ASYMMETRIC SYNTHESIS OF (*R*)(-)-DIMETHYL CITRAMALATE†

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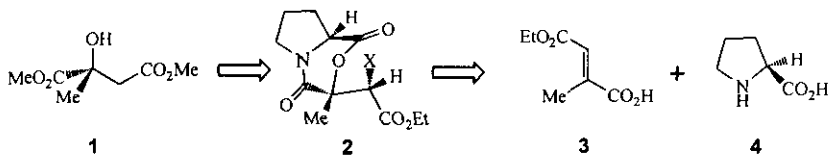
Abstract - An asymmetric synthesis of (*R*)(-)-dimethyl citramalate (**1**), involving halolactonization by using (*S*)(-)-proline as a chiral auxiliary, is reported.

For the last two decades, asymmetric synthetic methodology has been massively developed to prepare chiral building blocks which can be applied to the synthesis of biologically active natural products.[1] Several asymmetric syntheses of (*S*)(+)- or (*R*)(-)-dimethyl citramalate[2-5] and (*S*)(+)- or (*R*)(-)-citramalic acid,[5] chiral building blocks, have been reported. Even though most of them showed high ee, the overall chemical yields were relatively low due to their long synthetic steps. In this paper, we present an efficient asymmetric synthesis of (*R*)(-)-dimethyl citramalate (**1**) *via* halolactonization[7] by using (*S*)(-)-proline (**4**) as a chiral auxiliary (Scheme 1).

Scheme 1



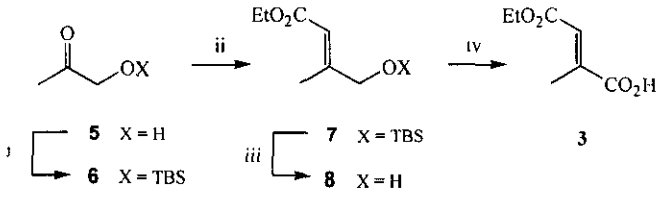
1 **2** **3** **4**

† Dedicated to Dr. Koji Nakanishi for the celebration of his 75th birthday.

The synthesis of (*R*)(-)-dimethyl citramalate (**1**) was accomplished by 6 steps sequence from the (*E*)-3-carboethoxy-2-methyl-2-butenoic acid (**3**) (Scheme 3).

3 was prepared in 63% overall yield over 4 steps from hydroxyacetone (**5**) (Scheme 2). **5** was protected with tributylsilyl chloride (TBSCl), followed by Wadsworth-Emmons reaction with triethyl phosphonoacetate gave **7**. Allylic alcohol (**8**) obtained by the deprotection of **7** was converted to the butenoic acid (**3**) by Jones oxidation.

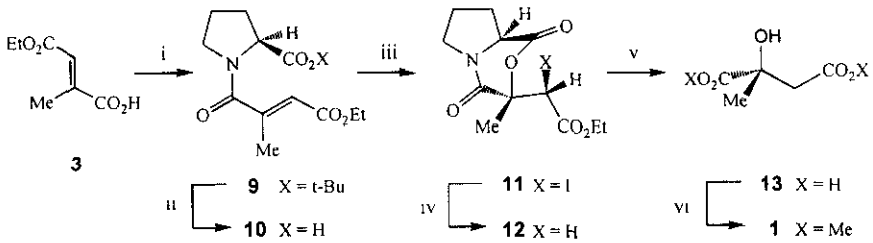
Scheme 2



i) TBSCl (1.0 eq), imidazole (2.0 eq), DMF, 73% ; ii) triethyl phosphonoacetate (1.1 eq), NaH (1.2 eq), THF, 92% ; iii) tetrabutylammonium florıde (1.1 eq), THF, 97% ; iv) CrO_3-1 5 M-H_2SO_4, acetone, 96%.

The coupling of **3** with (*S*)(-)-*t*-butyl prolinate[8] as a chiral auxiliary in the presence of diethyl phosphorocyanidate (DEPC) gave the amide (**9**) which was further transformed to **10**, substrate for halolactonization by treatment with trifluoroacetic acid. The diastereoselective halolactonization was attempted to get halolactone (**11**). In a previous report, (*S*)(-)-tigloylproline which has β-methyl group instead of β-carboethoxy group in **10** gave the corresponding bromolactone in 84% chemical yield and 95% de in NBS/DMF conditions.[7a,e]

Scheme 3



i) (*S*)(-)-*t*-butyl prolinate (1.0 eq), DEPC (1.1 eq), TEA (1.1 eq), DMF, 0 °C, 2 h, 100% ; ii) CF_3CO_2H, CH_2Cl_2, rt, 3 h, 98% ; iii) NIS (5 0 eq), DMF, 36 °C, 12 h, 83% ; iv) *n*-Bu_3SnH (1.2 eq), benzene, reflux, 0.5 h, 92% ; v) 6*N*-*aq*. HCl soln., reflux, 5 h, 100% , vi) CH_2N_2 (excess), MeOH, 50%, 2 step yield from **12**.

But the halolactonization of **10** did not proceeded in the same conditions.[7] It might be due to the electron deficiency on the double bond moiety by the electron withdrawing substituent, β-carboethoxy group.[9] In 1994, Guindon could get halolactone from the electron deficient olefin substituted with carboethoxy group by iodolactonization, I_2/AgOTf/$NaHCO_3$.[10] This method was not successfully applied to **10** but by using *N*-iodosuccinimide (NIS)/DMF conditions, iodolactone (**11**) (*vide infra*) could be prepared in 84% chemical yield.[9] The iodolactone (**11**) was reduced by *n*-Bu_3SnH to give lactone (**12**). Hydrolysis of **12** with 6*N*-aqueous HCl solution, followed by treatment with diazomethane gave the citramalate (**1**) ($[\alpha]^{22}_D$ -26.09 ° (c 0.30, $CHCl_3$) ; *lit.*,[11] 27.23 °, (c 0.30 $CHCl_3$)). Thus the citramalate (**1**) could be prepared in 37% overall yield and 98% ee over 6 steps from **3**. The absolute configuration of C(OCO)Me, one of the stereogenic centers of iodolactone (**11**) was assigned as *S* by chemical correlation with the citramalate (**1**) and the other stereogenic center, C(I)H was tentatively assigned as *S* in connection with halolactonization mechanism.[7a,e] The other enantiomer, (*S*)(+)-dimethyl citramalate can be prepared by using ethyl 3-carboxy-3-butenoate instead of the butenoic acid (**3**) *via* the same procedure.[7h,i] The high enantiomeric excess and chemical yield should make this method more practical than other procedure.

ACKNOWLEDGEMENT

This work was supported by the grant of the Resarch Center of New Drug Development of Seoul National University.

REFERENCES AND NOTES

1. S. Hanessian, 'Total Synthesis of Natural Products: The Chiron Approach', Pergamon Press, Inc., Oxford, 1983.
2. a) H. K. Spencerm and R. K. Hill, *J. Org. Chem.*, 1975, **40**, 217. b) C. Mioskowski and G. Solladie, *Tetrahedron*, 1980, **36**, 227. c) R. W. Stevens and T. Mukaiyama, *Chem. Lett.*, 1983,1799.

3. a) W. R. Kenan, Jr., *Tetrahedron, Lett.*, 1985, **26**, 3907. b) J. K. Whitesell, K. Nabona, and D. Deyo, *J. Org. Chem* , 1989, **54**, 2258. c) T. Akiyama, K. Ishikawa, and S. Ozaki, *Synlett.*, 1994, 275.

4. M. Gill and A. F. Smrdel, *Tetrahedron: Asymmetry,* 1990, **1**, 453.

5. H. Moorlag and R. M. Kellogg, *Tetrahedron: Asymmetry*, 1991, **2**, 705.

6. a) Y. Fujimoto, J. S. Yadav, and C. J. Sih, *Tetrahedron Lett.*, 1980, **21**, 2481 b) D. Seebach, R. Naef, and G. Calderari, *Tetrahedron*, 1984, **40**, 1313. c) R. Eck and H. Simon, *Tetrahedron*, 1994, **50**, 13641.

7. a) S. Terashima and S. S. Jew, *Tetrahedron Lett.*, 1977, **18**, 1005. b) S. Terashima, S. S. Jew, and K. Koga, *Chem. Lett* , 1977, 1109. c) S. Terashima, S. S. Jew, and K. Koga, *Tetrahedron Lett* , 1977, **18**, 4507. d) S. Terashima, S. S. Jew, and K. Koga, *Tetrahedron Lett.,* 1978, 4937. e) S. S. Jew, S. Terashima, and K. Koga, *Tetrahedron*, 1979, **35**, 2337. f) S. S. Jew, S. Terashima, and K. Koga, *Tetrahedron*, 1979, **35**, 2345. g) S. S. Jew, S. Terashima, and K. Koga, *Chem. Pharm. Bull.,* 1979, **27**, 2351. h) S. S. Jew, J. W. Kim, B. S. Jeong and Y. S. Cho, 'Advances in Organobromine Chemistry II: Asymmetric Synthesis of (*S*)-α-Substituted β-Bromo-α-hydroxy Acids,' ed. by J. R. Desmurs, B Gerard, and M. J. Goldstein, Elsevier, Amsterdam, 1995, pp. 171-173. i) S. S. Jew, H. O. Kim, B. S. Jeong, and H. G. Park, *Tetrahedron. Asymmetry*, 1997, **8**, 1187.

8. M. K. Dhaon and R. K. Olsen, *J. Org. Chem.*, 1982, **47**, 1962.

9. The reaction conditions for the halolactonization of **11** were investigated as follows.

11 ⟶ **12**

X	Reagent (eq)	Solvent	Base	Yield (%)
Br	NBS (3 5)	DMF	-	NR
Br	NBS (3 5)	MeCN	-	NR
Br	NBS (3 5)	DMF	*t*-BuOK	< 59
Br	NBS (3 5)	DMF	TEA	NR
I	*NIS (5 0)*	*DMF*	-	*84*

10. Y. Guindon, A. Slassi, E. Ghiro, G. Bantle, and G. Jung, *Tetrahedron Lett.*, 1992, **33**, 4257.

11. S. Yamada, K. Nakayama, and H. Takayama, *Tetrahedron Lett.*, 1981, **22**, 2591.

Received, 2nd May, 1997