CHEMISTRY LETTERS, pp. 81-84, 1986.

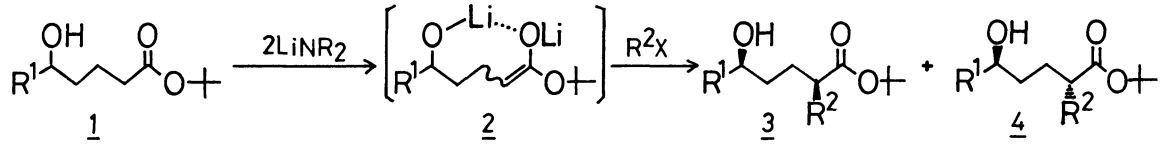
HIGHLY STEREOSELECTIVE ALKYLATION REACTION OF ESTER ENOLATES GENERATED FROM δ-HYDROXY CARBOXYLIC ACID ESTERS

Koichi NARASAKA and Yutaka UKAJI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

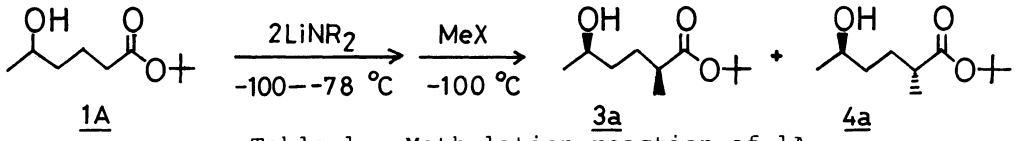
Alkylation reaction of lithium enolates generated from *t*-butyl esters of δ-hydroxy carboxylic acids by the treatment with lithium diethylamide in THF-HMPA proceeded stereoselectively to afford the corresponding *syn*-α-alkylated δ-hydroxy esters.

In recent years the synthetic challenges toward the syntheses of complex natural products have prompted extensive activity in controlling diastereoselectivity in acyclic compounds.[1] Concerning 1,3-chiral induction we have developed stereoselective methods for the preparation of *syn*-1,3-diols[2] and *syn*-3-amino-1-alkanols[3] from β-hydroxy ketones. Furthermore we have investigated the 1,4-chiral induction in acyclic systems,[4] and an efficient example of the 1,4-chiral induction directed by a hydroxyl group is realized in the stereoselective alkylation of δ-hydroxy esters.

The alkylation reaction of δ-hydroxy esters was studied based on the following hypothesis. When δ-hydroxy ester 1 is treated with 2 molar amounts of lithium amide, the resulting lithium enolate dianion 2 would form a 8-membered chelate by the interaction between lithium and oxygen atoms. Hence the successive alkylation reaction would be expected to proceed in a stereoselective manner.



By the above hypothesis, the stereoselective generation of E or Z-lithium enolate 2 should be indispensable for the high chiral induction. Therefore, we examined the generation of the enolate from 1 with LDA in THF or in THF-hexamethylphosphoric triamide (HMPA) and the trapping of each enolate with *t*-butyldimethylsilyl chloride according to the Ireland's procedure.[5] And in each case, the silyl enol ether of the different configuration was formed predominantly. Next, the lithium enolate generated from 1A in each solvent was alkylated with methyl iodide. When the alkylation reaction was performed in THF, none of the selectivity was observed. On the other hand, the alkylation of the enolate formed in THF-HMPA was found to proceed in high stereoselectivity to give a *syn*-alkylated product 3a.[6] Furthermore, it was noted that by the treatment of



1A 3a 4a

Table 1. Methylation reaction of 1A

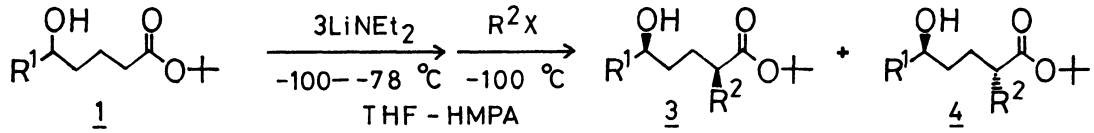
$LiNR_2$	Solvent	MeX	3a:4a
LDA	THF	MeI	56:44[a)]
LDA	THF-HMPA	MeI	87:13
LDA	THF-HMPA	Me_2SO_4	90:10
$LiNEt_2$	THF-HMPA	Me_2SO_4	92: 8

a) The reaction was performed at -78 °C.

t-butyl ester 1A with lithium diethylamide and dimethyl sulfate in THF-HMPA, higher stereoselectivity (3a:4a = 92:8) was realized (Table 1).

Based on these preliminary investigations, the stereoselective alkylation reaction of *t*-butyl 5-hydroxyhexanoate (1A) and *t*-butyl 5-hydroxynonanoate (1B) was examined in THF-HMPA. As shown in Table 2 the corresponding *syn*-δ-hydroxy-α-substituted esters 3 were found to be obtained in excellent stereoselectivity.

A typical experimental procedure is described for the methylation of *t*-butyl 5-hydroxyhexanoate: To a THF (9 mL) solution of lithium diethylamide (2.60 mmol)[7)] was added HMPA (0.87 mL, 5.20 mmol) at 0 °C under an argon atmosphere, and cooled to -100 °C. A THF (1.5 mL) solution of *t*-butyl 5-hydroxyhexanoate (163 mg, 0.87 mmol) was added to the mixture and stirred for 1 h at that temperature and gradually warmed to -78 °C during 1 h. Then the reaction mixture was cooled to



1 3 4

Table 2. Stereoselective preparations of *t*-butyl esters of δ-hydroxy-α-substituted carboxylic acids

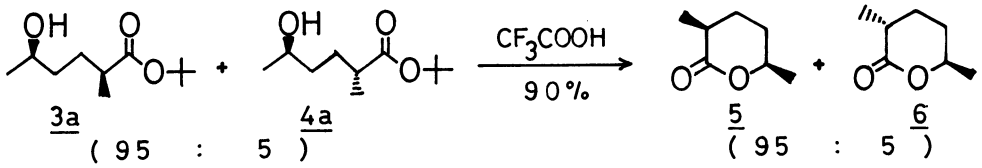
	R^1	R^2X	3:4	Total yield/%
a	CH_3	Me_2SO_4	92: 8	71
			95: 5	50[a)]
b	CH_3	*n*-BuI[b)]	93: 7	86
c	*n*-Bu	Me_2SO_4	92: 8	72
d	*n*-Bu	*n*-BuI[b)]	91: 9	75

a) Enolate formation was performed at -100 °C for 1 h.

b) After the addition of *n*-BuI, the reaction mixture was stirred for 1 h at -100 °C, and gradually warmed to -78 °C.

-100 °C, and a THF (2 mL) solution of dimethyl sulfate (342 mg, 2.71 mmol) was added. After being stirred for 70 min at -100 °C, the reaction was quenched with sat. aqueous NH_4Cl. Extraction with ether and purification by column chromatography on silica gel gave *syn*-*t*-butyl 5-hydroxy-2-methylhexanoate and the *anti*-isomer (total 124 mg, 71%) in a ratio of 92:8, respectively.[8]

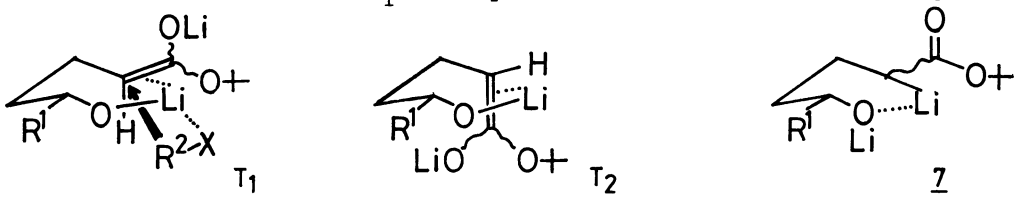
The stereochemistry of 3a and 3d was confirmed by the following observation. Acid treatment of the *syn*-alkylated ester 3a readily afforded the sex pheromone of the carpenter bee, (±)-*cis*-2-methyl-5-hexanolide (5).[9,10] The *syn*-ester 3d was also transformed to a *cis*-2-butyl-5-nonanolide, which was identical with the authentic *cis*-lactone derived from *cis*-2,5-dibutylcyclopentanone by the Baeyer-Villiger reaction.



3a + 4a (95 : 5) → 5 + 6 (95 : 5)

To confirm the influence of a hydroxyl group on the stereoselection, we examined the alkylation of *t*-butyl 5-hydroxynonanoate (1B) after the protection of the hydroxyl group as a *t*-butyldimethylsilyl ether. Although the alkylation reaction of the silyl ether proceeded smoothly, the ratio of the products was *ca.* 1:1 even when a mixture of THF-HMPA was employed as a solvent.

The effect of HMPA on the selectivity was also investigated. As mentioned before, we supposed that the stereoselection would depend on the configuration of the lithium enolate 2, and none of the stereoselection was observed in the alkylation of the enolate generated in THF. To the contrary, when the generation of the enolate from 1A in THF was followed by the addition of HMPA, the successive alkylation with dimethyl sulfate was found to proceed in remarkable selectivity (3a:4a = 81:19). The isomerization of the configuration of the enolate did not occur after the addition of HMPA by the enolate trapping examination with *t*-butyldimethylsilyl cholride. These observations indicate that the *syn*-stereoselection is controlled by the addition of HMPA without regard to the configuration of the generating lithium enolate. Accordingly, the 8-membered or 6-membered chelate of the *O*-lithium or α-*C*-lithium intermediate (2 or 7) would not be seemed to be an actual intermediate. It was reported that the regiochemistry of the enolate formation is regulated by lithium-arene π coordination.[11] The present results might be well explained by considering the chelate formation (T_1 or T_2) resulted from lithium-olefin π coordination in the enolate after the addition of HMPA.[12] Thus, the *syn*-alkylated ester 3 would be produced through the preferred transition state T_1 irrespective of the enolate configuration.



Thus the directing effect of a remote hydroxyl group on the stereoselectivity of the alkylation has good potential for use in organic synthesis.

The authors are grateful to Professor Teruaki Mukaiyama for valuable discussion during this work.

References

1) P. A. Bartlett, Tetrahedron, 36, 2 (1980).
2) K. Narasaka and F. C. Pai, Tetrahedron, 40, 2233 (1984).
3) K. Narasaka, S. Yamazaki, and Y. Ukaji, Chem. Lett., 1984, 2065.
4) T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, Tetrahedron Lett., 1978, 2741; M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and R. Steinbach, Angew. Chem., Int. Ed. Engl., 22, 989 (1983); S. R. Wilson and M. F. Price, Tetrahedron Lett., 24, 569 (1983).
5) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976).
6) The relative stereochemistry of δ-hydroxy-α-substituted esters is presented according to the Masamune's nomenclature using *syn* and *anti* terms; S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, Angew. Chem., Int. Ed. Engl., 19, 557 (1980).
7) When 2 molar amounts of lithium amide were employed, the yield of the products were remarkably decreased because of incomplete formation of the enolate.
8) Isomeric ratio was determined by capillary gas chromatography (PEG-HT).
9) Alkylation reaction of 5-hexanolide with methyl iodide gave 1:1 mixture of *cis*- and *trans*-2-methyl-5-hexanolide, see: W. H. Pirkle and P. E. Adams, J. Org. Chem., 44, 2169 (1979).
10) Recent stereoselective syntheses of *cis*-2-methyl-5-hexanolide, see: J. E. Bäckvall, S. E. Bystrom, and J. E. Nyström, the manuscript will be published in Tetrahedron; K. Mori and S. Senda, Tetrahedron, 41, 541 (1985).
11) G. H. Posner and C. M. Lentz, J. Am. Chem. Soc., 101, 934 (1979).
12) The role of HMPA is not explained clearly, but it would be supposed that the addition of HMPA transforms an aggregation form of the lithium enolate in THF.[13]
13) D. Seebach, R. Amstutz, and J. D. Dunitz, Helv. Chim. Acta, 64, 2622 (1981).

(Received November 13, 1985)