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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of β-hydroxy carboxylic acids: direct conversion of β-oxocarboxylic acids to enantiomerically enriched β-hydroxy carboxylic acids via neighboring group control

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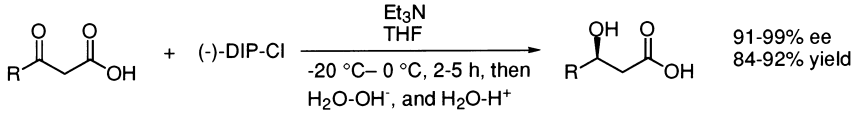
Abstract

β-Oxocarboxylic acids can be reduced to the corresponding β-hydroxy carboxylic acids employing DIP-Cl™ as a reducing agent. The β-carboxylic substituent exerts a remarkable neighboring group effect on the reduction. The reaction presumably proceeds in an intramolecular fashion through a 'rigid' bicyclic transition state assembly, which produces enantioselectivities approaching 99%.

Optically active β-hydroxy acids are important building blocks in organic synthesis, for example, in the syntheses of β-amino acids,[1] β-lactams,[2] and pheromones.[3] β-Hydroxy acids are also important subunits[4] of polyketide natural products such as amphotericin B,[5] tylosin[6] and rosaramicin.[7] Extensive effort in this field has resulted in fruitful synthetic methods for the synthesis of optically active β-hydroxy acids or their derivatives, utilizing, for example, aldol reactions,[8] and hydrogenation reactions.[9] We have been interested in developing a simple, straightforward, and generally applicable method for the enantioselective synthesis of β-hydroxy acids. Herein, we wish to report an efficient method to directly convert β-oxocarboxylic acids to chiral β-hydroxy carboxylic acids employing DIP-Cl™ as the reducing agent.



(1)

B-Chlorodiisopinocampheylborane is a remarkably versatile reducing agent in asymmetric synthesis.[10,11] This reagent has been successfully applied to a number of reduction reactions, including asymmetric reduction of ketones,[12] fluoroketones,[13] diketones,[14] α- and β-hydroxy ketones,[15] and

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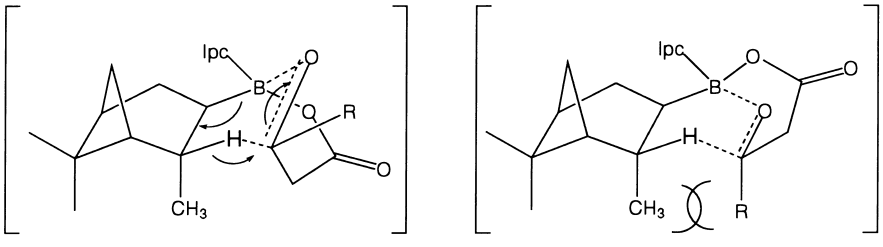
ortho-substituted amino-, hydroxy- and carboxylic benzophenones.[16] We have recently demonstrated that α-oxocarboxylic acids can be reduced in a highly enantioselective manner employing DIP-Cl™ as the reducing agent.[17] The reactions apparently took place in an intramolecular fashion via a neighboring group control, involving mixed boronate intermediates after ligand exchange.[17–19] Applying the same concept, we have achieved a methodology for the syntheses of enantiomerically enriched β-hydroxy carboxylic acids using highly enantioselective DIP-Cl™ reduction of β-oxocarboxylic acids.

In a sharp contrast to the DIP-Cl™ reduction of β-keto esters,[20] which occurred very sluggishly and generated low enantioselectivities, the DIP-Cl™ reduction of β-oxocarboxylic acids, in the presence of triethylamine, proceeds rapidly (in 1–5 h at −20–0°C) to afford the desired hydroxy carboxylic acids, with high enantioselectivities (91–99% ee) and with predictable absolute configuration. As we reported earlier, triethylamine significantly enhances the reaction rate.[17–19] A plausible mechanism for this reduction reaction may involve a 'rigid' bicyclic transition state assembly, as shown in Scheme 1.[17–19] One of the enantiotopic faces of the β-carbonyl is exposed to the reductive hydrogen via a 'locked' transition state. Of the two approaches, only one face (*Si*-face, assuming $-CH_2COOH$ is >R) approach of the β-carbonyl is favored since the R-group assumes an equatorial-like position in the six-membered ring which minimizes steric interaction. The *Re*-face (assuming $-CH_2COOH$ is >R) approach, on the other hand, is less favored due to the steric interaction between the axially (or axial-like) oriented R-group with the *endo*-methyl of the campheyl ligand. The preferred facial approach yields β-hydroxy carboxylic acids with the desired configuration shown in Eq. 1, which is consistent with the actual configuration observed in our results.



1. favored **2**. disfavored

Scheme 1.

As summarized in Table 1, β-oxocarboxylic acids[21] in methylene chloride are treated with triethylamine (1.0 equiv., −20°C, 5 min) and 1.2 equiv. of (−)-DIP-Cl™ (−20°C). Upon completion of the reaction (−20°C to 0°C for 1–5 h), the mixture is quenched with water. After basic hydrolysis, followed by acidic work-up, the desired optically active β-hydroxy carboxylic acids are obtained in 87–92% yield and 91–99% ee (Table 1). The absolute configurations of the products are determined by optical rotation through the comparison with literature.[8]

In summary, we have demonstrated that the β-carboxylic substituent exerts a remarkable neighboring group effect on the reduction of β-oxocarboxylic acids to their corresponding β-hydroxy carboxylic acids employing DIP-Cl™ as a reducing agent. This reaction presumably proceeds through a 'rigid' bicyclic transition state assembly, which leads to their enantioselective excesses approaching 99%.[22]

Acknowledgements

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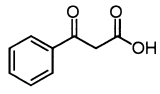
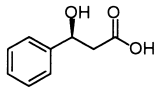
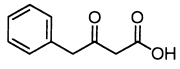
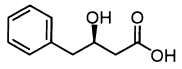
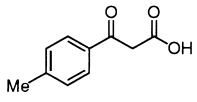
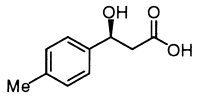
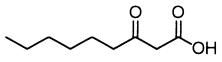
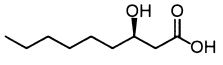
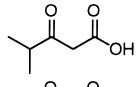
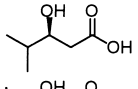
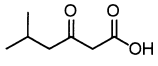
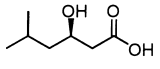
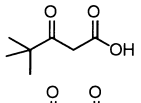
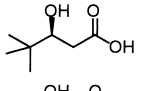
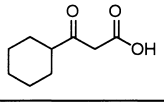
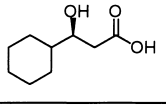
Table 1
Synthesis of β-hydroxy acids via DIP-Cl™ reduction of β-oxocarboxylic acids

Oxocarboxylic Acid	Product[a]	Yield %[b]	ee %[c]
		87	98
		88	91
		92	96
		88	95
		89	96
		92	>98
		91	>98
		89	97

(a). The absolute configuration was determined by the comparision with literature data.
(b). Isolated yield.
(c). The enantiomeric excess was determined by chiral HPLC employing either Chiralcel OD or AD columns (mobile phase: Hexane/IPA from 90/10 to 97/3) after conversion of the products to their corresponding methyl or benzyl esters.

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20. For example, treatment of 3-oxo-nonanoic acid benzyl ester with DIP-Cl™ for 5 h at 0°C, only less than 20% conversion with <40% ee was observed.
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22. The synthesis of (*R*)-(−)-3-hydroxyl-5-methyl hexanoic acid serves as an example. A solution of 5-methyl-3-oxo-hexanoic acid (2.0 g, 14.0 mmol, 1 equiv.) in CH_2Cl_2 (20 ml) was treated with Et_3N (2.0 ml, 14.0 mmol, 1 equiv.) at −20°C and stirred for 5 min followed by the addition of (−)-DIP-Cl™ (5.4 g, 16.7 mmol, 1.2 equiv. in 20 ml of CH_2Cl_2) slowly. The reaction mixture was gradually warmed up to 0°C and stirred at 0°C for 2 h (monitored by TLC, hexane:ethyl acetate:formic acid, 1:1:0.05). Upon the completion of the reaction, it was quenched with water, and basified with NaOH (10%) to pH>12; then extracted with *t*-butyl methyl ether (2×35 ml) and the organic layers were combined and washed with water (25 ml). The aqueous layers were then combined and acidified with HCl (2 N) to pH∼2 and extracted with ethyl acetate (3×80 ml). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, removal of solvents, the desired of (*R*)-(−)-5-methyl-hydroxyl hexanoic acid was obtained in 92% yield with >98% ee. $[\alpha]_D$= −15.8 (c=1.03, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$, δ=ppm, J=Hz), 4.16 (m, 1H), 2.53 (m, 2H), 1.81 (m, 1H), 1.53 (m, 1H), 1.23 (m, 1H), 0.93 (d, J=6.6, 6H). ^{13}C NMR (ppm), 177.6, 66.3, 45.5, 41.5, 24.4, 23.1, 22.0. The product (44 mg, 0.306 mmol, 1 equiv.) was treated with K_2CO_3 (46.4 mg, 0.336 mmol, 1.1 equiv.) and BnBr (57 mg, 0.336mmol, 1.1 equiv.) in DMF (2 ml) starting from 0°C to rt for 4 h; and then washed with saturated $NaHCO_3$ and NH_4Cl to obtain the desired benzylester derivative. HPLC studies (Chiralcel OD column, Hex/IPA=94/6, peaks at R=6.21 min and 7.70 min) revealed 99% ee.