Tetrahedron Letters,Vol.30,No.31,pp 4157-4160,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

[2,3]-WITTIG REARRANGEMENT ON CARBOHYDRATE TEMPLATE. NOVEL APPROACH TO CHIRAL SYNTHESIS OF 3-ALKYLMALIC ACIDS

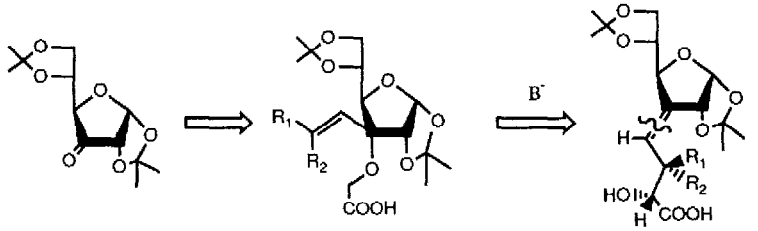
Katsumi Kakinuma* and Hui-Yin Li[1]

Department of Chemistry, Tokyo Institute of Technology
O-okayama, Meguro-ku, Tokyo 152, JAPAN

Summary: Dianion [2,3]-Wittig rearrangement of tertiary α-(allyloxy)-acetic acid systems on a carbohydrate template has achieved efficient chirality transfer to furnish diastereoselective chiral synthesis of 3-alkylmalic acid.

3-Alkylmalic acid derivatives, equivalent of aldol condensation products between glyoxylic acid and alkanoic acid derivatives, are important and useful building blocks for the syntheses of variety of natural products.[2,3] So far, however, approaches leading to the *threo*-aldol products seem to be insufficient so that further exploitation has been awaited. We report here a highly enantio- and diastereoselective method based upon the [2,3]-Wittig rearrangement on the chiral carbohydrate template (**1**). The reasons we chose **1** were because its stereochemical feature seems to allow rational prediction of the outcome of the rearrangement *vide post* and because it is readily available and recoverable after the desired bond construction.

Scheme 1



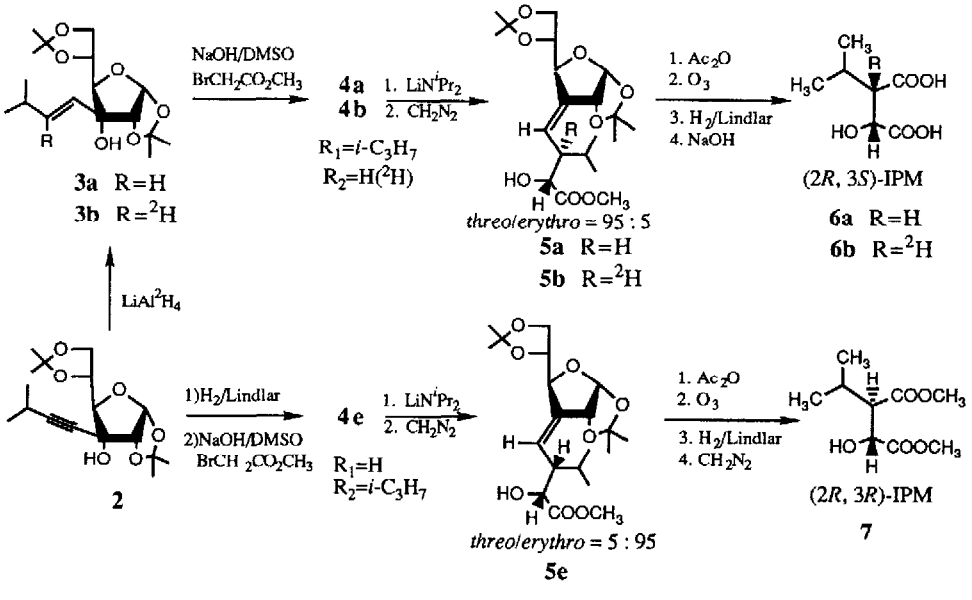
1 **4a-4g** **5**

R_1, R_2 = H, ^2H, CH_3, C_2H_5, or i-C_3H_7

Alkylation of **1** with 3-methyl-1-butynyl lithium yielded exclusively **2**[4] in 97% yield due to the steric hindrance of the 1,2-*O*-isopropylidene protecting group locating at the α-face of the furanose ring. Reduction with $LiAlH_4$ gave **3a** (J = 16.6 Hz) as a sole product (94%).[4] Only a few methods have been known so far to prepare α-(allyloxy)-acetic acids from primary and secondary alcohols.[5] We were successful to extend this reaction to the sterically congested tertiary alcohol in high yield. Treatment of **3a** with methyl bromoacetate, not bromoacetic acid, in the presence of pulverized NaOH in DMSO to afford **4a** (90%).[4]

The crucial step was the [2,3]-Wittig rearrangement reaction of the acid **4a**. Chirality transfer through the [2,3]-Wittig rearrangement of tertiary ethers has been reported only in a few cases and none of them has been concerned with the dianion [2,3]-Wittig rearrangement .[6] However, the desired rearrangement took place quite smoothly with efficient chirality transfer. Treatment of **4a** with three equivalent of LDA in THF at -78 °C and then at 0 °C for 10 min. Aqueous quenching followed by esterification with CH_2N_2 afforded a mixture of (2*R*,3*S*)-*threo*- **5a** and (2*R*,3*R*)-*erythro*-hydroxy acids in a ratio of 95:5 in 78% isolated yield. The geometry of the double bond of each product was separately determined by ^{1}H-NMR NOE difference spectroscopy. Although the coupling constant (J = 4.4 Hz) between the allylic methine proton and the oxymethine proton of **5a** would suggest a *threo*-configuration for the newly formed C-C bond, the stereochemistry was actually confirmed later. The *threo*-isomer was acetylated and then subjected to ozonolysis. The ozonide was decomposed with hydrogen in the presence of Lindlar catalyst to yield the monomethyl ester of **6a**.[4,7] Hydrolysis of the monoester afforded (2*R*,3*S*)-*threo*-D_S-3-isopropylmalic acid **6a** (48% overall yield from **5a**), mp 146-147°C, $[\alpha]_D^{23}$ -5.0°.[4,8] The 500 MHz ^{1}H-NMR spectrum of **6a** was completely identical with that of the authentic specimen obtained from the culture of a L-leucine auxotrophic mutant of *Neurospora crassa*. The absolute stereochemistry of **6a** was also confirmed by the enzymic assay with 3-isopropylmalate dehydrogenase (IPMDH) of thermophilic bacteria *Thermus thermophilus* HB-8.[9] IPMDH is currently under active research from enzymic, genetic as well as evolutionary interests.[10] (2*R*,3*S*)-[3-^{2}H]-3-isopropylmalic acid (**6b**)[4] was also synthesized similarly in high chiral purity and enrichment (93% atom based on 500MHz ^{1}H-NMR) from the deuterated olefin **3b**.[4,11]

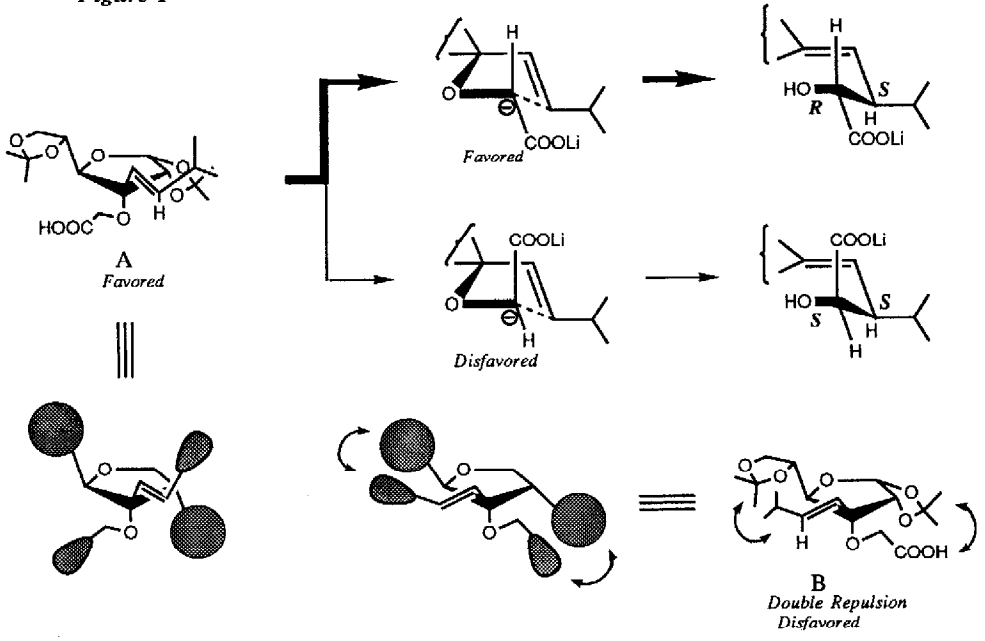
Scheme 2



The results described above prompted us to further examine the scope of this rearrangement. Apparently, the chirality transfer in the present approach *via* the dianion [2,3]-Wittig rearrangement is facilitated by the double steric interactions of the substituents between the C-3 position and the two isopropylidene protecting groups. The

conformation **A** but not conformation **B** should be favored because the β-alkenyl substitutent on C-3 tends to apart from the sterically demanding 5,6-*O*-isopropylidene group and the α-*O*-acetic acid moiety tends to apart from the 1,2-*O*-isopropylidene group (Figure 1). A transition state of an enveloped conformation with two substituents in pseudoequatorial positions is most likely.

Figure 1



When a *cis*-olefin **4g** was subjected to the rearrangement under the same conditions, the major product was the *erythro*-isomer (*erythro*/*threo* =95:5) as expected. Similarly the [2,3]-Wittig rearrangement of *E*- or Z-3-*C*-butenyl-α-D-allofuranose derivative underwent in 60-80% yield with high diastereoselectivity to give the *threo*- or *erythro*- product, respectively. However, the rearrangement of *trans*-3-*C*-propenyl-α-D-allofuranose afforded a mixture of products as summarized in the Table 1, whereas the *cis*-isomer turned out to give a single *erythro*-product . The bulkiness of ethyl or higher alkyl substituent is required for greater stereoselectivity in this chirality transfer reaction of the *trans*-allyl ether system. In the *cis*-olefin system, even methyl group can dictate the conformation of a transition state to afford a single *erythro*-isomer. The diastereoselection of the dianion [2,3]-Wittig rearrangement of alkenyloxyacetic acids was considered as an exception of the regular [2,3]-Wittig rearrangement and rather poor stereoselectivity was generally attained. By contrary, the present approach using the carbohydrate template controls the transition state of the reaction and makes the stereochemical outcomes predictable, i.e. *E*-to-*threo* and Z-to-*erythro*, with high diastereofacial selection. It should also be noted that the stereochemical outcome of the present reaction was just the same as those of the regular [2,3]-Wittig rearrangement. A similar *E*-to-*threo* selection of dianion [2,3]-Wittig rearrangement had only been observed in a steroid system .[5a,5d]

Table 1. Diastereoselectivity in [2,3]-Wittig Rearrangement

	Substrate		Yield(%)	Products			
				threo		*erythro*	
	R_1	R_2		*2R, 3S*	*2S, 3R*	*2S, 3S*	*2R, 3R*
4a	*i*-C_3H_7	H	78	95		5	
4b	*i*-C_3H_7	H	64	95		5	
4c	C_2H_5	H	63	95		5	
4d	CH_3	H	60	75		25	
4e	H	*i*-C_3H_7	66		5		95
4f	H	C_2H_5	89				100
4g	H	CH_3	56				100

It now appears that the [2,3]-Wittig rearrangement on the chiral template is among powerful tools for diastereoselective construction of chiral 3-alkylmalic acids.

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan. One of the author (H.Y.L) wants to thank the Fujisawa Foundation for financial support. We also wish to thank Professor T. Nakai for helpful discussions.

References and Notes

1. On leave from the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, People's Republic of China.
2. C. H. Heathcock, in "Asymmetric Synthesis" ed. by J. D. Morrison, Academic Press, New York (1984), Vol.3, p.111.
3. T.Yamada, K.Kakinuma, and T.Oshima, *Chem. Lett.*, 1745 (1987).
4. All new compounds have been characterized by ^{1}H-NMR and ^{13}C-NMR, IR, specific rotation and C, H combustion analysis.
5. a) T.Nakai, K.Mikami, S.Taya, Y.Kimura and T.Mimura, *Tetrahedron Lett.*, **22,** 69 (1981). b) K.Mikami, K.Kawamoto and T.Nakai, *Tetrahedron Lett.*, **27,** 4899 (1986). c) R.Paulissen, H.Reimlinger, E.Hayez, A.J.Hubert and P.Teyssie, *Tetrahedron Lett.*, **24**, 2233 (1973). d) M.Koreeda and D.J.Ricca, *J. Org. Chem.*, **27**, 4090 (1986).
6. a) T.Nakai and K.Mikami, *Chem. Rev.*, **86**, 885 (1986). b) J.A.Marshall and T.M.Jenson, *J. Org. Chem.*, **49**, 1707 (1984). c) M. Balestra. and J.Kallmerten, *Tetrahedron Lett.*, **29**, 6901(1988).
7. V.N.Odinokov, L.P.Zhemaiduk and G.A.Tolstikov, *Zh. Org. Khim.*, **14,** 54 (1978).
8. a) J.M.Calvo and S.R.Gross, *Methods Enzymol.*, **7A**, 791 (1970). b) R.O.Burns, H.E.Umbarger and S.R.Gross, *Biochemistry*, **2**, 1053 (1963).
9. We are grateful to Ms. N. Akutsu, Department of Life Science, Tokyo Institute of Technology, for this assay.
10. a) T.Yamada, K.Kakinuma, T.Endo and T.Oshima, *Chem . Lett.*, 1749 (1987). b) Y.Kagawa, H.Nojima, N.Nukina, M.Ishizuka, T.Nakajima, T.Yasuhara, T.Tanaka and T.Oshima, *J. Biol. Chem.*, **259**, 2956 (1984).
11. a) E.J. Corey, J.A.Katzenellenbogen and G.H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967). b) B. Grant and C. Djerassi, *J. Org. Chem.* , **39**, 968 (1974). K.Kakinuma, N.Imamura and Y.Saba, *Tetrahedron Lett.*, **23,** 1697 (1982).

(Received in Japan 12 May 1989)