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ENANTIOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE METOLACHLOR *VIA* ASYMMETRIC REDUCTION

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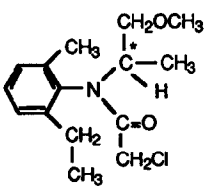
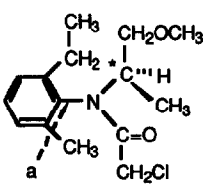
Abstract: Optically active metolachlor was prepared by chloroacetylation of the corresponding amine obtained by asymmetric reduction of the requisite imine with the chiral hydrides, such as Itsuno's reagent (4), Corey's reagent (5) and K glucoride (6).

Metolachlor (**1**) [2-chloro-N-(2-ethyl-6-methylphenyl)-N-(2-methoxy-1-methylethyl)acetamide] is one of the most intensively used herbicides in the chemical class of chloroacetamides.[1] This compound has four stereoisomers, the isomerism of which is based on a combination of a chiral center in the

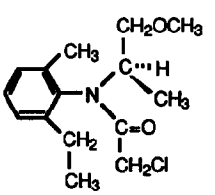


Metolachlor (**1**)

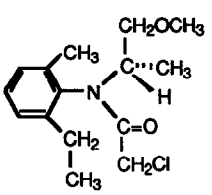


aR,*R (**1a**)

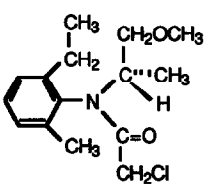
a = atropisomerism
* = chiral center



aS,*R (**1b**)



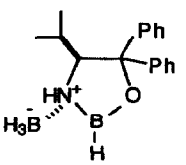
aS,*S (**1c**)



aR,*S (**1d**)

aliphatic side chain and a chiral axis between the phenyl group and the nitrogen atom.[2] Although the four stereoisomes differ in their ability to inhibit the growth of weeds, it is reported that the herbicidal activity is mainly influenced by the chiral center, the S isomers exhibiting higher activity than R isomers.[2]

Since optically active metolachlor could be easily prepared by chloroacetylation of the corresponding amine (**3**), several attempts were made to obtain this amine by using asymmetric hydrogenation of the corresponding imine (**2**).[3,4] However, no report on the preparation of the optically active amine by asymmetric reduction using chiral hydrides has appeared so far. Very recently, we reported the asymmetric reduction of N-substituted ketimine derivatives with a variety of chiral hydrides,[5] such as Itsuno's reagent (**4**)[6], Corey's reagent (**5**)[7], K glucoride (**6**)[8], Mosher's reagent (**7**)[9], and Sharpless' reagent (**8**).[10] In this reaction, we found that **4** reduced N-phenyl ketimine derivatives to the corresponding amines with high enantioselectivities. Accordingly, we applied the same reaction directly to the enantioselective synthesis of



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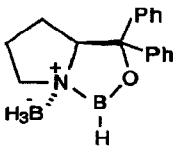

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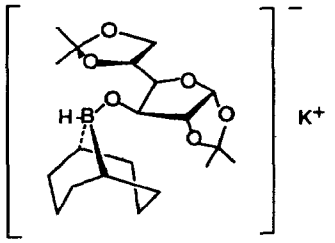

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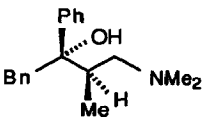
$LiAlH_4$ / Xc

Xc =



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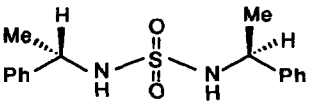

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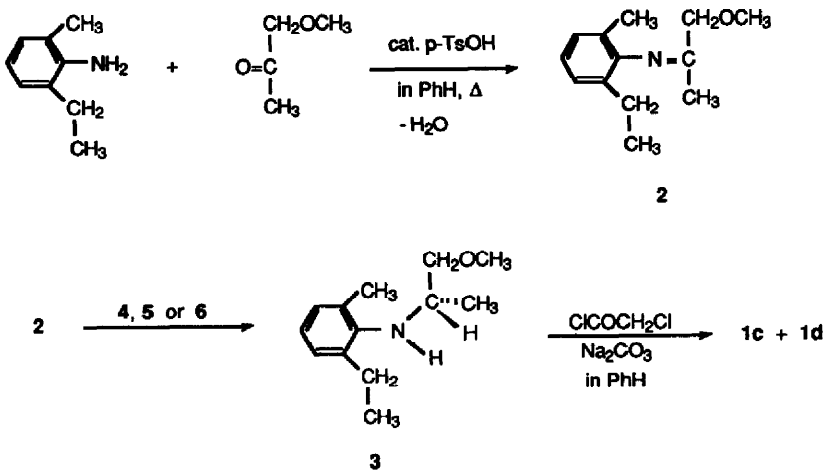
optically active metolachlor. The requisite imine (**2**) was prepared by condensation reaction of 2-ethyl-6-methylaniline and methoxyacetone in the presence of catalytic amounts of p-toluenesulfonic acid in benzene (scheme 1). The reduction procedure is as follows : To a solution of **4** (1 M, 3.3 ml, 3.3 mmol) in THF was added a solution of **2** (1.5 M, 2 ml, 3 mmol) in THF. The reaction mixture was stirred at 30 °C for 2 days and then excess hydride was destroyed by the addition of 1 M HCl solution. After THF was pumped off *in vacuo*, the reaction mixture was filtered. The filtrate was basified with 2 N NaOH and extracted with ether. The extract was washed with brine, dried over anhydrous K_2CO_3 and evaporated



Scheme 1

to give an oil residue. Column chromatography on silica gel (eluent: CH_2Cl_2) gave **3** (542 mg, 87 % yield) of a pale yellow syrup.[11] When this amine was reacted with chloroacetyl chloride in the presence of anhydrous sodium carbonate in benzene,[2] the product optically active metolachlor (**1**) was obtained quantitatively : a pale yellow syrup,[12] $[\alpha]_D^{22}$ - 5.61(*c* 2.1, hexane), 62 % ee based on $[\alpha]_D^{20}$ - 9.0 (*c* 2.073, hexane) of optical rotation of the diastereomeric mixture of the atropisomers (aRS. S, **1c** + **1d**) reported in literature.[2] On the other hand, **5** and **6** provided **1** with 52 % ee and 14 % ee, respectively. However, **6** and **7** did not reduce the imine(**2**).

Acknowledgement

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References and Notes

1. Lebaron, M. ; Mcfarland, J. E. ; Simoneaux, B. J. " *Herbicides* " Kearney, P.C. ; Kaufman, D.D. ed., chapter 7; Marcel Dekker Inc. : New York and Basel, 1988.
2. Mosher, H. ; Rihs , G. ; Sauter, H. *Z. Naturforsch. B 37*, **1982**, 451.

3. Spindler, F. ; Pugin, B. ; Blaser, H.-U. *Angew. Chem. Inter. Ed. Engl.* **1990**, 29, 558.

4. Kang, G.-J. ; Cullen, W. R. ; Fryzuk, M.D. ; James, B. R. ; Kutney, J.P. *J. Chem. Soc. Chem. Commun.*, **1988**, 1466.

5. Cho, B. T. ; Chun, Y. S. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 3200.

6. Itsuno, S. ; Nakano, M. ; Miyazaki, K. ; Masuda, H. ; Ito, K. ; Hirao, A. ; Nakahama, S. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 2039.

7. Corey, E. J. ; Bakshi, R. K. ; Shibata, S. *J. Am. Chem. Soc.* **1987**, 109, 5551.

8. K glucoride : Potassium 9 -*O* - (1,2;5,6 - di-*O* - isopropylidene - α - D - glucofuranosyl) - 9 - boratabicyclo[3.3.1]nonane ; Brown, H.C. ; Cho, B. T. ; Park, W. S. *J. Org. Chem.*. **1988**, 53, 1231.

9. Yamaguchi, S. ; Mosher, H. S. *J. Org. Chem.* **1973**, 38, 1870.

10. Hawkins, J. M. ; Sharpless, K. B. *J. Org. Chem.* **1984**, 49, 3861.

11. IR (neat, cm^{-1}) : 3032, 2922, 2823, 1463, 1441, 1255, 1143, 1119, 753 ; ^1H NMR (300 MHz, $CDCl_3$, δ) : 1.17 (d, 3 H, *J* 6.5 Hz, $C\underline{H}_3CH$-), 1.22 (t, 3 H, *J* 7.6 Hz, $C\underline{H}_3CH_2$-), 2.28 (s, 3 H, $C\underline{H}_3$-aromat.), 2.64 (q, 2 H, *J* 7.6 Hz, -$C\underline{H}_2CH_3$), 3.32-3.35 (unresloved peak, 6 H, -$C\underline{H}C\underline{H}_2O\underline{C}H_3$), 6.86-7.00 (m, 3 H, aromatic H).

12. IR (neat, cm^{-1}) : 2968, 2810, 1671, 1459, 1361, 1238, 1109, 785 ; ^1H NMR (300 MHz, $CDCl_3$, δ) : 1.15 (d, 2 H, *J* 7.0 Hz) and 1.17 (d, 1 H, *J* 7.0 Hz) for $C\underline{H}_3CH$-, 1.26 (t, 3 H, *J* 7.5 Hz, $C\underline{H}_3CH_2$-), 2.24 (s, 2 H) and 2.26 (s, 1 H) for aromatic $C\underline{H}_3$, 2.59 (m, 2 H, -$C\underline{H}_2CH_3$), 3.26 (s, 1 H) and 3.29 (s, 2 H) for -$OC\underline{H}_3$, 3.49 (dd, *J* 4.2 Hz and 6.5 Hz) and 3.51 (dd, *J* 4.2 Hz and 9.4 Hz) for one diastereomeric proton of -$CHC\underline{H}_2OCH_3$, 3.61 and 3.62 (s, 2 H, $C\underline{H}_2Cl$), 3.75 (dd, *J* 4.2 Hz and 9.4 Hz) and 3.94 (dd, *J* 4.2 Hz and 9.4 Hz) for one diastereomeric proton of -$CHC\underline{H}_2OCH_3$, 4.22 (m, 1 H, -$C\underline{H}CH_3$), 7.13-7.30 (m, 3 H, aromatic H) ; MS (CI) : m/e (%), 284 (M^+, 60), 252 (38), 250 (100), 218 (47), 178 (25), 162 (37), 73 (60).