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Efficient Intramolecular Asymmetric Reductions of α-, β-, and γ-Keto Acids with Diisopinocampheylborane[1]

P. Veeraraghavan Ramachandran,* Herbert C. Brown, and Sangeeta Pitre

Herbert C. Brown Center for Borane Research, Purdue University, West Lafayette, Indiana 47907-1393

chandran@purdue.edu

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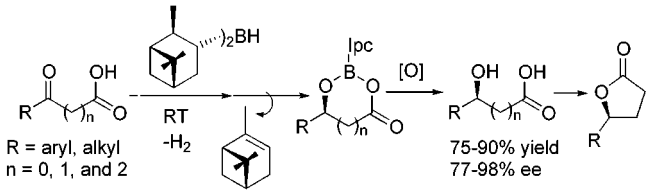
ABSTRACT



α-, β-, and γ-Keto acids are reduced with diisopinocampheylborane at room temperature to the corresponding hydroxy acids with predictable stereochemistry in very high ee. The γ-hydroxy acids produced were conveniently cyclized to the corresponding lactones. This provides a simple synthesis of 4-hexanolide, a component of the pheromone secreted by the female dermestid beetle *Trogoderma glabrum*.

The preparation of optically pure hydroxy esters or acids and their conversion to lactones are important processes in organic syntheses as a result of the significance of such molecules.[2] Asymmetric reduction of the corresponding ketones is an efficient route to achieve this goal. We had reported that one of our successful reagents, *B*-chlorodiisopinocampheylborane (Ipc_2BCl, DIP-Chloride, **1**) is very effective for the intramolecular asymmetric reductions of various classes of ketones, including keto acids.[3] The % enantiomeric excess (ee) achieved for the products from the reduction of *o*-acylbenzoic acids with **1** was inferior, attributed to a partial intermolecular reduction.[3] Utilizing the sodium salt of the keto acid or conducting the reaction in the presence of an amine circumvented this problem.[3] Carrying out the reduction with the parent diisopinocampheylborane (**2**) also solved the difficulty.[3] Utilizing our procedure, two separate reports on the reduction of α- and β-keto acids with **1** in the presence of amines have recently appeared.[4] We herein report the intramolecular reduction of aliphatic keto acids with **2**.

Reduction of α- and β-keto acids (**3** and **5**, respectively) with **2** provided essentially similar results as described with **1**.[4] However, the absence of hydrogen chloride in the medium makes the reduction with **2** more efficient. The workup is simple and the procedure can be applied to acid-sensitive molecules as well. Our results from α- and β-keto acids are summarized in Table 1.

The reduction was then extended to γ-keto acids. 3-Benzoylpropanoic acid (**7a**) was reduced with **2** within 36 h at room temperature. Workup provided 90% yield of the corresponding hydroxy acid **8a**, which was lactonized in the presence of trifluoroacetic acid to the corresponding γ-lactone **9a** in 90% yield and 94% ee in the *S*-isomer (Scheme 1).[5] The reduction of an aliphatic γ-keto acid, 4-oxopentanoic acid (**7b**), with **2** yielded the corresponding hydroxy acid **8b** in 98% ee. This was readily converted to the lactone **9b**.

We included the reduction of 4-oxohexanoic acid (**7c**) and

(1) Contribution 7 from the Herbert C. Brown Center for Borane Research.

(2) (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. (b) Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991** *32*, 4619. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

(3) (a) DIP-Chloride is the trademark of the Aldrich Chemical Co. (b) Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205.

(4) (a) Wang, Z.; La, B.; Fortunak, J. M.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1998** *39*, 5501. (b) Wang, Z.; Zhao, C.; Pierce, M. E.; Fortunak, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 225.

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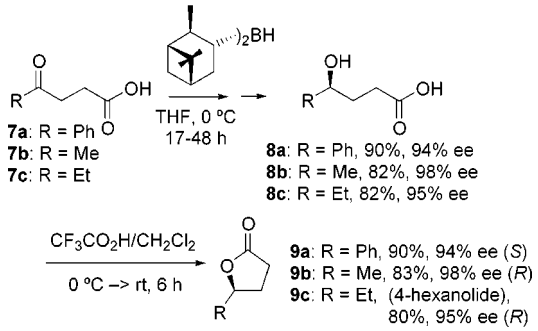
Table 1. Reduction of Keto Acids with (−)-Ipc$_2$BH (**2**)

keto acid R-CO-(CH$_2$)$_n$COOH			rxn time	hydroxy acid R-CH(OH)-(CH$_2$)$_n$COOH			
no.	*n*	R	h	no.	yield (%)	ee (%)	config[a]
3a	0	Ph	10	**4a**	82	95[b]	*R*
3b	0	*n*-Pr	6	**4b**	75	77[c,d]	*R*
5a	1	Ph	55	**6a**	85	92[d]	*S*
5b	1	Me	32	**6b**	75	92[d]	*R*
7a	2	Ph	36	**8a**	90	94[e]	*S*
7b	2	Me	17	**8b**	83	98[f]	*R*
7c	2	Et	48	**8c**	82	95[f,g]	*R*

[a] Determined by comparison of the optical rotations with those reported in the literature. [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 ethyl acetoxycarboxylate 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. [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.[8]

conversion to the corresponding γ-caprolactone, 4-hexanolide (**9c**), in 95% ee because of its importance as a component of the attractant pheromone of several *Trogoderma* species of dermestid beetles, such as *T. glabrum* and *T. granarium*.[6]

Scheme 1



δ-Keto acids did not undergo intramolecular reduction with **2**, even in refluxing THF. Thus, the intramolecular asymmetric reduction is limited to α-, β-, and γ-keto acids.

In conclusion, we have shown that diisopinocampheylborane is an excellent reagent for the intramolecular asymmetric reduction of aliphatic and aromatic α-, β-, and γ-keto acids. The hydroxy acids were obtained in 75−90% yields and 77−98% ee. The reduction of δ-keto acids does not proceed under the same conditions. This protocol has been utilized for the convenient synthesis of γ-lactones from the corresponding γ-keto acids.[7] The natural isomer of the insect pheromone of a dermestid beetle, 4-hexanolide, has also been synthesized.

Acknowledgment. Financial assistance from the United States Army Research Office (DAAG55-98-1-0405) is gratefully acknowledged.

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(5) The % ee and configuration are based on the optical rotation reported in the literature. Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365.

(6) (a) Mori, K.; Mori, H.; Sugai, T. *Tetrahedron* **1985**, *41*, 919 and references therein. (b) It has been shown that *T. granarium* responds to (*R*)-**9** only and not to its antipode or a racemic mixture.

(7) **Representative procedure** for the synthesis of 4-hexanolide. An oven-dried, 100 mL round-bottom flask equipped with a sidearm, magnetic stirring bar, and a connecting tube was cooled to room temperature in a stream of nitrogen. (−)-Ipc$_2$BH (**2**) (2.82 g, 10 mmol) was transferred to the flask in a glovebag, suspended in THF (10 mL) and stirred at 0 °C. 4-Oxohexanoic acid (1.3 g, 10 mmol) dissolved in a minimum amount of anhydrous THF was slowly added, at 0 °C, to the flask when evolution of hydrogen was observed. 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. The mixture was oxidized by the addition of 4 mL of 3 N NaOH and 4 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 the hydroxy acid (1.1 g, 82%), which was dissolved in CH_2Cl_2 (10 mL) and 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 **9c**, $[\alpha]^{20}_D = +50.63$ (*c* 1.5, MeOH), which corresponds to 95% ee in the (*R*)-isomer.[6]

(8) Jakovac, I. J.; Jones, J. B. *J. Org. Chem.* **1979**, *44*, 2165.