Reversed Stereochemical Control in the Presence of $CeCl_3$ and $TiCl_4$ in the Lewis Acid Mediated Reduction of α-Alkyl-β-keto Esters by Metal Hydrides. A General Methodology for the Diastereoselective Synthesis of *syn*- and *anti*-α-Alkyl-β-hydroxy Esters

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The Lewis acid-mediated reduction of α-alkyl-β-keto esters has been shown to proceed by different stereochemical control depending on the nature of the metal atom. Strongly chelating $TiCl_4$ led to the *syn* isomer in high diastereomeric excess in noncoordinating solvents (CH_2Cl_2) at −78 °C with BH_3·py as reducing agent, while nonchelating $CeCl_3$ gave a high excess of the *anti* isomer in coordinating solvents (THF) at the same temperature with lithium triethylborohydride ($LiEt_3BH$) as reducing agent. The methodology has been successfully utilized for obtaining important *syn*- and *anti*-α-alkyl-β-hydroxy esters with high diastereoselectivity.

Introduction

The stereochemical course in the reduction of the carbonyl group of ketones with an adjacent chiral center to the corresponding alcohol has long been studied.[1] Particularly, interest has been focused on the diastereoselective reduction of α-substituted β-functionalized carbonyl compounds.[2] Among these, the chemical[3] or enzymological[4] stereoselective reduction of α-substituted β-keto esters has been extensively studied in recent years. Accordingly, two strategies (chelation and nonchelation) have been developed that enabled the achievement of an opposite sense of diastereoselectivity by the appropriate choice of reducing systems. These methods have been successfully applied to a variety of natural product syntheses[5] including β-lactams[6] and β-lactone antibiotics.[7] Thus, the stereoselective reduction of the corresponding α-substituted β-keto ester to highly functionalized α-substituted β-hydroxy carboxylate represents an attractive alternative to stereoselective aldol condensation of various metal enolates, which has been successfully employed for such a purpose.[8]

In the course of our program to develop new synthetic Lewis acid-mediated reductions of β-functionalized carbonyl compounds with asymmetric α-carbon in their racemic form, we have found that the nature of the Lewis acid is instrumental in determining the stereochemical outcome of these reactions.[9] Herein we wish to report that the correct choice of hydrides, solvent, and especially Lewis acid allows us to obtain high stereoselective synthesis of α-substituted β-hydroxy esters. Our procedure represents a simple and effective alternative procedure for the highly diastereoselective synthesis of *syn*- or *anti*-α-alkyl-β-hydroxy esters through the reduction of the corresponding β-keto esters with BH_3·py or lithium triethylborohydride ($LiEt_3BH$) in the presence of $TiCl_4$ or dry $CeCl_3$, respectively (Scheme 1).

(1) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 1−24.
(2) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.
(3) (a) Sato, T.; Nishio, M.; Otera, J. *Synlett* **1995**, 965. (b) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169. (c) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5405. (d) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294. (e) Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1982**, *24*, 5385. (f) Sorrell, T. N.; Pearlman, P. S. *Tetrahedron Lett.* **1980**, *21*, 3963.
(4) (a) Dauchet, S.; Bigot, C.; Buisson, D.; Azerad, R. *Tetrahedron: Asymmetry* **1997**, *8*, 1735. (b) Shieh, W.-R.; Sih, C. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1259. (c) Jian-Xiu, G.; Gno-Qiang, L. *Tetrahedron* **1993**, *49*, 5805. (d) Servi, S. *Synthesis* **1990**, 1. (e) Nakamura, K.; Miyai, T.; Nagar, A.; Oka, S.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1179.
(5) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.
(6) (a) Shirai, F.; Nakai, T. *Chem. Lett.* **1989**, 445. (b) Wild, H.; Kant, J.; Walker, D. G.; Ojima, I.; Ternansky, R. J.; Morin, J. M., Jr.; Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-lactams*; Georg, G. I., Ed.; VCH Publishers: New York, 1993; and references therein.
(7) (a) Mead, K. T.; Park, M. *Tetrahedron Lett.* **1995**, *36*, 1205. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768. (d) Thompson, K. L.; Chang, M. N.; Chiang, Y.-C. P.; Yang, S. S.; Chabala, J. C.; Arison, B. H.; Greenspan, M. D.; Hauf, D. P.; Yudkovitz, J. *Tetrahedron Lett.* **1991**, *32*, 3337. (e) Chiang, Y. P.; Yang, S. S.; Heck, J. V.; Chabala, J. C.; Chang, M. N. *J. Org. Chem.* **1989**, *54*, 5708. (f) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925.
(8) (a) Bal, B.; Buse, C. T.; Smith, K.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 89. (b) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. *Org. Synth.* **1985**, *63*, 99. (c) Meyers. A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (d) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087.
(9) (a) Bartoli, G.; Bosco, M.; Cingolani, S.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1998**, *63*, 3624. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **1997**, *3*, 1941. (c) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L. *Tetrahedron Lett.* **1996**, *35*, 241.

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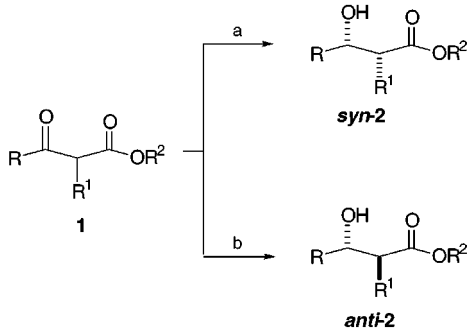
Table 1. Stereoselective Reduction of β-Keto Esters (1) to β-Hydroxy Esters with BH_3·py in the Presence of $TiCl_4$ in CH_2Cl_2 at −78 °C

Entry	R	R^1	R^2	Keto Ester	Overall yield (%)[c]	Product[a]	*syn*/*anti*[b]
1	Me	$PhCH_2$	Et	**1a**	93	**2a**	>99/1
2	Me	$EtO_2C(CH_2)_3$	Et	**1b**	89[d]	**2b**	95/5
3	Ph	Me	Et	**1c**	99	**2c**	>99/1
4	Ph	allyl	Et	**1d**	92	**2d**	>99/1
5	Ph	propargyl	Et	**1e**	95	**2e**	88/12
6	Ph	$MeCO(CH_2)_3$	Et	**1f**	57[d]	**2f**[e]	
7	Ph		Et	**1g**	86	**2g**[f]	
8	Me	$PhCH_2$	t-Bu	**1h**	94	**2h**	>99/1
9	Ph	allyl	t-Bu	**1i**	93	**2i**	>99/1

[a]By adding the BH_3·py complex to the solution of the CH_2Cl_2 solution of **1**/$TiCl_4$ complex at -78°C. [b]Determined by ^1H and ^{13}C-NMR spectroscopy. [c]Calculated on the mixture of diastereomers isolated by column chromatography. [d]2.5 Equivalents of $TiCl_4$. [e]3,6-Disubstituted δ-lactone was purified. [f]Cleavage of acetal moiety.

Scheme 1[a]

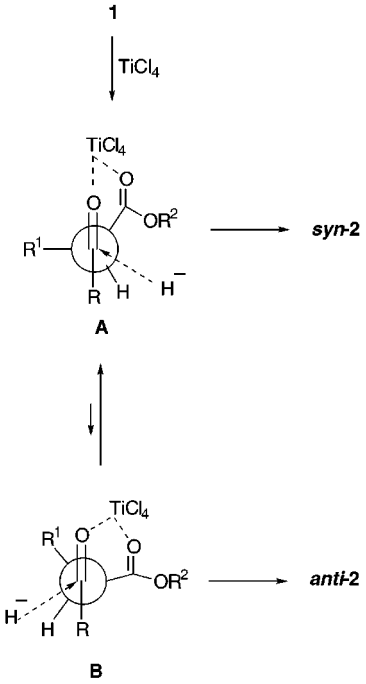


[a] Key: (a) $TiCl_4$ in CH_2Cl_2 at −78 °C, then BH_3·py; (b) $CeCl_3$ in THF at −78 °C, then $LiEt_3BH$.

Results and Discussion

The additions of nucleophiles to ketones are promoted by coordination of a Lewis acid to the carbonyl group, enhancing the electrophilicity of this moiety,[10] and borane−Lewis base complexes are finding an increasing role for this purpose.[11] It is also known that the reduction of α-substituted β-keto esters produces the *syn* diastereomer when a Lewis acid, which is able to coordinate to two additional ligands, is used.[12] We found that the reduction of α-alkyl-β-keto esters **1** in dichloromethane at low temperature (−78 °C) with BH_3·py[13] (1.5 equiv) in the presence of $TiCl_4$ (1.5 equiv) led to the prevalent formation of *syn*-α-alkyl-β-hydroxy esters (*syn*-**2**) (Table 1). The observed stereochemical course suggests a prevalent $TiCl_4$-induced chelation-controlled addition,[14] and the **1**−$TiCl_4$ complex can be represented by an equilibrium

Scheme 2



between the **A** and **B** conformations (Scheme 2). These species, involving 1 equiv of $TiCl_4$, should be the reactive intermediate, as suggested by the observation that addition of a second equivalent of Lewis acid has no influence on the diastereoselectivity (Table 1, entry 2). The high diastereoselectivity observed in this reduction is probably a consequence of the generally strong ability of titanium(IV) compounds to engage in chelation-controlled carbonyl addition.[15] It is obvious that every increase in bulkiness of R^1, shifting the conformational equilibrium toward the **A** conformation, increases the *syn*/*anti* ratio. In fact, the cylindrical symmetry of the alkynyl group in R^1 position reduces the unfavorable steric interaction between the R^1 substituent and the oxygen atom of the carbonyl group in conformation **B** (Table 1, entry 5).

(10) Sweeney, J. B. In *Comprehensive Organic Functional Group Transformation*; Katritzky, A. R., Meth-cohn, O., Rees, C. W., Eds.; Elsevier Science Ltd.: Oxford, 1995; Vol. 2, pp 52−82.

(11) (a) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, 1988. (b) Lane, C. F. *Aldrichim. Acta* **1973**, *6*, 51.

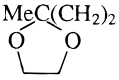
(12) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641.

(13) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868.

(14) Reviews on chelation- and nonchelation-controlled additions: (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (c) Jonas, V.; Frenking, G.; Reetz, M. T. *Organometallics* **1993**, *12*, 2110.

(15) Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 1994; pp 195−282.

Table 2. Stereoselective Reduction of β-Keto Esters (1) to β-Hydroxy Esters with $LiEt_3BH$ in the Presence of Dry $CeCl_3$ in THF at −78 °C

Entry	R	R^1	R^2	Keto Ester	Overall yield (%)[c]	Product[a]	Time	*anti*/*syn*[b]
1	Me	$PhCH_2$	Et	**1a**	92	**2a**	4.5 h	87/13
2	Me	$EtO_2C(CH_2)_3$	Et	**1b**	85	**2b**	5.0 h	87/13
3	Ph	Me	Et	**1c**	85	**2c**	4.0 h	91/9
4	Ph	allyl	Et	**1d**	90	**2d**	6.0 h	90/10
5	Ph	propargyl	Et	**1e**	90	**2e**	6.0 h	89/11
6	Ph	$MeCO(CH_2)_3$	Et	**1f**	55[d]	**2f**	5.0 h	
7	Ph		Et	**1g**	90	**2g**	6.0 h	64/36
8	Me	$PhCH_2$	t-Bu	**1h**	94	**2h**	5.5 h	99/1
9	Ph	allyl	t-Bu	**1i**	83	**2i**	6.0 h	97/3

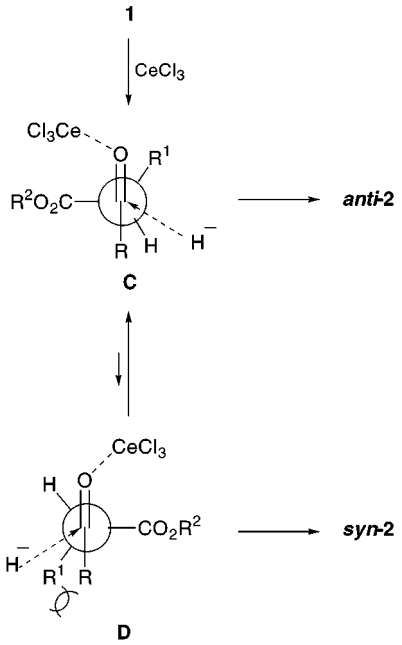
[a]By adding a 1M solution of $LiEt_3BH$ in THF to the THF solution of **1**-$CeCl_3$ complex at -78°C. [b]Determined by ^1H and ^{13}C-NMR spectroscopy. [c]Calculated on the mixture of diastereomers isolated by column chromatography. [d]3,6-Disubstituted δ-lactone was purified.

The reduction of β-keto esters **1** with BH_3·py in the presence of $TiCl_4$ was studied in different solvents such as CH_2Cl_2, THF, and Et_2O. Dichloromethane turned out to be a suitable solvent for the reduction, since the use of a coordinating solvent, such as THF and Et_2O, led to the complete loss of diastereoselectivity. To control diastereoselectivity, the reductions were executed at low temperature (−78 °C), as temperatures higher than −78 °C considerably lower both stereoselectivity and yields.

We also examined the reduction of α-substituted β-keto esters **1** with hydrides in the presence of dry cerium trichloride as the Lewis acid. We first tested the reduction of **1a** in dichloromethane with BH_3·py, a convenient reducing agent because of its solubility in many organic solvents, in the presence of dry $CeCl_3$. While the reducing system BH_3·py was highly efficient with $TiCl_4$, no reaction with $CeCl_3$ was observed, and at −78 °C the starting material was quantitatively recovered after 2 h. Prolonged reaction times and higher reaction temperatures were also ineffective. A complex between cerium(III) chloride and β-keto ester was formed, since the addition of the substrate to a suspension of the cerous salt resulted in a clear solution after about 1 h. Unfortunately, the paramagnetism of cerous salt prevented useful NMR information on the structure of this complex from being obtained.[16]

The reduction of α-alkyl-β-keto esters **1** proceeded successfully when a 1 M THF solution of $LiEt_3BH$ was employed in the presence of dry $CeCl_3$ and at low temperature (−78 °C). The reaction gave the expected α-alkyl-β-hydroxy esters **2** in almost quantitative yields, but with reversed stereoselectivity with respect to the BH_3·py/$TiCl_4$ system (Table 2). In this latter reducing system we observed that the important factor in the *syn*-selective reduction was the intermediary formation of stable titanium chelates. Therefore, for the *anti*-reduction, it is obvious that the use of Lewis acids having metals of high O-chelating ability are to be avoided. These findings then strongly support an open-chain mechanism, and the *anti* selectivity for the system $LiEt_3BH/CeCl_3$ may be explained by a Felkin−Ahn model[17−19] controlled reaction. In fact, the sterically demanding alkyl

Scheme 3



chains favor the **C** over the **D** conformation, and the hydride anion attacks the β-carbonyl at the opposite side to the bulky carboalkoxy group selectively leading to the *anti* isomer (Scheme 3). This explanation was further supported by the fact that *anti*-diastereoselecitivity was enhanced in the reduction of more bulky *tert*-butyl esters (Table 2, entries 8 and 9). For this reason, we believe that the cerium trichloride cannot participate in chelation when a six-membered transition state is involved, even though the $CeCl_3$ is apparently a good Lewis acid and its anhydrous form is highly hydroscopic.[20]

(16) Hubert-Pfalzgraf, L. G.; Machado, L.; Vaissermann, J. *Polyhedron* **1996**, *15*, 546.

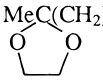
(17) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Einsenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(18) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(19) Bürgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956.

(20) The water molecule found in dry cerium(III) chloride seems to have no effect, since the material was highly efficient without a large excess of reducing agent. cf. Evans, W. J.; Feldaman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.

Table 3. ^{1}H NMR Chemical Shifts for the Carbinol Resonances of β-Hydroxy Esters (2)

Entry	R	R^1	R^2	Hydroxy Ester	*syn*-**2**	*anti*-**2**
1	Me	$PhCH_2$	Et	**2a**	4.30 (5.37 Hz)	4.05 (6.30 Hz)
2	Me	$EtO_2C(CH_2)_3$	Et	**2b**	3.95 (5.82 Hz)	3.90 (6.22 Hz)
3	Ph	Me	Et	**2c**	5.05 (4.43 Hz)	4.70 (8.46 Hz)
4	Ph	allyl	Et	**2d**	4.90 (5.97 Hz)	4.77 (6.70 Hz)
5	Ph	propargyl	Et	**2e**	4.90 (6.57 Hz)	4.80 (7.63 Hz)
6	Ph		Et	**2g**	4.95 (5.98 Hz)	4.75 (7.40 Hz)
7	Me	$PhCH_2$	t-Bu	**2h**	4.00 (5.49 Hz)	3.85 (6.44 Hz)
8	Ph	allyl	t-Bu	**2i**	4.84 (5.56 Hz)	4.74 (6.17 Hz)

[a]Data were reported as δ in ppm from Me_4Si, followed by the vicinal coupling costant. [b]By a reduction with $LiEt_3BH/CeCl_3$ only

Moreover, since Greeves et al.[21] have shown quite clearly that cerium(III) can be chelated by 1,2-diols, we have considered the possibility that the real reducing agent of the ketone moiety is not the Et_3BH^- anion. It may be, namely, that, since both $LiEt_3BH$ and $CeCl_3$ are required for efficient and diastereoselective reduction at −78 °C, the hydride of boron can reduce the $CeCl_3$ to CeH_nCl_{3-n} in a polar solvent such as THF. However, ^{1}H NMR measurements demostrated that, under these conditions, there was no generation of cerium hydride species *via* the transmetalation between cerium trihalide and lithium triethylborohydride.[22] In addition, Fukazawa et al.[23] have suggested that such hydrides species are unlikely to be the reducing agent in the reduction reactions with $LiAlH_4$ in the presence of $CeCl_3$; therefore, from our results, a similar behavior seems to be plausible.

The dry cerium(III) chloride, then, is not able to chelate with β-keto esters, but its presence is essential to obtain high yields and diastereoselectivities. In fact, the reaction of β-keto esters **1** with $LiEt_3BH$ alone[24] was slower and the yields were lower with respect to the same reaction carried out with $CeCl_3$. Reduction with short reaction times could be obtained at 0 °C, but it is detrimental to the diastereoselectivity and the yields, since an insoluble polymer is formed. At 0 °C in the presence of $CeCl_3$, the same low yields and low diastereoselectivity are observed. Cerium(III) trichloride is therefore essential in achieving high yields and diastereoselectivity, since it allows the reaction to be performed at low temperature. In these studies, THF was found to be a suitable solvent for the reaction, since the use of this coordinating solvent ensures good yields and high diastereoselectivity. On the other hand, the use of noncoordinating solvent such as CH_2Cl_2 caused a decrease in diastereoselectivity, even though an incomplete inversion to *syn* products was observed, as it was found in the presence of the powerful chelating $TiCl_4$. This would confirm the poor chelating ability of dry cerium(III) trichloride with these β-keto esters **1**.

Although several types of metal hydride complexes are available for this reduction of α-alkyl-β-keto esters, the lithium triethylborohydride was among the best. The data clearly reveal that $LiEt_3BH$ is an exceptionally powerful hydride reducing agent[25] and that it exibits a remarkable selectivity, a property normally considered to be characteristic of relatively mild reducing agent, such as lithium borohydride.[26]

The assignment for *syn* and *anti* diastereomers is based on the coupling constant between the α- and β-protons, which is usually slightly larger for the *anti* than *syn* isomer[27] (Table 3). Moreover, the stereochemistry of *syn* and *anti* diastereomers was fixed by using their ^{13}C NMR chemical shifts of carbinol carbon in comparison with the reported data.[28] It has also been showen that in the crude products the *syn*/*anti* ratios were very similar or identical to those of the purified β-hydroxy esters. Therefore, we can reasonably assume that the observed *syn*/*anti* ratio at the β-hydroxy ester stage reflects the diastereofacial selectivity of the addition step.

Further, on extending our procedure to obtain both *syn*- and *anti*-α-alkyl-β-hydroxy esters by reduction of the corresponding β-keto esters, the stereoselectivity of the reduction on β-keto esters **1** in the presence of other functionalities was examined. The isolated ester function is stable under our reaction conditions (Table 1, entry 2; Table 2, entry 2), whereas, when the β-keto ester substrate contains an acetal moiety (**1g**), the carbonyl group can be selectively reduced with the reducing system $LiEt_3BH/CeCl_3$ (Table 2, entry 7). On the other hand, we observed that if the reducing system BH_3·py/

(21) Greeves, N.; Pease, J. E.; Bowden, M. C.; Brown, S. M. *Tetrahedron Lett.* **1996**, *37*, 2675.

(22) Preparation of ^{1}H NMR sample: A 5-mm NMR tube charged with $CeCl_3 \cdot 7H_2O$ (79.4 mg, 0.21 mmol) was heated (140 °C) in vacuo (0.1 mmHg) for 2 h and charged with nitrogen. Then the tube was charged with dry THF-d_8 (0.75 mL) and frozen by liquid nitrogen. Next, a THF-d_8 solution of $LiEt_3BH$ (0.15 mL, 0.14 mmol) was added by syringe onto the solidified THF. Then the mixture was frozen again, and the tube was flame-sealed under vacuum. The ^{1}H NMR spectrum was measured after warming to −78 °C, it was referenced to residual tetrahydrofuran (δ 3.58 ppm, δ 1.73 ppm), and a broad new peak did not appear.

(23) Fukuzawa, S.; Fujinami, T.; Yamanchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929.

(24) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 4643.

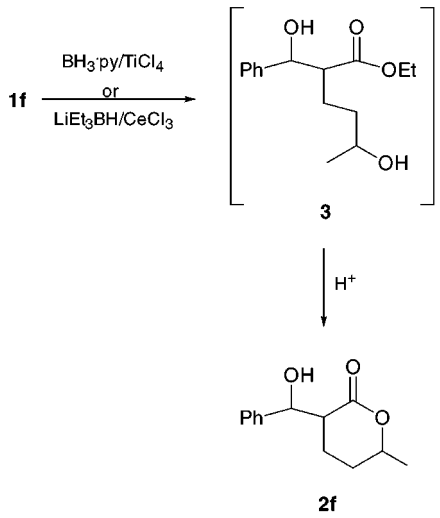
(25) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(26) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L. *Tetrahedron Lett.* **1996**, *37*, 7421.

(27) House, H. O.; Crumrine, D. S.; Teramishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(28) (a) Frater, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1277. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, T. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (c) Mulzer, J.; Zippel, M.; Brumtrup, G.; Segner, J.; Finke, J. *Liebigs Ann. Chem.* **1980**, 1108. (d) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

Scheme 4



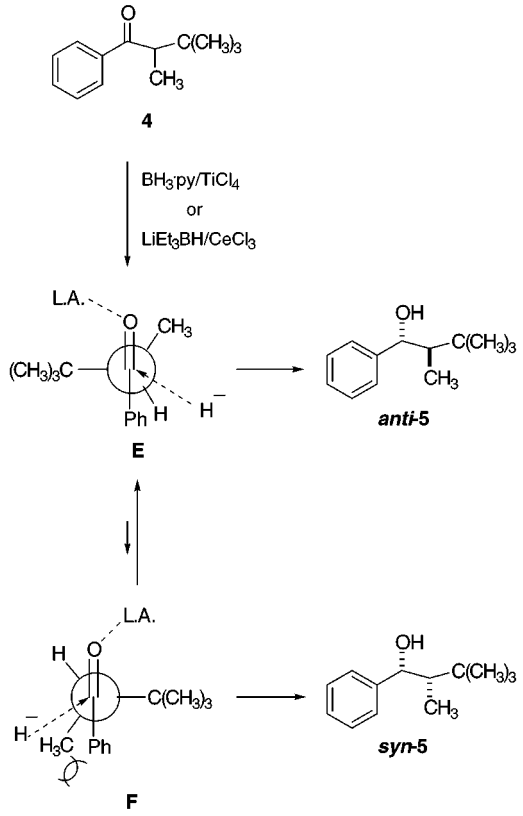
$TiCl_4$ was used, no selectivity was obtained, and the acetal moiety was also cleaved[29] (Table 1, entry 7). Unfortunately, both reducing systems are unsuccessful when the α-alkyl chain of the *β*-keto esters **1** contains another isolated carbonyl moiety (**1f**). Indeed, the reduction of both carbonyl groups provides dihydroxycarboxylates **3** (Scheme 4); however, no attempt to isolate this intermediate was undertaken. Instead, treatment with acid during workup directly afforded 3,6-disubstituted *δ*-lactone **2f** as mixture of diastereomers (Table 1, entry 6; Table 2 entry 6).

Finally, we have also examined our reducing systems, BH_3·py/$TiCl_4$ and $LiEt_3BH/CeCl_3$, with α-substituted carbonyl compounds that have no ability to chelate with metals. Our choice was ketone **4** because the *tert*-butyl group may be bulky enough to cause strong stereodifferentation beteween **E** and **F** conformations (Scheme 5). The high diastereoselectivity (*syn*-**5**/*anti*-**5** = 2:98 and 5:95 by ^{1}H NMR[30]) can be qualitatively understood by an open-chain mechanism, and the anti selectivity may explained by Felkin−Ahn's model. With this substrate, then, both $TiCl_4$ and $CeCl_3$ are not able to chelate, and they gave a high excess of the *anti* isomer with BH_3·py and $LiEt_3BH$ as reducing agent, respectively.

Conclusion

In summary, we have developed a straightforward approach for the synthesis both *syn*- and *anti*-α-alkyl-*β*-hydroxy esters, which are key intermediates for the stereoselective preparation of complex functionalized molecules, by Lewis acid-mediated reduction of α-alkyl-*β*-keto esters with metal hydrides. The nature of the Lewis acid was found to be pivotal in determining the outcome of these reductions. Strongly chelating $TiCl_4$ led largely to the syn diastereomer with BH_3·py as reducing agent, while nonchelating $CeCl_3$ gave an excess of the anti diastereomer with $LiEt_3BH$ as reducing agent. This would indicate that *β*-keto esters are probably just inadequate ligands for dry $CeCl_3$, and given the vast excess of polar THF solvent over the substrate, it is likely

Scheme 5



that complexation of the keto ester is unimportant in the case of these reduction conditions. Finally, it is noteworthy that our methodology can be carried out under standard procedures without any particular precaution and provides easy access to wide varieties of *β*-hydroxy carboxylates with high *syn* and *anti* diastereoselectivities.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 200 MHz using residual $CHCl_3$ (7.26 ppm) as reference. ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ (77.05 ppm) as reference. Mass spectra were measured at an ionizing voltage of 70 eV. All reactions were performed in flame-dried glassware under a positive pressure of nitrogen and stirred magnetically. Column and thin-layer chromatographies were carried out on silica gel (230−400 mesh ASTM) with the solvent system ethyl acetate in hexanes as eluent. Diastereomeric purity was determined by NMR analysis.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[31] *β*-Keto esters **1a** and **1c** were prepared by mono-C-alkylation of nonsubstituted *β*-keto esters with sodium alkoxide.[32] *β*-Keto esters **1d**, **1e**, and **1i** were prepared by a heterogeneous alkylation of ethyl and *tert*-butyl benzoyl acetate.[33] *β*-Keto esters **1b**, **1g**, and **1h** were prepared from the corresponding bromides via C-alkylation of nonsubstituted *β*-keto esters with NaH.[34] *β*-Keto ester **1f** was prepared through a cerium(III) chloride-catalyzed Michael reaction of the corresponding *β*-keto ester and methyl vinyl

(29) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997.
(30) (a) Arjona, O.; Pérez-Ossorio, R.; Pérez-Rubalcaba, A.; Quiroga, M. L. *J. Chem. Soc., Perkin Trans. 2* **1981**, 597. (b) Alvarez-Ibarra, C.; Arjona-Loraque, O.; Pérez-Rubalcaba, A.; Plumet, J. *Rev. R. Acad. Cienc. Exactas, Fis. Nat. Madrid* **1979**, 73.
(31) Armarego, W. L. F.; Perrin, D. D. In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
(32) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.
(33) Queignes, R.; Kirschleger, B.; Lambert, F.; Aboutaj, M. *Synth. Commun.* **1998**, *18*, 1213.
(34) (a) Kim, H.-O.; Carrol, B.; Lee, M. S. *Synth. Commun.* **1997**, *27*, 2505. (b) Reynolds, R. C.; Trask, T. W.; Sedwick, W. D. *J. Org. Chem.* **1991**, *56*, 2391.

ketone as acceptor.[35] The *tert*-butyl ketone **4** was obtained by means of the tertiary group introduction via the Friedel–Crafts alkylation of the corresponding trimethylsilyl enol ether according to reported procedure.[36] Other starting materials were commercially available, while *tert*-butyl benzoyl acetate was prepared according to the published procedure.[37]

General Procedure for Stereoselective Reduction of α-Alkyl-β-keto Esters 1 with BH_3·py in the Presence of $TiCl_4$. A representative experiment is as follows. To a cold (−78 °C) solution of β-keto esters **1** (1.0 mmol) in 10 mL of dry CH_2Cl_2 was added $TiCl_4$ (1.5 mmol, solution 1 M in CH_2Cl_2) to give immediately a clear solution, which was stirred for 15 min at this temperature. The complex BH_3·py (1.5 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 room temperature. 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 etheral layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography gave *syn*-α-alkyl-β-hydroxy esters **2**[38] contaminated by only a minor amount of the anti diastereomer. Diastereomeric purity was determined by NMR analysis, and reported yields listed in Table 1 are based on material isolated by flash column chromatography on silica gel using hexanes−EtOAc as the eluent system.

Ethyl (2*R,3*S**)-2-benzyl-3-hydroxybutanoate (*syn*-2a):** IR (neat) 3435, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.24 Hz), 1.26 (d, 3H, J = 6.43 Hz), 2.35 (bs, 1H, OH), 2.73−2.79 (m, 1H), 2.98 (d, 2H, J = 7.66 Hz), 4.13 (q, 2H, J = 7.22 Hz), 4.30 (after addition of D_2O, dq, 1H, J = 6.42, 5.37 Hz), 7.16−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.20, 25.15, 34.03, 52.05, 60.25, 68.33, 126.05, 128.16, 129.32, 139.23, 173.96; EI-MS *m*/*z* 222 (M^+), 204, 131 (100), 104, 91, 65, 51. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.22; H, 8.12.

Ethyl (5*R,6*S**)-5-ethoxycarbonyl-6-hydroxyeptanoate (*syn*-2b):** IR (neat) 3495, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.30 (m, 9H), 1.56−1.78 (m, 4H), 2.20 (t, 2H, J = 6.92 Hz), 2.51 (bs, 1H, 0H), 2.68−2.76 (m, 1H), 3.95 (t, 1H, J = 5.82 Hz), 4.10−4.20 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.39, 20.52, 21.57, 23.09, 26.96, 28.89, 34.19, 52.15, 60.79, 68.08, 173.56, 175.09; EI-MS *m*/*z* 231, 202, 128(100), 111, 101, 81. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.98; H, 8.23.

Ethyl (2*R,3*R**)-3-hydroxy-2-methyl-3-phenylpropanoate (*syn*-2c):** IR (neat) 3478, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 7.17 Hz), 1.19 (t, 3H, J = 7.00 Hz), 2.74−2.80 (m, 1H), 3.12 (bs, 1H, OH), 4.11 (q, 2H, J = 7.04 Hz), 5.06 (d, 1H, J = 4.43 Hz), 7.28−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.42, 14.55, 47.00, 61.18, 74.23, 126.53, 127.95, 128.70, 142.02, 176.25; EI-MS *m*/*z* 208 (M^+), 163, 107, 102(100), 91, 65, 51. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.27; H, 7.74. Found: C, 69.23; H, 7.70.

Ethyl (2*R,3*R**)-2-allyl-3-hydroxy-3-phenylpropanoate (*syn*-2d):** IR (neat) 3460, 1728, cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.00 Hz), 2.40−2.50 (m, 2H), 2.72−2.93 (m, 1H), 2.96 (bs, 1H,OH), 4.00 (q, 2H, J = 7.02 Hz), 4.90 (d, 1H, J = 5.97 Hz), 4.95−5.10 (m, 2H), 5.62−5.86 (m, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.55, 32.26, 53.33, 61.01, 74.51, 117.26, 126.77, 128.77, 128.89, 135.88, 141.96, 174.59; EI-MS *m*/*z* 234 (M^+), 193, 143, 91, 79 (100), 77, 41. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.75; H, 7.69.

Ethyl (2*R,3*R**)-3-hydroxy-3-phenyl-2-propargylpropanoate (*syn*-2e):** IR (neat) 3472, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 3H, J = 7.20 Hz), 2.50−2.65 (m, 3H), 2.85−2.95 (m, 1H), 4.01(q, 2H, J = 7.20 Hz), 4.90 (d, 1H, J = 6.57 Hz), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.49, 17.76, 52.90, 61.25, 70.37, 74.06, 82.05, 126.79, 128.35, 128.79, 141.90, 173.18; EI-MS *m*/*z* 232 (M^+), 204, 159, 115(100), 91. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.36, H, 6.91.

3-[Hydroxy(phenyl)methyl]-6-methyltetrahydro-2*H*-pyran-2-one (2f). Flash column chromatography (30% EtOAc in hexanes) afforded δ-lactone **2f** as a diastereomeric mixture. Our attempts to separate the diastereomers were unsuccessful: IR (neat) 3418, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, 3H J = 6.30 Hz), 1.93−2.03(m, 3H), 2.38−2.43 (m, 1H), 2.94−2.97 (m, 1H), 3.05 (bs, 1H, OH), 4.30−4.51 (m, 1H), 5.48 (d, 1H, J = 2.48 Hz), 5.54 (d, 1H, J = 2.99 Hz), 7.26−7.85 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.05, 25.81, 25.89, 30.14, 30.86, 47.31, 47.64, 70.72, 72.05, 73.00, 73.08, 126.20, 127.57, 128.13, 128.75, 142.03, 142.36, 171.96. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C, 70.86; H, 7.30.

Ethyl 2-Ethoxycarbonyl-5-(2-hydroxyethoxy)-1-phenylhexan-1-ol (2g). The reaction of **1g** with BH_3·py/$TICl_4$ gave **2g** as a diastereomeric mixture. Our attempts to separate the diastereomers were unsuccessful: IR (neat) 3419, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3H, J = 6.22 Hz), 1.27 (t, 3H, J = 6.95 Hz), 1.51−1.74 (m, 4H), 3.06−3.15 (m, 1H), 3.50−3.69 (m, 5H), 4.14 (q, 2H, J = 6.95 Hz), 4.35−4.49 (m, 1H), 4.53−4.65 (m, 1H), 6.02 (bs, 1H, OH), 7.10−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.49, 19.98, 20.05, 23.93, 24.35, 34.32, 34.68, 53.35, 53.81, 60.97, 61.04, 62.40, 70.01, 74.84, 74.95, 75.35, 76.41, 126.78, 126.85, 128.27, 128.77, 142.16, 142.25, 175.19. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.38; H, 8.77.

***tert*-Butyl (2*R**,3*S**)-2-benzyl-3-hydroxybutanoate (*syn*-2h):** IR (neat) 3508, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 6.38 Hz), 1.29 (s, 9H), 2.62−2.70 (m, 1H), 2.75 (bs, 1H, OH), 2.95 (dd, 2H, J = 6.24 and 3.05 Hz), 4.00 (q, 2H, J = 5.49 Hz), 7.17−7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.28, 27.80, 33.63, 54.75, 67.99, 81.07, 126.14, 128.19, 129.06, 139.23, 173.81; EI-MS *m*/*z* 232, 194, 131, 91(100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.93; H, 8.84.

***tert*-Butyl (2*R**,3*R**)-2-allyl-3-hydroxy-3-phenylpropanoate (*syn*-2i):** IR (neat) 3444, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 2.42 (t, 2H, J = 7.39 Hz), 2.64−2.74 (m, 1H), 3.01 (bs, 1H, OH), 4.84 (d, 1H, J = 5.56 Hz), 4.96−5.09 (m, 2H), 5.68−5.77 (m, 1H), 7.25−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.88, 32.17, 53.24, 74.16, 81.18, 116.57, 126.57, 127.72, 128.21, 135.57, 141.52, 173.42; EI-MS *m*/*z* 206, 143, 107(100), 77, 41. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.21; H, 8.42.

General Procedure for Stereoselective Reduction of α-Alkyl-β-keto Esters 1 with $LiEt_3BH$ in the Presence of Dry $CeCl_3$. A representative experiment is as follows. Finely ground $CeCl_3 \cdot 7H_2O$ (3.2 mmol) was dried by heating at 140 °C/0.1 Torr for 2 h,[39] and then it was suspended in 10 mL of dry THF and left to stir overnight at room temperature. At this temperature, a solution of **1** (1.0 mmol) in 5 mL of THF was added and left to stir for 1 h. Then it was cooled to −78 °C, and $LiEt_3BH$ (2.0 mmol, solution 1 M in THF) was added by syringe. The reaction mixture was then left to stir until TLC or GC indicated that no β-keto ester remained (Table 2). The reaction mixture was quenched with diluted HCl (10%) and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give *anti*-α-alkyl-β-hydroxy esters **2** contaminated only by a minor amount of the *syn* diastereomer. Diastereomeric purity was determined by NMR analysis, and reported yields listed in Table 2 are based on material isolated by flash column chromatography on silica gel using hexanes−EtOAc as the eluent system.

Ethyl (2*R,3*R**)-2-benzyl-3-hydroxybutanoate (*anti*-2a):** IR (neat) 3435, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.21 Hz), 1.30 (d, 3H, J = 6.19 Hz), 1.90 (bs, 1H, OH), 3.05−3.20 (m, 1H), 3.39 (d, 2H, J = 7.87 Hz), 4.05 (q, 1H, J = 6.30 Hz), 4.14 (q, 2H, J = 7.19 Hz), 7.20−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.20, 25.36, 34.10, 52.45, 60.12, 68.71, 126.15, 128.19, 129.32, 138.75, 174.37; EI-MS *m*/*z* 205, 157, 91(100),

(35) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617.

(36) Reetz, M. T.; Chatziiosifidis, I.; Hubner, F.; Heimbach, H. *Org. React.* **1984**, *31*, 101.

(37) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.

(38) Descriptors *R**,*S** indicate that diastereomeric compounds are obtained as racemates. We prefer this terminology to avoid the ambiguities that could arise from *syn*-*anti* descriptors.

(39) Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 231−250.

65, 51. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.21; H, 8.13.

Ethyl (5*R,6*R**)-5-ethoxycarbonyl-6-hydroxyeptanoate (*anti*-2b):** IR (neat) 3456, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16−1.31 (m, 9H), 1.56−1.75 (m, 4H), 2.30 (t, 2H, J = 6.75 Hz), 2.60 (bs, 1H, OH), 2.68−2.76 (m, 1H), 3.90 (after addition of D_2O, t, 1H, J = 6.22 Hz), 4.15 (q, 4H, J = 7.08 Hz); ^{13}C NMR ($CDCl_3$) δ 14.70, 14.75, 21.96, 23.13, 29.24, 34.51, 52.77, 60.81, 61.08, 68.75, 173.67, 175.59; EI-MS m/z 231, 202, 128 (100), 111, 101, 81. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.96, H, 8.22.

Ethyl (2*R,3*S**)-3-hydroxy-2-methyl-3-phenylpropanoate (*anti*-2c):** IR (neat) 3458, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, 3H, J = 7.20 Hz), 1.15 (t, 3H, J = 7.12 Hz), 2.75−2.83 (m, 1H), 2.96 (bs, 1H, OH), 4.16 (q, 2H, J = 7.12 Hz), 4.70 (d, 1H, J = 8.46 Hz), 7.31−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.62, 14.76, 47.62, 61.27, 76.91, 127.16, 128.31, 128.93, 142.09, 176.40; EI-MS m/z 208 (M^+), 163, 107, 102-(100), 91, 55. Anal. Calcd for $C_{12}H_{26}O_3$: C, 69.27; H, 7.74. Found: C, 69.25; H, 7.71.

Ethyl (2*R,3*S**)-2-allyl-3-hydroxy-3-phenylpropanoate (*anti*-2d):** IR (neat) 3460, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.00 Hz), 2.05−2.26 (m, 2H), 2.76−2.87 (m, 1H), 3.27 (d, 1H, J = 5.04 Hz, OH), 4.12 (q, 2H, J = 7.04 Hz), 4.77 (dd, 1H, J = 5.01 and 6.70 Hz), 5.00−5.05 (m, 2H), 5.60−5.70 (m, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.69, 34.26, 53.26, 61.14, 75.26, 117.70, 126.96, 128.45, 129.09, 134.92, 142.32, 175.04; EI-MS m/z 234 (M^+), 193, 143, 91, 79 (100), 77, 41. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.76; H, 7.70.

Ethyl (2*R,3*S**)-3-hydroxy-3-phenyl-2-propargylpropanoate (*anti*-2e):** IR (neat) 3462, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.02 Hz), 2.23−2.38 (m, 3H), 2.84−2.91 (m, 1H), 3.25 (bs, 1H, OH), 4.16 (q, 2H, J = 7.02 Hz), 4.80 (d, 1H J = 7.63 Hz), 7.27−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.13, 18.97, 51.39, 61.17, 70.80, 73.71, 80.25, 126.36, 128.18, 128.42, 140.94, 173.48; EI-MS m/z 232 (M^+), 204, 159, 115 (100), 91. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.34; H, 6.93.

Ethyl 2-[Hydroxy(phenyl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)butanoate (2g). Two diastereomeric β-hydroxy esters were obtained in a *anti*/*syn* ratio of 64:36 (90% yield) by the general procedure for reductions outlined above. These diastereomers were separable by flash column chromatography eluting with 20% EtOAc in hexanes mixture.

***Anti* diastereomer:** IR (neat) 3458, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 6.95 Hz), 1.32 (s, 3H), 1.45−1.62 (m, 2H), 1.83 (t, 2H, J = 7.68 Hz), 3.12−3.17 (m, 1H), 3.80−3.90 (m, 4H), 3.98 (bs, 1H, OH), 4.14 (q, 2H, J = 6.95 Hz), 4.75 (d, 1H, J = 7.40 Hz), 7.12−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.19, 23.56, 24.04, 36.97, 52.29, 60.51, 64.28, 64.84, 72.77, 108.02, 126.20, 127.55, 128.13, 141.59, 174.95. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.80; H, 8.15.

***Syn* diastereomer:** IR (neat) 3436, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7.00 Hz), 1.36 (s, 3H), 1.45−1.62 (m, 2H), 1.96 (t, 2H, J = 7.60 Hz), 3.20−3.29 (m, 1H), 3.82−3.95 (m, 4H), 4.26 (q, 2H, J = 7.01 Hz), 4.95 (d, 1H, J = 5.98 Hz), 6.10 (bs, 1H, OH), 7.18−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.25, 23.59, 24.19, 37.23, 52.92, 60.52, 64.86, 65.02, 72.98, 107.92, 126.70, 127.32, 128.15, 142.63, 175.23. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.82; H, 8.12.

***tert*-Butyl (2*R**,3*R**)-2-benzyl-3-hydroxybutanoate (*anti*-2h):** IR (neat) 3508, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 7.37 Hz), 1.33 (s, 9H), 2.55−2.63 (m, 1H), 2.93 (d, 2H, J = 7.06 Hz), 2.88 (bs, 1H, OH), 3.85 (dq, 1H, J = 7.34 and 6.44 Hz), 7.19−7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.71, 27.87, 35.60, 54.36, 67.72, 81.29, 126.26, 128.21, 129.06, 138.78, 174.22; EI-MS m/z 235, 194, 131(100), 103, 91. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; Found C, 71.90; H, 8.84.

***tert*-Butyl (2*R**,3*S**)-2-allyl-3-hydroxy-3-phenylpropanoate (*anti*-2i):** IR (neat) 3450, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.10−2.36 (m, 2H), 2.66−2.74 (m, 1H), 3.40 (bs, 1H, OH), 4.74 (t, 1H, J = 6.17 Hz), 4.96−5.10 (m, 2H), 5.61−5.78 (m, 1H), 7.25−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.50, 38.49, 53.49, 75.14, 81.86, 117.58, 126.89, 128.22, 128.82, 135.13, 142.55, 174.45; EI-MZ m/z 206, 143, 107(100), 105, 77, 41. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.21, H, 8.44.

2,3,3-Trimethyl-1-phenylbutan-1-ol (5). The reaction of **4** with BH_3·py/$TiCl_4$ or $LiEt_3BH/CeCl_3$ gave a 98:2 or 95:5 mixture of *anti*-**5** and *syn*-**5**, respectively. Diastereomeric purity was determined by NMR analysis: IR (neat) 3400 cm^{-1}; EI-MS m/z 192 (M^+), 118, 107 (100), 91, 57.

***anti*-5:** ^1H NMR ($CDCl_3$) δ 0.62 (d, 3H, J = 7.16 Hz), 1.02 (s, 9H), 1.75 (quint, 1H, J = 7.12 Hz), 1.89 (bs, 1H, OH), 4.62 (d, 1H, J = 7.43 Hz), 7.29−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.36, 29.23, 23.74, 49.30, 77.70; 127.82, 127.93, 128.73, 145.46.

***syn*-5:** ^1H NMR ($CDCl_3$) δ 0.51 (d, 3H, J = 7.08 Hz), 1.08 (s, 9H), 1.76 (quint, 1H, J = 7.00 Hz), 1.94 (bs, 1H, OH), 4.13 (d, 1H, J = 6.86 Hz), 7.29−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.05, 28.99, 33. 07, 50.98, 77.67, 126.91, 127.85, 128.51, 145.69.

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