Tetrahedron Letters, Vol.31, No.25, pp 3567-3570, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

# A NOVEL SYNTHESIS OF BOTH ENANTIOMERS OF α-HYDROXYCARBOXYLIC ESTERS AND AMIDES FROM (-)-1-CHLOROBUTYL *p*-TOLYL SULFOXIDE

Tsuyoshi Satoh, Ken-ichi Onda, and Koji Yamakawa*
Faculty of Pharmaceutical Sciences, Science University of Tokyo,
Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

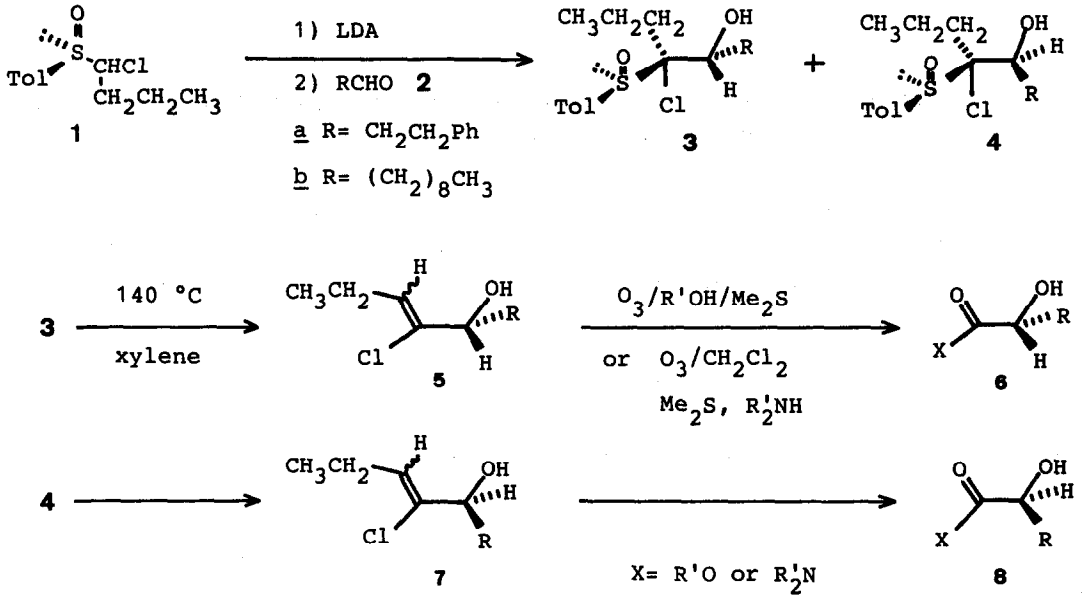
Summary Addition of the carbanion of (-)-1-chlorobutyl *p*-tolyl sulfoxide to aldehydes gave two adducts, which were converted to both enantiomers of α-hydroxycarboxylic esters or amides in two steps in high overall yields.

Much attention has been focused on asymmetric synthesis in modern synthetic organic chemistry and various kinds of chiral auxiliaries have been developed.[1] The use of optically active sulfoxides in asymmetric synthesis is relatively recent[2] and these fascinating chiral auxiliaries have not yet been put to full use in asymmetric synthesis.

Recently, we reported a novel synthesis of optically active epoxides and aziridines using optically active 1-chloroalkyl *p*-tolyl sulfoxides.[3] In continuation of our studies on the use of optically active 1-chloroalkyl p-tolyl sulfoxides in asymmetric synthesis, here we describe a novel synthesis of both enantiomers of α-hydroxycarboxylic esters and amides from (-)-1-chlorobutyl *p*-tolyl sulfoxide 1 and aldehydes (Scheme 1).

A representative example of this method is described below using hydrocinnamaldehyde 2a as the aldehyde. Treatment of (-)-1-chlorobutyl p-tolyl sulfoxide 1 (over 98% ee)[4] with LDA in THF at -55 °C followed by 2a afforded two products, which were easily separated by flash chromatography[5] to give the less polar adduct 3a and the more polar adduct 4a in 42% and 49% yields, respectively (3a: $[\alpha]_D^{25}$ -59.0° (C 0.8, acetone); 4a: $[\alpha]_D^{25}$ -157.8° (C 0.8, acetone)). The absolute stereochemistry of 3a and 4a was deduced as shown in Scheme 1 based on the experience gained from the study with α,β-epoxy sulfoxides,[3a] and it was later verified.

Thermal elimination of the sulfinyl group in 3a and 4a in refluxing xylene under $N_2$ for 10 to 15 min afforded cleanly the desired vinylchloride (E/Z mixture) 5a and 7a in 82% and 92 % yields, respectively (5a: $[\alpha]_D^{25}$ +11.7° (C 1.5, acetone); 7a: $[\alpha]_D^{25}$ -16.2° (C 1.0, acetone)). Ozonolysis of 5a in EtOH at -65 °C followed by reductive workup ($Me_2S$), then stirring at room temperature for 1 h gave ethyl (*R*)-2-hydroxy-4-phenylbutyrate (6a: X=OEt) in 88% yield as a colorless oil. The specific rotation of 6a (X=OEt; $[\alpha]_D^{25}$ -21.1° (C 1.0, $CHCl_3$) was in consistent with that of the reported value ($[\alpha]_D^{25}$ -21.6° (C 1.2, $CHCl_3$)[6a]; $[\alpha]_D^{25}$ -22.1° (C 1.0, $CHCl_3$)[6b]). The similar

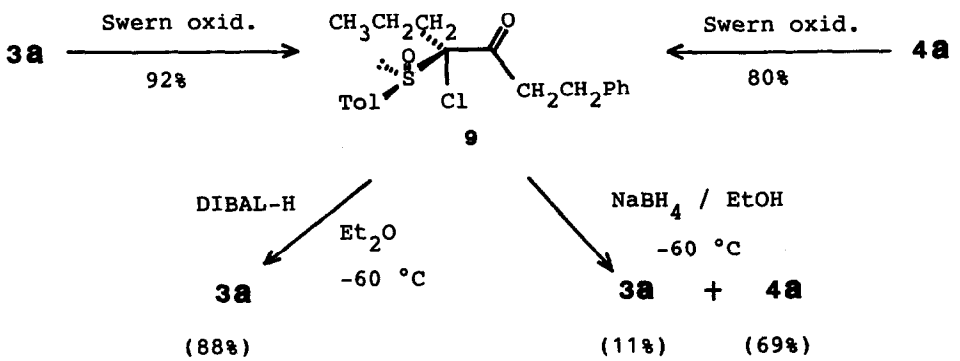



Scheme 1

treatment of 7a gave (*S*)-enantiomer 8a (X=OEt; $[\alpha]_D^{25}$ +21.3° (C 1.1, $CHCl_3$)) in 90% yield.

One can imagine that the intermediate of the ozonolysis of the vinylchloride must be an acylchloride. Actually, treatment of 5a with $O_3$ in dry $CH_2Cl_2$ at -65 °C followed by $Me_2S$ and piperidine gave optically active amide (6a: X=N$(CH_2)_5$) in 89% yield ($[\alpha]_D^{25}$ +7.3° (C 1.0, $CHCl_3$)). The similar treatment of 7a gave the enantiomer (8a: X=N$(CH_2)_5$; $[\alpha]_D^{25}$ -7.5° (C 1.6, $CHCl_3$) in 83% yield.

One problem of this method is the selectivity of the reaction of 1 with aldehydes; however, it was solved by the stereoselective reduction of the β-keto sulfoxide[7] 9 which was obtained from 3a or 4a by Swern oxidation




Scheme 2

(Scheme 2). If one needs (*R*)-enantiomer **6a**, undesired **4a** is oxidized to the β-keto sulfoxide **9** and then it is selectively reduced with diisobutylaluminum hydride (DIBAL-H) in ether at low temperature to give **3a** in 88 % yield. The reduction of **9** with $NaBH_4$ in EtOH at -60 °C gave predominately the other isomer **4a**; however, the selectivity was shown to be much lower than that with DIBAL-H. Representative results obtained by this method are summarized in Table 1.

As the asymmetric synthesis of the α-hydroxycarboxylic esters and amides is quite few[6] the method presented above becomes one of the most useful way for obtaining them in high enantiomeric excess.

Table 1. Synthesis of Chiral α-Hydroxy Carboxylic Esters and Amides from Vinylchlorides 5 and 7

| R | 5 or 7 (Yield/%)[a] | R'OH or $R'_2NH$ | 6 or 8 (Yield/%)[b] | $[\alpha]_D$, deg[c] |
|---|---|---|---|---|
| $CH_2CH_2Ph$ | 5a (82) | EtOH | 6a (88) | -21.1 |
| | 7a (92) | EtOH | 8a (90) | +21.3 |
| | 5a | MeOH | 6a (94) | -32.5 |
| | 7a | MeOH | 8a (94) | +30.9 |
| | 5a | piperidine | 6a (89) | +7.3 |
| | 7a | piperidine | 8a (83) | -7.5 |
| | 5a | $Et_2NH$ | 6a (76) | +16.9 |
| | 7a | $Et_2NH$ | 8a (74) | -17.3 |
| $(CH_2)_8CH_3$ | 5b (88) | MeOH | 6b (95) | -9.8 |
| | 7b (90) | MeOH | 8b (94) | +9.6 |
| | 5b | piperidine | 6b (90) | +8.7 |
| | 7b | piperidine | 8b (92) | -8.2 |

a) The yields in the thermal elimination of the sulfinyl group of 3 and 4.
b) The yields in the ozonolysis of 5 or 7 in alcohol or $CH_2Cl_2$.
c) All specific rotations were measured in $CHCl_3$ at 25 °C.

It is worth noting that in this method (-)-1-chlorobutyl *p*-tolyl sulfoxide 1 acts as a chiral auxiliary and also as an alkoxycarbonyl anion and a dialkylformamide anion equivalent.[9]

This work was supported by the Grant-in-Aid for Scientific Research (No. 01571168) from the Ministry of Education, which is gratefully acknoledged.

## References and Notes

1. J. W. ApSimon and R. P. Seguin, *Tetrahedron*, 35, 2797 (1979); J. W. ApSimon and T. L. Collier, *ibid.*, 42, 5157 (1986).
2. G. solladie, *Synthesis*, 1981, 185; G. H. Posner, In *Asymmetric Synthesis*; J. D. Morrison, Ed., Academic Press: New York, 1983; Chapter 8, Vol. 2, Part A, pp 225-241; K. Hiroi, *J. Syn. Org. Chem. Jpn.*, 41, 925 (1983); T. Koizumi, *ibid.*, 44, 102 (1986); H. Kosugi, *ibid.*, 45, 472 (1987); D. H. Hua, S. Venkataraman, R. A. Ostrander, G-Z. Sinai, P. J. McCann, M. J. Coulter, and M. R. Xu, *J. Org. Chem.*, 53, 507 (1988); Y. Arai, M. Yamamoto, and T. Koizumi, *Bull. Chem. Soc. Jpn.*, 61, 467 (1988); H. Kosugi, K. Tagami, A. Kakahashi, H. Kanna, and H. Uda, *J. Chem. Soc., Perkin Trans.* I, 1989, 935.
3. a) T. Satoh, T. Oohara, Y. Ueda, and K. Yamakawa, *J. Org. Chem.*, 54, 3130 (1989); b) T. Satoh, T. Sato, T. Oohara, and K. Yamakawa, *ibid.*, 54, 3977 (1989).
4. (-)-1-Chlorobutyl *p*-tolyl sulfoxide 1 was synthesized from (-)-chloromethyl *p*-tolyl sulfoxide (over 98% ee; see lit. 3a) with iodopropane using LDA as a base in THF at -60 to -30 °C in 88% yield as a diastereomeric mixture.
5. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 43, 2923 (1978).
6. a) Y-F. Wang, S-T. Chen, K-C. Liu, and C-H. Wong, *Tetrahedron Lett.*, 30, 1917 (1989); b) H. Urbach and R. Henning, *ibid.*, 25, 1143 (1984).
7. T. Satoh, A. Sugimoto, and K. Yamakawa, *Chem. Pharm. Bull.*, 37, 184 (1989) ; G. Solladie, G. Demailly, and C. Greck, *Tetrahedron lett.*, 26. 435 (1985); idem, *J. Org. Chem.*, 50, 1552 (1985); G. Solladie, C. Frechou, G. Demailly, and C. Greck, *ibid.*, 51, 1912 (1986).
8. J. K. Whitesell, *Acc. Chem. Res.*, 18, 280 (1985); H. Takahashi, T. Morimoto, and K. Achiwa, *Chem. Lett.*, 1987, 855; K. Mikami, M. Terada, and T. Nakai, *J. Am. chem. Soc.*, 111, 1940 (1989).
9. For a review: S. F. Martin, *Synthesis*, 1979, 633.

(Received in Japan 2 March 1990; accepted 19 April 1990)