Titanium and Boron Mediated Aldol Reactions of β-Hydroxy Ketones

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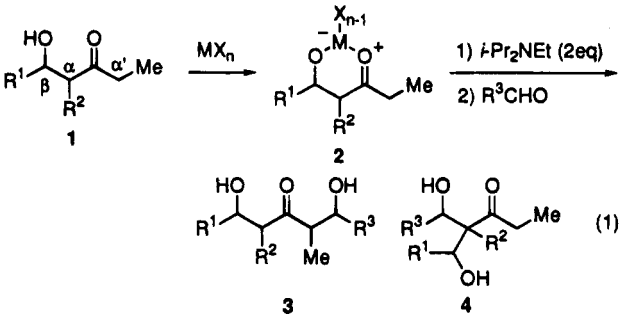
The reaction of enolates derived from titanium and boron complexes of β-hydroxy ketones with aldehydes afforded aldol products in good to excellent yields. Whereas the boron mediated reactions gave exclusively *anti* aldol products derived from the reaction at C_α, the titanium mediated reactions produced primarily *syn* aldol products from reaction at $C_{\alpha'}$. The product selectivities observed in the titanium mediated aldol reactions were highly dependent on the substitution pattern of the starting β-hydroxy ketone.

The aldol reaction is a powerful tool for the stereoselective construction of acyclic molecules.[1] Numerous approaches have been examined for controlling the stereochemical outcome of the reaction. Strategies for controlling enolate facial selectivity in the reaction with an achiral aldehyde have included the use of chiral auxiliaries,[2] conformational preferences of an enolate derived from a chiral ketone,[2,3] and internal metal chelation.[4,5] An alternative and previously unexamined means of controlling stereochemistry in the aldol reaction involves the generation and subsequent enolization of a metal (Ti(IV), B) complex **2** derived from a β-hydroxy ketone **1** and a Lewis acid. In addition to eliminating the need for a protecting group on the β-oxygen of the ketone substrate, this approach provides the opportunity to explore a variety of regio- and stereochemical outcomes (→ **3** and/or **4**) through the use of these readily formed complexes (eq 1).[6–8] Herein, we present a preliminary survey of aldol reactions of this type and report that moderate to excellent control can be obtained depending on the choice of metal and the initial ketone stereochemistry and substitution.[9]



1 2 3 4

The first substrate examined, 1-hydroxy-3-pentanone (**5**),[10] was chosen to evaluate the feasibility of the reaction as well as to determine what, if any, regiochemical issues needed to be addressed. Thus, $TiCl_4$[11,3b] was added to a methylene chloride solution of **5** at −78 °C. The resulting yellow slurry was warmed to 0 °C to insure complete complex formation. Treatment of the complex with *i*-Pr_2NEt (2.1 equiv) at −78 °C (deep red solution), followed by the addition of isobutyraldehyde, afforded a 62:38 mixture of regioisomers **6** and **7** in a combined 68% yield. The major regioisomer **6**, formed from the reaction at the α'-position, was produced as an 87:13 *syn:anti* mixture. Only the *anti* diastereomer **7** was produced from reaction at the α-position (entry 1, Table 1).

Syn-6 and **anti-6** were easily differentiated using the ^{1}H and ^{13}C NMR data of the corresponding primary TBS derivatives **8**.[12] The *anti* stereochemistry of **7** was proven using the ^{1}H and ^{13}C NMR data of the corresponding

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1995.

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(3) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (c) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127. (d) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182. (e) Evans, D. A.; Calter, M. A.; *Tetrahedron Lett.* **1993**, *34*, 6871.

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(8) For a related approach, see: Xiang, Y.; Olivier, E.; Ouimet, N. *Tetrahedron Lett.* **1992**, *33*, 457.

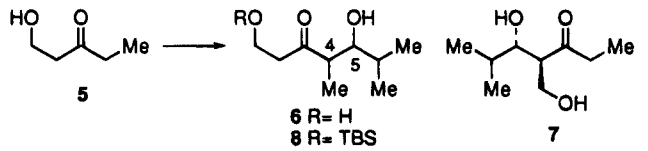
(9) For an examination of lithium mediated aldol reactions of β-hydroxy ketones, see: (a) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681. (b) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-b.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.

(10) Hitchcock, S. R.; Perron, F.; Martin, V. A.; Albizati, K. F. *Synthesis* **1990**, 1059.

(11) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215, and references therein.

0022-3263/95/1960-3013$09.00/0

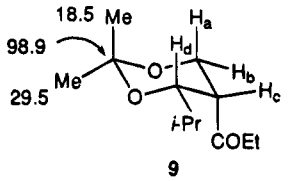
Table 1



ENTRY	CONDITIONS	YIELD (%)	RATIO (6:7)[a]
1	1) $TiCl_4$, -78 ° to 0 °C; *i*-Pr_2NEt, -78 °C, 30 min. 2) *i*-PrCHO, -78 °C	68	62 : 38 (*syn:anti*, 87:13) (only *anti*)
2	1) $TiCl_4$, -78 °C; *i*-Pr_2NEt, -78 ° to 0 °C, 5 min. 2) *i*-PrCHO, -78 °C	35[b]	100 : 0 (*syn:anti*, 92:8)
3	1) $PhBCl_2$, -78 ° to 0 °C; *i*-Pr_2NEt, -78 °C, 30 min. 2) *i*-PrCHO, -78 °C to rt	59	<5 : >95 (only *anti*)

[a] Ratios determined by GC analysis of the diacetates prepared from the crude product mixture.
[b] Yield calculated based on the ratio (^{1}H NMR) of **6** versus the inseparable 1-hydroxy-4-methyl-3,7-nonanedione (see text).

dimethyl acetonide derivative **9**. The ^{13}C NMR data of **9** was consistent with the chair conformation.[13] Additionally, no diaxial couplings were observed in the ^{1}H NMR spectrum.

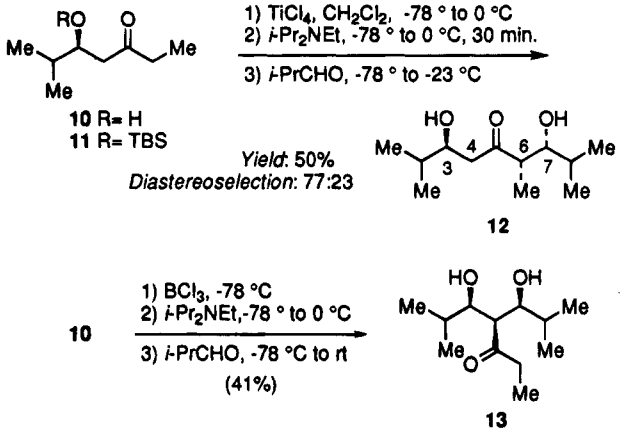


$J(H_a\text{-}H_c)$ = 3.8 Hz
$J(H_b\text{-}H_c)$ = 1.3 Hz
$J(H_c\text{-}H_d)$ = 3.2 Hz

When the titanium enolate derived from **5** was allowed to briefly warm to 0 °C,[9b] diol **6** was obtained in diminished yield but with comparable diastereoselectivity. Significantly, while none of the regioisomeric diol **7** was produced (entry 2, Table 1), a byproduct not observed in entry 1 (1-hydroxy-4-methyl-3,7-nonanedione) was also formed (22%). The formation of this compound can be explained by the apparent decomposition of the α-enolate at 0 °C to ethyl vinyl ketone and its subsequent 1,4-reaction with the regioisomeric α′-enolate.[14]

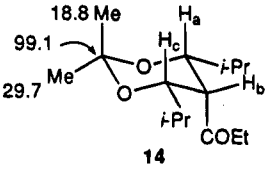
Next, hydroxy ketone **10**, containing an isopropyl group at the β-position, was examined. The titanium mediated aldol reaction of **10** with isobutyraldehyde produced diol **12** with 77:23 diastereoselectivity (50%) (Scheme 1).[15,16]

Scheme 1



Beta elimination of the intermediate aldolates was a problem with this reaction and increased with longer reaction times and at temperatures > −23 °C. Thus, a 12% yield of a mixture of *syn*/*anti* 3,4-anhydro and 6,7-anhydro aldol products was also obtained.[17] The stereochemical assignment of **12** was made on the basis of a direct comparison with material obtained after desilylation of the *minor* component from the known[3e] related boron mediated aldol reaction of silyloxy ketone **11**.[18]

The boron mediated aldol reactions of **5** and **10** with isobutyraldehyde were also examined. When the reaction with **5** was carried out using $PhBCl_2$,[19,3e] a 59% yield of **7** was obtained with excellent regio- and diastereoselectivity (entry 3, Table 1). Using the more Lewis acidic BCl_3,[20] the aldol reaction of **10** produced *meso* diol **13** as the major product (Scheme 1). As found with the boron mediated reaction of the unsubstituted β-hydroxy ketone **5**, none of the regioisomeric diols arising from reaction at the α′-position were detected. The ^{1}H and ^{13}C NMR data of the corresponding acetonide **14** confirmed the stereochemistry of **13**.[13]



$J(H_a\text{-}H_b) = J(H_b\text{-}H_c)$ = 3.0 Hz

In addition to the excellent regioselectivity obtained in the boron mediated reactions, the selective formation of *anti* aldol adducts from presumed *Z*(O)-enolates is significant.[1] This stereochemical outcome can be satisfactorily explained utilizing a boat transition state.[21,5e] With the presumed enolate locked in an *s*-cis conformation, a chair transition state would be inaccessible.

(12) (a)

	syn-8	*anti*-8
$J(H_4\text{–}H_5)$	2.7	7.2 Hz
C_5	75.9	78.2 ppm
C_4-Me	8.3	13.6 ppm

(b) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.
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(14) Quenching (saturated NH_4Cl) of the reaction mixture in the absence of an aldehyde produced a 21% yield of the byproduct.
(15) This result was obtained using 5.0 eq of isobutyraldehyde.
(16) Ratio determined by integration of the ^{1}H NMR spectrum of the product mixture after silica gel chromatography. Attempted GC analysis of the corresponding bisacetates resulted in partial elimination. Ratio refers to **12** versus the sum of the other isomers.
(17) A quantitative recovery of 4-deutero-1-hydroxy-3-pentanone was obtained when the enolate was quenched with 5% DCl/D_2O suggesting the regioselective generation of a stable enolate.
(18) A reversal of selectivity in the aldol reactions of protected versus unprotected substrates has previously been observed: ref 9a.
(19) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729.
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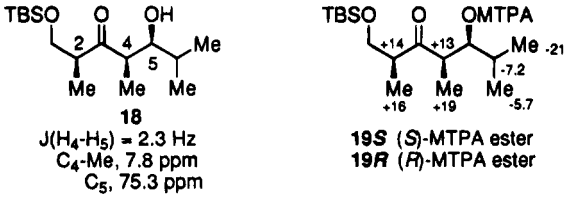
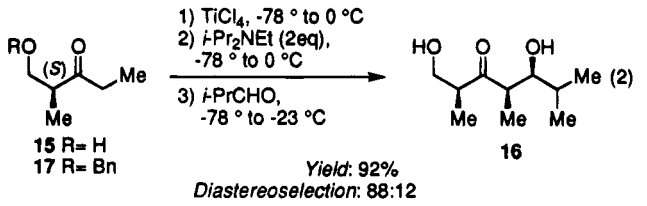


Figure 1. Diagnostic NMR data for **18**, and $\Delta\delta$ values ($\delta_S - \delta_R$) for MTPA esters **19*S*** and **19*R***.

Hydroxy ketone **15**, containing an α-methyl group, was prepared in optically active form from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate.[22] The titanium mediated aldol reaction of **15** with isobutyraldehyde produced the *syn,syn* aldol product **16** in 92% yield and with 88:12 diastereoselectivity (eq 2).[23] This result is analogous to the chelation controlled aldol reaction of **17** with aldehydes using tin(II) triflate.[4b]



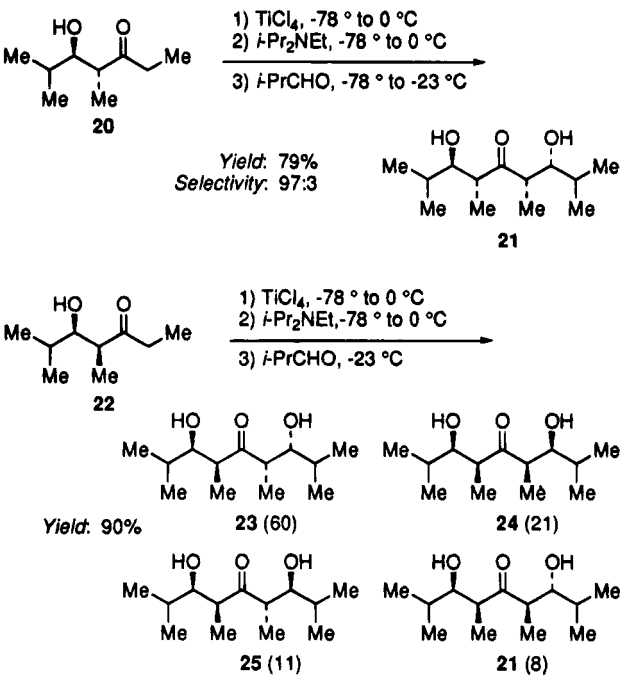
The 4,5 *syn* stereochemistry of **16** was confirmed using the ^1H and ^{13}C NMR data of primary TBS derivative **18**.[12b] The 5-(*S*) stereochemistry was assigned using chemical shift data of Mosher esters **19*S*** and **19*R***, derived from diastereomerically pure **18**, thus proving the overall *syn, syn* relative stereochemistry (Figure 1).[24] This analysis also confirmed that no epimerization of the α-center had occurred during enolization.

Finally, the titanium mediated aldol reactions of the epimeric α,β-disubstituted β-hydroxy ketones **20** and **22** with isobutyraldehyde were examined. With *anti* ketone **20**, excellent stereocontrol was achieved as a 97:3 mixture of known[3b] diol **21** and an *anti* aldol product was produced in 79% yield under standard conditions (Scheme 2). In contrast, *syn* ketone **22** produced a gross mixture (60:21:11:8) of the known[3b] diols **23**, **24**, **25**, and **21**, respectively, in 90% yield.

The results obtained with ketones **20** and **22** appear to be consistent with the trends observed for the monosubstituted ketones **10** and **15**. The titanium mediated aldol reaction with ketone **10** produces, as the major product, the *syn* aldol product that is *anti* to the β-isopropyl group. The major product from the reaction with ketone **15** is the *syn* aldol product that is *syn* to the α-methyl group. These substituent effects appear to be additive as diol **21** is formed almost exclusively from **20**.

In summary, the reactions of enolates derived from titanium and boron complexes of β-hydroxy ketones with aldehydes produce aldol products in good to excellent yields. Whereas the boron mediated reactions produce exclusively *anti* aldol products from reaction at C_α, the titanium mediated reactions produce primarily *syn* aldol products from reaction at $C_{\alpha'}$. In addition, product selectivities observed in the titanium mediated aldol reactions appear to be highly dependent on the substitution pattern of the starting β-hydroxy ketone.

Scheme 2



Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise indicated) at 300 MHz and 75 MHz, respectively. Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh). CH_2Cl_2, *i*-Pr_2NEt, and Et_3N were distilled from CaH_2 under N_2. Analytical GC was performed using a DB-5 5% phenylmethyl silicon column (15 m × 0.53 mm × 1.5 μM film thickness) (J&W Scientific Inc.). Samples were injected at 100 °C, and, after 1 min, the column temperature was raised 10 °C/min to a final temperature of 250 °C. Hydroxy ketones **5**[10] and **22**[3b] were prepared according to the published procedures.

Typical Procedure for Acetylating the Crude Diol Mixtures. To a solution of *ca.* 10–15 mg of the crude diol mixture in *ca.* 0.5–1.0 mL of CH_2Cl_2 at rt under N_2 was added 20–24 drops of Et_3N followed by 10–12 drops of Ac_2O and a few crystals of DMAP. The reaction mixture was stirred at rt for 30–60 min whereupon it was diluted with Et_2O and washed successively with 10% aqueous HCl, H_2O, and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude diacetate mixture was analyzed by GC.

(4*R,5*S**)-1,5-Dihydroxy-4,6-dimethyl-3-heptanone (*syn*-6) and (4*S**,5*S**)-1,5-Dihydroxy-4,6-dimethyl-3-heptanone (*anti*-6). Entry 1, Table 1.** To a solution of 164.3 mg (1.61 mmol) of 1-hydroxy-3-pentanone (**5**) in 6.4 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.19 mL (1.77 mmol) of $TiCl_4$. The resulting yellow slurry was warmed to 0 °C. After 45 min, the slurry was recooled to −78 °C, and 0.59 mL (3.38 mmol) of *i*-Pr_2NEt was slowly added. After 30 min, 0.18 mL (1.93 mmol) of isobutyraldehyde was added to the deep red solution at −78 °C. The reaction mixture was kept at −78 °C for 4 h and then quenched by the addition of saturated aqueous NH_4Cl. The mixture was stirred vigorously while warming to rt. After 30 min, enough water was added to dissolve the solids, and the resulting mixture was extracted with EtOAc (3×). The combined extracts were dried over $MgSO_4$ and concentrated. An aliquot (~10–15 mg) of the crude material was removed and peracetylated. GC analysis of the bisacetate mixture

(22) (a) Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(23) GC analysis of the diacetates prepared from the crude diol mixture indicated an 88:8:4 ratio of isomers. The 4,5 relative stereochemistry of the 8% isomer is believed to be *anti* based upon ^1H and ^{13}C NMR data of the primary TBS ether ($J(H_4-H_5) = 7.2$ Hz; C_5, 78.0 ppm);[12b] however, the overall relative stereochemistry of this product has not been determined.

(24) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(25) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162.

indicated a 54:8:38 mixture produced from ***syn*-6**, ***anti*-6**, and **7**, respectively. The crude material was purified by flash chromatography on silica gel. Elution with 4:1 Et_2O–hexanes, 100% Et_2O, and finally 5:1 Et_2O–EtOAc afforded 122.1 mg (44%) of **6** and 66.6 mg (24%) of **7**. ***Syn*-6**: IR (thin film) ν 3409, 1704 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 3.87 (2H, m), 3.60 (1H, dd, J = 8.6, 3.0 Hz), 2.76 (2H, m), 2.74 (1H, qd, J = 7.2, 3.0 Hz), 1.68 (1H, d sept, J = 8.6, 6.7 Hz), 1.13 (3H, d, J = 7.2 Hz), 1.02 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 215.6, 76.1, 57.6, 48.7, 42.9, 30.7, 19.0, 18.9, 8.6; HRMS for $C_9H_{19}O_3$ [$(M + H)^+$] calcd 175.1334, found 175.1336.

Entry 2, Table 1. To a solution of 168.0 mg (1.64 mmol) of 1-hydroxy-3-pentanone (**5**) in 6.6 mL of dry CH_2Cl_2 at −78 °C, under N_2 was added 0.20 mL of $TiCl_4$. After 15 min, 0.60 mL (3.45 mmol) of i-Pr_2NEt was slowly added to the yellow slurry at −78 °C. The resulting deep red solution was then warmed to 0 °C for 5 min and recooled to −78 °C, and 0.18 mL (1.97 mmol) of isobutyraldehyde was added. The color of the reaction mixture faded slightly over time. After 3 h at −78 °C, the reaction mixture was diluted with saturated aqueous NH_4Cl. The resulting mixture was stirred vigorously at rt for 30 min. Enough water was added to dissolve the solids, and the mixture was extracted with EtOAc (3×). The combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 5:1 Et_2O–hexanes followed by Et_2O, and finally 5:1 Et_2O–EtOAc afforded 136.1 mg of a mixture of ***syn*/*anti*-6** (35%, 92:8) and 1-hydroxy-4-methyl-3,7-nonanedione (22%). The yields were calculated based on the ^1H NMR ratio (75:25) of **6**:1-hydroxy-4-methyl-3,7-nonanedione. Data for the dione: IR (thin film) ν 3474, 1710 cm^{-1}; ^1H NMR δ 3.85 (2H, br q, J = 5.3 Hz), 2.71 (2H, m), 2.58 (2H, m), 2.42 (4H, m), 1.95 (1H, m), 1.66 (1H, m), 1.11 (3H, d, J = 7.0 Hz), 1.04 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 214.9, 211.0, 57.8, 45.7, 42.6, 39.3, 35.9, 26.2, 16.2, 7.7.

(3*S,4*S**)-3-Hydroxy-4-(hydroxymethyl)-2-methyl-5-heptanone (7). Entry 3, Table 1.** To a solution of 535.0 mg (5.24 mmol) of 1-hydroxy-3-pentanone (**5**) in 21 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.71 mL (5.50 mmol) of $PhBCl_2$. The resulting colorless solution was warmed to 0 °C. After 30 min, the solution was recooled to −78 °C, and 1.92 mL (11.0 mmol) of i-Pr_2NEt was slowly added, producing a colorless slurry. After 30 min, 0.71 mL (7.86 mmol) of isobutyraldehyde was added at −78 °C. The reaction mixture was allowed to slowly warm to rt. After 40 h, the reaction mixture was recooled to 0 °C and diluted with 6 mL of MeOH and 2 mL of 30% aqueous H_2O_2. The mixture was warmed to rt for 2 h and concentrated *in vacuo*. The residue was diluted with saturated aqueous NH_4Cl and extracted with EtOAc (4×). The combined extracts were dried over $MgSO_4$ and concentrated. A small aliquot (~10–15 mg) was peracetylated, and the acetates were analyzed by GC. The *trans* isomer from **7** predominated (>95%). Trace amounts (<5%)of ***syn*/*anti*-6** were also detected. The remainder of the crude material was purified by flash chromatography on silica gel. Elution with 3:1 Et_2O–hexanes afforded 536.4 mg (59%) of pure **7**: IR (thin film) ν 3429, 1706 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 3.92 (2H, d, J = 5.2 Hz), 3.51 (1H, dd, J = 7.0, 4.6 Hz), 2.99 (1H, td (apparent q), J = 5.2, 4.6 Hz), 2.66, 2.57 (2H, ABX, J_{AB} = 18.5, J_{AX} = 7.2, J_{BX} = 7.2 Hz), 1.74 (1H, oct, J = 6.8 Hz), 1.06 (3H, t, J = 7.2 Hz), 0.98 (3H, d, J = 6.7 Hz), 0.91 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 216.5, 76.6, 62.2, 54.8, 38.1, 31.6, 19.4, 17.2, 6.8. Anal. Calcd for $C_9H_{18}O_3$ (2.15% H_2O found): C, 60.71; H, 10.43. Found: C, 60.62; H, 10.27.

(3*S,4*S**)-3-Acetoxy-4-(acetoxymethyl)-2-methyl-5-heptanone:** ^1H NMR δ 5.06 (1H, dd, J = 7.4, 5.3 Hz), 4.26, 4.20 (2H, ABX, J_{AB} = 11.1, J_{AX} = 5.6, J_{BX} = 8.5 Hz), 3.19 (1H, ddd, J = 8.5, 7.4, 5.7 Hz), 2.52 (2H, q, J = 7.3 Hz), 2.03 (3H, s), 2.03 (3H, s), 1.87 (1H, sept d, J = 6.8, 5.3 Hz), 1.05 (3H, t, J = 7.3 Hz), 0.93 (3H, d, J = 6.8 Hz), 0.93 (3H, d, 6.7 Hz).

(4*R,5*S**)-1-((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyl-5-hydroxy-3-heptanone (*syn*-8) and (4*S**,5*S**)-1-((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyl-5-hydroxy-3-heptanone (*anti*-8).** To a solution of 163.9 mg (0.941 mmol) of diol **6** (~9:1, *syn*:*anti*) in 2.5 mL of dry CH_2Cl_2 at rt under N_2 was added 0.16 mL of Et_3N followed by 170 mg of TBSCl and a catalytic amount of DMAP. After 2 days, starting diol was still present, and 0.16 mL of i-Pr_2NEt, TBSCl (~100 mg) and DMAP (~1 mg) were added. After 3 h, starting diol was completely consumed. The reaction mixture was diluted with Et_2O and poured into 5% aqueous HCl. The organic extract was washed with H_2O and brine, the aqueous washes were reextracted once with Et_2O, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 5:1 to 4:1 to 3:1 hexanes–Et_2O afforded 127.4 mg of ***syn*-8**, 24.7 mg of ***anti*-8** (total, 56%), and 56.8 mg (22%) of 4,5-anhydro-**8**. ***Syn*-8**: IR (thin film) ν 3493, 1707, 1093 cm^{-1}; ^1H NMR δ 3.91 (2H, dd (apparent t), J = 6.4, 5.8 Hz), 3.59 (1H, br dt, J = 8.7, 3.0 Hz), 2.84 (1H, d, J = 3.4 Hz), 2.74 (1H, qd, J = 7.1, 2.7 Hz), 2.69 (2H, m), 1.67 (1H, d sept, J = 8.7, 6.7 Hz), 1.12 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 6.5 Hz), 0.88 (9H, s), 0.86 (3H, d, J = 6.7 Hz), 0.06 (6H, s); ^{13}C NMR δ 214.7, 75.9, 59.2, 48.9, 43.8, 30.5, 25.8, 19.2, 18.9, 18.2, 8.3. Anal. Calcd for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18. Found: C, 62.32; H, 11.13. ***Anti*-8**: ^1H NMR δ 3.91 (2H, m), 3.46 (1H, m), 2.78 (1H, pent, J = 7.2 Hz), 2.80–2.62 (3H, m), 1.76 (1H, sept d, J = 6.8, 4.5 Hz), 1.10 (3H, d, J = 7.1 Hz), 0.96 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.7 Hz), 0.88 (9H, s), 0.06 (6H, s); ^{13}C NMR δ 215.1, 78.2, 58.7, 49.5, 45.2, 30.3, 25.8, 20.0, 18.2, 15.7, 13.6.

(2*S,3*S**)-6-Dimethyl-2-(1-methylethyl)-3-(1-propanone)-1,5-dioxolane (9).** A solution of 89.2 mg (0.512 mmol) of diol **7** in 2 mL of 2,2-dimethoxypropane containing a catalytic amount of PPTS was stirred at rt under Ar. After 20 h, the reaction was heated to 85 °C. After 4 h at 85 °C, the reaction was allowed to cool to rt, and the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel. Elution with 5:1 hexanes–Et_2O afforded 88.8 mg (81%) of acetonide **9** as a colorless oil: IR (thin film) ν 1696 cm^{-1}; ^1H NMR δ 4.13, 3.91 (2H, ABX, J_{AB} = 12.5, J_{AX} = 3.8, J_{BX} = 1.3 Hz), 3.51 (1H, dd, J = 10.0, 3.3 Hz), 2.81 (2H, q, J = 7.2 Hz), 2.46 (1H, ddd (apparent td), J = 3.8, 3.3, 1.3 Hz), 1.55 (1H, dsept, J = 10.0, 6.6 Hz), 1.47 (6H, s), 1.04 (3H, t, J = 7.2 Hz), 0.93 (3H, d, J = 6.5 Hz), 0.87 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 212.2, 98.9, 75.5, 61.2, 50.1, 36.4, 31.1, 29.5, 19.5, 18.5, 18.0, 7.3. Diagnostic ^{13}C NMR peaks were assigned using an HETCOR NMR experiment.

(±)-3-Hydroxy-2-methyl-5-heptanone (10). To a solution of 7.0 mL (50.0 mmol) of i-Pr_2NEt in 125 mL of THF at 0 °C under N_2 was slowly added 31.3 mL of 1.6 *M* n-BuLi in hexanes. After 10 min, the LDA solution was cooled to −78 °C and 4.48 mL (50.0 mmol) of methyl ethyl ketone was slowly added. After 45 min, 5.0 mL (55.0 mmol) of isobutyraldehyde was slowly added to the enolate at −78 °C. After 30 min, the reaction was quenched at −78 °C by the addition of 100 mL of 5% aqueous HCl. After warming, the mixture was extracted with Et_2O and washed with H_2O and brine, the aqueous washes were reextracted once with Et_2O, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 2:1 hexanes–Et_2O followed by 3:2 hexanes–Et_2O afforded 5.43 g (75%) of hydroxy ketone **10** as a colorless oil: IR (thin film) ν 3457, 1711 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 3.81 (1H, ddd, J = 9.3, 5.7, 2.8 Hz), 2.60, 2.49 (2H, ABX, J_{AB} = 17.3, J_{AX} = 2.8, J_{BX} = 9.3 Hz), 2.48 (2H, q, J = 7.3 Hz), 1.68 (1H, sept d, J = 6.9, 5.7 Hz), 1.07 (3H, t, J = 7.3 Hz), 0.94 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.9 Hz); ^{13}C NMR δ 212.8, 72.1, 45.4, 36.6, 32.9, 18.1, 17.5, 7.3. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.31; H, 11.15.

(3*S,6*S**,7*R**)-3,7-Dihydroxy-2,6,8-trimethyl-5-nonanone (12).** To a solution of 223.0 mg (1.55 mmol) of hydroxy ketone **10** in 6.2 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.19 mL (1.70 mmol) of $TiCl_4$. The yellow slurry was warmed to 0 °C. After 30 min, the resulting cream colored slurry was cooled to −78 °C, and 0.57 mL (3.25 mmol) of i-Pr_2NEt was slowly added. The resulting light orange slurry was warmed to 0 °C. After 30 min, the deep red solution was cooled to −78 °C, and 0.70 mL (7.73 mmol) of isobutyraldehyde was added dropwise. The reaction mixture was warmed to −23 °C and stirred at −23 to −18 °C for 5.75 h (the color faded slightly over time). The reaction was quenched by the addition

of saturated aqueous NH_4Cl. The resulting mixture was stirred vigorously at rt for 1 h, and enough water was added to dissolve the solids. The resulting mixture was extracted with EtOAc (3×), and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 3:2 followed by 1:1, and finally 1:2 hexanes−Et_2O afforded 168.8 mg (50%) of aldol products, with **12** predominating (diastereoselection 77:23), and 36.4 mg (12%) of a mixture of *syn*/*anti* 3,4-anhydro-**12** and 6,7-anhydro-**12**. A sample of pure **12** was obtained by subjecting the product mixture to flash chromatography again: IR (thin film) ν 3444, 1702 cm^{-1}; ^1H NMR ($CDCl_3$−D_2O) δ 3.85 (1H, m), 3.62 (1H, dd, J = 8.7, 2.9 Hz), 2.74 (1H, qd, J = 7.1, 2.9 Hz), 2.62 (2H, m), 1.69 (2H, m), 1.12 (3H, d, J = 7.1 Hz), 1.03 (3H, d, J = 6.6 Hz), 0.95 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.7 Hz), 0.87 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 216.3, 75.9, 72.6, 49.2, 44.6, 33.1, 30.7, 19.2, 18.9, 18.3, 17.7, 8.5. Anal. Calcd for $C_{12}H_{24}O_3$ (1.21% H_2O found): C, 65.82; H, 11.18. Found: C, 66.20; H, 11.29.

(3*S,6*R**,7*S**)-3,7-Dihydroxy-2,6,8-trimethyl-5-nonanone.** To a solution of 666.0 mg (2.58 mmol) of (±)-5-((*tert*-Butyldimethlsilyl)oxy)-6-methyl-3-heptanone (**11**) in 10.3 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.40 mL (3.09 mmol) of $PhBCl_2$.[3e] To the clear, colorless solution was added 0.58 mL (3.35 mmol) of *i*-Pr_2NEt. After 30 min at −78 °C, the solution was warmed to 0 °C. After 30 min, the slightly yellow solution was recooled to −78 °C, and 0.28 mL (3.09 mmol) of isobutyraldehyde was added. After 2 h, the reaction was quenched at −78 °C by the addition of 8 mL of MeOH. The mixture was warmed to 0 °C, and 3 mL of 30% aqueous H_2O_2 was added. The resulting mixture was allowed to gradually warm to rt overnight. The mixture was concentrated *in vacuo*, and the residue was extracted with Et_2O and washed successively with 10% aqueous HCl, H_2O, and brine. The aqueous washes were reextracted once with Et_2O, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 1:1 Et_2O−hexanes followed by 2:1 Et_2O−hexanes afforded 458 mg (82%) of the (3*S**,7*S**) diol and **12**. The ratio was comparable to the reported ratio (87:13)[3e] as judged by ^1H NMR analysis. Pure (3*S**,7*S**) diol was obtained by recrystallization from hexanes. IR (min oil mull) ν 3452, 3401, 1711 cm^{-1}; ^1H NMR ($CDCl_3$−D_2O) δ 3.84 (1H, m), 3.55 (1H, dd, J = 8.6, 2.9 Hz), 2.73 (1H, qd, J = 7.2, 2.9 Hz), 2.64 (2H, m), 1.69 (2H, m), 1.14 (3H, d, J = 7.1 Hz), 1.02 (3H, d, J = 6.5 Hz), 0.95 (3H, d, J = 6.9 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 217.0, 76.3, 72.1, 48.6, 44.8, 33.0, 30.6, 18.9, 18.9, 18.3, 17.6, 8.8. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.73; H, 10.91.

(3*R,4*R**,1′*S**)-3-Hydroxy-4-(1′-hydroxy-2′-methylpropyl)-2-methyl-5-heptanone (13).** To a solution of 218.2 mg (1.51 mmol) of hydroxy ketone **10** in 4.5 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 1.6 mL of 1.0 *M* BCl_3 in CH_2Cl_2. After 30 min, 0.55 mL (3.18 mmol) of *i*-Pr_2NEt was slowly added to the slightly cloudy, light yellow mixture at −78 °C. After 20 min, the clear, colorless reaction mixture was warmed to 0 °C. After 15 min, the resulting yellow solution was recooled to −78 °C, and 0.21 mL (2.27 mmol) of isobutyraldehyde was added. The reaction mixture was allowed to slowly warm to rt. By TLC, there appeared to be no reaction until the temperature reached rt. After 24 h at rt, the reaction mixture was cooled to 0 °C, and 5 mL of MeOH followed by 1.5 mL of 30% aqueous H_2O_2 were added. The resulting mixture was stirred overnight at rt and then concentrated *in vacuo*. The residue was diluted with EtOAc and washed successively with 10% aqueous HCl, 5% aqueous $NaHCO_3$, and brine. The aqueous washes were reextracted once with EtOAc, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 3:1, 2:1, and finally 1:1 hexanes−Et_2O afforded 132.7 mg (41%) of diol **13**. The material was further purified by recrystallization from hexanes: mp 47−48 °C; IR (min oil mull) ν 3524, 3366, 1703, 1690 cm^{-1}; ^1H NMR δ 3.58 (2H, br q, J = 6.5 Hz), 3.04 (1H, t, J = 5.4 Hz), 2.81 (2H, d, J = 7.4 Hz), 2.63 (2H, q, J = 7.2 Hz), 1.72 (2H, oct, J = 6.7 Hz), 1.04 (3H, t, J = 7.2 Hz), 0.95 (6H, d, J = 6.8 Hz), 0.94 (6H, d, J = 6.6 Hz); ^{13}C NMR δ 218.9, 77.3, 54.1, 40.4, 31.4, 19.4, 16.9, 6.7. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.69; H, 11.50.

(2*R,3*R**,4*S**)-2,4-Bis-(1-methylethyl)-6-dimethyl-3-(1-propanone)-1,5-dioxolane (14).** A mixture of 23.7 mg (0.110 mmol) of diol **13** and a few crystals of PPTS in 2 mL of 2,2-dimethoxypropane was stirred at rt for 2 h and at 85 °C for 2 h. The reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel. Elution with 15:1 hexanes−Et_2O afforded 22.6 mg (80%) of acetonide **14** as a colorless solid: mp 85−87 °C; IR (min oil mull) ν 1692 cm^{-1}; ^1H NMR δ 3.40 (2H, dd, J = 10.0, 3.0 Hz), 2.76 (2H, q, J = 7.2 Hz), 2.63 (1H, t, J = 3.0 Hz), 1.49 (3H, s), 1.46 (2H, m), 1.43 (3H, s), 0.99 (3H, t, J = 7.2 Hz), 0.94 (6H, d, J = 6.4 Hz), 0.86 (6H, d, J = 6.7 Hz); ^{13}C NMR δ 212.0, 99.1, 76.5, 53.2, 37.7, 31.2, 29.7, 19.7, 18.8, 18.0, 7.1. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.38; H, 11.38.

(+)-(*S*)-*N*-Methoxy-*N*-methyl-3-hydroxy-2-methylpropionamide. The published procedure[22a] was slightly modified. To a suspension of 20.69 g (212 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride in 212 mL of benzene at 0 °C under N_2 was slowly added 106 mL of 2.0 *M* $AlMe_3$ in toluene via an addition funnel. The ice bath was removed, and the golden yellow solution was stirred at rt for 1 h. A solution of 10.02 g (84.8 mmol) of (2*S*)-methyl 3-hydroxy-2-methylpropionate in 50 mL of benzene was added via cannula with the aid of a 1 × 5 mL rinse. The resulting solution was heated to reflux for 2 h. The orange reaction mixture was cooled to 0 °C and carefully quenched by the *slow* addition of 1 *N* aqueous HCl (~180 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3×), and the combined extracts were dried over $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography on silica gel. Elution with 3:1 Et_2O−EtOAc followed by 15:1 CH_2Cl_2−MeOH afforded 10.06 g (81%) of the desired amide as a light yellow oil: $[\alpha]_D$ +52° (*c* 0.98, $CHCl_3$); IR (thin film) ν 3428, 1639, 1465 cm^{-1}; ^1H NMR δ 3.73 (2H, m), 3.73 (3H, s), 3.21 (3H, s), 3.05 (1H, m), 2.63 (1H, br), 1.17 (3H, d, J = 7.2 Hz); ^{13}C NMR δ 176.7, 64.8, 61.5, 37.6, 32.0, 13.6. Anal. Calcd for $C_6H_{13}NO_3$ (2.62% H_2O found): C, 47.68; H, 8.96; N, 9.27. Found: C, 47.91; H, 9.03; N, 9.30.

(−)-(*S*)-1-Hydroxy-2-methyl-3-pentanone (15). To a solution of 4.53 g (30.78 mmol) of the amide in 60 mL of THF at 0 °C under N_2 was slowly added 71 mL of 1.0 *M* EtMgBr in THF.[22b] The reaction mixture was kept at 0 °C for 1 h and then allowed to warm to rt. After stirring overnight, the reaction mixture was diluted with 5% aqueous HCl. The mixture was extracted with Et_2O, and the extract was washed with brine. The aqueous washes were reextracted twice with Et_2O, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography on silica gel. Elution with 1:1 Et_2O−hexanes followed by 2:1 Et_2O−hexanes afforded 2.35 g (66%) of hydroxy ketone **15** as a colorless oil: $[\alpha]_D$ −22° (*c* 0.85, $CHCl_3$); IR (thin film) ν 3440, 1709 cm^{-1}; ^1H NMR ($CDCl_3$−D_2O) δ 3.74, 3.65 (2H, ABX, J_{AB} = 11.1, J_{AX} = 7.4, J_{BX} = 4.3 Hz), 2.77 (1H, pent d, J = 7.3, 4.3 Hz), 2.59, 2.48 (2H, ABX, J_{AB} = 18.0, J_{AX} = J_{BX} = 7.3 Hz), 1.13 (3H, d, J = 7.3 Hz), 1.06 (3H, t, J = 7.3 Hz); ^{13}C NMR δ 215.5, 64.2, 47.7, 34.7, 13.2, 7.3. Anal. Calcd for $C_6H_{12}O_2$ (1.54% H_2O found): C, 61.09; H, 10.43. Found: C, 61.26; H, 10.07.

(2*S*,4*R*,5*S*)-1,5-Dihydroxy-2,4,6-trimethyl-3-heptanone (16). To a solution of 117.6 mg (1.53 mmol) of hydroxy ketone **15** in 6.1 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.18 mL (1.68 mmol) of $TiCl_4$. The yellow solution was warmed to 0 °C (yellow slurry). After 30 min, the slurry was cooled to −78 °C, and 0.56 mL (3.21 mmol) of *i*-Pr_2NEt was slowly added, producing a deep red solution that was subsequently warmed to 0 °C. After 30 min, the enolate was cooled to −23 °C, and 0.17 mL (1.83 mmol) of isobutyraldehyde was added. After 2 h, the reaction was quenched at −23 °C by the addition of saturated aqueous NH_4Cl. The resulting mixture was stirred at rt for 3 h and diluted with enough water to dissolve the solids. The resulting mixture was extracted with

EtOAc (3×), and the combined extracts were dried over $MgSO_4$ and concentrated. An aliquot (~10–15 mg) was removed and peracetylated. GC analysis of the crude diacetate mixture showed the ratio of stereoisomers to be 88:8:4. The remainder of the crude diol mixture was purified by flash chromatography on silica gel. Elution with 2:1 was followed by 3:1 Et_2O–hexanes, and finally 100% Et_2O afforded 254.4 mg of a mixture of **16** and the major of the two minor isomers and 10.9 mg of the most minor isomer: total yield 265.3 mg (92%); IR (thin film) ν 2967, 1703 cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 3.80, 3.62 (2H, ABX, J_{AB} = 10.6, J_{AX} = 8.6, J_{BX} = 4.2 Hz), 3.64 (1H, m), 3.06 (1H, dqd, J = 8.5, 7.1, 4.2 Hz), 2.90 (1H, qd, J = 6.9, 2.8 Hz), 1.71 (1H, m), 1.08 (3H, d, J = 7.0 Hz), 1.07 (3H, d, J = 7.2 Hz), 1.04 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 218.5, 75.7, 64.7, 48.0, 46.2, 30.7, 19.3, 19.0, 13.6, 8.0. Anal. Calcd for $C_{10}H_{20}O_3$: C, 68.80; H, 10.71. Found: C, 63.56; H, 10.63.

(2*S*,4*R*,5*S*)-1,5-Diacetoxy-2,4,6-trimethyl-3-heptanone: ^1H NMR δ 5.05 (1H, dd, J = 6.6, 5.5 Hz), 4.21, 4.09 (2H, ABX, J_{AB} = 11.0, J_{AX} = 7.4, J_{BX} = 6.0 Hz), 3.11 (1H, dqd, J = 7.4, 7.2, 6.0 Hz), 3.01 (1H, qd, J = 7.0, 5.4 Hz), 2.05 (3H, s), 2.03 (3H, s), 1.85 (1H, oct, J = 6.7 Hz), 1.13 (3H, d, J = 7.2 Hz), 1.08 (3H, d, J = 7.0 Hz), 0.94 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.7 Hz).

(+)-(2*S*,4*R*,5*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-hydroxy-2,4,6-trimethyl-3-heptanone (18). To a solution of 53.1 mg (0.282 mmol) of diol **16** (containing a small amount of the major of the two minor diastereomers) in 1 mL of dry CH_2Cl_2 at 0 °C under N_2 was added ~50 μL (0.35 mmol) of Et_3N followed by 51 mg (0.35 mmol) of TBSCl and a catalytic amount of DMAP. The reaction mixture was stirred at rt overnight, diluted with Et_2O, and poured into 5% aqueous HCl. The Et_2O extract was washed with H_2O and brine, and the aqueous washes were reextracted once with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 6:1 followed by 5:1 hexanes–Et_2O afforded 54.8 mg of diastereomerically pure **18** and 20.6 mg of a mixture of the two diastereomers: total yield: 75.4 mg (88%). **18**: $[\alpha]_D$ +46° (*c* 0.92, $CHCl_3$); IR (thin film) ν 3510, 1701 cm^{-1}; ^1H NMR δ 3.75, 3.56 (2H, ABX, J_{AB} = 9.5, J_{AX} = 9.2, J_{BX} = 4.7 Hz), 3.60 (1H, dt, J = 9.1, 2.5 Hz), 3.03 (2H, m), 2.83 (1H, qd, J = 7.1, 2.3 Hz), 1.66 (1H, d sept, J = 9.2, 6.6 Hz), 1.07 (3H, d, J = 7.1 Hz), 1.01 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.9 Hz), 0.85 (9H, s), 0.83 (3H, d, J = 6.7 Hz), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR δ 218.9, 75.3, 66.6, 48.4, 46.6, 30.2, 25.8, 19.7, 18.8, 18.3, 13.5, 7.8. Anal. Calcd for $C_{16}H_{34}O_3Si$: C, 63.52; H, 11.33. Found: C, 63.35; H, 11.12.

Minor isomer: ^1H NMR δ 3.82, 3.56 (2H, ABX, J_{AB} = 9.9, J_{AX} = 8.5, J_{BX} = 4.8 Hz), 3.48 (1H, m), 2.96 (1H, m), 2.86 (1H, quint, J = 7.2 Hz), 2.66 (1H, d, J = 6.5 Hz), 1.72 (1H, m), 1.10 (3H, d, J = 7.2 Hz), 1.01 (3H, d, J = 7.1 Hz), 0.97 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.7 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR δ 218.6, 78.0, 65.4, 48.9, 48.2, 30.2, 25.9, 20.1, 18.3, 15.8, 13.4, 13.3.

(*S*)- and (*R*)-MPTA esters of 18: The esters were prepared using 9.5–10.0 mg of diastereomerically pure **18**, 2.6 equiv of (*R*)- and (*S*)-MPTA chloride, 3.0 equiv of Et_3N, and 3.0 equiv of DMAP in 0.5 mL of dry CH_2Cl_2. After complete reaction (TLC) the reaction mixtures were quenched by the addition of 5 drops of 3-(dimethylamino)propylamine. The mixtures were diluted with ether and washed successively with 5% aqueous HCl, H_2O, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Analysis of the ^1H NMR spectra of the crude esters revealed each ester to be diastereomerically pure. The esters were purified by flash chromatography on silica gel. Elution with 6:1 hexanes–Et_2O provided the pure esters.

(2*S*,4*R*,5*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-((*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy)-2,4,6-trimethyl-3-heptanone (19*S*): ^1H NMR δ 7.58 (2H, m), 7.41 (3H, m), 5.38 (1H, t, J = 5.7 Hz), 3.79, 3.59 (2H, ABX, J_{AB} = 9.8, J_{AX} = 7.1, J_{BX} = 5.7 Hz), 3.55 (3H, q, J_{H-F} = 1.2 Hz), 3.06 (1H, qd, J = 7.1, 6.0 Hz), 2.95 (1H, m), 1.90 (1H, m), 1.07 (3H, d, J = 7.1 Hz), 1.05 (3H, d, J = 7.0 Hz), 0.88 (3H, d, J = 6.8 Hz), 0.87 (9H, s), 0.82 (3H, s), 0.034 (3H, s), 0.026 (3H, s).

(2*S*,4*R*,5*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-((*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetoxy)-2,4,6-trimethyl-3-heptanone (19*R*): ^1H NMR δ 7.58 (2H, m), 7.39 (3H, m), 5.38 (1H, dd, J = 6.8, 4.8 Hz), 3.76, 3.56 (2H, ABX, J_{AB} = 9.8, J_{AX} = 7.4, J_{BX} = 5.5 Hz), 3.55 (3H, q, J_{H-F} = 1.1 Hz), 3.02 (1H, pent, J = 7.1 Hz), 2.91 (1H, m), 1.92 (1H, m), 1.02 (3H, d, J = 7.1 Hz), 1.01 (3H, d, J = 7.0 Hz), 0.90 (3H, d, J = 6.9 Hz), 0.89 (3H, d, J = 6.8 Hz), 0.86 (9H, s), 0.029 (3H, s), 0.020 (3H, s).

(3*R,4*R**)-2,4-Dimethyl-3-hydroxy-5-heptanone (20).** This compound was prepared using the conditions described by Brown.[25] To a solution of 2.87 g (13.50 mmol) of dicyclohexylchloroborane in 270 mL of pentane at 0 °C under N_2 was added 1.88 mL (13.50 mmol) of Et_3N and 1.32 mL (13.11 mmol) of 3-pentanone. After 1 h at 0 °C, the white slurry was cooled to −78 °C, and 1.25 mL (13.76 mmol) of isobutyraldehyde was slowly added. After 2 h at −78 °C, the reaction was quenched by the addition of 26 mL of MeOH and 4.3 mL of 30% aqueous H_2O_2 (dropwise). The mixture was warmed to 0 °C (30 min), and then to rt. After 3 h, the mixture was concentrated *in vacuo*, and the residue was extracted with Et_2O and washed with H_2O and brine. The aqueous washes were reextracted once with Et_2O, and the combined extracts were dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography on silica gel. Elution with 3:1 followed by 2:1 hexanes–Et_2O afforded 1.265 g (64%) of hydroxy ketone **20** as a colorless oil. Spectroscopic data was in accord with that published:[9a] ^1H NMR ($CDCl_3$–D_2O) δ 3.44 (1H, dd, J = 6.6, 5.0 Hz), 2.78 (1H, pent, J = 7.1 Hz), 2.60, 2.48 (2H, ABX, J_{AB} = 18.2, J_{AX} = J_{BX} = 7.2 Hz), 1.73 (1H, d sept, J = 8.7, 6.7 Hz), 1.12 (3H, d, J = 7.2 Hz), 1.05 (3H, t, J = 7.2 Hz), 0.95 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.7 Hz); ^{13}C NMR δ 217.1, 78.3, 48.1, 36.1, 30.5, 19.9, 15.9, 14.5, 7.4.

(2*R,3*R**,5*S**,6*R**)-3,7-Dihydroxy-2,4,6,8-tetramethyl-5-nonanone (21).** To a solution of 243.0 mg (1.54 mmol) of hydroxy ketone **20** in 6.2 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.19 mL (1.69 mmol) of $TiCl_4$. The resulting yellow solution was warmed to 0 °C. After 30 min, the cream colored slurry was cooled to −78 °C and 0.56 mL (3.22 mmol) of *i*-Pr_2NEt was slowly added. Upon warming to 0 °C, the typical deep red solution formed. After 30 min, the enolate was cooled to −78 °C, and 0.17 mL of isobutyraldehyde was added. The reaction mixture was stirred at −78 °C for 2 h and at −23 °C for 4 h and quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was stirred at rt overnight, and enough water was added to dissolve the solids. The mixture was extracted with EtOAc (3×), and the combined extracts were dried over $MgSO_4$ and concentrated. An aliquot (~10–15 mg) of the crude diol mixture was removed and acetylated. GC analysis indicated a 97:3 ratio of diacetates produced from diol **21** and an *anti* diol. The crude material was purified by flash chromatography on silica gel. Elution with 2:1, 3:2, and 1:2 hexanes–Et_2O afforded 279 mg (79%) of diol **21** and the minor *anti* diol. Diol **21** was isolated in diastereomerically pure form by recrystallization from hexanes. Spectral data was in accord with that previously published:[3b] mp 67–68 °C; IR (min oil mull) ν 3491, 3434, 1704 cm^{-1}; ^1H NMR δ 3.65 (2H, m), 2.97 (2H, m), 2.85 (1H, qd, J = 7.0, 2.5 Hz), 1.79 (1H, m), 1.70 (1H, m), 1.08 (3H, d, J = 7.0 Hz), 1.05 (3H, d, J = 7.0 Hz), 1.03 (3H , d, J = 6.9 Hz), 0.99 (3H, d, J = 6.9 Hz), 0.91 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 219.7, 78.3, 75.6, 49.1, 47.0, 30.5, 29.5, 19.9, 19.7, 19.0, 14.5, 14.3, 7.9. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.85; H, 11.45.

Titanium Mediated Aldol Reaction of Hydroxy Ketone 22. To a solution of 243.8 mg (1.54 mmol) of hydroxy ketone **22** in 6.2 mL of dry CH_2Cl_2 at −78 °C under N_2 was added 0.19 mL (1.69 mmol) of $TiCl_4$. The resulting yellow suspension was warmed to 0 °C for 30 min and recooled to −78 °C, and 0.56 mL of *i*-Pr_2NEt was added. Upon warming to 0 °C, the typical deep red-orange solution formed. After 30 min, the enolate was cooled to −23 °C, and 0.17 mL of isobutyraldehyde was added. After 1 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and stirred at rt for 45 min. Enough water was added to dissolve the solids. The mixture was extracted with EtOAc (3×), and the combined

extracts were dried over $MgSO_4$ and concentrated. An aliquot (~10–15 mg) of the crude diol mixture was removed and peracetylated. GC analysis of the crude diacetate mixture indicated a 60:21:11:8 mixture of diacetate stereoisomers produced from diols **23**, **24**, **25**, and **21**, respectively. The remainder of the crude material was purified by flash chromatography on silica gel. Elution with 2:3, 2:1, and 3:1 Et_2O–hexanes afforded 318.3 mg (90%) of a mixture of diols **23**, **24**, **25**, and **21**.

The assignment of the peaks in the GC was made in the following manner: The purified mixture of diols was peracetylated. The diacetate mixture was then purified by flash chromatography on silica gel. Elution with 5:1, 4:1, 3:1, and finally 2:1 hexanes–Et_2O provided the diacetate corresponding to **23** in diastereomerically pure form. Spectral data was in accord with that previously published.[3b] The diacetate from **21** was assigned based on the previous experiment. The diacetates corresponding to **24** and **25** were obtained as a mixture. The diacetate of **24** was independently prepared in diastereomerically pure form[3b] in order to differentiate the two GC peaks corresponding to the diacetates of **24** and **25**.

(3*R,4*S**,6*S**,7*R**)-3,7-Diacetoxy-2,4,6,8-tetramethyl-5-nonanone:** mp 68–70 °C; ^1H NMR δ 4.88 (2H, dd, J = 9.0, 2.9 Hz), 3.15 (2H, qd, J = 6.7, 2.9 Hz), 2.00 (6H, s), 1.89 (2H, m), 1.01 (6H, d, J = 6.9 Hz), 0.99 (6H, d, J = 7.0 Hz), 0.90 (6H, d, J = 6.6 Hz); ^{13}C NMR δ 211.9, 170.6, 77.5, 45.4, 29.7, 20.7, 19.1, 19.0, 8.8.

Supplementary Material Available: ^1H NMR spectra of compounds ***syn/anti*- 6**, **1-hydroxy-4-methyl-3,7-nonanedione**, **7**, ***syn*-8**, ***anti*-8**, **9**, **12**, **(3*S**,6*R**,7*S**)-3,7-dihydroxy-2,6,8-trimethyl-5-nonanone**, **13**, **14**, **16**, **18**, **19*S***, **19*R***, and **21** (15 pages). This material is contained in libraries on microfilm, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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