Pergamon

Tetrahedron Letters 39 (1998) 5501–5504

TETRAHEDRON LETTERS

Enantioselective Synthesis of α-Hydroxy Carboxylic Acids: Direct Conversion of α-Oxocarboxylic Acids to Enantiomerically Enriched α-Hydroxy Carboxylic Acids via Neighboring Group Control

Zhe Wang*, Brittany La[1] and Joseph M. Fortunak

DuPont Merck Pharmaceutical Company, Research & Development

Chambers Works, Deepwater, NJ 08023.

Xian-Jun Meng[2] and George W. Kabalka

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996

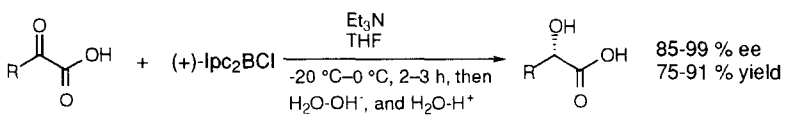
Dedicated to Professor E. J. Corey on the occasion of his 70th birthday

Received 6 April 1998; revised 28 May 1998; accepted 2 June 1998

Abstract: α-Oxocarboxylic acids can be reduced to the corresponding α-hydroxy carboxylic acids employing DIP-Cl™ as a reducing agent. The α-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%.

© 1998 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd. All rights reserved.

Optically active α-hydroxy acids are important building blocks in organic synthesis, for example, in the syntheses of glycols,[3] α-halo esters[4] and epoxides.[5] α-Hydroxy acids have also been widely employed as starting materials for the synthesis of complex molecules, such as prostaglandins[6] and angiotensin converting enzyme (ACE) inhibitors.[7] Considerable effort in this field has resulted in several synthetic[8,9] and enzymatic[10] methods for the synthesis of optically active α-hydroxy acids. We have been interested in developing a simple, straightforward, and generally applicable method for the enantioselective synthesis of α-hydroxy acids. Herein, we wish to report an efficient method to directly convert α-oxocarboxylic acids to chiral α-hydroxy carboxylic acids employing DIP-Cl™ as the reducing agent.



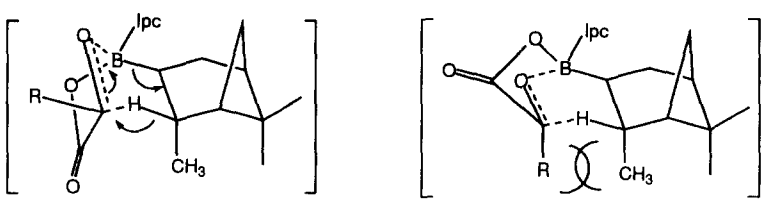
B-Chlorodiisopinocampheylborane is a remarkably versatile reducing agent in asymmetric synthesis.[11,12] This reagent has been successfully applied to a number of reduction reactions, including

0040-4039/98/$19.00 © 1998 The DuPont Merck Pharmaceutical Company.
Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(98)01162-9

asymmetric ketone reductions,[13,14] fluoroketone reductions[15] and the syntheses of C_2 -symmetric auxiliaries.[16] Brown recently reported the reduction reactions of α- and β-hydroxy ketones[17] employing DIP-Cl™ as the reducing agent. The reactions apparently took place *via* ketoalkyl diisopinocamphenyl-borinate intermediates. Those observations are consistent with our reports related to allylboration of α-hydroxy ketones[18] and α-oxoacids[19] in which we postulated that the allylboration occurred in an intramolecular fashion *via a neighboring group control* involving mixed boronate intermediates after ligands exchange. Applying the same concept, we have achieved a methodology for the syntheses of enantiomerically enriched α-hydroxy carboxylic acids using highly enantioselective DIP-Cl™ reduction of α-oxocarboxylic acids.

In contrast to the DIP-Cl™ reduction of α-keto esters,[20] which occurred rather sluggishly and generated low enantioselectivities, the DIP-Cl™ reduction of α-oxocarboxylic acids, in the presence of triethyl amine, proceeds rapidly (in 2-3 h at -20 °C- 0 °C) to afford the desired hydroxy carboxylic acids, with high enantioselectivities (85-98% ee) and with predictable absolute configuration. As we reported earlier, triethylamine significantly enhances the reaction rate. A plausible mechanism for this reduction reaction may involve a "rigid" bicyclic transition state assembly, as shown in Scheme 1.[18,19] One of the enantiotopic faces of the α-carbonyl is exposed to the reductive hydrogen via a "locked" transition state. Of the two approaches, the *Re*-face approach of the α-carbonyl is favored since the R-group assumes an equatorial-like position in the six-membered ring which minimizes steric interaction. The *Si*-face approach, on the other hand, is less favored due to the steric interaction between the axial-like oriented R-group with the endo-methyl of the campheyl ligand. The preferred *Re*-face approach yields α-hydroxy carboxylic acids with the S-configuration, which is in consistent with the actual configuration observed in our results.

Scheme 1

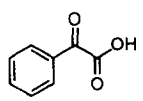
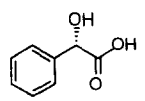
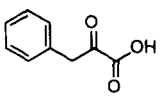
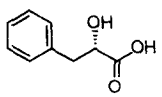
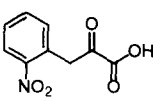
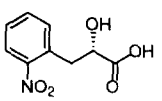
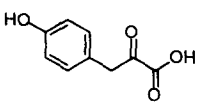
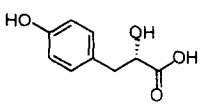
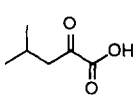
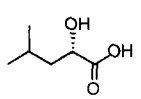
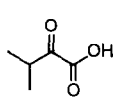
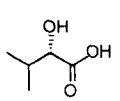
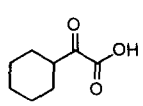
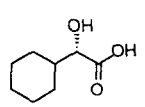


1, favored **2**, disfavored

As summarized in Table 1, α-oxocarboxylic acids in either THF or methylene chloride are treated with triethylamine (1.0 equivalent, -20 °C, 5 minutes) and 1.2 equivalent of (+)-DIP-Cl™ (-20 °C). Upon completion of the reaction (-20 °C to 0 °C for 2–3 h), the mixture is quenched with water. After basic hydrolysis, followed by acidic workup, the desired optically active (S)-α–hydroxy carboxylic acids are obtained in 65-91% yield and 85-98% ee (Table 1). The absolute configurations of the products are determined by optical rotation through the comparison with the authentic samples.

In summary, we have demonstrated that the α-carboxylic substituent exerts a remarkable neighboring group effect on the reduction of α-oxocarboxylic acid to its corresponding α-hydroxy carboxylic acid employing DIP-Cl™ as a reducing agent. This reaction presumably proceeds through a "rigid" bicycle transition state assembly, which leads the enantioselectivity excess approaching to 99%.

Table 1. Synthesis of α-Hydroxy Acids *via* DIP-Cl ™ Reduction of α-Oxocarboxylic Acids

Oxocarboxylic Acid	Product	Yield %[a]	ee %[b]
		91	96
		70	90
		74	95
		78	93
		65	89
		65	85
		88	98

(a). Isolated yield.
(b). The enantiomeric excess were determined either by NMR after converting the products to their methyl esters and then to their corresponding Mosher esters, or by optical rotation with authentic samples.

ACKNOWLEDGMENT:

BL would like to thank Mr. Silvio Campana for his technical guidance during her summer intern research. She also acknowledges her summer internship and the financial support from the DuPont Merck summer intern program.

REFERENCES:

1. Current address: Department of Chemistry, Wesleyan University, Middletown, CT 06459.
2. Current address: DuPont Co.; Agricultural Division, Newark, DE 19713.
3. Prelog, V.; Wilhelm, M.; Bright, D. B. *Helv. Chim. Acta* **1954**, *37*, 221.
4. Lee, J. B.; Downie, I. M. *Tetrahedron* **1967**, *23*, 359.
5. Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *25*, 933.
6. Grieco, P. A.; Takigawa, T.; Vedananda, T. R. *J. Org. Chem.* **1989**, *50*, 3111.
7. (a) Iwasaki, G.; Kimura, R.; Numao, N.; Kondo, K. *Chem. Pharm. Bull.* **1989**, *37*, 280.
   (b) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143.
8. (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
   (b) Duan, X. F.; Yin, C. L. *Synth. Comm.* **1997**, *27*, 825
9. Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435.
10. Adam, W.; Lazarus, M.; Boss, B.; Saha-Mollor, C. R.; Humpf, H.-U.; Schreier, P. *J. Org. Chem.* **1997**, *62*, 7841, and references cited therein.
11. (a) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*. 16. (b) Brown, H. C.; Ramachandran, P. V. *Pure Appl. Chem.* **1994**, *66*. 201.
12. Zhao, M.; King, A. O.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 2641.
13. (a) Brown, H. C.; Ramachandran, P. V. *Organometal. Chem.* **1995**, *500*, 1.
14. (a) Shieh, W.-C.; Cantrell, W. M.; Carlson, J. A. *Tetrahedron Lett.* **1995**, *36*, 3797.
    (b) Ramachandran, P. V.; Malhotra, S. V.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 957, and the references cited therein.
15. Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41.
16. Sablong, R.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937 and the references cited therein.
17. Ramachandran, P. V.; Lu, Z.-H.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 761.
18. Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 1945.
19. (a) Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 4619.
    (b) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677.
20. Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
21. The synthesis of (S)-mandelic acid serves as an example. A solution of benzoformic acid (2.04 g, 13.6 mmol, 1 eq.) in THF (50 ml) was treated with Et_3N (1.9 ml, 13.6 mmol, 1 eq.) at -20 °C and stirred for 5 minutes followed by the addition of (+)-DIP-Cl (5.24 g, 16.3 mmol, 1.2 eq. in 20 ml of THF) slowly. The reaction mixture was gradually warmed up to room temperature ant stirred at r.t. for 3 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; and extracted with *t*-butyl methyl ether (2 x 35 ml) and the organic layers were combined and washed with water (25 ml). The aqueous layers were then combined and acidified with HCl (2N) to pH~2; and extracted with ethyl acetate (3 x 80 ml). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, removal of solvents and silica gel plug filtration (hexane/ethyl acetate/formic acid = 1/1/0.05), the desired S-mandelic acid was obtained in 91% yield with 96% ee. $[\alpha]_D$= +150 (c=2.8, H_2O), ^{1}H-NMR (300 MHz, $CDCl_3$ + DMS)-d_6, δ=ppm, J=Hz), 7.33-7.26 (m, 2H), 7.20-7.14 (m, 3H), 4.98 (s, 1H). ^{13}C-NMR (ppm), 175.0, 139.1, 128.2 (2C), 127.9 (2C), 126.6, 72.6. The product (2 mg) was treated with diazomethane; and then Mosher chloride to form a mandelic acid methyl ester Mosher derivative. its ^{1}H-NMR studies (peaks at δ = 6.12 and 6.09) revealed 96% ee.