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Selective Reductions. 59. Effective Intramolecular Asymmetric Reductions of α-, *β*-, and *γ*-Keto Acids with Diisopinocampheylborane and Intermolecular Asymmetric Reductions of the Corresponding Esters with *B*-Chlorodiisopinocampheylborane

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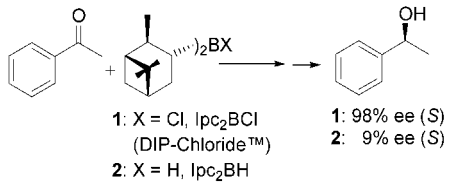
A comparison of the stereochemistry of the products obtained from the intramolecular asymmetric reduction of a series of keto acids with (−)-diisopinocampheylborane and intermolecular asymmetric reduction of the corresponding series of keto esters with (−)-*B*-chlorodiisopinocampheylborane ((−)-DIP-Chloride) has been made. The stereochemistry of the hydroxy acids from the reduction of keto acids is dependent only on the enantiomer of the reagent used. The stereochemistry of the products from the reduction of keto esters is also consistent, except those of aliphatic α-keto esters. α-, *β*-, and *γ*-keto acids provide the corresponding hydroxy acids in 77−98% ee, and the α- and *γ*-keto esters afford the hydroxy esters in 82−≥99% ee. *β*-Keto esters do not undergo reduction. Although the reduction of *δ*-keto acids does not proceed under the same reaction conditions, the reduction of *δ*-keto esters is facile. All of the products from the reduction of *γ*-keto acids and esters and *δ*-keto esters were converted to the corresponding lactones. This study revealed that DIP-Chloride is an efficient reagent for the reduction of α-keto esters at low temperatures.

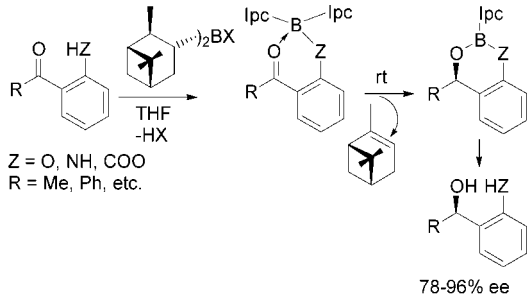
Introduction

B-Chlorodiisopinocampheylborane (Ipc_2BCl, DIP-Chloride, **1**) is very effective for the intermolecular asymmetric reduction of various classes of ketones, such as aralkyl ketones (eq 1), α-hindered ketones, and perfluoroalkyl ketones.[1] It has been applied for the preparation of intermediates for several important pharmaceutical compounds.[2]



(1)

In contrast, the parent diisopinocampheylborane (**2**) is a very poor reagent for intermolecular asymmetric reductions (eq 1).[3] However, we have recently reported that both of these reagents are very effective for intramolecular asymmetric reductions of *o*-acylphenols, -anilines, and -benzoic acids (eq 2).[4] In all of these intramolecular reductions, the product alcohols were obtained in opposite stereochemistry as compared to the intermolecular reduction of the corresponding heteroalkylated acyl derivatives with **1**.[4] We noticed that while the intramolecular asymmetric reduction provided similar % ee for the product alcohols in the case of *o*-acylphenols and-anilines, the % enantiomeric excesses (ee) for the products from the reduction of *o*-acylbenzoic acids with reagent **2** were superior. This was attributed to a partial intermolecular reduction due to an inherent equilibrium between the keto acid and the HCl produced early in the reaction.[4c] This problem was circumvented by utilizing the sodium salt of the keto acid or conducting the reaction in the presence of an amine.[4c]



(2)

The above intramolecular reductions were then extended to aliphatic systems, such as hydroxy ketones and keto acids. The intramolecular asymmetric reduction of

(1) (a) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (b) For a review on DIP-Chloride, see: Ramachandran, P. V.; Brown, H. C. In *Reductions in Organic Chemistry*; Abdel-Magid, A. A., Ed.; ACS Symposium Series No. 641; American Chemical Society: Washington, DC, 1996; Chapter 5.

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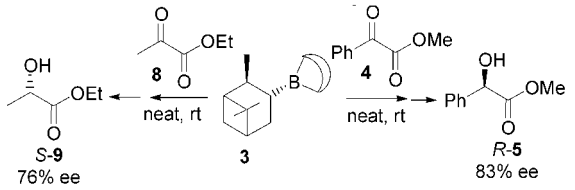
α- and *β*-hydroxy ketones with **1** and **2** provides the corresponding diols in high ee.[5] However, *γ*-hydroxy ketones did not undergo reduction even in refluxing THF. Similarly, aliphatic keto acids undergo asymmetric reduction with **1** and **2**.[6] However there has been no comparison of the stereochemistry of the products obtained from the corresponding keto esters, although it is believed to be opposite. We undertook to examine this and found that the reversal of stereochemistry is not general. We observed differences in the stereochemistry of the products from the reduction of aromatic and aliphatic keto esters themselves with **1**. This study also established that **1** is a much superior reagent than earlier reported for the reduction of α-keto esters. The details of our study are described below.

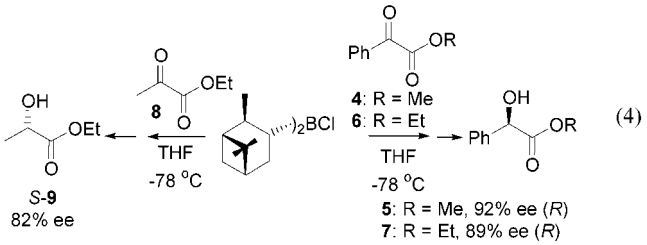
Results and Discussion

Reduction of α-Keto Esters. More than a decade ago, we had reported the reduction of methyl benzoylformate (**4**) with (−)-**1** (prepared from (+)-α-pinene) in THF at −25 °C to (*R*)-methyl mandelate (**5**). On the basis of a gas chromatographic analysis of the corresponding α-methoxy-α-(trifluoromethyl)phenyl acetate, we had reported an ee of 70%.[1a] *R*-Alpine−borane (**3**) reduces **4** to (*R*)-**5** under neat conditions at room temperature (rt) in 83% ee (eq 3).[7] The mode of action of **1** and **3** is believed to be similar. By reducing a series of α-keto esters, we had established that **3** is an efficient reducing agent for this class of ketones (eq 3). However, we had not examined the efficacy of **1** for the reduction of other α-keto esters. During the current project, we had to compare the stereochemistry of the products from the reduction of keto esters and acids.



(3)

A reexamination of the reduction of **4** with (−)-**1** at −25 °C and analysis of **5**, this time using a Chiralcel OD-H column[8] with HPLC, revealed an ee of 84%. The optical rotation, $[\alpha]_D^{25}$ −127.88 upon comparison with that reported in the literature confirmed the *R*-configuration and ee of the hydroxy ester.[9] Since the reduction was complete within 1 h, we performed the experiment at −78 °C with the hope of improving the ee. The reaction was complete in 2 h, and workup provided (*R*)-**5** in 92% ee. To verify the generality of this reduction with **1**, we carried out the reduction of ethyl benzoylformate (**6**) with (−)-**1** at −78 °C and obtained (*R*)-ethyl mandelate (**7**) in 89% ee (eq 4).

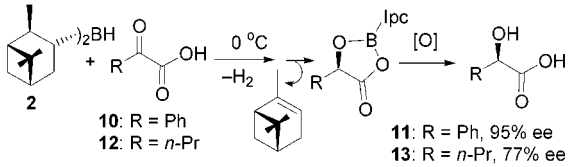


(4)

An aliphatic α-keto ester, ethyl pyruvate (**8**), was reduced by (−)-**1** at −78 °C to (*S*)-ethyl lactate (**9**). A comparison of the rotation of **9** with the literature data[10] revealed an optical purity of 82% (eq 4). Surprisingly, we obtain opposite stereochemistry for the products from the reduction of aromatic and aliphatic α-keto esters with **1**. This is similar to what we had observed for the reduction of these keto esters with **3** as well (eq 3).[7] Thus, we have now established that **1** is an efficient reagent for the reduction of α-keto esters at −78 °C.

Reduction of α-Keto Acids. Either enantiomer of 3-substituted 1(3*H*)-isobenzofuranones (phthalides) can be obtained via an intermolecular asymmetric reduction of 2-acylbenzoates or the intramolecular reduction of the corresponding 2-acylbenzoic acids with **1** followed by lactonization.[4c] Higher ee can be achieved by the reduction of acylbenzoic acids with **2** since this process avoids an undesirable equilibrium between the keto acid and HCl.

To determine whether the reversal in stereochemistry observed in the reduction of aryl and alkyl α-keto esters with **1** is comparable to the reduction of the corresponding keto acids with **2**, we treated benzoylformic acid (**10**) with an equivalent of **2** (prepared from (+)-α-pinene) in THF at 0 °C. Immediate evolution of 1 equiv of hydrogen, followed by an intramolecular reduction within 10 h, provided the intermediate, which was oxidized under alkaline conditions to obtain mandelic acid (**11**) in 82% yield (eq 5). Conversion to the corresponding methyl ester and HPLC analysis using a Chiralcel OD-H column revealed an ee of 95% for (*R*)-**5**. As can be seen, there is no reversal in the stereochemistry as compared to the reduction of the aryl keto ester!



(5)

We then compared the reduction of an aliphatic keto acid, 2-oxopentanoic acid (**12**), with **2**, which was complete within 12 h, and alkaline H_2O_2 workup provided (*R*)-2-hydroxypentanoic acid (**13**) in 77% ee (eq 5), on the basis of the optical rotation reported in the literature.[11]

(4) (a) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141. (b) Ramachandran. P. V.; Malhotra, S. V.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 956. (c) Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417.

(5) Ramachandran, P. V.; Lu, Z. H.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 761.

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(7) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.

(8) Chiralcel OD-H is a product of Chiral Technologies, Inc., Exton, PA.

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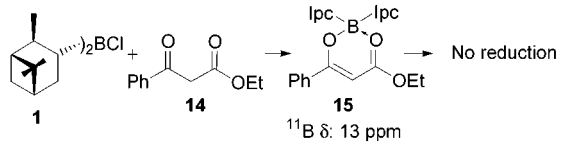
The % ee was further confirmed by ^{1}H NMR spectroscopic analysis of the corresponding acetate in the presence of Eu(hfc)$_3$. Thus, the stereochemistry of the product hydroxy acid depends only on the enantiomer of reagent **2** used and not on the nature (aromatic or aliphatic) of the keto acid reduced. It is noteworthy that there is a reversal in the stereochemistry of the product as compared to the product from the reduction of the corresponding keto ester with **1**. As can be seen from the stereochemistry of the products of reduction of β- and γ-keto acids described below, the exception to the generality is the reduction of aliphatic keto esters with **1**.

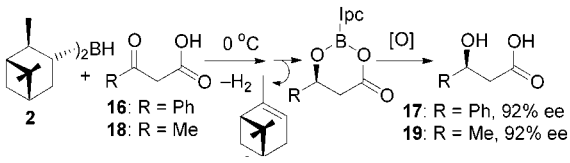
Reduction of α-Keto Esters. We have already shown that **1** is incapable of reducing β-keto esters with an enolizable α-hydrogen atom.[1] Upon mixing the reagent with ethyl benzoyl acetate (**14**), 1 mol of hydrogen chloride was liberated and a strong six-membered chelate (**15**; ^{11}B NMR δ 13 ppm) was formed (eq 6). There was no further change in the ^{11}B NMR spectrum, even after leaving the reaction mixture at room temperature for several days, indicating no further reaction.



(6)

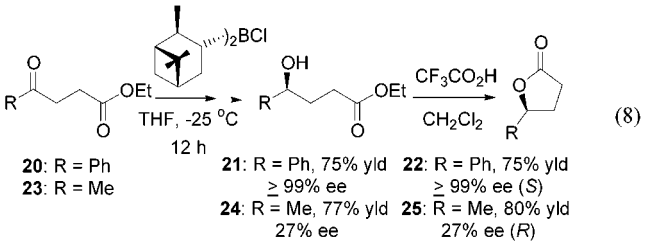
Reduction of α-Keto Acids. In contrast, we expected smooth intramolecular reduction of β-keto acids with **2**. The reduction of benzoylacetic acid (**16**) with **2** was complete within 55 h, and alkaline H_2O_2 workup provided the product hydroxy acid **17** in 85% yield (eq 7). The optical rotation revealed that we had obtained the (*S*)-hydroxy acid in 92% ee. The ee was confirmed by conversion of the product to the benzyl ester and analyzing on a Chiralcel OD-H column using an HPLC. The reduction of an aliphatic β-keto acid, 3-oxo-butanoic acid (**18**), with **2** was complete in 32 h, and the usual workup provided the corresponding hydroxy acid **19** in 75% yield. Conversion of this hydroxy acid to the corresponding benzyl ester and comparison of the maximum rotation reported in the literature[12] revealed an optical purity of 92% in the *R*-isomer (eq 7). The % ee was confirmed by the HPLC analysis of the benzyl ester on a Chiralcel OD-H column.

The stereochemistry of the product hydroxy acids is similar for the α- and β-keto acids. Although we have no way of comparing it with that of the corresponding β-hydroxy esters, the predictability of the product stereochemistry is a useful feature of this reduction.



(7)

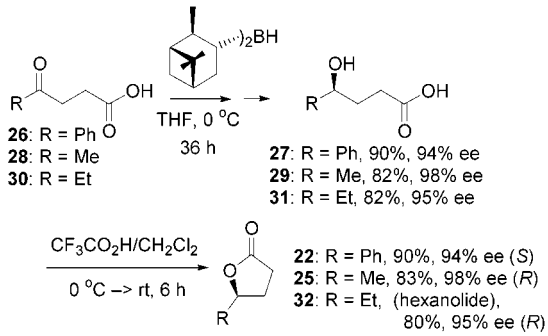
Reduction of γ-Keto Esters. Unlike β-keto esters, the reduction of γ-keto esters is facile with **1**. Since **1** provides high ee for the alcohols from the reduction of aryl ketones, we examined the reduction of ethyl 3-benzoylpropanoate (**20**) with **1** in THF at −25 °C. The reaction was complete in 12 h, and workup provided the product γ-hydroxy ester **21** in 75% yield (eq 8). We converted this to the corresponding γ-lactone **22** by treatment with a catalytic amount of trifluoroacetic acid to determine the optical purity and the stereochemistry. The optical rotation[13] of **22** revealed a purity of ≥99% in the *S*-isomer, which was confirmed by HPLC analysis on a Chiralcel OD-H column. The configurations of **21** and **22** are as expected for a reduction with **1**.



(8)

The reduction of an aliphatic γ-keto ester (**23**) provided the corresponding hydroxy ester **24** in 27% ee. This is expected on the basis of the ineffectiveness of **1** to reduce aliphatic ketones. Cyclization of **24** provided the corresponding lactone **25** in 27% ee.

Reduction of γ-Keto Acids. The reduction of 3-benzoylpropanoic acid (**26**) with **2** was complete within 36 h. Workup provided 90% yield of the corresponding hydroxy acid **27**. This was lactonized in the presence of trifluoroacetic acid to the corresponding γ-lactone **22** in 90% yield (eq 9). The % ee of the lactone as determined by HPLC analysis on a Chiralcel OD-H column is 94%. A comparison of the optical rotation of **22** with that reported in the literature[13] revealed it to be the *S*-isomer, similar to the alcohol obtained from the reduction and hydrolysis of **20** with **1**.



(9)

The reduction of an aliphatic γ-keto acid, 4-oxopentanoic acid (**28**), with **2** resulted in the formation of the corresponding hydroxy acid **29** in 98% ee, as determined by its conversion of to γ-methyl-γ-lactone (*R*-**25**) and comparison of the optical rotation with the literature data[14] (eq 9). Thus the reduction of aliphatic γ-keto acids, followed by esterification of the acid, is an excellent alternative for the reduction of aliphatic γ-keto esters with **1**.

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TABLE 1. Reduction of Keto Esters with (−)-Ipc$_2$BCl

keto ester RCO(CH2)$_n$COOR				reactn cond		hydroxy ester RCH(OH)(CH$_2$)$_n$COOR			
no.	n	R	R′	time, h	temp, °C	no.	% yield	% ee	config[a]
4	0	Ph	Me	<1	−25	**5**	87	84[b]	R
4	0	Ph	Me	1	−78	**5**	89	92[b]	R
6	0	Ph	Et	1	−78	**7**	79	89[b]	R
8	0	Me	Et	1	−78	**9**	75	82[c]	S
14	1	Ph	Et	24	−25	chelate formation, no reacn			
14	1	Ph	Et	24	−25	chelate formation, no reacn			
20	2	Ph	Et	12	−25	**21**	75	≥99[d]	S
23	2	Me	Et	12	25	**24**	77	27	R
33	3	Ph	Et	12	−25	**34**	77	98[d]	S

[a] Determined by comparison of the optical rotation with that reported in the literature. See the text. [b] % ee determined by the HPLC analysis of the hydroxy ester on a Chiralcel OD-H column. [c] % ee determined by comparison of the optical rotation. [d] % ee determined by HPLC analysis of the corresponding lactone on a Chiralcel OD-H column.

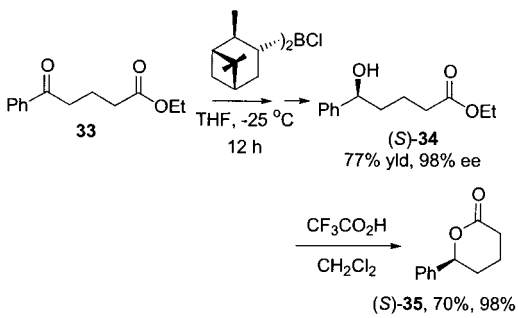
TABLE 2. Reduction of Keto Acids with (−)-Ipc$_2$BH

keto acid RCO(CH$_2$)$_n$COOH				hydroxy acid RCH(OH)(CH$_2$)$_n$COOH			
no.	n	R	reacn time, h	no.	% yield	% ee	config[a]
10	0	Ph	10	**11**	82	95[b]	R
12	0	*n*-Pr	12	**13**	75	77[c]	R
16	1	Ph	55	**17**	85	92[d]	S
18	1	Me	32	**19**	75	92[d]	R
26	2	Ph	36	**27**	90	94[e]	S
28	2	Me	17	**29**	82	98[f]	R
30	2	Et	17	**31**	82	95[f,g]	R
36	3	Et	24[h]				

[a] Determined by comparison of the optical rotation with that reported in the literature. See the text. [b] % ee determined by the HPLC analysis of the hydroxy ester on a Chiralcel OD-H column. [c] % ee determined by ^{1}H NMR spectroscopic analysis of the acetate in the presence of Eu(hfc)$_3$. [d] % ee determined by HPLC analysis of the corresponding benzyl ester on a Chiralcel OD-H column. [e] % ee determined by HPLC analysis of the corresponding lactone on a Chiralcel OD-H column. [f] % ee determined by comparison of the optical rotation. See the text. [g] % ee determined by ^{1}H NMR spectroscopic analysis (in the presence of Eu(hfc)$_3$) of the diol obtained by opening the lactone with excess MeLi.[16] [h] There was no reaction even in refluxing THF.

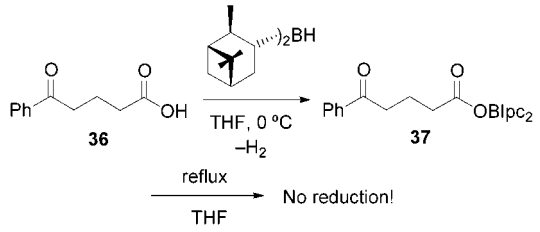
The possibility of the formation of both aliphatic and aromatic γ-lactones in high ee via the asymmetric reduction of γ-keto acids with **2** prompted us to include the reduction of 4-oxohexanoic acid (**30**) as well since the corresponding lactone, 4-hexanolide (**32**), is a component of the pheromone secreted by the female dermestid beetle *Trogoderma glabrum*. We obtained the hydroxy acid **31** in 95% ee, which was converted to the pheromone without any loss of optical activity.

Reduction of γ-Keto Esters. Reduction of ethyl 4-benzoylbutanoate (**33**) with **1** in THF at −25 °C was complete in 12 h, and the usual workup provided the corresponding δ-hydroxy ester **34**. The enantiomeric excess was determined by converting this to the corresponding δ-phenyl-δ-lactone **35** (eq 10). A comparison of the rotation with that reported in the literature[15] revealed an optical purity of 98% in the *S*-isomer, which was confirmed by HPLC analysis on a Chiralcel OD-H column. The stereochemistry of **34** and **35** is as would be expected for the reduction of such a ketone with **1**.



(10)

Reduction of γ-Keto Acids. When a δ-keto acid, 4-benzoylbutanoic acid (**36**), was mixed with **2**, evolution of 1 molar equiv of hydrogen was observed with the concurrent formation of the diisopinocampheylborinate **37** as indicated by the ^{11}B NMR spectrum. However, unlike in the case of α-, β-, and γ-keto acids, no intramolecular reduction was observed (eq 11). Heating the THF solution to reflux made no difference. Thus, the intramolecular asymmetric reduction is limited to α-, β-, and γ-keto acids.



(11)

The reduction of all of the keto esters is summarized in Table 1, and that of keto acids is summarized in Table 2.

Conclusions

In conclusion, we have studied the intramolecular asymmetric reduction of a series of α-, β-, and γ-keto acids with (−)-diisopinocampheylborane and intermolecular asymmetric reduction of the corresponding series of keto

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esters with (−)-*B*-chlorodiisopinocampheylborane and compared the stereochemistry of the products obtained. The hydroxy derivatives were obtained in 77−≥99% ee. The stereochemistry of the products is independent of the keto acids and esters in all cases, except in the case of aliphatic α-keto esters. This study has revealed that DIP-Chloride is an efficient reagent for the reduction of α-keto esters in 82−92% ee. The reduction of δ-keto acids does not proceed under the same reaction conditions, and the reduction of δ-keto esters is facile. γ- and δ-lactones were prepared from the product γ-hydroxy acids and esters and δ-hydroxy esters.

Experimental Section

General Methods. All operations were carried out under an inert atmosphere. Techniques for handling air- and moisture-sensitive materials have been previously described.[17] The ^{1}H and ^{11}B NMR spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. The optical rotations were measured using a Rudolph Autopol III polarimeter.

Materials. THF was distilled from sodium benzophenone ketyl. β-Keto acids were prepared according to a literature procedure.[18] γ- and δ-keto acids were prepared from the corresponding esters by base hydrolysis. Enantiomerically pure (−)-Diisopinocampheylborane was prepared from (+)-α-pinene and borane−methyl sulfide according to the literature procedure.[19]

General Procedure for the Intramolecular Reduction of Keto Acids with Ipc_2BH. All of the procedures were carried out in an inert atmosphere. An oven-dried, 100 mL round-bottom flask equipped with a sidearm, magnetic stirring bar, and connecting tube was cooled to room temperature in a stream of nitrogen. (−)-Ipc_2BH (**2**) (2.82 g, 10 mmol) was transferred to the flask in a glovebag and suspended in THF (10 mL), and the mixture was stirred at 0 °C. The keto acid (10 mmol) dissolved in minimum amount of anhydrous THF was slowly added, at 0 °C, to the flask when evolution of hydrogen was noticed. The ^{11}B NMR of the resultant clear solution showed a peak at δ 52 ppm. The mixture was warmed to room temperature. The progress of the reaction was monitored by ^{11}B NMR spectroscopy, which revealed a peak at δ 32 ppm when the reaction was complete. Upon completion of the reaction, the mixture was oxidized by the addition of 4 mL of 3 N NaOH and 2 mL of 30% H_2O_2. The aqueous layer was separated, washed several times with Et_2O to remove organics, and acidified using 1.0 M aqueous HCl. The product hydroxy acid was extracted with EtOAc (3 × 40 mL). The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Removal of solvents afforded reasonably pure hydroxy acid, which was further purified for recording the optical rotation.

General Procedure for the Intermolecular Reduction of Keto Esters with (−)-DIP-Chloride. All of the procedures were carried out in an inert atmosphere. An oven-dried, 100 mL round-bottom flask equipped with a sidearm, magnetic stirring bar, and connecting tube was cooled to room temperature in a stream of nitrogen. To this was added 11 mmol (3.5 g) of (−)-DIP-Chloride ((−)-**1**) and THF (11 mL), and the mixture was cooled to −78 °C, followed by the addition of 10 mmol of the α-keto ester. A yellow color developed indicating a complex formation. The ^{11}B NMR spectrum of a methanolyzed aliquot of the reaction mixture (δ 32 ppm) indicated progressive disappearance of **1**. The reagent was consumed in 2 h when the mixture was warmed to 0 °C and treated with 2.2 equiv of diethanolamine. This mixture was filtered through a silica gel and chromatographed to isolate pure hydroxy ester.

The reaction of γ- and δ-keto esters were carried out at −25 °C.

Preparation of Lactones from Hydroxy Acids and Hydroxy Esters. The following procedure for the synthesis of 4-hexanolide is representative. The hydroxy acid **31** prepared as described above (1.1 g, 82%) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C, followed by the addition of 4 drops of trifluoroacetic acid. Stirring for 6 h at room temperature completed the lactonization, and the reaction was worked up with aqueous sodium bicarbonate. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to yield 0.76 g (80%) of **32**, $[\alpha]_D^{20} = +50.63$ (*c* 1.5, MeOH), which corresponds to 95% ee in the (*R*)-isomer.[20]

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