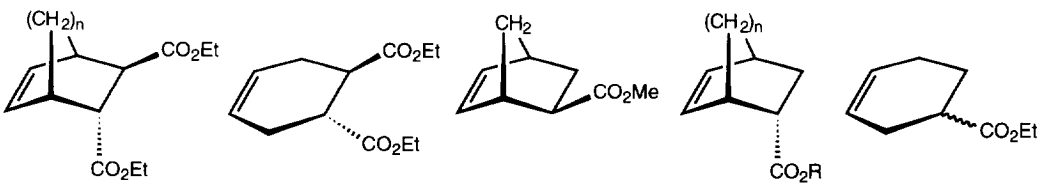
Abstract: Simple mono- and bicyclic olefins, readily available by the Diels-Alder methodology, are subjected to osmium-catalyzed asymmetric dihydroxylation with the aim to achieve kinetic resolution of the Diels-Alder adducts. The stereoselectivity factor **s** varies from 1.1 to 2.5. An effective procedure is developed to reconvert the *cis*-vicinal diols into the corresponding alkenes.

INTRODUCTION

The Diels-Alder methodology for the synthesis of cyclohexenes and cyclohexene derived structures is one of the most versatile and widely used synthetic operations in organic chemistry. Innumerable natural product syntheses are based on this [4+2]-cycloaddition usually starting from relatively simple cycloadducts[1]. For a successful use of the Diels-Alder reaction cycloadducts in enantiopure form with the desired absolute configuration are of great importance. For this reason considerable effort is spent on asymmetric Diels-Alder cyclizations using chiral dienes or/and dienophiles, or chiral catalysts with variable results[2]. Optical resolution often is an alternative to achieve this goal. Especially enzymatic kinetic resolution has broadened the synthetic utility of simple Diels-Alder adducts. We recently showed that bicyclic ester **1**, which is the Diels-Alder adduct of cyclopentadiene and fumaric diethyl ester, can conveniently be resolved using pig's liver esterase (PLE)[3].



1 (n = 1)
2 (n = 2)

3

4

5 (n = 1, R=Et)
6 (n = 2, R=Me)

7

Fig. 1: Mono- and bicyclic Diels-Alder adducts

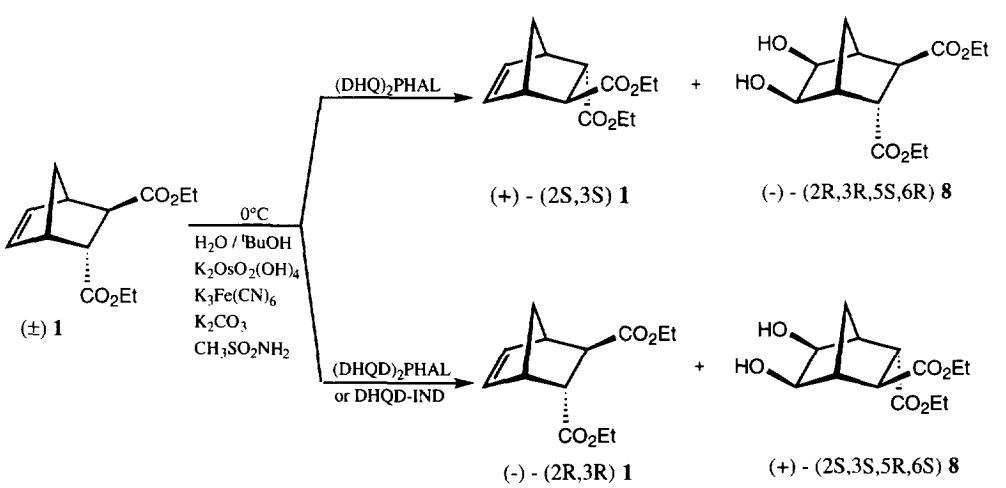
However, this resolution appeared to be very dependent on the nature of the substrate and in fact failed for adducts **2**,**4** and **5**.

Recently, Sharpless and coworkers[4] published an improved procedure for the osmium-catalyzed asymmetric dihydroxylation of olefins applying a single set of reaction parameters for a wide range of olefins. The use of sulfonamide to accelerate the hydrolysis of the initially formed monoglycolate-osmate ester and employing phtalazine as a new ligand generally leads to *cis*-vicinal diols with enantiomeric purities up to 99%[4,5]. This finding prompted us to study this osmium tetroxide-cinchona alkaloid system for the asymmetric *cis*-dihydroxylation of Diels-Alder cycloadducts **1-7**. Since effective reconversion of *cis*-diols into the corresponding alkenes has been reported[6], successful asymmetric dihydroxylation of the chiral Diels-Alder adduct **1-7** could be attractive for optical resolution of these cyclic olefins.

RESULTS AND DISCUSSION

Strategy

In determining which ligand should be used as the chiral auxiliary in the osmium tetroxide-catalyzed asymmetric *cis*-dihydroxylation[4], we were confronted with the problem that our substrates **1-7** are *cis*-disubstituted olefins, which are the most difficult substrates in the dihydroxylation process[7]. The most widely applied chiral ligands are the pseudoenantiomers 1,4-bis(9-O-dihydroquinine) phtalazine ((DHQ)$_2$PHAL) and 1,4-bis(9-O-dihydroquinidine) phtalazine ((DHQD)$_2$PHAL), which for *cis*-olefins usually gave diols with rather low optical purities[5c,8]. Better results were obtained with 9-O-indolinylcarbamoyl dihydroquinidine (DHQD-IND), an auxiliary especially developed for the asymmetric oxidation of *cis*-disubstituted olefins[9]. However, this ligand seems to be effective only for non-cyclic *cis*-olefins as the dihydroxylation of indene, the only *cis*-olefin studied with the double bond incorporated in a ring system, gave the corresponding *cis*-diol with an enantiopurity of only 16%.[10]



Scheme 1: Partial asymmetric dihydroxylation of **1** using different chiral ligands

Attempts to improve the asymmetric dihydroxylation of *cis*-olefins by variation of the ligands only led to inductions comparable to those obtained with DHQD-IND, $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ ligands[11]. Recently, Takano *et al.*[12] obtained satisfacory results for a *meso*-cyclic diene, using the latter two chiral auxiliaries. These results prompted us to first establish the effectiveness of all three ligands mentioned above in the asymmetric dihydroxylation of *cis*-alkenes **1-7**. Diethyl bicyclo[2.2.1]hept-5-ene-*trans*-dicarboxylate **1** was selected as the model compound (Scheme 1).

Table 1: Kinetic resolution of racemic **1** *via* asymmetric dihydroxylation under different catalytic conditions using various cinchona alkaloid ligands.

Entry	Ligand (eq.)[a]	time (h)	conv. (%)	recovered olefin **1** $[\alpha]^{D}_{20}$ (c, in $CHCl_3$)	recovered olefin **1** cy[b] (%)	recovered olefin **1** ee[c] (%)	obtained diol **8** $[\alpha]^{D}_{20}$ (c, in $CHCl_3$)	obtained diol **8** cy[b] (%)	obtained diol **8** ee[c] (%)
1	$(DHQ)_2PHAL$ (0.005)[d]	51	72	+ 14.3 (0.92)	25	11	- 0.7 (1.22)	55	5
2	$(DHQ)_2PHAL$ (0.01)	20	73	+ 31.5 (1.04)	21	23	- 1.2 (1.05)	48	9
3	$(DHQD)_2PHAL$ (0.01)	7.5	51	- 25.5 (1.05)	48	20	+ 3.0 (1.00)	41	20
4	$(DHQD)_2PHAL$ (0.01)	16	96	- 76.9 (1.22)[e]	3	76	+ 0.7 (1.37)	92	5
5	$(DHQD)_2PHAL$ (0.05)[f]	4	83	- 70.0 (0.96)	14	55	+ 2.2 (1.01)	78	16
6	$(DHQD)_2PHAL$ (0.1)[f]	4	99	g	g	g	g	g	g
7	DHQD-IND (0.02)[h]	8	36	- 22.5 (1.09)	52	19	+ 4.3 (0.99)	31	31
8	DHQD-IND (0.02)[h]	9	43	- 31.7 (1.27)	55	25	+ 3.9 (1.00)	40	27

[a]The amounts of the components necessary for the asymmetric dihydroxylation, other than the ligand, are described in the general procedure. The number of equivalents of the ligand used (0.01 equiv. $(DHQ)_2PHAL$ normally present in the AD-mix α and 0.01 equiv. $(DHQD)_2PHAL$ in the AD-mix β) was taken relative to the initial amount of olefin. [b]Isolated chemical yields. [c]Enantiomeric excesses were determined by ^1H-NMR experiments using $Eu(hfc)_3$ as chiral shift reagent and correlating the measured optical rotations. [d]The amounts of all AD-reagents were halved, corresponding to 0.5 equiv. of AD-mix α. [e]This optical rotation is not entirely correct as the recovered olefin could not be purified further than 95% pure according to GC. [f]The relative amounts of both the ligand and the osmium reagent were increased five-fold (entry 5) and ten-fold (entry 6), respectively. [g]No attempts were made to obtain the olefin and diol separately. [g]0.02 equiv. is the recommanded relative amount for DHQD-IND[9,13].

The results collected in Table 1 show that both the rate of the dihydroxylation and the optical yield are extremely low when only half of an equivalent of the AD-mix is applied (Table 1, entry 1). Better results were obtained when the usual amount of the ligand (0.01 eq.) was used (entry 2). However, the enantiopurity of the remaining olefin **1** is still low at a conversion of 73%. Slightly better results were obtained with $(DHQD)_2PHAL$ as a ligand (entries 3,4). This observation is a generally observed tendency[5]. After 7.5 h 50% conversion was reached and both recovered olefin **1** and the corresponding diol **8** were obtained in 20% ee. A nearly complete conversion was observed after 16 h. Even at this high conversion the optical purity of recovered olefin **1** remained disappointingly low. A five- or a ten-fold increase of the combination of ligand $(DHQD)_2PHAL$ and the osmium reagent relative to the other components of the AD-mix led to a much faster dihydroxylation of **1** but no improvement of the enantioselectivity was observed (entries 5,6). With DHQD-IND as the chiral auxiliary both the rate of dihydroxylation and the enantioselectivity are comparable with those observed for $(DHQD)_2PHAL$ (entries 7,8).

These first results show that dihydroxylation of bicyclic alkenes such as **1** using AD-mix is possible albeit with modest enantioselectivity. Based upon the outcome of the above experiments the asymmetric dihydroxylation of mono- and bicyclic olefins **2-7** was investigated by taking one equivalent of AD-mix β containing the relative amounts $(DHQD)_2PHAL$ and $K_2OsO_2(OH)_4$ as recommended[4].

Synthesis

Most substrates were readily available by a Diels-Alder reaction of the appropriate diene and dienophile[3,14,15]. Only the preparation of bicyclic mono-esters **4,5,6** deserves some comment.

Reacting cyclohexadiene with ethyl acrylate afforded a 6:1 mixture of ethyl *endo*- and *exo*-bicyclo[2.2.2]octene carboxylates. The *endo*-isomer was obtained by selective iodolactonization of the corresponding mixture of *endo/exo*-acids[3,16]. After separation from the remaining *exo*-acid, the lactone was reduced with zinc to give the *endo*-carboxylic acid which on esterification with diazomethane afforded pure *endo*-ester **6**. Unfortunately, the corresponding *exo*-ester could not be obtained pure and therefore is not included in this study. In a similar way pure *exo*-bicyclo[2.2.1heptene ester **4** was prepared starting from a 3:1 endo/exo mixture of ethyl bicyclo[2.2.1]hept-5-ene 2 carboxylates. A sufficient amount of pure *endo*-ester **5** was obtained from the original *endo/exo*-mixture by column chromatography.

Dihydroxylations

The dihydroxylations of mono- and bicyclic olefins **1-7** were generally carried out until a conversion of about 50% had been reached. The progress of the reaction was followed by gas chromatography and the conversion determined as the quotient of the absolute amount of the produced diol and the sum of the absolute amounts of the diol and remaining olefin. Comparison of the analytical GC values with the isolated amounts of olefins and diols clearly showed that it was absolutely necessary to calibrate the GC response. This calibration was performed for olefin **1** and diol **8**, resulting in two calibration lines with an excellent correlation factor (R_f=0.99991) and linearity over the whole dynamic range. As expected the response factor for the olefin **1** is higher than for diol **8**, giving a quotient of 0.622. It is noteworthy that upon extrapolation of the calibration curve of diol **8** there is a dead volume, which can only be explained by assuming that a fixed amount of the diol remains on the column. Decomposition is not likely as the peaks of the diols are perfectly sharp and symmetrical. For all sets of olefins and diols the degrees of conversion, as collected in Tables 1 and 2, were calculated with correction for the response difference and the dead volume of the diol determined for olefin **1** and diol **8**. This is legitimate because of the close analogy of the olefins **1-7** and their corresponding diols (Table 2). The calculated degrees of conversion were in accordance with the isolated amounts of olefins and diols.

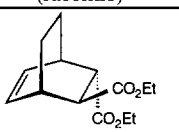
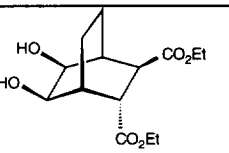
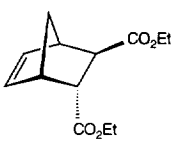
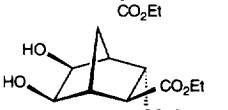
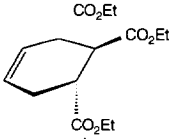
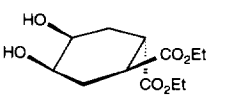
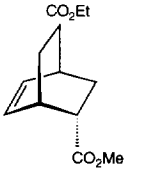
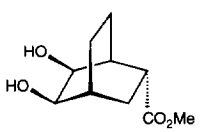
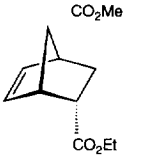
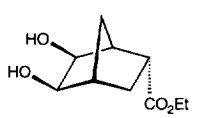
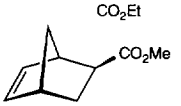
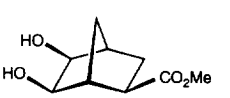
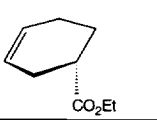
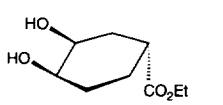
The structures of the diols **8-14** were established by ^{1}H-NMR spectroscopy. For all bicyclic esters these dihydroxylations are completely diastereoselective as the result of steric blocking of one face of the olefinic unit either by an ester function or by an ethylene bridge, which is sterically more demanding than a methylene bridge. Hence, dihydroxylation of bicyclic esters **1,2,4,5** and **6** exclusively gave *exo*-diols **8,9,11,12** and **13** (Table 2).

Enantioselective dihydroxylation of the cyclohexene *trans*-diester **3** leads to just one pair of diastereomeric diols **10**. Only for cyclohexene ester **7** a 2:1 mixture of diastereomeric diols **14** was formed. Apparently the

ester function in **7** does not shield one of the olefinic faces to such an extent that complete diastereoselectivity is attained here.

The *exo*-structure of diols **8**,**9**,**11**,**12** and **13** could unambiguously be proven by ^{1}H-NMR NOE studies on diol **13** which showed that there is a clear NOE-contact between the hydroxyl protons and $H_{7,syn}$, the bridge

Table 2: Kinetic resolution of various olefins *via* asymmetric dihydroxylation applying one equivalent of AD-mix β.

	recovered olefin						obtained diol			
Entry	substrate[a] (racemic)	nr.	time (h)	conv. (%)	cy[b] (%)	ee[c] (%)	product[a]	nr.	cy[b] (%)	ee[c] (%)
1		**2**	16	28	56	13		**9**	22	11
2		**2**	24	36	49	11		**9**	28	11
3		**2**	48	55	40	12		**9**	42	10
4		**1**	7.5	51	48	20		**8**	41	20
5		**1**	16	96	3	76		**8**	92	5
6		**3**	6	23	66	31[c]		**10**	21	7[d]
7		**3**	8	69	28	41[c]		**10**	54	4[d]
8		**6**	20	57	37	10		**11**	42	1.5
9		**5**	8	70	27	14		**12**	60	9
10		**4**	8	55	37	35		**13**	47	20
11		**7**	2	48	e	e		**14**	38	f
12		**7**	4	95	e	e		**14**	78	f

[a]Absolute configurations of the olefinic substrates were determined by comparing the sign of the measured optical rotation with the values reported in literature[3,14,17]. The absolute configuration of the corresponding diol is opposite to that of the olefin. [b]Isolated chemical yields. [c]Enantiomeric excesses were determined by ^{1}H-NMR experiments using Eu(hfc)$_3$ as chiral shift reagent. [d]The absolute configurations of olefin **3** and its corresponding diol are unknown. The drawn configurations were arbitrarily chosen. [e]No accurate values were obtained due to purification problems. [f]Both possible pairs of diastereomers of **14** were formed in a ratio of about 2:1.

proton in *syn*-position with respect to both hydroxy moieties. Furthermore, proton $H_{3,down}$ has a strong NOE-contact with H_5 and/or H_6, the protons vicinal to the alcohol functions. Of the aforementioned diols diol **13** has the double bond sterically least hindered for *endo*-attack and yet no *endo*-positions for the hydroxy moieties have been found, allowing to state that diols **8,9,11,12** and **13** all have the *exo*-structure.

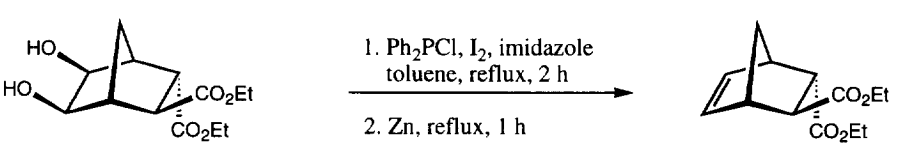
The data collected in Table 2 show that all substrates **1-7** undergo dihydroxylation with AD-mix β although at rather low rates. The highest conversion rates are observed for the monocyclic olefins **3** and **7**. In the bicyclic series the experimental data clearly show that an increase of the bridge size slows down the dihydroxylation reaction (compare entries 1,2 and 8,9). These observations may be explained by the increased steric bulkiness at the *convex* face of the olefinic unit in going from cyclohexenes to bicyclo[2.2.1]heptenes to bicyclo[2.2.2]octenes. As expected, not much difference in rate is observed for the mono-and diester of the cycloalkenes.

The enantioselectivity observed for the asymmetric dihydroxylation reaction is rather disappointing in all cases. At about 50% conversion modest optical yields up to 41% for the remaining olefin (entries 6,7 and 10) and up to 20% for the newly formed diol (entries 4,10) were obtained. The stereoselectivity factor s, which correlates the conversion and the enantiomeric excess[18], varies from 1.1 to 2.5 for entries 1-12, and this is far too low to make these dihydroxylation reactions attractive for optical resolution purposes. The poor enantioselectivity observed here seems to be typical for kinetic resolutions *via* the asymmetric dihydroxylation methodology because thusfar only comparably low s-values were obtained[5,7c,19]. Better results were achieved sofar only with the double-helical fullerene C_{76}[20].

For the structures **1-7** the enantiofacial differentation is apparently too small for effective chiral induction using AD-mix β. The stereogenic centres which cause the chiral dissymmetry of these cyclic olefins are probably too far away from the reaction centre ('*meso*-effect'[9]). Interestingly however, there is some distinct influence of the configuration of these remote chiral centers on the transition state as illustrated by the significant differences in optical yields in the enantioselective dihydroxylation of the *exo*- and *endo*-bicyclo[2.2.1]heptene monoester (entries 9,10). Since these structures are conformationally rigid these results suggest that dihydroxylation of cycloalkene esters **1-7** using the AD-mix β proceeds through a transition state which has only limited flexibility, confirming that the low enantioselectivity found for the substrates **1-7** is indeed caused by the so-called '*meso*-effect'.

Reconversion

Although the asymmetric dihydroxylation of cycloalkene esters does not yet fulfil the requirements for a practical resolution of Diels-Alder adducts, we established an effective procedure for the reconversion of the



(+) - (2S,3S,5R,6S) **8** (+) - (2S,3S) **1**

Scheme 2: Olefination of *cis*-vicinal diol

diol function to the alkene without loss of optical purity. Diol (+)-**8** (ee = 20%) which was chosen as the model compound, was treated with chlorodiphenyl phosphine and iodine[6] to give the vicinal iodo diphenylphosphinate that was not isolated but immediately reductively eliminated with zinc to afford alkene (+)-**1** in an excellent overall yield of 90%. The optical purity of this alkene was fully retained thus no racemization had occurred during this eliminative process.

Concluding remarks

We demonstrated that the sequence of dihydroxylation and reductive reconversion of the diol moiety to the alkene function is an efficient chemical process which, in principle, would allow optical resolution of cycloalkenes produced by the Diels-Alder methodology. However, the enantioselectivity of the asymmetric dihydroxylation of a range of Diels-Alder adducts using AD-mix β is still too low to be of practical use. More effective osmium ligand complexes will have to be designed. Following the sequence as described above, alkene **1** was obtained with an optical purity of 20% starting from racemic **1**.

Sofar no bicyclic diols either completely or partially resolved have been reported. With the exception of diols **12** and **13**[21] the resulting diols were not described previously.

EXPERIMENTAL SECTION

General __ Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AM-400 and a Bruker AC-100, using $CDCl_3$ as an internal standard. For mass spectra a double focussing VG 7070E mass spectrometer was used. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O 1108 Elemental Analyzer. Optical rotations were measured with a Perkin Elmer 241 Polarimeter. GLC was conducted with a Hewlett-Packard HP5890II gas chromatograph, using a capillary column (HP1, 25m x 0.31mm x 0.17μm). Flash chromatography was carried out at a pressure of *ca.* 1.5 bar, a column length of 15-30 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60H. All solvents used were dried and distilled according to standard procedures.

General procedure for the asymmetric dihydroxylation.__ All dihydroxylation reactions were performed at a scale of 5 mmol of olefin.

Three equivalents of $K_3Fe(CN)_6$ (4.94 g, 15 mmol), 3.0 equiv. of K_2CO_3 (2.07 g, 15 mmol), 1.0 equiv. of $CH_3SO_2NH_2$ (0.48 g, 5 mmol), 0.01 equiv. of $(DHQD)_2PHAL$ (0.039 g, 0.05 mmol), and 0.002 equiv. of $K_2OsO_2(OH)_4$ (0.0037 g, 0.01 mmol) were dissolved in water (25 mL, 5 mL/mmol) and t-BuOH (25 mL, 5 mL/mmol). This heterogeneous solution was cooled to 0°C and 1 equiv. of olefin (5 mmol) was added to the suspension at once. After stirring the reaction mixture at 0°C for number of hours indicated in Table 1 and 2 the reaction was quenched by adding 12 equiv. of Na_2SO_3 (7.5 g, 60 mmol) and the reaction mixture was stirred for an additional hour at room temperature. Subsequently the reaction mixture was diluted with ethyl acetate (50 mL) and extracted with water (3x). The aqueous fractions were then extracted with ethyl acetate (3x). The combined organic layers were concentrated *in vacuo*, the residue dissolved in diethyl ether and extracted with

water (1x) and brine (1x). Then the ether fraction was dried over Na_2SO_4 and concentrated *in vacuo*, resulting in a mixture of the starting olefin and the corresponding diol.

Diethyl *exo,exo*-5,6-dihydroxybicyclo[2.2.1]heptane-*trans*-2,3-dicarboxylate (8) The mixture of olefin **4** (n=1) and diol **8** was separated by flash chromatography, starting with n-hexane:ethyl acetate = 5:1. After the olefin had eluted the eluent was changed to n-hexane:ethyl acetate = 1:5. Diol **8** was isolated as a white crystalline compound. m.p.: 37-39°C. IR (CCl_4): ν 3400 (O-H), 1725 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.16 (overlapping q, ^{3}J=7.0Hz, 4H, O-CH_2-), 3.85 A of AB (d, ^{3}J=5.7Hz, 1H, H_5 or H_7), 3.76 B of AB (d, ^{3}J=5.7Hz, 1H, H_5 or H_7), 3.49 (br.s., 1H, -OH), 3.39 (br.s., 1H, -OH), 3.19 (t, ^{3}J=5.1Hz, 1H, H_2), 2.70 (d, ^{3}J=5.4Hz, 1H, H_3), 2.55 (d, ^{3}J=3.5Hz, 1H, H_1), 2.48 (s, 1H, H_4), 1.86 A of AB (d, ^{2}J=11.0Hz, H_9), 1.42 B of AB (d, ^{2}J=11.0Hz, H_9), 1.28 (t, ^{3}J=7.0Hz, 3H, -CH_3), 1.26 (t, ^{3}J=7.0Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.7 and 173.6 (C=O), 73.2 and 70.0 (C_5 and C_6), 61.14 and 61.06 (O-CH_2), 48.3, 46.4, 46.1 and 44.8 (C_1, C_2, C_3 and C_4), 31.6 (C_7), 14.1 (-CH_3). EI/MS: *m/e* (%) 254 (2, M^+-H_2O), 227 (45, M^+-OEt), 198 (36, M^+-COOEt-H), 82 (100, $C_5H_6O^+$). EI/HRMS: *m/e* 254.11534 (calc. for $C_{13}H_{18}O_5$ (M^+-H_2O): 254.1154).

Diethyl *exo,exo*-5,6-dihydroxybicyclo[2.2.2]octane-*trans*-2,3-dicarboxylate (9) The mixture of olefin **2** and the corresponding diol was separated by flash chromatography, as described for **8**. The diol was obtained as a waxy compound. IR (CCl_4): ν 3410 (O-H), 1725 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.16 (overlapping q, ^{3}J=7.1Hz, 4H, O-CH_2-), 3.97 A of AB (dd, ^{2}J=7.9Hz, ^{3}J=3.0Hz, 1H, H_5 or H_6), 3.82 B of AB (d, ^{2}J=7.9Hz, 1H, H_5 or H_6), 3.19 (dd, ^{3}J=7.2Hz, ^{3}J=2.3Hz, 1H, H_2 or H_3), 3.16 (br.s., 1H, -OH), 3.07 (br.s., 1H, -OH), 3.00 (d, ^{3}J=7.2Hz, 1H, H_2 or H_3), 2.28 (br.s., 1H, H_1 or H_4), 2.22-2.19 (m, 1H, H_1 or H_4), 1.93-1.77 (m, 2H, H_7 and/or H_8), 1.43-1.37 (m, 1H, H_7 or H_8), 1.27 (t, ^{3}J=7.1Hz, 7H, -CH_3 and H_7 or H_8). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.0 and 173.6 (C=O), 67.0 and 64.5 (C_5 and C_6), 61.1 (O-CH_2-), 42.6 and 41.7 (C_2 and C_3), 34.7 (C_1 and C_4), 17.6 (C_7 and C_8), 14.1 (-CH_3). EI/MS: *m/e* (%) 287 (100, M^++1), 269 (37, M^++1-H_2O), 241 (8, M^+-OEt), 223 (11, M^+-OEt-H_2O), 96 (20, $C_6H_8O^+$). EI/HRMS: *m/e* 286.1415 (calc. for $C_{14}H_{22}O_6$ (M^+): 254.1416).

Diethyl *syn*-4,5-dihydroxycyclohexane-*trans*-1,2-dicarboxylate (10) The mixture of olefin **3** and the corresponding diol was separated by flash chromatography, as described for **8**. The diol was obtained as a slightly yellow oil. IR (CCl_4): ν 3410 (O-H), 1720 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.13 (q, ^{3}J=7.1Hz, 2H, O-CH_2-), 4.12 (q, ^{3}J=7.1Hz, 2H, O-CH_2-), 4.01 (br.s., 1H, H_4), 3.70 (ddd, ^{3}J=10.1Hz, ^{3}J=3.8Hz, ^{3}J=3.2Hz, H_5), 3.03 (ddd, ^{3}J=12.0Hz, ^{3}J=11.2Hz, ^{3}J=4.0Hz, 1H, H_2), 2.74-2.67 (m, 3H, H_1 and -OH), 2.23 A of AB (dt, ^{2}J=14.1Hz, ^{3}J=4.0Hz, 1H, H_3), 2.03 A of AB (dt, ^{2}J=12.6Hz, ^{3}J=3.8Hz, 1H, H_6), 1.83 B of AB (q, ^{3}J=12.0Hz, 1H, H_6), 1.60 B of AB (ddd, ^{2}J=14.1Hz, ^{3}J=12.0Hz, ^{3}J=2.4Hz, 1H, H_3), 1.25 (t, ^{3}J=7.1Hz, 3H, -CH_3), 1.24 (t, ^{3}J=7.1Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.9 and 173.8 (C=O), 70.3 and 67.9 (C_4 and C_5), 60.83 and 60.75 (O-CH_2-), 43.0 and 38.4 (C_1 and C_2), 32.9 and 30.3 (C_3 and C_6), 14.1 (-CH_3). EI/MS: *m/e* (%) 261 (5, M^++1), 242 (6, M^+-H_2O), 216 (50, M^++1-OEt), 197 (86, M^+-OEt-H_2O), 188 (55, M^++1-COOEt), 29 (100, $CH_3CH_2^+$). EI/HRMS: *m/e* 242.11549 (calc. for $C_{12}H_{18}O_5$ (M^+-H_2O): 242.1154).

Methyl *exo,exo*-5,6-dihydroxybicyclo[2.2.2]octane-*endo*-2-carboxylate (11) The mixture of olefin **6** and the corresponding diol was separated by flash chromatography, starting with n-hexane:ethyl acetate = 10:1. After the olefin had eluted the eluent was changed to pure ethyl acetate. The diol was obtained as a yellowish oil. IR (CCl_4): ν 3390 (O-H), 1725 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 2H, H_5 and H_7), 3.69 (s, 3H, -O-CH_3), 2.87 (br.s., 1H, -OH), 2.85 (br.s., 1H, -OH), 2.70-2.65 (m, 1H, H_2), 2.0-1.2 (m, 8H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.9 (C=O), 67.3 and 64.6 (C_5 and C_6), 51.8 (O-CH_3), 40.2 (C_2), 34.3 and 30.8 (C_1 and C_4), 25.5 (C_3), 18.2 and 17.3 (C_7 and C_8). EI/MS: *m/e* (%) 200 (3, M^+), 182 (29, M^+-H_2O), 168 (51, M^+-CH_3OH), 150 (33, M^+-CH_3OH-H_2O), 96 (100, $C_6H_8O^+$). EI/HRMS: *m/e* 200.10490 (calc. for $C_{10}H_{16}O_4$ (M^+): 200.1049).

Ethyl *exo,exo*-5,6-dihydroxybicyclo[2.2.1]heptane-*endo*-2-carboxylate (12) The mixture of olefin **5** and the corresponding diol was separated by flash chromatography, starting with n-hexane:ethyl acetate = 5:1. After the olefin had eluted the eluent was changed to pure ethyl acetate. The diol was obtained as a white solid. m.p.: 63-66°C (66-67°C[21]). IR (CCl_4): ν 3390 (O-H), 1730 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.14 (q, ^{3}J=7.1Hz, 2H, O-CH_2-), 3.79 (s, 2H, H_5 and H_7), 3.20 (s, 2H, -OH), 2.71 (dt, ^{3}J=11.5Hz, ^{3}J=5.0Hz, 1H, H_2), 2.46 (br.s., 1H, H_1), 2.20 (d, ^{3}J=4.0Hz, 1H, H_4), 1.91 (dd, ^{2}J=10.5Hz, ^{3}J=1.6Hz, 1H, H_7), 1.70 (ddd, ^{2}J=13.2Hz, ^{3}J=11.5Hz, ^{3}J=5.0Hz, 1H, H_3), 1.53 (ddd, ^{2}J=13.2Hz, ^{3}J=5.3Hz, ^{3}J=2.4Hz, 1H, H_3), 1.27 (t, ^{3}J=7.1Hz, 4H, -CH_3 and H_9). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.1 (C=O), 74.0 and 70.7 (C_5 and C_6), 60.6 (O-CH_2-), 46.5 (C_2), 43.7 and 42.6 (C_1 and C_4), 33.5 (C_7), 27.4 (C_3), 14.2 (-CH_3). EI/MS: *m/e* (%) 182 (8, M^+-H_2O), 155 (27, M^+-OEt), 82 (100, $C_5H_6O^+$). EI/HRMS: *m/e* 182.09430 (calc. for $C_{10}H_{14}O_3$ (M^+-H_2O): 182.0943).

Methyl *exo,exo*-5,6-dihydroxybicyclo[2.2.1]heptane-*exo*-2-carboxylate (13) The mixture of olefin **4** and the corresponding diol was separated by flash chromatography, starting with n-hexane:ethyl acetate = 3:1. After the olefin had eluted the eluent was changed to pure ethyl acetate. The diol was obtained as a white crystalline compound. m.p.: 49-52°C (50-53°C[21]). IR (CCl_4): ν 3400 (O-H), 1730 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 2H, H_5 and H_6), 3.68 (s, 3H, O-CH_3), 3.40 (br.s., 1H, -OH), 3.27 (br.s., 1H, OH), 2.42 (s, 1H, H_1), 2.23-2.19 (m, 2H, H_2 and H_4), 1.86 A of AB (dt, ^{2}J=13.2Hz, ^{3}J=5.0Hz, 1H, H_{3up}), 1.75 A of AB (d, ^{2}J=10.8Hz, 1H, H_{7syn}), 1.40-1.34 (m, 2H, H_{3down} and H_{7anti}). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.6 (C=O), 73.81 and 73.77 (C_5 and C_6), 52.0 (O-CH_3), 47.2 (C_2), 42.7 and 41.8 (C_1 and C_4), 29.8 and 29.0 (C_3 and C_7). EI/MS: *m/e* (%) 186 (1, M^+), 168 (38, (M^+-H_2O), 154 (100, M^+-CH_3OH). EI/HRMS: *m/e* 186.08927 (calc. for $C_9H_{14}O_4$ (M^+): 186.0892.

Ethyl *syn*-3,4-dihydroxycyclohexane-1-carboxylate (14) The mixture of olefin **7** and the corresponding diols were separated by flash chromatography, starting with n-hexane:ethyl acetate = 10:1. After the olefin had eluted the eluent was changed to n-hexane:ethyl acetate = 1:3. This resulted in the isolation of the diol as a colorless oil, which contained all four possible enantiomers as was indicated by NMR-experiments using Eu(hfc)$_3$ as a chiral shift reagent. IR (CCl_4): ν 3410 (O-H), 1730 (C=O) cm^{-1}. EI/MS: *m/e* (%) 188 (1, M^+), 170 (5, M^+-H_2O), 159 (2, M^+-Et), 143 (20, M^+-OEt), 116 (24, M^++1-COOEt), 97 (100, $C_6H_9O^+$).

Diethyl bicyclo[2.2.1]hept-5-ene-*trans*-2,3-dicarboxylate (**1**) A solution of diol **8** (0.55 g, 2.0 mmol) and imidazole (0.55 g, 8.0 mmol) in toluene (50 mL) was heated under reflux, then chloro diphenylphosphine (0.86 mL, 4.8 mmol) was added. After 10 minutes iodine (1.22 g, 4.8 mmol) was gradually added and the reaction mixture was heated under reflux for 2 h. Subsequently, an excess of zinc powder was added at room temperature and the reaction mixture was heated under reflux for an additional hour. The reaction was stopped by filtration over celite, and the residue was washed with 3N HCl (aq.). The aqueous phase was extracted with ethyl acetate (3x). The organic fractions were washed with saturated aqueous $NaHCO_3$-solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (n-hexane : ethyl acetate = 10:1) of the residue resulted in the isolation of **1** as a yellowish oil (0.44 g, 90%). IR (CCl_4): 3070 (C-H, unsat.), 1730 (C=O) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.28 (dd, ^{3}J=3.2Hz, ^{3}J=5.6Hz, 1H, H_5 or H_6), 6.07 (dd, ^{3}J=2.8Hz, ^{3}J=5.6Hz, 1H, H_5 or H_6), 4.17 (q, ^{3}J=7.0Hz, 2H, O-CH_2-), 4.10 (dq, ^{3}J=7.0Hz, ^{3}J=2.0Hz, 2H, O-CH_2-), 3.37 (t., ^{3}J=4.1Hz, 1H, H_3), 3.26 (s, 1H, H_1 or H_4), 3.12 (s, 1H, H_1 or H_4), 2.67 (dd, ^{3}J=4.5Hz, ^{3}J=1.6Hz, 1H, H_2), 1.62 A of AB (d, ^{3}J=8.7Hz, 1H, H_7), 1.45 B of AB (dd, ^{3}J=8.7Hz, ^{3}J=1.6Hz, 1H, H_7), 1.28 (t, ^{3}J=7.0Hz, 3H, -CH_3), 1.26 (t, ^{3}J=7.0Hz, 3H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.4 and 173.3 (C=O), 137.5 and 135.0 (C_5 and C_6), 60.8 and 60.5 (O-CH_2-), 47.9, 47.7, 47.2 and 45.7 (C_1, C_2, C_3 and C_4), 47.2 (C_7), 14.2 (-CH_3). EI/MS: *m/e* (%) 239 (4, M^++1), 193 (14, M^+-OEt), 173 (34, M^+-C_5H_5), 165 (16, M^+-COOEt), 66 (100, $C_5H_6^+$). EI/HRMS: *m/e* 238.12055 (calc. for $C_{13}H_{18}O_4$ (M^+): 238.1205).

REFERENCES AND NOTES

1. (a) Helmchen, G.; Goeke, A.; Kreisz, S.; Krotz, A.; Lauer, G.H.; Linz, G. Cyclopentanoid Natural Products *via* Asymmetric Diels-Alder Reactions. In *Studies in Natural Products Chemistry*, Vol. 8. Elsevier Science Publishers B.V.: Amsterdam, 1991; 139. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.*, **1993**, *93*, 741. (c) Fringuelli, F.; Tatichi, A. *Dienes in the Diels-Alder Reaction*. Wiley: New York, 1990. (d) Desimo, G.; Tacconi, G.; Barco, A.; Pollini, G.P. Natural Products Synthesis through Pericyclic Reactions. In *ACS Monograph Series*, No. 180, 1983.
2. (a) Paquette, L.A. *Asymmetric Synthesis*, Vol. 3; Morrison J.D. Ed.; Academic Press: Orlando, 1984, Chapter 7. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.*, **1984**, *23*, 876. (c) Trost, B.M.; O'Krongly, D.; Belletire, J.L. *J. Am. Chem. Soc.*, **1980**, *102*, 7595. (d) Corey, E.J.; Ensley, H.E. *J. Am. Chem. Soc.*, **1975**, *97*, 6908. (e) Kagan, H.B.; Riant, O. *Chem. Rev.*, **1992**, *92*, 1007. (f) Lohray, B.B.; Bhushan, V. *Angew. Chem.*, **1992**, *104*, 740. (g) Deloux, L.; Srebnik, M. *Chem. Rev.*, **1993**, *93*, 673.
3. Van Gastel, F.J.C.; Klunder, A.J.H.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas*, **1991**, *110*, 175.
4. 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 and references cited therein.
5. For recent reviews on asymmetric dihydroxylation reaction, see: (a) Lohray, B.B. *Tetrahedron: Asymm.*, **1992**, *3*, 1317. (b) Johnson, R.A.; Sharpless, K.B. Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetric Synthesis* ; Ojima, I. Ed.; VCH Publishers: New York, 1993; 227. (c) Kolb, H.C.;

VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.*, **1994**, *94*, 2483. (d) Balavoine, G.G.A.; Manoury, E. *Appl. Organomet. Chem.*, **1995**, *9*, 199.

6. (a) Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.*, **1988**, *53*, 6126. (b) Liu, Z.; Classon, B.; Samuelsson, B. *J. Org. Chem.*, **1990**, *55*, 4273.
7. (a) Sharpless, K.B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.*, **1991**, *56*, 4585. (b) Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1993**, *115*, 8463. (c) Crispino, G.A.; Makita, A.; Wang, Z.-M.; Sharpless, K.B. *Tetrahedron Lett.*, **1994**, *35*, 543.
8. (a) Jeong, K.-S.; Sjö, P.; Sharpless, K.B. *ibid.*, **1992**, *33*, 3833. (b) Soderquist, J.A.; Rane, A.M.; López, C.J. *ibid.*, **1993**, *34*, 1893. (c) VanNieuwenhze, M.S.; Sharpless, K.B. *ibid.*, **1994**, *35*, 843. (d) Ko, S.Y.; Malik, M.; Dickinson, A.F. *J. Org. Chem.*, **1994**, *59*, 2570.
9. Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1992**, *114*, 7568.
10. While this research was in progress Wang *et al.* published on the asymmetric dihydroxylation of a series of conjugated cyclic *cis*-disubstituted olefins that gave only moderate results with a few exceptions. Wang, Z.-M.; Kakiuchi, K.; Sharpless, K.B. *J. Org. Chem.*, **1994**, *59*, 6895.
11. (a) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.*, **1992**, *33*, 4021. (b) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennani, Y. *J. Org. Chem.*, **1993**, *58*, 1991.
12. Takano, S.; Yoshimitsu, T.; Ogasawara, K. *ibid.*, **1994**, *59*, 54.
13. The ligand DHQD-IND is not commercially available. The synthesis of DHQD-IND was performed as described in the supplementary material of Ref. 9.
14. (a) Koch, H. *Mh. Chem.*, **1962**, *93*, 1343. (b) Inukai, T.; Kasai, M. *J. Org. Chem.*, **1965**, *30*, 3567. (c) Devine, P.N.; Oh, T. *J. Org. Chem.*, **1992**, *57*, 396.
15. The synthesis of **3** and **7** was an improved version of the procedure of Ref. 14b and Ref. 14c. One equivalent of $AlCl_3$ was added to a solution of diethyl fumarate or ethyl acrylate in benzene (500 mL/mol). The reaction vessel was equipped with a reflux condenser, cooled to -80°C and directly connected to a gas cylinder containing 1,3-butadiene. Slowly condensing the gas while the reaction mixture was well stirred resulted in a slightly exothermal reaction. After 1.5 h the excess of 1,3-butadiene was allowed to evaporate. Then the reaction mixture was diluted with ethyl acetate and extracted with water (3x). The combined water layers were again extracted with ethyl acetate. The organic fractions were dried over Na_2SO_4 and concentrated *in vacuo*.
16. (a) Ver Nooy, C.D.; Rondestvedt Jr., C.S. *J. Am. Chem. Soc.*, **1955**, *77*, 3583. (b) Van Tamelen, E.E.; Shamma, M. *ibid.*, **1954**, *76*, 2315.
17. (a) Varech, D.; Jacques, J. *Tetrahedron*, **1972**, *28*, 5671. (b) Nakazaki, M.; Naemura, K.; Kondo, Y. *J. Org. Chem.*, **1979**, *44*, 16. (c) Cervinka, O.; Kriz, O. *Collection Czechoslov. Chem. Commun.*, **1968**, *33*, 2342. (d) Berson, J.A.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J. Am. Chem. Soc.*, **1961**, *83*, 3986.
18. Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.*, **1988**, *18*, 249.
19. (a) Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.*, **1993**, *34*, 3911. (b) VanNieuwenhze, M.S.; Sharpless, K.B. *J. Am. Chem. Soc.*, **1993**, *115*, 7864. (c) Ward, R.A.; Procter, G. *Tetrahedron Lett.*,

1992, *33*, 3363. (d) Crispino, G.A.; Makita, A.; Wang, Z.-M.; Sharpless, K.B. *Tetrahedron Lett.*, **1994**, *35*, 543.

20. Hawkins, J.M.; Meyer, A. *Science*, **1993**, *260*, 1918.
21. Bazbouz, A.; Christol, H.; Coste, J.; Plénat, F. *Bull. Soc. Chim. Fr.*, **1978**, *II*, 305-311.

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