Protocols for the Preparation of Each of the Four Possible Stereoisomeric α-Alkyl-β-hydroxy Carboxylic Acids from a Single Chiral Aldol Reagent[1]

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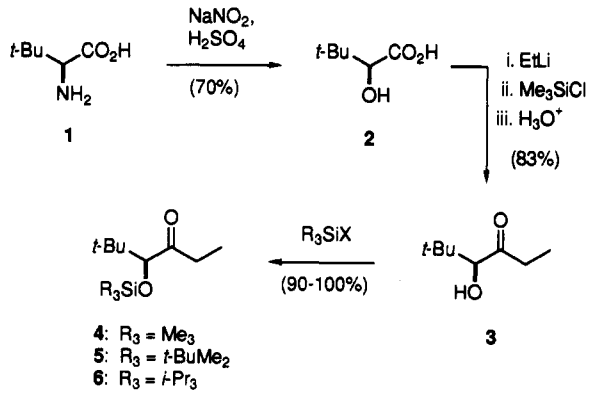
Protocols have been devised whereby all four possible stereoisomeric α-alkyl-β-hydroxy carboxylic acids can be derived from a single aldol reagent, hydroxy ketone **3**. Compound **3**, obtained in enantiomerically homogeneous form in 50% overall yield from *tert*-butylglycine (**1**), is used for aldol reactions in the form of its trimethylsilyl and *tert*-butyldimethylsilyl derivatives, **4** and **5**. The *Z* lithium and *Z* boron enolates of **4** react with various aldehydes to give aldols **8** and **9**, respectively. Deprotonation of **4** by bromomagnesium 2,2,6,6-tetramethylpiperidide (MTMP) gives the *E* enolate, which may be trapped by trimethylsilyl chloride to obtain the *E* silyl enol ether **11**. The *E* bromomagnesium enolate of **4** reacts with aldehydes to give aldols of structure **15**. Transmetalation of the bromomagnesium enolate of keto ether **5** is accomplished by reaction with (triisopropoxy)titanium chloride. The resulting *E* (triisopropoxy)titanium enolate reacts with aldehydes to provide aldols of structure **17**. The aldols resulting from the foregoing reactions are hydrolyzed to keto diols **19–22**, which are oxidized to the stereoisomeric α-methyl-β-hydroxy carboxylic acids **23–26**.

The reaction of a chiral enolate with a prochiral aldehyde can give rise to four diastereomeric aldols.[3] The stereochemical outcome of such a reaction is governed by three factors: (1) the configuration, *E* or *Z*, of the enolate; (2) which of the enolate diastereotopic faces reacts; (3) which of the aldehyde enantiotopic faces reacts. Variable 1 is independent of the other two since, in principle, the double-bond geometry can be established prior to addition of the aldehyde. Variables 2 and 3 are usually coupled, however. For example, many aldol reactions are known to proceed through six-centered transition states in which the alkyl group of the aldehyde preferentially occupies an "equatorial" position in the chairlike transition structure.[4] For the extreme case in which R of the aldehyde occupies *only* the equatorial position, there remain only two possible chairlike transition structures each for the *E* and *Z* enolates (cf. Scheme I).[5] Which of these predominates is a function of the steric and electronic properties of R*, the chiral moiety of the chiral enolate.[6]

In principle, one could convert a given chiral ketone $R^*COCH_2CH_3$ into each of its four possible diastereomeric aldol products by regulating the stereochemistry of enolate formation and by selecting whether it reacts on its *si* or *re* face. In this paper, we demonstrate the first case of such total stereochemical control.

Compound (*S*)-**4**, previously reported in racemic form,[7,8] is prepared in 50% overall yield from L-*tert*-butylglycine (**1**)[9] by diazotization to the α-hydroxy acid **2**,[10] reaction of this material with excess ethyllithium to obtain hydroxy ketone **3**, and silylation with *N*-(trimethylsilyl)imidazole.[11] The analogous reagent **5** was obtained by reaction of **3** with *tert*-butyldimethylsilyl chloride. The triisopropylsilyl derivative (±)-**6** was prepared by reaction of (±)-**3** with triisopropylsilyl triflate.



The lithium enolate of **4** was prepared by treatment of the ketone with lithium diisopropylamide (LDA) in THF at −78 °C for 2.5 h. To this solution was added 1.0 equiv of tetramethylethylenediamine (TMEDA). After 2 min the aldehyde was added, and after an additional 8 min the reaction was quenched. This optimized procedure gave aldols of structure **8** in 75–80% yield. With isobutraldehyde (**7b**), pivalaldehyde (**7c**), and benzaldehyde (**7d**) the stereoselectivity was >95:5. The relative stereochemistry of the major aldol **8d** was ascertained by single-crystal X-ray analysis of the keto diol obtained by hydrolysis of

(1) Paper 53 in the series Acyclic Stereoselection. For paper 52, see: Mori, I.; Ishihara, K.; Nozaki, K.; Flippin, L. A.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107.

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(3) For this statement to be rigorously true, the reacting atom of the chiral enolate must be prostereogenic; the carbonyl group of an aldehyde is prostereogenic of necessity.

(4) See, inter alia: (a) Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R *Top. Stereochem.* **1982**, *13*, 1. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press, Inc.: New York, 1984; Vol 3, p 111.

(5) In other words, prostereogenicity of the aldehyde and enolate faces is coupled through the steric properties of the Zimmerman six-centered transition state. The phenomenon is usually referred to as "simple diastereoselection": Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(6) This phenomenon is referred to as "diastereofacial selectivity": Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296.

(7) (a) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077. (b) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290. (c) Heathcock, C. H.; Arseniyadis, S. *Tetrahedron Lett.* **1985**, *26*, 6009; **1986**, *27*, 777 (Erratum).

(8) An analogous reagent having a cyclohexyl group instead of the *tert*-butyl group has been prepared in both enantiomeric forms; (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566; (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568.

(9) Compound **1**, also known as L-*tert*-leucine, is available in 500-g quantities from Degussa AG, Weissfrauenstrasse 9, Frankfurt am Main, D-6000 Frankfurt 11, Federal Republic of Germany.

(10) Arndt, F.; Noller, C. R.; Bergsteisson, I. *Organic Synthyses*; Wiley: New York, 1943; Collect. Vol. 2, p 165. The distillation step was omitted; the ethereal solution was simply decanted onto KOH pellets three times or until the KOH remained free-flowing.

(11) Compound **3** is the major product of the Rubottom workup. Rubottom, G.; Kim, C. *J. Org. Chem.* **1983**, *48*, 1550. However, it is contaminated with some of the corresponding alcohol, necessitating the silylation step.

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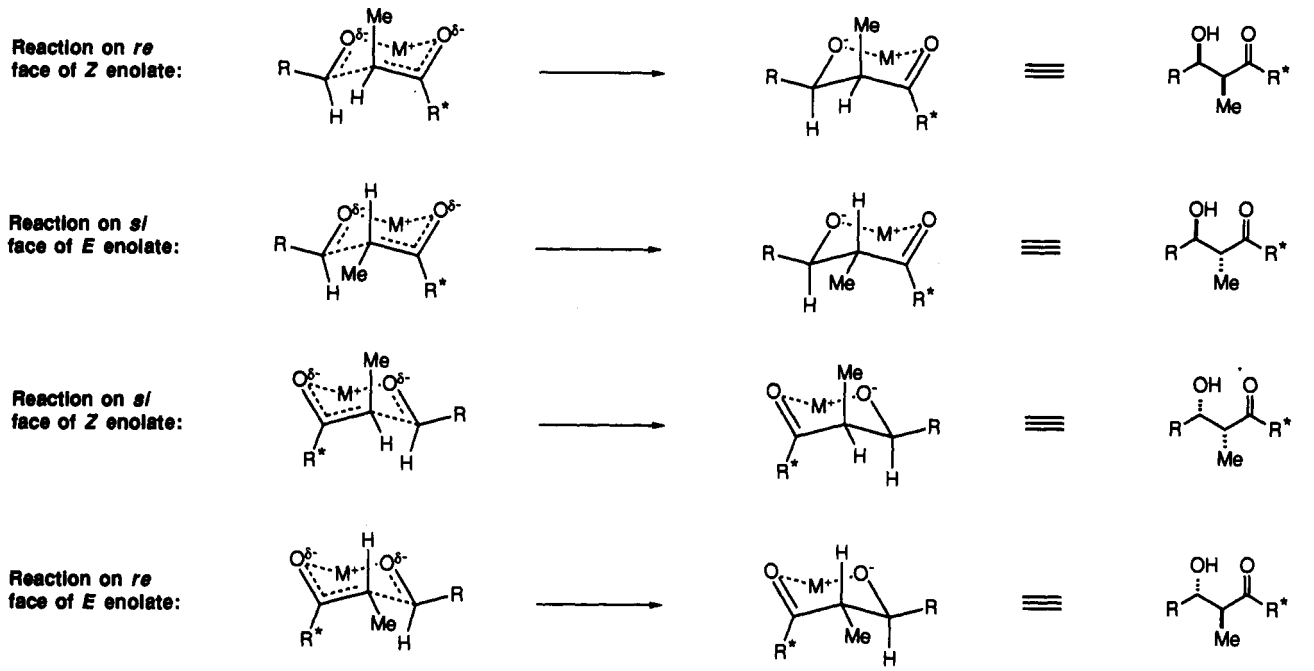
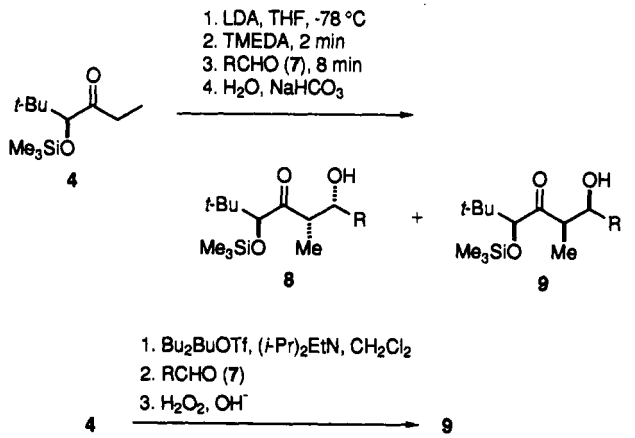
Scheme I

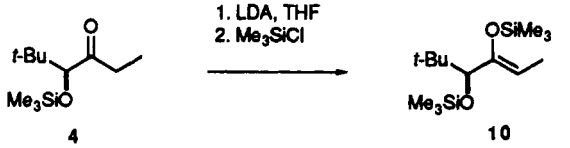


its racemic counterpart, (±)-**8d** (vide infra). With 3-(benzyloxy)propanal (**7e**) the stereoselectivity was 95:5, with the minor isomer being aldol **9e**.[12] The corresponding boron enolate of **4**, prepared in the conventional manner,[13] reacted with aldehydes **7b–e** to give aldols of structure **9** in 80–88% yield. In each case the stereoselectivity was >95:5. For aldols **9b** and **9d** the relative stereochemistry follows unabiguously from the known absolute configuration of **2**, coupled with the fact (vide infra) that they are converted into enantiomers (**24b** and **24d**) of the known β-hydroxy acids **23b** and **23d** (see the Experimental Section).



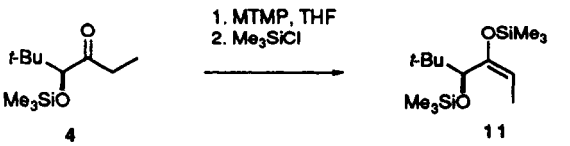
b: R = *i*-Pr; **c**: R = *t*-Bu; **d**: R = Ph; **e**: R = $PhCH_2OCH_2CH_2$

The fact that the both lithium and boron enolates give only the syn relative configuration at the newly created aldol centers is in accord with a large body of fact[4] and provides strong circumstantial evidence that both have the *Z* configuration.[14] Silylation of the lithium enolate provided the silyl enol ether **10**. The effect of cation on



diastereofacial preference is understood in terms of Scheme II.[15] The chelation of the lithium cation by the enolate and silyloxy oxygens causes the chiral enolate to have a distinct facial bias, with the *si* face shielded by the *tert*-butyl group. If the lithium cation is coordinated simultaneously by the enolate, carbonyl, and silyloxy oxygens, reaction through the Zimmerman–Traxler six-centered transition state[16] would give aldols of structure **8**, as is observed. Because of its two alkyl ligands, boron cannot simultaneously coordinate to all three oxygens. In this case, we believe that the enolate adopts a conformation wherein the two C–O bonds are antiperiplanar for dipolar reasons.[17] To the extent that this conformation is important, the *re* face of the enolate is shielded by the *tert*-butyl group and aldols **9** are produced.

The *E* magnesium enolate of **4**, obtained by adding the ketone to a solution of *N*-(bromomagnesio)-2,2,6,6,-tetramethylpiperidine (MTMP) in THF at −5 °C, reacted with trimethylsilyl chloride to give the isomeric silyl enol ether **11**. A possible rationale for the unique ability of this base



(12) Earlier reports on the use of racemic **3** (ref 7) reported lower diastereoselectivity than is obtained using the optimized protocol given here.

(13) (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (b) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Ibid.* **1977**, 153. (c) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (d) Hirama, M.; Masamune, S. *Tetrahedron Lett.* **1979**, 2225. (e) Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229. (f) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.

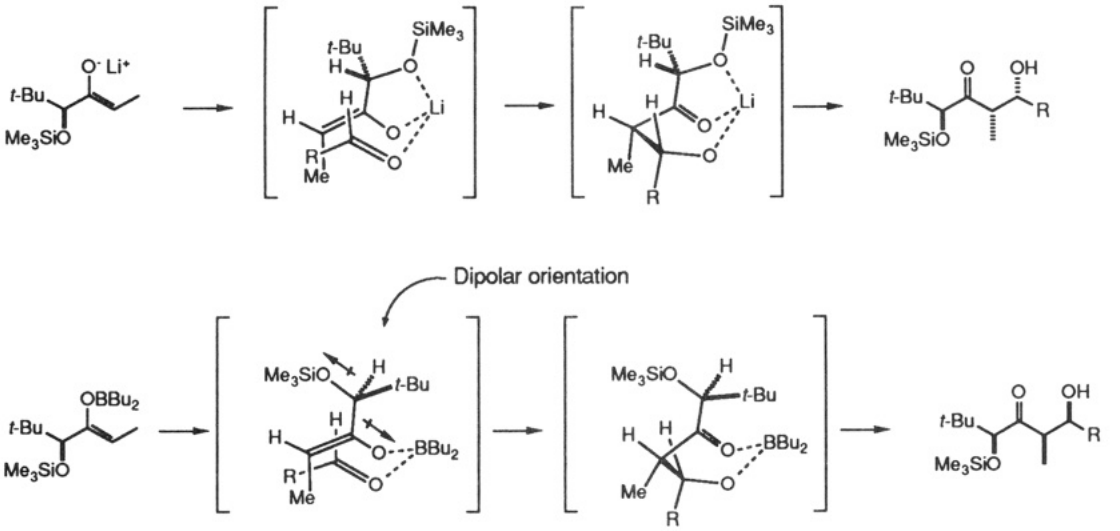
(14) The Evans convention is used to describe enolate confuguration: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, p 11.

(15) For an early exposition of this rationale, see: Heathcock, C. H. In *ACS Symposium Series, No. 185, Asymmetric Reactions and Processes in Chemistry*, Eliel, E. L., Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982, p 55.

(16) Zimmerman, H.; Traxler, M. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(17) Masamune and coworkers (see ref 8a) have advanced a purely steric argument to account for the diastereofacial preference of the boron enolate of a similar α-silyloxy ketone.

Scheme II



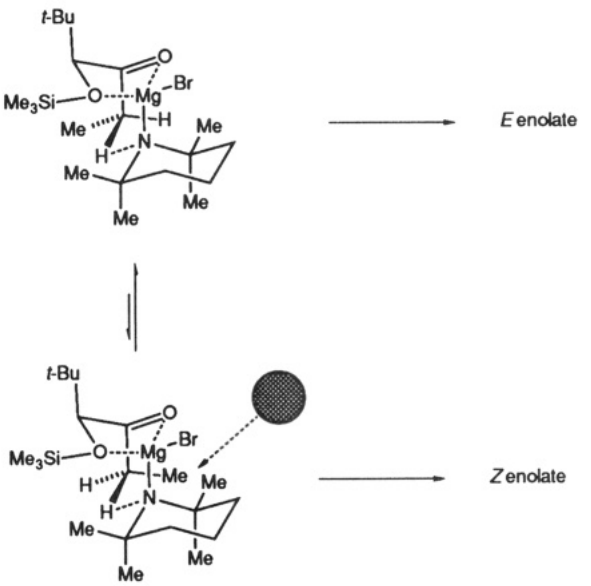
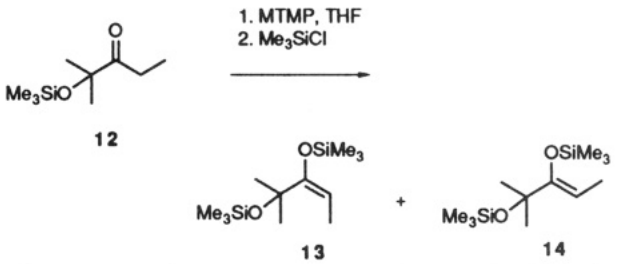


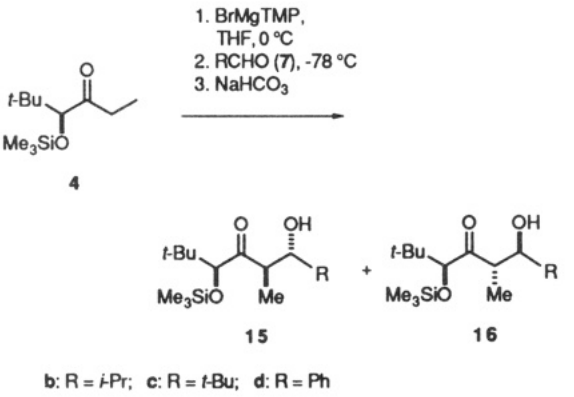
Figure 1. Coordination of magnesium by the α-silyloxy and carbonyl oxygens gives a rigid spirocyclic geometry that causes severe non-bonded interactions between one of the tetramethylpiperidine methyl groups and the α′-methyl group in the conformation leading to the *Z* enolate.

to produce the *E* enolate is suggested in Figure 1. The importance of the α-alkoxy group was shown by the fact that MTMP also deprotonated ketone **12**[5,18] to give a 7:1 mixture of *E* and *Z* enolates, which were converted into silyl enol ethers **13** and **14**. For comparison, LDA reacts with ketone **12** to give only the *Z* enolate.



12 **13** **14**

Reaction of the *E* magnesium enolate with aldehydes **7b–d** gave aldols **15** and **16** in ratios of 92:8 to 95:5 and yields of 75–85%. The relative stereochemistry of the major aldol from benzaldehyde was ascertained by single-crystal X-ray analysis of the keto diol obtained by hydrolysis of its racemic counterpart, (±)-**15d** (vide infra).



4 **15** **16**

b: R = *i*-Pr; **c**: R = *t*-Bu; **d**: R = Ph

To obtain the fourth possible aldol, it was necessary to transmetalate the *E* magnesium enolate with a metal that does not undergo the three-point coordination depicted in Scheme II. The ideal species would be the *E* boron enolate. However, numerous attempts to exchange magnesium for boron did not succeed and attempts to prepare the *E* boron enolate directly from ketone **4** by the method of Brown and co-workers[19] were also unsuccessful.

Eventually we found conditions whereby magnesium can be replaced by titanium. Thus, a solution of the magnesium enolate of **5** and triisopropoxytitanium chloride in a mixture of hexamethylphosphoric triamide (HMPA), dioxane, and THF was sonicated at 25–45 °C for 4 h. The use of $(i\text{-PrO})_3\text{TiCl}$ for enolate exchange was adapted from the work of Siegel and Thornton, who performed a similar exchange with a lithium enolate.[20,21] Each of the additives

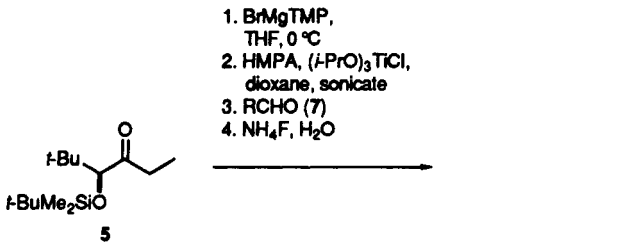
(18) Bal, B.; Buse, C. T.; Smith, K.; Heathcock, C. H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 185.

(19) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. J. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(20) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722.

(21) With ketone **4**, the standard Siegel–Thornton protocol gave no change in product ratio, implying that transmetallation did not occur. When titanation of the magnesium enolate was attempted at room temperature a 1:1 mixture of keto diols was obtained as the only product. This result implied that the transmetalation conditions caused desilylation, with a resulting deleterious effect on aldol stereoselectivity. For this reason, we investigated the use of more hardy silyl protecting groups. We were unable to deprotonate the triisopropylsilyl derivative **6** with MTMP. This led us to the use of the *tert*-butyldimethylsilyl derivative **5**, which served admirably.

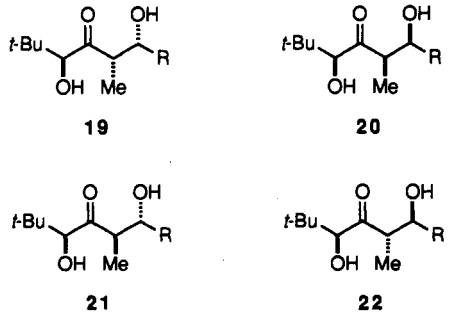
(HMPA, dioxane) and the sonication period was shown to be necessary by appropriate control experiments. By this protocol, benzaldehyde **7d** gave aldols **17d** and **18d** in a ratio of 1:4. However, aldehydes **7a**, **7b**, and **7c** gave **17a**/**18a**, **17b**/**18b**, and **17c**/**18c** in ratios of <5:95 and 85–88% yield. For aldols **17b** and **17d** the relative stereochemistry follows unambiguously from the known absolute configuration of **2**, coupled with the fact that they are converted into enantiomers (**26b** and **26d**) of the known β-hydroxy acids **25b** and **25d** (see the Experimental Section).



a: R = Me; **b**: R = *i*-Pr; **c**: R = *t*-Bu; **d**: R = Ph.

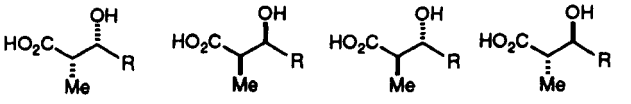
Scheme III depicts our view of the transition structures for the reactions of the *E* magnesium and titanium enolates. We believe that magnesium, like lithium, engages in three-point coordination, leading through the Zimmerman–Traxler transition state predominantly to aldol **15**. The titanium enolate, on the other hand, behaves like the boron enolate, thereby providing aldol **16** (or **17**, in the case of the *tert*-butyldimethylsilyl ether) as the major product.

As part of the characterizations of the aldols **8**, **9**, **15**, and **17**, those derived from benzaldehyde and isobutyraldehyde were hydrolyzed to the corresponding keto diols (**19b**, **19d**, **20b**, **20d**, **21b**, **21d**, **22b**, **22d**). The crystalline diols **19d** (lithium enolate) and **21d** (magnesium enolate) were characterized by single-crystal X-ray analysis.[22]



b: R = *i*-Pr; **c**: R = *t*-Bu; **d**: R = Ph

Keto diols **19b–22b** and **19d–22d** were oxidized by periodic acid or sodium periodate (see the Experimental Section) to obtain β-hydroxy acids **23b–26b** and **23d–26d**, thus demonstrating the ability to synthesize all four of the possible stereoisomers of a given α-alkyl-β-hydroxy carboxylic acid from a single enantiomer of hydroxy ketone **3**.



b: R = *i*-Pr; **d**: R = Ph

Experimental Section

General. Unless otherwise noted, materials were obtained from commerical suppliers and used without further purification. Ether, dioxane, and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Diisopropylamine, 2,2,6,6-tetramethylpiperidine, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), 2,6-lutidine, and diisopropylethylamine were distilled from CaH_2 immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 and stored over 4-Å molecular sieves. All reactions involving organometallic reagents were conducted under a N_2 or Ar atmosphere. The normal processing of organic extracts consisted of washing the extract with water and brine, drying over $MgSO_4$, filtration, and concentration with a rotary evaporator. Boiling points and melting points (Pyrex capillary) are uncorrected. Concentrations for rotation data are given as g/100 mL of solvent. All NMR spectra were measured in $CDCl_3$ solution. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane; coupling constants are expressed in hertz. Enantiomeric excesses (ee) were determined by HPLC with a Pirkle-type 1-A semi-prep column and 10% ether/hexanes as eluant, unless otherwise specified. Flash chromatography refers to the procedure of Still, Kahn, and Mitra.[23]

(±)-2-Hydroxy-3,3-dimethylbutanoic Acid. Pinacolone (20 g, 0.2 mol) was weighed into a flask equipped with a thermometer, a condenser, and a gas outlet tube. Two drops of concentrated HCl were added, and gaseous Cl_2, dried by passage through H_2SO_4, was bubbled through the pinacolone. The HCl gas generated was absorbed by passing the exit gas through aqueous NaOH and the temperature of the reaction mixture was maintained below 60 °C with a water bath. As the reaction neared completion, the mixture solidified. The reaction mixture was heated to 60 °C to melt the solids and Cl_2 addition was continued until the reaction maintained a yellow color. After an additional 1 h at 60 °C 20% aqueous NaOH (48 g, 1.2 mol) was added with stirring, and the temperature was maintained at 60 °C for 12 h. The reaction mixture was allowed to cool to room temperature and was extracted with 100 mL of ether. The aqueous layer was acidified (pH 2) with concentrated HCl and extracted with ether (3 × 150 mL). Normal workup gave 25.8 g (98%) of a solid, off-white product. Recrystallization from benzene gave 23.7 g (90%) of white crystals, mp 86.5–87 °C (lit.[24] mp 87–88 °C). IR (Nujol): 3100, 2950, 1765, 1740, 1640 cm^{-1}. ^1H NMR (250 MHz): δ 3.90 (s, 1), 1.02 (s, 9).

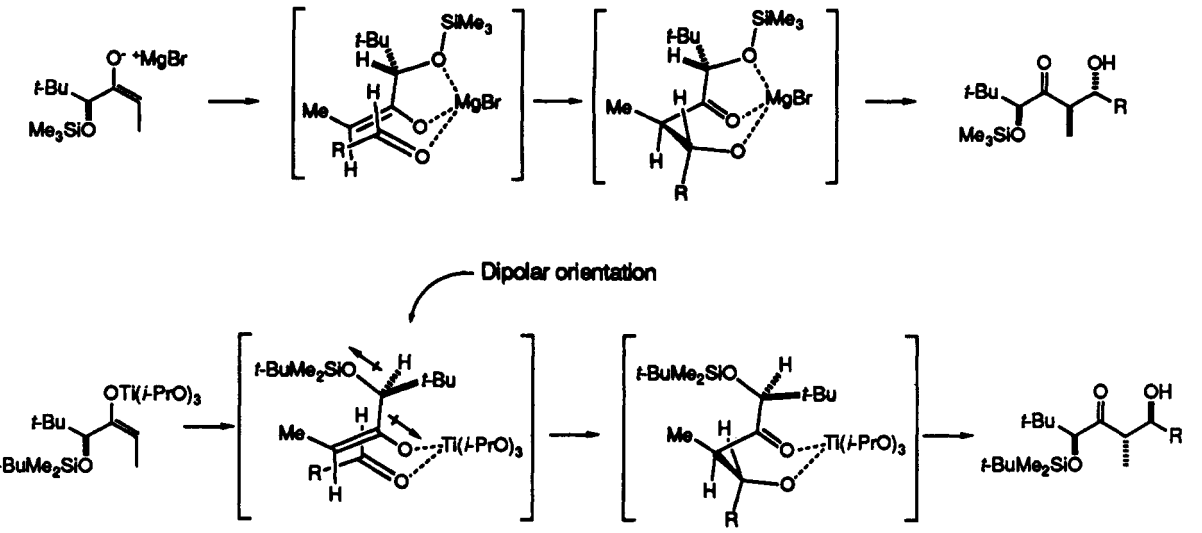
(*S*)-(+)-2-Hydroxy-3,3-dimethylbutanoic Acid (2). To a solution of L-*tert*-leucine (1, 30 g, 0.229 mol) in 345 mL of 1 N H_2SO_4, cooled to 0 °C, was added over 2.5 h a solution of 23.7 g (0.34 mol) of $NaNO_2$ in 83 mL of water. The temperature was maintained below 5 °C during the addition, and the mixture was refrigerated until evolution of N_2 ceased (24 h). The solution was saturated with $(NH_4)_2SO_4$ and extracted with ether (3 × 75 mL). Normal workup gave 29.6 g of a yellow solid. Recrystallization from benzene yielded 20.2 g (67%) of acid **2**, mp 49–51 °C (lit.[24] mp 51–52 °C). $[\alpha]_D$: +3.9° (*c* = 1, CH_3OH) [lit.[24] $[\alpha]_D$ +4.5° (*c* = 4, H_2O)]. IR (Nujol): 3100, 2950, 1765, 1740, 1640 cm^{-1}. ^1H NMR (250 MHz): δ 3.90 (s, 1), 1.02 (s, 9).

(*S*)-(+)-4-Hydroxy-5,5-dimethyl-3-hexanone (3). A solution of 15 g (0.11 mol) of (*S*)-(+)-2-hydroxy-3,3-dimethylbutanoic acid (**2**) in 500 mL of anhydrous ether (500 mL) was cooled to −60 °C. Ethyllithium (2 × 250 mL, 0.9 M, 0.44 mol) was added dropwise from an addition funnel to the stirring reaction mixture over a period of 1 h, at such a rate as to maintain the reaction temperature below −50 °C. The solution was allowed to stir at −60

(22) ORTEP representations of the structures of these two compounds are presented as Figures 2 and 3 in the supplementary material. In the case of **19d** the unit cell contains reciprocally hydrogen-bonded enantiomeric molecules.

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(24) Tanabe, T.; Yajima, S.; Imaida, M. *Bull. Soc. Chim. Jpn.* **1968**, *41*, 3178.

Scheme III



°C for 3 h and then was stirred at room temperature for 36 h. The mixture was cooled to 0 °C, and the reaction was quenched with 220 mL (188.1 g, 1.7 mol) of freshly distilled trimethylsilyl chloride. The cooling bath was removed, and the mixture was stirred for 12 h. The product was hydrolyzed by the addition of 2 L of saturated NH_4Cl solution, and the resulting mixture was stirred for 18 h. The layers were separated, and the aqueous phase was extracted with ether (4 × 500 mL). Normal workup gave 40 g of a light yellow oil, which was purified by flash chromatography (1:4 ether/hexanes) to give 83% of the product as a clear oil. $[\alpha]_D$: +94.5° (c = 2.2, $CHCl_3$). ^1H NMR (300 MHz): δ 0.97 (s, 9), 1.09 (t, 3, J = 7.2), 2.42–2.63 (m, 2), 3.21 (br, s, 1), 3.87 (br s, 1). ^{13}C NMR (50 MHz): δ 7.65, 26.20, 35.15, 35.45, 83.71. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.78; H, 11.09.

Application of the identical procedure to (±)-2 provided (±)-3.

(*S*)-(−)-5,5-Dimethyl-4-[(trimethylsilyl)oxy]-3-hexanone (4). A solution of 6.5 g (45 mmol) of (*S*)-(−)-3 and 7.3 mL (50 mmol) of *N*-(trimethylsilyl)imidazole in 5 mL of CH_2Cl_2 was kept at room temperature for 1 h and then treated with 10 mL of H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL). Normal workup of the combined organic solutions gave 10 g of a yellow oil which was purified by flash chromatography (2.5:97.5 ether–hexanes as eluant) to give 8.8 g (90%) of the 4 as a clear liquid. $[\alpha]_D$: −59.8° (c = 1, $CHCl_3$). IR (film): 2980, 1725, 1268, 1110. ^1H NMR (250 MHz); δ 3.62 (s, 1), 2.50 (q, 2, J = 7.0), 0.98 (t, 3, J = 7.0), 0.88 (s, 9), 0.09 (s, 9). ^{13}C NMR (50 MHz): δ −0.21, 0.36, 7.14, 26.08, 32.11, 34.93, 85.72. Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.11; H, 11.11. Found: C, 60.99; H, 11.19.

(*S*)-(−)-5,5-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-3-hexanone (5). A solution of 6 g (41 mmol) of (*S*)-(−)-3, 12.5 g (83 mmol) of *tert*-butyldimethylsilyl chloride, 11.3 g (166 mmol) of imidazole, and 0.5 g (4.1 mmol) of DMAP in 200 mL of CH_2Cl_2 (200 mL) was heated at reflux for 12 h. The reaction mixture was poured into 200 mL of a saturated $NaHCO_3$ solution layered with 200 mL of 30–60 petroleum ether. The layers were separated and the aqueous phase was extracted with petroleum ether (2 × 50 mL). Normal workup of the combined organic layers gave 12 g of a yellow oil which was purified by flash chromatography (2.5:97.5 ether–hexanes as eluant) to give 9.6 g (90%) of 5 as a clear liquid. $[\alpha]_D$: −53.9° (c = 1.1, $CHCl_3$). IR (film): 1710 cm^{-1}. ^1H NMR (300 MHz): δ −0.07 (s, 3), −0.01 (s, 3), 0.87 (s, 9), 0.92 (s, 9), 0.97 (t, 3, J = 7.2), 2.48 (dq, 2, J = 2.1, 7.2), 3.60 (s, 1). ^{13}C NMR (50 MHz): δ −5.21, −4.97, 7.26, 17.96, 25.74, 26.27, 32.16, 35.10, 85.92. Anal. Calcd for $C_{14}H_{30}O_2Si$: C, 65.06; H, 11.70. Found: C, 65.15; H, 11.65.

(±)-5,5-Dimethyl-4-[(triisopropylsilyl)oxy]-3-hexanone (6). To a solution of 0.50 g (3.5 mmol) of (±)-3 in 5 mL of CH_2Cl_2 at −78 °C was added 0.6 mL (5.2 mmol) of 2,6-lutidine and 1.1 mL (4.2 mmol) of triisopropylsilyl trifluoromethanesulfonate. The solution was allowed to warm to 0 °C, stirred for 20 min, and was quenched by addition of 2 mL of saturated $NaHCO_3$. The reaction mixture was poured onto 10 mL of CH_2Cl_2 layered with 5 mL of H_2O. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were worked up in the normal manner to obtain a pungent oil that was purified by flash chromatography (2.5:97.5 ether–hexanes as eluant) to yield 1.0 g (100%) of (±)-6 as a clear oil. IR (film): 1710 cm^{-1}. ^1H NMR (400 MHz): δ 0.92 (s, 9), 1.00 (t, 3, J = 7.30), 1.04–1.05 (br s, 21), 2.39–2.65 (m, 2), 3.91 (s, 1). ^{13}C NMR (100 MHz): δ 7.30, 13.00, 18.14, 18.18, 26.52, 32.75, 35.44, 86.95. Anal. Calcd for $C_{17}H_{36}O_2Si$: C, 67.94; H, 12.08. Found: C, 68.13; H, 11.97.

General Procedure for Lithium-Mediated Aldol Reactions. A solution of 0.15 mL (0.11 g, 1.1 mmol) of diisopropylamine and 2 mL of THF was cooled to −78 °C, and *n*-butyllithium (2.5 M in hexanes, 0.44 mL, 1.1 mmol) was added dropwise. After 10 min, ketone 4 (0.27 mL, 0.22 g, 1.0 mmol) was added dropwise. The solution was allowed to stir for 2.5 h at −78 °C, and TMEDA (0.27 mL, 0.21 g, 1.8 mmol) was added in one portion. After 2 min the aldehyde (2.0 mmol) was added dropwise.[25] The mixture was allowed to stir for 8 min at −78 °C, and the reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$. The mixture was allowed to warm to room temperature, the layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organics were washed with 20 mL of ice-cold 1% HCl and 10 mL of saturated $NaHCO_3$ solution (1 × 10 mL). After drying and removal of solvent the aldol products were obtained as clear to light yellow oils. Diastereomeric ratios were determined by integration of diagnostic peaks in the ^1H NMR spectra of the crude products. Purification was effected by flash chromatography, 5.95 ether–hexanes as eluant, unless otherwise specified.

(−)-(3*S*,5*S*,6*R*)-6-Hydroxy-2,2,5,7-tetramethyl-3-[(trimethylsilyl)oxy]-4-octanone (8b), 70% yield. $[\alpha]_D$: −26.2° (c = 1, $CHCl_3$). IR (film): 3560, 2990, 2910, 1710 cm^{-1}. ^1H NMR (250 MHz): δ 0.13 (s, 9), 0.80 (d, 3, J = 7.0), 0.91 (s, 9), 1.01 (d, 3, J = 7.0), 1.04 (d, 3, J = 7.0), 1.60–1.80 (m, 1), 3.24–3.34 (m, 2), 3.66 (s, 1), 3.69 (s, 1). ^{13}C NMR (50 MHz): δ 0.34, 10.11, 18.59, 19.69, 26.51, 30.31, 35.32, 40.88, 75.63, 86.32. Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.50; H, 11.11. Found: C, 62.86; H, 11.14.

(−)-(3*S*,5*S*,6*S*)-6-Hydroxy-2,2,5,7,7-pentamethyl-3-[(trimethylsilyl)oxy]-4-octanone (8c), 80% yield. $[\alpha]_D$: −19.3° (c = 4.4, $CHCl_3$). ^1H NMR (400 MHz): δ 0.15 (s, 9), 0.92 (s, 9), 0.96 (s, 9), 1.10 (d, 3, J = 7), 3.19 (s, 1), 3.35 (q, 1, J = 7.0), 3.41 (s, 1), 3.74 (s, 1). ^{13}C NMR (100 MHz): δ 0.51, 11.42, 26.69, 27.31, 35.54, 35.60, 40.99, 76.36, 85.91. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.12; H, 11.32.

(−)-(1*S*,2*S*,4*S*)-1-Hydroxy-1-phenyl-2,5,5-trimethyl-4-[(trimethylsilyl)oxy]-3-hexanone (8d), 80% yield, 98% ee.

(25) Although the use of 2.0 equiv of aldehyde is preferred for inexpensive aldehydes, the lithium and boron enolate reactions can also be carried out with 1.0 equiv of aldehyde with essentially the same results; yields may be about 5% lower. With the magnesium enolate, the aldol yield seems to be about 10% lower if 1.0 equiv of aldehyde is employed.

$[\alpha]_D$: −1.6° (c = 1, $CHCl_3$). IR (film): 3560, 3000, 1720, 1280, 1125, 910, 870, 730 cm^{-1}. ^1H NMR (250 MHz): δ 0.14 (s, 9), 0.99 (d, 3, J = 7.0), 1.02 (s, 9), 3.29 (dq, 1, J = 7.0, 1.7), 3.77 (s, 1), 3.98 (s, 1), 5.08 (d, 1, J = 1.7), 7.39–7.31 (m, 5). ^{13}C NMR (50 MHz): δ 0.46, 10.62, 26.68, 35.51, 46.56, 71.83, 86.54, 125.83, 127.08, 128.10, 141.26. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.14; H, 9.26.

(+)-(3*S*,5*S*,6*R*)-8-(Benzyloxy)-3,6-dihydroxy-2,2,5-trimethyl-4-octanone (Keto Diol Corresponding to 8e). The aldol reaction of the lithium enolate of (*S*)-(−)-**6** with 3-(benzyloxy)propanal was carried out by the general procedure, but the trimethylsilyl derivative was not isolated. Instead, the crude material was desilylated by stirring 15 min at room temperature with 5 drops of 1% HCl in 5 mL of CH_3OH. The diol was purified by flash chromatography, 10–20–50% ether–hexanes as gradient eluant to give **8e** in 75% yield. The ^1H NMR spectrum indicated that the product was contaminated with 5% of **9e**, identified by comparison of several discernible resonances with those in the analogous spectrum of the only product from the boron enolate reaction (vide infra). $[\alpha]_D$: +146.8° (c = 2.7, $CHCl_3$). IR (film): 3440, 1710 cm^{-1}. ^1H NMR (400 MHz): δ 0.97 (s, 9), 1.09 (d, 3, J = 6.7), 1.62–1.79 (m, 2), 3.05 (dq, 1, J = 11, 6.7), 3.30 (br s, 1), 3.45 (br s, 1), 3.61 (dt, 1, J = 3.8, 9.0), 3.92 (ddd, 1, J = 2.7, 4.5, 9.1), 4.08 (d, 1), 4.50 (s, 2), 7.33 (m, 5). ^{13}C NMR (100 MHz): δ 10.62, 25.30, 33.04, 35.04, 50.09, 69.14, 73.29, 73.41, 84.17, 127.72, 127.84, 128.47, 137.58. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.45; H, 9.08.

General Procedure for Boron-Mediated Aldol Reactions. To a solution of 0.27 mL (0.22 g, 1.0 mmol) of ketone **4** in 5 mL of CH_2Cl_2 at −78 °C under N_2 was added 0.224 mL (0.18 g, 1.4 mmol) of diisopropylethylamine and 0.26 mL (0.33 g, 1.2 mmol) of di-*n*-butylboryltrifluoromethanesulfonate (Aldrich, distilled immediately prior to use; 50–55 °C, 0.5 mmHg). The resulting solution was warmed to 0 °C, stirred for 2.5 h, and cooled to −78 °C, and the aldehyde (2.0 mmol) was added dropwise.[25] The solution was allowed to warm to room temperature and stirred for 1.5 h, and reaction was quenched by the addition of 5 mL of pH 7 phosphate buffer solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The solvent was removed and the slushy orange product was dissolved in a mixture of 3 mL of CH_3OH and 1 mL of 30% H_2O_2 at 0 °C. The resulting solution was allowed to stir at 0 °C for 2 h, 10 mL of H_2O was added, and the methanol was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (5 × 10 mL), and the combined organic layers were treated in the normal manner to obtain the products as clear to orange oils. Ratios of diasteromers were determined by integration of the relevant peaks in the ^1H NMR spectrum of the crude materials. Purification was effected by flash chromatography (5.95 ether–hexanes as eluant, unless otherwise specified) to give the aldol products.

(−)-(3*S*,5*R*,6*S*)-6-Hydroxy-2,2,5,7-tetramethyl-3-[(trimethylsilyl)oxy]-4-octanone (9b), 70% yield. $[\alpha]_D$: −35.6° (c = 0.8, $CHCl_3$). IR (film): 3560, 2990, 2910, 1710, 1270 cm^{-1}. ^1H NMR (250 MHz): δ 0.11 (s, 9), 0.92 (d, 3, J = 7.0), 0.92 (s, 9), 1.02 (d, 3, J = 7.0), 1.03 (d, 3, J = 6.5), 1.80–1.95 (m, 1), 3.16–3.30 (m, 2), 3.35 (d, 1, J = 7.0), 3.80 (s, 1). ^{13}C NMR (50 MHz): δ 0.36, 8.65, 18.58, 19.99, 26.55, 30.54, 35.46, 42.46, 75.85, 85.62. Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.50; H, 11.11. Found: C, 62.45; H, 11.13.

(+)-(3*S*,5*R*,6*S*)-3,6-Dihydroxy-2,2,5,7,7-pentamethyl-4-octanone (22c). The aldol reaction required 2.5 h for completion. Oxidation of the crude product resulted in desilylation, giving keto diol **22c**, rather than its silyl ether **9c**. Purification was effected by flash chromatography (10–20–30% ether–hexanes gradient elution) to give **22c** as a clear oil in 80% yield. $[\alpha]_D$: +134.1° (c = 2.0, $CHCl_3$). ^1H NMR (400 MHz): δ 0.96 (s, 9), 0.98 (s, 9), 1.19 (d, 3, J = 7.2), 3.05–3.15 (br s, 1), 3.11 (q, 1, J = 7.2), 3.60 (s, 1), 4.03 (s, 1), 5.13 (s, 1). ^{13}C NMR (100 MHz): δ 10.98, 26.40, 27.11, 35.25, 36.07, 45.40, 75.76, 81.68. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.88; H, 11.32.

(−)-(1*R*,2*R*,4*S*)-1-Hydroxy-1-phenyl-2,5,5-trimethyl-4-[(trimethylsilyl)oxy]-3-hexanone (9d), 85% yield, 98% ee. $[\alpha]_D$: −84° (c = 1.0, $CHCl_3$). Mp: 89–90 °C. IR (film): 3560, 3000, 1720, 1280 cm^{-1}. ^1H NMR (250 MHz): δ 0.17 (s, 9), 0.91 (d, 3, J = 7.0), 0.95 (s, 9), 3.27 (dq, 1, J = 7.0, 1.7), 3.43 (s, 1), 3.87 (s, 1), 5.08 (d, 1, J = 1.7), 7.33-7.35 (m, 5). ^{13}C NMR (50 MHz): δ 0.39, 9.14, 26.53, 35.53, 48.00, 71.99, 85.69, 125.69, 127.09, 128.15, 141.26. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.12; H, 9.44.

(−)-(3*S*,5*R*,6*S*)-8-(Benzyloxy)-6-hydroxy-2,2,5-trimethyl-3-[(trimethylsilyl)oxy]-4-octanone (9e), 85% yield; purified with 3:7 ether–hexanes as eluant. $[\alpha]_D$: −23.7° (c = 1.2, $CHCl_3$). IR (film): 3505, 1700, 1110 cm^{-1}. ^1H NMR (400 MHz): δ 0.11 (s, 9), 0.93 (s, 9), 1.10 (d, 3, J = 7.1), 1.59–1.75 (m, 2), 1.79–1.90 (m, 1), 3.04 (dq, 1, J = 2.4, 7.1), 3.62 (t, 2, J = 6), 3.82 (s, 1), 4.00–4.06 (m, 1), 4.51 (s, 2), 7.31 (s, 5). ^{13}C NMR (100 MHz): δ 0.013, 9.75, 26.56, 34.27, 35.58, 46.06, 67.82, 68.57, 73.15, 85.30, 127.51, 127.61, 128.29, 138.22, 218.30. Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.32; H, 9.47. Found: C, 66.36; H, 9.31.

(±)-(*Z*)-5,5-Dimethyl-3,4-bis[(trimethylsilyl)oxy]-2-hexene (10). A solution of 0.15 mL (1.1 mmol) of diisopropylamine in 2 mL of THF was cooled to −78 °C, and *n*-butyllithium (2.5 *M* in hexanes, 0.44 mL, 1.1 mmol) was added dropwise. After 10 min, 0.27 mL (0.22 g, 1.0 mmol) of ketone (±)-**4** was added dropwise. The solution was stirred for 30 min at −78 °C, and 0.5 mL (0.36 g, 3.6 mmol) of triethylamine was added, followed by 0.5 mL (5.5 mmol) of trimethylsilyl chloride. The resulting solution was stirred at −78 °C for 2 h, allowed to warm slowly to room temperature, and stirred overnight. The reaction mixture was diluted with 1 mL of saturated $NaHCO_3$, and 10 mL of ether was added. The layers were separated and the aqueous layer was extracted with two 10-mL portions of petroleum ether. The dried solution was carefully evaporated (bath temperature at or below room temperature). The resulting silyl enol ether was purified by flash chromatography on silica gel, using petroleum ether as eluant, to give 0.28 g (100%) as an oil. ^1H NMR (300 MHz): δ 0.11 (s, 9), 0.20 (s, 9), 0.88 (s, 9), 1.51 (d, 3, J = 6.3), 3.52 (s, 1), 4.71 (q, 1, J = 6.7). ^{13}C NMR (75 MHz): δ 0.66, 1.17, 10.9, 27.6, 35.7, 82.6, 104.4, 152.2. Anal. Calcd for $C_{14}H_{32}O_2Si_2$: C, 58.27; H, 11.18. Found: C, 58.53; H, 11.24.

(±)-(*E*)-5,5-Dimethyl-3,4-bis[(trimethylsilyl)oxy]-2-hexene (11). To a solution of 0.52 mL (3.0 mmol) of 2,2,6,6-tetramethylpiperidine in 1.0 mL of THF was added 1.9 mL of 1.45 M ethylmagnesium bromide (2.8 mmol) in THF. The solution was refluxed for 48 h and cooled to 0 °C. A solution of 0.20 mL (0.16 g, 1.0 mmol) of ketone **4** in 1.0 mL of THF was added over 30–60 min with a syringe pump. The resulting solution was stirred for 1.5 h at 0 °C, and triethylamine (0.5 mL, 3.6 mmol) and trimethylsilyl chloride (0.5 mL, 5.5 mmol) were added. The resulting solution was allowed to warm to room temperature and stirred overnight. To the resulting mixture was added 2 mL of saturated $NaHCO_3$ and 10 mL of petroleum ether. The layers were separated, and the aqueous phase was extracted with two 10-mL portions of petroleum ether. After drying and careful removal of solvent (bath temperature at or below room temperature), the silyl enol ether was purified by flash chromatography with petroleum ether as eluant to give 0.28 g (100%) of product as a light oil. ^1H NMR (300 MHz): δ 0.09 (s, 9), 0.17 (s, 9), 0.89 (s, 9), 1.59 (d, 3, J = 7.1), 3.95 (s, 1), 4.58 (q, 1, J = 7.1). ^{13}C NMR (75 MHz): δ 0.39, 0.61, 12.2, 27.0, 36.2, 82.6, 102.2, 152.1. Anal. Calcd for $C_{14}H_{32}O_2Si_2$: C, 58.27; H, 11.18. Found: C, 58.39; H, 11.27.

Deprotonation of Ketone 12 with MTMP. Application of the foregoing procedure to the α-(trimethylsilyl)oxy ketone **12**[5,18] gave a 2:1 mixture of silyl enol ethers **13** and **14** in quantitative yield. However, if deprotonation was carried out by keeping a solution of **12** and MTMP in THF at −78 °C for 30 min, compounds **13** and **14** were obtained in a ratio of 7:1. Anal. Calcd for $C_{12}H_{28}O_2Si_2$: C, 55.32; H, 10.83. Found: C, 55.56; H, 10.62. The compounds were not separated, but their NMR resonances could be discerned from the spectra of the mixture of isomers. The resonances of the minor isomer, **14**, were identical with those previously reported.[5]

(±)-(*E*)-4-Methyl-3,4-bis[(trimethylsilyl)oxy]-2-pentene (13). ^1H NMR (300 MHz): δ 0.13 (s, 9), 0.17 (s, 9), 1.34 (s, 6), 1.74 (d, 3, J = 7.3), 4.57 (q, 1, J = 7.3). ^{13}C NMR (75 MHz): δ 0.42, 2.46, 12.4, 29.9, 77.1, 101.1, 155.9.

(±)-(*Z*)-4-Methyl-3,4-bis[(trimethylsilyl)oxy]-2-pentene (14). ^1H NMR (300 MHz): δ 0.13 (s, 9), 0.21 (s, 9), 1.34 (s, 6), 1.52 (d, 3, J = 6.7), 4.87 (q, 1, J = 6.7). ^{13}C NMR (75 MHz): δ 1.1, 2.8, 11.4, 29.1, 75.3, 98.3, 156.6.

General Procedure for Magnesium-Mediated Aldol Reactions. An oven-dried 5-mL Wheaton vial was flushed with N_2 and 0.26 mL (1.5 mmol) of 2,2,6,6-tetramethylpiperidine, and 0.5 mL of dry THF and ethylmagnesium bromide (1.2 M in THF, 1.16 mL, 1.4 mmol) were added. The vial was capped securely and heated with stirring at 80 °C for 24 h. The resulting solution was cooled to 0 °C, and 0.10 mL (0.08 g, 0.50 mmol) of ketone **4** in 0.25 mL of THF was added over a 30–60-min period with a syringe pump. The solution was stirred for 1.5 h at 0 °C after the addition was complete. The enolate solution was then cooled to −78 °C and the aldehyde (2 mmol) was added dropwise.[25] After 30 min, the reaction was quenched by pouring the reaction mixture into 5 mL of saturated $NaHCO_3$ solution. The layers were separated, and the aqueous phase was extracted with ether (5 × 10 mL). The combined organic layers were washed with 10 mL each of 1% cold HCl and saturated $NaHCO_3$ solutions. After drying, the solution was concentrated to yield the product as a clear oil. Ratios of diastereomers were determined by integration of the relevant peaks in the ^1H NMR spectra of the crude products. Purification was accomplished by flash chromatography (5:95 ether–hexanes as eluant, unless otherwise specified).

(−)-(3*S*,5*R*,6*R*)-6-Hydroxy-2,2,5,7-tetramethyl-3-[(trimethylsilyl)oxy]-4-octanone (15b), 75% yield. $[\alpha]_D$: −19.8° (*c* = 1, $CHCl_3$). IR (film): 3560, 3000, 1710 cm^{-1}. ^1H NMR (250 MHz): δ 0.14 (s, 9), 0.81 (d, 3, *J* = 7.0), 0.92 (s, 9), 1.02 (d, 3, *J* = 7.0), 1.05 (d, 3, *J* = 7.0), 1.6–1.8 (m, 1), 3.25–3.40 (m, 2), 3.68 (s, 1), 3.70 (s, 1). ^{13}C NMR (50 MHz): δ 0.46, 10.50, 18.52, 20.01, 26.63, 30.43, 35.58, 41.00, 75.74, 86.42. Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.50; H, 11.11. Found: C, 62.61; H, 11.06.

(−)-(3*S*,5*R*,6*S*)-3-Hydroxy-2,2,5,7,7-pentamethyl-3-[(trimethylsilyl)oxy]-4-octanone (15c). $[\alpha]_D$: −5.2° (*c* = 0.25, $CHCl_3$). ^1H NMR (300 MHz): δ 0.17 (s, 9), 0.93 (s, 9), 0.98 (s, 9), 1.25 (d, 3, *J* = 7.1), 3.13 (dq, 1, *J* = 5.1, 7.1), 3.35 (dd, 1, *J* = 5.1, 7.0), 3.57 (d, 1, *J* = 7.0), 3.90 (s, 1). ^{13}C NMR (50 MHz): δ 0.61, 17.86, 26.78, 26.98, 35.84, 35.98, 43.77, 83.15, 84.85. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.27; H, 11.45.

(−)-(1*S*,2*R*,4*S*)-1-Hydroxy-1-phenyl-2,5,5-trimethyl-4-[(trimethylsilyl)oxy]-3-hexanone (15d), 80% yield, 98% ee. $[\alpha]_D$: −22.3° (*c* = 0.66, $CHCl_3$). IR (film): 3560, 3000, 1720, 1280 cm^{-1}. ^1H NMR (250 MHz): δ 0.16 (s, 9), 0.93 (d, 3, *J* = 7.1), 0.96, (s, 9), 2.75 (d, 1, *J* = 4.3), 3.30 (dq, 1, *J* = 8.7, 7.1), 3.91 (s, 1), 4.80 (dd, 1, *J* = 4.3, 8.7), 7.25–7.32 (m, 5). ^{13}C NMR (50 MHz): δ −0.005, 2.44, 14.91, 26.73, 35.99, 50.35, 84.85, 126.89, 127.87, 128.40, 142.22. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.08; H, 9.32. Found: C, 67.28, H, 9.26.

General Procedure for Titanium-Mediated Aldol Reactions. An oven-dried 25-mL Schlenk-type reaction tube with male joint and female 90° angled adapter was flushed with N_2 and charged with 0.57 mL (3.1 mmol) of 2,2,6,6-tetramethylpiperidine, 4 mL of THF, and 1.9 mL of 1.45 M ethylmagnesium bromide in THF (2.8 mmol). The stopcocks were closed securely, and the reaction mixture was heated at 80 °C for 24 h. The solution was cooled to 0 °C, and 0.26 g (1.0 mmol) of ketone **5** in 4 mL of THF was added over a 30-min period. The resulting solution was allowed to stir for 2.5 h at 0 °C, and 4 mL (22 mmol) of HMPA, 4 mL of dioxane, and 2.6 mL (10.9 mmol) of neat triisopropoxytitanium chloride were added sequentially. The solution was clear yellow or brown upon addition of triisopropoxytitanium chloride. The mixture was sonicated for 2 h (25–45 °C bath temperature) in a Branasonic Laboratory Sonicator and cooled to 0 °C, and the aldehyde (2.0 mmol) was added dropwise. The resulting solution was stirred for 2 h at 0 °C and then poured into 25 mL of saturated NH_4F solution. The layers were separated, and the aqueous layer extracted with 20 mL of ether. The tenacious emulsion that formed was destroyed by filtration of the aqueous layer. The solid precipitate was rinsed thoroughly with ether, and the layers of the combined filtrates were separated. The aqueous layer was further extracted with two 20-mL portions of ether. The combined organics were dried and concentrated as usual to obtain the crude aldol products. Ratios of diastereomers were determined by integration of the relevant peaks in the ^1H NMR. Purification was effected by flash chromatography (5:95 ether–hexanes as eluant, unless otherwise specified).

(+)-(3*S*,5*S*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-2,2-dimethyl-4-heptanone (17a). $[\alpha]_D$: +10.1° (*c* = 0.8, $CHCl_3$). ^1H NMR (300 MHz): δ 0.08 (s, 3), 0.12 (s, 3), 0.92 (s, 9), 0.96 (s, 9), 0.97 (d, 3, *J* = 2.2), 1.22 (d, 3, *J* = 6.4), 2.84–3.20 (m, 1), 3.52 (d, 1, *J* = 4.6), 3.70 (dd, 1, *J* = 1.6, 4.6), 4.88 (dq, 1, *J* = 6.4, 7.8). ^{13}C NMR (100 MHz): δ −4.36, −3.16, 10.42, 17.94, 18.66, 26.34, 27.31, 35.90, 39.35, 70.76, 83.37. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.36; H, 11.09.

(+)-(3*S*,5*S*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-2,2,5,7-tetramethyl-4-octanone (17b). $[\alpha]_D$: +34.6° (*c* = 0.90, $CHCl_3$). IR (film): 3560, 3000, 1710 cm^{-1}. ^1H NMR (400 MHz): δ 0.017 (s, 3), 0.053 (s, 3), 0.87 (d, 3, *J* = 6.8), 0.95 (s, 9), 0.98 (d, 6, *J* = 6.8), 0.98 (s, 9), 1.71 (d, 1, *J* = 4.6), 1.82 (d sept 1, *J* = 6.8, 2.6), 3.10 (dq, 1, *J* = 9.4, 6.8), 3.62 (ddd, 1, *J* = 9.4, 4.6, 2.6), 3.90 (s, 1). ^{13}C NMR (100 MHz): −4.23, −3.76, 14.03, 14.67, 18.37, 20.12, 26.03, 26.68, 29.06, 35.79, 45.98, 78.56, 86.76, 216.07. Anal. Calcd for $C_{18}H_{38}O_3Si$: C, 65.40, H, 11.60. Found: C, 65.65; H, 11.54.

(+)-(3*S*,5*S*,6*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-2,2,5,7,7-pentamethyl-4-octanone (17c). $[\alpha]_D$: +51.9° (*c* = 0.32, $CHCl_3$). ^1H NMR (300 MHz): δ 0.04 (s, 3), 0.06 (s, 3), 0.96 (s, 9), 0.96 (s, 9), 9.97 (s, 9), 1.12 (d, 3, *J* = 6.6), 2.30–2.40 (br s, 1), 3.29 (dd, 1, *J* = 6.6, 7.9), 3.40 (d, 1, *J* = 7.9), 3.86 (s, 1). ^{13}C NMR (50 MHz): δ −3.65, −3.58, 18.29, 18.40, 26.07, 26.69, 26.83, 35.69, 35.92, 44.08, 82.48, 86.37. Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70. Found: C, 66.72; H, 11.42.

(+)-(1*R*,2*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-1-phenyl-2,5,5-trimethyl-3-hexanone (17d). $[\alpha]_D$: +38.9° (*c* = 1.0, $CHCl_3$). IR (film): 3560, 1720 cm^{-1}. ^1H NMR (250 MHz): δ 0.013 (s, 3), 0.056 (s, 3), 0.81 (d, 3, *J* = 7.0), 0.93 (s, 9), 1.00 (s, 9), 2.23 (d, 1, *J* = 1.7), 3.23 (dq, 1, *J* = 11.0, 7.0), 4.00 (s, 1), 7.70 (dd, 1, *J* = 1.7, 11.0), 7.32–7.35 (m, 5). ^{13}C NMR (50 MHz): δ −4.47, −3.92, 15.28, 18.33, 25.90, 26.02, 26.63, 35.80, 49.96, 78.32, 86.91, 126.96, 128.07, 128.48, 216.21. Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.96. Found: C, 69.46; H, 9.85.

General Procedure for Hydrolysis and Oxidation of Aldol Products. Method A: Periodic Acid. The experimental procedure was identical with the literature procedure.[18] Methyl esters were prepared by treating an ethereal solution of the crude acid with ethereal diazomethane. Purification was effected by flash chromatography, 10:90 ether–hexanes as eluant.

Method B: Sodium Periodate. The aldol products were desilylated by one of two methods, depending on whether the substrate was a trimethylsilyl or a *tert*-butyldimethylsilyl ether. In the former case the trimethylsilyl group was removed by stirring the aldol products with 5 drops of 1% HCl in 5 mL of CH_3OH per mmol aldol product for 15–30 min at 0 °C. The methanol was removed with a rotary evaporator. The residue was dissolved in ether and dried ($MgSO_4$), and the solvent was removed to obtain the diol product. *tert*-Butyldimethylsilyl groups were removed by treating the aldol product with 5 mL/mmol aldol of 95:5 CH_3CN–HF (48% aqueous solution) for 2–4 h at room temperature. The CH_3CN was removed and the residue was dissolved in ether. The ether solution was dried and concentrated in the normal manner to obtain the diol product.

The diol product was dissolved in 2:1 CH_3OH–H_2O (5 mL per mmol of diol) and 5–10 equiv of $NaIO_4$ was added with stirring. The reaction mixture was allowed to stir at room temperature until TLC (50:49.5:0.5 hexanes–ether–HOAc) showed no starting material remaining. The solid residue was dissolved in a minimum amount of H_2O, and the solution was extracted with $CHCl_3$ (5 × 20 mL). The combined organic extracts were processed as usual to obtain the β-hydroxy acids in 60–90% yields.

(3*S*,5*S*,6*R*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (19b). ^1H NMR (400 MHz): δ 0.89 (d, 3, *J* = 6.7), 0.98 (s, 9), 1.02 (d, 3, *J* = 6.6), 1.08 (d, 3, *J* = 5.8), 1.67 (m, 1), 2.38 (d, 1, *J* = 3.6), 3.07 (dq, 1, *J* = 6.7, 3.5), 3.23 (d, 1, *J* = 7.3), 3.37 (ddd, 1, *J* = 7.5, 3.6, 3.5), 4.00 (d, 1, *J* = 7.3). ^{13}C NMR (75 MHz, C_6D_6): δ 8.8, 18.9, 19.3, 26.3, 31.4, 36.0, 47.4, 76.6, 82.9, 217.3).

(1*S*,2*S*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (19d). Mp: 112–112.5 °C. ^1H NMR (400 MHz): δ 0.94 (s, 9), 1.13 (d, 3, *J* = 6.7), 2.64 (br s, 1), 3.00 (d, 1, *J* = 6.5), 3.19 (dq, 1, *J* = 6.7, 6.7), 3.59 (d, 1, *J* = 6.2), 4.81 (d, 1, *J* = 5), 7.35 (m, 5). ^{13}C NMR (75 MHz): δ 10.44, 26.34, 36.13, 52.15, 74.72, 84.19, 126.01, 128.03, 128.50, 141.12, 220.9.

(3*S*,5*R*,6*S*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (20b). ^1H NMR (400 MHz): δ 0.82 (d, 3, *J* = 6.8), 0.98 (s, 9), 1.02 (d, 3, *J* = 6.5), 1.13 (d, 3, *J* = 7.2), 1.68 (m, 1), 3.02 (dq, 1, *J* =

1.6, 7.3), 3.10 (br s, 1), 3.30–3.50 (br s, 1), 3.51 (dd, 1, J = 1.6, 9.1), 4.01 (s, 1). ^{13}C NMR (75 MHz, C_6D_6): δ 9.7, 18.9, 19.5, 26.3, 30.7, 36.0, 45.7, 75.4, 82.3, 220.0.

(1*R*,2*R*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (20d). ^{1}H NMR (300 MHz): δ 0.94 (s, 9), 1.09 (d, 3, J = 7.2), 3.14–3.25 (br m, 2), 3.25–3.38 (br s, 1), 3.93 (s, 1), 5.11 (d, 1, J = 3.8), 7.25–7.40 (m, 5). ^{13}C NMR (75 MHz): δ 11.2, 26.2, 36.0, 50.8, 72.5, 82.4, 126.1, 127.6, 128.2, 141.2, 218.6.

(3*S*,5*S*,6*S*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (21b). ^{1}H NMR (400 MHz): δ 0.88 (d, 3, J = 6.8), 0.93 (d, 3, J = 6.8), 0.95 (s, 9), 0.97 (d, 3, J = 6.9), 1.82 (double septet, 1, J = 6.9, 2.1), 2.93–2.94 (m, 1), 3.29–3.36 (m, 1), 3.49–3.53 (m, 1), 3.67 (d, 1, J = 2.3), 4.49 (br s, 1). ^{13}C NMR (100 MHz): δ 12.46, 14.47, 19.78, 26.38, 29.95, 35.89, 47.26, 80.34, 85.58, 218.1.

(1*S*,2*R*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (21d). ^{1}H NMR (250 MHz): δ 0.76 (d, 3, J = 6.9), 0.96 (s, 9), 3.38 (d, 1, J = 2.8), 3.42–3.52 (m, 1), 3.72 (d, 1, J = 2.6), 4.53 (d, 1, J = 2.7), 4.55 (d, 1, J = 2.7), 7.35–7.36 (m, 5). ^{13}C NMR (75 MHz): δ 13.37, 26.15, 35.27, 48.31, 78.62, 84.70, 126.86, 128.36, 128.54, 141.75, 217.70.

(3*S*,5*S*,6*S*)-3,6-Dihydroxy-2,2,5,7-tetramethyl-4-octanone (22b). ^{1}H NMR (400 MHz): δ 0.88 (d, 3, J = 6.7), 0.96 (d, 3, J = 6.9), 0.99 (s, 9), 1.01 (d, 3, J = 6.8), 1.77 (dq, 1, J = 3.5, 6.9), 2.28–2.30 (m, 1), 3.04 (d pent, 1, J = 1.7, 6.8), 3.41 (d, 1, J = 7.1), 3.43–3.47 (m, 1), 4.04 (dd, 1, J = 1.2, 7.1). ^{13}C NMR (100 MHz): δ 12.50, 14.53, 19.77, 26.39, 29.99, 35.91, 47.19, 80.41, 85.61.

(1*R*,2*S*,4*S*)-1,4-Dihydroxy-2,5,5-trimethyl-1-phenyl-3-hexanone (22d). ^{1}H NMR (300 MHz): δ 0.87 (d, 3, J = 6.7), 0.99 (s, 9), 2.62 (br s, 1), 3.17 (dq, 1, J = 8.8, 6.7), 3.19 (d, 1, J = 2.0), 4.06 (s, 1), 4.59 (d, 1, J = 8.8), 7.30–7.35 (m, 5). ^{13}C NMR (75 MHz): δ 12.78, 26.38, 35.89, 51.40, 79.27, 85.80, 126.57, 128.32, 128.57, 142.09, 218.2.

(−)-(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic Acid (23b). $[\alpha]_D$: −9.5° (c = 0.4, H_2Cl22). Th ^{1}H NMR spectrum of this material was identical to that reported.[26] ^{13}C NMR (50 MHz): δ 14.59, 16.09, 19.75, 30.67, 42.65, 78.04, 180.96.

(−)-(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (23d). $[\alpha]_D$: −29.3° (c = 0.8, $CHCl_3$). [lit. $[\alpha]_D$ −29.5° (c = 2.03, $CHCl_3$)].[27] ^{1}H NMR (400 MHz): δ 1.16 (d, 3, J = 7.2), 2.85 (dq, 1, J = 3.9, 7.2), 5.19 (d, 1, J = 3.9), 7.27–7.37 (m, 5). ^{13}C NMR (100 MHz): δ 10.27, 46.16, 73.37, 125.93, 127.66, 128.35, 141.01, 180.85.

(+)-(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoic Acid (24b). $[\alpha]_D$ +9.1° (c = 2.2, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of this material were identical with those obtained for its enantiomer, **23b**.

(+)-(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (24d). $[\alpha]_D$: +28.5° (c = 1.2, $CHCl_3$). [lit. $[\alpha]_D$ +29.5° (c = 1.27, $CHCl_3$)].[26] The ^{1}H and ^{13}C NMR spectra were identical with those of its enantiomer, **23d**.

(−)-(2*R*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic Acid (25b). $[\alpha]_D$: −14.3° (c = 1.0, $CHCl_3$). The ^{1}H NMR spectrum of this material was identical with that reported.[18] ^{13}C NMR (50 MHz): δ 9.69, 18.72, 19.02, 30.62, 41.77, 76.93, 181.27.

(−)-(2*R*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (25d). $[\alpha]_D$: −17.5° (c = 2.3, $CHCl_3$). ^{1}H NMR (400 MHz): δ 1.00 (d, 3, J = 7.2), 2.84 (dq, 1, J = 7.2, 9.0), 4.75 (d, 1, J = 9.0), 5.70–6.10 (br s, 1), 7.29–7.39 (m, 5). ^{13}C NMR (100 MHz): δ 14.40, 47.20, 76.60, 126.84, 128.40, 128.80, 141.16, 180.72. Compound **25d** was identified by comparison of its ^{1}H NMR spectrum with that reported.[28]

(+)-(2*S*,3*S*)-3-Hydroxy-2,4-dimethylpentanoic Acid (26b). $[\alpha]_D$: +14.1° (c = 1.1, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra of this material were identical with those obtained for the enantiomer, **25b**.

(+)-(2*S*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (26d). $[\alpha]_D$: +17.8° (c = 2.0, $CHCl_3$). The ^{1}H and ^{13}C NMR spectra were identical with those of the enantiomer, **25d**.

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Supplementary Material Available: Figures 2 and 3 (ORTEP drawings of keto diols **19** and **21**) and ^{1}H and ^{13}C NMR spectra of keto diols **19b**, **19d**, **20b**, **20d**, **21b**, **21d**, **22b**, and **22d** (17 pages). Ordering information is given on any current masthead page.

(26) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Organic Synthyses*; Wiley: New York, 1990, Collect. Vol. VII, p 190.

(27) Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296.

(28) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

Stereocontrolled Preparation of *cis*- and *trans*-2,6-Dialkylpiperidines via 1-Acyldihydropyridine Intermediates. Synthesis of (±)-Solenopsin A and (±)-Dihydropinidine

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The stereoselective reduction of 1-(*tert*-butoxycarbonyl)-4-chloro-2,6-dialkyl-1,2-dihydropyridines **6** and **22** was studied. Reduction of **6** with Et_3SiH/TFA gave the *cis*-2,6-dialkyl-1,2,5,6-tetrahydropyridine **7** as the major product. The stereoselectivity was reversed by reducing **6** with $NaBH_3CN$/TFA, which gave predominantly the *trans*-2,6-dialkyltetrahydropyridine **10**. Catalytic hydrogenation of **7** and **10** gave the corresponding *N*-Boc-*cis*(or *trans*)-2,6-dialkylpiperidines. Regioselective hydrogenation of **6** gave the 1,2,3,4-tetrahydropyridine **18**, which on treatment with $NaBH_3CN$/TFA provided a 90:10 mixture of *trans*- and *cis*-piperidines **15** and **16**. More vigorous hydrogenation of **6** afforded the *cis*-piperidine **15** with 96% stereoselectivity. Similar stereoselective reductions of dihydropyridine **22** were carried out. Stereoselective reductions of dihydropyridines **6** and **22** were utilized in the synthesis of (±)-solenopsin A and (±)-dihydropinidine from 4-chloropyridine in six and five steps, respectively.

Alkaloids containing a 2,6-disubstituted piperidine ring are abundant in nature and many exhibit significant biological activity.[2] Numerous cis-2,6-disubstituted piperidines can be stereoselectively prepared by simple reduction

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