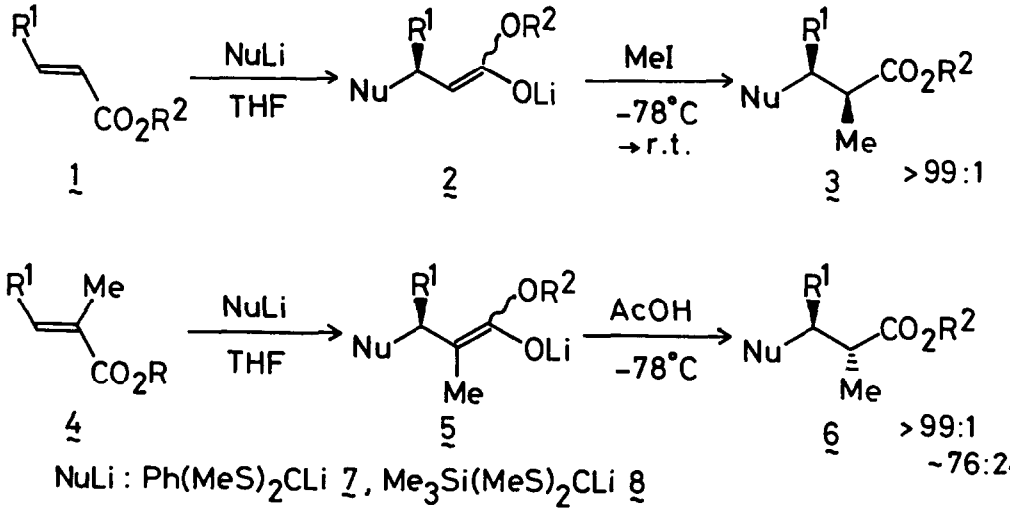
Tetrahedron Letters,Vol.26,No.25,pp 3031-3034,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

HIGHLY DIASTEREOSELECTIVE TANDEM ALKYLATION OF ACYCLIC α,β-UNSATURATED ESTERS BASED ON THE NOVEL USE OF DITHIOACETAL UNIT

Hisashi Kawasaki, Kiyoshi Tomioka,* and Kenji Koga
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: Highly diastereoselective tandem alkylation process of acyclic α,β-unsaturated esters was developed based on the novel use of dithioacetal as a stereocontrolling unit.

Development of the stereoselective alkylation process in acyclic structures is a focused and challenging area of current investigations and methodologies based on the 1,2-asymmetric induction concepts have been well documented.[1,2] However, diastereoselective alkylation of enolates with simple chirality at the β-position has received much less attention.[1b] Quite recently Fleming and Yamamoto reported their results on the diastereoselective alkylation of enolates.[3,4] In connection with our studies on the asymmetric tandem alkylation and its application to the total synthesis of cytotoxic neolignan (-)-megaphone,[5] we now report the highly efficient 1,2-asymmetric induction through the conjugate addition of dithioacetal based nucleophiles to α,β-unsaturated esters and subsequent methylation or protonation of the corresponding enolates.



Conjugate addition of lithiated di(methylthio)acetals (7 and 8)[5,6] to

α,β-unsaturated esters (**1** and **4**) in THF at low temperature (-78°C for **7** and -20°C for **8**) is the common step in the reaction. Subsequent methylation of enolate **2** with methyl iodide at -78°C to room temperature afforded **3** as a single isomer in every case (runs 1,3,5,7).[7,8] On the other hand, protonation of enolate **5** with acetic acid gave **6** as a major diastereomer (runs 2,4,6,8).[7,8] The results are summarized in Table 1. Products **3** and **6** were purified by silica gel column chromatography and stereochemistry of the products was assigned by converting **3** to known compounds.[8]

Alkylation of enolate **2** and protonation of enolate **5** take place in the same stereochemical sense, with electrophile attacking anti to the bulky dithioacetal based nucleophile for steric reason as shown in Figure 1,[3,4,9] in accord with theoretical predictions by Houk.[10] Highly sterically demanding characteristic feature of dithioacetal based nucleophile should be responsible for increase of selectivity in comparison with Fleming's[3] and Yamamoto's[4] results.

Alternative explanation by chelate control may be precluded from the following experiments. Addition of HMPA (6 eq. THF/HMPA=5/1 (v/v)) to the reaction (run 3) afforded **3** as a single isomer. The same reaction using methyl cis-cinnamate (NuLi=**7**) afforded **3** as a single isomer in 85% yield. Alkylation of E-lithioenolate[2k] formed by deprotonation (LDA in THF) of the ester, prepared in 94% yield by conjugate addition of **7** to **1b** and subsequent protonation, also afforded **3** as a single isomer in 80% yield. These data imply the coordination of sulfur group to lithium cation to form seven membered chelate not to be important. As bulkiness of R^1 in **4** increases (Ph>Me), selectivity is becoming lower in the protonation of **5** (runs 2 vs 4, 6 vs 8). These data support the steric control is dominant.

It is essential to use t-butyl ester to achieve clean conjugate addition of **8** to cinnamates (**1c** and **4c**) and stereochemical outcome is not affected by the change of R^2 in **1** and **4** as shown in runs 7 and 8.

It is interesting to note that since trimethylsilyldi(methylthio)acetal group can be reduced to methyl and this acetal works as a bigger group than phenyl in a stereochemical sense as shown in runs 7 and 8, this acetal can be considered as a "big methyl."[11] Furthermore, enantioselective conjugate addition reaction using **7** and **8** to **1** has been developed,[12] the present methodology is applicable to the synthesis of optically active **3** and **6**.

Application of the present highly diastereoselective tandem alkylation process to the biologically active natural product synthesis is the subject of current investigations.

Table 1. Ratios of diastereomers **3** and **6** in the conjugate addition and subsequent methylation for **1** and protonation for **4**

Run	Substrate **1, 4**	R1	R2	NuLi **7, 8**	Yield/%[a]	Isomer ratios[b] **3:6**
1	**1a**	Me	Me	$Ph(MeS)_2C$	86	99: 1[c]
2	**4a**	Me	Me	$Ph(MeS)_2C$	87	4:96[c]
3	**1b**	Ph	Me	$Ph(MeS)_2C$	75	99: 1[d]
4	**4b**[e]	Ph	Me	$Ph(MeS)_2C$	70	13:87[d]
5	**1a**	Me	Me	$Me_3Si(MeS)_2C$	76	99: 1[f]
6	**4a**	Me	Me	$Me_3Si(MeS)_2C$	51	1:99[f]
7	**1c**[g]	Ph	t-Bu	$Me_3Si(MeS)_2C$	88	99: 1[h]
8	**4c**[i]	Ph	t-Bu	$Me_3Si(MeS)_2C$	79	24:76[h]

a) Yields refer to chromatographically purified products mixture of **3** and **4**. b) Ratios (**3:4**) were determined by ^{1}H-NMR and/or by isolation. No isomer was detected when 99:1 ratio is described. c) assigned by converting **3** into dl-2,3-dimethyl-1,4-diphenyl-1,4-butanedione (i. NaOH-aq. EtOH; ii. $HgCl_2$-$CaCO_3$ in aq. CH_3CN; iii. PhLi in THF). See ref. 21. d) Predicted from the stereochemical course of the other reactions described here and from ^{1}H-NMR of the major diastereomer. e) T. B. Strzalko, Tetrahedron, 29, 4199 (1973). f) assigned by converting **3** (protodesilylated product obtained in 83% yield from **1a** by in situ treatment with $(n\text{-Bu})_4NF$) into dl-dimethylsuccinic acid (i. $HgCl_2$-$CaCO_3$ in aq. CH_3CN; ii. Jones oxidation; iii. KOH in aq. EtOH). W. A. Bone and W. H. Perkin, J. Chem. Soc., 69, 253 (1896). g) E. M. Kaiser and R. A. Woodruff, J. Org. Chem., 35, 1198 (1970). h) assigned by converting **3** (protodesilylated product (75%)) into dl-erythro-2-methyl-3-phenylbutyric acid (i. Raney nickel in EtOH; ii. CF_3COOH). S. A. Theine and J. G. Traynham, J. Org. Chem., 39, 153 (1974). i) Prepared by hydrolysis of **4b** and esterification with t-BuOH (DCC-DMPA/CH_2Cl_2).

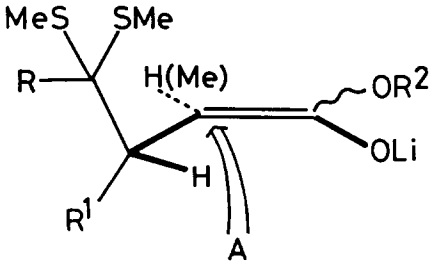


Fig. 1

References and Notes

1. For reviews, see: a) M. T. Reetz, Angew. Chem. Int. Ed. Engl., 23, 556 (1984); b) D. A. Evans, "Asymmetric Synthesis," ed. by J. D. Morrison, Academic Press, New York, Vol. 3, 1984, p. 1; c) C. H. Heathcock, ibid., p. 111; d) E. L. Eliel, ibid., Vol. 2, 1983, p. 125; e) K. Tomioka and K. Koga, ibid., p. 201; f) T. Mukaiyama, "Organic Reactions," 28, 203 (1982); g) S. Masamune and W. Choy, Aldrichimia Acta, 15, 47 (1980).
2. Leading references for the stereoselective syntheses of 2,3-disubstituted carbonyl compounds with carbon-carbon bond formation: a) F. E. Ziegler and A. Kneisley, Tetrahedron Lett., 26, 263 (1985); b) J. L. Belletire, E. G. Spletzer, and A. R. Pinhas, ibid., 25, 5969 (1984); c) M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, ibid., 25, 5661 (1984); d) N. Saya, K. Azuma, K. Mikami, and T. Nakai, ibid., 25, 565 (1984); e) S. E. Denmark and M. A. Harmata, J. Org. Chem., 48, 3369 (1983); f) Y. Tamaru, Y. Amino, Y. Furukawa, M. Katagiri, and Z. Yoshida, J. Am. Chem. Soc., 104, 4018 (1982); g) K. K. Mahalanabis, M. Mumtaz, and V. Snieckus, Tetrahedron Lett., 23, 3971 (1982); h) D. P. Curran, J. Am. Chem. Soc., 104, 4024 (1982); i) D. Seebach and J. Golinski, Helv. Chim. Acta, 64, 1413 (1981); j) G. B. Mpango, K. K. Mahalanabis, Z. Mahdavi-Damghani, and V. Snieckus, Tetrahedron Lett., 1980, 4823; k) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976); l) C. W. Perry, M. V. Kalnins, and K. H. Dectcher, J. Org. Chem., 37, 4371 (1972).
3. a) I. Fleming and J. J. Leiw, J. Chem. Soc. Chem. Commun., 1985, 149; b) H.-F. Chow and I. Fleming, Tetrahedron Lett., 26, 397 (1985); c) W. Bernhard, I. Fleming, and D. Waterson, J. Chem. Soc. Chem. Commun., 1984, 28.
4. Y. Yamamoto and K. Maruyama, J. Chem. Soc. Chem. Commun., 1984, 904.
5. K. Tomioka, H. Kawasaki, Y. Iitaka, and K. Koga, Tetrahedron Lett., 26, 903 (1985).
6. D. Seebach, M. Kolb, and B.-Yh. Gröbel, Chem. Ber., 106, 2277 (1973).
7. Satisfactory analytical and spectroscopic data were obtained for all new compounds described in this communication. Compounds **3** and **6** are racemic.
8. See footnotes in Table 1.
9. F. Johnson, Chem. Rev., 68, 375 (1968).
10. a) M. N. Paddon-Row, N. G. Rondon, and K. N. Houk, J. Am. Chem. Soc., 104, 7162 (1982); b) P. Garamella, N. G. Rondon, M. N. Paddon-Row, and K. N. Houk, ibid., 103, 2438 (1981); c) E. M. Burgess and C. L. Liotta, J. Org. Chem., 46, 1703 (1981).
11. For the utility of di(methylthio)acetal in organic synthesis, see: B. M. Trost and T. Sato, J. Am. Chem. Soc., 107, 719 (1985).
12. K. Tomioka, M. Sudani, Y. Shinmi, and K. Koga, Chemistry Lett., 1985, 329.

(Received in Japan 23 March 1985)