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Oxazaborolidine-catalysed reduction of alk-2-ene-1,4-diones. A convenient access to chiral 1,4-diols

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Dedicated with best wishes to *Prof. Satoru Masamune* on the occasion of his 70th birthday

Abstract

An efficient method for the preparation of C_2-symmetric, chiral alk-2-ene-1,4-diols (**4**) has been achieved, based on the borane-mediated reduction of symmetric alk-2-ene-1,4-diones (**2**) in the presence of oxazaborolidine (*R*)-**1**. In general, the presence of the double bond in **2** has been beneficial (compared with the related saturated 1,4-diketones **3**) not only as far as the stereoselectivity in the reduction step is concerned, but also because it allowed us to remove *meso*-**4** by chomatography and/or to improve the stereochemical purity of several resulting mixtures of diols **4** by Sharpless' epoxidation. Enantioenriched compounds **4** have been readily reduced to saturated diols with negligible loss of optical purity. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric synthesis; Diols; Oxazaborolidines; Reduction

1. Introduction

Over the last years there has been much interest in the development of new and more efficient chiral reagents and catalysts to be applied to organic synthesis [1,2]. In this context, C_2-symmetric 1,4-diols and their derivatives have proved to be useful building blocks for the preparation *inter alia* of 2,5-disubstituted pyrrolidines [3-6], thiolanes [7], and phosphine ligands of interest for asymmetric hydrogenation [8-10]. These 1,4-diols have been obtained either from the chiral pool [11,12], by enzymatic resolutions of mixtures of *meso* and racemic isomers [13-16], by electrochemical Kolbe-type coupling of chiral ß-hydroxy acids [17], or by addition of diorganozincs to γ-alkoxy aldehydes in the presence of a chiral Lewis acid [18]. The stereoselective reduction of symmetric 1,4-diketones appears, obviously, as an attractive approach to chiral 1,4-diols. In fact, one might expect much higher enantioselectivities –from

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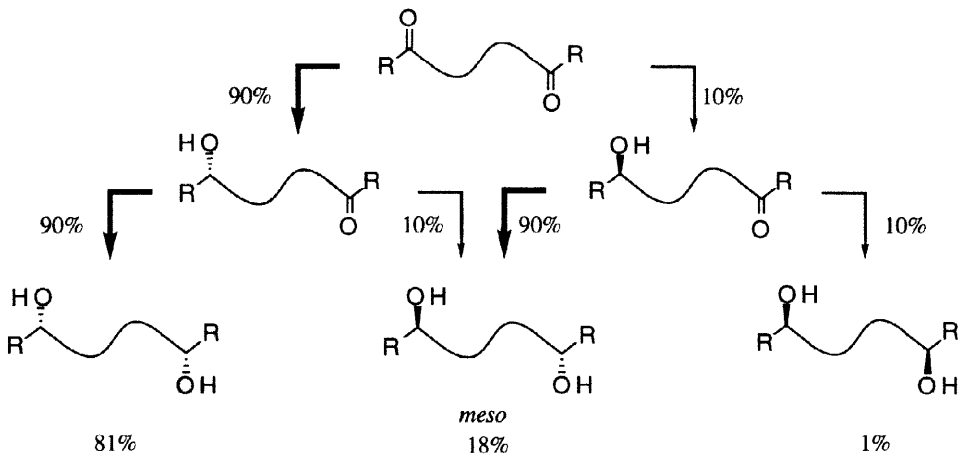
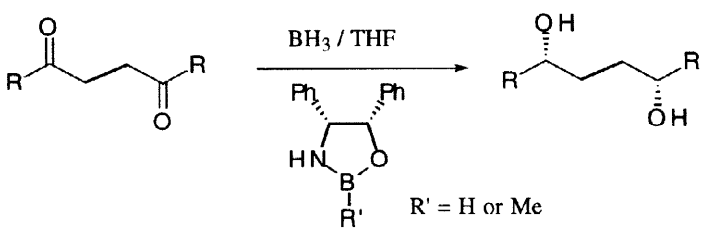
a statistical point of view– than those noted for related monoketones, since most of the minor enantiomer formed in the first reduction would become a *meso* compound after the second reduction. Thus, the enantiopurity of the final diols would be enhanced at the expense of the formation of potentially removable *meso* byproducts. For instance, assuming that both the first and second reductions run independently with a moderate 90:10 facial selectivity, enantiomerically enriched diol should be obtained in 82% yield and 97.6% e.e. besides 18% of *meso* compound (see Scheme 1) [19].

Scheme 1



However, wonderful this sounds, the utilisation of this strategy has been limited [5,20-25] and it has seldom been applied to 1,4-diketones. For instance, (*S*,*S*)-hexane-2,5-diol has been successfully prepared from parent hexane-2,5-dione by baker's yeast reduction [26] and by asymmetric hydrosilylation catalysed by a chiral rhodium complex [27]. In this connection, Quallich et al. have reported [28] the borane-mediated reduction of a number of alkane-1,4-diones in the presence of (4*R*,5*S*)-4,5-diphenyl-1,3,2-oxazaborolidines with good to excellent *dl*:*meso* ratios and enantioselectivities for aromatic and hindered diketones (Scheme 2, R = Ph or R = Bu^t).

Scheme 2



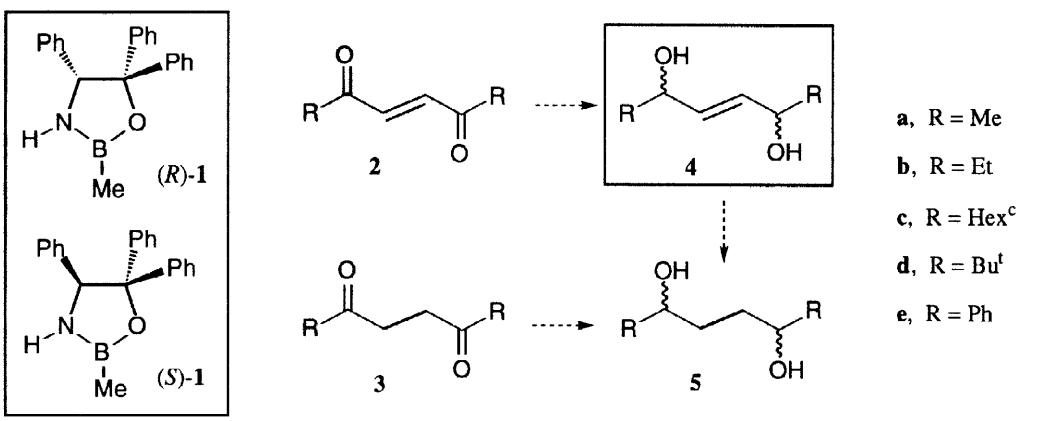
	dl/*meso* ratio	e.e.
R = Ph	84/16	99%
R = Bu^t	80/20	97%
R = Me	69/31	17% ⇦

Nevertheless, the reported stereoselectivity for hexane-2,5-dione (Scheme 2, R = Me) under similar conditions was much lower, probably due to the fact that the steric hindrance

around both sides of both carbonyl groups are quite similar and the catalyst cannot efficiently discriminate between them. Thus, a process that would provide a general and practical route to chiral 1,4-diols would be desirable yet.

Our previous experience on the reduction of α,ß-unsaturated ketones catalysed by (*R*)- and (*S*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidines, (*R*)- and (*S*)-**1** [29,30], indicates that the ethylenic moiety of these ketones behaves as a group "larger" than the saturated chain in such processes. Accordingly, we envisaged that oxazaborolidine-mediated reduction of alk-2-ene-1,4-diones (**2**) could be much more efficient in terms of stereoselectivity than the reduction of the corresponding saturated diketones **3** (see Scheme 3). In addition, the resulting allylic diols **4** are versatile intermediates amenable to conversion not only to saturated diols **5** but also to other useful chiral synthons. Thus, we undertook a systematic study on reduction of unsaturated diketones **2a–e** with borane in the presence of (*R*)-**1** [31]. For the sake of comparison, related saturated diketones **3a–e** were also included. We wish to report here our findings in this connection.

Scheme 3



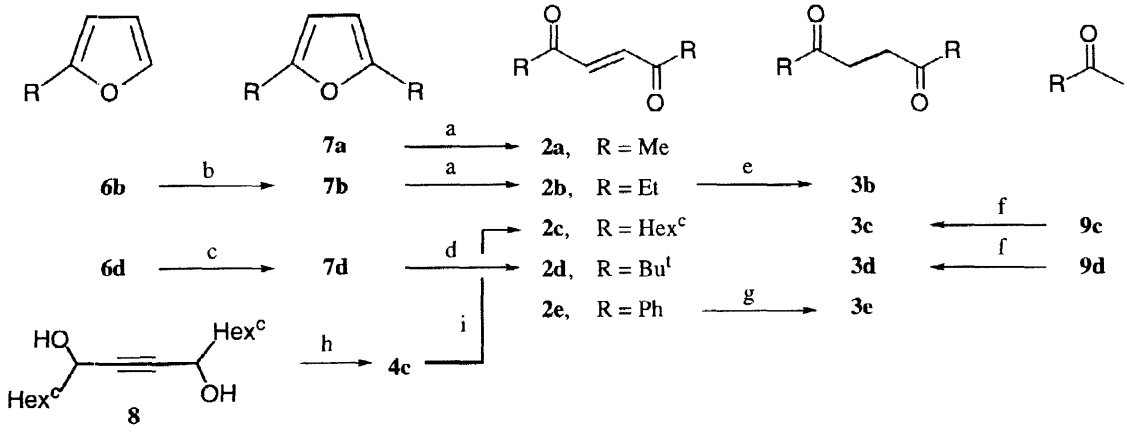
2. Results and Discussion

Preparation of 1,4-Diketones

A series of unsaturated diketones, **2**, with increasing steric demand in going from **2a** (R = Me) to **2d** (R = Bu^t), were synthesized in order to investigate their performance in oxazaborolidine-mediated asymmetric reductions. As shown in Scheme 4, most of these diketones were readily obtained by oxidative cleavage of the corresponding 2,5-dialkylfurans (**7**) with Br_2 in H_2O/acetone (**2a,b**) or with bleach (**2d**) [32]. As far as **2c** is concerned (Hex^c means cyclohexyl), we obtained a better overall yield by means of a two-step process starting from 1,4-dicyclohexylbut-2-yne-1,4-diol (**8**) [31]. The required 2,5-dialkylfurans, in turn, were obtained from the known 2-alkylfurans **6b** and **6d** by alkylation using butyl-lithium in hexane-

THF to deprotonate the furan ring (**7b**) and by Friedel-Crafts alkylation (**7d**), respectively.[1] 1,4-Diphenylbutene-1,4-dione (**2e**), also studied in this work, is commercially available.

Scheme 4[a]



[a]Reagents: (a) Br_2, H_2O-acetone 1:2, –20 °C to r.t. (b) i) BuLi, THF, –15 °C; ii) EtBr, –15 °C to r.t. (c) Bu^tBr, $AlCl_3$, CCl_4, –20 °C. (d) bleach, H_2O-CH_2Cl_2, r.t. (e) H_2, Pd/C, MeOH. (f) i) LDA, THF, –78 °C; ii) $CuCl_2$ anh., DMF. (g) $SnCl_2$, aq. HCl-EtOH. (h) $LiAlH_4$, THF, Δ. (i) Swern oxidation.

Regarding saturated diketones **3**, hexane-2,5-dione (**3a**) is commercially available. Compounds **3c** and **3d** were readily obtained by oxidative dimerisation of the appropriate methyl ketone lithium enolates by $CuCl_2$ [34,35]. Since the same process, when applied to butanone enolate to obtain **3b**, gave a mixture of regioisomers, we prepared **3b** by reduction of the corresponding ethylenic diketone **2b**; **3e** was similary obtained from **2e**, as described in the literature [36].

Reduction of Diketones

When we carried out the reduction of **2a** (1.0 mmol) with BH_3:SMe_2 (2.2 mmol) and (*R*)-**1** (2.0 mmol) in THF at 0 °C,[2] the allylic diol **4a** was obtained in essentially quantitative yield and, as expected, with better stereoselectivities (86:14 *dl/meso* ratio, 99% e.e.) than those obtained in the reduction of saturated diketone **3a** to diol **5a** (68:32 *dl/meso* ratio, 92% e.e.). It is to be noted that the stereoselectivity decreased when the reduction of **2a** was performed with only 1.0 equiv. or 0.2 equiv. of (*R*)-**1** (77:23 *dl/meso* ratio, 95% e.e. and 69:31 *dl/meso* ratio,

[1]Attempts to obtain **7c** and **7d** by a double Friedel-Crafts alkylation from furan led to low yields and considerable resinification. Another attempt to get **7c** by double nucleophilic alkylation of 2,5-dilithiofuran [33] was also unsuccessful.

[2]When reductions were carried out at lower temperatures or changing the order of addition (slow addition of BH_3:SMe_2 to the mixture of diketone and catalyst), worse results were recorded.

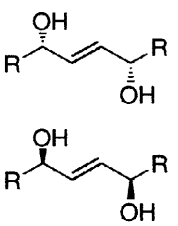
81% e.e., respectively).

Similar trends were observed in the reduction of the remaining diketones. Whereas good to excellent enantioselectivities were noted for unsaturated diketones **2b–e** (up to 99% e.e., when 2 equiv. of (*R*)-**1** were used, see Table 1), poor results were generally obtained in the reduction of the corresponding saturated diketones **3** (see Table 2). Therefore, alk-2-ene-1,4-diones **2** were more suitable starting materials for obtaining chiral 1,4-diols than their saturated analogues **3**. In addition, in most cases the undesired *meso*-**4** diols could be readily removed by flash chromatography from their corresponding (*S,S*)-stereoisomers, increasing in this way the purity of the final product.[3]

Table 1

Reduction of diketones 2 with BH_3:SMe_2 in the presence of (*R*)-1[a]

entry	diketone	yield	*dl*/*meso* ratio[b]	e.e.[b]	major diol[c]
1	**2a**, R = Me	98% (93%)	86:14 (69:31)	99% (81%)	(*S,S*)-**4a**
2	**2b**, R = Et	85% (75%)	72:28 (67:33)	91% (88%)	(*S,S*)-**4b**
3	**2c**, R = Hex[c]	83% (75%)	71:29 (61:39)	82% (65%)	(*S,S*)-**4c**
4	**2d**, R = Bu^t	85% (98%)	87:13 (85:15)	99% (98%)	(*S,S*)-**4d**
5[d]	**2e**, R = Ph	84% (47%)	62:38 (55:45)	92% (82%)	(*S,S*)-**4e**

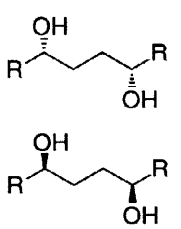


[a]Reactions were carried out by slow addition of diketone (1.0 mmol) to a mixture of BH_3:SMe_2 (2.2 mmol) and catalyst (2.0 mmol) in THF at 0 °C. Within parentheses values using 0.2 mmol of catalyst.
[b]Determined by HPLC and/or ^{19}F NMR analysis of the corresponding Mosher diesters.
[c]Absolute configuration was established by comparison of the sign of the specific rotations of these diols after hydrogenation with those given in the literature (see Experimental Section).
[d]Stereoselectivity determined by HPLC using a reverse phase chiral column Chiracel OD-R.

Table 2

Reduction of diketones 3 with BH_3:SMe_2 in the presence of (*R*)-1[a]

entry	diketone	yield	*dl*/*meso* ratio[b]	e.e.[b]	major diol[c]
1	**3a**, R = Me	92%	68:32	92%	(*S,S*)-**5a**
2	**3b**, R = Et	80%	58:42	46%	(*S,S*)-**5b**
3	**3c**, R = Hex[c]	75%	67:33	45%	(*R,R*)-**5c**
4	**3d**, R = Bu^t	78%	58:42	40%	(*S,S*)-**5d**
5	**3e**, R = Ph	91% (95%)	93:7 (91:9)	99% (98%)	(*S,S*)-**5e**



[a]Reactions were carried out by slow addition of diketone (1.0 mmol) to a mixture of BH_3:SMe_2 (2.2 mmol) and catalyst (2.0 mmol) in THF at 0 °C. Within parentheses values using 0.2 mmol of catalyst.
[b]Determined by HPLC and/or ^{19}F NMR analysis of the corresponding Mosher diesters.
[c]Absolute configuration was established from the sign of the specific rotation of each diol (see Experimental Section).

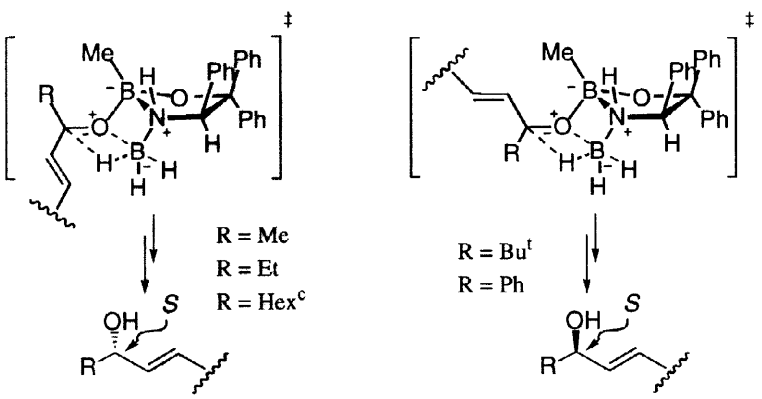
[3]In our hands, the *dl*-**5** and *meso*-**5** stereoisomers could not be separated by chromatography, except for the case of **5d**.

With regard to the results summarised in Table 1 some remarks should be pointed out:

(i) It seems reasonable that better stereoselectivities were achieved in compounds **2a** (R = Me) and **2d** (R = Bu^t) in which the R groups are clearly smaller and bigger, respectively, than the olefinic moiety. In contrast, **2c** or **2e** gave worse results, which suggests that cyclohexyl or phenyl groups are not so markedly discriminated against the double bond.

(ii) As far as the stereochemical course of the reaction is concerned, the observed configuration of diols **4** may be explained, according to the mechanism proposed by Corey et al. [37,38] for similar oxazaborolidine mediated reactions, by the transition state shown in Scheme 5, in which the double bond moiety –acting as a bigger group than Me, Et, or cyclohexyl– is located far from the Me group on the boron atom. The opposite relationship of effective size applies for bulkier Bu^t and Ph groups.

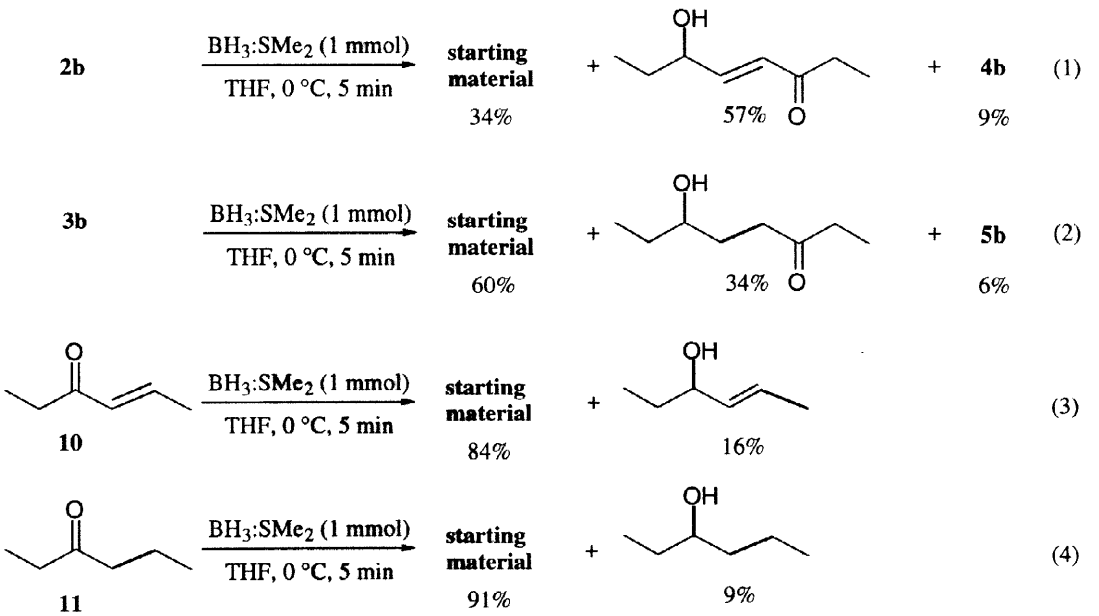
Scheme 5



(iii) Although a decrease in the amount of oxazaborolidine (*R*)-**1** from 2 equiv. to 0.2 equiv. does not affect too much the stereoselectivity of the reduction of **2d**, in most cases it does. This fact can be related with an increasing significance of the uncatalysed reduction by borane as the relative amount of (*R*)-**1** decreases. In this regard, some control experiments carried out in our laboratory suggest that the uncatalysed reduction of relatively more reactive diketones **2** may compete with the desired oxazaborolidine-catalysed process to a greater extent than in the case of the well-known reduction of simple monoketones [37]. Thus, as shown in Scheme 6, BH_3:SMe_2 (1 mmol) in THF reduced one of the carbonyl groups of **2b** very quickly (eq. 1, 57% of ketol with 1 mmol of BH_3:SMe_2 within 5 min), but the second one more slowly (9% of **4b** within 5 min, as shown in Scheme 6, eq. 1, and only ~22 % of diol with 2 mmol of

BH_3:SMe_2, within 1 h).[4] Instead, in a parallel experiment under similar conditions **3b** was reduced to a lesser extent (eq 2, 40% of starting material is transformed into alcohol or diol). On the other hand, monoketones **10** and **11** were more resistant to the reduction by borane (eq. 3 and 4, respectively).

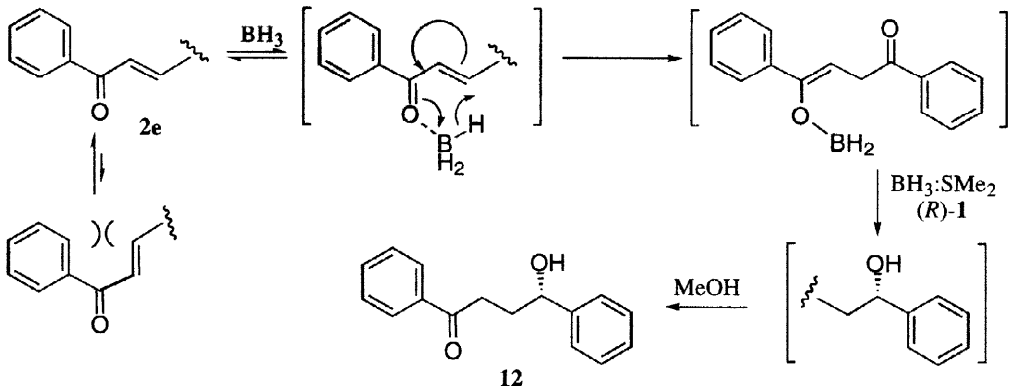
Scheme 6



(iv) In sharp contrast with the remaining instances, reduction of 1,4-diphenylbutane-1,4-dione (**3e**) gave better chemical yield and stereoselectivity than that of its related olefinic diketone **2e**. From the stereochemical point of view, this is not surprising since one can expect a larger diference of steric hindrance between a Ph group and a saturated chain (in **3e**) than between the Ph group and an olefinic moiety (in **2e**). Regarding the low chemical yield –specially when only 0.2 equiv. of oxazaborolidine were present–, it can be explained by the competitive formation of 4-hydroxy-1,4-diphenylbutan-1-one (**12**), isolated together with the expected diol **4e** in the reduction of **2e**. This hydroxy ketone probably arises from the conjugate reduction of the enone system by borane (see Scheme 7). This result could be related with a more prevailing trend of **2e** to adopt the *s-cis* conformation, needed for such a conjugated addition, than other diketones **2**.

[4]The fast uncatalysed reduction of the first carbonyl group can explain the diastereoselectivity obtained (*dl/meso* ratio) in borane-reductions of diketones **2** catalysed by **1**, which is lower than expected from statistical arguments on the basis of results for monoketones [29]. Obviously, an increase in the unselective reduction of the first carbonyl group causes a larger amount of the *meso* diol.

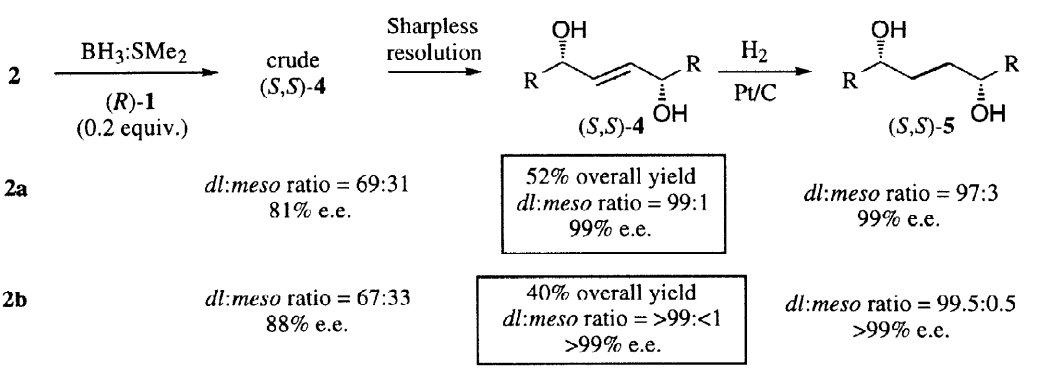
Scheme 7



*Sharpless Epoxidation of Enantiomerically Enriched Diols **4a** and **4b***

Since it was not possible to remove the *meso* stereoisomer by chromatography from the mixture of diols **4a**, or it was difficult for **4b**, we improved its diastereomeric and enantiomeric purity (up to 99:1 *dl:meso* ratio, 99% e.e.) by Sharpless epoxidation under controlled conditions [39]. Accordingly, a sample of diols **4a** (containing ~63% of the *S,S*-isomer, 69:31 *dl:meso* ratio, 81% e.e.) arising from reduction of **2a** under catalytic conditions (0.2 equiv. of (*R*)-**1**) was treated with 0.50 equiv. of (–)-diethyl tartrate, 0.40 equiv. of titanium(IV) isopropoxide and 0.50 equiv. of *tert*-butyl hydroperoxide in CH_2Cl_2 for 2 days at –20 °C. After work-up, recovered diol **4a** showed a 99:1 *dl:meso* ratio and 99% e.e. (52% overall yield from diketone **2a**). Thus, the sequence outlined above, based on the reduction of **2a** emerges as a suitable choice to obtain highly enantioenriched (*R,R*) or (*S,S*)-hexane-2,5-diol by using (*S*)-**1** or (*R*)-**1**, respectively.[5] In a similar way it was possible to obtain (*S,S*)-**4b** enantiomerically pure (see Scheme 8).

Scheme 8



[5]Obviously, Sharpless epoxidation protocol can be applied to the mixture of diols derived from the reduction of **2a** with achiral $NaBH_4$, but in this case overall conversions below 20% are necessary to reach highly enantiopure **4a**.

Catalytic hydrogenation of diols 4

In general, catalytic hydrogenation (50 atm of H_2, Pt/C, MeOH or AcOEt) of chiral diols **4a–d** gives the corresponding saturated diols **5a–d** in good yields and negligible loss of optical purity. It is worth noting that lower hydrogen pressures were ineffective for relatively hindered olefins **4c** and **4d** using either Pd/C or Pt/C as catalysts. On the other hand, a set of hydrogenations carried out with **4a** revealed that the use of Pd/C and/or 1 atm. pressure of hydrogen led to a decrease of yield, owing to the formation of 5-15% of 5-hydroxyhexan-2-one derived from the migration of the double bond.

3. Conclusions

In summary, a synthetic route to symmetric chiral 1,4-diols, based on the borane-mediated reduction of alk-2-ene-1,4-diones **4** catalysed by oxazaborolidine **1**, followed by catalytic hydrogenation, has been developed. In general, this approach has appeared to be more efficient that the reduction of the related saturated 1,4-diketones, **3**, not only as far as the stereoselectivity in the reduction step is concerned, but also because it allowed us to remove *meso*-**4** by chomatography and/or to improve the optical purity of some mixtures of diols **4** by Sharpless epoxidation.

Acknowledgements

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Experimental Section

All the solvents were distilled from an appropriate drying agent and stored under nitrogen atmosphere. The crude products were purified by column chromatography on silica gel of 230-400 mesh (flash chromatography). Thin-layer chromatograms were performed on HF 254 silica gel plates (using the eluents indicated after the R_f values). Melting points are uncorrected. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at 200 MHz and 50.3 MHz, respectively; chemical shifts are given in ppm with respect to internal TMS, and J values are quoted in Hz. Infrared spectra were measured on a Perkin-Elmer 681 on NaCl plates (film) or in KBr; only the most significant absorptions, in cm^{-1}, are indicated. Microanalyses were performed by the Serveis Científico-Tècnics (Universitat de Barcelona). Chemical ionisation mass spectra (NH_3) are given in *m/z*. Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter in an appropiate solvent. 2,5-Diethylfuran (**7b**) [40], diketones **2d** [41], **3d** [35], and **3e** [42], as well as oxazaborolidine **1** [30] were prepared according to published procedures. 2,5-Dimethylfuran (**7a**), ketones **10** and **11**, and diketones **2e** and **3a** are commercially available.

Unsaturated ketones (2).

(*E*)-Hex-3-ene-2,5-dione (2a) [43,44]. To a solution of 4.0 g (42 mmol) of 2,5-dimethylfuran in acetone/H_2O (2:1, 50 mL) at –20 °C, vigorously stirred, 6.65 g (42 mmol) of bromine were added dropwise. Afterwards, the cooling bath was removed and the reaction mixture was allowed to warm to r.t. Three hours later, TLC showed that only the *E* isomer of the hex-3-ene-2,5-dione was present. The reaction mixture was poured into ethyl ether and saturated aq. $NaHCO_3$. The organic layer was separated and washed with more aq. $NaHCO_3$ and then brine. After drying (Na_2SO_4), the solvent was eliminated *in vacuo* and the crude product was purified by flash chromatography (99:1 CH_2Cl_2/MeOH) to yield 3.76 g (80%) of (*E*)-hex-3-ene-2,5-dione. m.p. 75–76 °C (lit. [44] 76 °C); R_f 0.70 (99:1 CH_2Cl_2/MeOH); ^{1}H NMR δ 2.40 (s, 6H), 6.80 (s, 2H); ^{13}C NMR δ 27.8, 137.7, 198.4; IR (KBr) 1670.

(*E*)-Oct-4-ene-3,6-dione (2b). The reaction was performed as described above for **2a**. Yield 60%; m.p. 50–51 °C; R_f 0.30 (2:1 CH_2Cl_2/hexane); ^{1}H NMR δ 1.14 (t, 6H, J = 7.2 Hz), 2.69 (q, 4H, J = 7.2 Hz), 6.89 (s, 2H); ^{13}C NMR δ 8.1, 35.3, 136.5, 201.6; IR (KBr) 1680. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.38; H, 8.61.

(*E*)-1,4-Dicyclohexylbut-2-ene-1,4-dione (2c). To a solution of 3 g (17.6 mmol) of bis(trimethylsilyl) acetylene in 5 mL of anh. THF was added a solution of 260 mg of "anhydrous" tetrabutylammonium fluoride [45] in 0.5 mL of anh. THF under Ar. The mixture was cooled to –20 °C and 4.44 mL (36.7 mmol) of cyclohexanecarboxaldehyde were added dropwise. After 1 h, 30 mL of a 1:1 AcOH/H_2O solution were added and the resulting mixture was stirred at r.t. overnight. It was then extracted with CH_2Cl_2, washed with aq. $NaHCO_3$ and brine, dried, and concentrated *in vacuo*. The residue was purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to afford 2.88 g (65%) of 1,4-dicyclohexylbut-2-yne-1,4-diol (**8**) as a mixture of stereoisomers: m.p. 105–106 °C (lit. [46] 102–106 °C); R_f 0.18 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR δ 0.60–1.32 (m, 10H), 1.35–1.95 (m, 12H), 2.90 (bs, 2H), 4.11 (d, 2H, J = 8.6 Hz); ^{13}C NMR δ 23.4, 25.9, 26.4, 28.1, 28.6, 44.0, 67.1, 86.8; IR (KBr) 3700–3010, 2910, 1450, 1010. MS (CI) *m/z* (rel. int. %): 268 (M^++18, 100).

To a solution of 1.00 g (4.0 mmol) of **8** in 20 mL of anh. THF, 455 mg (12 mmol) of $LiAlH_4$ were added and the resulting mixture was heated to reflux. The progress of the reaction was monitored by TLC. After 5 h, the mixture was cooled to 0 °C and then cautiously quenched by dropwise addition of 2 mL of ethyl acetate followed by 10 mL of 2 M aq. solution of sodium and potasium tartrate. The mixture was stirred at r.t. overnight and then poured into CH_2Cl_2 and brine. The aqueous layer was extracted with more CH_2Cl_2 and the organic layers were dried ($MgSO_4$) and concentrated to afford 784 mg (78%) of crude (*E*)-1,4-dicyclohexylbut-2-ene-1,4-diol (**4c**) as a mixture of stereoisomers which was used in the next reaction.

150 μL (2.11 mmol) of DMSO were added slowly to a solution of 92 μL (1.05 mmol) of oxalyl chloride in 2 mL of anh. CH_2Cl_2 at –78 °C under Ar. After 5 min at this temperature, 119 mg (0.48 mmol) of **4c** in 1 mL of anh. CH_2Cl_2 added dropwise and the solution was stirred for 20 min. Afterwards, 670 μL (4.81 mmol) of Et_3N were added and the mixture was stirred for 1 h and then it was allowed to warm to r.t. The suspension was diluted with more CH_2Cl_2 and then extracted with *p*H 7 phosphate buffer. The organic layer was washed

with brine, dried ($MgSO_4$), and the solvent was eliminated *in vacuo*. The residue was purified by flash chromatography (2:1 CH_2Cl_2/hexane) to afford 106 mg (87%) of (*E*)-1,4-dicyclohexylbut-2-ene-1,4-dione (**2c**): m.p. 58–60 °C; R_f 0.24 (CH_2Cl_2); ^{1}H NMR δ 1.05–1.50 (m, 10H), 1.55–2.00 (m, 10H), 2.50–2.70 (m, 2H), 7.03 (s, 2H); ^{13}C NMR δ 25.4, 25.7, 28.1, 50.0, 135.1, 202.5; IR (KBr) 1675. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.56; H, 9.40. MS (CI) *m/z* (rel. int. %): 266 (M^++18, 100).

Saturated ketones (3).

Octane-3,6-dione (3b) [46]. 25 mg of Pd/C (5%) were added to a solution of 550 mg (3.9 mmol) of (*E*)-oct-4-ene-3,6-dione (**2b**) in 20 mL of MeOH. The system was purged and the mixture was shaken under a hydrogen atmosphere. After 2 h, TLC revealed the disappearance of the starting alkene. Filtration through a pad of Celite® and evaporation of the solvent gave a crude. Chromatography on silica gel (9:1 CH_2Cl_2/hexane) gave 483 mg (97%) of saturated diketone **3b**: colourless oil; R_f 0.25 (9:1 CH_2Cl_2/hexane); ^{1}H NMR δ 1.06 (t, 6H, J = 7.2 Hz), 2.50 (q, 4H, J = 7.2 Hz), 2.69 (s, 4H); ^{13}C NMR δ 7.7, 35.6, 35.8, 210.1; IR (film) 1700.

1,4-Dicyclohexylbutan-1,4-dione (3c) [46]. This product was prepared according to an adaptation of Seagusa's procedure [35]. Under Ar, a solution of diisopropylamine (2.1 mL, 15 mmol) in anh. THF (10 mL) was treated with *n*-butyllithium (9.0 mL of 1.6 M hexane solution, 14.4 mmol) at –78 °C, and after 15 min, 1.66 mL (12.0 mmol) of cyclohexyl methyl ketone were added dropwise to the resulting THF solution of lithium diisopropylamide (LDA). After 30 min, anhydrous $CuCl_2$ (1.61 g, 12 mmol) dissolved in 16 mL of DMF were added at once. The dark solution was stirred for an additional 30 min and then allowed to warm to r.t. over 1 h. The reaction was quenched by addition of 0.5 M aq. HCl and the acidic solution was extracted with diethyl ether (50 mL). The ether extract was washed twice with water and dried over $MgSO_4$. Concentration and column chromatography (6:4 CH_2Cl_2/hexane) afforded 1.17 g (78%) of pure 1,4-dicyclohexylbutan-1,4-dione (**3c**): colourless oil; R_f 0.31 (CH_2Cl_2); ^{1}H NMR δ 1.05–1.50 (m, 10H), 1.60–2.00 (m, 10H), 2.30–2.60 (m, 2H), 2.70 (s, 4H); ^{13}C NMR δ 25.7, 25.9, 28.5, 34.0, 50.8, 212.6; IR (film) 1700. MS (CI) *m/z* (rel. int. %): 268 (M^++18, 100), 251 (M^++1, 65).

General procedure for reduction of unsaturated diketones 2 with BH_3:SMe_2 catalysed by (*R*)-1: Reduction of (*E*)-oct-4-ene-3,6-dione (2b). A solution of **2b** (175 mg, 1.25 mmol) in THF (2 mL) was slowly added (ca. 1 mmol/h) to a solution of (*R*)-**1** (2.5 mmol) and BH_3:SMe_2 (275 μL, 2.75 mmol) in THF (2 mL) at 0 °C under Ar. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. Reaction was cautiously quenched by slow addition of MeOH (1 mL) at 0 °C. The solution was stirred for 15 min at r.t. and then concentrated under vacuum. The residue was purified by flash chromatography (1:1 hexane/AcOEt) to yield 154 mg (85%) of a mixture of diols. Samples of enantioenriched (3*S*,4*E*,6*S*)-4-octen-3,6-diol and *meso*-(*E*)-4-octen-3,6-diol were isolated in the chromatography. An analytical sample of the crude was treated with an excess of (*S*)-Mosher acid chloride (derived from (*R*)-acid) [46] to give a mixture of Mosher diesters. The analysis by HPLC (Tracer Spherisorb S3W column, 0.9 mL/min, hexane/THF 99:1, t_R (*R,R*) = 15.5 min, t_R (*R,S*) = 17.9 min, t_R (*S,S*) = 17.2 min) revealed a 72:28 *dl/meso* ratio and a 91% e.e.

A similar reduction using a molar ratio (*R*)-**1**/diketone = 0.2 led to a mixture of diols in 75% yield, with a *dl/meso* ratio of 67:33 and 88% e.e. of (*S,S*)-**4b**.

(3*S*,4*E*,6*S*)-Oct-4-ene-3,6-diol [(*S,S*)-4b]. Colourless oil; R_f 0.15 (1:2 hexane/AcOEt); $[\alpha]^{20}_D$ +27.4 (*c* 1.2, MeOH); ^{1}H NMR δ 0.90 (t, 6H, *J* = 7.4 Hz), 1.54 (m, 4H), 3.04 (bs, 2H, OH), 3.98 (m, 2H), 5.61 (dd, 2H, *J* = 1.8, 3.9 Hz); ^{13}C NMR δ 9.7, 29.8, 73.8, 133.9; IR (film) 3320, 2980, 1460, 1120. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.58; H, 10.88. MS (CI) *m/z* (rel. int. %): 162 (M^++18, 100).

***meso*-(*E*)-Oct-4-ene-3,6-diol (*meso*-4b).** Colourless oil; R_f 0.20 (1:2 hexane/AcOEt); ^{1}H NMR δ 0.92 (t, 6H, *J* = 7.4 Hz), 1.55 (dt, 4H, *J* = 7, 7.4 Hz), 2.80 (bs, 2H, OH), 4.02 (m, 2H), 5.69 (dd, 2H, *J* = 1.8, 3.3 Hz); ^{13}C NMR δ 9.7, 29.9, 73.2, 133.1; IR (film) 3350, 2970, 1460, 1130. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.42; H, 11.44. MS (CI) *m/z* (rel. int. %): 162 (M^++18, 100).

Reduction of (*E*)-hex-3-ene-2,5-dione (2a). Reduction was performed according to the procedure employed for **2b**, to afford a 98% yield of a mixture of diols **4a**. It was not possible to remove the *meso*-**2b** from this mixture by flash chromatography. An analytical sample of the crude was treated with an excess of (*S*)-Mosher acid chloride to give a mixture of Mosher diesters. The analysis by HPLC (Tracer Spherisorb S3W column, 0.9 mL/min, hexane/THF 98.5:1.5, t_R (*R,R*) = 26.6 min, t_R (*R,S*) = 29.6 min, t_R (*S,S*) = 28.2 min) revealed a 86:14 *dl/meso* ratio and 99% e.e. [(*S,S*)-**4a** as the major stereoisomer].

A similar reduction using equimolar amounts of (*R*)-**1** and diketone led to a mixture of diols in 90% yield with *dl/meso* ratio of 77:23 and 95% e.e.

When a molar ratio (*R*)-**1**/diketone = 0.2 was used, a mixture of diols in 93% yield with *dl/meso* ratio of 69:31 and 81% e.e. was obtained.

Reduction of (*E*)-1,4-dicyclohexylbut-2-ene-1,4-dione (2c). Reduction of **2c** was performed according to the procedure employed for **2b**, to yield a mixture of diols **4c**. Samples of enantioenriched (1*S*,2*E*,4*S*)-1,4-dicyclohexylbut-2-ene-1,4-diol [(*S,S*)-**4c**] and *meso*-(*E*)-1,4-dicyclohexylbut-2-ene-1,4-diol were isolated during the chromatography (98:2 CH_2Cl_2/MeOH). An analytical sample of the crude product was treated with an excess of (*S*)-Mosher acid chloride to give the mixture of Mosher diesters. The ^{19}F NMR analysis revealed a 71:29 *dl/meso* ratio and 82% e.e. of (*S,S*)-**4c**.

A similar reduction using a molar ratio (*R*)-**1**/diketone = 0.2 led to a mixture of diols in 75% yield, with *dl/meso* ratio of 61:39 and 65% e.e. of (*S,S*)-**4c**.

(1*S*,2*E*,4*S*)-1,4-Dicyclohexylbut-2-ene-1,4-diol [(*S,S*)-4c]. m.p. 117–120 °C; R_f 0.60 (95:5 CH_2Cl_2/MeOH); $[\alpha]^{20}_D$ +39.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 1.05–1.50 (m, 12H), 1.55–2.00 (m, 10H), 3.75 (m, 2H), 5.56 (dd, 2H, *J* = 2.1, 4.2 Hz); ^{13}C NMR (CD_3OD) δ 27.3, 27.7, 30.0, 45.2, 78.0, 134.0; IR (KBr) 3225, 2910, 1450. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.39; H, 11.39. MS (CI) *m/z* (rel. int. %): 270 (M^++18, 100).

***meso*-(*E*)-1,4-Dicyclohexylbut-2-ene-1,4-diol (*meso*-4c).** m.p. 132–135 °C; R_f 0.76 (95:5 CH_2Cl_2/

MeOH); ^{1}H NMR (CD_3OD) δ 1.05–1.50 (m, 12H), 1.55–2.00 (m, 10H), 3.87 (m, 2H), 5.69 (dd, 2H, J = 1.8, 3.6 Hz); ^{13}C NMR (CD_3OD) δ 27.2, 27.3, 29.9, 45.3, 77.7, 133.8; IR (KBr) 3225, 2910, 1460. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.88; H, 10.93.

Reduction of (*E*)-2,2,7,7-tetramethyloct-4-ene-3,6-dione (2d). Reduction was performed according to the procedure employed for **2b** to afford 85% yield of a mixture of diols **4d**. Samples of enantioenriched (3*S*,4*E*,6*S*)-2,7-dimethyloct-4-ene-3,6-diol [(*S*,*S*)-**4d**] and *meso*-(*E*)-2,7-dimethyloct-4-ene-3,6-diol were isolated by chromatography (6:4 hexane/AcOEt). An analytical sample of the crude product was treated with an excess of (*S*)-Mosher acid chloride to give the mixture of Mosher diesters. The analysis by HPLC (Tracer Spherisorb S3W column, 0.9 mL/min, hexane/THF 99.6:0.4, t_R (*R*,*R*) = 22.3 min, t_R (*R*,*S*) = 16.5 min,t_R (*S*,*S*) = 15.7 min) revealed a 87:13 *dl/meso* ratio and 99% e.e.

A similar reduction using a molar ratio (*R*)-**1**/diketone = 0.2 led to a mixture of diols in 98% yield with *dl/meso* ratio of 85:15 and 98% e.e.

(3*S*,4*E*,6*S*)-2,2,7,7-Tetramethyloct-4-ene-3,6-diol [(*S*,*S*)-4d]. m.p. 120–121 °C; R_f 0.27 (6:4 hexane/AcOEt); $[\alpha]^{20}_D$ –55.2 (*c* 2.17, MeOH); ^{1}H NMR (CD_3OD) δ 0.95 (s, 18H), 3.72 (dd, 2H, J = 2.4, 4.5 Hz), 4.93 (bs, 2H), 5.70 (dd, 2H, J = 2.4, 4.5 Hz); ^{13}C NMR (CD_3OD) δ 26.4, 35.8, 81.6, 133.3; IR (KBr) 3290, 2940, 1460,. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.74; H, 12.04. MS (CI) *m/z* (rel. int. %): 218 (M^++18, 100).

***meso*-(*E*)-2,2,7,7-Tetramethyloct-4-ene-3,6-diol (*meso*-4d).** m.p. 102–105 °C; R_f 0.35 (6:4 hexane/AcOEt); ^{1}H NMR (CD_3OD) δ 0.95 (s, 18H), 3.75 (dd, 2H, J = 1.8, 3.6 Hz), 4.93 (bs, 2H), 5.78 (dd, 2H, J = 1.8, 3.6 Hz); ^{13}C NMR (CD_3OD) δ 26.4, 36.0, 81.2, 133.0; IR (KBr) 3250, 2960, 1460. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.90; H, 12.27. MS (CI) *m/z* (rel. int. %): 218 (M^++18, 100).

Reduction of (*E*)-1,4-diphenylbut-2-ene-1,4-dione (2e). Reduction of **2e** was performed according to the procedure employed for **2b**, to afford a 84% yield of a mixture of diols **4e**. The analysis of the mixture of diols by HPLC using a reverse phase chiral column Chiracel OD-R (0.9 mL/min, MeOH/H_2O 9:1, t_R (*R*,*R*) = 8.1 min, t_R (*R*,*S*) = 8.7 min,t_R (*S*,*S*) = 9.21 min) revealed a 62:38 *dl/meso* ratio and 92% e.e.

A parallel reduction using a molar ratio (*R*)-**1**/diketone = 0.2 led to a mixture of diols in 47% yield with *dl/meso* ratio 55:45 and 82% e.e. 4-Hydroxy-1,4-diphenyl-1-butanone (**12**) was also isolated in 31% yield.

(*E*)-1,4-Diphenylbut-2-ene-1,4-diol (mixture of stereoisomers) [48]. R_f 0.30 (1:1 hexane/AcOEt); ^{1}H NMR δ 1.93 (bs, 2H), 5.22 (m, 2H), 5.98 (m, 2H), 7.15–7.40 (m, 10H); ^{13}C NMR δ *dl*-isomer: 74.5, 126.7, 127.9, 128.8, 133.8, 143.1; *meso*-isomer: 74.41, 126.8, 128.0, 128.8, 133.5, 143.1; IR (film) 3460, 3010, 1490, 1450. MS (CI) *m/z* (rel. int. %): 223 (M^++1-H_2O, 100), 258 (M^++18, 15).

4-Hydroxy-1,4-diphenyl-1-butanone (12) [49]. Colourless oil; R_f 0.36 (1:1 hexane/AcOEt); ^{1}H NMR δ 2.20 (m, 2H), 3.12 (t, 2H, J = 8.6 Hz), 4.85 (t, 1H, J = 8.0 Hz), 7.2–7.6 (m, 8H), 7.93 (m, 2H); ^{13}C NMR δ 33.6, 35.3, 73.9, 126.3, 127.9, 128.6, 128.9, 129.0, 133.6, 137.3, 144.9, 201.2.

Typical procedure for the Sharpless epoxidation of enantiomerically enriched diols 4. Epoxidation of 4a. A solution of 319 mg (2.8 mmol) of diols **4a** (arising from reduction of **2a** in the presence of 0.2 mmol of (*R*)-**1**, containing ca. 63% of (*S,S*)-**4a**, 69:31 *dl:meso* ratio, 81% e.e.) and 240 μL (1.4 mmol) of (–)-diethyl tartrate in 5 mL of anh. CH_2Cl_2 was dried by stirring for 2 h in the presence of powdered, activated 4 Å molecular sieves [39]. The solution was added via cannula to another flask containing further powdered 4 Å molecular sieves by using additional 5 mL of CH_2Cl_2 for washing the first flask. The solution was cooled to –20 °C, 333 μL (1.12 mmol) of $Ti(OPr^i)_4$ were added, and the solution was stirred for 2 h. Then, 460 μL (1.4 mmol) of *tert*-butyl hydroperoxide 3 M in isooctane, previously stored over 4 Å molecular sieves, were added and the mixture was stirred for 2 days at that temperature. TLC was not useful for following the advance of the reaction. The reaction was quenched by addition of an aqueous solution of 3.3 g of $FeSO_4 \cdot 7H_2O$ and 1.0 g of tartaric acid in 10 mL of deionised water. Afterwards, the mixture was allowed to warm to r.t. and was extracted repeatedly with portions of 10 mL of CH_2Cl_2 (8–10 times) due to the solubility of diol **4a** in water. The combined organic phases were concentrated and the residue was purified by flash chromatography (9:1 CH_2Cl_2/hexane) to afford 168 mg (84% of the overall amount of (*S,S*)-stereoisomer in the sample, 52% overall yield from diketone **2a**, 99:1 *dl/meso* ratio, 99% e.e.) of (2*S*,3*E*,5*S*)-hex-3-ene-2,5-diol [(*S,S*)-**4a**]: colourless oil [50]; R_f 0.26 (AcOEt); $[\alpha]^{20}_D$ +14.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR δ 1.25 (t, 6H, *J* = 6.4 Hz), 3.58 (bs, 2H), 4.26 (m, 2H), 5.66 (m, 2H); ^{13}C NMR δ 23.1, 68.1, 134.0; IR (film) 3530, 3010, 1485, 1445. MS (CI) *m/z* (rel. int. %): 134 (M^++18, 100).

Epoxidation of 4b. When the same procedure described above for **4a** was applied to a mixture of **4b** containing ca. 62% of (*S,S*)-**49**, a sample of almost pure (*S,S*)-**4b** (41% overall yield from diketone **2b**, 99.6:0.4 *dl/meso* ratio, >99.5% e.e.) was obtained. $[\alpha]^{20}_D$ +30.0 (*c* 1.2, MeOH).

Reduction of 1,4-diphenylbutane-1,4-dione (3e). A solution of 1,4-diphenylbutane-1,4-dione (119 mg, 0.5 mmol) in THF (2 mL) was slowly added to a solution of (*R*)-**1** (1 mmol) and BH_3:SMe_2 (110 μL, 1.1 mmol) in THF (2 mL) at 0 °C under Ar. Upon completion of the addition, TLC revealed the disappearance of the starting ketone. The solution was partitioned with aq. 1 M HCl (2 mL) and diethyl ether (5 mL). The organic layer was decanted, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue, containing almost pure **5e**, was subjected to flash chromatography (1:1 hexane/AcOEt) to yield 110 mg (91%). An analytical sample of the crude was treated with an excess of (*S*)-Mosher acid chloride to give a mixture of Mosher diesters. The analysis by HPLC (Tracer Spherisorb S3W column, 0.9 mL/min, hexane/THF 98.5:1.5, t_R (*R,R*) = 21.5 min, t_R (*R,S*) = 24.6 min, t_R (*S,S*) = 30.3 min) revealed a 93:7 *dl/meso* ratio and 99% e.e. [(*S,S*)-**5e** as the major stereoisomer]. A similar reduction using a molar ratio (*R*)-**1**/diketone = 0.2 led to a mixture of diols in 95% yield, with *dl/meso* ratio of 91:9 and 98% e.e.

(*S,S*)-1,4-Diphenylbutane-1,4-diol [(*S,S*)-5e]. m.p. 74-75 °C, $[\alpha]^{20}_D$ –47.8 (*c* 1.2, $CHCl_3$) [lit. [5] m.p. 74.6–75.3 °C; $[\alpha]^{20}_D$ –58.5 (*c* 1, $CHCl_3$)]; R_f 0.20 (1:1 hexane/ AcOEt); ; ^{1}H NMR δ 1.77–1.95 (m, 4H), 2.68 (bs, 2H), 4.75 (m, 2H), 7.26–7.35 (m, 10H); ^{13}C NMR δ 35.9, 74.2, 125.7, 127.2, 128.2, 144.6; IR (KBr) 3280, 2900, 1450. MS (CI) *m/z* (rel. int. %): 260 (M^++18, 80).

General procedure for hydrogenation of enantioenriched diols 4: hydrogenation of (*S,S*)-4a. To a solution of 100 mg (0.86 mmol) of diol (*S,S*)-**4a** (99:1 *dl/meso* ratio, 99% e.e.) in 20 mL of EtOH, 10 mg of 5% Pt /C were added and the suspension was shaken under 50 atm of hydrogen for 2 h. Afterwards, the mixture was filtered through a pad of Celite®, the solvent was eliminated *under vacuo* and the residue was purified by flash chromatography through a short path of silica gel to yield 82 mg (81%) of hexane-2,5-diol. An analytical sample was treated with an excess of (*S*)-Mosher acid chloride to give the mixture of Mosher diesters. The analysis by HPLC (Tracer Spherisorb S3W column, 0.9 mL/min, hexane/THF 97.5:2.5, t_R (*R,R*) = 23.1 min, t_R (*R,S*) = 20.2 min, t_R (*S,S*) = 16.5 min) revealed a 97:3 *dl/meso* ratio and 99% e.e.

(*S,S*)-Hexane-2,5-diol [(*S,S*)-5a]. Colourless oil; R_f 0.21 (99:1 CH_2Cl_2/MeOH); $[\alpha]^{20}_D$ +32.7 (*c* 1, $CHCl_3$) [lit. [51] m.p. 53–53.3 °C; $[\alpha]^{20}_D$ +35.1 (*c* 9.49, $CHCl_3$)]; ^{1}H NMR δ 1.21 (d, 6H, *J* = 6.0 Hz), 1.25 (bs, 2H), 1.59 (m, 4H), 3.85 (m, 2H); ^{13}C NMR δ 23.4, 35.9, 68.0. MS (CI) *m/z* (rel. int. %): 136 (M^++18, 100), 119 (M^++1, 41).

(*S,S*)-Octane-3,6-diol [(*S,S*)-5b]. m.p. 49–51 °C (lit. [8] m.p. 51–52 °C); R_f 0.30 (1:2 hexane/AcOEt); $[\alpha]^{20}_D$ +27.5 (*c* 1, $CHCl_3$) [lit. [8] +22.8 (*c* 1, $CHCl_3$)]; ^{1}H NMR δ 0.94 (t, 6H, *J* = 7.4 Hz), 1.49 (m, 4H), 1.65 (m, 4H), 2.55 (bs, 2H), 3.46 (m, 2H); ^{13}C NMR δ 9.9, 30.4, 33.5, 73.6. MS (CI) *m/z* (rel. int. %): 164 (M^++18, 100), 147 (M^++1, 55).

(*S,S*)-1,4-Dicyclohexylbutane-1,4-diol [(*S,S*)-5c]. m.p. 116–118 °C; R_f 0.30 (95:5 CH_2Cl_2/MeOH); $[\alpha]^{20}_D$ –12.5 (*c* 0.6, $CHCl_3$) for 82% e.e. [lit. [9] +22.0 (*c* 1, $CHCl_3$) for (*R,R*)-isomer]; ^{1}H NMR δ 0.90–1.95 (m, 24H), 2.50 (bs, 2H), 2.05–2.20 (m, 2H), 3.36 (m, 2H); ^{13}C NMR δ 26.7, 26.8, 27.0, 28.2, 29.7, 31.3, 44.4, 77.1. MS (CI) *m/z* (rel. int. %): 272 (M^++18, 100), 255 (M^++1, 61).

(*S,S*)-2,2,7,7-Tetramethyloctane-3,6-diol [(*S,S*)-5d]. m.p. 155–156 °C; R_f 0.44 (6:4 hexane/AcOEt); $[\alpha]^{20}_D$ –44.4 (*c* 0.94, MeOH) [lit. [28] –34.3 (*c* 1, MeOH)]; ^{1}H NMR (CD_3OD) δ 0.91 (s, 18H), 1.43 (m, 2H), 1.77 (m, 2H), 2.55 (bs, 2H), 3.25 (m, 2H); ^{13}C NMR (CD_3OD) δ 26.4, 29.4, 36.0, 80.2. MS (CI) *m/z* (rel. int. %): 220 (M^++18, 100), 203 (M^++1, 44).

Reductions with BH_3:SMe_2 of mono- and diketones (without (*R*)-1). Reductions were carried out by addition of BH_3:SMe_2 (100 μL, 1.0 mmol) to a solution of 1 mmol ketone (**10** or **11**) or diketone (**2b** or **3b**) in 2 mL of anh. THF at 0 °C under Ar. After 5 min, 300 μL of MeOH were cautiously added and the solvent was removed *in vacuo* to obtain a crude which was analysed by TLC and ^{1}H NMR by comparison with authentic samples of alcohols.

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