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STEREOSELECTIVITY IN THE ALDOL REACTION

THE USE OF CHIRAL AND ACHIRAL OXAZOLINES AS THEIR BORON AZAENOLATES

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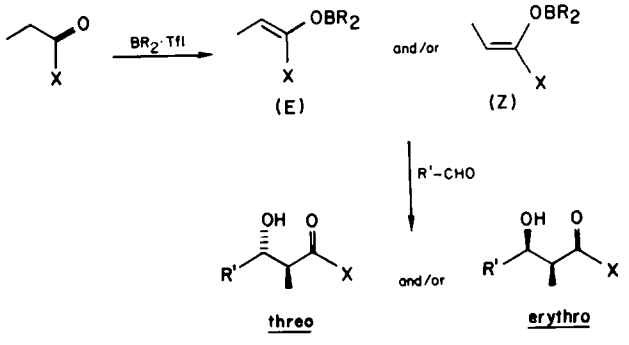
Abstract—Chiral oxazolines, as their boron enolates derived from various boron triflates, react with aldehydes to give *erythro*-selectivity (97% + %) with enantiomeric purities of 50–60%. Achiral oxazolines as their boron enolates derived from diisopinocampheylborane give, on reaction with aldehydes, β-hydroxy esters with high *threo*-selectivity (90 + %) in 77–85% ee. A variety of structurally different oxazolines were also studied and many show high *erythro*-selectivity.

The synthetic challenges in recent years to reach complex natural products has prompted extensive activity in controlling diastereoselectivity in open chain compounds.[1] Among the reagents utilized with greatest success are the boron enolates shown in their most general form in Scheme 1. From the first examples of Fenzyl[2] to the extensive work of Masamune[3] and others,[4] the Lewis-acid nature of boron enolates have shown that they are indeed a technique which should be seriously considered when acyclic stereocontrol is required.

An important goal for the aldol reaction is not only to achieve high diastereoselectivity (*erythro* vs *threo*) but to also achieve high enantioselectivity, thus allowing the preparation of a single enantiomer of either the *threo* or *erythro* product. This has recently been accomplished by Evans in an elegant approach using a chiral imide **1** as its boron enolate derivative.[5] Thus, the dibutylboron enolate **2** of the chiral imide reacts with aldehydes, shown in its most favorable conformation to give greater than 99% of the *erythro* product **3** possessing > 99% enantiomeric excess. Because of the success encountered in our laboratory using both chiral[6] and achiral[7] oxazolines we investigated their behavior as boron enolate derivatives[8] in an attempt to assess their utility in reaching β-hydroxy acids with high diastereo- and enantioselectivity.

Treatment of 2-ethyl-4, 4-dimethyl-2-oxazoline **4** with diisopinocampheylborane triflate **5** according to the method of Mukaiyama[9] gave the boron azaenolate **6**. Without isolation, the latter was cooled to −78° in ether and treated with 1.0 equiv of an aldehyde. The alkylated oxazoline **7** was recovered after aqueous quench (pH7) and hydrogen peroxide treatment. Without purification **7** was hydrolyzed in acid to the carboxylic acid and treated with diazomethane to furnish the β-hydroxyesters **8**. Although the yields for the four step sequence were only moderate, the *threo*-selectivity of the hydroxy acids was excellent



Scheme 1.

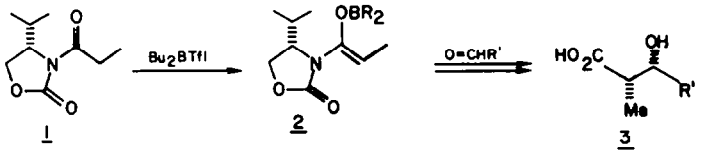
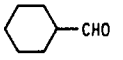
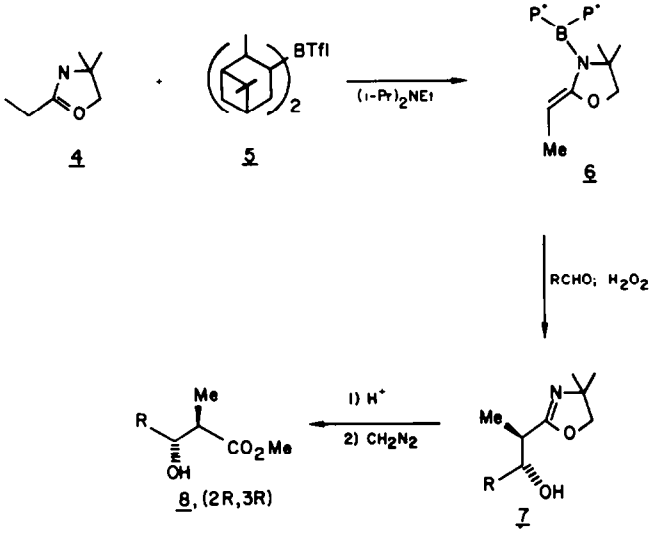
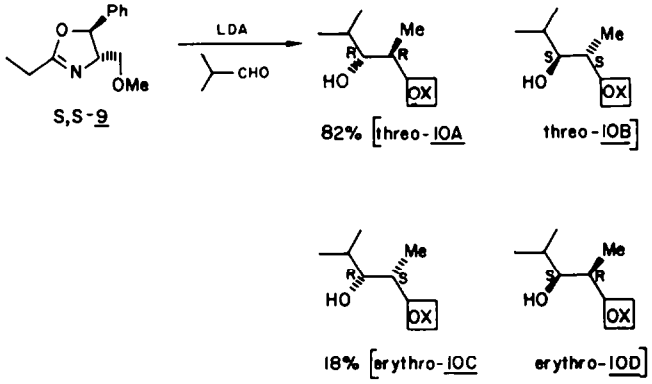


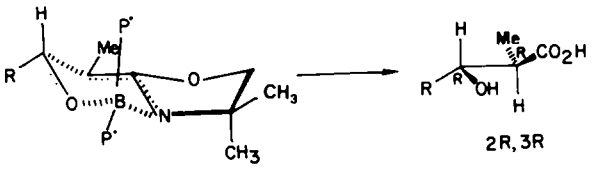
Table 1. Threo-β-hydroxyesters 8

RCHO	Threo:Erythro, %	%ee, Threo	Overall Yield From 4
EtCHO	92:8	77	26
PrCHO	91:9	77	22
n-PentCHO	90:10	77	25
i-PrCHO	91:9	85	36
	95:5	84	31
t-BuCHO	94:6	79	29



(Table 1). The pure *threo*-product was obtained using preparative gas chromatography and subjected to enantiomeric analysis by chiral shift reagents monitoring the OMe signal at 4.08 ppm (major) and 4.13 ppm (minor). In order to assess the absolute configuration of *threo*-**8**, the chiral oxazoline **9** was metalated with LDA (−78°) and treated with isobutyraldehyde to give an 82:18 mixture of *threo* to *erythro* oxazolines.[10] Each of the four diastereomers were isolated pure by medium pressure liquid chromatography[11] and hydrolyzed to the acid and esterified with diazomethane. The esters derived from **10C** and **10D** were identical to the *erythro* esters reported by Evans[5] and may be assigned the 2*S*, 3*R* and 2*R*, 3*S* configurations. For *threo* 10*A* and 10*B*, these were assigned by treating **10A** with 2 eq of t-butyllithium (THF, −78°) and quenching with acetic acid. HPLC analysis showed only a mixture of **10A** and **10C**. Similar.y **10B** was epimerized to give a mixture of **10B** and **10D**. Since it may be safely assumed that only the α-carbon in **10A** and **10B** were metalated it may also be concluded that **10A** possessed the 2*R*, 3*R* configuration while **10B** possessed the 2*S*, 3*S* configuration. Since all the β-hydroxyesters in Table 1 showed the same behavior toward the chiral shift reagent they may be assigned 2*R*, 3*R*

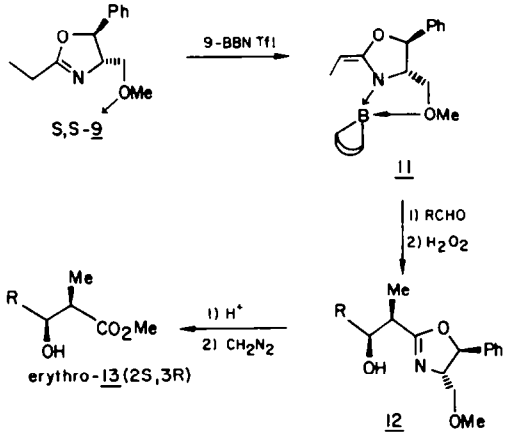




Scheme 2.

except for the last entry (t-BuCHO) which is assigned 2*R*, 3*S* because of the priority rule. In order to rationalize the high *threo* selectivity and the high ee's (~80%), one may consider the following transition state based on the Zimmerman model[12] (Scheme 2). In the transition state, the CO of the aldehyde complexes with boron such that the R in the aldehyde assumes an "equatorial" position. This results in minimum nonbonded interaction with the chiral ligand and provides alkylation from the si-face of the aldehyde. Approach to the re-face results in an "axial" orientation of the R-group and leads to serious interaction with the chiral ligand on boron.

We next turned to the chiral oxazoline **9** and transformed it into its boron enolate derived from 9-BBN, **11**. Thus, the chirality of the boron aza-enolate now resides in the oxazoline as opposed to the previous study where the chirality was present on boron. Reaction of **11** with various aldehydes, gave after work-up the alkylated oxazolines **12**. No attempts were made to separate **12** since gas chromatography indicated that the ratio of diastereomers was quite high. Thus, **12** was directly hydrolyzed and treated with diazomethane to give the hydroxyesters **13**. The ratios of esters by gc showed 95–98% *erythro* isomer formed (Table 2). Although the *erythro*-selectivity in Table 2 is quite favorable, the enantioselectivity (% ee) is only modest. Solvent changes from ether to hexane had little effect on the stereochemical results and appears to only effect the chemical yields.



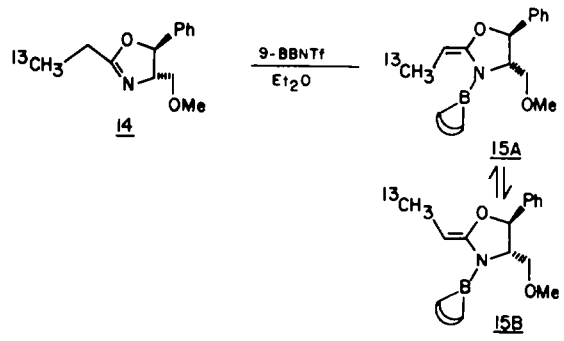
In order to gain an insight into the reversal of stereochemistry when the chirality is on boron (*threo*) as opposed to chirality on the oxazoline (*erythro*), we considered the possibility of a reversal in the enolate geometry. We had previously observed in chiral imines that equilibrating the lithio imines of acyclic ketones gave rise to a reversal in enantioselectivity.[13] Since these boron enolates **6** and **11** were formed under kinetic conditions, we chose to examine their behavior after equilibration. To this end the boron enolate **11** was heated to reflux for 2 hr prior to addition of the aldehydes in Table 2. However, the only event that ensued was a slight lowering of the *erythro–threo* ratios to ~85:15 with no significant change in the % ee's of **13**. Thus, no important changes occurred even after equilibration. The problem which arose at this point is whether or not any equilibration *or* changes in enolate geometry had occurred during heating. This was addressed by preparing ^{13}C-enriched oxazoline **14** as previously described[14] and transforming it into its boron aza-enolate **15**. Only a single ^{13}C signal for the Me group was evident and as the temperature rose and sub-

Table 2. Erythro β-hydroxyesters **13** from **9**

RCHO	Solvent	Erythro:Threo[a]	%ee[b]	Overall Yield From 9
EtCHO	Et_2O	95:5	40	44
i-PrCHO	Et_2O	98:2	29	68
i-PrCHO	Et_2O-Hex	98:2	41	42
i-PrCHO	Hexane	97:3	46	28
t-BuCHO	Et_2O	97:3	60	60
t-BuCHO	Hexane	97:3	71	24

a) Determined by gas chromatography. b) Determined by chiral shift reagent without excluding 2-5% of threo isomer. All possessed the 2S,3R configuration based on comparison with ref. 5, except the last two entries which are 2S,3S due to a change in priority.

Table 3. ^{13}C-NMR of **15A**, **15B** ratios[a]

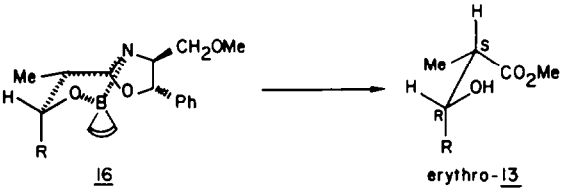


T°	Time	Ratios 15A (8.64 ppm):15B (9.34 ppm)
-75°	0	1:0
-50°	5 min.	1:0
-25°	20 min.	1:0
0°	30 min.	8.7:1
25°	45 min.	1.3:1
25°	After 3 h @32°	1.0:2.1

a) The oxazoline 14 contained 52% ^{13}C at methyl.

sequent reflux was initiated a final ratio of two Me signals remained (Table 3). Under kinetic boron enolate formation, therefore, only a single enolate was present (singlet at 8.64 ppm) whereas after standing at 0° to room temperature the other enolate **15B** began to increase until after heating the ethereal solution, the major enolate was **15B**. Thus a significant reversal had occurred yet the *erythro–threo* ratios were not affected significantly by the change in enolate geometry. Since **15B** is less crowded than **15A** about the double bond, it is reasonable to assume that **15B** is the thermodynamically favored boron enolate, yet only by a ratio of 2:1. One must therefore conclude that the stereoselectivity of this aldol process is dependent on factors other than enolate geometry. Evans has also described the equilibration of E and Z enolates by heating or standing for periods of time.[14] The *erythro* products from this reaction may be reasonably rationalized by invoking the chair transition state possessing the minimum number of non-bonded interactions (Zimmerman model) **16**. However, it is not readily apparent why the enantioselectivity is only 40–70% ee. This may be due to the substituents on the oxazoline ring (phenyl and methoxymethyl) both of which provide undesirable steric factors. However, since the 2S, 3R enantiomer is the major product, perhaps the methoxymethyl is chelated to some degree to the boron affixing the boron to the side shown in **16**. Chelation of boron by the methoxymethyl itself generates a strained 6-5-5 ring system which suggests that a longer chain bearing the OMe group would make the chelate more stable.

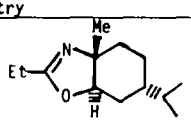
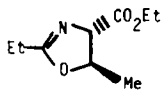
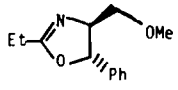
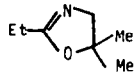
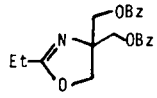
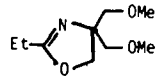
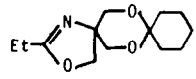
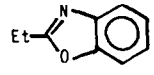
A further study was undertaken to assess the nature of the oxazoline structure and various substituents toward diastereoselection. In this regard, the boron enolates of various oxazolines, both chiral and achiral, were studied. Their reaction with isobutyraldehyde to give the methyl ester of 2,



4-dimethyl-3-hydroxypentanoic acid is given in Table 4. The most striking fact that appears in Table 4 is the almost exclusive preponderance of the *erythro* hydroxy acid regardless of oxazoline or boron structure. In entry 6 the use of 9-BBN as the source of the boron enolate, gives a modest *threo*-selectivity. As described in Table 2, those reactions which provide high *erythro*-product also give modest enantioselectivity which augers for the comparable transition state leading to the *erythro* isomer. Only in the *threo*-selective products (Table 1) is there a meaningful level of enantioselectivity, even though a single boron enolate appears to be involved (Table 3) for the *erythro*-selective process. From Table 4 it is also seen that introduction of two oxygen substituents (entry 5–7) appears to reduce the diastereoselectivity significantly, whereas the presence of a fused aromatic (entry 8) provides for high diastereoselectivity. The nature of the boron substituents are also a factor since in entry 8 the dicyclopentyl boron reduces selectivity relative to the i-P_2B or the 9-BBN. Once again the degree of diastereoselection seems to have no relation to the degree of enantioselection and this is clearly seen throughout Table 4.

The conclusions drawn by Heathcock[1] that diastereoselectivity is fairly high if the enolate geometries are fixed apparently does not apply to oxazolines. The complexity of the molecule with two

Table 4. Various oxazolines as their B-azaenolates in reaction with isobutyraldehyde and the *erythro–threo* (E–T) ratios

Entry	Boron Triflate[a]	E:T[b]	%ee[c]	conf[d]	Overall Yield, %[e]
1) 	Cp_2BTf	91:9	36	2R,3S	60
	9-BBNTf	97:3	58	2R,3S	60
2) 	9-BBNTf	98:2	57[g]	2S,3R	47
3) 	Cp_2BTf	77:23	64	2S,3R	50
4) 	i-P_2BTf	82:18	9	2S,3R	25
	Cp_2BTf	90:10	--	--	55
	9-BBNTf	99:1	--	--	32
5) 	9-BBN	71:29	--	--	69
6) 	i-P_2BTf	66:34	f		21
	9-BBNTf	39:61	--	--	73
7) 	i-P_2BTf	51:49	f		46
8) 	i-P_2BTf	98:2	27	2R,3S	26
	9-BBNTf	96:4	--	--	38
	Cp_2BTf	65:35	--	--	45

a) Cp_2BTf = dicyclopentylborontriflate; i-P_2BTf = diisopinocampheylboron-triflate. b) Reactions run using oxazoline, borontriflate, diisopropyl amine, ether, -78° to -20°, 1.5 h; isobutyraldehyde added at -78°; details given in Experimental. E-T ratios determined by gc. c) Determined by chiral shift reagent. d) Determined by similar behavior of shifts using shift reagents. e) Based on starting oxazoline. f) Not determined due to poor E-T selectivity. g) Corrected for 83% ee in starting oxazoline.

hetero atoms (ligands) as well as externally placed heteroatoms as found in the oxazolines in this study adds to the complexities of the aldol process when one departs from simple oxygen-boron enolates.

EXPERIMENTAL

2-Ethyl-4, 4-dimethyl-2-oxazoline **4**[7] and (4*S*, 5*S*)-2-ethyl-4-methoxy-methyl-5-phenyl-2-oxazoline **9**[16] were prepared as previously described. Diisopinylcamphenylborane was prepared in 99.8% ee as described by Brown.[17] Dicyclopentylboryltriflate was prepared according to Evans.[15]

Diisopinocamphenylboryl trifluoromethanesulfonate **5**. A soln of 13.5 g diisopinocamphenylborane in 250 ml hexane was treated at 0° with 7.1 g (47 mmol) of trifluoromethane sulfonic acid in a dropwise fashion. Hydrogen gas evolution was observed during the addition and the mixture stirred at 0° for 3 hr and then room temp overnight. Evans[15] has cautioned against an induction period which results in a rapid exotherm in the Mukaiyama procedure.[18] However at 0°, the reaction in this case proceeded with slow, but steady H_2 evolution without any problem.

After stirring overnight, a small amount of solid material appeared. The solvent was evaporated and the residue was used without further purification; IR (hexane) 1414, 1243, 1212, 1145, 930, 720, 605 cm^{-1}.

β-Hydroxyesters **8**

General procedure. To a soln of **5** (2.5 g, 5.7 mmol) in 42 ml ether cooled to −78°, was added **4** (0.72 g, 5.7 mmol) and diisopropylethylamine (0.73 g, 5.7 mmol) under N_2. The mixture was stirred at −78° for 1 hr during which the trialkylammonium triflate precipitated. Stirring was continued at −20° for 30 min and then the aldehyde (5.7 mmol) was added at −78° in a dropwise fashion. After stirring the mixture at −78° for 2 hr and −20° for 1 hr, 10 ml of phosphate buffer (pH 7), 22 ml MeOH, and 10 ml 30% H_2O_2 was added (~0°). The mixture was stirred for 45 min and then extracted with ether affording, after drying and evaporation, crude **7** which was hydrolyzed as follows. The ethereal residue was heated in 50 ml of 3N H_2SO_4 at reflux for 12 hr and the soln, after cooling, extracted with ether (3 × 30 ml). The ether layer was washed with 5% K_2CO_3 (3 × 20 ml) and the alkaline extract was acidified with 6 N H_2SO_4 and extracted (3 × 30 ml) with ether. After wash-

ing the ethereal layer with brine and drying ($MgSO_4$) the ether was removed and the residue treated with excess diazomethane. Bulb-to-bulb distillation gave the oily β-hydroxyesters which were purified to pure *threo*-esters using preparative gas chromatography (35% DEGS, 1-m column at temps between 140–200° with the flow at 40 ml/min). In the case of pivaldehyde, baseline separation was achieved with a 1-m column of 1% SE-30 at 110°.

Enantiomeric excess determination. Ten mg of the *threo*-5-hydroxyester and 10 mg of Tris-[3-(heptafluoropropyl)-hydroxymethylene]-d-camphorato Europium were dissolved in 0.4 ml $CDCl_3$. The OMe singlet was seen as separate signals δ 4.08 (major enantiomer) and δ 4.13 (minor enantiomer). The ratio was obtained by peak height and area. All the *threo* compounds in Table 1 showed similar peak separations.

Physical Data for **8** *in Table* **1**

(−)-threo-*Methyl 2-methyl-3-hydroxypentanate.* b.p. 90°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −9.9° (*c* 1.28, $CHCl_3$): δ 0.83–1.18 (m, 3), 1.25 (d, 3), 1.38–1.80 (m, 2), 2.61 (quintet, J = 7 Hz, 1), 2.60 (bs, 1), 3.46–3.90 (m, 1), 3.76 (s, 3); IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

(−)-threo-*Methyl 2-methyl-3-hydroxyhexanate,* b.p. 90°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −2.5° (*c* 1.03, $CHCl_3$), NMR ($CDCl_3$): δ 0.83–1.20 (m, 3), 1.26 (d, 3), 1.30–1.80 (m, 4), 2.60 (quintet, J = 7 Hz, 1), 2.58 (d, 1), 3.46–3.96 (m, 1), 3.76 (s, 3); IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

(−)-threo-*Methyl 2-methyl-3-hydroxyoctanate.* b.p. 100°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −3.1° (*c* 1.03, $CHCl_3$), NMR ($CDCl_3$): δ 0.76–1.15 (m, 3), 1.20–1.82 (m, 8), 1.26 (d, 3), 2.61 (quintet, J = 7 Hz, 1), 2.55 (d, 1), 3.5–4.00 (m, 1), 3.76 (s, 3), IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

(−)-threo-*Methyl* 2, 4-*dimethyl-3-hydroxypentanate.* b.p. 90°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −12.5° (*c* 1.04, $CHCl_3$): δ 0.96 (d, 3), 1.00 (d, 3), 1.25 (d, 3), 1.44–1.98 (m, 1), 2.43 (bs, 1), 2.72 (quintet, J = 7 Hz, 1), 3.26–3.58 (m, 1), 3.73 (s, 3), IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

(−)-threo-*Methyl 2-methyl-3-hydroxy-3-cyclohexylpropionate.* b.p. 80°/0.1 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −8.1° (*c* 1.05, $CHCl_3$), NMR ($CDCl_3$): δ 0.90–2.15 (m, 11), 1.25 (d, 3), 2.72 (quintet, = 7 Hz, 1), 2.50 (d, 1), 3.18–3.62 (m, 1), 3.74 (s, 3), IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

(−)-threo-*Methyl* 2, 4, 4-*trimethyl-3-hydroxypentanate.* b.p. 95°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −21.2° (*c* 1.01, $CHCl_3$), NMR ($CDCl_3$): δ0.90 (s, 9), 1.26 (d, 3), 2.76 (quintet, J = 7 Hz, 1), 3.05–3.40 (b, 2), 3.70 (s, 3), IR (film) 3500 (OH), 1740 (C=O) cm^{-1}.

Separation of **10A-10D.** The oxazoline **9** (2.19 g, 10 mmol) was dissolved in THF and cooled to −78°. A soln of lithium diisopropylamide (11 mmol) in 20 ml THF was added dropwise and after 1 hr a soln of isobutyraldehyde (0.79 g, 11 mmol) in 10 ml THF was added. The mixture was stirred at −78° for 2 hr and quenched in 100 ml water and extracted with ether, dried (Na_2SO_4) and concentrated to give **10A–10D** (2.65 g. 91%). The ratio of diastereomers was determined by HPLC (18.3:1.0:2.4:2.2). All four were separated using medium pressure liquid chromatography[11] (silica gel, 20% acetone–80% hexane, 13 ml/min) or on a Waters Prep 500 (10% acetone–90% hexane).

Compound threo-**10A.** NMR (CCl_4) δ 1.00 (J = 7 Hz, 3), 1.03 (d, J = 7 Hz, 3), 1.23 (d, J = 7 Hz, 3), 1.83 (octet, J = 7 Hz, 1), 268 (quintet, J = 7 Hz, 1), 3.43 (s, 3), 3.27–3.80 (m, 4), 4.06 (m, 1), 5.27 (d, J = 7 Hz, 1), 7.30 (s, 5).

Compound threo-**10B.** The NMR spectrum is virtually identical to **10A** except the doublet at 1.23 is shifted downfield to 1.33. The characteristic *threo*- quintet at 2.68 ppm was still present.

Compound erythro-**10C.** The major spectral difference is the absence of the quintet at 2.68 ppm and its replacement by a doublet of triplets (J = 3, 7 Hz).

Compound erythro-**10D.** This is virtually superimposable on **10C** showing the characteristic *erythro* doublet of triplets (J = 3, 7 Hz) at 2.60 ppm.

Epimerization of threo **10A** *to* erythro **10C.** A soln of **10A** (50 mg) in 2 ml THF cooled to −78° was treated with 1 ml of THF soln containing 0.21 ml (2.2 equiv) t-BuLi. The mixture was stirred for 1 hr and quenched with 0.1 ml of AcOH at −78°. The soln was poured into 5% aq NaOH and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$) and concentrated to give an oil, 50 mg. HPLC analyses [μ-porasil, $CHCl_3$ containing 0.07% EtOH, 2 ml/min UV (254)] showed a mixture of **10A** and **10C**, compared to pure, previously separated **10A** and **10C**. A similar experiment starting with **10B** gave, after epimerization a mixture of **10B** and **10D**. This confirmed that **10A**, **10C** and **10B**, **10D** differed only at the α-carbon.

Erythro-β-*hydroxyesters* **13**

General procedure. To the chiral **9** (0.89 g, 4.0 mmol) and diisopropylethylamine (0.52 g, 4.0 mmol) in 10 ml ether was added 9-BBN triflate[9] (1.08 g, 4.0 mmol) in a dropwise fashion at −78° under N_2. The mixture was stirred for 2 hr at −78° and the aldehydes (4.0 mmol) in Table 2 were added dropwise at −78°. Stirring was continued at this temp for 3 hr and MeOH (20 ml), phosphate buffer (pH 7, 9 ml), and 30% H_2O_2 (9 ml) were added sequentially. After 45 min at 0° and the work up, as described for the *threo* esters **8** accomplished, there was obtained the oxazolines **12** as oily products. Without further purification, the crude oxazolines were heated to reflux in 4.5 N H_2SO_4 for 12–14 hr. Isolation of the β-hydroxy esters **13** followed the procedure used above for **8**. No attempts were made to exclude the 2–5% *threo* ester impurities during the determination of enantiomeric excess. The % ee was determined using the *erythro*-esters **13** (23 mg, 2–5% *threo*-**13**), Tris-3 [(heptafluoropropyl)hydroxymethylene]-d-comphorato Europium (9 mg) dissolved in 0.5 ml $CDCl_3$. The C–CH_3 doublet at C-2 was separated and appeared at δ 1.74 (minor enantiomer) and δ 1.98 (major enantiomer). The % ee was calculated from peak heights and areas. All the *erythro*-esters **13** in Table 2 showed similar NMR behavior.

Physical data for erythro-β-*hydroxyesters* **13**

(+) - *Methyl* - 2 - *methyl* - 3 - *hydroxypentanoate.* B.p. 93°/18 mm[19] (bulb-to-bulb), $[\alpha]_D^{23}$ 1.4° (*c* 2.7, $CHCl_3$), 40% ee (contained 5% of *threo*-isomer); NMR ($CDCl_3$): δ 0.82–1.12 (m, 3), 1.20 (d, 3), 1.32–1.80 (m, 2), 2.40 (s, 1), 2.59 (d of q, J = 4 Hz, 7 Hz, 1), 3.72 (s, 3), 3.72–3.96 (m, 1).

(−)-erythro *Methyl* 2, 4-*dimethyl-3-hydroxypentanoate.* $[\alpha]_D^{23}$ −2.7° (*c* 1.15, $CHCl_3$), NMR ($CDCl_3$): δ 0.92 (d, 3), 1.26 (d, 3) 1.45–2.10 (m, 1), 2.60 (d, 1), 2.73 (d of q, J = 4 Hz, 7 Hz, 1) 3.60 (d of d, J = 4 Hz, 8 Hz, 1). 3.73 (s, 3).

(−)-erythro *Methyl* 2, 4-*trimethyl-3-hydroxypentanoate.* B.p. 94°/18 mm (bulb-to-bulb), $[\alpha]_D^{23}$ −6.6°, 60% ee (contains 3% of *threo* isomer), NMR ($CDCl_3$): δ 0.92 (s, 9), 1.26 (d, 3), 2.18 (bs, 1), 2.70 (d of q, J = 4 Hz, 1), 3.62 (d, 1), 3.64 (s, 3).

Oxazoline preparations from Table 4

Entry 1. To a soln of 1-amino-2-menthanol[20] (2.26 g) in dichloroethane (25 ml) was added triethylorthopropionate (2.78 g) and the mixture allowed to reflux for 24 hr. The solvent was removed *in vacuo* to yield a yellow oil. Bulb-to-bulb distillation (125°, 15 mm) gave 2.33 gr (84%) of the oxazoline, IR (neat) 1625 cm^{-1}, NMR ($CDCl_3$): δ 3.7 (d of d, 1) along with an assortment of overlapping signals.

Entry 2 was prepared as described.[21]

Entry 3 is **9** whose preparation has already been reported.[16]

Entry 4 was prepared as described.[7]

Entries 5, 6, 7. A mixture of tris-(hydroxymethyl)- aminomethane (36.3 g, 0.3 mol) and ethyl orthopropionate (68.7 g, 0.39 mol) in 100 ml dimethylformamide was heated to 90–100° for 18 hr. The solvent was removed *in vacuo* and the bis-hydroxymethyloxazoline was collected as a solid and recrystallized from CH_2Cl_2, 34 gr (71%); NMR ($CDCl_3$): δ 1.21 (t, 3), 2.38 (q, 2), 3.62 (s, 4), 4.20 (s, 2) and 4.62 (s, 2).

(Found: C, 52.40; H, 7.76. Calc for $C_7H_{13}NO_3$: C, 52.81; H, 8.20%).

The ethers (entries 5, 6, 7) were all prepared from the above oxazoline diol as follows:

Entry 5. The oxazoline diol (5.0 g), t-BuOK (8.4 g) and benzyl bromide (12.7 g) were dissolved in 50 ml DMF and stirred at 0° for 3 hr followed by stirring at ambient overnight. The mixture was concentrated and washed with water and then 5% HCl to remove the basic product. Neutralization of the aqueous soln with 10% NaOH and ether extraction gave an oil after drying (Na_2SO_4) and concentration. Bulb-to-bulb distillation at 160° (0.05 mm) provided 8.0 g (75%) of the dibenzyl ether. NMR ($CDCl_3$): δ 1.20 (t, 3) 2.32 (q, 2), 3.40–3.78 (m, 4), 4.22 (s, 2), 4.56 (s, 4), 7.30 (br.s, 10).

Entry 6. As above, 10 g oxazoline diol in 200 ml THF at 0° was treated with 27.5 g *t*-BuOK and then 34.7 g MeI. After stirring overnight at ambient, work-up gave 5.2 g (41%) of an oil in bulb-to-bulb distillation (90°, 15 mm). NMR ($CDCl_3$): δ 1.21 (s, 3), 2.36 (q, 2), 3.26–3.62 (m, 4), 3.40 (s, 6), 4.15 (s, 2).

Entry 7. In toluene (50 ml), *p*-toluene sulfonic acid monohydrate (6.0 g) was heated to reflux with a Dean Stark trap for 1 hr. Oxazoline diol (5.0 g) and cyclohexanone (6.2 g) were then added to the toluene soln and heated to reflux for 4 hr. After cooling, the mixture was poured into 5% aq NaOH and work-up as above gave an oil which was distilled (bulb-to-bulb) at 130° (15 min). NMR ($CDCl_3$): δ 1.20 (t, 3), 1.34–2.30 (m, 10), 2.35 (q, 2), 3.54 (d of d, 2), 4.12 (d, 2). (Found: C, 65.45; H, 9.05. Calc for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.85%).

Entry 8. A mixture of *o*-aminophenol (5.0 g) and ethyl orthopropionate (10.5 g) in 10 ml DMF was heated overnight at 100°. Bulb-to-bulb distillation (80°, 15 mm) gave an oil (6.1 g, 90%). NMR ($CDCl_3$; δ 1.5 (t, 3), 3.0 (q, 2), 7.1–7.9 (m, 5). (Found: C, 73.25; H, 6.47. Calc for C_9H_9NO: C, 73.44; H, 6.17%).

Aldol reaction of i-*butyraldehyde with oxazolines in Table* 4. These reactions were carried out in the same manner as described in the General Procedure for **8** and **13** mentioned above.

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