Stereochemistry of an Oxidative 1,4-Fragmentation of γ-Stannyl Alcohols with a Hypervalent Organoiodine Compound and the Synthesis of *erythro*-6-Acetoxyhexadecan-5-olide

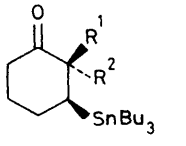
Masahito Ochiai,[a] Tatsuzo Ukita,[b] Yoshimitsu Nagao,[a] and Eiichi Fujita*[a]

[a] *Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan*
[b] *Department of Synthetic Chemistry, Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., Yodogawa-Ku, Osaka 532, Japan*

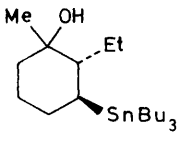
Iodine(III)-mediated oxidative 1,4-fragmentation of the 2,3-*trans*- and 2,3-*cis*-3-stannyl alcohols, (**6a,b**) and (**6c**), proceeds stereospecifically to give the *E*- and *Z*-enals, (**7**) and (**8**), respectively, and stereoselective synthesis of the mosquito pheromone, *erythro*-6-acetoxyhexadecan-5-olide (**5**), starting from the *E*-enal (**7**), was accomplished.

1,4-Fragmentation reactions provide a useful tool for the stereoselective synthesis of acyclic and macrocyclic compounds.[1,2] The stereochemistry and yields of the products, and the reaction rates depend upon the stereochemical arrangement of nucleofugal and electrofugal groups,[1] especially in one-step synchronous fragmentations.[3] Iodine(III)-mediated oxidative 1,4-fragmentation of the cyclic γ-stannyl alcohols has been reported to give unsaturated carbonyl compounds in good yields.[4] We have now examined the stereochemical course of the fragmentation reaction and the results obtained have been applied to the synthesis of *erythro*-6-acetoxyhexadecan-5-olide (**5**).[5]

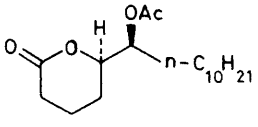
Conjugate addition of tributylstannyl-lithium to cyclohex-2-en-1-one in tetrahydrofuran (THF) followed by alkylation of the resulting lithium enolate with n-decyl iodide afforded the *trans*-ketone (**1**) stereoselectively in 47% yield. A similar stereochemical outcome was observed in the synthesis of 3-(dimethylphenylsilyl)-2-methylcyclohexan-1-one from cyclohex-2-en-1-one.[6,7] The $LiAlH_4$ reduction of (**1**) produced a mixture of stereoisomers, from which 2,3-*trans*-alcohols (**6a**) and (**6b**) were isolated by silica gel column chromatography using hexane–ethyl acetate (10:1) in 51 and 29% yields, respectively. The relative stereochemistry of these alcohols was determined using ^1H and ^{13}C n.m.r. spectroscopic data: (**6a**) δ_H 3.36 (dt, *J* 4, 10 Hz, C-1–H), δ_C 73.9 [$^3J(^{119}Sn–^{13}C)$ 63 Hz, C-1]; (**6b**) δ_H 3.93 (dt, *J* 4, 2.5 Hz, C-1-H), δ_C 67.5 [$^3J(^{119}Sn–^{13}C)$ 43 Hz, C-1]. Karplus-type dependence of vicinal $^{119}Sn–^{13}C$ coupling has been demonstrated to exist in a series of stereochemically rigid organotin compounds.[8] 2,3-*cis*-Alcohol (**6c**) was synthesized as follows: isomerization of (**1**) with NaOH in dioxane–MeOH–water afforded an inseparable mixture of *trans*- and *cis*-ketones, (**1**) and (**2**), in a 62:38 ratio (96% yield), which was reduced with $LiAlH_4$ in THF to give (**6a**), (**6b**), and (**6c**) in a 43:21:36 ratio (96% yield).[9]



(**1**) R^1 = H, R^2 = n-$C_{10}H_{21}$
(**2**) R^1 = n-$C_{10}H_{21}$, R^2 = H
(**3**) R^1 = H, R^2 = Et



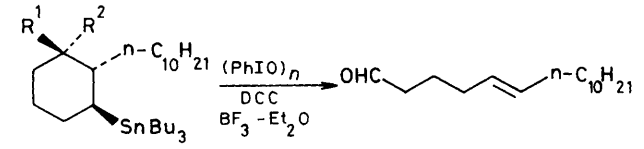
(**4**)



(**5**)

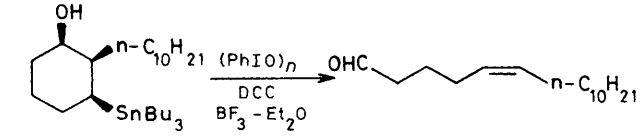
Oxidative 1,4-fragmentation of γ-tributylstannyl alcohols (**6**) was found to proceed in a completely stereospecific manner: the 2,3-*trans*-alcohol (**6a**) on treatment with iodosylbenzene, dicyclohexylcarbodiimide (DCC), and boron trifluoride–diethyl ether in dichloromethane at room temperature for 2 h afforded the *E*-enal (**7**)† in 77% yield, after purification by preparative t.l.c. using hexane–ethyl acetate (9:1); (**6b**) on the same treatment gave (**7**) in 91% yield. The

† *Selected spectroscopic data:* (**7**), i.r. (neat): 2700, 1730, 965, and 720 cm^{-1}; ^1H n.m.r. (400 MHz; $CDCl_3$): δ 0.88 (t, 3H, *J* 6.5 Hz), 1.20—1.38 (m, 16H), 1.70 (quint., 2H, *J* 7.0 Hz), 1.97 (q, 2H, *J* 7.0 Hz), 2.03 (q, 2H, *J* 7.0 Hz), 2.42 (dt, 2H, *J* 2.0 and 7.0 Hz), 5.34, 5.43 [AB type, each 1H, *J* 15.1 Hz; each signal showed a vicinal coupling (t, *J* 7.0 Hz)], and 9.77 (t, 1H, *J* 2.0 Hz); mass spectrum *m/z* 238 (M^+), 220, 194, 166, 98, 82, and 54; M^+: found, 238.2308 (calc. for $C_{16}H_{30}O$, 238.2296).



(**6a**) R^1 = OH, R^2 = H (**7**)

(**6b**) R^1 = H, R^2 = OH



(**6c**) (**8**)

400 MHz ^{1}H n.m.r. spectra of the products from the fragmentation of (**6**) did not show any signals due to *Z*-enal (**8**). On the other hand, 2,3-*cis*-alcohol (**6c**) gave only the *Z*-enal (**8**)‡ in 45% yield. Thus, the stereochemistry of oxidative fragmentation products depends entirely upon the relative configuration between the substituent at C-2 and tributylstannyl group at C-3; the configuration of the hydroxy group has no effect. Similarly 1,4-fragmentation of an epimeric mixture of alcohol (**4**), prepared from the ketone (**3**) by the reaction with methyl-lithium in THF, gave *E*-non-3-en-8-one stereoselectively in 69% yield. The latter has been shown to be an important intermediate for the synthesis of *endo*-brevicomin.[10]

Stereoselective synthesis of *erythro*-6-acetoxyhexadecan-5-olide (**5**), the major component of a mosquito oviposition attractant pheromone, from the fragmentation product (**7**) was carried out: oxidation of the *E*-enal (**7**) with sodium chlorite[11] at room temperature for 17 h gave *E*-hexadec-5-enoic acid in 84% yield. Epoxidation of the olefinic acid by treatment with *m*-chloroperbenzoic acid in toluene–cyclohexane at room temperature for 6 h, lactonisation of the resulting oxirane by heating in toluene–cyclohexane at reflux for 24 h, and subsequent acetylation with acetic anhydride in pyridine at room temperature for 48 h afforded the desired compound (**5**) in 40% yield. The structure of (**5**) was confirmed by the comparison of the 400 MHz ^{1}H n.m.r. spectrum with that of the authentic pheromone.

We are grateful to Prof. K. Mori for a gift of the n.m.r. spectrum of the pheromone.

Received, 3rd December 1984; Com. 1708

‡ *Selected spectroscopic data:* (**8**), i.r. (neat): 2720 and 1720 cm^{-1}; ^{1}H n.m.r. (400 MHz; $CDCl_3$): δ 0.88 (t, 3H, *J* 6.8 Hz), 1.20—1.38 (m, 16H), 1.70 (quint., 2H, *J* 7.0 Hz), 2.00 (br. q, 2H, *J* 7.0 Hz), 2.08 (br. q, 2H, *J* 7.0 Hz), 2.43 (dt, 2H, *J* 1.5 and 7.0 Hz), 5.31, 5.42 [AB type, each 1H, *J* 11.0 Hz; each signal showed vicinal and allylic couplings (tt, *J* 7.0 and 1.5 Hz)], and 9.77 (t, 1H, *J* 1.5 Hz); mass spectrum *m/z* 238 (M^+), 220, 194, 166, 98, 68, and 54; M^+: found, 238.2312 (calc. for $C_{16}H_{30}O$, 238.2296).

References

1 C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, 1976, **6**, 1; C. A. Grob, *ibid.*, 1969, **8**, 535.
2 T. Wakabayashi and K. Watanabe, *J. Synth. Org. Chem., Jpn.*, 1980, **38**, 853.
3 P. Deslongchamps, 'Stereoelectronic Effects in Organic Chemistry,' Pergamon Press, Oxford, 1983, p. 257.
4 M. Ochiai, T. Ukita, Y. Nagao, and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 1984, 1007.
5 B. R. Laurence and J. A. Pickett, *J. Chem. Soc., Chem. Commun.*, 1982, 59; C. Fuganti, P. Grasselli, and S. Servi, *ibid.*, 1982, 1285; K. Mori and T. Otsuka, *Tetrahedron*, 1983, **39**, 3267.
6 I. Fleming, 7th International Symposium on Organosilicon Chemistry, Japan, Kyoto, 1984, 1B1130.
7 'Carbon-Carbon Bond Formation,' ed. R. L. Augustine, Marcel Dekker, New York, 1979, vol. 1, p. 220.
8 D. Doddrell, I. Burfitt, W. Kitching, M. Bullpitt, C.-H. Lee, R. J. Mynott, J. L. Considine, H. G. Kuivila, and R. M. Sarma, *J. Am. Chem. Soc.*, 1974, **96**, 1640; G. Wickham, H. A. Olszowy, and W. Kitching, *J. Org. Chem.*, 1982, **47**, 3788.
9 Similar stereoselectivity has been observed on the reduction of *cis*-2,3-dimethylcylcohexan-1-one with KBH_4; W. Cocker, T. B. H. McMurry, and E. R. Simmons, *J. Chem. Soc.*, 1965, 3022.
10 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1981, vol. 4, p. 72.
11 B. S. Bal, W. E. Childers, and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091.