Regio-, Diastereo-, and Enantio-selective Condensation of Chiral Vinylic Borates with Aldehydes

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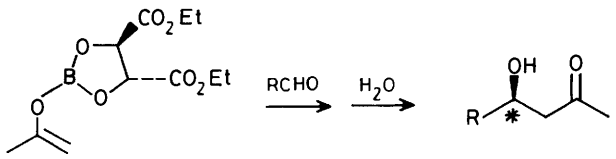
A regio- and diastereo-selective synthesis of enantiomerically enriched *syn*-ketols is reported, starting from homochiral 2-(but-2-en-2-yloxy)-1,3,2-dioxaborolanes and aldehydes.

The development of highly stereocontrolled aldol condensations has been a challenging undertaking during the last decade.[1] In particular, the presence of 3-hydroxy-2-methylcarbonyl units in biologically active molecules, such as several macrolide and ionophore antibiotics,[2] gave impetus to the design of chiral enolates which take part in diastereo- and enantio-selective additions to carbonyl compounds.[3] While simple diastereoselection† largely depends on the geometry of the enolate and on the metal used,[1,3,4] the control of the absolute configuration of the newly formed stereogenic centres requires the presence of chirality on the enolate. The main solutions given to the latter problem involve the use of (*i*) chiral auxiliaries covalently bonded to the carbon framework of the enolate, (*ii*) metal atoms as stereogenic centres, or (*iii*) chiral ligands bonded to the metal.[5] Promising results have been reported in the last couple of years, with this last approach, using ketone or thioester boron enolates containing chiral alkyl groups connected to the boron atom.[6] Following this method the ketone or thioester is enolised with a Hünig base and *O*-borylated with the appropriate chiral boron triflate. In the case of unsymmetrically substituted ketones these conditions will give rise to enolisation at the less hindered side of the carbonyl group (kinetic enolate). This paper reports a complementary approach based on boron chemistry to a regio-, diastereo-, and enantio-selective aldol condensation of the butanone 'thermodynamic' enolate with aldehydes.

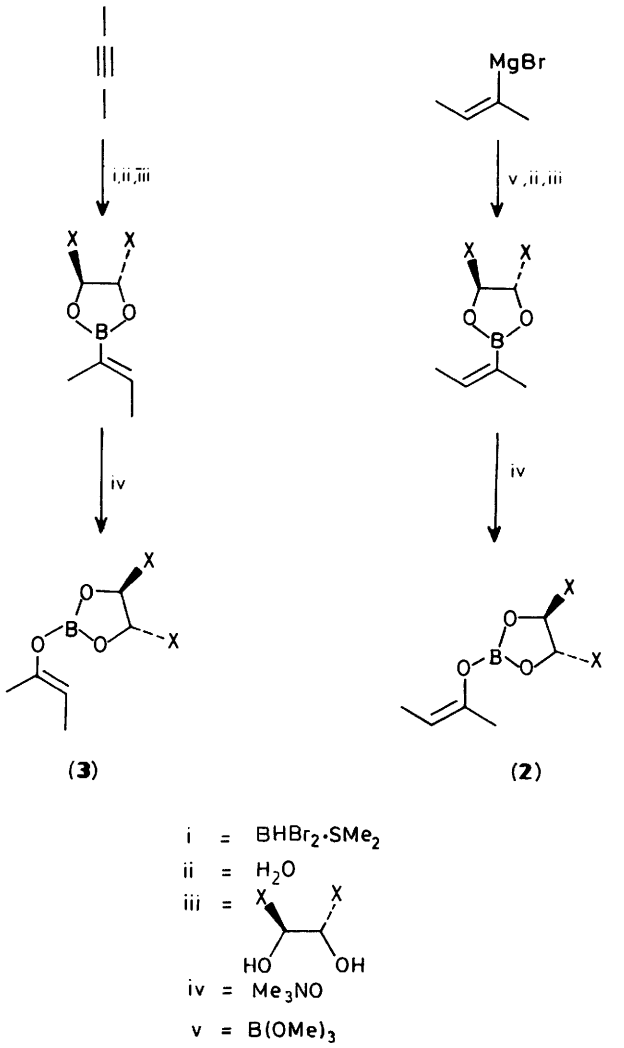
We recently described a simple procedure to prepare optically active ketols (derived from the condensation of acetone with aldehydes[7]) which involves the reaction of the chiral 2-isopropenyloxy-1,3,2-dioxaborolane (**1**) with aldehydes (Scheme 1).



(**1**)

Scheme 1.

Here we report the preparation of (*Z*)-2-(but-2-en-2-yloxy)-1,3,2-dioxaborolane (**2**) and of (*E*)-2-(but-2-en-2-oxy)-1,3,2-dioxaborolane (**3**) (see Scheme 2), and the diastereoconvergent synthesis of enantiomerically enriched *syn*-ketols by condensing (**2**) and (**3**) with aldehydes (Scheme 3). The homochiral diols used for the preparation of (**2**) and (**3**) are: (*a*) di-isopropyl(*R,R*)-tartrate, (*b*) dicyclohexyl (*R,R*)-tartrate, (*c*) (*S,S*)-1,4-diphenoxybutane-2,3-diol, and (*d*) (*S,S*)-1,4-ditosyloxybutane-2,3-diol.



Scheme 2.

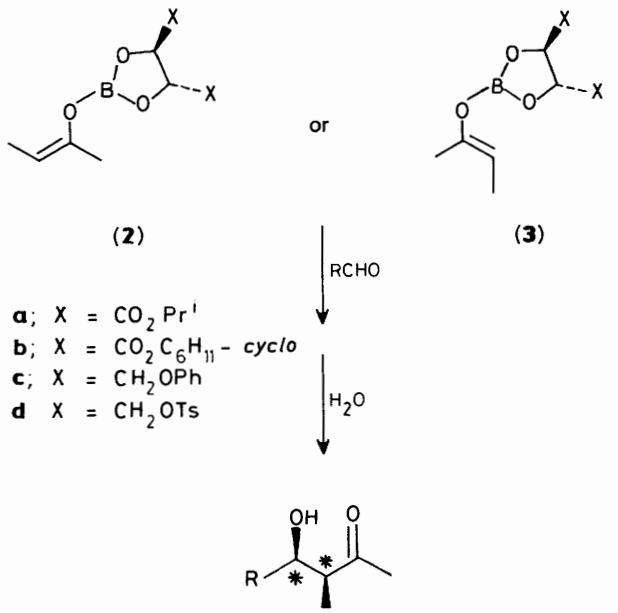
The conformations of (**2**) and (**3**) drawn in Scheme 2 are supported by theoretical calculations carried out by several groups[8] showing that *Z*-(**2**) adopts a S-*trans* (W-shaped) ground-state conformation, while *E*-(**3**) exists in a more stable S-*cis* (U-shaped) conformation. Among the results summarized in Table 1, we first take into account the reactions with benzaldehyde (runs 1—5) leading to *syn*-4-hydroxy-3-methyl-4-phenylbutan-2-one.

† The Masamune *syn-anti* nomenclature is used in this paper both for simple diastereoselectivity and for diastereofacial selectivity (Cram/*anti*-Cram relationships) (see ref. 4).

Table 1. Addition of vinylic borates (**2**) and (**3**) to prochiral aldehydes[a]

Run	Aldehyde	Vinylic borate[c]	Reaction time (h)	*Syn* ketol[b] Yield (%)[d]	$[\alpha]_D$[e]	E.e. (%)
1	PhCHO	(**2a**)	30	43[f]	−12.6	25
2	PhCHO	(**3a**)	10	64, 75[g]	−33.3	65
3	PhCHO	(**3b**)	14	65	−33.5	66
4	PhCHO	(**3c**)	14	45	+2.2	4
5	PhCHO	(**3d**)	14	55	+15.5	30
6	n-C_5H_{11}CHO	(**3a**)	14	74[g]	−13.5	72
7	n-C_5H_{11}CHO	(**2a**)	25	45	−5.7	30
8	Et_2CHCHO	(**3a**)	20	47	−14.9	58

[a] All reactions are carried out at −50 °C in dichloromethane. [b] The ^1H and ^{13}C n.m.r. spectra failed to reveal the *anti* product which was estimated to be < 5% by h.p.l.c. analysis. [c] The crude vinylic boronates are used unless otherwise stated. [d] Yields were not optimized and refer to the starting vinylic borate. They are determined on the ketol purified by flash chromatography. [e] (*c* 1 in $CHCl_3$). [f] Yield was 20% after 10 h. [g] The distilled vinylic boronate was used.



Scheme 3.

The absolute configuration of the stereogenic centres of this ketol was established on the basis of the known facial preference of chiral vinylic borates,[7] allylic boronates[9] and stannanes,[10] and allenyl boronates[11] containing (*R,R*)-tartrates as chiral ligands; we presumed that the *Si* face of the aldehyde would preferentially react with (**2a**) and (**3a,b**). Thus, the laevorotatory product of runs 1—3 should be (3*S*,4*S*)-4-hydroxy-3-methyl-4-phenylbutan-2-one.*

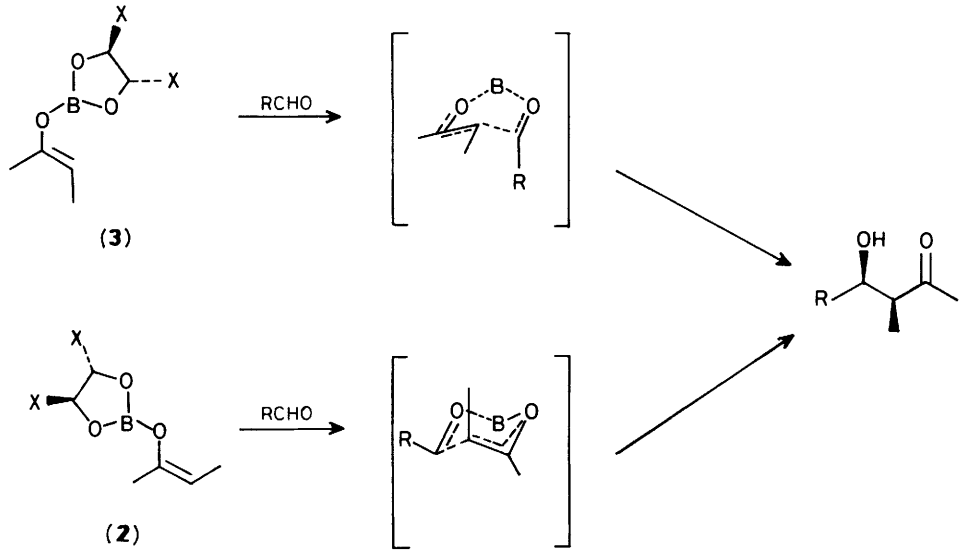
The condensation is diastereoconvergent since *Z* and *E* vinylic borates (**2**) and (**3**) afford the same *syn*-ketol unambiguously identified by n.m.r. spectroscopy.[12] Such behaviour was reported by Hoffmann[13] and Scolastico[14] for prochiral vinylic borates. The diastereoconvergency of (**2**) and (**3**) may result from either the intermediacy of two different transition states or from an equilibration of the *E* and *Z* isomers, particularly a *Z* to *E* rate determining conversion, since *E*-(**3**) reacts much faster than *Z*-(**2**). The latter hypothesis seems less likely since it has been demonstrated that the same butanone boron enolates esterified with pinacol are not configurationally labile.[13] More probably, according to Hoffmann,[13] the condensation of *E*-(**3**) with an aldehyde occurs *via* a boat-like transition state, while *Z*-(**2**) adopts a chair-like transition state (Scheme 4). It should be noted that the two transition states are pseudo-conformers, that is to say they have the same *cis* relative configurations at the incipient stereogenic centres, and hence they will afford the same *syn*-ketol. In contrast *E* and *Z* crotyl boronates[15] and boranes[16] give, upon reaction with aldehydes, *anti* and *syn* homoallylic alcohols respectively in excellent diastereoisomeric excess.

With respect to control of the absolute configuration of the newly formed stereogenic centres, we see that the addition of the *Z* vinylic borate (**2a**) to benzaldehyde is both slower and less enantioselective than the corresponding reaction for *E*-(**3a**), using the same chiral auxiliary (runs 1, 2).

The ground-state conformations of (**2**) and (**3**) account for their different enantioselectivities as a result of differences in the distances between the nucleophilic carbon of the enolate and the stereogenic centres (C-4 and C-5) of the 1,3,2-dioxaborolane ring. These distances, estimated on the basis of previously reported calculations[8] and standard crystallographic data, were *ca.* 5.9 and 5.7 Å for S-*trans*-(**2a**) and 5.3 and 4.6 Å for S-*cis*-(**3a**). Finally, we observe that the extent of asymmetric induction (runs 2 and 3) is unaffected by the bulkiness of the ester group, whilst the use of the ethers (**3c,d**) as auxiliary ligands instead of the esters (**3a,b**) has a dramatic effect both in terms of absolute asymmetric induction and of facial preference. The absence of any effect arising from replacement of an isopropyl group by a cyclohexyl group in the neat asymmetric induction (runs 2 and 3), and the necessity for a C=O group to be present on the 1,3,2-dioxoborolane ring to ensure preferential attack on the *Si* face of the aldehyde, leads us to believe that the alkoxycarbonyl substituents are oriented in such a way as to point the carbonyl oxygen toward the approaching aldehyde. When the aldehyde RCHO approaches the vinylic borate directing its oxygen towards boron,[17] it will offer the enolate the face (*Si* face) that keeps the R group as far as possible from the ester carbonyl groups in order to minimize repulsive through-space interactions between R and the oxygen lone pairs.

Since, among the vinylic borates examined, *E*-(**3a**) gives the best results in terms of enantioselectivity in the condensation with benzaldehyde, we turned our attention to the reactions of (**3a**) with other model aldehydes. Thus, we examined hexanal and 2-ethylbutanal as typical examples of linear and α-branched enolisable aldehydes (runs 6 and 8). In these cases

* Enders[5c] has recently reported for 98% pure (4*S*,5*S*)-5-hydroxy-4-methyl-5-phenylpentan-3-one, the (−) optical rotation sign, $[\alpha]_D^{22}$ −16.0 (*c* 1.3 in benzene). In the same solvent and conditions *syn*-4-hydroxy-3-methyl-4-phenylbutan-2-one obtained in run 2 of Table 1 has $[\alpha]_D^{22}$ −34.5 (*c* 1.3 in benzene).

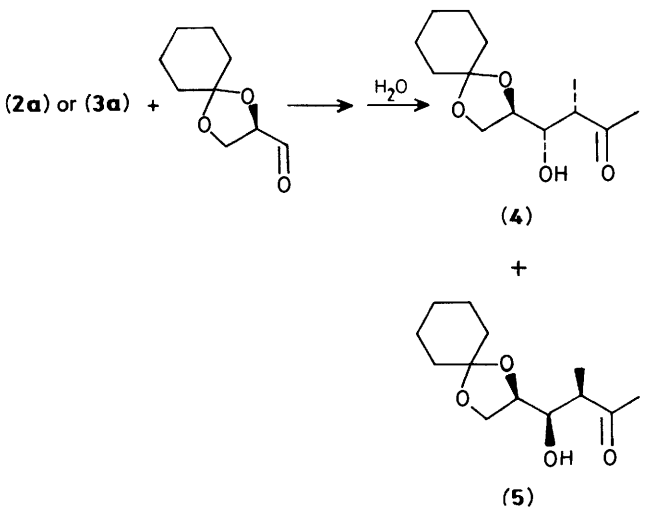


Scheme 4. Chiral ligands omitted in the transition state structures for clarity

too, *syn*-ketols deriving from the probable attack on the *Si* face of the aldehyde are obtained with more than 95% diastereoisomeric excess (d.e.) and in fair enantiomeric excess (e.e.).

As seen with benzaldehyde, *Z*-(**2a**) confirms, in the reaction with hexanal (run 7), the same *syn*-selectivity exhibited by *E*-(**3a**), as well as its inferior enantioface differentiating ability. Moreover, the lack of side-product in the reactions of (**2a**) and (**3a**) with enolisable aldehydes is worth noting; in fact only unchanged aldehyde remains, little more than traces of unsaturated ketones or hexanal self-condensation products being detected.

The last aldehyde we checked was 2,3-*O*-cyclohexylidene-D-glyceraldehyde, a frequently used probe for testing doubly stereodifferentiating reactions.[18] We studied the condensation of this substrate with *Z*-(**2a**) and *E*-(**3a**) containing both (*R,R*)- and (*S,S*)-di-isopropyl tartrates as the auxiliary ligand, and obtained only the ketols (**4**) and (**5**) (Scheme 5). These results are summarized in Table 2. It is known that protected glyceraldehydes react with most nucleophiles to give the *anti* derivatives predicted by the Felkin-Ahn model[19] (see Figure), including the reactions with chiral or achiral allylic boronates.[9,20] The Felkin-Ahn model requires that the *Si* face



Scheme 5.

Table 2. Addition of (**2a**) and (**3a**) to 1,2-*O*-cyclohexylidene-D-glyceraldehyde[a]

Run	Vinylic borate	Tartrate configuration	Reaction time (h)	Overall yield (**4**) + (**5**) (%)[b]	(**4**):(**5**)[c]
1	(**2a**)	(*R,R*)	24	55	99:1
2	(**2a**)	(*S,S*)	24	46	80:20
3	(**3a**)	(*R,R*)	12	54	99:1
4	(**3a**)	(*S,S*)	12	48	68:32

[a] All reactions are carried out at −50 °C in dichloromethane. [b] Yields were not optimized and refer to the starting vinylic boronate. [c] Determined by h.p.l.c. analysis (see Experimental section).

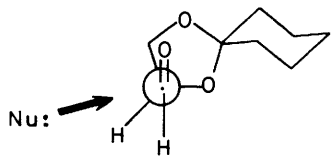


Figure.

of glyceraldehyde react; since the same *Si* face is preferred by the vinylic borate derived from natural tartaric acid, it was not unexpected to find that D-glyceraldehyde and (**2a**) and (**3a**) containing (*R,R*)-tartrates act as a matched pair to give virtually pure (**4**) (runs 1 and 3). In contrast, the facial preferences of D-glyceraldehyde and (**2a**) or (**3a**) containing (*S,S*)-tartrates counteract, the result being the formation of significant amounts of (**5**), but to a lesser extent when the less selective *Z*-(**2**) is used (runs 2 and 4).

In conclusion, the aldol condensation procedure reported here is a clean reaction which affords *syn*-ketols as the sole products. Moreover *syn*-ketols are obtained in enantiomerically enriched forms, the absolute configurations and the e.e. levels depending on the chiral auxiliary. Even if the e.e. values are somewhat inferior in comparison to those obtained with other chiral auxiliaries,[6] our best results are obtained with the cheap and commercially available di-isopropyl tartrate. Finally although we have specifically reported on the condensation of butanone enolates, the procedure has much wider applicability thanks to the number of routes to vinylic boronates and borates which have recently appeared in the literature.[21]

Experimental

I.r. spectra were measured on a Perkin-Elmer PE 682 spectrophotometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ at 90 MHz on a Varian EM390 instrument; ^{13}C n.m.r. spectra were recorded in $CDCl_3$ at 20 MHz on a Varian FT80A instrument. Chemical shifts are given relative to Me_4Si as internal standard. Optical rotations were measured on a Perkin-Elmer PE241 polarimeter. Mass spectra were measured at 70 eV on a VG 7070E instrument. High pressure liquid chromatography (h.p.l.c.) was performed with a Hewlett-Packard Liquid Chromatograph 1090 with a solvent flow of 0.5 ml min^{-1} using a Pirkle covalent D-naphthylalanine column (25 cm × 4.6 mm internal diameter). Analytical thin layer chromatography (t.l.c.) was performed on 5 × 10 cm plates coated with a 0.2 mm layer of silica gel (Merck Kieselgel 60 F_{254}). Products were purified by flash chromatography on 230—400 mesh silica gel (Merck). All reactions were conducted in flame-dried glassware under argon.

All solvents were purified before use, and dichloromethane was distilled over CaH_2 and P_2O_5. (*R,R*)-Tartrates, (*S,S*)-tartaric acid, and trimethyl borate were obtained by Janssen; but-2-yne, $BHBr_2{\cdot}SMe_2$, benzaldehyde, 2-ethylbutanal, and hexanal were purchased from Aldrich and used as received. Trimethylamine oxide dihydrate (Aldrich) was made anhydrous by azeotropic distillation in *N,N*-dimethylformamide.[22] (*Z*)-2-Bromobut-2-ene was obtained 96% pure by spinning band distillation (b.p. 84—85 °C) on a Perkin-Elmer 251 Auto Annular Still apparatus of the commercially available mixture of (*E*)- and (*Z*)-2-bromobut-2-ene (Aldrich). (*S,S*)-1,4-Diphenoxybutane-2,3-diol[23] and (*S,S*)-1,4-ditosyloxybutane-2,3-diol[24] were prepared from (*R,R*)-tartaric acid according to the procedure of Seebach. 2,3-*O*-Cyclohexylidene-D-glyceraldehyde was prepared from D-mannitol.[25]

Di-isopropyl (4R)-trans-2-[(E)-*But*-2-*en*-2-*yl*]-1,3,2-*dioxaborolane*-4,5-*dicarboxylate*.—A 1 l three-necked round-bottom flask fitted with a 200 ml dropping funnel, argon inlet, and efficient magnetic stirring bar, was charged with freshly distilled dry ether (350 ml) and trimethyl borate (23 ml, 200 mmol), and cooled at −78 °C. A 1M solution of (*Z*)-but-2-en-2-ylmagnesium bromide (100 ml) in dry tetrahydrofuran (THF) was pressure transferred with argon to the dropping funnel and added during 1 h to the vigorously stirred reaction mixture at −78 °C. Stirring was continued for a further 5 h, then the reaction mixture was warmed to −10 °C. The reaction was hydrolysed with water (150 ml) and the pH of the aqueous layer was adjusted to neutrality by adding 1M H_2SO_4. The boronic acid was extracted with ether and the extract dried ($MgSO_4$) and concentrated under reduced pressure. When almost all the solvent had been removed, the evaporator was filled with argon (*dried boronic acid is pyrophoric*) and the residue was treated with dichloromethane–cyclohexane (1:1). Small amounts of boric acid were not soluble in this solvent mixture and were filtered off. The solution was again concentrated to give the crude but-2-en-2-yl boronic acid (5.8 g, 60%). The boronic acid was dissolved in anhydrous dichloromethane (40 ml) and treated with (*R,R*)-di-isopropyl tartrate (12.2 g, 52 mmol) with vigorous stirring. After a few minutes the reaction mixture became turbid from the formation of water. Anhydrous $MgSO_4$ was added and the mixture was allowed to stand for 24 h. Filtration and distillation of solvent left the title (*E*)-boronate as an oil (14.9 g, 100%); δ_H 6.3 (1 H, m, 2′-H), 5.13 (2 H, m, CH_3CHCH_3), 4.82 (2 H, s, 4-H, 5-H), 1.6—2.2 (6 H, m, 3′-H, 1′-Me), 1.3 (12 H, d, CH_3CHCH_3); δ_C 169.2, 145.0, 77.7, 69.8, 22.0, 21.7, and 17.3.

Di-isopropyl (4R)-trans-2-[(Z)-*But*-2-*en*-2-*yl*]-1,3,2-*dioxaborolane*-4,5-*dicarboxylate*.—A solution of $BHBr_2{\cdot}SMe_2$ in dichloromethane (1M; 90 ml) was added over 2 h to a stirred solution of but-2-yne (5 g, 92 mmol) in dichloromethane (30 ml) under argon. The reaction was allowed to proceed at 0 °C overnight after which the mixture was poured into water (100 ml) and the pH adjusted to neutrality by addition of $NaHCO_3$ (1M). The aqueous phase was extracted with ether (× 3) and the combined organic phases were dried ($MgSO_4$), and evaporated. The crude solid residue (5.85 g, 65%) was dissolved in dichloromethane (30 ml) and treated under argon with (*R,R*)-di-isopropyl tartrate (12.9 g, 55 mmol). After a few minutes the formation of water drops became apparent; $MgSO_4$ was added and the reaction mixture was stirred overnight at 20 °C. The mixture was then filtered and evaporated to give the crude title (*Z*)-boronate (15.7 g, 100%) which could be used directly for the next oxidation step (better yields are obtained using the distilled boronate), b.p. 140—145 °C/0.2 mmHg (Found: C, 56.5; H, 7.7. $C_{14}H_{23}BO_6$ requires C, 56.4; H, 7.8%); δ_H 6.63 (1 H, m, 2′-H), 5.13 (2 H, m, CH_3CHCH_3), 4.73 (2 H, s, 4-H, 5-H), 1.75 (6 H, s and d, 3′-H, 1′-Me), and 1.32 (12 H, d, CH_3CHCH_3); δ_C 169.3, 143.8, 77.9, 69.8, 21.7, 14.5, and 13.2; *m/z* 256 (27%, $M^+ - C_3H_6$), 214 (70), 169 (100), 124 (73), 115 (15), 109 (23), 96 (30), 84 (20), 67 (15), and 54 (18). All these peaks refer to the ^{11}B containing ions.

By the same esterification procedure the following 2-[(*Z*)-but-2-en-2-yl]boronates were prepared and used as crude products without further purification for the oxidation step, since any attempts to distil them led to extensive decomposition.

Dicyclohexyl (4*R*)-trans-2-[(Z)-*but*-2-*en*-2-*yl*]-1,3,2-*dioxaborolane*-4,5-*dicarboxylate*. δ_H 6.62 (1 H, m, 2′-H), 4.95 (2 H, m, CH_2CHCH_2), 4.81 (2 H, s, 4-H, 5-H), 1.7 (6 H, s and d, 3′-H, 1′-Me), and 1.8—1.15 (20 H, m).

(4S)-trans-2-[(Z)-*but*-2-*en*-2-*yl*]-4,5-*diphenoxymethyl*-1,3,2-*dioxaborolane*. δ_H 7.2 (4 H, m, Ph), 6.95 (6 H, m, Ph), 6.65 (1 H, m, 2′-H), 4.65 (2 H, t, *J* 4 Hz, 4-H, 5-H), 4.1 (4 H, d, *J* 4 Hz, CH_2O), and 1.7 (6 H, s, and d, 3′-H,1′-Me).

(4S)-trans-2-[(*Z*)-*but*-2-*en*-2-*yl*]-4,5-*ditosyloxymethyl*-1,3,2-*dioxaborolane*. δ_H 7.77 (4 H, d, *J* 8.5 Hz, ArH), 7.32 (4 H, d, *J* 8.5 Hz, ArH), 6.4 (1 H, q, *J* 6.2 Hz, 2′-H), 4.38 (2 H, t, *J* 3 Hz, 4-H, 5-H), 4.12 (4 H, d, *J* 3 Hz, CH_2O), 2.42 (6 H, s, CH_3Ar), 1.69 (3 H, d, *J* 6.2 Hz, 3′-H), and 1.56 (3 H, s, 1′-Me).

Synthesis of (−)-syn-4-*Hydroxy*-3-*methyl*-4-*phenylbutan*-2-*one* (*Table* 1, *run* 2): *Typical Procedure*.—A 100 ml round-bottom three-necked flask connected through a Firestone valve to an argon or a vacuum line, equipped with a magnetic stirring bar, was charged with di-isopropyl (4*R*)-*trans*-2-[(*Z*)-but-2-en-2-yl)-1,3,2-dioxaborolane-4,5-dicarboxylate (2.98 g, 10 mmol) and anhydrous dichloromethane (20 ml). Anhydrous trimethylamine oxide (0.75 g, 10 mmol) was added in three portions with stirring and cooling with a water-bath at 10 °C. After 1 h at room temperature, the flask was cooled to 0 °C and most of the solvent and trimethylamine were evaporated under reduced pressure. The residue was dissolved in dichloromethane (10 ml), and the solution cooled to −78 °C, and treated with benzaldehyde (1.17 g, 11 mmol). The mixture was stirred for 14 h while the temperature was raised to −50 °C and quenched with a buffered phosphate solution (pH 7) (10 ml). The crude residue was extracted with ether, and the extract dried (Na_2SO_4) and evaporated. The crude residue was chromatographed (cyclohexane–ether, 9:1) to give the title ketol as an oil (1.3 g, 73%) (Found: C, 74.2; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); $\nu_{max.}$ 3 400, 3 050, 1 710, 1 600, 910, 750, and 710 cm^{-1}; δ_H 7.25 (5 H, s, Ph), 5.05 (1 H, d, *J* 4 Hz, 4-H), 3.4 (1 H, br s, OH), 2.77 (1 H, dq, $J_{3,4}$ 4 Hz, $J_{3,3\text{-Me}}$ 7 Hz, 3-H), 2.05 (3 H, s, 1-H), and 1.07 (3 H, d, *J* 7 Hz, 3-Me); δ_C 213.4, 142.3, 128.2, 127.3, 126.1, 73.4, 53.6, 29.3, and 10.6; *m/z* 178 (8%, M^+), 160 (16), 107 (32), 106 (76), 105 (80), 77 (82), 72 (97), and 43 (100). The yield of this

reaction, which was repeated several times, was affected by the dryness of both the solvent and of the trimethylamine oxide.

The e.e. was determined by ^{1}H n.m.r. spectroscopy after conversion of the title ketol into the Mosher's ester. The following signals were split: OCH_3 at 3.5 and 3.43 p.p.m., $COCH_3$ at 1.96 and 1.9 p.p.m., and $CHCH_3$ at 1.2 and 1.09 p.p.m. respectively.

According to the same general procedure the following ketols were obtained using hexanal, 2-ethylbutanal and 2,3-*O*-cyclohexylidene-D-glyceraldehyde respectively.

(−)-syn-4-*Hydroxy*-3-*methylnonan*-2-*one*, oil (Found: C, 69.6; H, 11.8. $C_{10}H_{20}O_2$ requires C, 69.7; H, 11.7%); $\nu_{max.}$ 3 450 and 1 710 cm^{-1}; δ_H 3.95 (1 H, m, 4-H), 2.9 (1 H, br s, OH), 2.55 (1 H, dq, $J_{3,4}$ 3.3 Hz, $J_{3,3\text{-Me}}$ 7.3 Hz, 3-H), 2.15 (3 H, s, 1-H), 1.15—1.7 (8 H, m, aliph.), 1.05 (3 H, d, *J* 7.3 Hz, 3-Me), and 0.9 (3 H, t, 9-H); δ_C 213.5, 71.3, 51.4, 34.3, 31.9, 29.1, 25.8, 22.7, 14.1, and 10.0; *m*/*z* 157 (3%, $M^+ - CH_3$), 154 (7), 101 (14), 83 (12), 72 (100), 57 (20), 55 (22), 45 (96), and 43 (91). The e.e. was established through h.p.l.c. analysis (isopropyl alcohol–hexanes, 4:6) of a sample of the corresponding 3,5-dinitrobenzoates. Two peaks were observed at 12.2 (major) and 14.1 min.

(−)-syn-5-*Ethyl*-4-*hydroxy*-3-*methylheptan*-2-*one*, oil (Found: C, 69.8; H, 11.6. $C_{10}H_{20}O_2$ requires C, 69.7; H, 11.7%); $\nu_{max.}$ 3 470, 2 960, 2 940, 2 880, 1 705, 1 460, 1 380, 1 355, 1 015, 980, and 960 cm^{-1}; δ_H 3.8 (1 H, m, 4-H), 2.7 (1 H, dq, $J_{3,4}$ 3.4 Hz, $J_{3,3\text{-Me}}$ 7.2 Hz, 3-H), 2.6 (1 H, d, *J* 4.2 Hz, OH), 2.2 (3 H, s, 1-H), 1.65 (1 H, m, 5-H), 1.2—1.5 (4 H, m, CH_3CH_2), 1.15 (3 H, d, *J* 7.2 Hz, 3-Me), and 0.9 (6 H, m, CH_3CH_2); δ_C 213.5, 72.1, 48.5, 42.4, 28.6, 21.0, 20.2, 10.3, 10.2, and 9.6; *m*/*z* 154 (5%, $M^+ - H_2O$), 101 (69), 100 (8), 72 (94), 71 (9), 59 (13), 57 (16), 55 (19), and 43 (100). The e.e. was established through h.p.l.c. analysis (hexane–isopropyl alcohol, 99.5 : 0.5, eluant flow 0.6 ml min^{-1}) of a sample of the corresponding 3,5-dinitrobenzoates. Two peaks were observed at 38.4 and 39.7 (major) min.

(2R)-2-[(1S,2S)-1-*Hydroxy*-2-*methyl*-3-*oxobutyl*]-1,4-*dioxaspiro*[4.5]*decane* (**4**). The crude reaction mixtures corresponding to the runs reported in Table 2 were analyzed by h.p.l.c. (isopropyl alcohol hexane, 2:8). The peaks corresponding to (**4**) and (**5**) were observed at 7.7 and 8.6 min respectively. The two diastereoisomers (**4**) (lower R_F) and (**5**) were separated by column chromatography using dichloromethane–ether, 9:1. Data for (**4**): oil (Found: C, 64.5, H, 9.1. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.15%); $[\alpha]_{365}^{23}$ −84° (*c* 0.44 in benzene); $\nu_{max.}$ 3 450 and 1 715 cm^{-1}; δ_H 3.7—4.3 (4 H, m, 2-H, 3-H, 1′-H), 2.8 (1 H, m, 2′-H), 2.45 (1 H, d, OH), 2.25 (3 H, s, 4′-H), 1.1—1.9 (10 H, m), and 1.2 (3 H, d, *J* 7.5 Hz, 2′-Me); δ_C 213.1, 109.9, 74.8, 72.1, 67.2, 47.8, 34.8, 29.0, 25.2, 24.1, 23.8, 21.7, and 9.7; *m*/*z* 242 (3%, M^+), 214 (14), 169 (13), 141 (26), 127 (39), 109 (52), 84 (100), 56 (16), and 43 (35).

(2R)-2-[(1R,2R)-1-*Hydroxy*-2-*methyl*-3-*oxobutyl*]-1,4-*dioxaspiro*[4.5]*decane* (**5**). An analytically pure specimen of this product could not be obtained since traces of di-isopropyl tartrate could not be removed even after several chromatographic runs: δ_H 3.7—4.2 (3 H, m, 2-H, 3-H, 1′-H), 3.25 (1 H, d, OH), 2.7 (1 H, m, 2′-H), 2.25 (3 H, s, 4′-H), 1.2—1.9 (10 H, m), and 1.2 (3 H, d, *J* 7 Hz, 2′-Me); δ_C 213.5, 109.8, 76.2, 71.7, 65.8, 50.1, 34.7, 26.9, 25.1, 24.0, 23.8, 21.7, and 12.2.

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