Tetrahedron Letters,Vol.26,No.7,pp 861-864,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00
©1985 Pergamon Press Ltd.

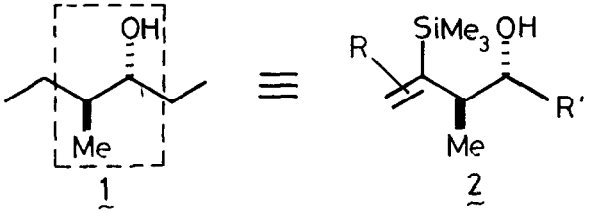
ENANTIO- AND DIASTEREO-CONTROLLED SYNTHESIS OF (+)- AND (-)-ELDANOLIDE BASED ON ASYMMETRIC PINACOL-TYPE REARRANGEMENT

Keisuke Suzuki, Takeshi Ohkuma, and Gen-ichi Tsuchihashi*

Department of Chemistry, Faculty of Science and Technology,
Keio University, Hiyoshi, Yokohama 223, Japan

Summary: *Highly enantio- and diastereo-controlled synthesis of chiral pheromone, eldanolide, was accomplished in both enantiomeric forms, via organoaluminum-mediated asymmetric pinacol-type rearrangement followed by stereoselective reduction.*

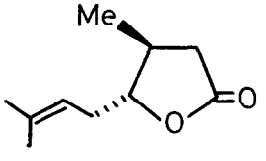
Stereo-defined β-methyl alcohol 1 constitutes a common subunit in various natural products.



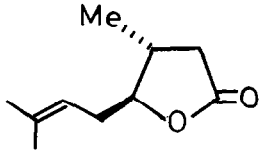
1 ≡ 2

We have reported a novel and highly stereoselective approach to this class of stereostructure in the form of chiral *threo*-β-methyl homoallylic alcohol 2. Thereby, the stereo-regulations are executed by (1) the asymmetric pinacol-type rearrangement promoted by Et_3Al (enantio-control),[1a] and (2) the highly *threo*-selective reduction of α-alkenyl ketones (diastereo-control),[1b] utilizing Me_3Si group as an efficient controlling factor. Moreover, availability of both (R)- and (S)-lactate esters of high enantiomeric purities, in conjunction with this process, provides a facile and general access to the chiral building block 2 in both enantiomeric forms,[1c] which satisfies the basic criterion in the synthesis of optically active insect pheromones.[2]

In this communication, we wish to report a total synthesis of (+)- and (-)-eldanolide 3, a wing gland pheromone of african sugar-cane borer Eldana saccharina (Wilk.),[3] by way of the methodology stated above.



(3S,4R)-3
— natural



(3R,4S)-3
— unnatural

(3S,4R)-(+)-Eldanolide (natural) (3): As the natural eldanolide was shown to possess (3S,4R)-stereochemistry,[3b] our synthesis of this enantiomer started with the (S)-lactamide derivative 4, easily available from (S)-ethyl lactate.[1] Condensation of 4 with 3-methyl-2-butenyl-1-magnesium bromide under carefully controlled conditions (1.5 equiv. /THF, 0°C, 4.0 h) gave the prenylated ketone 5 in 80 % yield. The regioisomeric ratio of this prenylation reaction was 20 / 1 (allylation at *primary* vs *tertiary* position)[4] and these isomers were easily separated with flash chromatography on silica gel (hexane/AcOEt 97/3).[5] Next, introduction of the vinylsilane moiety, the latent migrating group, was performed by the use of organocerium reagent[6] to afford 6 in 91 % yield. The same transformation using the corresponding lithium or magnesium reagents was unsatisfactory due to the highly enolizable nature of the ketone 5 and the yields were less than 40 %. The ethoxyethyl group was removed to afford 7.[7]

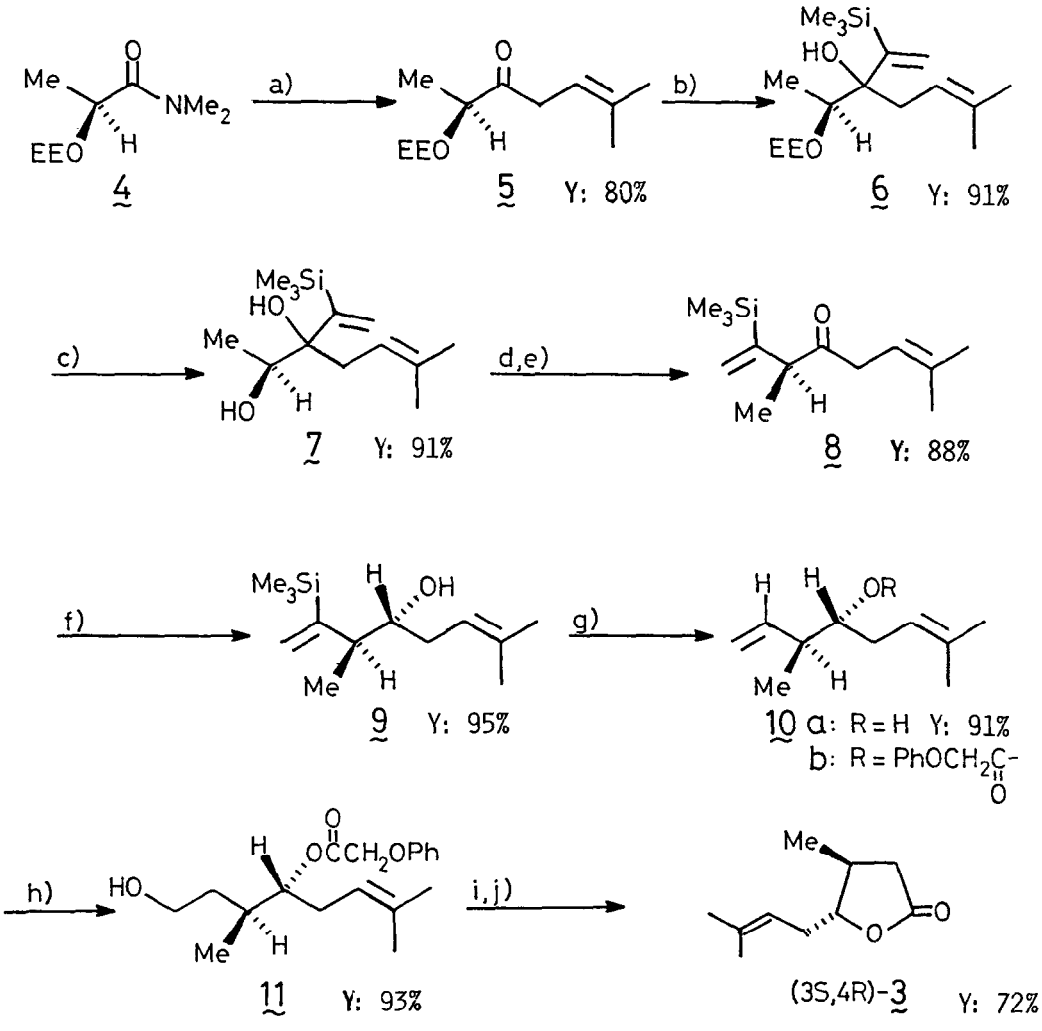
With the diol 7 in hand, the pinacol-type rearrangement was carried out under the conditions previously stated:[1a] Mesylation of 7 with MsCl-Et_3N gave the corresponding *sec*-mesylate in essentially quantitative yield. After simple extractive purification, the mesylate was treated with Me_3Al[8] in CH_2Cl_2 (1.5 equiv., -78°C, 0.5 h) to afford the rearranged α-alkenyl ketone 8[9] in 88 % yield after purification on silica-gel column chromatography (hexane/AcOEt 97/3).

Stereoselective reduction of the α-alkenyl ketone 8 was effected by $LiB(C_2H_5)_3H$ (Super-Hydride)(2.0 equiv. / THF, -78°C; H_2O_2) to result in the exclusive formation of *threo*-9 (*threo/erythro* = >99/1 by glc),[10] while the same reduction with L-Selectride, the preferred reagent in our model study,[1b] was rather sluggish. Reduction with DIBAL was also highly stereoselective in this case (*threo/erythro* 53/1). In any case, highly *threo*-selective reduction of 8 provided diastereomerically pure *threo*-9, which is reasonably understood in terms of the Felkin-Anh's model.[11] Thus, the key intermediate 9 was obtained with high enantiomerical and diastereomerical purities.[12]

Conversion of 9 into eldanolide was accomplished as follows; the Brook-type rearrangement of 9 gave the desilylated alcohol 10a in 91 % yield, which was converted to phenoxyacetate 10b quantitatively. Selective hydroboration of 10b with dicyclohexylborane followed by oxidation gave the alcohol 11 in 93 % yield. Finally, alcohol 11 was oxidized to carboxylic acid, which in turn was converted to eldanolide 3 by successive base-acid treatment ($[\alpha]_D^{28}$ +58.1°(c 1.29, MeOH), lit. $[\alpha]_D^{20}$ +51.5°(c 1.15, MeOH)[3b]). Thus, a highly stereo-controlled synthesis of (3S,4R)-(+)-eldanolide was achieved based on asymmetric pinacol-type rearrangement in an overall yield of 30 %.[13]

(3R,4S)-(-)-Eldanolide (unnatural) (3): Availability of (R)-series of methyl lactate[14] allowed an access to the antipode of the pheromone, (3R,4S)-(-)-eldanolide *via* the completely same sequence described above; $[\alpha]_D^{23}$ -57.5° (c 1.37, EtOH) (lit. $[\alpha]_D^{21}$ -52.4°(c 1.51, EtOH),[3b] $[\alpha]_D^{21}$ -55.9°(c 0.81, EtOH)[15a]).

Chiral synthesis of eldanolide has been reported by three groups up to the present,[3b,15a,b] the synthesis reported herein adds a novel and highly efficient approach to this chiral pheromone.



a) $Me_2C{=}CHCH_2MgBr$ / THF, 0°C, slow addition during 1.5 h, then 2.5 h at 0°C, b) $H_2C{=}C(SiMe_3)Li - CeCl_3$ / THF - Et_2O - hexane (4/1/1), -78°C, 0.5 h, c) cat. PPTS/ MeOH, rt, 1 h, d) MsCl - Et_3N / CH_2Cl_2, 0°C, 5 min, e) Me_3Al / CH_2Cl_2, -78°C, 0.5 h, f) $LiB(C_2H_5)_3H$ / THF, -78°C, 5 min; H_2O_2, g) cat. NaH / HMPA, rt, 10 min; $PhOCH_2COCl$ / pyridine-CH_2Cl_2, rt, 10 min, h) cyclo-$(C_6H_{11})_2BH$ / THF, 0°C, 3h; H_2O_2, pH 7 phosphate buffer, i) CrO_3 / pyridine, rt, 12 h, j) LiOH / EtOH-H_2O; dil HCl.

Acknowledgment

The present authors are grateful to Dr. Yasushi Yokoyama, Yokohama National University, for providing us the spectroscopic data of eldanolide, and to Dr. Tsuneo Imamoto, Chiba University, for valuable information on the organocerium reagent. Thanks are also due to Dr. Shuichi Mitamura, Chemical Research Lab., Nippon Steel Corp., for measurement of ^{13}C NMR.

References and Notes

1) a) K. Suzuki, E. Katayama, and G. Tsuchihashi, Tetrahedron Lett., 25, 1817 (1984).
b) K. Suzuki, E. Katayama, and G. Tsuchihashi, *ibid.*, 25, 2479 (1984).
c) G. Tsuchihashi, K. Tomooka, and K. Suzuki, *ibid.*, 25, 4253 (1984).

2) K. Mori, "The Total Synthesis of Natural Products," J. ApSimon Edn., Vol. 4, pp 1-183, J. Wiley & Sons, N. Y. (1981).

3) a) G. Kunesch, P. Zagatti, J. Y. Lallemand, A. Debal, and J. P. Vigneron, Tetrahedron Lett., 22, 5271 (1981).
b) J. P. Vigneron, R. Méric, M. Larchevêque, A. Debal, G. Kunesch, P. Zagatti, and M. Gallois, *ibid.*, 23, 5051 (1982).

4) Regioisomeric behavior of substituted allylic organometallics; see G. Courtois and L. Miginiac, J. Organomet. Chem., 69, 1 (1974). Although this type of allylation could be a reversible process and the product composition may be a function of time, no detailed study on this point was done in the present case; for the reversibility of the reaction, see F. Barbot and Ph. Miginiac, Bull. Chim. Soc. Fr., 1977, 113.

5) W. C. Still, M. Kahn, and M. Mitra, J. Org. Chem., 43, 2923 (1978).

6) T. Imamoto, Y. Sugiura, and N. Takiyama, Tetrahedron Lett., 25, 4233 (1984).

7) Diol 7 was an approximately 1/1 mixture of diastereomers, which was further used without separation.

8) Although Et_3Al worked equally well, slightly better yield was achieved by the use of Me_3Al.

9) 8: Bp 65-75°C / 0.25 mmHg (bath temp.); ^1H NMR (CCl_4): δ = 0.10 (s, 9H), 1.05 (d, J=9Hz, 3H), 1.55 (s, 3H), 1.65 (s, 3H), 2.85 (d, J=8.5Hz, 2H), 3.2 (q, J=9Hz, 1H), 4.95-5.3 (m, 1H), 5.45 (d, J=3Hz, 1H), 5.55 (d, J=3Hz, 1H); IR (neat): 1715 cm^{-1}; $[\alpha]_D^{27}$ +194° (c 1.01, $CHCl_3$).

10) *Threo*-9: Bp 60-70°C / 0.1 mmHg (bath temp.); ^1H NMR (CCl_4): δ = 0.10 (s, 9H), 0.85 (d, J= 9Hz, 3H), 1.2 (broad, 1H), 1.55 (s, 3H), 1.65 (s, 3H), 1.7-2.5 (m, 3H), 3.3 (dt, J_1=4.5Hz, J_2= 7.5Hz, 1H), 4.9-5.2 (m, 1H), 5.3 (d, J=3Hz, 1H), 5.55 (d, J=3Hz, 1H); $[\alpha]_D^{26}$ -11° (c 2.02, $CHCl_3$); high-resolution MS: Found: *m/e* 211.1500. Calcd for $C_{12}H_{23}OSi$: 211.1516 $(M-CH_3)^+$. Glc conditions: PEG-20M, 1m × 5mm, 110°C; the authentic mixture of *threo/erythro*-9 was prepared by the reduction of 8 at relatively higher temperature with $LiAlH_4$ in refluxing Et_2O.

11) F. Sato *et al.* independently reported this sense of diastereofacial selection; see F. Sato, Y. Takeda, H. Uchiyama, and Y. Kobayashi, J. Chem. Soc., Chem. Commun., 1984, 1132.

12) The ee of the intermediate 9 was estimated by HPLC analysis of its MTPA ester (J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).) to be over 98 % ee in both (S)- and (R)-9, respectively. Conditions: ZORBAX SIL 4.6mm × 25cm (DuPont) hexane/ CH_2Cl_2 95/5. These results were further confirmed by 100 MHz ^{13}C NMR measurements of the esters; we are indebted to Associate Professor Kazuhiko Saigo and Dr. Noriyuki Yonezawa, the University of Tokyo, for the measurements.

13) Eldanolide 3: Bp 80-90°C / 2 mmHg (bath temp.); ^1H NMR ($CDCl_3$) : δ = 1.13 (d, J=6Hz, 3H), 1.61 (s, 3H), 1.73 (s, 3H), 2.0-2.9 (m, 5H), 4.03 (dt, J_1=J_2=6Hz, 1H), 5.0-5.3 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 17.66, 17.93, 25.79, 32.18, 35.10, 37.00, 87.06, 118.04, 135.27, 176.44; IR (neat): 1780 cm^{-1}; high-resolution MS: Found: *m/e* 168.1120. Calcd for $C_{10}H_{16}O_2$, 168.1149 (M^+).

14) (R)-Methyl lactate was kindly donated from Daicel Chem. Ind., Ltd.

15) a) T. Uematsu, T. Umemura, and K. Mori, Agric. Biol. Chem., 47, 597 (1983).
b) Y. Yokoyama and M. Yunokihara, Chem. Lett., 1983, 1245.

(Received in Japan 13 November 1984)