BCl_3- and $TiCl_4$-Mediated Reductions of β-Hydroxy Ketones

Christopher R. Sarko, Scott E. Collibee, Allison L. Knorr, and Marcello DiMare*

Department of Chemistry, University of California, Santa Barbara, California 93106

Received August 22, 1995[⊗]

Syn-selective reduction protocols for β-hydroxy ketones are described exploiting the intermediacy of titanium and boron chelates derived from $TiCl_4$ and BCl_3, respectively. Reductions are conducted at −78 °C in CH_2Cl_2 using a wide range of CH_2Cl_2-soluble reducing agents. Added acid-scavenging agents are detrimental to reaction selectivity. An $A^{(1,3)}$-like interaction involving the stereocenter responsible for asymmetric induction provides conformational biasing of the intermediate chelates necessary for high diastereoselectivity.

Introduction

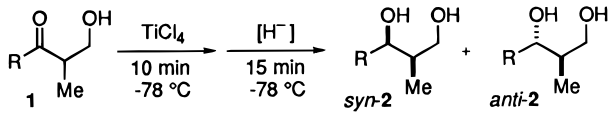
Recently there has been much activity exploiting the presence of proximal hydroxyl groups to control the diastereoselectivity and enantioselectivity of organic reactions.[1] In particular, hydroxyl-directed reductions have been intensively investigated because of the desire to control syn and anti 1,3-diol relationships found in polyacetate- and polypropionate-derived natural products.[2] Having recently developed a protocol to allow the diastereoselective reduction of β-alkoxy ketones,[3] we turned our attention to β-hydroxy ketones. In this paper, the development of $TiCl_4$- and BCl_3-mediated protocols for the syn-selective reduction of some β-hydroxy ketones is reported. $A^{(1,3)}$-like interactions appear to dictate intermediate chelate conformation and hence are responsible for the diastereoselectivity observed in these reductions.

Results and Discussion

$TiCl_4$-Mediated Reductions. Given previous experience in these laboratories,[3] initial experiments were conducted using $TiCl_4$ as the chelating agent and substrates where an adjacent stereocenter would dictate the course of asymmetric induction and the flanking carbonyl substituent was large or sp^2-hybridized (vide infra). As envisaged, the β-hydroxy ketone substrate would first be combined with $TiCl_4$ to form an intermediate chelate **A**, which would then be treated with the desired reducing agent (eq 1). This is akin to what could be called a two-component approach as outlined by Reetz for chelation control.[4]

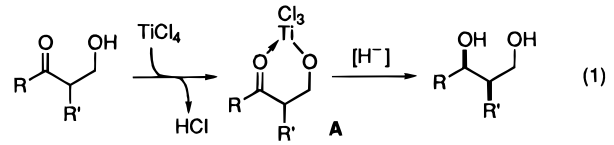
The presumed generation of HCl was worrisome given the presence of Brønsted acid sensitive substrates and nucleophiles. Indeed, initial reductions conducted at 0−25 °C gave large amounts of elimination products. Reducing reaction temperatures to −78 °C, however, improved selectivity and yield. Table 1 displays the

Table 1. $TiCl_4$-Mediated Reductions of β-Hydroxy Ketones 1a and 1b



	1a (R = Ph)		**1b** (R = *t*-Bu)	
reductant	syn:anti[a]	yield (%)[b]	syn:anti[a]	yield (%)[b]
pyr·BH_3	>99:1	81	98:2	84
Et_4NNCBH_3	98:2	85	97:3	88
Bu_4NBH_4	98:2	79	97:3	86
BH_3·THF	56:44	87	58:42	84
morpholine·BH_3	87:13	86	89:11	78
t-$BuNH_2$·BH_3	86:14	84	85:15	82
DIBALH	93:7	80	91:9	76

[a] Determined by ^1H NMR. [b] Isolated yield of diastereomeric mixture.



(1)

results of $TiCl_4$-mediated reductions of ketones **1a** (R = Ph) and **1b** (R = *t*-Bu) using a standard protocol: a cold (−78 °C) CH_2Cl_2 solution of ketone was treated with 1.0 equiv of $TiCl_4$ (10 min), 1.0 equiv of reducing agent (15 min), and then dilute aqueous HCl. The results are notable in that only BH_3·THF failed to provide useful levels of diastereocontrol consistent with a chelation-controlled process.[5] Further, only Me_3N·BH_3 of the nucleophiles screened led to no observed addition.[6]

Although many of the reducing agents used in Table 1 are known to generate hydrogen upon exposure to HCl, no gas evolution was noted during reductions. This suggested that **B** not **A** is the predominate intermediate chelate in reductions (eq 2), because chelate **B** is expected to be a much weaker acid than the HCl generated upon forming **A**. The intermediacy of **B** is reasonable because the elimination of HCl from **B** to afford **A** comes at a

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

(1) For an excellent survey of directed chemistry, see: Hoveyda, A.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(2) For the most recent work in this area, see the following and references cited therein: (a) Bonini, C.; Racioppi, R.; Righi, G.; Rossi, L. *Tetrahedron: Asymmetry* **1994**, *5*, 173−176. (b) Kaneko, Y.; Matsuo, T.; Kiyooka, S. *Tetrahedron Lett.* **1994**, *35*, 4107−4110. (c) Mohr, P. *Tetrahedron Lett.* **1991**, *32*, 2219−2222. (d) Bonini, C.; Bianco, A.; Di Fabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75−80. (e) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190−5192. (f) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

(3) Sarko, C. R.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1994**, *59*, 705−706.

(4) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468.

(5) Stereochemical assignments were made using ^1H and ^{13}C NMR spectroscopies, see: (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324. (b) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294−4299.

(6) The alkylating agents $AlMe_3$ and $ZnEt_2$ were substituted successfully for reducing agents with the syn-to-anti ratio exceeding 98:2 and 74−87% yields.

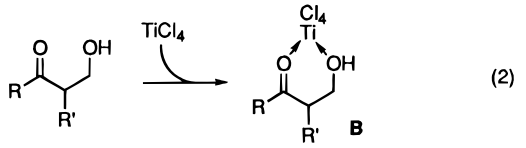
0022-3263/96/1961-0868$12.00/0

Table 2. Effect of Amine Bases on $TiCl_4$-Mediated Reductions of 1a (R = Ph)

base	conversion (%)[a]	syn:anti[a]	yield (%)[b]
none	100	98:2	85
Et_3N	81	94:6	89
2,6-di-*t*-Bu-pyridine	76	96:4	87
2,6-lutidine	57	96:4	87
pyridine	43	93:7	85

[a] Determined by ^1H NMR. [b] Combined yield of recovered starting material and product.

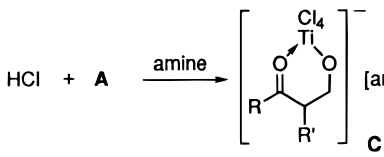
price. Strong H−Cl (102 kcal/mol[7]) and Ti−O (115 kcal/mol[8]) bonds are formed in making **A**, but at the expense of comparably strong O−H (109 kcal/mol[7]) and Ti−Cl (103 kcal/mol[8]) bonds. In addition, titanium(IV) goes from a six-coordinate to a five-coordinate state when it is known to prefer the former.[9] The validity of this analysis is seen in the crystallographically characterized adducts $[TiCl_4(HSC_5H_9)_2]$[10] and $[SnCl_4(C_6H_{11}OH)_2]$[11] and in the report of Maier and co-workers that combining $TiCl_4$ and 4-hydroxy-3,3-dimethyl-2-pentanone gives a solid without the generation of HCl.[12]



(2)

The effect of amines on $TiCl_4$-mediated Et_4NNCBH_3 reductions of **1a** was examined (Table 2). A standard procedure was followed: a cold (−78 °C) CH_2Cl_2 solution of ketone **1a** was treated with 1.0 equiv each of $TiCl_4$ (10 min), amine (5 min), and Et_4NNCBH_3 (15 min) and then dilute aqueous HCl. No precipitates were observed, and interestingly, amines slowed the rate of reduction in a structurally dependent manner. These observations are difficult to explain if chelate **A** was the predominate intermediate. The HCl present due to the formation of **A** should generate amine hydrochloride salts, which are often insoluble in CH_2Cl_2 at −78 °C (e.g., pyridinium chloride). The absence of precipitates, though, does not rule out salt formation. Amine hydrochloride salts and $TiCl_4$ are known to give organic soluble salts such as [amine·H][$TiCl_5$] or [amine·H]$_2$[$TiCl_6$].[13] Thus, the absence of precipitates can be explained by the formation of chelates **C** (eq 3). The dependence of reduction rate on amine structure, however, cannot be explained by this. In chelates **C**, the protonated amine is serving only as a counterion, and its structure should be irrelevant.

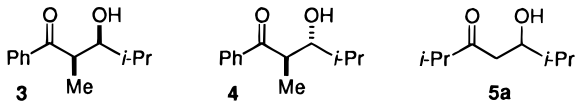
If chelate **B** was the predominate chelate, the effect of amine structure can be explained. The acidity of the chelated hydroxyl group of **B** is enhanced by its association with titanium, but even a large increase of 10 pK_a units would still leave pyridine only half-protonated in



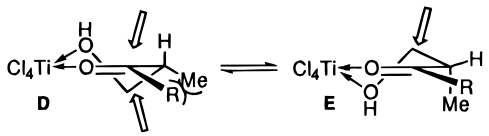
(3)

its presence. Pyridine, an excellent ligand, would thus be available to compete with β-hydroxy ketone for binding sites on titanium, slowing reduction rates. Poorer ligands and stronger bases such as Et_3N would be expected to deprotonate **B** to give **C**. The attenuated Lewis acidity of the titanium present in **C** compared to that in **B** would then account for the slightly slower rates of reduction in the presence of bases such as Et_3N.

Extension of the $TiCl_4$-mediated reduction procedure to other β-hydroxy ketones met with mixed results. Reduction of ketones **1c** (R = C_6H_{11}) or **1d** (R = CH_3) using pyr·BH_3 gave 76:24 (89%) and 63:37 (87%) syn-to-anti ratios, respectively.[14] The reduction protocol also shows pairing of the matched/mismatched type; namely, ketone **3** is reduced with high syn selectivity (98:2, 86%) by Et_4NNCBH_3, while its diastereomer **4** showed little selectivity (67:33, 86%). Reduction of ketone **5a**, which lacks a substituent at the 2-position, was similarly unselective. These results parallel those of Oishi and Nakata using $Zn(BH_4)_2$.[15]



The diastereoselectivity afforded by reduction of chelates **B** parallels that observed with the related β-alkoxy ketone chelates, which adopt half-chair conformations (eq 4).[3,16] When R is small (e.g., **1c** and **1d**), conformer **D** is favored. Since **D** displays no clear facial biasing of the ketone, low reduction selectivity results. When R is large or is an sp^2-hybridized center (e.g., **1a** and **1b**), conformer **E** is favored because it avoids the destabilizing $A^{(1,3)}$-like interaction[17] present in **D** (e.g., the interaction of an ortho carbon of a phenyl group with the stereogenic methyl group). The pseudoaxial methyl group of **E** affords facial biasing of the ketone carbonyl leading to the syn reduction product. With the $TiCl_4$ chelate of ketone **5a**, no diastereoselectivity is observed upon reduction because there is no $A^{(1,3)}$-like interaction to favor one of the two expected half-chair conformers. The substituents within the organic fragment are too far apart, and the chloride ligands of titanium are too far away from the organic fragment.

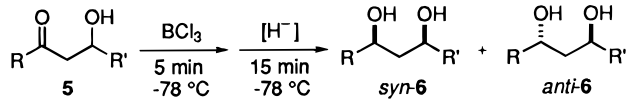


(4)

BCl_3-Mediated Reductions. The failure of $TiCl_4$-mediated reductions of β-hydroxy ketones where 1,3-asymmetric induction was desired pointed toward a boron-based chelating agent. The absence of conforma-

(7) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 2nd ed.; Plenum: New York, 1984; Part A, p 11.
(8) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 37.
(9) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256−272.
(10) Winter, C. H.; Lewkebandara, T. S.; Proscia, J. W.; Rheingold, A. L. *Inorg. Chem.* **1993**, *32*, 3807−3808.
(11) Fournet, F.; Theobald, F. *Inorg. Chim. Acta* **1981**, *52*, 15−21.
(12) Maier, G.; Seipp, U.; Kalinowski, H.-O.; Henrich, M. *Chem. Ber.* **1994**, *127*, 1427−1436.
(13) McAuliffe, C. A.; Barratt, D. S. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1987; Vol. 3, Chapter 31.
(14) Similarly, reduction of ketones **1c** and **1d** with Et_4NNCBH_3 led to 69:31 (84%) and 60:40 (81%) syn-to-anti ratios, respectively.
(15) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.
(16) Sarko, C. R.; Haase, C.; DiMare, M.; Ziller, J. W. Submitted for publication.
(17) (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

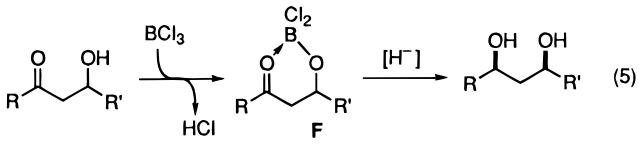
Table 3. BCl_3-Mediated Reductions of β-Hydroxy Ketones 5b−f



ketone	R	R′	reductant	ratio[a] syn:anti	yield[b] (%)
5b	Ph	C_6H_{13}	Bu_4NBH_4	94:6	81
5b	Ph	C_6H_{13}	Et_4NNCBH_3	95:5	80
5b	Ph	C_6H_{13}	pyr·BH_3	92:8	90
5b	Ph	C_6H_{13}	Me_3N·BH_3	92:8	87
5c	Ph	*i*-Pr	Bu_4NBH_4	93:7	79
5c	Ph	*i*-Pr	Et_4NNCBH_3	94:6	84
5c	Ph	*i*-Pr	pyr·BH_3	>95:5	72
5c	Ph	*i*-Pr	Me_3N·BH_3	93:7	90
5d	Ph	Ph	Bu_4NBH_4	>95:5	68
5d	Ph	Ph	Et_4NNCBH_3	95:5	81
5d	Ph	Ph	pyr·BH_3	>95:5	71
5d	Ph	Ph	Me_3N·BH_3	94:6	96
5e	Ph	Me	Bu_4NBH_4	>95:5	65
5e	Ph	Me	Et_4NNCBH_3	>95:5	75
5e	Ph	Me	pyr·BH_3	>95:5	74
5e	Ph	Me	Me_3N·BH_3	>95:5	77
5f	Me	Ph	Bu_4NBH_4	90:10	78
5f	Me	Ph	Et_4NNCBH_3	84:16	91
5f	Me	Ph	pyr·BH_3	81:19	71
5f	Me	Ph	Me_3N·BH_3	81:19	75

[a] Determined by ^{1}H NMR. [b] Isolated yield of diastereomeric mixture.

tionally biasing interactions within the organic fragment in this situation indicated that the substituents of the chelating agent must fulfill this role. Boron chelates then are logical candidates because of the short B−O bond (ca. 1.35 Å) as demonstrated most effectively by the procedures of Narasaka[18] and Prasad.[19] A shortcoming of these procedures is their reliance on pyrophoric trialkylboranes to give dialkylalkoxyborane intermediate chelates. We rationalized that chlorides could replace the alkyl groups of these intermediate chelates, affording a more convenient and practical procedure. The application of commercially available BCl_3 to the syn-selective reductions of β-hydroxy ketones follows (eq 5). The origin of diastereocontrol in this and related systems is also discussed.



(5)

Table 3 shows the result of the application of the following protocol to ketones **5b**−**f**: a cold (−78 °C) CH_2Cl_2 solution of ketone was treated with 1.0 equiv each of BCl_3 (1.0 M, CH_2Cl_2, 5 min) and then reductant. After the reduction was complete (2 h), the solvent was removed. Silica gel and methanol were then added to the reaction flask, and the resulting mixture was stirred for at least 6 h. This workup effectively cleaves intermediate boronate esters under mild conditions. In contrast to the $TiCl_4$-mediated reductions, the range of useful reducing agents was limited in BCl_3-mediated reductions. 9-BBN and DIBALH failed to give any 1,3-diols. THF·BH_3, *t*-$BuNH_2$·BH_3, and morpholine·BH_3 afforded 1,3-diols, but the preference for the syn 1,3-diol was relatively low.[20] As HCl generation is unavoidable if intermediate chelates are to form, the range of behavior displayed by reductants may be due to their modification by this species. Temperature is an important factor in these reductions. Selectivity and yields diminish when reductions are performed at higher temperatures. The use of the coordinating solvent THF led to the complete loss of reduction diastereoselectivity.

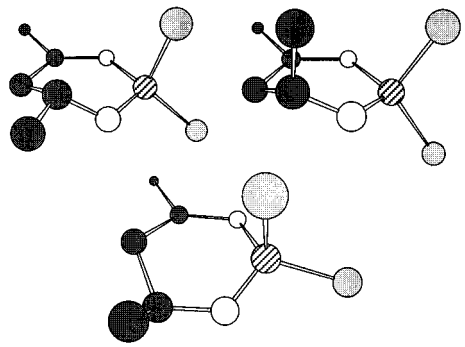


Figure 1. Ab initio minimized structures for conformers of the chelate derived from BCl_3 and 4-hydroxy-2-pentanone: (top left) half-chair conformer with stereogenic methyl oriented pseudoequatorial; (top right) same with stereogenic methyl oriented pseudoaxial; (bottom) boat conformer. Hydrogen atoms have been omitted for clarity.

To support the presence of conformationally biasing interactions in **F** (eq 5), the chelate derived from BCl_3 and 4-hydroxy-2-pentanone was examined by ab initio computational methods (see Experimental Section). Three minima were found (Figure 1). Two of the minima are half-chair conformers that differ in the orientation of the stereogenic methyl group. The conformer with a pseudoequatorial methyl group is favored by 4.18 kcal/mol. The disfavored conformer is destabilized by a close contact between the pseudoaxial chloride and methyl groups, which are separated by 3.48 Å (sum of van der Waals radii is 3.75 Å). This 4.18 kcal/mol destabilization is 1.84 kcal/mol greater[21] than that predicted for the 1,3-diaxial interaction between the chloride and methyl groups of *cis*-1-chloro-3-methylcyclohexane. Interestingly, a boat conformer was found to be only 3.56 kcal/mol less stable than the most stable half-chair conformer.[22] The lack of eclipsing H−H interactions presumably stabilizes it.

Experimental support for the preceding was obtained by a VT-NMR experiment.[23] ^{1}H NMR spectra of a mixture of ketone **5c** and BBr_3[24] in CD_2Cl_2 (ca. 0.1 M) at −80 °C revealed a new species with the systematic downfield shifts characteristic of a Lewis acid chelate

(18) (a) Narasaka, K.; Pai, F.-C. *Chem. Lett.* **1980**, 1415−1418. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233−2238.

(19) (a) Prasad, K.; Chen, K.; Hardtmann, G. E.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158. (b) Prasad, K.; Chen, K.; Hardtmann, G. E.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926. (c) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803−805.

(20) BCl_3-mediated reduction of **5b** afforded the following syn-to-anti ratios: morpholine·BH_3, 88:12; *t*-$BuNH_2$·BH_3, 80:20; THF·BH_3, 87:13.

(21) Derived from molecular mechanics (PCMODEL Version 4.51; Serena Software, Bloomington, IN 47402), strain energies (kcal/mol) for the following isomers of 1-chloro-3-methylcyclohexane: cis, all equatorial +7.19, all axial +10.63; trans, chloride axial +7.63, methyl axial +8.96.

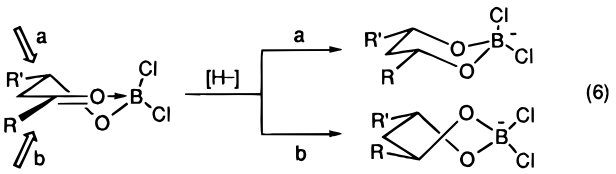
(22) Another boat conformer with the stereogenic methyl occupying a pseudoaxial site could not be found.

(23) Prasad and co-workers failed to detect the chelate intermediate predicted for their system using ^{11}B NMR; see ref 19b.

(24) The use of BBr_3 (bp 90 °C) was to avoid the expense and volatility of BCl_3 (bp 12.5 °C).

having formed.[25,26] For example, the methylene hydrogens of **5c** resonate at 3.01 and 3.16 ppm and at 3.31 and 4.09 ppm after treatment with BBr_3.[27] Similarly, the aryl hydrogens ortho to the carbonyl group of **5c** resonate at 7.96 ppm and at 8.36 ppm after treatment with BBr_3. If this intermediate chelate adopted the lowest energy conformer predicted computationally, the dihedral angles between the hydrogen of the hydroxy-bearing β carbon and the methylene hydrogens of the α carbon would be 51 and 170°. The observed coupling constants of 2.0 and 10.5 Hz are consistent with these values.

The half-chair conformer indicated above as an intermediate agrees with the previously proposed mechanisms for this class of chelate-controlled reductions. The lack of obvious facial biasing observed in this intermediate, however, does not explain the asymmetric induction observed. In analogy to cyclic iminium salt and cyclohexanone enolate chemistry,[28] product development control is suggested (eq 6). Attack of hydride by path **a** gives the boronate anion of the major syn 1,3-diol in a chair conformation, while attack of hydride by path **b** gives the boronate anion of the minor anti 1,3-diol in a twist conformation. Although the presence of so many heteroatoms makes the analogy to the twist and chair forms of cyclohexane tenuous, ab initio calculations show that the chair boronate anion derived from *syn*-2,4-pentanediol (eq 6; R, R′ = Me) is 3.20 kcal/mol[29] more stable that the twist boronate anion derived from *anti*-2,4-pentanediol (see Experimental Section).



(6)

Conclusions

Two diastereoselective reduction procedures have been developed for β-hydroxy ketones. When $TiCl_4$ is used as the chelating agent, the β-hydroxy ketone must be α substituted and the flanking carbonyl substituent large or sp^2-hybridized if highly diastereoselective reduction is to occur. The resulting 1,3-diols have the newly formed hydroxyl syn to the α substituent. When BCl_3 is used as the chelating agent, β-hydroxy ketones are reduced with high diastereoselectivity to give syn 1,3-diols. The avoidance of an $A^{(1,3)}$-like interaction appears responsible for the high diastereoselectivity in both protocols. With $TiCl_4$ as a chelating agent, a half-chair conformer is favored that strongly biases approach of the reducing agent. With BCl_3 as a chelating agent, a half-chair conformer is strongly favored that is subject to product development controlled reduction. Hopefully, the protocols developed will be of use to synthetic chemists, and the interactions apparently responsible for diastereocontrol can be used as design elements in new reactions.

Experimental Section

^1H NMR spectra were acquired at 199.98 MHz in $CDCl_3$ and referenced to residual $CHCl_3$ unless otherwise noted. ^{13}C NMR spectra were acquired at 50.29 MHz in $CDCl_3$ and referenced to $CDCl_3$. Coupling constants are reported in Hz. All reactions were conducted in oven-dried (130 °C) glassware under a dry nitrogen atmosphere. Stereochemical assignments were accomplished by direct comparison to the literature or by use of spectroscopic methods.[5] Compound **1d**, 1.0 M BCl_3 in CH_2Cl_2, and $TiCl_4$ were purchased from Aldrich Chemical Company. Chromatography refers to "flash" chromatography on SiO_2.

General $TiCl_4$ Reduction Procedure. To a cold (−78 °C) solution of ketone (1.0 mmol) in 10 mL of CH_2Cl_2 was added $TiCl_4$ (111 μL, 1.0 mmol) to give immediately a bright yellow solution, which was stirred 10 min at this temperature. The nucleophile (1.0 mmol) in 5 mL of CH_2Cl_2 was then added. After 15 min, 25 mL of 1 N HCl was added, and the reaction was warmed to rt. The organic layer was separated, the aqueous layer was washed with CH_2Cl_2, and the combined organics were concentrated *in vacuo*. The resulting residue was partitioned between Et_2O and H_2O. The ethereal layer was washed with water and brine, dried over anhyd Na_2SO_4, and concentrated *in vacuo*. Chromatography gave diastereomeric mixtures of diols in 84−96% yield.

General BCl_3 Reduction Procedure. To a cold (−78 °C) solution of ketone (0.5 mmol) in 5 mL of CH_2Cl_2 was added prechilled BCl_3 (0.5 mmol, 1 M CH_2Cl_2). After 5 min, reductant was added, and the reaction was stirred for 2 h. While still cold, CH_3OH was added (gas evolution evident), and the reaction vessel was then allowed to warm to rt. After concentration *in vacuo*, silica gel (ca. 0.75 g) and CH_3OH (ca. 10 mL) were added, and the resulting slurry was stirred overnight.[30] Chromatography gave diastereomeric mixtures of diols in 70−90% yield.

1-Hydroxy-2,4,4-trimethyl-3-pentanone (1b). A cold (−78 °C) solution of LDA generated by the addition of *n*-BuLi (12.0 mL, 1.6 M hexanes) to $(i\text{-Pr})_2NH$ (2.05 g, 20 mmol) in 20 mL of THF was transferred to ethyl propionate (5.0 g, 18.0 mmol) in 10 mL of cold (−78 °C) THF. After 1 h, pivaldehyde (1.72 g, 20.0 mmol) was added in one portion. The resulting solution was stirred for 30 min at −78 °C, warmed slowly to rt where it remained 90 min, and then treated with 30 mL of saturated aqueous NH_4Cl. The products were extracted into CH_2Cl_2, dried over anhyd Na_2SO_4, concentrated *in vacuo*, and chromatographed (15% EtOAc:hexanes) to give 2.51 g (74%) of ethyl 3-hydroxy-2,4,4-trimethylpentanoate[31] as a colorless oil.

This ester was then dissolved in 100 mL of Et_2O and chilled (0 °C). Solid LAH (0.51 g, 13.5 mmol) was added portionwise over 15 min, and the reaction was warmed to rt. After 2 h, 0.5 mL of water, 0.5 mL of 10% NaOH, and then 1.5 mL of water were added sequentially. Water was added to the reaction, which was then extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, concentrated *in vacuo*, and chromatographed (20% EtOAc:hexanes) to give 1.67 g (84%) of 2,4,4-trimethyl-1,3-pentanediol (see below).

Oxidation of the preceding diol to **1b** was accomplished using the procedure of Stevens and co-workers.[32] To a solution of the above diol in glacial AcOH (6.6 mL) was added aqueous 20% NaOCl (6.6 mL) in a dropwise manner over a 1-h period. An ice bath was used to maintain the reaction temperature between 15 and 25 °C. The mixture was stirred for 1 h after

(25) See, for example: (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847−3849. (b) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5480−5482. (c) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281−284.

(26) See Experimental Section for more details.

(27) The ^1H NMR spectra of uncomplexed ketone **5c** were acquired in $CDCl_3$ at rt. Our experience is that chemical shifts of such compounds are not greatly dependent on temperature or the chlorinated solvent used.

(28) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; pp 209−221, 274−284.

(29) This is a large part of the 4.6−6.2 kcal/mol destabilization of the twist form of cyclohexane relative to the chair form, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 689−690.

(30) Six hours of stirring is sufficient at this point. If an ester is present in the substrate, transesterification has been observed with the longer reaction time.

(31) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309−2315.

(32) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030−2032.

the addition was complete. Saturated aqueous $NaHSO_3$ was added until the color of the reaction mixture changed from pale yellow to white and the mixture gave a negative KI−starch test. The resulting mixture was poured into an ice−brine mixture and extracted with Et_2O. The combined organic layers were washed with 10% aqueous NaOH. The combined aqueous washes were back extracted with Et_2O. All the organic extracts were combined, dried over anhyd Na_2SO_4, concentrated *in vacuo*, and chromatographed (10% EtOAc: hexanes) to give 1.46 g (90%) of **1b**: ^{1}H NMR δ 3.57 (dd, J = 7.54, 10.6, 1H), 3.35 (dd, J = 4.9, 10.6, 1H), 3.19−3.03 (m, 1H), 2.56 (br s, 1H), 1.09 (s, 9H), 0.98 (d, J = 7.1, 3H); ^{13}C NMR δ 220.10, 65.16, 44.65, 41.68, 25.78, 14.84; IR (film) 3504 (br), 2969, 2877, 1700 (vs), 1479, 1457, 1465, 1049, 1070, 1029 cm^{-1}; MS-CI *m/z* (relative intensity) 145 (MH, 9), 127 (9), 103 (23), 87 (27) 57 (100); HRMS-CI m/z calcd for $C_8H_{17}O_2$ (MH) 145.1228, found 145.1229.

3-Hydroxy-1-cyclohexyl-2-methyl-1-propanone (1c). The same series of steps used for the preparation of **1b** was used to prepare **1c**. Substitution of cyclohexanecarboxaldehyde (2.24 g, 20.0 mmol) for pivaldehyde followed by chromatography (15% EtOAc:hexanes) gave 2.62 g (68%) of ethyl 3-hydroxy-3-cyclohexyl-2-methylpropanoate as a colorless oil.[31] Reduction with LAH (0.63 g, 16.5 mmol) and chromatography (20% EtOAc:hexanes) gave 1.68 g (80%) of 1-cyclohexyl-2-methyl-1,3-propanediol (see below). Oxidation and chromatography (10% EtOAc:hexanes) gave 1.51 g (93%) of **1c**: ^{1}H NMR δ 3.70 (dd, J = 6.8, 10.1, 1H), 3.53 (dd, J = 4.4, 10.1, 1H), 2.98−2.80 (m, 1H), 2.46 (m, 2H), 1.90−1.55 (m, 4H), 1.40−1.10 (m, 6H), 1.05 (d, J = 6.5, 3H); ^{13}C NMR δ 218.14, 64.35, 49.75, 46.08, 28.50, 27.90, 25.65, 13.29; IR (film) 3830, 2942, 2864, 1711, 1456, 1380, 1152, 1046, 1003, 896 cm^{-1}; MS-CI *m/z* (relative intensity) 171 (MH, 20), 129 (88), 111 (22), 83 (132); HRMS-CI *m/z* calcd for $C_{10}H_{19}O_2$ (MH) 171.1385, found 171.1382.

***rel*-(1*S*,2*R*)-2-Methyl-1-phenyl-1,3-propanediol (*syn*-2a).**[33] General reduction was performed on **1a**:[33,34] ^{1}H NMR δ 7.41−7.23 (m, 5H), 4.92 (d, J = 5.2, 1H), 3.65−3.21 (m, 3H), 2.63 (br s, 2H), 2.08 (m, 1H), 0.83 (d, J = 7.7, 3H); ^{13}C NMR δ 142.63, 128.15, 127.83, 127.20, 126.75, 126.15, 76.45, 66.28, 41.30, 10.73.

***rel*-(2*R*,3*S*)-2,4,4-Trimethyl-1,3-pentanediol (*syn*-2b).**[35] General reduction was performed on **1b**: ^{1}H NMR δ 3.90−3.71 (m, 2H), 3.36 (m, 1H), 2.24 (br s, 2H), 1.90 (m, 1H), 1.02 (d, J = 7.3, 3H), 0.92 (s, 9H); ^{13}C NMR δ 84.93, 69.96, 35.83, 35.35, 26.24, 13.02.

***rel*-(1*R*,2*R*)- and *rel*-(1*R*,2*S*)-1-Cyclohexyl-2-methyl-1,3-propanediol (*syn*- and *anti*-2c).**[35] General reduction was performed on **1c**: ^{1}H NMR δ 3.87−3.41 (m, 3H), 2.62 (m, 1H), 1.86−1.12 (m, 11H), 0.83 (d, J = 6.9, 3H), 0.72 (d, J = 6.3, 3H); ^{13}C NMR δ 81.42, 78.21, 67.66, 65.75, 40.68, 40.56, 36.19, 35.55, 30.07, 29.67, 28.90, 26.45, 25.99, 25.78, 13.92, 8.86.

***rel*-(2*R*,3*R*)-2-Methyl-1,3-butanediol (*syn*-2d).**[36] General reduction was performed on **1d**: ^{1}H NMR δ 3.52−3.74 (m, 3H), 2.95 (br s, 1H), 2.55 (br s, 1H), 1.62 (m, 1H), 1.29 (d, J = 6.3, 3H), 0.92 (d, J = 7.5, 3H); ^{13}C NMR δ 76.45, 69.06, 41.76, 22.01, 15.65.

***rel*-(1*S*,2*R*,3*S*)-2,4-Dimethyl-1-phenyl-1,3-pentanediol.**[37] General reduction was performed on **3**:[38] ^{1}H NMR δ 7.27−7.35 (m, 5H), 5.01 (d, J = 2.7, 1H), 3.51 (dd, J = 1.9, 9.4, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.03 (d, J = 6.9, 3H), 0.83 (d, J = 7.0, 3H), 0.80 (d, J = 7.0, 3H); ^{13}C NMR δ 143.92, 128.63, 127.52, 126.24, 83.17, 79.35, 41.58, 32.21, 20.12, 19.41, 4.65.

***rel*-(1*S*,2*R*,3*R*)-2,4-Dimethyl-1-phenyl-1,3-pentanediol.**[37] General reduction was performed on **4**:[38] ^{1}H NMR δ 7.27−7.35 (m, 5H), 4.96 (d, J = 3.3, 1H), 3.51 (d, J = 9.0, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 0.99 (d, J = 6.9, 3H), 0.81 (d, J = 6.9, 3H), 0.76 (d, J = 6.9, 3H); ^{13}C NMR δ 133.38, 128.72, 128.29, 125.87, 79.19, 76.22, 43.37, 31.21, 19.96, 16.96, 15.97.

Reductions of *β*-Hydroxy Ketones 5. *β*-Hydroxy ketones **5a**,[2f] **5c**,[39] **5d**,[39] **5e**,[40] and **5f**[41] were prepared by aldol reactions similar to that reported for **5b** (see below) and matched physical characteristics previously reported for them. The corresponding BCl_3-mediated reduction products *syn*-**6a**,[42] *syn*-**6c**,[43] *syn*-**6d**,[44] and *syn*-**6e**[44] similarly matched physical characteristics previously reported for them.

3-Hydroxy-1-phenyl-1-nonanone (5b). To a cold (−78 °C) solution of *i*-Pr_2NH (4.80 mL, 36.6 mmol) in 150 mL of THF was added a solution of *n*-BuLi (19.5 mL, 1.6 M hexanes). After 30 min, a solution of acetophenone (3.60 mL, 51.5 mmol) in 15 mL of THF was added followed 60 min later by a solution of heptanal (4.8 mL, 34.4 mmol) in 15 mL of THF. This was stirred for 5 min and then treated with 50 mL of saturated aqueous NH_4Cl. After warming to rt, the resultant mixture was extracted with ether (4 × 100 mL). The combined organic extracts were washed with 50 mL of brine, dried over anhyd $MgSO_4$, and chromatographed (20% EtOAc:hexanes) to give 3.20 g (44%) of **5b** as a white solid: mp 28−29 °C; ^{1}H NMR δ 0.84 (t, J = 6.5, 3H), 1.09−1.67 (m, 10H), 2.90−3.16 (m, 2H), 3.32 (s, 1H), 4.17 (m, 1H), 7.36−7.57 (m, 3H), 7.88−7.93 (m, 2H); ^{13}C NMR δ 14.0, 22.3, 25.6, 29.0, 31.8, 36.4, 45.0, 67.6, 127.8, 128.2, 133.2, 136.3, 200.5; IR (neat) 3420, 2925, 2859, 1684, 1605, 1582, 1450, 1212, 1020, 757, 691 cm^{-1}; HRMS-CI *m/z* calcd for $C_{15}H_{23}O_2$ (MH) 235.169805, found 235.170563.

***rel*-(1*S*,3*S*)-1-Phenyl-1,3-nonanediol (*syn*-6b).** Ketone **5b** (92 mg, 0.392 mmol) was reduced using the standard BCl_3 procedure and Et_4NNCBH_3. Chromatography (20% EtOAc: hexanes) afforded *syn*-**6b** (74 mg) in 81% yield: mp 67−69 °C; ^{1}H NMR δ 0.83 (t, J = 6.5, 3H), 1.12−1.81 (m, 10H), 3.28 (s, 2H), 3.37−3.89 (m, 2H), 4.79−4.85 (m, 2H), 7.12−7.37 (m, 5H); ^{13}C NMR δ 14.1, 22.5, 25.3, 29.2, 31.8, 38.0, 45.1, 72.9, 75.3, 125.6, 127.4, 128.3, 144.4; IR (neat) 3290, 2915, 2852, 1464, 1366, 1075, 1020, 1002, 756, 700 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{24}O_2$ 236.177630 (M), found 236.178375.

Chelate from BBr_3 and Ketone 5c. Ketone **5c** (20 mg, 0.104 mmol) was placed in an NMR tube equipped with a J. Young valve, frozen in liquid nitrogen, and then evacuated to 150 mTorr. A solution of BBr_3 (33.8 mg, 0.135 mmol) in CD_2Cl_2 (1.0 mL) was then vacuum transferred to the NMR tube, which was kept in liquid nitrogen until placed in the chilled NMR probe: ^{1}H NMR (500 MHz, CD_2Cl_2, −80 °C) 1.02 (d, J = 6.8, 3H), 1.04 (d, J = 6.8, 3H), 1.92 (m, 1H), 3.31 (dd, J = 10.5, 20.0, 1H), 4.09 (dd, J = 2.0, 20.0, 1H), 4.41 (ddd, J = 2.0, 7.2, 10.5, 1H), 7.72 (app. t, J = 8.0, 2H), 8.00 (t, J = 7.5, 1H), 8.36 (d, J = 8.0, 2H). As the sample was warmed, two sets of new signals appeared at the expense of the those assigned to the chelate formed from BBr_3 and ketone **5c**. The two new compounds were very similar, present in equal amounts, and only differentiated because one displayed line broadening at 15 °C.

Computational Method. All structures were optimized at the RHF/6-31G* level of theory[45] using the Gaussian 92 suite of programs.[46] Frequency calculations were performed

(33) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411−1415.
(34) Zimmerman, H. E.; English, J., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 2294−2300.
(35) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279−8281.
(36) White, J. D.; Theramongkol, P.; Kuroda, C.; Engebrecht, J. R. *J. Org. Chem.* **1988**, *53*, 5909−5921.
(37) Bloch, R.; Gilbert, L.; Girard, C. *Tetrahedron Lett.* **1988**, *29*, 1021−1024.
(38) Stille, J. K.; Labadie, S. S. *Tetrahedron* **1984**, *40*, 2329−2336.
(39) Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T. *J. Org. Chem.* **1991**, *56*, 1631−1635.
(40) Oare, D. A.; Henderson, M. A.; Sanner, M. A., Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132−157.
(41) Surov, I.; Jund, H. *Acta Chem. Scand. Ser. B* **1986**, *40*, 831−838.
(42) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761−3770.
(43) Kiyooka, S.; Kurada, H; Yajoi, S. *Tetrahedron Lett.* **1986**, *27*, 3009−3012.
(44) Todesco, R.; Bockstaele, D. V.; Gelen, J.; Martens, H.; De Schryer, F. C. *J. Org. Chem.* **1983**, *48*, 4963−4968.
(45) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *16*, 217−219.
(46) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92, Revision B*; Gaussian Inc.: Pittsburgh, PA 1992.

at the same level. All optimized geometries proved to be minima, and energies were corrected for zero-point energies (unscaled). No restrictions were placed on the molecules during geometry optimizations.

Acknowledgment is made to the University of California and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. C.R.S. acknowledges the support of a John H. Tokuyama Fellowship, and M.D. thanks the American Cancer Society for a junior faculty research award.

Supporting Information Available: ^{1}H NMR spectra are available for **1b**, **1c**, **5b**, and *syn*-**6b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951549X