When esters **1a,b** were irradiated in the presence of ephedrine (runs 12-16), not only were the observed de very close to the ee obtained by irradiation of an achiral ester such as isopropyl 2,4-dimethyl-2-pentenoate **1f**[5b] (run 23) but also the configuration of the new asymmetric center could be deduced from the model proposed to rationalize enantioselectivities.[5b] When bulky esters **1c-e** were irradiated, the protonation, either with (+)- or (-)-ephedrine, occurs on the less hindered side. When the configuration of the new asymmetric center was expected to be the same, that is, either from the protonation of the less crowded face of the chiral dienol or as determined from the model developed for the enantioselective photodeconjugation of achiral esters in the presence of aminoalcohols (runs 18, 19, and 22), the de was similar to those observed in the absence of chiral additives. By contrast, where mismatched interactions were expected (runs 17, 20, and 21), the observed diastereoselectivities were considerably lowered.

High Diastereofacial Selectivity in Nucleophilic Additions to Chiral Acylsilanes[1]

Masahisa Nakada, Yasuharu Urano, Susumu Kobayashi, and Masaji Ohno*

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

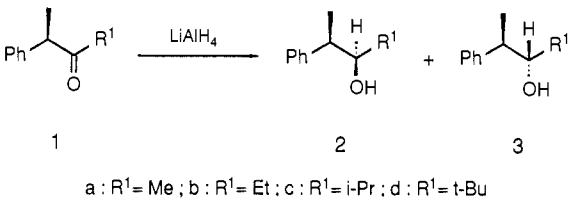
Received February 1, 1988

Asymmetric induction in nucleophilic additions to chiral aldehydes and ketones is a topic of great interest, and chiral aldehydes have been used more conveniently for the construction of many useful chiral synthons in natural product syntheses.[2] However, when the α-chiral carbonyl compounds have no ability to coordinate with metals, the 1,2-asymmetric induction is generally modest, and some more elegant approaches have been advanced recently.[2,3] In our case, it became necessary to explore more effective construction of syn moiety in the total synthesis of a new macrolide, rhizoxin.[4]

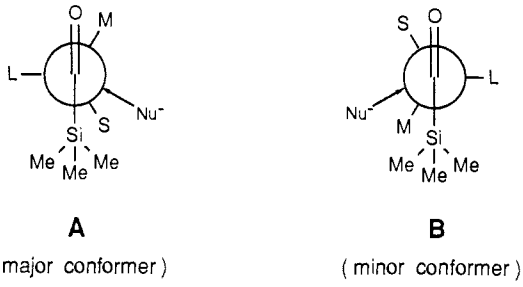
In this communication, we report that α-chiral acylsilanes show exceptional diastereofacial preferences in nucleophilic additions followed by stereospecific protiodesilylation with F^- anion to afford Cram-type isomers **7**.

The important observation and explanation by Chêrest, Felkin, and Prudent that asymmetric induction increases markedly in the series of compounds **1** (R^1 = Me, Et, *i*-Pr, and *t*-Bu) as the size of R increases[5] suggests to us to start with an aldehyde equivalent having a bulky group R^1 (Scheme I), and, chiral acylsilanes[6] were selected to be one of the most ideal chiral carbonyl compounds because of the following three characteristic points; (1) the trimethyl silyl group may be bulky[7] enough to cause strong ster-

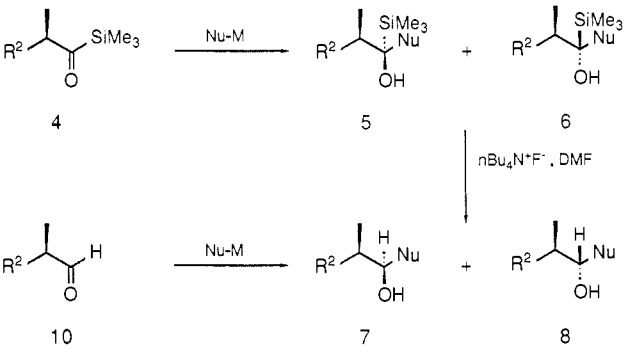
Scheme I



Scheme II



Scheme III



eodifferentiation between A and B (Scheme II), (2) the silyl group can be stereospecifically replaced with hydrogen after nucleophilic additions, and (3) the acylsilanes and α-hydroxysilanes are both considered to be easy to handle and stable (Scheme III). Thus, α-chiral acylsilane **4** (R^2 = Ph)[8] was treated with *n*-BuLi in THF at -78 °C for 5 min, affording a mixture of α-hydroxysilanes[9] **5** and **6**. The diastereomer ratio was estimated to be >100:1.[10] Subsequent treatment of the crude α-hydroxysilanes with TBAF (*n*-$Bu_4N^+F^-$)[11,12] in DMF at room temperature gave the known desilylated products **7** and **8** in a ratio of >100:1.[13,14] For comparison, the syn and anti isomers **7** and **8** were obtained from the reaction of **10** (R^2 = Ph) and *n*-BuLi in a ratio of 5:1.[15] On the

(1) Dedicated to Prof. E. J. Corey of Harvard University on the occasion of his 60th birthday.

(2) For recent papers, see: (a) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353 and references cited therein. (b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2819. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

(3) (a) Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 7199. (b) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667. (c) Yamamoto, Y.; Yamada, J. *J. Am. Chem. Soc.* **1987**, *109*, 4395.

(4) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M.; Iwasaki, S.; Okuda, S. *29th Symposium on the Chemistry of Natural Products*; Aug. 26-28, 1987; *Sapporo. Abstr.* p 110.

(5) (a) Cherest, M.; Felkin, H.; Prodent, N. *Tetrahedron Lett.* **1968**, 2199, 2205. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

(6) For preparation of acylsilanes, see: (a) Brook, A. G.; Duff, J. M.; Jones, D. F.; Davis, N. R. *J. Am. Chem. Soc.* **1967**, *89*, 431. (b) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434. (c) Reich, H. J.; Rusek, J. J.; Olson, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 2225. (d) Kang, J.; Lee, J. H.; Kim, K. S.; Jeong, J. U.; Pyun, C. *Tetrahedron Lett.* **1987**, *28*, 3261. (e) Kuwajima, I.; Arai, M.; Sato, T. *J. Am. Chem. Soc.* **1977**, *99*, 4181. (f) Kuwajima, I.; Kato, M.; Sato, T. *J. Chem. Soc., Chem. Commun.* **1978**, 478. (g) Hosomi, A.; Hashimoto, H.; Sakurai, H.; *J. Organomet. Chem.* **1979**, *175*, c1 and references cited therein.

(7) For examples of stereocontrolling methods using steric bulkiness of TMS group, see: (a) Hasan, J.; Kishi, Y.; *Tetrahedron Lett.* **1980**, *21*, 4229. (b) Wilson, S. R.; Hague, M. S.; Mistra, R. N. *J. Org. Chem.* **1982**, *47*, 747. (c) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *J. Am. Chem. Soc.* **1985**, *107*, 5541.

(8) (a) Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791. (b) Brook, A. G. *Adv. Organometallic Chem.* **1968**, *7*, 95. (c) Brook, A. G.; Quiglay, M. A.; Peddele, G. J. D.; Schwartz, N. V.; Warner, C. M. *J. Am. Chem. Soc.* **1960**, *82*, 5102.

(9) α-Hydroxysilanes were prepared and well characterized in the study of Brook rearrangement, see: Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77 and references cited therein.

(10) The ratio was determined by 400 MHz ^1H NMR analysis of the reaction mixture.

(11) TBAF (*n*-$Bu_4N^+F^-\cdot 3H_2O$, purchased from Aldrich) was used. TBAF (1 M solution in THF, Aldrich) was also effective. In THF, the reaction proceeded more slowly.

(12) During the present methdology was developed as an essential part for the total synthesis of a new macrolide, rhizoxin, a high stereoselective addition of nucleophiles to 2-(phenylthio)-3-phenyl-1-(trimethylsilyl)-1-propanone, see: Reich, H. J.; Holton, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 314. This prompted us to publish our own results.[4]

(13) The ratio was determined by 400 MHz ^1H NMR and GLC analysis.

(14) For base-induced protiodesilylation of α-hydroxysilanes in cyclic system, see: Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K.; *J. Am. Chem. Soc.* **1982**, *104*, 6809.

(15) (a) Of using crown ethers, see: Yamamoto, Y.; Maruyama, K.; *J. Am. Chem. Soc.* **1985**, *107*, 6411. (b) Of using R_4Pb, see: ref 3c.

0002-7863/88/1510-4826$01.50/0

Table I. Diastereomer Ratios in the Reactions of Nucleophiles with α-Chiral Acylsilanes

entry	R^2 (**4**)	Nu–M[a]	conditions[b]	yield[c] % (5 + 6)	α-hydroxysilane ratio[d] 5:6	yield[e] % (7 + 8)	product ratio[f] 7:8
1	Ph	*n*-Bu–Li	A	92	>100:1	89	>100:1[g]
2	Ph	Me–Li	A	96	>40:1	76	>40:1
3	Ph	allyl–TMS	B	68	>100:1	56	>1001[g]
4	Ph	allyl–MgBr	A	96	11:1	85	11:1[g]
5	1-cyclohexenyl	*n*-Bu–Li	A	56	>30:1	40	>30:1
6	1-cyclohexenyl	Me–Li	A	69	>100:1	69	>100:1
7	1-cyclohexenyl	allyl–TMS	B	50	>30:1	40	>301
8	1-cyclohexenyl	allyl–MgBr	A	69	11:1	39	11:1
9	cyclohexyl	*n*-BuLi	A	98	15:1	80	15:1
10	cyclohexyl	Me–Li	A	77	21:1	61	21:1
11	cyclohexyl	allyl–TMS	B	96	>100:1	79	>100:1
12	cyclohexyl	allyl–MgBr	A	93	3.5:1	75	3.5:1

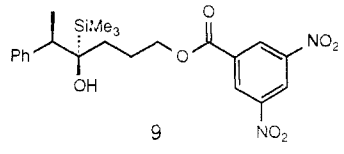
[a] Nucleophiles (2 equiv) were used. [b] A: THF, −78 °C, 5 min; B: CH_2Cl_2, $TiCl_4$ (1 equiv), −78 °C, 5 min. [c] Isolated yield. [d] Determined by 400 MHz ^1H NMR. [e] Isolated yield from **4**. [f] Determined by 400 MHz ^1H NMR. [g] Determined by GLC analysis.

Table II. Diastereomer Ratios in the Reactions of Nucleophiles with α-Chiral Aldehydes

entry	R^2 (**10**)	Nu–M[a]	conditions[b]	yield[c] % (7 + 8)	product ratio[d] 7:8
1	Ph	*n*-Bu–Li	A	91	5:1[e]
2	Ph	Me–Li	A	91	4:1
3	Ph	allyl–TMS	B	90	2:1[f]
4	Ph	allyl–MgBr	A	92	1.7:1[f]
5	1-cyclohexenyl	*n*-Bu–Li	A	40	16:1
6	1-cyclohexenyl	Me–Li	A	49	1.9:1
7	1-cyclohexenyl	allyl–TMS	B	61	1:1
8	1-cyclohexenyl	allyl–MgBr	A	54	2.5:1
9	cyclohexyl	*n*-Bu–Li	A	96	3.5:1
10	cyclohexyl	Me–Li	A	75	2:1
11	cyclohexyl	allyl–TMS	B	84	1.5:1
12	cyclohexyl	allyl–MgBr	A	59	2:1

[a] Nucleophiles (2 equiv) were used. [b] A: THF, −78 °C, 5 min; B: CH_2Cl_2, $TiCl_4$ (1 equiv), −78 °C, 5 min. [c] Isolated yield. [d] Determined by 400 MHz ^1H NMR. [e] Reference 3c. [f] Determined by GLC analysis.

other hand, the diastereomers **5** and **6** were also prepared in a ratio of 1:>50 from the reaction of **1** (R^1 = *n*-Bu) and TMSLi,[16] and then treatment of the mixture with TBAF afforded **7** and **8** in a ratio of 1:>50.[14] The protiodesilylation mentioned above was assumed to proceed with complete retention (>99%).[13] This supposition was verified by single-crystal X-ray analysis of the 3,5-dinitrobenzoate derivative of the major diastereomer of α-hydroxysilanes prepared from **4** and allyltrimethylsilane by the present methodology (entry 3, Table I),[17,18] which indeed showed it to be **9**. The extension of these reactions using various α-chiral silanes and nucleophiles was performed, representative results are shown in Table I, and direct nucleophilic additions to aldehydes **10** are also shown for comparison in Table II.



9

The results clearly showed that acylsilanes with a phenyl group at the α-position to the carbonyl group afford syn products with highly remarkable selectivity not accessible by simple addition to chiral aldehydes, and those with the cyclohexenyl and cyclohexyl groups showed less selectivity but generally much better than that of direct additions to aldehydes. Our results can be accommodated within the general framework of Felkin's model for 1,2-asymmetric induction. However, steric effects alone cannot explain the results, and an electronic effect (σ*-orbital energies) is considered to contribute equally to the stereodifferentiation.[17-19]

Thus, the utility of acylsilanes as aldehyde equivalents and the highly stereospecific protiodesilylation of α-hydroxysilanes with F^- enable us to construct syn isomers or Cram-type isomers,[20] and, considering that α-hydroxysilanes are also accessible by other methods,[21] the overall stereocontrolling methods via α-hydroxysilanes in acyclic systems are quite effective and are now applied toward the total synthesis of rhizoxin.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid for Co-operative Research A 61303017 from the Ministry of Education, Science, and Culture of Japan. We are grateful to Prof. Y. Iitaka for X-ray analysis of **9**, Prof. Hisashi Yamamoto for the detailed information of the preparation of **10** (R^2 = 1-cyclohexenyl), and Satoshi Sonoda for experimental help at the early stage.

Registry No. 1 (R^1 = *n*-Bu), 103189-52-2; **4** (R^2 = Ph), 114634-03-6; **4** (R^2 = 1-cyclohexenyl), 114634-04-7; **4** (R^2 = cyclohexyl), 114634-05-8; **5** (R^2 = Ph; Nu = *n*-Bu), 114634-06-9; **5** (R^2 = Ph; Nu = Me), 114634-07-0; **5** (R^2 = Ph; Nu = allyl), 114634-08-1; **5** (R^2 = 1-cyclohexyl; Nu = *n*-Bu), 114634-09-2; **5** (R^2 = 1-cyclohexyl; Nu = Me), 114634-10-5; **5** (R^2 = 1-cyclohexyl; Nu = allyl), 114634-11-6; **5** (R^2 = cyclohexyl; Nu = *n*-Bu), 114634-12-7; **5** (R^2 = cyclohexyl; Nu = Me), 114634-13-8; **5** (R^2 = cyclohexyl; Nu = allyl), 114634-14-9; **6** (R^2 = Ph; Nu = allyl), 114634-17-2; **6** (R^2 = 1-cyclohexenyl; Nu = allyl), 114634-18-3; **6** (R^2 = cyclohexyl; Nu = allyl), 114634-19-4; **6** (R^2 = cyclohexyl; Nu = *n*-Bu), 114634-22-9; **6** (R^2 = Ph; Nu = *n*-Bu), 114634-24-1; **7** (R^2 = Ph; Nu = *n*-Bu), 56844-72-5; **7** (R^2 = Ph; Nu = Me), 40960-66-5; **7** (R^2 = Ph; Nu = allyl), 74333-47-4; **7** (R^2 = 1-cyclohexenyl; Nu = *n*-Bu), 114222-04-7; **7** (R^2 = 1-cyclohexenyl; Nu = Me), 114222-00-3; **7** (R^2 = 1-cyclohexenyl; Nu = allyl), 114634-15-0; **7** (R^2 = cyclohexyl; Nu = *n*-Bu), 114222-08-1; **7** (R^2 = cyclohexyl; Nu = Me), 114222-06-9; **7** (R^2 = cyclohexyl; Nu = allyl), 114634-16-1; **8** (R^2 = Ph; Nu = allyl), 74333-46-3; **8** (R^2 = 1-cyclohexenyl; Nu = allyl), 114634-20-7; **8** (R^2 = cyclohexyl; Nu = allyl), 114634-21-8; **8** (R^2 = cyclohexyl; Nu = *n*-Bu), 114222-09-2; **8** (R^2 = Ph; Nu = *n*-Bu), 56844-77-0; **8** (R^2 = Ph; Nu = Me), 56907-39-2; **8** (R^2 = 1-cyclohexenyl; Nu = *n*-Bu), 114222-05-8; **8** (R^2 = 1-cyclohexenyl; Nu = Me), 114222-01-4; **8** (R^2 = cyclohexyl; Nu = Me), 114222-07-0; **9**, 114634-23-0; **10** (R^2 = Ph), 34713-70-7; **10** (R^2 = 1-cyclohexenyl), 114221-81-7; **10** (R^2 = cyclohexyl), 97859-57-9; allyltrimethylsilane, 762-72-1.

Supplementary Material Available: Structural and physical data for all new compounds, X-ray data for **9**, and the structure of rhizoxin (15 pages). Ordering information is given on any current masthead page.

(16) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063.

(17) The crystalline benzoate **9** was prepared from **8** (see: entry 3, Table I) by four-step reactions (allyltrimethylsilane/$TiCl_4$, BH_3·SMe_2, H_2O_2–NaOH, and 3,5-dinitrobenzoylchloride/Py) in a good overall yield and purified by recrystallization from methanol, mp 104–105 °C.

(18) The important effect of σ*-orbital energies in diastereoface differentiation in additions to α-chiral aldehydes is persuasively well discussed by Heathcock and Lodge in ref 2.

(19) A preliminary study showed that the diastereoselectivity in the cases of **4** (R^2 = *n*-alkyl) and β-chiral acylsilanes was not high.

(20) Some nucleophiles cause rearrangement. For the rearrangement of 1-(trimethylsilyl)allylic alkoxides, see: Endo, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495 and references cited therein.

(21) (a) For the hydroboration of vinylsilane, see: de Jesus, M.; Rusario, O.; Larson, G. L. *J. Organomet. Chem.* **1977**, *132*, 301. (b) For the dipolar addition of acetonitrile oxide with vinylsilane, see: Bankov, J. I.; Burlachenko, G. S.; Lutsenko, I. F. *J. Organomet. Chem.* **1965**, *3*, 478. (c) For the epoxide ring opening of epoxysilane, see: Hudrlik, P. F.; Arcoleo, J. P.; Schwartz, R. H.; Mistra, R. N.; Rona, R. J. *Tetrahedron Lett.* **1977**, 591.